THE UNIVERSITY OF QUEENSLAND

AUSTRALIA

Impact of drug warning system on prescriptions

Suvimol Niyomnaitham

MD, MSCE

A thesis submitted for the degree of Doctor of Philosophy at

The University of Queensland in 2014

School of Pharmacy

Abstract

The emergence of a serious adverse effect from a recently marketed drug is a great concern. The earlier we can detect and evaluate those unwanted effects, the better we can prevent them. Regulatory authorities play an important role in detecting, assessing and informing healthcare professionals and consumers on drug safety issues. Regulatory authorities use drug safety warnings as a communication tool for notifying prescribers about the risk and providing the recommendation for their practices. Expected outcomes of drug safety warnings are prescribers' awareness of these risks and a change in their prescribing according to the safety information. However, effectiveness of these safety warnings on clinical practice had been reviewed and led to recommendation for reform in Australia.

Several studies in the US and Europe have investigated the effect of regulatory warnings on clinical practice with the ultimate aim to improve the effectiveness of drug warning systems. To date limited studies are available on the effects of regulatory warning systems in Australia. Given global access to medicines and the importance of timely post-marketing surveillance on new drugs, drug safety regulation has an international focus. Medicine use in Australia is influenced not only by the local drug authority, Therapeutic Goods Administration (TGA), but also key international drug regulatory bodies such as the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Therefore, an understanding of the impact of national and international drug warnings on clinical practice is needed. Recent drug warnings on risks related to the thiazolidinedione drug class (rosiglitazone and pioglitazone) and the proposed drug-drug interaction between clopidogrel and proton pump inhibitors (PPIs) provide excellent case studies to assess the impact of drug safety warnings on medicine use in Australia.

First, a time series analysis was used to examine the changes of rosiglitazone and pioglitazone use after the release of international and local warnings. The impact size of each warning on i) dispensing patterns in the Pharmaceutical Benefit Scheme (PBS)—national dispensing database and ii) prescribing patterns in the AsteRx clinical database was investigated using an auto regressive, integrated, moving average (ARIMA) statistical model. The PBS data displayed a nationwide trend of drug dispensing, whereas the prescribing trend in the AsteRx provided more specific details on switching choices and other factors associated with prescribing decisions. For warnings on a definite and serious

cardiovascular effect related to rosiglitazone, a decline in the use of rosiglitazone was observed immediately after the warning from the FDA and EMA in May 2007. No significant further effect on the use of rosiglitazone was observed following the warning by the TGA, announced in December 2007. Warnings on the risk of bladder cancer, a low incidence outcome related to long-term pioglitazone treatment in June–July 2011 did not have any significant effect on the ongoing decline of pioglitazone use.

Second, a similar time-series analysis was used to assess the effect of warnings regarding a possible drug-drug interaction between clopidogrel and proton pump inhibitors in AsteRx coprescribing data. Compared to the warnings on adverse effects of thiazolidinediones, warnings regarding the clopidogrel-PPI interaction were inconsistent, largely due to the conflicting and inconclusive clinical evidence. The FDA and EMA suggested avoiding concomitant esomeprazole and omeprazole with clopidogrel in 2009, and recommended use of pantoprazole. However, the TGA refrained from providing specific advice. Although esomeprazole was the most commonly coprescribed PPIs with clopidogrel in Australian clinical practice during 2006–2012, an increasing trend of coprescribing pantoprazole was observed after international warnings in 2009. This increasing trend found to be a result of switching from omeprazole and esomeprazole to pantoprazole.

The third component of this thesis developed and piloted a survey tool to elicit the beliefs and behaviour of Australian prescribers in response to safety warnings. Results show that a large proportion of survey responders did not receive any direct drug safety communication from the TGA (e.g. TGA's safety advisory email or TGA's website). NPS MedicineWise and Australian prescriber were popular sources of drug safety information among survey participants. The changes in patterns of rosiglitazone and pioglitazone corresponded to a high awareness of the cardiovascular risk associated with rosiglitazone and a low awareness of the bladder cancer risk related to pioglitazone. Despite a non-specific warning from the TGA, half of responders knew of the interaction between clopidogrel and PPIs.

These results suggest that changes in patterns of concerned drugs were associated with international warnings, which may get through to Australian prescribers via NPS MedicineWise or other medical associations. In summary, the impact on drug use depends on the intensity and clarity of warnings as well as the certainty, severity and prevalence of adverse effects. This thesis expands the current understanding of the impact of regulatory

safety warnings on prescriptions and also provides the scope for possible improvement to the warning system in Australia.

Declaration by author

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

I have clearly stated the contribution of others to my thesis as a whole, including statistical assistance, survey design, data analysis, significant technical procedures, professional editorial advice, and any other original research work used or reported in my thesis. The content of my thesis is the result of work I have carried out since the commencement of my research higher degree candidature and does not include a substantial part of work that has been submitted to qualify for the award of any other degree or diploma in any university or other tertiary institution. I have clearly stated which parts of my thesis, if any, have been submitted to qualify for another award.

I acknowledge that an electronic copy of my thesis must be lodged with the University Library and, subject to the policy and procedures of The University of Queensland, the thesis be made available for research and study in accordance with the Copyright Act 1968 unless a period of embargo has been approved by the Dean of the Graduate School.

I acknowledge that copyright of all material contained in my thesis resides with the copyright holder(s) of that material. Where appropriate I have obtained copyright permission from the copyright holder to reproduce material in this thesis.

Suvimol Niyomnaitham

Publications during candidature

Peer-reviewed paper

Niyomnaitham S, Page A, Caze AL, Whitfield K, Smith AJ. Utilisation trends of rosiglitazone and pioglitazone in Australia before and after safety warnings. *BMC Health Services Research 2014, 14:151*

Niyomnaitham S, Caze AL, Whitfield K, Smith AJ. Impact of regulatory warnings on prescribing rosiglitazone and pioglitazone in Australia. *Submitted to Research in Social & Administrative Pharmacy 2014*

Niyomnaitham S, Caze AL, Smith AJ. Pattern of the concomitant use of antisecretory drugs with clopidogrel in Australia including changes after the international clopidogrel-PPI warnings. *Submitted to Pharmacoepidemiology and Drug Safety 2014*

Conference abstracts: poster presentations

Niyomnaitham S, Caze AL, Whitfield K, Smith A. Changes in coprescribing antisecretory drugs with clopidogrel in clinical practices. Australasian Pharmaceutical Science Association Conference, Dunedin, New Zealand, December 2013.

Niyomnaitham S, Caze AL, Whitfield K, Smith A. Utilization and government subsidized cost of antisecretory drugs among elderly in Australia and New Zealand. International Conference of Pharmacoepidemiology, Taiwan, October 2014.

Conference abstracts: oral presentation

Niyomnaitham S, Caze AL, Whitfield K, Smith A. Changes in the prescribing of rosiglitazone and pioglitazone following safety warnings. National Medicines Symposium, Brisbane, Australia, May 2014.

Publications included in this thesis

Publication entitled "**Utilisation trends of rosiglitazone and pioglitazone in Australia before and after safety warnings**. BMC Health Services Research 2014, 14:151" was incorporated as Chapter 3.

Contributors	**Statement of contribution**
Author Suvimol Niyomnaitham (Candidate)	Designed experiments (80%) Analysis of data (90%) Wrote the paper (80%)
Author Alesha J Smith	Designed experiments (10%) Wrote and edited paper (12.5%)
Author Adam La Caze	Designed experiments (5%) Wrote and edited paper (2.5%)
Author Karen Whitfield	Designed experiments (5%) Wrote and edited paper (2.5%)
Author Andrew Page	Analysis of data (10%) Edited paper (2.5%)

Submitted manuscript entitled "**Impact of regulatory warnings on prescribing rosiglitazone and pioglitazone in Australia**." was incorporated as Chapter 4.

Contributors	**Statement of contribution**
Author Suvimol Niyomnaitham (Candidate)	Designed experiments (80%) Analysis of data (100%) Wrote the paper (85%)
Author Alesha J Smith	Designed experiments (10%)

	Wrote and edited paper (5%)
Author Adam La Caze	Designed experiments (5%) Wrote and edited paper (5%)
Author Karen Whitfield	Designed experiments (5%) Wrote and edited paper (5%)

Submitted manuscript entitled "**Pattern of the concomitant use of antisecretory drugs with clopidogrel in Australia including changes after the international clopidogrel-PPI warnings**" was incorporated as Chapter 5.

Contributors	**Statement of contribution**
Author Suvimol Niyomnaitham (Candidate)	Designed experiments (85%) Analysis of the data (100%) Wrote the paper (90%)
Author Alesha J Smith	Designed experiments (10%) Wrote and edited paper (5%)
Author Adam La Caze	Designed experiments (5%) Wrote and edited paper (5%)

Contributions by others to the thesis

Dr Alesha Smith was the principle advisor of my PhD academic committee, which included Dr Adam La Caze and Dr Karen Whitfield as associate advisors. All three advisors supervised all processes of study designs, data collection, and data analysis.

Statement of parts of the thesis submitted to qualify for the award of another degree

None.

Acknowledgements

I would like to express my gratitude to my supervisor Dr Alesha Smith for the opportunity to do my PhD under her supervision. With her academic guidance and encouragement I had a great learning experience throughout my PhD.

I would like to thank my advisors Dr Adam La Caze and Dr Karen Whitfield for their academic help and feedback throughout the project. Their support and kindness are essential for my PhD.

I would also like to thank Dr Samantha Hollingworth for her advice on the database, Dr Andrew Page for his advice on statistical analyses, and Justine Broadley for the New Zealand data extraction.

Thank you to the School of Pharmacy and staffs for their assistance in the administrative during my PhD candidature.

My gratitude goes to the PhD funding board Faculty of Medicine Siriraj Hospital, Mahidol University and University of Queensland International tuition fee scholarship for financial support during my PhD.

Many thanks to my friends—Tew, Nel, Kitty, and Bonnie who are my Australian family and provide me with their help and support.

My most wonderful family who did not quite understand what I was doing but still provides unconditionally support and encouragement throughout my life and PhD.

Keywords

Drug safety warning, regulatory authority, Therapeutic Goods Administration, drug utilisation, clopidogrel, proton pump inhibitors, thiazolidinedione, rosiglitazone, pioglitazone

Australian and New Zealand Standard Research Classifications (ANZSRC)

ANZSRC code: 160508 Health Policy, 60%

ANZSRC code: 111709 Health Care Administration, 30%

ANZSRC code: 111711 Health Information Systems (incl. Surveillance), 10%

Fields of Research (FoR) Classification

FoR code: 1117 Public Health and Health Services, 100%

Table of Contents

List of figures

List of tables

List of Abbreviations used in the thesis

ACF	Autocorrelation functions
ACS	Acute coronary syndrome
ADP	Adenosine diphosphate
ADR	Adverse drug reaction
ARIMA	Auto-regressive, integrated, moving average model
ATC	WHO anatomical therapeutic chemical classification
AUC	Area under the curve
CAD	Coronary artery disease
CDER	Center for Evaluation and Research
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CYP	Cytochrome P450
DDD	Defined Daily Dose
DES	Drug-eluting stent
DHPC	Direct Health Professional Communication
DPP-4	Dipeptidyl peptidase-4 inhibitor
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
GORD	Gastro-oesophageal reflux disease
GP	General practitioner
H2RA	Histamine 2 receptor antagonist
IRR	Incidence rate ratio
MACE	Major adverse cardiovascular event
MI	Myocardial infarction
NPS	National prescribing service

NSAID	Non-steroidal anti-inflammatory drug
NSTE	Non ST-segment elevate myocardial infarction
NYHA	New York Heart Association
PACF	Partial autocorrelation functions
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PCI	Percutaneous catheter intervention
PhVWP	PharmacoVigilance Working Party
PI	Product information
PPI	Proton pump inhibitor
PRI	Platelet reactivity index
RCT	Randomized control trial
RPBS	Repatriation Pharmaceutical Benefits Scheme
RR	Rate ratio
SAG	Scientific advisory group
TGA	Therapeutic Goods Administration
TZD	Thiazolidinedione
UK	United Kingdom
US	United States of America
VASP	Vasodilator-stimulated phosphoprotein

Chapter 1. Introduction

1. Drug safety warning system

A drug safety warning system helps to create a virtual community in the form of a network of stakeholders who communicate with each other on unwanted adverse drug reactions (ADRs) of medicines in post-marketing situations. The system consists of a set of activities taken by different parties, with the aim of improving the safety of medicine use and preventing drug-related harms.

1.1 Why is a drug warning system needed?

Pharmaceutical development has provided better medical treatment but a greater risk has also been encountered. Studies indicate that ADRs may occur in 16.88% of patients during hospitalisation and 20–70% of those events are related to preventable pharmacological properties of the involved medicines (Kongkaew et al. 2008; Miguel et al. 2012). A systemic review showed that 2–4% of all hospital admissions in Australia were from adverse drug reactions (Runciman et al. 2003). At least 80,000 drug-related hospitalisations were estimated annually in Australia, of those numbers between 32% and 69% were considered preventable events (Roughead 1999; Kalisch et al. 2012). Approximately 3–30% of all adverse drug reactions are caused by drug–drug interactions and result in hospitalisation or morbidity every year, making their early identification vital (Stanton et al. 1994; Dechanont et al. 2014; Iyer et al. 2014).

Monitoring risks of innovative products is necessary based on the fact that the pre-approval data of newly-marketed drugs is not enough to establish a complete risk-benefit profile (Berlin et al. 2008). Preclinical testing of a compound in laboratories and animals suggests possible therapeutic and adverse effects for testing in humans. Clinical testing in approximately 1,000–3,000 human participants during the drug development process is limited in the length of time, sample size, and certain subgroups of patients (Stricker et al. 2004). Moreover, clinical trials of some chronic diseases measure biomarkers or surrogates as study outcomes instead of clinical endpoints. For example, the level of haemoglobin A1c is often used as a surrogate outcome to measure the effect of new drugs for diabetes (Phillips et al. 2001; Gerstein et al. 2006). Therefore, the real risk and benefit of these medicines are not entirely known at the end of the approval process.

Clinical trials required for the current drug approval process are generally divided into 3 phases. Phase I trials are conducted in a small number of healthy volunteers (20–100) to determine the pharmacodynamics, pharmacokinetics and intoxicated dosage in humans. Typically 100–300 patients who have the target disease are included in the Phase II testing to obtain the efficacy and possible side effects. The daily dosage and regimen are also identified in Phase II. During Phase III trials, ten to thousands of patients (depending on prevalence of the disease) are randomly assigned the treatments to examine the rate of primary outcomes and to generate adverse event profiles. Although a larger number of patients are exposed to a drug in Phase III testing, only relatively frequent adverse events can be detected. For example, a total of 3000 patients would provide a 95% chance of detecting any adverse events, which occur in at least one out of 1000 exposed patients. A smaller sample of 1000 patients would detect any adverse events that occur at a rate of 6 in 1000 patients (Berlin et al. 2008).

Therefore the sample sizes in these premarketing phases are insufficient to detect less common adverse events or establish a full safety profile at the time of approval (Wahab et al. 2013). There are several other reasons why adverse reactions emerge after approval and widespread use of a drug (WHO 2004). For example, some adverse drug events are only identified in specific groups of patients who were excluded in pre-marketing studies, e.g. the elderly, children, and pregnant women. Other comorbidities and concomitant medicines (both for the same indication or others) can also modify the effect of drugs and enhance some adverse reactions. Moreover, the delayed effects from exposure to certain drugs are impossible to identify in a limited premarketing period. For instance, the incidence of developing bladder cancer related to more than a 2 year-exposure to pioglitazone (Mamtani et al. 2012) and carcinoma of the reproductive system from a 20 year-exposure to diethylstibestrol (Herbst et al. 1971).

A suitable system is essential to ensure the safety of post-marketing drug use. Such a system should involve monitoring safety signals, gathering data, evaluating the association between adverse events and the drug concerned, balancing the risk-benefit profile, and preventing adverse events (WHO 2004).

1.2 Components and objectives of a drug warning system

Safety issues can emerge at any stage throughout the drug lifecycle and be obtained from different data sources. Consequently, the practice of drug safety monitoring and warning requires a complex relationship between a wide range of partners. These partners include patients, health professionals, regulatory bodies, policy makers, and the pharmaceutical industry. Each partner needs to understand their role in contributing to the information on the risk related to drug use and how to respond to potential harms of the drugs available in the market (WHO 2000).

Pharmacovigilance tools are usually employed to approach the safety issue related to the use of drugs after approval. WHO defines pharmacovigilance as "*the science and activities mainly emphasized on the detection, assessment, understanding and prevention of adverse effects of postmarketing pharmaceutical products*" (WHO 2000). The two main components of a drug warning system are risk identification and risk minimisation.

1.2.1 Risk identification

Risk identification is the first half of a drug warning system focusing on identifying safety signals and characterising the risks related to drug use in populations (WHO 2004; Strom 2006). Specific aims of risk identification are:

- To early detect the adverse drug effects and interactions
- To identify the possible association between adverse effects and the concerned drug
- To classify the severity of the adverse effects
- To evaluate the risk and benefit of the concerned drug in each population group

Data on adverse events or risk related to the use of a drug can be obtained from spontaneous reports, electronic databases, and data collected in post-marketing studies (Strom 2006). Spontaneous adverse event reports are unsolicited reports of clinical observations in patients administered the product outside a formal clinical study (Ahmad 2003). These reports are acquired directly from consumers or healthcare professionals through the established voluntary spontaneous reporting systems from drug manufacturers or regulatory agencies. Studies show increasing reporting activities through spontaneous reporting systems in many countries (Kimura et al. 2011; Srba et al. 2012), which can be

linked and contribute to global pharmacovigilance databases. However, signals from spontaneous reporting systems require careful analyses from regulatory authorities and industry before they can be used to inform decision making.

Adverse effects are also collected from the growing availability of electronic health databases such as claims-based health insurance (e.g. Medicaid-Medicare in the United States) (Rodriguez et al. 2001) and medical practice databases (e.g. the General Practices Research Database in the United Kingdom) (Garcia Rodriguez et al. 1998). Recently, the Asian Pharmacoepidemiology Network (AsPEN) was formed as a multi-national research network to promptly identify and validate emerging safety issues. Participating countries include Taiwan, Japan, Korea, Hong Kong, China, Singapore and Australia as well as collaborating nations: Sweden and the USA (Andersen et al. 2013). Currently, eight different databases from six countries have been used in collaboration between AsPEN nations to conduct pharmacoepidemiology studies. These databases provide a proactive approach to detecting adverse effects and a better chance of establishing a relationship between prescriptions and diagnoses at the patient level. However, a substantial amount of time is needed after the marketing of a new drug in order to obtain information on the adverse events. Typically, the adverse events identified from databases are used to generate hypotheses for further investigation (Strom 2005).

In many countries including Australia pharmaceutical companies are obligated to conduct Phase IV clinical trials or post-marketing studies on the safety and monitoring of their products (WHO 2004). The collection of adverse event data during observational studies or clinical trials also provides information on possible adverse events even when safety was not the main outcome of interest. For example, the incidence of cardiovascular events in a clinical study investigating the primary gastrointestinal endpoint of rofecoxib (Vioxx®)—a cyclooxygenase-2 selective inhibitors—was found to be higher than a traditional non-steroidal anti-inflammatory drug (NSAID) (Mukherjee et al. 2001). The association between adverse effects and specific conditions or certain characteristics can be investigated using data from these observational or randomised clinical studies (WHO 2004).

The emerging serious cardiovascular events related to Vioxx® along with other withdrawn drugs have raised media attention on the effectiveness of post-marketing surveillance (Olsen et al. 2009). Risk identification as a part of drug warning systems has been

extensively reviewed and is under increasing pressure by the public for a reform (Ray et al. 2006; Olsen et al. 2009; McGee et al. 2012). Pharmaceutical companies together with drug authorities are demanding close monitoring and characterisation of the severity of adverse effects. Close cooperation is required with academia to identify the signals and conduct further analysis investigating these signals and determining an association. The evaluation of risk and benefit data from the risk identification process informs what regulatory action takes place.

1.2.2 Risk minimisation

After a drug safety risk has been identified and evaluated, risk minimisation strategies are needed to prevent these unwanted events related to the use of the drug concerned. The risk minimisation process requires industry, regulatory authorities, healthcare providers, and consumers to interact through the use of effective communication methods (WHO 2004; Strom 2006). The specific aims of risk minimisation are:

- To decide the action needed to reduce risk or increase benefit of using the concerned drug
- To communicate the risks or interventions
    - To promote understanding of the risk of the concerned drug to the public
    - To improve rational use of the concerned drug in specific conditions or in populations who benefit from that medicine
    - To provide practical implications and different therapeutic strategies for prescribing decisions
    - To provide education or clinical training related to the concerned drug and other therapeutic options available

Both the regulator and manufacturer are responsible for responding to safety issues and informing the public. The drug label (or package insert, patient information leaflet, product information) is the official route for providing information to practitioners and patients (Meadows 2002; WHO 2004; Edwards et al. 2012). However, the content on the drug label is drafted by the pharmaceutical industry and requires time consuming negotiations and modifications (Ray et al. 2006). Without notification from the supplier or drug regulator, most of practitioners and consumers would not know that changes had been made to drug labels. Therefore, drug safety communications in various forms are used to alert health

care professionals and patients on this emerging risk of a medicine. The choice of communication depends on the urgency and severity of the safety issue (WHO 2004). One of the biggest challenges is to translate important safety information into clinical practice (Ray et al. 2006). Drug safety communication should specify the use of medicine in patients with different risk profiles including treatment strategies and choices.

Changes to prescribing or use of the drug do not always appear to follow the recommendations on the safety communication (Lexchin 2005). In Canada, the 2000 change in the contraindication of cerivastatin product to include the risk of rhabdomyolysis did not slow down its prescribed rate before it was withdrawn in 2001. This growth in prescribing might have been increased by the huge spend on the marketing campaign on cerivastatin (Lexchin 2005). Continued follow-ups of communication from evolving safety evidence among diverse populations have substantial effects in refining the efficient use of the drug (Esterly et al. 2011). In order to enhance prescribing decisions for health care providers, medical associations together with academia have the ability to revise clinical guidelines and provide infrastructure to enhance the knowledge for risk benefit assessment (Edwards et al. 2012).

Cases of liver failure and death were reported spontaneously soon after the 1997 introduction of troglitazone for the treatment of type 2 diabetes mellitus in the United States (Gitlin et al. 1998). As a result of the increasing number of cases, four “Dear Healthcare Professional” letters were sent by the manufacturer to doctors countrywide to recommend they monitor liver enzymes in patients taking troglitazone (Graham et al. 2001). The manufacturer and the US drug authority updated the label and recommended monitoring hepatic enzymes. Subsequently, the pharmaceutical company decided to withdraw this drug from the market in 1999. After its withdrawal, researchers from health care, insurance companies and academia conducted observational studies and found that the risk related to troglitazone was actually much smaller than what was estimated from the spontaneous reports (Graham et al. 2001).

There is no single system in place for the dissemination of safety information (Woosley 2000). Globalisation and increasing use of the internet have all contributed to enhanced communication across borders and the way people access medical products and information (WHO 2004). However, these various sources presenting different risk conclusions can create difficulties for clinical practice. National regulators have the

responsibility for making judgements of acceptance and action towards risks for public safety.

2. Role of regulatory authorities on drug safety warnings

There are diverse views of risk and benefit among pharmaceutical industry, medical experts, healthcare professionals, and consumers (i.e. where some value the benefit of the drug differently from the others). Emerging adverse events associated with a drug can lead to fear among patients and the immediate discontinuation of drug use or the switching to another drug class (de Vries et al. 1998).

Regulatory bodies play an important role in investigating an emerging event and ensuring understanding of the situation by all stakeholders. Governments of most developed countries have increased their involvement in regulatory actions in order to ensure the safety of drugs and public confidence in using the medications (WHO 2004). The majority of regulatory authorities are established by governments as part of the public section (or public authority) to protect the health of general population from the industry sector and potential risks from their products. The role of the regulatory authority is to enact legislation and establish the rules by which the industry must act, including the development process, licensing of the drug, monitoring safety, and marketing of the products. The regulation of the medical products involves three primary areas: quality, safety and effectiveness. Regulators approach these topics by making evidence-based decisions and balancing risk-benefit profiles from the public perspective (Strom 2006; TGA 2014).

In addition to the approval of new drugs, regulatory authorities undertake the judgment on acceptable limits of risk related to marketed products. Actions taken by the regulators to ensure the safety of drugs in the market range from termination of the licence, suspension of marketing/licence, changes to product indications, adding a warning to the product information or labelling, or putting the drug on a watch list, depending on the risk/benefit assessment (FDA 2009; TGA 2014).

When an emerging signal is detected, regulatory agencies need to determine if the adverse event is a result of the drug. Regulatory authorities therefore implement several approaches (depending on the system in each country) to re-evaluate risk and benefit of the drug concerned. After a benefit-risk assessment if the risk outweighs the benefit, the

regulator can remove the drug of the market. However, if the risk is not certain or can be minimised by specific strategies, a removal is not necessary and safety information can be updated on the drug label in accordance with decisions by the regulatory authority.

Regulatory processes differ according to the nation in which the authority is established as such decisions in regard to a drug causing concern can also differ. For example, rosiglitazone, an antidiabetic drug with an increased risk of cardiovascular event, was withdrawn throughout Europe whereas it is still in the US market with warnings and some restrictions. Restriction programs are used to limit access in a specific population or to closely monitor drug exposure. Prescribers or patients are required to enrol into a specialised program for access to the drug. The AVANDIA-Rosiglitazone Medicines Access Program is one such program established by the American regulatory authority, the Food and Drug Administration (FDA), in order to assess authority restricted medicines (FDA 2010). The challenge is to minimise the removal of potentially useful products (as a result of false signals) whilst, acting in a fast enough manner to prevent additional harm from a delay in withdrawal. The delay in the withdrawal of Vioxx® is one example of this challenge as there were more than 139,000 cardiovascular and cerebrovascular cases reported involved with Vioxx treatment prior to removal (Armstrong 2006; Olsen et al. 2009).

Regulatory warnings

National regulators have a major role in raising public awareness of drug safety. Furthermore, they are involved in providing the recommendation and developing the health policy with regards to the use of concerning medicines (FDA 2007). Regulatory activities have been extended to include communication of risk, benefit, and effectiveness of medical products to healthcare providers, patients and the public. Improving the public's understanding of the risk is also essential to achieve the expected outcome of the safe use of medicines (Yu et al. 2010; Thomas et al. 2013).

Safety communication from a regulatory authority, also called a regulatory warning is a risk minimisation tool utilised to help prevent further harm from a concerned product. An effective safety communication must operate under a publicly trusted system in order to satisfy all parties including pharmaceutical industry, government, health professionals, and consumers (WHO 2000; Strom 2006). Safety communications need to consider the differences in perception and understanding of healthcare professionals and lay people.

Medical experts require sufficient scientific evidence of safety and appropriate recommendations for their practice, while patients may need to be assured about the concerned medicine. The pressure regulatory bodies have been under regarding the effectiveness of regulatory actions toward an emerging risk of a medical product and the release of risk communications has led to an increased transparency in the regulatory process, in order to gain more public trust and understanding (Ray et al. 2006; Cook et al. 2009; Buckley et al. 2011; TGA 2011; McGee et al. 2012; Health_Canada 2013).

2.1 International regulatory authorities

Each country has their own national drug warning system to take into account the differences in legislative requirements, distribution, drug use (e.g. indications, dose, availability), genetics and health care systems. Drug safety communications issued by each national authority is an intervention tool that aims to minimise the risk related to the concerned drug in addition to updated labelling.

There are several methods for delivering safety communications (Nkeng et al. 2012). Among the most widely known safety communications are ‘Direct Healthcare Professional’ (DHCP) letters so-called ‘Dear Doctor’ letters released by the United States Food and Drug Administration (FDA) and Health Canada (FDA ; MedEffect™). Similarly, ‘Dear Healthcare Professional communications’ (DHPCs) are issued by several authority bodies (Mol et al. 2010; Piening et al. 2012). A study from the Netherlands showed an increase in the number of DHPC letters issued in the past decade. This increase is likely a result from a greater awareness by the public, media, regulatory bodies and other stakeholders as well as the proactive screening of large databases (Mol et al. 2010).

Another communication strategy is a ‘Black Box Warning’ that is mostly used by the FDA to indicate a serious adverse event or life-threatening risk of a medicine. Box warnings or Black box warnings are also used on drug labels in the UK and Australia but with a less frequent and higher threshold for issue compared to the US (Buckley et al. 2011).

Safety alerts and public advisory warnings are commonly announced by the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom (UK), the FDA, and Health Canada (FDA ; MedEffect™ ; MHRA). The Pharmaceutical and Medical Devices Agency (PMDA) in Japan usually uses ‘Pharmaceuticals safety information’ and a ‘Yellow Letter’ for emergent safety communications, and a ‘Blue Letter’ for rapid safety

communication (PMDA). ‘Press Release’ and ‘Public statement’ are the terms used by the European Medicines Agency (EMA). In Australia, the safety communication of an emerging risk is distributed by the Therapeutic Goods Administration (TGA). Some communication is directly targeted to patients such as the patient alert cards in the UK.

The global connection of drug information and the rapid spread of safety communications between national regulatory authorities is well recognised with medical media and online drug information resources frequently publishing drug safety warnings released by the major regulatory bodies. Hence, it is likely that prescribers would receive these new safety communications from a range of international sources. The FDA and the EMA are the key regulatory authorities, which are under the spotlight of the media and medical experts. This is due to the United States and the European Union being the two main regions that have early access to innovative products (Nkeng et al. 2012; Moore et al. 2014). Clinical trials for new drugs and post-marketing surveillance data are essential sources for development of benefit-risk profiles (FDA ; FDA ; Xu et al. 2014). Data collection on adverse events in addition to the increasing resources for research infrastructure from manufactures, academia, and regulatory bodies provide further opportunity to investigate the emerging risk of medicines (Mol et al. 2013). Cardiovascular adverse events associated with rofecoxib were collected from clinical trials and reports in the US during 1999–2002, while there was no report in Australia. This is likely to have resulted in the time difference seen between warnings issued by the FDA in 2002 and by the TGA in 2003 (Wahab et al. 2014).

Decisions on the registration and risk management of new medicines by less resourced regulatory agencies are often based on either the FDA or EMA. Moreover, the FDA and the EMA collaborate on the development of new guidelines and risk management plans including risk minimisation activities. The initial release and implementation of these guidelines occurred in 2006 with the aim to improve the regulatory intervention in instances of individual safety issues of a concerned drug (FDA ; EMA 2005; Zomerdijk et al. 2012). The safety warning processes of the FDA and the EMA including public opinions on their performances are reviewed below. The process of drug safety warnings in Australia by the TGA is also discussed in the following section.

2.1.1 U.S. Food and Drug Administration

The Food and Drug Administration (FDA) is an agency of the Department of Health and Human Services of the United States. Its purpose is the regulation and supervision of food, tobacco, dietary supplements, cosmetics and medical products by approving, restricting, issuing safety warnings, and recalling products (FDA 2012). The Center for Drug Evaluation and Research (CDER) is responsible for the collection of adverse drug reaction reports, regulation of advertising for the approved drug indication, and providing information to health professionals and consumers. The CDER also conducts post-marketing drug surveillance from data collected in the Adverse Event Reporting System (AERS), the monitoring system of licensed drugs' safety after distribution into the market (FDA 2014).

If an adverse event is reported and a trend begins to emerge, an advisory committee will form to investigate and issue recommendations. Depending on the adverse effect and/or medicine that is reviewed, certain offices (e.g. Office of Surveillance and Epidemiology, Office of Biostatistics) and divisions (e.g. Division of Metabolism and Endocrine Products, Division of Cardiology Products) will review the evidence and/or conduct their own analyses, eventually comparing their analyses to those of the pharmaceutical companies. This information will be provided to the over-seeing advisory committee who evaluates and votes for the appropriate actions regarding the adverse effect (FDA). Regulatory actions range from market withdrawal to minor revisions to the drug's label.

Significant funds and workforce have been put into post-marketing drug safety monitoring since the withdrawal of rofecoxib (Vioxx®). Rofecoxib was approved by the FDA in May 1999. Preliminary results of the Vioxx GI Outcome Research (VIGOR) study in 2000 showed a four times higher risk of cardiovascular disease in the Vioxx group over the naproxen group. However, authors interpreted this as a coronary protective effect of naproxen over the risk of Vioxx (Armstrong 2006). Following this study, in April 2002, the FDA required labelling changes in the "Precautions section" of Vioxx to recognise the potential of cardiovascular effects instead of a more serious "Black Box Warnings" (FDA 2002). After being marketed for 5 years, heart attacks and strokes were shown to be significantly associated with Vioxx, finally, the pharmaceutical company voluntarily withdrew Vioxx in September 2004 (FDA 2004). A number of on-going trials on rofecoxib were discontinued. The APPROVe (Adenomatous Polyp Prevention on Vioxx) study that

showed a two times higher risk of fatal cardiovascular events compared to the placebo group was discontinued (Bresalier et al. 2005; Armstrong 2006).

The whole drug approval and monitoring process was under scrutiny and required major reform. In 2005, the Drug Safety and Effectiveness Monitoring program (DSEM) and the Drug Safety Oversight Board (DSB) were created to assist CDER in handling emerging drug safety concerns. The Institute of Medicine of the National Academies was assigned to assess the US drug safety system and later release recommendations for improvement (FDA 2005). The FDA also created the Risk Communication Advisory Committee in 2007 to advise on methods of effective risk communication (FDA 2009). The Food and Drug Administration Amendments Act of 2007 was implemented to improve transparency and communication on post-marketing drug safety information.

The FDA launched the FDA's Transparency Initiative in June 2009 and three phases have since been implemented to increase the transparency on decision-making processes of the agency (FDA 2011). Since then more reports on the FDA's assessments and semi-raw data from the AERS were released online. However, these early signal postings were opposed by physicians due to the concern that patients would stop taking these medicines without adequate causality being ascribed to the signal (Lofstedt et al. 2013).

Safety communications from the FDA

The FDA communicates new safety information through a combination of methods under 'Alerts'/'Safety Alerts' and 'Drug Safety Communications'. 'Public Health advisory' aims to inform the general public on new risks associated with a medical product and to advise consumers on the medicines concerned. More targeted communication such as 'Information for Healthcare Professional' sheet or 'Dear Healthcare Provider' letters are directed to the main prescribers of concerned products including details on scientific evidence and specific strategies for the treatment of conditions (FDA). The FDA is known for their timely response to emerging concerns and their reinforcement of messages over time; Early Communications, Follow-up Early Communications, and Reminders are often released by the FDA.

The FDA has opened several channels to enhance the communication of safety information to health professionals and consumers. The "Drug Safety and Availability" page on FDA's website provides Drug Safety Communications including new drug

warnings, drug recalls and drug label changes; moreover, there are easy ways to access the information via an email subscription for Recalls, Mobile Apps for Recalls, FDA on Facebook, FDA Drug Info on Twitter, FDA on Flickr, Drug Safety Podcasts and FDA Patient Safety News Video Broadcasts (FDA). The FDA's announcements also often appear in both medical and non-medical media.

The impacts of risk communication issued by the FDA on drug use have been frequently investigated. Although the FDA communication is generally rapid and more detailed, the inconsistent effects of box warnings from the FDA have been highlighted in several studies (Matlock et al. 2011; Dusetzina et al. 2012). The adherence to warnings or recommendations issued by the FDA depends on several factors. For example, the content of warnings must be summarised and focused directly on the risk and its management, including alternative treatment options to receive a targeted and widespread response (Dusetzina et al. 2012).

2.1.2 European Medicines Agency

The European Medicines Agency (EMA) is the European Union body responsible for: 1) inspecting good manufacturing practice, good laboratory practice and pharmacovigilance (pre- and post-marketing) of a new product; 2) coordinating the European Union's pharmacovigilance system in monitoring the safety of medicines; and 3) conducting scientific assessment of a particular medicine on behalf of the European Union (EMA). The EMA is located in London and formed in 1995 in an attempt to harmonise the existing regulatory bodies in European nations. The EMA has a different approach to that of the centralised methodology of the FDA, as it incorporates a network of expertise and resources throughout the European Union for scientific assessment of medicines (EMA 2005).

The Committee for Medicinal Products for Human Use (CHMP) was established to prepare the Agency's opinions on all questions concerning medicines. It is composed of 27 voting members of the EMA (Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, United Kingdom) and non-voting members (Norway, Iceland and Liechtenstein) chosen for their expertise regarding medicine evaluation. A Pharmacovigilance Working

Party (PhVWP) has the responsibility of evaluating the potential adverse drug reactions and reporting these to CHMP. CHMP initiates internal peer-review for the assessment of adverse events based on scientific evidence, necessary quality, safety, efficacy, and benefit/risk-balance model for making recommendations for changes, suspension, or withdrawal of the drug (EMA 2009). A panel within the CHMP known as the Scientific Advisory Group (SAG) provides independent recommendations on scientific or technical issues relevant to that product, such as, SAG on Diabetes/Endocrinology or SAG on Cardiovascular issue (EMA 2014). After the evaluation of each concern, a full report and recommendation called a European public assessment report (EPAR) is published on the Agency's website (EMA).

In 2010, the EMA was under pressure to increase the transparency and accessibility of information to the public (Lancet 2010). Risks associated with Vioxx, Avandia and Mediator were examples of public criticism on a lack of disclosure of information from the regulator and the regulatory relationship with industry (Bouder 2011). Strategies to improve the transparency of the regulatory environment on risk communication were discussed by the EMA and were included on the 'Road map to 2015' as a guideline document (EMA 2010). The establishment of an independent risk communication advisory board, a strategic view on transparency, the involvement of the public on risk communication and the evaluation of communication messages are suggested strategies for the EMA (Bouder 2011).

Safety communications from the EMA

Numerous safety communications are utilised by the EMA. European Public Assessment Reports (EPAR) contain a full risk and benefit assessment of the product and an update summary of product characteristics that is published on the EMA's website. The Press Office under CHMP makes announcements with media representatives called a 'Press release' or 'Public advisory' related to an emerging risk and recommendation from the EMA. These communications contain the review process and time, up-to-date information, and recommendations related to the products concerned. With a similar purpose to the 'Press release', Questions and Answers (Q&As) documents also provide risk and benefit assessments of the drug concerned on the EMA website. Specific communications to healthcare professionals by the EMA are termed 'Direct Health Professional Communications' (DHPC) or a 'Dear Doctor letter' (EMA).

All risk communications are published on the EMA's website. The subscription of RSS (Rich Site Summary) feeds, monthly e-mail newsletter, audio and YouTube video are also available for healthcare professionals and consumers. National regulators in the European Union also adapt and combine the EMA communication with their own (EMA).

Each of the EMA risk communications aims to describe the possible risk and benefit in using the concerned drug for targeted audiences but often tend to repeat standardised messages (Bouder 2011). However, these communications were observed to be unclear with regards to the expected benefits, magnitude and certainty of the risk communication. Inadequate information on the seriousness, baseline risk and recommendation on what action to take have also been a public concern (EMA 2009; Suvarna 2011). Suggested solutions are: improving templates of risk communication, targeted communication tools for various audiences/purposes, and better-informed benefit/risk decisions (e.g. risk stratification for healthcare professionals) and improving methods of message distribution (Suvarna 2011).

2.2 The Australian regulatory authority

2.2.1 Therapeutic Goods Administration

The Therapeutic Goods Administration (TGA) is a division of the Australian Government Department of Health. The TGA ensures the safety, efficacy, and manufacturing quality of prescription medicines, vaccines, biological, blood and tissue products, medical devices, *in vitro* diagnostic devices, over-the-counter medicines, and complementary medicines (TGA 2014). The establishment of the TGA was to integrate the Therapeutic Goods Administration Laboratories into the 1989 legislation of Therapeutic Goods for the full authority control of premarketing assessment, licensing, and post-marketing assessment of pharmaceutical products. The TGA is a major component of Australia's National Medicines Policy and is developing the national regulatory framework to align with international regulatory systems (WHO 2004).

The TGA structure comprises of three major groups: marketing authorisation, monitoring & compliance, and regulatory support. The marketing authorisation group is responsible for the approval of new therapeutic products for sale in Australia. The monitoring and compliance group ensures that approved products meet the mandatory standards

throughout their lifecycle. The regulatory support group supplies the legal, financial, technology & management information, parliamentary, and human resource services for all regulatory processes (TGA).

Drug safety warnings, including monitoring and reviewing the concerns, falls to the monitoring and compliance group. When there is an emerging risk of a medical product, an Advisory Committee on the Safety of Medicines (ACSOM) is formed by the TGA. The members of ACSOM are selected for their knowledge and skills relevant to the drug of concern such as clinical pharmacology, biostatistics, and clinical expertise. The ACSOM assesses the evidence on the adverse events and provides the risk management plans for the TGA (TGA 2014). Unlike the EMA and FDA, the TGA does not conduct any new analyses. The TGA's decision is based on the conclusion by advisory committee who assesses safety issued from adverse event notification, published articles, and manufacturer's information.

The range of TGA regulatory actions in response to a safety concern include: withdrawing/suspending/recalling a drug from the market, requesting an investigation from the manufacturers and requesting changes to product information (PI). The TGA is unable to make any change on the PI as it is the property of the manufacturer. The TGA can request that the drug sponsor updates the safety information on the PI; however, the process of discussion and agreement between authority and supplier may take time. If an emerging adverse effect needs an urgent response, other regulatory actions would be required for preventing further harm (Cook et al. 2009). Therefore, risk communications are necessary in order to alert health care professionals and consumers of an emerging risk (TGA).

A previous review found that the PI for thyroid-related medicines failed to reflect an updated contraindication and dose recommendation from the medical literature and international guidelines (Stockigt 2007). This review also recommended that the process of updating the PI needed to be modified and required more of a proactive approach from the TGA in collaboration with suppliers and specialist clinicians. The "Box warning" on the product information was rarely used by the TGA. The TGA reserved it for the possible side effect, which is considered to be extremely necessary to alert the public. The content of Australian box warnings were shown to be succinct compared to the U.S. box warnings which are 10 times longer with a large amount of clinical evidence and practical

recommendations while only a few sentences of the negative effects were provided on the warning section in Australia (Buckley et al. 2011).

In comparison with other industrialised countries, an attempt to improve the transparency of the TGA regulatory process has been delayed (Lancet 2010; FDA 2011; Health_Canada 2013). In November 2010, a review panel was formed to improve the transparency and understanding of TGA's regulatory processes and decisions due to the perception that the TGA did not provide sufficient information to the public regarding TGA activities. In July 2011, the TGA transparency review was published under the Parliamentary Secretary for Health and Ageing. One topic from the TGA transparency review highlighted the difficulties in getting information about suspect products to consumers and health providers (TGA 2011). This review reflected community concern on two separate recent safety issues of poly-implant prosthetic breast implants and joint replacements. It indicated that a lack of effectiveness of the TGA's regulatory communication had caused potential harm to the public (McGee et al. 2012; Bonython 2014). The review also attacked the internal processes of the TGA in their delayed regulatory response to emerging safety information and following up on the issues concerned. It was suggested that the TGA develop an effective warning system to alert the public and to provide appropriate information on either the products under investigation or product recalls. The safety alerts needed timely distribution to health practitioners through jurisdictional and prescribing association networks (TGA review-recommendation 15–18) (TGA 2011).

Since then, the TGA has been focusing on improving the transparency of regulatory decision-making processes as a part of the TGA reforms (TGA_reforms 2012). The early warning system is established as part of TGA's proactive approach to monitoring the safety of medicines. It was implemented in 2013 as a joint project between the TGA and the New Zealand Medicines and Medical Devices Safety Authority (Medsafe–the regulatory authority in New Zealand) to include current and historical information on safety concerns for medical products. Information on the decision criteria used, content of communication, publications and the update process of communication are available on the Trans-Tasman Early Warning System: Processes in Australia and New Zealand. Although this is a joint project on adverse event reports and regulatory processes, the communications themselves are separated between the two countries (TGA 2013).

Safety communications from the TGA

Safety communications issued by the TGA are divided into monitoring communication and alerts communication. The monitoring communication underlines the potential safety concerns that the TGA has detected, even if they are in the early stages of investigation and little information is known. The monitoring communication aims to encourage practitioners, patients, and researchers to provide more data and clinical experiences related to these concerns (TGA 2013).

The alert communications alert healthcare professionals and consumers to new safety information following the outcome of the TGA's investigation. An alert communication on a concerned medicine is under 'Alerts', 'Recalls', and 'Safety information'. 'Alerts' and 'Safety information' may not necessarily indicate that the medicine is unsafe to use. The TGA expects healthcare professionals to use their clinical judgment in applying the safety communication to individual patients.

The TGA issues a safety advisory message under 'Alerts' published on the TGA's website, which includes information on the emerging event, any changes to product information or labelling and recommended use of the medicine to health professionals and consumers. Healthcare professionals and consumers can also subscribe to the 'TGA-SAFETYINFO' list to receive a notification email for any new TGA safety alerts (TGA_Alerts).

The Medicine Safety Update is an article providing practical information and advice on emerging drug safety for health professionals. It is published every 2 months on the TGA's website and appears in each edition of the Australian Prescriber Journal. The Medicine Safety Update replaced the Australian Adverse Drug Reactions Bulletin in 2010 (TGA).

There is a difference in the timing of issued warnings between the FDA, EMA and TGA. For example, the FDA sent a warning letter to health professionals on the ischemic heart disease related to Vioxx in May 2002 (FDA 2002) but it was not until October 2003 when the first TGA Alert was issued. During that gap, the dispensing of rofecoxib continually increased in Australia. Some of the reasons behind the delay might be due to the fact that the spontaneous reporting signal on cardiovascular adverse events was not detected in Australia until the end of 2002 and there were no medical publications on the cardiovascular risk or stroke until 2005 (Armstrong 2006; Wahab et al. 2014).

As the majority of prescription medicines are subsidised by the Australian Government, the risk management strategy is extended to limiting access to the Pharmaceutical Benefits Scheme (PBS). The restriction of authorised prescribers and changes to restriction criteria on the PBS are also applied in response to safety concerns. However, changes to the PBS subsidy may be delayed until a series of warnings have been issued or the evidence is conclusive. For example, a change to flucloxacillin prescribing was observed after the issuing of warnings and multiple initiatives on the PBS subsidy to improve drug use (Roughead et al. 1999).

There are several other ways to improve prescribing behaviour of concerned drugs. The TGA cooperates with the Quality Use of Medicines Policy arm of the national medicines policy through organisations such as the National Prescribing Service, which helps to distribute updated safety information. The NPS also provides educational programmes and resources to enhance the understanding and appropriate use of medicines to healthcare professionals and consumers (Gadzhanova et al. 2013). Examples of these programmes are the printed/online Australian Prescriber publication for health care professionals and the NPS RADAR mail-out on new drugs (NPS 2014). Updated safety information on the PI endorsed by the TGA is also published in other sources such as MIMS (monthly index of medical specialties), Australian Medicines Handbook, Therapeutic Guidelines, and NHMRC Clinical Practice Guidelines Portal.

3. Evaluation of the impact of drug safety warnings

Drug safety communications are utilised as intervention tools of the risk minimisation plan to raise awareness of the risk and to minimise the occurrence of risks associated with drugs in real-world settings. Regulatory agencies employ several methods to inform healthcare professionals of drug-related problems as stated above. Each communication method is chosen for different target audiences and various responses depending on the safety issue. This project focuses on the impacts of drug safety warnings on clinical practice. As there is no established design to evaluate the impact of drug safety warnings, several study designs and statistical analyses have been employed to examine these influences. Reviews of common types of safety warnings, expected outcomes, outcome measurements, study designs and statistical analyses are provided below.

3.1 Types of safety warnings

Previous research investigated the impacts of several types of safety warnings such as Black box warning, Public health advisory, Dear Healthcare Provider letter issued by the FDA; Press release, Public advisory, Dear Healthcare Professional Communication by the EMA or European regulators; Safety Alerts by other national regulators on different outcomes of clinical practice (Piening et al. 2012). A number of articles have evaluated more than one warning in the range of one to eight per article. The most frequently assessed warnings are the Black box warning in the US. While Dear Healthcare Professional Communications are more frequently evaluated in other places, followed by Public Health Advisories and Safety Alerts (Dusetzina et al. 2012; Piening et al. 2012).

3.2 Content and expected outcome of drug safety warnings

The contents of a warning usually contain results of a regulatory evaluation on the risk-benefit profile and recommendations on the use of the drug concerned. For warnings targeted at healthcare professionals, two main purposes are to raise their awareness of the safety issue and (if required) to change clinical practice. The expected outcomes of regulatory warnings on the changes to clinical practice are usually indicated in the recommendations.

In addition to raising awareness, other expected outcomes of drug safety warnings are to encourage risk reporting, to prevent prescribing in specific groups of patients, to prevent concomitant use of drugs with their potential interaction, to encourage baseline and follow-up laboratory tests, and to prevent serious adverse events from drug use (Dusetzina et al. 2012; Piening et al. 2012). The following section provides a review of the expected outcomes related to the warning's content.

3.2.1 Warning on drug use in subpopulations

Examples of safety warnings issued for preventing the use of drug in certain populations are: the Black box warnings regarding the risks of atypical antipsychotic use among elderly with dementia, the warning on the use of selective serotonin reuptake inhibitors (SSRIs) related to increased suicidal rate in children and adolescents, and the warning on thiazolidinedione drug class in patients with congestive heart failure (FDA 2007). Specific

subpopulation warnings usually include recommendations to avoid the concerned drug in high-risk patients and providing alternative treatment options.

An expected outcome should be a decrease in the use of the concerned drug among the high-risk subpopulations and unchanged use among other groups of patients who may benefit from this drug. An increased use of alternative treatments and a reduction of adverse events in high-risk patients are also expected (Dusetzina et al. 2012).

3.2.2 Warnings on drug-drug interactions

To prevent concomitant use in the case of a drug-drug interaction or contraindication, the warnings usually list potential combinations and suggest a substitute if needed. Examples are the 'Dear Doctor' letters sent by the FDA to professionals listing drugs contraindicated for use with cisapride due to an increased risk of cardiac arrhythmias (Guo et al. 2003) and the warning on the concurrent use of terfenadine and some macrolides (e.g. erythromycin, ketoconazole) (Thompson et al. 1996). Recently, the warnings on the potential drug interaction between clopidogrel and drugs with CYP2C19 enzyme inhibitory effects were issued by the FDA and EMA (EMA 2009; FDA 2009). Similar to the previous warning, a decreased concurrent use of the drug-drug interaction is an expected outcome as well as substitution for the contraindicated medicine. Many studies indicate that a change in co-prescribing in response to drug interaction warnings often takes months or years (Weatherby et al. 2002; Guo et al. 2003). For instance, an obvious decline in the contraindicated use of cisapride was not seen until after the third warning by the FDA (Weatherby et al. 2002; Guo et al. 2003). Despite serious cardiac warnings on the drug interaction, a decline in the coprescribing of contraindicated macrolides with terfenadine occurred slowly with the largest effect observed eighteen months following the first warning (Thompson et al. 1996).

3.2.3 Recommendation for increased monitoring

If certain complications are associated with the concerned drug, clinical monitoring or laboratory tests are recommended. Prior to the market withdrawal of trosiglitazone regarding hepatotoxicity, 'Dear Healthcare Professional' letters recommended that the liver function should be monitored in patients taking trosiglitazone (Graham et al. 2001; Cluxton et al. 2005). Other laboratory tests suggested by regulators are metabolic screening (e.g.

glucose testing) in patients starting second-generation antipsychotic drugs (Morrato et al. 2010) and a tuberculin skin testing among infliximab users for a complication of latent tuberculosis (Vaughn et al. 2012). Apart from an increase in laboratory orders, an increase in follow-up visits for patients taking antidepressants are also suggested. Nevertheless, these expected effects were found to vary and were not necessarily consistent with the warnings. Studies on laboratory monitoring show unchanged rates of glucose testing in antipsychotic users moreover, rates of liver enzyme monitoring were shown to be lower in a certain group of practitioners following the FDA advice (Graham et al. 2001).

3.2.4 Warnings on adverse events of concerned drugs

In general population warnings on adverse events associated with use of a concerned drug prescribers are required to be cautious when using these medicines in all patients. Examples of drugs with serious adverse effect warnings are: third generation oral contraceptives associated with venous thromboembolism, droperidol regarding the risk of a cardiac arrhythmia, and the thiazolidinedione drug class (rosiglitazone and pioglitazone) associated with an increased risk of congestive heart failure (de Vries et al. 1998; Habib et al. 2008). Expected outcomes are a reduction of drug use in general or in patients with the high risk of developing adverse events if other treatments are available. A retrospective analysis showed a significant decline in droperidol use and a significant increase in ondansetron use (similar treatment effect as droperidol) for postoperative nausea and vomiting prophylaxis as suggested on the Black box warning in 2001 (Wax et al. 2007).

3.3 Consequences of drug safety warnings

Previous studies have assessed the intended and unintended consequences of drug safety warnings. The intended effects are a reduction in the number of prescriptions in populations at risk or a decrease in adverse events related to the concerned drug. For example, a decline of atypical antipsychotic drug use was observed in elderly with dementia in the year following the FDA advisory on an increased mortality (Dorsey et al. 2010) and the dispensing of contraindicated drugs among cisapride users decreased after the issuing of ‘Dear Doctor’ letters (Smalley et al. 2000).

The unintended consequences of drug warnings were also observed, particularly from the warnings on SSRIs and third-generation oral contraceptives (Piening et al. 2012).

Decreased use of SSRIs was reported in adults—the group of patients who would benefit from this treatment. A sharp fall in the all prescribing of third generation contraceptive pills occurred in the UK immediately after a press release concerning the safety of certain drugs in the same class (Flett et al. 1998). These consequences were spill-over effects of warnings to other subpopulations or other members of the same drug class (Ceilley et al. 2009). The UK primary care database showed decreased rates of depression diagnoses in adolescent, which implied that GPs were cautious when making diagnoses following the warning (Wijlaars et al. 2012).

3.4 Measuring the outcomes of drug safety warnings

Previous studies have measured the changes in clinical practice as the outcomes of drug safety warnings. Healthcare utilisation, clinical diagnoses, and health behaviours are often assessed to indicate the impact of drug safety warnings (Dusetzina et al. 2012; Piening et al. 2012). The outcomes of interest can vary from a simple change in the number of prescriptions to complex social behaviours.

Outcomes of studies depend on the purposes of warnings and the availability and accessibility of health information (Piening et al. 2012). Changes in patterns of healthcare utilisation and health outcome can be investigated using quantitative analyses. Healthcare utilisation includes drug utilisation, indication of drug use, use of other health care services (e.g. healthcare visits (Morrato et al. 2008), laboratory testing), etc. Primary outcomes regarding health utilisation used in the measurement of impact of warnings are listed below.

3.4.1 Drug utilisation of a concerned drug or therapeutic class

Changes in the use of the concerned drug are the most common outcomes assessed to investigate the impact of drug safety warnings (Dusetzina et al. 2012). Previous studies applied drug utilisation methods to measure changes in drug volume and standard daily requirement of concerned drug as the outcomes. In North American and Europe, Drug Use Evaluation and Drug Utilisation Review are terms used in criteria-based evaluation of drug use to ensure the appropriate drug therapy according to the current guideline or recommendation (Ratanawijitrasin 2002). Volume of drug use and amount of standard

dose use (defined daily dose) in a population are frequently used to calculate trends of drug use overtime.

Volumes of drug use

A common measurement in drug utilisation studies is the volume of drugs recorded in health databases (NHS 2012). Number of prescriptions, number of items, number of patients prescribed/dispensed drugs are counted without taking strengths, formulations or doses into account. Therefore the comparison between different time periods, groups of drugs, individual drugs, or studied population are difficult. For example, a prescription/package that may have contained 14 tablets in 2008 may increase to 30 tablets in 2012 plus changing doses. The trend of actual consumption would be misleading if only volumes of drug were compared over time (WHO 2003).

When the population size is known (defined cohort) or prescriptions of all therapeutic drugs can be identified during the study period, the proportion/rate of prescriptions or patients can be compared over time periods as well as between individual drugs or drug class (Strom 2005).

Numbers of prescriptions and items are often collected for administrative purposes and obtained from wholesale or retail pharmacy prescription/dispensing data. Whereas numbers of patients prescribed the concerned drugs are acquired from medical records and medical claims database (Strom 2005).

WHO anatomical Therapeutic Chemical Defined Daily Dose (ATC/DDD)

Comparative utilisation among different populations over time can be examined by the World Health Organization Anatomic Therapeutic Chemical (ATC)/Defined Daily Dose (DDD) system (Magrini et al. 1997; WHO 2013). The ATC system comprises of 5 classification levels, for example A10BG02 is the ATC code for rosiglitazone:

1st level indicates an anatomical main group e.g. A—*Alimentary tract and metabolism*

2nd level indicates a therapeutic subgroup e.g. A10—*Drug used in diabetes*

3nd level indicates a pharmacological subgroup e.g. A10B—*Blood glucose lowering drugs*

4th level indicates a chemical therapeutic subgroup e.g. A10BG—*Thiazolidinediones*

5th level indicates a chemical substance e.g. A10BG02—*Rosiglitazone*

The defined daily dose (DDD) is a medical meaningful unit assigned for each ATC code and provides an assumed average daily maintenance dose for a drug in adults. The DDD designated for all drugs are available on the WHO's website (WHO 2013). DDDs per population per day are usually calculated from national pharmacy claims databases to compare drug utilisation between these jurisdictions (Tett et al. 2013).

Advantages of DDDs (Wertheimer 1986)

- Able to work with gross drug statistics at various levels of the health chain
- Allows comparisons between drugs in the same therapeutic class and between different health care settings or geographic areas
- Can evaluate trends over time
- Relatively easy and inexpensive

Disadvantages of DDDs (Wertheimer 1986)

- DDD is a technical unit of comparison but not a recommended dose
- DDDs do not reflect actual prescribing patterns (Number of prescriptions of each dosage will vary)
- DDD varies with drugs that have >1 indication, various doses, are used in combination with other drugs, do not take into account compliance variation
- There is no designated DDD for children
- There is no designated DDD for topical preparations

3.4.2 Discontinuation rates or substitutes for the concerned drug

Discontinuation of a concerned drug following the warnings is often used as an outcome, especially when an alternative treatment has been suggested in the recommendation. Prevalence/incidence of discontinuation and the substituted drug are compared before and after the warnings. For example, a decline in the rate of co-prescribing contraindicated drugs with cisapride was observed after the warning (Smalley et al. 2000; Guo et al. 2003). Prevalence of switches from third to second generation oral contraceptives was higher after the warnings on deep vein thrombosis associated with third generation oral contraceptives (de Vries et al. 1998).

Discontinuation and switching data can be obtained from electronic medical records and large health-claims databases such as the UK health improvement network and Medicaid program in the USA.

3.4.3 Diagnosis and clinical outcomes

Some safety warnings encourage screening for complications associated with drug use, for example, an increased diagnosis of diabetes from blood glucose screening in patients initiating second-generation antipsychotic drugs (Morrato et al. 2010). Withdrawal of COX-2 inhibitor were associated with a temporally decline of myocardial infarction admissions but reversed the previous decreases in gastrointestinal haemorrhage hospitalisations (Wheeler et al. 2009). More cases of thrombotic thrombocytopenic purpure were reported after the issue of a Dear Health Professional letter in Italy (Malgarini et al. 2000).

Diagnosis data must be linked to prescribing records in order to investigate their relationship. Linked data are available in health claims databases, electronic medical databases, and medical records. Fully linked databases are difficult to obtain in a large population, especially in Australia.

3.4.4 Other health care services

Other healthcare services used as measurement outcomes of drug safety warnings are; numbers of practice visits, referral to specialists, and laboratory testing (Graham et al. 2001).

After the FDA's recommendations on the close monitoring in patients who start antidepressants, the frequency of visits did not increase compared to before the warning (Morrato et al. 2008; Busch et al. 2010). A shift in care provided from primary care to psychiatrist was seen after the warning of antidepressant use (Valuck et al. 2009). The rate of liver function testing in troglitazone users and metabolic screening in patients who started antipsychotic drug was expected to increase following the safety warnings although compliance could not be achieved (Graham et al. 2001; Morrato et al. 2010).

3.5 Analytic methods

After outcomes of interest are defined, the next step is a method for data analysis. Several analyses have been used to evaluate the impact of drug safety warnings. They can be divided into quantitative and qualitative approach.

Quantitative approach

A quantitative approach aims to quantify the trends or time course of drug use at different levels of heath settings: national, urban, rural, or institutional. Study designs may be prospective, such as randomised control trials (RCTs) or retrospective. A RCT assesses the impact of a safety warning on expected outcome as an intervention by comparing the assigned intervention arm to a control arm. Both arms are subjected to the same biases and allow us to investigate the causal effect of a safety warning (Piening et al. 2012). However, it is often not feasible due to several factors such as ethical issues, time constraints, and high cost (Majumdar et al. 2003). Retrospective studies use previously collected data from existing databases or medical records. A before and after comparison of data over the warning period is used to measure the impact of the safety warning.

Two categories of available data that are divided by the collective methods are cross sectional data and continuous data. The cross sectional data only provides the prevalence of interested outcomes at one point (or more) in time either before or after a safety warning. The post-intervention prevalence may not have the comparative baseline (pre-intervention period). Examples include information from surveys and prescribing audits. Continuous data are routinely collected for administrative purposes such as electronic medical databases and health or pharmacy claims databases. These data provide an advantage in detecting the underlying secular trends before the intervention period.

Statistical analyses are chosen according to the availability of the data. Examples of designs used in previous studies are provided below (Lunde PKM 1987; Piening et al. 2012).

3.5.1 Interrupted time series designs

The interrupted time series design is a powerful quasi-experimental approach to provide an estimate of the impact of safety warnings (intervention). Data are collected at multiple

time points before and after an intervention to detect whether the intervention has a significantly greater effect than any underlying secular trend. This design accounts for the long-term non-periodic variation of observation before the warning, which is expected to continue after the warning. It is considered to be the best available study design for evaluating the impact of a new regulatory warning, policy, or guideline (Wagner et al. 2002; Piening et al. 2012). The intervention effect is estimated by comparing the trend after the intervention to the trend in pre-intervention period. There are a wide variety of techniques that can be used based upon the characteristics of the data, number of observations and the existence of autocorrelation. The most frequent analyses are the auto regressive moving average model and segmental time series regression.

1) The auto regressive moving average model (ARIMA)

The auto regressive moving average (ARIMA) model has been used to investigate the trend of time-series data and the impact of health care interventions on trends of drug use (Ferrand et al. 2011; Langley et al. 2011; Ruiter et al. 2012). The impact of the intervention on subsequent observations can be detected as permanent abrupt, permanent gradual, or abrupt temporary. The ARIMA model incorporates the past values and directions over a period of time to better describe the trend of data. Apart from detecting the secular trend, the ARIMA detects the higher degree of correlation such as seasonal trend. However confounding effects on data are assumed to be similar both before and after the intervention periods. The ARIMA (*p,d,q*) model is an applied time-series model developed by Box-Jenkins (Box 1976; Griffiths et al. 2000) to forecast future observations that occur at equal time intervals and determine the effect of an intervention in time series data. Firstly, the integration process is differenced (*d*) to make stationary data. The Dickey-Fuller test can also be used to confirm the stationary data (Dickey 1979). The autoregressive model of order *p* explains the accumulated effect of the preceding data and moving average model of order *q* indicates the most recent random shock carried over from one period to the next. The appropriate model (*p, q*) is obtained from the visibility to the plots of autocorrelation functions (ACF) and partial autocorrelation functions (PACF) of time-series values (McDowall 1980). The best fitted model for analysis is examined using the Bayesian Information Criteria (Schwarz 1978).

The fact that the ARIMA model is not supported by any theoretical model or structural relationship raises questions on its reliability. It can be challenging to achieve a high level

of accuracy for a chosen model ARIMA (p,d,q) as it depends on selecting appropriate values for variables p, d and q. The results may vary from one researcher to another due to different levels of skill and experience of each researcher. However, other modeling approaches also share this type of criticism. The utilisation of the ARIMA model has been widespread since the method was incorporated into a number of commonly used statistical software such as STATA, SAS and R. The major advantage of the ARIMA method is that it is based on autocorrelation; thus, the data can be fitted into either a linear model, an exponential smoothing model or both (Griffiths et al. 2000).

2) Segmented time series regression

Segmented time series regression is used to estimate changes in the proportion of events by comparing post-intervention trends to pre-intervention trends (baseline slope) (Wagner et al. 2002). This analysis controls for the autocorrelation (first order correlation) or secular trend. Common segmented regression models estimate coefficients, which correspond to the trends of pre-implementation and post-implementation periods. Typically, at least 12 data points before and after the intervention are recommended to evaluate seasonal variation. For example, a significant association between the FDA advisory and a change in the trend of patients seen by psychiatrist as a declining trend at 1.8% per year before the warnings is significantly different from a declining trend at 3.5% per year after the warnings using a t test analysis (Morrato et al. 2008; Dorsey et al. 2010; Wijlaars et al. 2012).

3.5.2 Poisson regression

Poisson regression analysis is the association between count data/rate data and the intervention (exposure). Count data are the count of events occurring and rate data are the count of events occurring to a particular unit of observation, divided by the unit's exposure. Examples are co-dispensing/co-prescribing rate occurring among cisapride users before and after the warnings (Guo et al. 2003). Poisson regression is used to determine the overall association between antidepressant prescription rates and suicide rates, adjusted for sex and age, during the periods preceding and immediately following the public health warnings (Wijlaars et al. 2012).

3.5.3 Logistic regression

This analysis categorises the outcomes that occurred during the period before and after the warning as a binary response. Predicted outcomes during the post-warning period are compared with the baseline (pre-warning) using logistic regression. Logistic regression measures the relationship between outcomes and the period of warnings. For example, there was no increase in the recommended outpatient visits among children starting antidepressants following the warning (Guo et al. 2003; Busch et al. 2010). The use of droperidol for postoperative nausea and vomiting prophylaxis significantly decreased after the Black box warning (Wax et al. 2007).

All analyses need to consider adjusting for other influences such as scientific reports, media coverage, and industry promotion. This can be multifaceted and difficult to achieve, therefore additional qualitative research can help to interpret quantitative data and explain the complex reality of a given situation.

Qualitative approach

Qualitative research generally provides an understanding of a problem or issue from the perspective of the particular population it involves. It is an effective way of obtaining information on the opinions, behaviours, and social contexts of target populations. Previous research evaluated the impact of drug safety warnings by assessing practitioners' knowledge, attitudes, beliefs, or experiences regarding safety communications. The measurement outcomes are: the degree of awareness of the risk associated with medicine (or recent updated labelling) and awareness of the specific recommendation; the agreement and satisfaction with the content provided in communication messages; and the impact of warnings on alterations to clinical practice. Studies in clinicians suggested high levels of awareness for a Black box warning on antidepressants but low levels of awareness of the recommended strategies (Richardson et al. 2007; Bhatia et al. 2008). An online survey reported that specialists had higher awareness regarding the Black box warning on long-acting beta-agonists (LABAs) compared to primary care physicians; however, a smaller proportion of specialists agreed with the warning (Karpel et al. 2009). About half of survey participants considered changing their practice after the FDA alert regarding suicidality and antiepileptic drugs (Shneker et al. 2009).

To date, there have been little or no studies on the impact of the safety warnings among Australian prescribers therefore qualitative research will help to provide a more in-depth understanding of prescribing behaviour and the structure of the drug warning system used by practitioners. Several methods of obtaining data are available for different types of questions .

3.5.4 Questionnaire and Survey Methods

Questionnaires or a survey-based design is the most common method for qualitative studies assessing prescribers' knowledge, attitudes and beliefs regarding safety warnings (Feldman et al. 2011). Selected populations are primarily general practitioners or primary care physicians and the main prescribers of drugs. The selected population in previous studies are often convenience samples such as attendees of the conference or members of a medical association (Paschall et al. 2008; Phipps et al. 2011).

In person, mail or telephone surveys are the best form when high response rates are needed; however, they are more time consuming, higher cost, and more difficult to code data (Bonevski et al. 2011). Web-based surveys are versatile and widely dispersed in social settings. Participants are autonomous on a web-based survey therefore it allows researchers to control for bias both from investigators and responders (Wright 2005). This type of survey is suitable when there is a limited budget and/or time; however, low response rates are the main concern. The increasing challenge of survey-based studies is the low response rate especially in general practitioners, which have been as low as 5% in previous papers (Karpel et al. 2009). Non-responders may cause selection bias (or socially-desirable response bias) and have an effect on generalisability and potential validity of the findings (Paschall et al. 2008). Systemic reviews of strategies to improve survey responses suggested that incentives, shorter questionnaires, pre-notification, follow-up contact with a copy of questionnaires could increase survey response rates (Edwards et al. 2009).

Combined qualitative and quantitative analysis was used to interpret the results from the survey study. The comments and free text answers were collected for further interpretation and discussion while the responses were collected in the form of categorical variables. These results were presented as numbers and percentages among responders and were

quantitatively analysed using statistical tests. Pearson chi-square and Fisher exact tests are often used to evaluate the relationships between variables (Lydersen et al. 2003).

3.5.5 Interviews

Interviews either face-to-face or by telephone are optimal for collecting data on individuals' status, experience and perspectives. It can achieve higher response rates compared to other designs (Bowling 2005). However, interviews involve social interactions that may result in decreased confidentiality and anonymity in answering, especially when sensitive issue are being assessed (Bowling 2005). Interviews are a more appropriate forum for open-ended questions to gauge the idea of participants of that topic and invite more in-depth opinions. Interview data can be a useful mechanism for developing closed questions for a survey of the larger participants (Fowler et al. 2002).

3.5.6 Focus groups

Focus groups are efficient in generating broad overviews of issues among groups represented. Participants are free to discuss their opinions, attitudes towards the topic of interest and can often bounce ideas and opinions off each other. Focus groups can create the external validity when using participants from similar backgrounds or with shared interests. However, focus groups do have disadvantages, they can evoke social desirability bias and are often difficult to organise/coordinate with multiple participants. Often a few people can dominate the discussion leading to limited exploration of everyone's viewpoints. Only a few focus groups have been used to examine the effect of drug warnings, one of those was to assess the influence of a Black box warning on the changes in providers' practice on adolescent depression (Richardson et al. 2007).

4. Australian healthcare system

The healthcare system in Australia is primarily provided and funded by the Federal Government, Department of Health; however elements of system such as public hospitals are operated by State Governments. The National health policy aims to provide all Australians with accessible and affordable health care, additionally, all individuals have a choice of private health insurance (e.g. Life Health Cover, Medicare Levy Surcharge).

Medicare and the Pharmaceutical Benefits Scheme (PBS) are the two main healthcare funding systems operated by the Australian Government (Medicare).

4.1 Medicare

Medicare is a universal public health insurance scheme instituted in 1984 to provide free or subsidised health care treatment under the Medical Benefits Scheme (MBS). Medicare covers 100% of treatment and accommodation costs if you are a public patient in a public hospital. For medical services outside the hospital, 100% of MBS fee for a general practitioner, 85% for the specialist, optometrists, and dentists (in specific circumstances) can be reimbursed although these reimbursements are capped and therefore patient co-payments vary at the discretion of the provider (Medicare).

4.2 Pharmaceutical Benefits Scheme

The Pharmaceutical Benefits Scheme (PBS) is the national formulary that provides affordable access to necessary medicines covering most medical conditions. Most of medicines listed on the PBS are prescribed by community medical practitioners and dispensed by community pharmacists. The government reimburses products listed on the PBS for all Australian citizens by paying a portion of the cost of medicines. The cost of the full scheme is financed from consolidated revenue, which is from the taxpayer (PBS 2012).

In order to be available on the PBS, a medicine must be approved for sale in Australia by the TGA based on medicine's safety, efficacy, and manufacturing quality. Then most pharmaceutical suppliers products will apply for a PBS listing for their product. The Pharmaceutical Benefits Advisory Committee (PBAC), an independent expert committee, evaluates medicines using a cost-effectiveness analysis to determine whether its benefit is better or comparable to the available subsidised medicines at an acceptable price. If it is deemed acceptable the PBAC will recommend the subsidised conditions and price listing to the Government for funding on the PBS (Figure 1). PBS listing conditions correspond to clinical indications approved by the TGA when products are registered for marketing (PBS 2012).

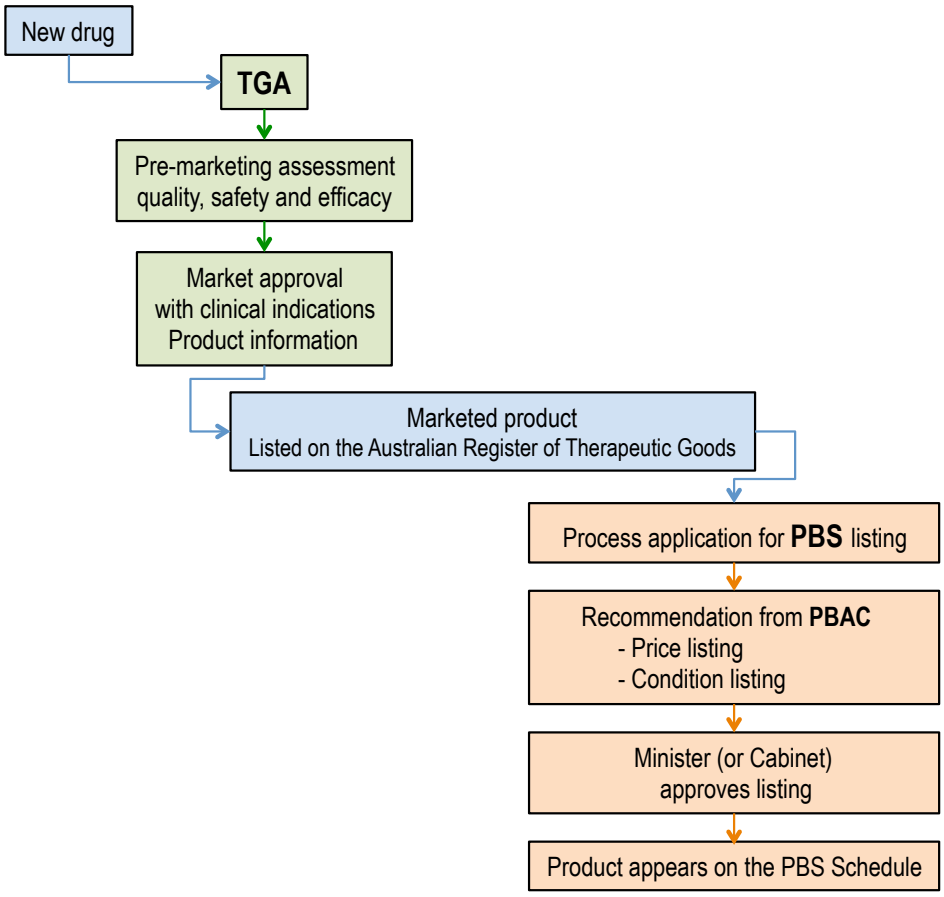


Figure 1. Processes of drug approval and the PBS subsidised listing

Drugs listed on the PBS are categorised into three levels of restriction (PBS):

- Unrestricted benefits—The drug has no restrictions on its therapeutic uses. It may be used for whichever therapeutic condition that is considered appropriated by prescribers
- Restricted benefits—The drug is only subsidised for specific therapeutic conditions listed
- Authority required benefits—The drug is subsidised if prescribing reasons comply with the listed restrictions according to the efficacy, safety, and economic analyses. Authority required benefits are divided into two categories:
  - 'Authority required'—The dispensing needs a telephone or written approval from the Department of Human Services or Department of Veterans' Affairs.
  - 'Authority required (STREAMLINED)'—Items do not require approval. Instead, a four digit streamlined authority code has to be included on the prescription according to the PBS restriction criteria.

Usually, new-entry medicines are listed as Authority Required Benefits due to the limited experience with the drug. The PBS listings may be reclassified depending on extended evidence of benefits and risks. This process closely reflects the updated data from the TGA and the product information (PBS).

All Australian residents and those who qualify for a Medicare card are eligible for PBS subsidised medicines. There are two types of PBS beneficiaries: general and concession. Concession beneficiaries are Australian social security recipients and most aged pensioners (aged above 65 years) and the remainder are general beneficiaries (Centrelink 2014). Patient contributions for the PBS are updated annually. When dispensed a medicine, patients pay the lowest value of either; the total cost of the medicine or a fixed co-payment. As of 1 January 2014, general beneficiaries contributed a co-payment of up to AU$36.90 for each dispensing with the general safety net threshold (maximum co-payment) of AU$1421.20 per year, when they then pay concession beneficiary co-payment amounts) compared to a considerably lower AUD$6.00 (maximum AU$360) for concession beneficiaries. The Government absorbs the remaining drug costs (PBS 2014).

Besides the PBS, the Repatriation Pharmaceutical Benefits Scheme (RPBS) is a separate scheme administered and subsidised by the Department of Veteran's Affairs (DVA). The RPBS provides pharmaceutical supplies for veterans and their dependants at a concessional rate. Those who are eligible for a DVA card can be reimbursed for all medicines listed on both the PBS and RPBS (DVA).

5. Available sources of data in Australia

5.1 PBS database

The PBS database is a national administrative database that records reimbursed medicines by the Australian Government. Products subsidised by the PBS are assigned PBS codes, which are specific for each formulation. The PBS codes indicate; chemical name, strength, maximum quantities (e.g. tablets), maximum numbers of repeats, and dispensed price. These data are regularly updated in the Schedule of Pharmaceutical Benefits (PBS 2014).

Available data on the PBS database are; amount of dispensing, cost of dispensing, and period of drug dispensed. All dispensings are recorded as aggregated, de-identified data

using the PBS codes (Medicare). Drug dispensing data on the PBS database are publicly available (Medicare) and are frequently used in research studies to investigate the utilisation trends in Australia such as antidepressants and antisecretory drugs (Hollingworth et al. 2010; Islam et al. 2014).

Only subsidised drugs that cost more than the co-payment of each beneficiary are available in the database. At the time of writing the dispensing costs of all drugs listed on the PBS are higher than $6 in 2014 therefore all dispensings for concession beneficiaries are captured in the database. If the dispensing cost is under the general co-payment for example, pantoprazole, which cost $18.40 in 2014, then there is no record of any dispensings to general beneficiaries. Whereas 'expensive' medicines such as esomeprazole, which cost $38.32 in 2014, all dispensings will be recorded for both concession and general beneficiaries (PBS 2014).

Similar to other pharmacy claims databases, the PBS was designed for pharmacy reimbursements. It does not link to clinical data at a patient level to provide information such as; patient characteristics, reason for dispensing, and other co-prescribed medicines. The dispensing data may not represent the actual prescribing trend in clinical practice because patients may choose not to fill the prescription (primary non-compliance) (Beardon et al. 1993; Shrank et al. 2010). Another limitation is that the dispensing data do not guarantee the actual consumption by patients (secondary non-compliance) (Roughead et al. 2007).

5.2 AsteRx database

The AsteRx database has collected clinical data from more than one hundred medical practices in all states of Australia since 2003. As of May 2012, demographic data of over half a million patients and 1,121 doctors were recorded as de-identified information. There are a total of seven million prescriptions including details on prescribing date, chemical name, strength, quantity, and drug codes (WHO Anatomical Therapeutic Chemical Classification (ATC) system codes and PBS codes). Other information such as diagnoses, consultations, and laboratory results are recorded in free text (Gilard et al. 2008).

There are a total of 13 files in the AsteRx database.

- The “Consult” file includes three variables: the “consultID”—a unique identification number of consultation, “consultDate”—date of consultation and “consultreasonDetail”—a free text of the details on the “consultID”.
- The “Diagnosis” file includes the “diagnosisID”, “diagnosisdate” and “diagnosis”—a free text.
- The “DoctorCD” file indicates the details of doctors in the AsteRx. This file composes of “DoctorID”, “state”—practicing state, “gender”, “YearofGrad”—year of graduation and “Qualifications”.
- The “Practice” file includes the details of practice sites: “PracticeID”, number of doctors, postal code and state.
- The “ReferralsCDM” file records the information on the category of referral doctors such as general practitioners and specialist type.
- The “ServiceRequestCDM” file records any service the practice site gave to the patients in free text.
- The “ScriptCDM” file indicates the details on the prescription. It composes of “ScriptID”—a unique identification number of the prescription”, “DoctorID”, “Scriptdate”—date of prescription, “Drugname”—generic or trade name of the drug, strength, dose, frequency, instructions, quantity, repeats, “scriptreason”—reason of this prescription, “pbstype”—PBS subscription according to the PBS website, “atccode”—Anatomical Therapeutic Chemical (ATC) code as recommended by the World Health Organization (WHO), “DrugID”—a unique identification number of the drug that links to the AsteRx drug reference, and “pbscode”—an identification number of the formulation as listed on the PBS website.
- The “ScriptRxCDM” file includes “reasonDeletion”—the reasons of a cessation of drug and “ceasedDate”—date of drug deletion/drug cessation.
- The “ImmunisationCDM” file indicates the details of immunisation of the patients.
- The “MeasureCDM” file includes other measurements that were recorded in the AsteRx.
- The “Pathology” file records the details of pathology sites, doctor who sent the tissue and date of sent tissue in free text.
- The “PathologyAtom” file indicates the pathology result.

- The “Patient” file includes “PatientID”—a unique identification number of patient, gender, “yearofbirth”—year of birth, “monthofbirth”—month of birth, “pensionstatus” —status of patients’ pension and “Smoker”—smoking status of the patient (ex-smoking or non-smoking) and number of years of smoking.

The AsteRx clinical database provides prescribing data which links to patients’ demographics, prescribers’ characteristic, clinical diagnoses, and other co-prescribed medicines. These data can be used to investigate the prescribing or co-prescribing trends, more specific details on switching choices and other clinical factors associated with prescribing decisions (AsteRx 2012).

5.3 DVA database

The Australian Government Department of Veterans’ Affairs (DVA) administrative health claims database collects health services that are provided for all veterans and their eligible dependants (e.g. spouses, widows or widowers, and children) (DVA). The DVA database is assessed for research conducted by the University of South Australia and their collaborators (Wahab et al. 2014).

According to statistics in 2011, the database contains an estimated eighty million pharmacy records, two hundred million medical service records, and six million hospital admissions for three hundred thousand patients. Data include patient characteristics such as age, sex, date of birth, date of death and residential status. DVA populations are 60% male and predominately elderly aged between 80 and 85 years. Medical consultations, pathology, hospital admissions, and diagnoses associated with the hospitalisation subsidised by DVA are also available. Hospitalisations are recorded using the WHO international Classification of disease, 10^{th} revision (ICD-10). Prescriptions dispensed and subsidised by the PBS and RPBS for the DVA clients are recorded on the pharmacy claims information using WHO Anatomical Therapeutic Chemical (ATC) classification codes (DVA 2011; Pratt et al. 2013).

Apart from veterans’ health studies, research conducted using DVA data include medical problems, medicines use in geriatrics and other pharmacoepidemiology studies (Pratt et al. 2013).

5.4 BEACH program

The Bettering the Evaluation and Care of Health (BEACH) program is a general practice activity database that has been collected since 1998. It aims to provide accurate and timely data to various users including government, pharmaceutical industry, external organisation, and researchers for investigating GP/patient encounter information.

A cross-sectional, paper based data collection system developed and validated by the University of Sydney is used to compile the data. The collection process is performed by randomly sampling one thousand general practitioners (GPs) annually across Australia and then recording one hundred consecutive consultations from each GP. As of July 2012, there were approximately 1,400,000 GP-patient encounter records in the BEACH database (BEACH 2012).

The BEACH database contains the interrelationships of data variables including:

- Encounter characteristics
- Characteristics of GPs (e.g. age, gender, years in practice, size of practices, computer use, location of practice)
- Characteristics of patients seen by GPs (e.g. age, gender, healthcare coverage, status to the practice (new/seen))
- Up to three visiting reasons
- Up to four problems managed at the consultation
- Treatment provided for each problem managed
- Drugs prescribed, drug supplied by the GP, dosage regimen, over the counter drug advised, clinical procedures
- Referrals to specialists and allied health services
- Test orders including pathology and radiology

Other supplementary data is often nominated for collection by BEACH stakeholders e.g. smoking status, alcohol consumption, and body mass index. External organisations can also specify topics for data collection and data analysis (BEACH 2012).

The BEACH collects data from random sample all over Australia, thus it provides general information on the prevalence of diseases and the clinical activities taking place in Australian general practice. Examples of studies utilising these data are common sexual

transmitted infections and their management (Johnston et al. 2004), musculoskeletal problems seen in adolescents seen by GPs (Henschke et al. 2014), and presentations that led to long consultations in children (Cooke et al. 2013; Freed et al. 2013). Other kinds of research that use the BEACH database are reliability and validity of GP records and development of tools for improving management.

Since the information captured on the BEACH database is cross-sectional data, it can not be used to examine the trend or the changes over time. Not all prescribing drugs are recorded for each visit therefore a complete pattern of medicine use cannot be assessed.

6. Chapter conclusion

Given the public attention to the TGA's safety communication and the necessary of drug safety warnings, this research aims to gain the comprehensive impacts of current drug safety warnings on clinical practice in Australia. Both quantitative and qualitative studies were conducted using recent drug safety warnings as case studies.

Quantitative studies presented the impact size and direction of each drug safety warning on patterns of actual drug use using an interrupted time series analysis. Rates of events (e.g. switch and stop) before and after the warnings are also assessed using regression models (Piening et al. 2012). Currently, available databases for the patterns of drug use in Australia are the PBS database and AsteRx database. The publically available online PBS data records all prescriptions dispensed to Australian residents therefore the patterns of national drug consumption can be calculated using DDD/inhabitant/day during the period of interest. This data source lacks information on individual-linked drug use and diagnosis-linked data that are captured in the clinical database, AsteRx. The AsteRx database can be used to examine concomitant drugs in individual patients, incidence/prevalence of events, duration of treatment, prescribers, and prescribing correlation. The AsteRx database is currently accessible for research conducted in the School of Pharmacy, the University of Queensland.

A qualitative study assessed prescribers' perspective on the overall drug warning system and towards recent drug safety warnings. Findings from a combined interview and survey study among Australian prescribers has been used to improve the understanding of the

impacts of drug safety warnings on prescribing decisions and better explain the changes in the quantitative studies.

The next chapter will describe the recent drug safety warnings that may have significant impacts on the trends of drug use in Australia.

Chapter 2. Recent drug safety warnings

Overview

Diabetes mellitus and cardiovascular disease are two high-burden diseases in developed countries (Squires 2011). Prevalence of diabetes has increased in Australia from 2.4% in 1995 to 4.2% in 2011. The data from the Australian Health Survey showed that approximately 1 million Australians had diabetes in 2011–2012 and 84.9% of those had type 2 diabetes (ABS 2012). Good glycemic control can prevent chronic complications of diabetes such as nephropathy, retinopathy, peripheral vascular disease, and cardiovascular/cerebrovascular diseases, which contribute greatly to the burden of disease and health care expenditure (UKPDS 1998; Bach et al. 2014). Cardiovascular disease is the primary cause of death in patients with type 2 diabetes as well as the leading cause of death among Australians since 2000 (Statistics 2012).

Significant resources have been invested to develop new drugs for better controlling and preventing complications of diabetes and cardiovascular disease; however new treatments may come with unpredictable complications.

Case study 1. Thiazolidinediones

In the US, the number of patients treated with antidiabetic drugs increased by 42.9% from 2003–2012 with much of this growth consisting of prescriptions for thiazolidinediones (rosiglitazone and pioglitazone) and dipeptidyl peptidase 4 inhibitors (DPP-4) (Hampp et al. 2014). Other antidiabetic treatments such as sulfonylureas, metformin, alpha glucosidase inhibitors and insulin have been extensively used with acceptable safety.

During the expanding use of thiazolidinediones, a meta-analysis from Nissen et al. suggested an increased risk of myocardial infarction (MI) related to rosiglitazone treatment in May 2007 (Nissen et al. 2007). Pioglitazone, on the other hand, showed no evidence of an increase in ischemic heart events and seemed to be a better alternative to rosiglitazone (Lincoff et al. 2007). However, in 2011 the long-term use of pioglitazone was found to be associated with an increased risk of bladder cancer (Lewis et al. 2011). Regulatory bodies from around the world have announced a series of safety warnings related to the use of thiazolidinediones.

Case study 2. Clopidogrel and proton pump inhibitor interaction

Since the availability of clopidogrel in 1997, this effective antiplatelet agent became the fastest growing pharmaceutical product across the globe (Committee 1996; ims 2011). A combination of clopidogrel and aspirin or 'dual antiplatelet therapy' is well recognised as the standard treatment and prevention for acute coronary syndrome. However, an increased risk of gastrointestinal bleeding, especially in patients with a history of gastrointestinal conditions and the elderly, is associated with this dual antiplatelet therapy (Yusuf et al. 2001; Steinhubl et al. 2002; Ng et al. 2008). Antisecretory agents such as proton pump inhibitors (PPI) and histamine-2 receptor antagonists (H2RA) are usually coprescribed with antiplatelet agents to prevent these gastrointestinal complications (Kushner et al. 2009). For the last decade, clopidogrel (Plavix®) and proton pump inhibitors, particularly esomeprazole (Nexium®) were in the top five pharmaceutical product sales and highest expenditure worldwide (Chevarley 2010; ims 2011).

In 2006, *in vitro* studies indicated a decrease in platelet inhibitory effect of clopidogrel related to PPI treatment (Gilard et al. 2006). Literature had been extensively published on the pharmacodynamic evidence of this interaction but clinical studies could not provide consistent outcomes (Kwok et al. 2013). The key international regulators issued several warnings on the drug interaction between clopidogrel and PPIs. However, the contents in the warnings have been modified over time with conflicting messages across nations.

Studies in the US and Europe have investigated the impact of their regulatory warnings on the use of thiazolidinediones and the coprescribing of proton pump inhibitors with clopidogrel but the patterns of use in Australian were unknown. Chapter 3–6 will present studies conducted using Australian data, this chapter will provide background information on the details of the medicines involved and their safety warnings.

1. Thiazolidinediones

Thiazolidinediones (TZDs) were approved based on their efficacy in decreasing HbA1c in patients with type 2 diabetes without long-term data on safety and clinical outcomes (Aronoff et al. 2000; Phillips et al. 2001). Troglitazone (Rezulin®) was the first TZD approved by the FDA in 1997; however, shortly after its launch into the market severe hepatotoxicity effects were reported (Gitlin et al. 1998; FDA 2000). Regulatory warnings

were issued on this side effect including liver function monitoring, subsequently, troglitazone was withdrawn from the market in March 2000 (FDA 2000). In 1999, the FDA approved rosiglitazone (Avandia®) and pioglitazone (Actos®), which did not share troglitazone's risk of hepatotoxicity (FDA 1999; FDA 2000). TZDs were considered as a third-line choice for type 2 diabetes treatment when metformin or a sulfonylurea were contraindicated or intolerable (NICE 2003). Although, pioglitazone and rosiglitazone showed similar glycaemic effects in their suggested therapeutic doses, pioglitazone was associated with better improvements in lipid profiles compared to rosiglitazone (Diamant et al. 2003; Goldberg et al. 2005).

Mechanism of action

Thiazolidinediones (TZDs) have a different mechanism of action to pre-existing antidiabetic agents. They improve insulin sensitivity by acting as modifiers of peroxisome proliferator-activated receptor gamma (PPAR–γ) or PPAR–γ agonists, regulating selective ligands of the nuclear transcription factor. PPAR receptors are found at the key sites of insulin resistance tissues including adipose tissue, skeletal muscle, and liver (Spiegelman 1998; Olefsky 2000).

Activation of the PPAR–γ responsive gene improves the regulation of glucose production, transport, and utilisation as well as the regulation of fatty acid metabolism. They promote endogenous and exogenous insulin sensitivity in muscle, fat, and liver. In *in-vitro* studies, pioglitazone acts like a partial PPAR-α agonist, while rosiglitazone has a pure PPAR–γ agonist effect (Yki-Jarvinen 2004).

Glycaemic control

The effect of TZDs on blood sugar control is progressive, and typically results in a decline of HbA1c in the region of 0.5–1.5% over one to three months. Rosiglitazone and pioglitazone have been used as an oral monotherapy or in combination with metformin, sulfonylureas, or insulin, which lead to further decreases in the level of HbA1c.

Adverse effects

The main side effects of TZDs are weight gain, fluid retention, oedema, and dilutional anaemia, which result from the PPAR–γ activities on various tissues. Weight gain after six months of treatment may be due to increased peripheral fat mass and fluid retention. The

fluid retention and oedema may cause by increased endothelial cell permeability as well as a renal effect of PPAR–γ. Because of fluid accumulation, the TZDs treatment is significantly associated with an exacerbation of congestive heart failure (Benbow et al. 2001). Therefore congestive heart failure is a contraindication of TZDs. In 2002, TZDs were not recommended in patients with New York Heart Association (NYHA) functional classification stages III and IV (Nesto et al. 2003).

Macular oedema has been associated with TZDs and typically resolves rapidly after drug cessation (Ryan et al. 2006; Liazos et al. 2008). TZDs also appear to be associated with a higher risk of peripheral fracture in women and bone loss in elderly women (Kahn et al. 2006; Schwartz et al. 2006; Grey et al. 2007).

1.1 Rosiglitazone

1.1.1 Availability of rosiglitazone in Australia

Rosiglitazone (Avandia®) was approved by the TGA in 2000 for type 2 diabetes treatment in patients with inadequate glycaemic control through lifestyle measures, sulfonylureas or metformin. It was first listed on the PBS in November 2003 and subsidised as a dual oral therapy with either metformin or a sulfonylurea. Patients must have a contraindication or intolerance to either metformin or a sulfonylurea and inadequate control of blood glucose (HbA1c>7% with metformin or sulfonylureas) to qualify for PBS subsidised treatment. Rosiglitazone's PBS listing extended to triple therapy with metformin and a sulfonylurea in April 2005 and for use in combination with insulin in August 2005. Fixed dose combination tablets of rosiglitazone with metformin were listed on the PBS in July 2006 (PBS 2006; PBS 2008).

In late 2008, the PBS revoked the subsidised conditions of rosiglitazone for the triple oral therapy and the use in combination with insulin (PBS 2008). Subsequently in March 2011, the PBS changed the restriction criteria for rosiglitazone from Authority Required (STEAMLINE) to Authority Required for dual oral therapy, which requires telephone approval prior to the dispensing of rosiglitazone.

1.1.2 Rosiglitazone and cardiovascular events

On 21 May 2007, a meta-analysis was published concerning a significantly elevated risk of MI and cardiovascular mortality related to rosiglitazone therapy (Nissen et al. 2007). Two further meta-analyses were published in 2007: one observed an increased risk of cardiovascular events with rosiglitazone, and one was inconclusive (Diamond et al. 2007; Singh et al. 2007).

An interim analyses of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial, prospectively designed to evaluate the risk of cardiovascular outcomes between rosiglitazone in combination with metformin or sulphonylurea and dual therapy of metformin and sulphonylurea, had inconclusive findings with regards to cardiovascular events and rosiglitazone (Home et al. 2007).

A FDA briefing document published their evaluation of three meta-analyses on myocardial ischemic events related to rosiglitazone, which concluded that there was an increased risk of MI and mortality associated with rosiglitazone use, particularly in patients exposed to long term nitrate treatment and insulin (FDA 2007).

A retrospective evaluation from GSK, the manufacturer of rosiglitazone, on cardiovascular events of short-term, double blind, randomised studies of rosiglitazone found an increased incidence of congestive heart failure in patients prescribed rosiglitazone with sulfonylureas or insulin. This evaluation also observed greater events of myocardial ischemia in rosiglitazone treatment compared to placebo or other diabetes drugs (Cobitz et al. 2008).

The RECORD study could not confirm the risk of myocardial infarction and overall cardiovascular morbidity or mortality of rosiglitazone; however, most of the studied patients had an incomplete follow-up status for the primary endpoint—first cardiovascular hospitalisation or cardiovascular death (Home et al. 2009).

On 28 June 2010, an updated meta-analysis from Nissen et al. and a retrospective observational study by Graham et al. were published which again raised the cardiovascular concerns of rosiglitazone (Graham et al. 2010; Nissen et al. 2010).

1.1.3 Safety warnings on cardiovascular events

U.S. Food and Drug Administration

The FDA issued an alert on the potential increased risk of myocardial ischemia on the same date as Nissen's publication (21 May 2007) (FDA 2007). On 30 July 2007, the joint committee of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the FDA assembled to discuss the cardiovascular risk of rosiglitazone. The FDA concluded that there was an increased risk of congestive heart failure and MI using three meta-analyses. Analysis of these results suggested that rosiglitazone users with long-term nitrate treatment and concomitant insulin therapy were at higher risk of myocardial infarction and cardiovascular mortality (Rosen 2007). On 14 August 2007, the FDA issued a Black box warning to emphasise the exacerbation of heart failure related to rosiglitazone treatment (FDA 2007). In November 2007, the precautions section for concomitant use of nitrate or insulin on the rosiglitazone label was updated.

In September 2010, the joint committee evaluated the recently updated data available on the cardiovascular risk of rosiglitazone and voted to allow rosiglitazone to stay on the market while the EMA suspended rosiglitazone throughout Europe. The restriction program took full effect in November 2011. The FDA requested GSK to convene an independent expert panel to re-investigate the RECORD study and evaluate the integrity of the study findings. In June 2013, the re-adjudicated results of RECORD were unchanged from the findings in 2008 and the FDA joint committee reassured the accuracy of these results. Following the discussion and recommendations from the joint committee, the FDA eased the restrictions of rosiglitazone in the USA (FDA 2013).

European Medicines Agency

A few days after the publication by Nissen et al. and the warning by the FDA, the European Medicines Agency (EMA) announced a press release on the cardiac safety of rosiglitazone (EMA 2007). The updated product information and warning stated that rosiglitazone may be associated with an increased risk of ischemic events and should not be used in patients with myocardial ischemic symptoms. Another press release was issued to confirm the positive benefit-risk balance for rosiglitazone and pioglitazone in treatment of type 2 diabetes on 18 October 2007 (EMA 2007). During 2007–2008 the EMA re-evaluated the benefits and risks of rosiglitazone using the data up to July 2008 and decided that the evidence regarding the link between rosiglitazone and ischemic heart disease was inconclusive.

In January 2008, a press release was issued by the EMA to recommend new warnings and contraindications for rosiglitazone in patients with ischemic heart disease and/or peripheral arterial disease (EMA 2008). On 9 July 2010, the EMA Diabetes/Endocrinology Scientific Advisory group (SAG) started to assess the updated available data and analysed the usage of rosiglitazone in the THIN database. The EMA concluded that the risk of rosiglitazone outweighed its benefits and recommended the suspension of all rosiglitazone containing products on 23 September 2010 (EMA 2010).

Therapeutic Goods Administration

The Therapeutic Goods Administration (TGA) approved the change on the product information that rosiglitazone should not be added to therapy in patients receiving insulin on 17 August 2007. The TGA considered the available data of three meta-analyses from Nissen et al., the FDA and the manufacturer as well as an interim analysis of the ongoing RECORD study when actioning the changed PI and Alerts. In December 2007, the TGA requested a box warning: "*The use of AVANDIA/AVANDAMET is not recommended in patients with known ischaemic heart disease, particularly in those taking nitrates. AVANDIA/AVANDAMET has been shown to be associated with an increased risk of myocardial ischaemia (angina, infarction) in pooled short-term clinical studies, particularly in those who needed several antidiabetic drugs or nitrates. See Precautions*" (TGA 2007). On 24 September 2010, the TGA published an advisory statement to reinforce the Box Warning (TGA 2010).

1.2 Pioglitazone

Pioglitazone seems to have a favourable effect on cardiovascular events. A PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) randomised controlled trial focused on vascular outcomes of pioglitazone found a reduction in the composite of all-cause mortality, non-fatal MI, and stroke in patients with high risk of macrovascular events (Dormandy et al. 2005). A meta-analysis pooled individual patient data from pioglitazone clinical trials and found a reduction in composite outcomes of all-cause mortality, myocardial infarction and stroke (Lincoff et al. 2007).

1.2.1 Availability of pioglitazone in Australia

The TGA approved pioglitazone for use as a monotherapy and in combination with sulfonylureas, metformin or insulin on 6 February 2001. Pioglitazone was listed on the PBS in November 2003 with the same criteria as rosiglitazone, dual oral therapy with metformin or a sulfonylurea. Additionally, the pioglitazone listing was wider than rosiglitazone in 2004 allowing an initiation in combination with insulin in patients with inadequate control of blood glucose, despite concomitant use of insulin and oral hypoglycemic drugs. In November 2007, the PBS listing of pioglitazone was extended to triple therapy with metformin and a sulfonylurea under Authority Required (STREAMLINED) (PBS 2007).

1.2.2 Pioglitazone and bladder cancer

A small increase in the number of bladder cancer cases in patients taking pioglitazone compared to control was observed in the PROactive meta-analysis (0.15% compared to 0.07% respectively), but it was concluded that these cases were unlikely related to drug (Dormandy et al. 2005). In March 2011, a French study reported a significantly increased risk of bladder cancer in patients exposed to pioglitazone compared to other antidiabetic medicines with higher risk in those exposed for more than twelve months, subsequently this study was published in June 2011 (Maladie 2011). Another retrospective cohort study showed a significant risk of developing bladder cancer among patients who took pioglitazone for more than two years (Lewis et al. 2011).

1.2.3 Safety warnings on bladder cancer

The EMA started a review on the risk of bladder cancer related to pioglitazone in March 2011. On 9 June 2011, the French regulatory authority decided to suspend pioglitazone-containing products in France (EMA 2011). On 21 July 2011, the EMA issued a warning for pioglitazone on the small increased risk of bladder cancer. EMA recommended that pioglitazone should not be used in patients with history of bladder cancer or with uninvestigated macroscopic haematuria (EMA 2011).

The FDA also requested a retrospective cohort study among pioglitazone users in March 2011 (Lewis et al. 2011). On 15 June 2011, the FDA announced that using pioglitazone for more than one year might be associated with an increased risk of bladder cancer. The

FDA recommended that pioglitazone should not be used in patients with active bladder cancer, and that practitioners should use pioglitazone with caution in patients with history of bladder cancer (FDA 2011).

On 18 July 2011, the TGA issued a safety advisory on the increased risk of bladder cancer associated with the use of pioglitazone for more than one year (TGA 2011). Health professionals were advised: *"Do not use pioglitazone in patients with bladder cancer or a history of bladder cancer. Consider the risk of bladder cancer in all patients treated with pioglitazone."*

1.3 Impact of regulatory warnings on thiazolidinediones in other countries

The usage of both rosiglitazone and pioglitazone were assessed after the emerging myocardial infarction risk of rosiglitazone. The EMA reported a decline in rosiglitazone in many countries from the assessment of drug usage during 2008–2010 (EMA 2010). Studies on the impact of EMA press releases and DHPCs showed a significant decrease in the dispensing of rosiglitazone after the 2007–2008 warnings in the Netherlands (Ruiter et al. 2012). Studies using the UK databases found a sharp decrease in rosiglitazone prescription numbers and an increase in switching to pioglitazone following the warnings on cardiac events of rosiglitazone (Hall et al. 2011; Leal et al. 2013). Most of the studied data depicted a transient increase in pioglitazone use during the intensive warnings of rosiglitazone in 2007–2008 as a result of an increase in the number of pioglitazone initiations and new users of pioglitazone (Shah et al. 2008).

In the US, pharmacy claims databases were accessed to evaluate TZD after the FDA warnings. The average number of claims per day per million members for rosiglitazone decreased dramatically after May 2007 while pioglitazone remained flat through 2007–2008. On the other hand, sitagliptin claims increased 5-fold during 2007 (Starner et al. 2008).

Some studies assessed the adverse events associated with rosiglitazone and found a decline in monthly rates of these events after November 2007. A study assessing the reason for switching found that switching from pioglitazone to other antidiabetic drugs was more common in patients with heart failure conditions and that switching from rosiglitazone was more likely in patients with ischemic heart disease, heart failure, insulin treatment, or a recent sulphonylurea prescription (Hall et al. 2011).

Various analytical models such as ARIMA model, Logistic regression and Poisson regression were used to examine the outcomes of interest, which include; number of users/prescriptions/dispensing, prevalence/incidence of prescriptions (e.g. person-years), proportion of all antidiabetic drug users, rate of switching, new users, number of initiations, and diagnoses/laboratory details related to the recommendations provided in the warnings (Ehrenstein et al. 2013).

2. Clopidogrel and proton pump inhibitors interaction

Overview

In 2009, the FDA and EMA announced a possible interaction between clopidogrel and PPIs, later that year, the FDA recommended against the concomitant use of omeprazole and esomeprazole with clopidogrel. The TGA refrained from any specific comment aside from the following update on the Consumer Product Information "consult your doctor before using these two drugs" in October 2011. Most *in vitro* studies have shown that omeprazole and esomeprazole reduce measures of the antiplatelet efficacy of clopidogrel. The considerable diversity in evidence on the risk of cardiovascular outcomes of concomitant clopidogrel and PPI therapy in clinical studies has led to a debate regarding the clinical applicability of the interaction.

2.1 Antiplatelet agents

Antiplatelet therapy is used for secondary prevention of coronary artery diseases and thrombotic cerebrovascular by inhibition of platelet aggregation in arterial thrombosis (Steinhubl et al. 2002; Patrono et al. 2008). Antiplatelet drugs are grouped according to their mechanisms of platelet inhibition: irreversible cyclooxygenase inhibitors, adenosine diphosphate receptor inhibitors (thienopyridiens), phosphodiesterase inhibitors, glycoprotein IIb/IIIa receptor antagonists, reversible P2Y12 antagonists (Eikelboom et al. 2012). Patients may benefit from different antiplatelet regimens; however, aspirin and clopidogrel are common oral antiplatelet therapies in patients with artherothrombosis with or without vascular intervention (Steinhubl et al. 2002; Kushner et al. 2009; Eikelboom et al. 2012).

2.1.1 Aspirin

Aspirin is a non-steroidal anti-inflammatory drug often used as an analgesic, antipyretic and anti-inflammatory drug (Eikelboom et al. 2012). The antiplatelet activity of low-dose aspirin (75–375 mg daily) was acknowledged in the 1960s as prolonged bleeding time (Weiss et al. 1967). Aspirin 100 mg tablets and 300 mg effervescent tablets are subsidised on the PBS.

Low dose aspirin inhibits platelet aggregation due to its irreversible inactivation of the cyclooxygenase (COX) -1 enzyme, which is a key enzyme in thromboxane A2 production. Thromboxane A2 induces platelet aggregation and vasoconstriction. In contrast, much larger daily doses of aspirin are required to inhibit the COX-2 dependent anti-inflammatory pathway rather than the antiplatelet pathway (Awtry et al. 2000).

Roles in the prevention of atherothrombosis

Daily dose of aspirin 75–100 mg is recommended for the long term prevention of serious atherothrombotic events (Collaboration. 2002). In primary prevention or prophylaxis of atherothrombosis, low dose aspirin yielded a 12% relative risk reduction in the incidence of major vascular events, particularly non-fatal myocardial infarction (MI). However, the benefits of aspirin in patients with a high risk of major thrombotic events need to be weighed against the risk of major bleeding (Baigent et al. 2009).

For secondary prevention in patients with existing vascular conditions, the benefits of aspirin exceed the bleeding risk (Baigent et al. 2009). Long-term aspirin therapy is recommended for patients with acute coronary syndrome (ACS) unless aspirin is contraindicated (Aroney et al. 2008). Even so, aspirin is considered to have a weaker inhibitory effect on platelet aggregation compared to other antiplatelet drugs. Thus it is used in combination with other antiplatelet drugs (Yusuf et al. 2001).

2.1.2 Clopidogrel

Overview

Clopidogrel is a second-generation thienopyridine. Clopidogrel is a prodrug that needs metabolic activation through the hepatic cytochrome (CYP) 450 system to generate active metabolites. Clopidogrel's metabolic pathways can be interfered with by other drugs that

share the same CYP450 enzyme (e.g. CYP2C19 drug interaction with PPIs). The first-generation agent, ticlopidine, was limited in use due to serious hematological toxicity and was replaced by clopidogrel. The antiplatelet effect of the newest thienopyridine, prasugrel, is more potent than clopidogrel and is not disturbed by polymorphisms in CYP2C19 or the concomitant use of PPIs (Brandt et al. 2007; Farid et al. 2008).

Pharmacokinetics and pharmacodynamics

Clopidogrel is an inactive prodrug therefore its therapeutic efficacy depends on its two-step oxidative process. First, hepatic CYP450 isoenzymes CYP1A2, CYP2B6, and CYP2C19 transform clopidogrel into 2-oxo-clopidogrel. Subsequently CYP2B6, CYP2C9, CYP2C19, and CYP3A4 oxidise 2-oxo-clopidogrel into a highly labile active metabolite (Figure 2) (Savi et al. 1994; Savi et al. 1998; Savi et al. 2000).

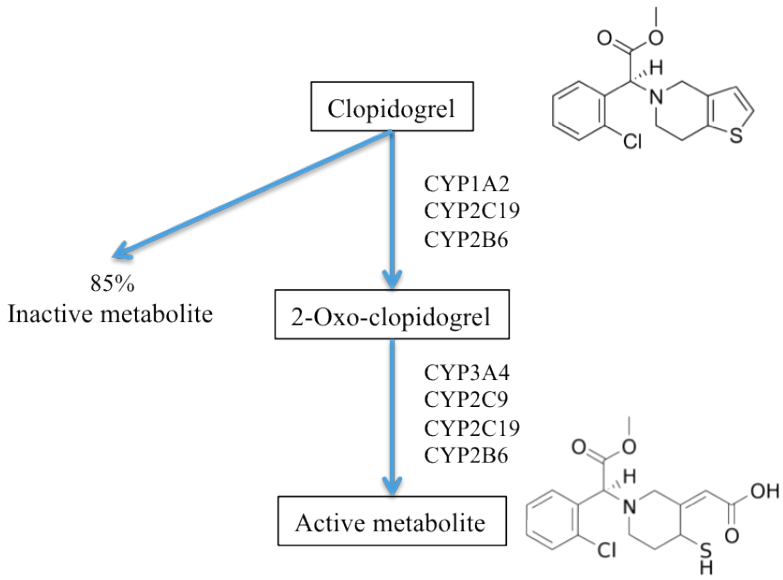


Figure 2. Clopidogrel metabolism

The active metabolite of clopidogrel is a potent inhibitor of adenosine diphosphate (ADP)-induced platelet aggregation (Defreyn et al. 1991). It reduces the amount of platelet ADP binding sites by selective and irreversible blockade of the platelet ADP $P2Y_{12}$ receptor (Savi et al. 1992; Savi et al. 1998; Savi et al. 2000).

At a maintenance dose of 75 mg daily, clopidogrel reaches steady state after 4–7 days and inhibits approximately 50–60% of platelet aggregation. A loading dose of 300–600 mg achieves the same levels of platelet aggregation within 4–24 hours (Gurbel et al. 2003;

Patrono et al. 2004; Gurbel et al. 2005; Lev et al. 2007; Kim et al. 2008; Kushner et al. 2009; Patrono et al. 2011).

Clopidogrel resistance

Mechanisms underlying variable or insufficient responses to clopidogrel have been attributed to multiple factors (Gurbel et al. 2003; Muller et al. 2003; Gurbel et al. 2005). These include impaired gastric absorption of clopidogrel, increased reactivity of resting platelets, up-regulation of other platelet activation pathways, CYP450 isoenzymes activity, genetic polymorphisms of the CYP2C19 allele, and drug-drug interactions (Kim et al. 2008; Holmes et al. 2011; Shmulevich et al. 2011). Recently, CYP2C19 metabolic activity was shown to be the key to the pharmacodynamic response and clinical efficacy of clopidogrel (Angiolillo et al. 2007). The CYP2C19 loss-of-function allele (*2 to *8 CYP2C19 allele) is responsible for more than 90% of poor metabolisers (Cayla et al. 2011; Holmes et al. 2011). Patients with genetic polymorphisms of the CYP2C19 allele could not convert clopidogrel to its active metabolites. Studies suggested that CYP2C19 loss-of-function allele is associated with the risk of cardiovascular events in clopidogrel-treated patients (Collet et al. 2009; Simon et al. 2009; Hulot et al. 2010; Simon et al. 2011). *In vitro* studies revealed impaired antiplatelet activity of clopidogrel by the concomitant use with CYP3A4- and CYP2C19-metabolised drugs (Zahno et al. 2010). Recent clinical studies have been trying to establish whether the interaction is clinically significant (Almadi et al. 2011; Ogilvie et al. 2011; Aihara et al. 2012).

Side effects

Clopidogrel is generally well tolerated with minor side effects such as stomach upset, diarrhoea and constipation (Committee 1996). Although clopidogrel can cause easy bleeding/bruising, the risk of upper gastrointestinal bleeding is less likely compared to low-dose aspirin. Clopidogrel rarely causes serious hematologic reactions (e.g. thrombotic thrombocytopenic purpura, neutropenia), which are of major concern in the thienopyridine drug class (Pereillo et al. 2002).

Roles in prevention of atherothrombosis

The Clopidogrel vs Aspirin in Patients at risk for Ischemic Events (CAPRIE) trial compared the efficacy and safety of clopidogrel (75 mg/day) with aspirin (325 mg/day). Clopidogrel

treatment was more effective in reducing the risk of MI, ischemic stroke or vascular mortality than those in the aspirin treatment group with a similar overall incidence of haemorrhagic events (Committee 1996). Several randomised clinical trials have shown the comparative efficacy and safety profiles of clopidogrel in reducing cardiovascular events compared to aspirin or placebo (Committee 1996; Collaboration. 2002; Diener et al. 2004; Berger et al. 2009).

Patients with coronary, cerebrovascular or peripheral arterial disease who cannot tolerate low-dose aspirin can use clopidogrel (75 mg daily) as an alternative antiplatelet. Frequently, clopidogrel is given with aspirin to reduce the risk of severe cardiovascular events in patients with acute coronary artery syndromes and after coronary intervention (Collaboration. 2002; Gurbel et al. 2005; Smith et al. 2006; Patrono et al. 2008; Patrono et al. 2011).

As the distinct and complementary pathways of platelet activation and aggregation, a combination of aspirin and a thienopyridine the so-called “dual antiplatelet therapy” is shown to have clinical benefit in high-risk clinical settings (Yusuf et al. 2001; Steinhubl et al. 2002; Diener et al. 2004; Chen et al. 2005; Sabatine et al. 2005; Bhatt et al. 2006; Berger et al. 2009). The combination of aspirin and clopidogrel consistently reduces the risk of cardiovascular events in ACS patients undergoing percutaneous coronary intervention (PCI) (CURE) (Steinhubl et al. 2002), patients with unstable angina/non-ST-segment-elevation myocardial infarction (CURE) (Yusuf et al. 2001), and acute myocardial infarction with ST-segment elevation (CLARITY, COMMIT) (Chen et al. 2005; Sabatine et al. 2005).

National and international guidelines recommended the combination of low dose aspirin and clopidogrel (75mg daily) for at least 12 months in patients with ACS after undergoing percutaneous coronary intervention (PCI) with or without stent. Continuation of clopidogrel beyond 15 months maybe considered in patients undergoing PCI with drug-eluting stent placement (Aroney et al. 2008; Kushner et al. 2009; Chew et al. 2011).

Studies have reported an increased risk in upper gastrointestinal bleeding complications due to dual therapy compared to the same dose of aspirin alone or clopidogrel alone (Diener et al. 2004; Hsu et al. 2011). Antiplatelet therapy is correlated with various

hemorrhagic complications, and upper gastrointestinal bleeding is the most frequent bleeding site (Trenk 2009).

Availability of clopidogrel in Australia

In November 1999, clopidogrel 75 mg tablet (Plavix® and Iscover®) was listed on the PBS subsidised formulary for the secondary prevention of ischemic cerebral stroke or transient cerebral ischemic events and the secondary prevention of myocardial information or unstable angina in patients with a history of cerebrovascular ischaemic episodes while on therapy with low-dose aspirin, or with contraindications to low-dose aspirin (such as gastrointestinal bleeding, allergy). In 2009, the listing of clopidogrel was extended to the treatment of acute coronary syndromes and the use following stent insertion in patients without a prior history of acute coronary syndrome in combination with aspirin (PBS 2009). In 2010, clopidogrel was listed as fifth-highest PBS drug by total cost to Australia (PBS 2010).

2.2 Antisecretory agents

Only two classes of drugs, proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H2RAs), are available as antisecretory agents for treating gastric acid-related disorders. Both drug classes inhibit gastric acid secretion but have different modes-of-action and metabolic pathways (Schafer et al. 2010).

2.2.1 Proton pump inhibitors

Overview

PPIs are recognised as efficient acid suppressants for the treatment of acid related gastrointestinal disorders (Welage et al. 2000). PPIs are shown to be more effective in the treatment of complicated gastric/duodenal ulcers, Zollinger-Ellison syndrome, erosive esophagitis and gastroesophageal reflux disease (GORD) compared to H2RAs (Torguson R ; Welage et al. 2000).

A duration of 4–8 weeks of PPI therapy is recommended in dyspepsia, GORD, peptic ulcer and mild to moderate esophagitis. Continuous PPI therapy is recommended for sever esophagitis and Barrett's esophagus, Zollinger-Ellison syndrome, scleroderma, and strictures (NICE 2004). For the eradication of *Helicobacter pylori* (*H. pylori*), PPIs play a

key role in triple therapy with two antibiotics (clarithromycin and amoxicillin/metronidazole) for 1 week and continued PPI treatment for up to 8 weeks (Gillen et al. 2004). PPI therapy is also useful in healing and preventing stress- and NSAID-induced ulcerations until NSAID treatment is stopped (Singh et al. 2005). Patients with a high risk of gastrointestinal bleeding particularly the elderly and patients with multidrug therapy often require long-term PPI treatment. Thus, they have a higher possibility of PPIs interacting with other drugs (Singh et al. 2005; Blume et al. 2006).

Availability in Australia

Five proton pump inhibitors are subsidised on the PBS but are not funded for all indications. Omeprazole and lansoprazole were launched in 1994, followed by pantoprazole (1995), rabeprazole (Pariet®) (2001) and esomeprazole (Nexium®) in August 2002. As at January 2014, all five PPIs are PBS subsidised as 'Restricted Benefits' for peptic ulcers and GORD. Esomeprazole 40 mg is listed as 'Authority Required benefits' on the PBS for Zollinger-Ellison syndrome and scleroderma. Only esomeprazole and omeprazole are subsidised for *H. pylori* eradication (PBS). As a class, PPIs are continuously among the top 10 most commonly subsidised medicines in Australia based on prescription numbers, daily dose and cost to the Government (PBS 2010).

Pharmacodynamics and pharmacokinetics

PPIs are designed to diffuse and inhibit gastric acid secretion at the surface of parietal cells in the stomach. PPIs irreversibly inactivate the gastric hydrogen, potassium-adenosine triphosphate (H+, K+-ATPase) enzyme system, also called the proton pump, which is the end stage of acid production (Kahrilas et al. 2000). The suppressive effect of PPIs last for 24 to 72 hours with once daily dosing and increases with repeated once daily dosing to plateau after 4 days.

PPIs are rapidly absorbed, highly protein bound, and extensively metabolised in the liver by cytochrome P450, particularly CYP2C19 and CYP3A4 (Blume et al. 2006). Each PPI has different substitutions on its pyridine and/or benzimidazole groups and some pharmacokinetic pathways. However, all PPIs are very similar in their pharmacological properties.

Drug-drug interaction

Although PPIs are metabolised via cytochrome P450, the inhibitory potency of each PPI is dependent on different enzymes (Li et al. 2004; Ogawa et al. 2010). The most extensively studied PPI drug interactions are omeprazole and pantoprazole (Blume et al. 2006; Wedemeyer et al. 2014). Omeprazole is the most potent *in vitro* inhibitor of CYP2C19 and a moderate inhibitor of CYP3A4 (Li et al. 2004), while pantoprazole has a considerably lower potential for drug interactions (Singh et al. 2005; Blume et al. 2006). Omeprazole increases the plasma concentration of warfarin, diazepam, phenytoin, while pantoprazole is not likely to interact with these medicines. The interaction profiles of lansoprazole and rabeprazole were limited in studies; however, they appear to have a less potential than omeprazole (Wedemeyer et al. 2014).

Side effects

Although PPIs are largely well tolerated, incidence of rare but serious adverse effects has been described in research studies. Chronic treatment with PPIs has been associated with increased risks of bone fractures, especially at high doses (Yang et al. 2006; Gray et al. 2010); the FDA requested these risks be added to the label in 2010 and the EMA in 2012. Meta-analyses and observational studies found an increased risk of community-acquired pneumonia in patients receiving PPIs and moreover, a recent meta-analysis shows an association with a higher dose PPI and short duration (<30 days) (Laheij et al. 2004; Johnstone et al. 2010; Eom et al. 2011; Giuliano et al. 2012). Patients using PPIs are reported to have an increased risk of a *Clostridium difficile* infection from meta-analysis studies (Dial et al. 2004; Leonard et al. 2007). The FDA issued a safety alert on *Clostidium difficile*—associated diarrhoea and the pneumonia associated with PPIs in 2012. Hypomagnesaemia, vitamin B12 deficiency, iron deficiency, thrombocytopenia, rhabdomyolysis and acute interstitial nephritis have also been associated with the long-term use of PPIs (Ali et al. 2009; Wilhelm et al. 2013).

2.2.2 Histamine 2 receptor antagonists

The long availability of H2RA including known safety and efficacy profiles has led to accessibility of these medicines over the counter in many countries; however, proton pump inhibitors are replacing H2RA in clinical practice (Klinkenberg-Knol et al. 1995). H2RAs are considered to be less effective in decreasing gastric acid than PPIs, which shut down the final step of acid secretion (Lanas et al. 2007).

Availability in Australia

Cimetidine, famotidine and ranitidine were made available on the PBS prior to 1992 followed by nizatidine in 1993. Currently, only famotidine and ranitidine are available over-the counter in Australia.

Drug-drug interaction

Cimetidine is the prototype H2RA; however, its clinical use is restricted by its adverse effects and drug-drug interactions. Cimetidine can increase a variety of drugs that metabolise via CYP1A2, CYP2C6, CYP2D9, and CYP3A4 enzymes. Ranitidine interferes minimally with hepatic metabolism of other drugs with an affinity of only 10% that of cimetidine. Famotidine and nizatidine have no significant drug interactions via CYPs therefore making them safe for use with other drugs (Sabesin 1993; Hatlebakk et al. 1996).

Side effects

Side effects of H2RAs occur in a small proportion of patients with the most common being headache, dizziness, diarrhoea, constipation, and muscular pain. Using cimetidine is associated with reversible endocrine side effects including gynecomastia and galactorrhea due to its nonsteroidal antiandrogen properties. Ranitidine has minimal side effects and none of the antiandrogenic and prolactin-stimulating effects of cimetidine (Sabesin 1993; Lev et al. 2007).

2.3 Concomitant use of clopidogrel and proton pump inhibitors

Gastrointestinal bleeding has been examined as one of the most common causes of life-threatening complications after acute coronary syndrome (ACS) (Liberopoulos et al. 2006). Gastrointestinal bleeding is usually precipitated by antithrombolytic, anticoagulation, or antiplatelet therapy and infrequently by colonic ischemia induced by hypo-perfusion. There are many other potential factors associated with an increased risk for upper GI bleeding in ACS patients including older age, previous GI events, and the use of other precipitating medicines such as NSAIDs (Ali et al. 2009).

PPIs or H2RAs are often prescribed prophylactically to prevent gastrointestinal haemorrhage or complications in patients taking antiplatelet drugs (Lev et al. 2007;

Schafer et al. 2010). In the CURE study, major GI bleeding occurred in 1.33% of patients on dual therapy compared to 0.75% in aspirin alone during the 12-month follow-up. Studies have shown that the use of PPI prophylaxis significantly lowers the risk of clinical upper GI bleeding and is more effective compared to H2RAs (Mehta et al. 2001; Ali et al. 2009; Pongprasobchai et al. 2009; Yasuda et al. 2009). One study showed that esomeprazole (PPI) is superior to famotidine (H2RA) in preventing upper GI complications related to aspirin, clopidogrel, enoxaparin, or thrombolytics (Ng et al. 2012).

Studies suggest PPIs have benefit in patients who need a dual antiplatelet therapy, especially aspirin and clopidogrel to prevent the risk of gastric bleeding complications (Abraham et al. 2010; Barkun et al. 2010). The American College of Cardiology Foundation/American College of Gastroenterology/American Heart Association (ACCF/ACG/AHA) 2010 expert consensus recommended the use of a PPI to reduce GI bleeding among patients who require antiplatelet therapy with a history of upper GI bleeding and multiple risk factors for GI bleeding. They did not suggest the routine use of either a PPI or a H2RA for prophylaxis in patients with low risk of GI bleeding (Abraham et al. 2010).

2.4 Interaction between clopidogrel and proton pump inhibitors

The clopidogrel-PPI interaction was first demonstrated by Gilard and colleagues in 2006. They found an *in vitro* reduction of antiaggregatory platelet response of clopidogrel in PCI patients taking PPI treatment (Gilard et al. 2006). Since then, several pharmacodynamics studies have extensively analysed the clopidogrel-PPI interaction (Table 1). The clinical relevance of this interaction has been evaluated in observational studies and randomised trials but the clinical importance remains uncertain (Table 2).

2.4.1 *In vitro* studies on clopidogrel-PPI interaction

In vitro or pharmacodynamic studies use surrogate markers such as of clopidogrel efficacy on platelet aggregation as outcomes. The Omeprazole Clopidogrel Aspirin (OCLA) trial randomised patients who had undergone elective PCI with stent and who received 75 mg daily of aspirin and clopidogrel and either omeprazole 20 mg daily or placebo. The antiplatelet effect of clopidogrel was measured using the vasodilator-stimulated phosphoprotein (VASP) phosphorylation assay to provide a platelet reactivity index (PRI)

on day 1 and 7. The mean PRI was significantly higher in omeprazole treatment, demonstrating less effective antiplatelet aggregation of clopidogrel (less clopidogrel response) (Gilard et al. 2008). The potential interaction of the PPI class effect was investigated by the PPI And Clopidogrel Association (PACA) study. The PACA compared pantoprazole to omeprazole treatment in patients talking aspirin 75 mg and clopidogrel 150 mg using VASP-PRI and adenosine diphosphate-induced aggregation (ADP-Ag) for platelet reactivity. Pantoprazole has significantly less effect on platelet responsiveness to clopidogrel than omeprazole but no significant difference in platelet reactivity (Cuisset et al. 2009). Researchers hypothesised that omeprazole may interact adversely with clopidogrel at the level of CYP2C19; thus, omeprazole inhibits the conversion of clopidogrel to the active anticoagulating form (Cuisset et al. 2009; Ho et al. 2009). A randomised placebo-controlled crossover study among healthy subjects tried to address the argument about whether this interaction was a PPI class effect or CYP2C19 inhibiting effect on clopidogrel. Results showed that active metabolites of clopidogrel and platelet response were significantly decreased in the omeprazole group when the clopidogrel dosage was increased or administered 12hr apart from omeprazole. The PRI did not significantly change in the pantoprazole group leading the authors to conclude that an interaction between clopidogrel and omeprazole exists but not pantoprazole (Angiolillo et al. 2011). Esomeprazole is the S-isomer omeprazole which is assumed to have similar metabolic pathways and effects as omeprazole (Richter et al. 2001; FDA 2009), although studies have not been able to provide consistent effects of esomeprazole treatment on clopidogrel's antiplatelet efficacy (Siller-Matula et al. 2009; Neubauer et al. 2010; Fernando et al. 2011; Hsu et al. 2011).

Table 1. *In vitro* studies of clopidogrel and PPIs

Study	Design	Patients (n)	Treatment	Outcome	Results
Gilard (Gilard et al. 2008)	Randomised, Double-Blind (OCLA)	Elective PCI (124)	Omeprazole vs. placebo	VASP-PRI	**PRI: placebo 39.8%, omeprazole: 51.4%, p<0.0001**
Cuisset (Cuisset et al. 2009)	Randomised (PACA)	NSTE MI who Undergoing PCI (104)	Omeprazole vs. pantoprazole	VASP-PRI, ADP-Ag	**PRI: pantoprazole 36%, omeprazole 48%, p=0.007** APD-Ag: pantoprazole 50 U+/-18%, omeprazole 52 U+/-15%, p=0.29

Siller-Matula (Siller-Matula et al. 2009)	Non-randomised study design.	CAD with undergoing PCI (300)	Pantoprazole vs. esomeprazole vs. non-PPI	VASP-PRI, ADP-Ag	PRI&APD-Ag: pantoprazole 50%&47U, esomeprazole 54%&42U, non-PPI 49%&41U, No significance
Neubauer (Neubauer et al. 2010)	Retrospective	48 hr after PCI with stent (336)	Pantoprazole vs. omeprazole/ esomeprazole vs. without PPI	Impedance aggregome-try (in Ohm), Clopidogrel low-response (%)	Non-PPI 2.75 Ohm&21.9%, pantoprazole 2.33Ohm&16.4%, omeprazole/esomeprazole 3 Ohm&30.8% No significance
Angiolillo (Angiolillo et al. 2011)	Four-way crossover	Healthy volunteers (282)	Omeprazole vs. placebo 0,12 h apart Pantoprazole vs. placebo	MPA, VASP-PRI, ADP-AG	Metabolic drug-drug interaction between **clopidogrel and omeprazole** and but not pantoprazole
Ferreiro JL (Ferreiro et al. 2011)	Randomized crossover study	Healthy volunteers (20)	Pantoprazole vs. placebo	Aggregometry, VerifyNow P2Y(12) system	No significance
Fernando (Fernando et al. 2011)	Randomised to esomeprazole or placebo	CAD (31)	Esomeprazole vs. placebo	VASP, PRI, PRU	Esomeprazole attenuation antiplatelet effects (p< 0.01)
Funch-Brentano (Funck-Brentano et al. 2013)	Randomised three-period crossover	Healthy subjects (36)	Omeprazole Rabeprazole Placebo	VASP-PRI	No significance
Hsu (Hsu et al. 2011)	Randomised controlled	CAD (165)	Esomeprazole vs. no PPI	ADP-induced platelet aggregation test	No significance

VASP-PRI: Vasodilator-stimulated phosphoprotein platelet reactivity index; PRI: Platelet reactivity index; NSTE MI: Non ST-elevated Myocardial infarction; ADP-Ag: Adenosine diphosphate induced platelet aggregation; CAD: Coronary artery disease; PCI: Percutaneous coronary artery intervention; CLR: Clopidogrel low-response; PRU: Platelet reactivity units; MPA: Mean platelet aggregation; PPI: proton pump inhibitor.

2.4.2 Clinical studies on the clopidogrel-PPI interaction

Although pharmacodynamic studies show PPIs affecting platelet function, inconsistent findings from clinical studies mean it is difficult to establish the clinical importance of this clopidogrel-PPI interaction.

In 2009, a retrospective cohort study in Veterans Affairs medical records investigated 8,205 patients who were hospitalised for ACS. 63.9% of patients were coprescribed a PPI (mainly omeprazole and rabeprazole) at any time point during cloidogrel treatment. The concomitant use of a PPI and clopidogrel was associated with an increased risk of rehospitalisation for ACS and all-cause mortality (OR 1.25, 95% CI 1.11–1.41) (Ho et al. 2009). Analyses of PPIs as a class from post hoc studies and retrospective studies found an increased risk of major adverse cardiovascular event (MACE) associated to PPI treatment in ACS patients with or without PCI (Dunn SP 2008; Charlot et al. 2010; Evanchan et al. 2010; Gupta et al. 2010; Kreutz et al. 2010; van Boxel et al. 2010; Dunn et al. 2013). A nationwide Danish cohort study observed an increased risk of adverse cardiovascular events associated with PPI use in ACS patients, regardless of clopidogrel use (Charlot et al. 2010). Whereas, a post hoc of TRITON-TIMI38 and other observational studies show no significant association of the clinical cardiovascular outcomes and PPI treatment in ACS patients taking clopidogrel (O'Donoghue et al. 2009; Rassen et al. 2009; Gaspar et al. 2010; Ray et al. 2010; Garcia Rodriguez et al. 2013). One study focused on pantoprazole, the less potent inhibitor of CYP2C19, and did not find a significantly increased risk of cardiovascular events as found in other PPIs (Juurlink et al. 2009). However, another study from Stockl et al. reported that pantoprazole was also associated with an increased risk of cardiovascular outcomes in patients with a stent implantation (Stockl et al. 2010). The COGENT trial, the only RCT to date, comparing clopidogrel alone and combination of clopidogrel and omeprazole, found no significant increase in the risk of cardiovascular outcomes in the combination group. However, upper GI bleeding was observed to significantly decrease in the omeprazole treatment group (HR 0.34, 95%CI 0.18–0.63, p=0.001). Unfortunately, this RCT was terminated early due to bankruptcy of the sponsor therefore the number of subjects recruited and follow up times were less than expected (Bhatt et al. 2010). The use of retrospective observational studies may also be limited by confounding due to diverse baseline characteristics and limited compliance data. Moreover, sample sizes were insufficient or follow-up time was too limited in all

randomised clinical trials to confirm the clinical relevance of this interaction. Details of some of these studies are provided below (Table 2).

Table 2. Clinical studies on the clopidogrel-PPI interaction

Study	Study design	Patients (n)	Treatment	Outcome	Results
Bhatt (Bhatt et al. 2010)	Randomized double-blind (COGENT)	ACS or undergoing PCI (3873)	Omeprazole vs. placebo	MACE, UGIB 106 days	MACE-HR 0.99, 95% CI 0.68–1.44 **UGIB-HR 0.34,95%CI 0.18–0.63** Underpowered, Ran out of finances
Dunn (Dunn SP 2008) (Abstract)	Post hoc Randomized double blind (CREDO)	Elective PCI (1053)	PPIs	MACE 1 year	**OR 1.633, 95%CI 1.015–2.627**
Ho (Ho et al. 2009)	Retrospective cohort	ACS (8205)	PPIs vs. without PPI	Mortality or rehospitalis-ation for ACS	**OR 1.25, 95%CI 1.11–1.41**
O`Donogh ue (O'Donogh ue et al. 2009)	Post hoc Randomized double blind (TRITON-TIMI38)	Undergoing PCI (6795)	PPIs	MACE	No significance
Juurlink (Juurlink et al. 2009)	Nested-case-control	MI (734 cases, 2057controls)	Omeprazole, pantoprazole, lansoprazole, rabeprazole	Death; reMI Up to 3 months	**OR 1.27, 95%CI 1.03–1.57 for OME-LANSO-RABE group** OR 1.02, 95%CI 0.7–1.47 for PANTO group
Rassen (Rassen et al. 2009)	Retrospective Cohort	ACS or PCI (18565)	PPIs	MACE 6 months	MI or Death: RR 1.22, 95% CI 0.99–1.51; for death, RR 1.20, 95% CI 0.84–1.70; for revascularization, RR 0.97, 95% CI 0.79–1.21
Charlot (Charlot et al. 2010)	Nationwide Danish cohort	First MI (56406)	Clopidogrel: PPIs vs. without PPI non-	MACE 1 year	**HR 1.29, 95%CI 1.17–1.42 in clopidogrel** **HR 1.29, 95%CI, 1.21–1.37 in**

			clopidogrel: PPIs vs. without PPI		**non-clopidogrel**
Kreutz (Kreutz et al. 2010)	Retrospective cohort	Undergone PCI with stent (Medco 16,690)	PPI vs. clopidogrel alone (omeprazole, esomeprazole, pantoprazole, lansoprazole)	Major cardiovascular events within 1 yr.	**HR 1.51, 95%CI 1.39–1.64**
Zairis (Zairis et al. 2010)	Retrospective Cohort	Elective PCI (588)	Omeprazole	MACE 1 year	HR 1.1, 95% CI 0.6–1.8
Gupta (Gupta et al. 2010)	Retrospective Cohort	PCI (315)	Omeprazole, lansoprazole, rabeprazole	MACE 4 years	**OR 1.95, 95%CI 1.09–3.49**
Gaspar (Gaspar et al. 2010)	Retrospective Cohort	ACS (802)	Omeprazole, lansoprazole, rabeprazole	MACE 6 months	No significance
Evanchan (Evanchan et al. 2010)	Retrospective	MI with PCI (5794)	Omeprazole, esomeprazole, pantoprazole, lansoprazole	MI 1 year	**OR 1.78, 95% CI 1.55–2.07**
Ray (Ray et al. 2010)	Retrospective Cohort	ACS with PCI (20596)	PPIs	MACE, UGIB 1 year	MACE-HR 0.99, 95%CI 0.82–1.19 **UGIB-HR 0.50, 95%CI 0.39–0.65**
Stockl (Stockl et al. 2010)	Retrospective Cohort	MI or stent implantation (2066)	Pantoprazole vs. others	MACE 1 year	**PPIs: HR1.93; 95%CI, 1.05–3.54; p=0.03** **Pantoprazole: HR 1.91; 95%CI, 1.19–3.06; p=0.008**
Van Boxel (van Boxel et al. 2010)	Retrospective Cohort	New clopidogrel users (18,139)	PPIs	MACE, peptic ulcer (PU)	**MACE-HR 1.75, 95% CI 1.58–1.94** **Low incidence of PU but increase PU disease-HR 4.76, 95%CI 1.18–19.17**
Harjai (Harjai et al. 2011)	Retrospective Cohort	PCI (1210)	PPIs	MACE 6 months	No significance

Simon (Simon et al. 2011)	Retrospective cohort (FAST-MI)	MI (3670)	PPIs	MACE	OR 0.90, 95%CI 0.60–1.35
Hsiao (Tsai et al. 2011)	Retrospective cohort study	ACS taking clopidogrel and aspirin (9753)	PPIs vs. no PPI	ACS re-hospitalization 1 year	No significance
Aihara (Aihara et al. 2012)	Retrospective Propensity Score Matching	Underwent PCI (1000)	PPIs vs. without PPI	MACE	No significance
Bhurke (Bhurke et al. 2012)	Retrospective Cohort	ACS (10,101)	PPIs	MI, PCI, ACS	**HR 1.44, 95%CI 1.24–1.67**
Schmidt (Schmidt et al. 2012)	Population-based cohort	PCI (12001)	Clopidogrel users: PPIs vs. without PPI clopidogrel non-users: PPIs vs. without PPI	MACE 1 year	HR 1.24, 95% CI 0.97–1.58 for clopidogrel users HR 1.26, 95% CI 0.97–1.63 for clopidogrel non-users
Garcia Rodriguez (Garcia Rodriguez et al. 2013)	Population-based cohort study in THIN, GPRD	Clopidogrel monotherapy and dual antiplatelet therapy (42,542)	Clopidogrel: PPIs vs. without PPI Dual antiplatelet: PPIs vs. without PPI	MI, coronary death Peptic ulcer bleeding (PUB)	CV-PPI+mono clop: RR 1.06, 95%CI 0.47–2.36 CV-PPI+dual: RR 0.8, 95%CI 0.47–1.37 UGIB-PPI+dual-RR 0.66, 95%CI 0.27–1.6
Hsu (Hsu et al. 2011)	Randomised controlled	CAD (165)	Esomeprazole vs. no PPI	MACE, Recurrent peptic ulcer	No significance in MACE Reduced recurrent of peptic ulcers

ACS: Acute coronary syndrome; MACE: Major adverse cardiac event; UGIB: Upper gastrointestinal bleeding; HR: Hazard ratio; VASP-PRI: Vasodilator-stimulated phosphoprotein platelet reactivity index; PRI: Platelet reactivity index; NSTE MI: Non ST-elevated Myocardial infarction; ADP-Ag: Adenosine diphosphate induced platelet aggregation; CAD: Coronary artery disease; PCI: Percutaneous coronary artery intervention; CLR: Clopidogrel low-response; PRU: Platelet reactivity units; MPA: Mean platelet aggregation; PPI: proton pump inhibitor.

Despite a concern on the antiplatelet effects of clopidogrel related to PPIs, several studies suggested that PPIs and H2RA are associated with a reduction in the risk of upper GI bleeding and recurrent peptic ulcer in CAD patients who are also taking clopidogrel and aspirin (Ng et al. 2008; Bhatt et al. 2010; Hsu et al. 2011; Kwok et al. 2011). A double-

blind, randomised, controlled trial suggests that esomeprazole is better than famotidine in preventing GI complications in patients taking a combination of aspirin, clopidogrel, and either enoxaparin or thrombolytics (Ng et al. 2011).

Meta-analyses also could not provide conclusive evidence on the cardiovascular events of concomitant use of clopidogrel and PPIs. Meta-analysis studies by Kwok et al concluded that both platelet function and clinical studies of the clopidogrel-PPI interaction were considerably heterogeneous in their study designs, baseline characteristics and drug exposure, thus no clear interaction could be determined (Kwok et al. 2011; Kwok et al. 2013). Siller-Matula et al. also found heterogeneity in the overall analyses but after a sensitivity analysis assessment, concluded that concomitant PPI with clopidogrel may influence the risk of the cardiovascular events (Siller-Matula et al. 2010). Another meta-analysis by Chen concluded that PPIs were associated with an attenuated antiplatelet effect of clopidogrel in *in vitro* studies but a lack of compatibility between clinical studies (Chen et al. 2011) (Table 3).

Table 3. Meta-analysis studies on the clopidogrel-PPI interaction

Study	Study design	Patients (n)	Treatment	Outcome	Result
Kwok (Kwok et al. 2010)	Meta-analysis	Post-PCI 23 studies (93,278)	PPI vs. no PPI	MACE	No significant due to unmeasured confounders
Siller-Matula (Siller-Matula et al. 2010)	Meta-analysis	25 studies (159,138)	PPIs vs. no PPI	MACE, MI, Mortality, GI bleeding	**MACE-RR 1.29, 95%CI 1.15–1.45** **MI-RR 1.31, 95%CI 1.12–1.53** Mortality-RR 1.04,95%CI 0.93–1.16 **GI bleeding-RR 0.5, 95%CI 0.37–0.69**
Chen (Chen et al. 2011)	Meta-analysis	13 studies (31,073)	PPIs vs. no PPI	MACE	**RR 1.49, 95%CI 1.43–1.55 fixed-effects model** **RR 1.40, 95%CI 1.15–1.70 random-effects model**

Pharmacodynamic studies on the interaction between clopidogrel and PPIs in 2008 led to the warnings of concomitant use of clopidogrel and all PPIs (Dunn SP 2008; Gilard et al. 2008). Once studies suggested an effect of omeprazole but not pantoprazole on the platelet function of clopidogrel, the class effect of PPIs was reconsidered (Juurlink et al. 2009; Sibbing et al. 2009; Siller-Matula et al. 2009). The possible explanation for this observation is that the metabolic activation of clopidogrel was interfered with via the CYP2C19 activities of the higher inhibitory potency of omeprazole. As the clinical impact of the clopidogrel-PPI interaction remains conflicting, the risk of PPIs on secondary prevention of cardiovascular events of clopidogrel must be balanced with the benefit in preventing GI bleeding. Several articles and guidelines suggest pantoprazole as a preferable choice if a PPI is required with clopidogrel.

2.5 Regulatory warnings on the clopidogrel-PPI interaction

Between the first in vitro study from Gilard to Angiolillo's study (as shown in Table 1), studies were continuously being published on the clopidogrel-PPI interaction, it was during this time that a series of warnings were made from the FDA and EMA according to this updated information (Gilard et al. 2008; Angiolillo et al. 2011). Both the FDA and EMA went from the PPI drug class warnings to more specific warnings on omeprazole and esomeprazole. A lack of clinical evidence on this interaction may be the cause of hesitation from the TGA to take action.

2.5.1 Warnings from the U.S. Food and Drug Administration

In January 2009, the FDA issued an early communication warning recommending that healthcare providers should re-evaluate the initiation or continuation of PPI treatment in patients taking clopidogrel (FDA 2009). The FDA also mentioned that there was no evidence of any change in antiplatelet activity of clopidogrel by concomitant use with H2RAs (with an exception of cimetidine).

In November 2009, the FDA issued a public health advisory on clopidogrel-omeprazole interaction and updated labelling for clopidogrel and omeprazole. This announcement recommended avoiding omeprazole and clopidogrel together at any time of the day. This recommendation was based on studies showing that omeprazole reduced clopidogrel's anti-clotting effect through the CYP 2C19 enzyme and this inhibitory effect was present

even when taking 12 hours apart (Angiolillo et al. 2011). The FDA informed health professionals that they did not have enough information about the inhibitory effect of PPIs other than omeprazole; however, it was suggested that other potent CYP2C19 inhibitors should be avoided including esomeprazole. H2RAs, except cimetidine, were suggested if a drug to reduce acid was needed. The update of the clopidogrel drug label was processed by Sanofi-Aventis and Bristol-Myers Squibb (FDA 2009). The FDA also published details mentioning the Angiolillo et al. study and COGENT study as well as other alternatives for healthcare professionals.

The FDA published three 'Considerations for Healthcare Professionals' and recommendations listed below in November 2009 (FDA 2009).

- "The concomitant use of omeprazole and clopidogrel should be avoided because of the effect on clopidogrel's active metabolite levels and anti-clotting activity. Patients at risk for heart attacks or strokes, who are given clopidogrel to prevent blood clots, may not get the full protective anti-clotting effect if they also take prescription omeprazole or the OTC form (Prilosec OTC).
- Separating the dose of clopidogrel and omeprazole in time will not reduce this drug interaction.
- Other drugs that should be avoided in combination with clopidogrel because they may have a similar interaction include: esomeprazole (Nexium), cimetidine (which is available by prescription Tagamet and OTC as Tagamet HB), fluconazole (Diflucan), ketoconazole (Nizoral), voriconazole (VFEND), etravirine (Intelence), felbamate (Felbatol), fluoxetine (Prozac, Serafem, Symbyax), fluvoxamine (Luvox), and ticlopidine (Ticlid).
- At this time FDA does not have sufficient information about drug interactions between clopidogrel and PPIs other than omeprazole and esomeprazole to make specific recommendations about their co-administration. Healthcare professionals and patients should consider all treatment options carefully before beginning therapy.
- There is no evidence that other drugs that reduce stomach acid, such as most H2 blockers ranitidine (Zantac), famotidine (Pepcid), nizatidine (Axid), except cimetidine (Tagamet and Tagamet HB—a CYP2C19 inhibitor) or antacids interfere with the anti-clotting activity of clopidogrel. Ranitidine and famotidine are available by prescription

and OTC to relieve and prevent heartburn and antacids are available OTC to relieve heartburn.

- Talk with your patients about the OTC medicines they take. Be aware that patients may be taking non prescription forms omeprazole and cimetidine."

In October 2010, after the COGENT study was published (Bhatt et al. 2010), the FDA issued a reminder for healthcare professionals to avoid concomitant use of clopidogrel and omeprazole. The FDA emphasised that the interaction between clopidogrel and PPIs was not a class effect. A weak inhibitor of CYP2C19 such as pantoprazole should be considered as an alternative PPI (FDA 2010).

Several safety labelling changes of clopidogrel related to PPIs were approved by FDA Center for Drug Evaluation and Research (CDER) including; October 2009—add omeprazole as drug interactions of clopidogrel, August 2010—avoid omeprazole and suggest pantoprazole as alternative, and December 2011—avoid omeprazole and esomeprazole with clopidogrel (FDA 2013).

In December 2011, the FDA updated labelling for clopidogrel and esomeprazole, which extended to avoid esomeprazole with clopidogrel due to the CYP2C19 interaction and that it is a component of omeprazole.

2.5.2 Warnings from the European Medicines Agency

In May 2009, the EMA issued a warning on the interaction between clopidogrel and PPIs, in which PPIs may reduce the antiplatelet effect of clopidogrel. The Committee for Medicinal Products for Human Use and the Pharmacovigilance Working Party recommended an amendment to the product information of clopidogrel "*Discourage concomitant use of PPIs unless absolutely necessary*" (EMA 2009). In March 2010, EMA issued a public statement replacing the class warning of PPIs with a more specific PPI warning for concomitant use of omeprazole or esomeprazole with clopidogrel based on two studies, which were completed at the end of August 2009. They stated as "no solid grounds" were present or little evidence was available the class warning of PPIs was unjustified (EMA 2010). Both the FDA and EMA stated that there were no data indicating an interaction between H2RA and clopidogrel.

2.5.3 Warnings from the Therapeutic Goods Administration

While the issue of the clopidogrel-PPI interaction had been extensively investigated and debated among researchers and drug authorities, the TGA refrained from any announcement. In October 2011 the TGA made its first recommendation regarding the interaction, stating "*It would be misleading if consumers are only warned about this particular interaction and not other interactions and may assume that they do not need to check if they are not taking clopidogrel."* Therefore the TGA issued advisory statement 223 "*Ask your doctor or pharmacist before use if you are taking other medicines regularly*", which the TGA said it was adequate to cover all possible interactions between clopidogrel and PPIs (TGA 2011).

The above releases demonstrate that the detail in EMA and FDA warnings are much more comprehensive than the Australian TGA warning, which is only two sentences long and lacks guidance about specific management strategies or alternative choices for healthcare professionals and consumers. It may be worthwhile alerting healthcare professionals and consumers, who are making a decision on the use of these medicines, to the emerging data on CYP2C19 activity related to the clopidogrel interaction and possible reduction of efficacy in antiplatelet aggregation.

Due to the widespread use of proton pump inhibitors and clopidogrel, the mixed signals expressed by drug authorisations, and the inconclusive research around this co-prescribing, it is unknown how this information has affected prescribing practices.

Objectives and hypotheses of this thesis

Overview

The purpose of this thesis was to expand the understanding of the impact of drug safety warnings on clinical practice in Australia. To date, there has been no study on the effects of drug safety warnings on drug use or prescribing decisions in Australia. We lack a comprehensive overview of the effectiveness of the Australian drug warning system in reducing the risks of new medicines. For these reasons, the aims of this PhD were: 1) to compare the timing and content of Australian regulatory warnings and warnings from major international drug authorities, 2) to investigate the impact of local and international regulatory warnings on the pattern of drug use in Australia, and 3) to evaluate prescribers' awareness and response to drug safety warnings.

Two recent drug safety warnings on adverse effects related to the thiazolidinedione drug class and on a drug interaction between clopidogrel and proton pump inhibitors (PPIs) provide excellent case studies to assess the impact of drug safety warnings on clinical practice in Australia.

Firstly, the studies in Chapter 3&4 investigated a series of regulatory warnings on an increased risk of serious cardiovascular events related to rosiglitazone and regulatory warnings on a small increase risk of bladder cancer related to the long-term use of pioglitazone. The impact of warnings on drug use was analysed in two databases: Pharmaceutical Benefit Scheme (PBS) in Chapter 3—contains dispensing data from the national subsidised formulary and AsteRx in Chapter 4—a clinical database collected from medical practices. Several additional factors that may influence the pattern of drug use were also identified and included in analyses.

To examine the impact of warnings with different degree of certainty, the second study in Chapter 5 investigated warnings on the clopidogrel-proton pump inhibitors interaction. This drug interaction warning was complicated by conflicting and inconclusive clinical evidence. We investigated changes to the pattern of antisecretory drugs co-prescribed with clopidogrel in the AsteRx database after the safety warnings.

A qualitative approach was taken in Chapter 6 to assess prescribers' perspective on drug safety warnings in Australia. This study used a combination of interviews and survey tools to assess the sources of drug safety information among practitioners. The outcome

expanded the understanding of drug warning systems and their influence on prescribers. To better explain the patterns of drug use and prescribing decisions, the degree of awareness of warnings and responses to warnings in Chapters 3&4 (thiazolidinediones) and Chapter 5 (clopidogrel-PPI) were examined.

The primary and secondary outcomes of the impact of warnings on dispensing and prescribing patterns in Chapter 3–5 are explored by incorporating into findings from the survey. All results from this thesis are discussed in Chapter 7.

1. Objectives

The following objectives were proposed:

I. To evaluate warnings on adverse effects of the thiazolidinedione drug class
   a. To compare the timing and content of warnings between local authority—the TGA and international authorities—the FDA and EMA
   b. To investigate the impact of warnings from the TGA, FDA and EMA on the changes in national dispensing patterns of the thiazolidinedione drug class in the PBS
   c. To investigate the impact of warnings from the TGA, FDA and EMA on the changes in prescribing details in patients using thiazolidinediones in the AsteRx database

II. To evaluate warnings on drug interaction between clopidogrel and proton pump inhibitors
   a. To compare the timing and content of interaction warnings between local authority—the TGA and international authorities—the FDA and EMA
   b. To investigate the impact of interaction warnings from the TGA, FDA and EMA on the on patterns of antisecretory coprescribing with clopidogrel in the AsteRx database
   c. To identify other factors related to adverse effects that influenced patterns of the thiazolidinedione drug class use

III. To assess prescribers' perspectives toward drug safety warnings
   a. To determine sources of drug safety information among participants
   b. To obtain participants' opinions on local drug safety warnings

c. To examine the awareness and response towards two recent drug warnings

2. Hypotheses

The following hypotheses were tested based on the above objectives:

I. Warnings on adverse effects of the thiazolidinedione drug class

a. Drug safety warnings from the FDA, EMA and TGA would be similar in timing and content.

b. Patterns of thiazolidinedione use would significantly decrease after warnings from the FDA, EMA, and TGA.

c. More patients would stop rosiglitazone after the FDA, EMA and TGA warnings. Patients who stop rosiglitazone after the warnings would switch to a non-thiazolidinedione antidiabetic medicine.

II. Drug interaction warnings between clopidogrel and proton pump inhibitors

a. Drug safety warnings from the FDA, EMA and TGA would be similar in timing and content.

b. There would be a significant decrease in proton pump inhibitor coprescribing with clopidogrel after the first issue of interaction warnings from the FDA, EMA, and TGA and (maybe) specific reduction in omeprazole and esomeprazole due to differences in the content of the warnings.

c. There would be other factors influencing coprescribing patterns such as a rapid growth of new products and other clinical conditions.

III. Prescribers' perspective

a. Prescribers use multiple sources of drug safety information, including the TGA warnings. There would be multiple sources of drug safety information used by participants; however, the TGA would be the most assessable and reliable source.

b. Prescribers regularly receive drug safety communications from the TGA via either the TGA's subscription email or the TGA's website.

c. Prescribers have a high awareness on the thiazolidinedione and clopidogrel-PPI warnings. Prescribers have changed their prescribing in response to the

safety warnings. Prescriber awareness and response will correlate with the changes in pattern of drug use in Chapters 3&4 and Chapter 5.

Chapter 3. The impact of thiazolidinedione warnings on the dispensing of PBS items

1. Synopsis

This study investigates the impact of warnings on adverse events of thiazolidinediones on the national patterns of drug use in the PBS database. Warnings on myocardial infarction events of rosiglitazone announced by the FDA and EMA in May 2007 were associated with a significant decrease in rosiglitazone utilisation in Australia. A decline in rosiglitazone use was observed prior to TGA warnings in December 2007. Findings in this chapter suggest that Australian prescribers may have acted in response to scientific evidence or international safety warnings (EMA, FDA), prior to the TGA warning. Minor effects on the pattern pioglitazone utilisation were observed following bladder cancer warnings in June–July 2011.

2. Overview

As of 2014, there are seven classes of drugs used in Australia for the treatment of lowering blood sugar levels (PBS 2014). Current clinical guidelines recommend initiating metformin as first line therapy concurrent with lifestyle intervention and titrating to maximally effective dose over 1–2 months (Nathan et al. 2006; NICE 2011). There is no consensus on which drug should be used if metformin fails to achieve glycaemic goals. Usually, oral hypoglycaemic drugs will be added and followed by insulin to maintain HbA1c below the recommendation for each condition. Table 4 summarises the currently available agents and subsidy restrictions on the PBS for the treatment of type 2 diabetes (PBS 2014).

Table 4. Available drugs for treatment of type 2 diabetes in Australia

Drug class	Generic name	PBS listing
Biguanides	Metformin	No restriction
Sulfonylureas	Glibenclamide Gliclazide, gliclazide MR	No restriction

	Glimepiride Glipizide	
Alpha glucosidase inhibitors	Acarbose	No restriction
Thiazolidinediones	Rosiglitazone	November 2003—Dual oral therapy with metformin or a sulfonylurea April 2005—Triple oral therapy with metformin and a sulfonylurea August 2005—In combination with insulin November 2008—Revoked triple therapy and in combination with insulin March 2011—Authority Required for dual oral therapy
	Pioglitazone	November 2003—Dual oral therapy with metformin or a sulfonylurea 2004—In combination with insulin November 2007— Authority Required (STREAMLINED) for triple therapy with metformin and a sulfonylurea
Dipeptidyl peptidase 4 (DPP-4) inhibitors	Vildagliptin Saxagliptin Sitagliptin Linagliptin	1 November 2011—Authority Required (STREAMLINED) for triple oral combination with metformin and a sulfonylurea 1 April 2014—Authority Required (STREAMLINED) for dual oral therapy with metformin or a sulfonylurea
	Alogliptin	1 December 2013—Authority

		Required (STREAMLINED) for triple or dual oral therapy with metformin or a sulfonylurea
Combination tablets	Metformin/glibenclamide	No restriction
	Metformin/rosiglitazone	Listed in July 2006
	Metformin/sitagliptin Merformin/vildagliptin	Listed in August 2009
Insulin		No restriction
Incretin mimetics	Exenatide Liraglutide	Authority required (streamlined): in combination with metformin and/or a sulfonylurea
Sodium-glucose transporter inhibitors (SGLT2)	Canagliflozin Dapagliflozin	-

Previous research showed that biguanides had the highest rate of oral anti-diabetic drug consumption using the PBS/RPBS data in 2011, comprising 43.6% of all oral antidiabetic drugs (a total of 12.6 DDD/1000inhibitants/day). Sulfonylureas were the second most dispensed oral drugs contributing to 41% of all dispensing (11.9 DDD/1000inhibitants/day) followed by thiazolidinediones at 5.9% of all oral antidiabetic drugs (1.7 DDD/1000inhibitants/day) (Sylvain Pichetti 2013).

2.1 Warnings on cardiovascular risk related to rosiglitazone

Since a meta-analysis by Nissen suggested an elevated risk of myocardial infarction and cardiovascular deaths associated with rosiglitazone therapy on 21 May 2007 (Nissen et al. 2007), a series of warnings on cardiac events were issued by the FDA, EMA and TGA as listed in a chronological order below.

21 May 2007—The FDA issued an alert on rosiglitazone. This alert included an ongoing FDA review of clinical data. The FDA suggested that healthcare professionals should

consider this and other available data when making individual treatment decisions for their patients with type 2 diabetes.

23 May 2007—The EMA press release stated that the risk of cardiac ischaemic events was included in the EU product information in September 2006. Prescribers were reminded to adhere to the restrictions for use in patients with cardiac disease. Patients were suggested not to stop rosiglitazone and discuss with their doctor at their next regular visit.

14 August 2007—The FDA requested the manufacture revise the rosiglitazone label highlighting an increased risk of congestive heart failure.

18 October 2007—The EMA press release confirmed the positive benefit-risk balance for rosiglitazone treatment in patients with type 2 diabetes.

14 November 2007—The FDA updated the WARNING SECTION of the rosiglitazone label to include myocardial ischemic events.

December 2007—The TGA requested a Box Warning on the product information stating that rosiglitazone was not recommended in patients with known ischemic heart disease particularly in those who need several antidiabetic drugs or nitrates.

24 January 2008—The EMA press release recommends a new warning stating that “the use of rosiglitazone in patients with ischemic heart disease and/or peripheral arterial disease is not recommended”.

23 September 2010—The FDA restricted access and distribution of rosiglitazone.

23 September 2010—The EMA suspended all rosiglitazone-containing products throughout Europe.

24 September 2010—The TGA published an advisory statement to reinforce the Box Warning in the previous approved product information.

2.2 Warnings on the risk of bladder cancer related to pioglitazone

9 June 2011—The EMA press release announced ongoing review on a small increased risk of bladder cancer related to pioglitazone that had caused the suspension of pioglitazone in France.

15 June 2011—The FDA suggested that pioglitazone should not be used in patients with active bladder cancer and to use with caution in patients with history of bladder cancer.

18 July 2011—The TGA stated that "*Do not use pioglitazone in patients with bladder cancer or a history of bladder cancer."* Healthcare providers should consider the risk of bladder cancer in all patients treated with pioglitazone.

21 July 2011—The EMA advised healthcare professionals to avoid pioglitazone in patients with history of bladder cancer or with uninvestigated macroscopic haematuria.

In the present study, the Defined Daily Dose (DDD), a unit of drug utilisation recommended by the WHO is used to represent the assumed maintenance dose per day for rosiglitazone and pioglitazone in adults and to compare drug usage between different drugs and different periods (Wertheimer 1986; WHO 2013). The analysis of thiazolidinediones (TZDs) consumption structures is presented as monthly DDDs per 1000inhabitants per day of rosiglitazone and pioglitazone over the study period. DDDs for rosiglitazone is 6 mg (ATC code: A10BG02) and pioglitazone is 30 mg (ATC code: A10BG03) according to the WHO ATC/DDD system (WHO 2013). Table 5 lists thiazolidinedione-containing products, PBS codes assigned to each item, pack size, and dispensed price available on the PBS (PBS 2014). The dispensed prices of all thiazolidinedione-containing products were over both the concession and general co-payment thresholds during the study period therefore all dispensing data were captured in the PBS database.

Table 5. Details of rosiglitazone and pioglitazone listed on the PBS in 2011

Name and strength	PBS code	Pack size	Dispensed price
Rosiglitazone 4 mg	8689H	28	$61.52
Rosiglitazone 8 mg	8690J	28	$91.19

Rosiglitazone 2 mg with 500 mg metformin	9059T	56	$64.32
Rosiglitazone 2 mg with 1000 mg metformin	9060W	56	$66.96
Rosiglitazone 4 mg with 500 mg metformin	9061X	56	$93.99
Rosiglitazone 4 mg with 1000 mg metformin	9062Y	56	$96.63
Pioglitazone 15 mg	8694N	28	$53.00
Pioglitazone 30 mg	8695P	28	$77.62
Pioglitazone 45 mg	8696Q	28	$99.01

3. Chapter aims

This chapter aims to evaluate the warnings of adverse effects related to the thiazolidinedione drug class

Specific aim 1: To compare the timing and content of warnings between local authority—the TGA and international authorities—the FDA and EMA.

Specific aim 2: To investigate the impact of warnings from the TGA, FDA and EMA on the changes in national dispensing patterns of the thiazolidinedione drug class in the PBS.

4. Published Manuscript entitled "Utilisation trends of rosiglitazone and pioglitazone in Australia before and after safety warnings"

The manuscript entitled "Utilisation trends of rosiglitazone and pioglitazone in Australia before and after safety warnings" is published in the BMC Health Services Research, 14:151 (2014) (Appendix 1).

The co-authors contributed to the manuscript as follows: PhD candidate, Suvimol Niyomnaitham, designed the study under the supervision of Dr Alesha Smith, Dr Adam La

Caze, and Dr Karen Whitfield. The PhD candidate performed all data collection and data analysis with biostatistics help from Dr Andrew Page. Suvimol Niyomnaitham took the lead role in manuscript preparation and writing. All co-authors revised the manuscript for intellectual content and approved the final manuscript. The manuscript presented in this chapter has been adjusted to fit the overall style of the thesis.

Utilisation trends of rosiglitazone and pioglitazone in Australia before and after safety warnings

Suvimol Niyomnaitham[1,2*], Andrew Page[3], Adam La Caze[1], Karen Whitfield[1], Alesha J. Smith[1,4]

[1]School of Pharmacy, University of Queensland, Australia, [2]Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand, [3]School of Pharmacy, University of Otago, New Zealand

ABSTRACT

Background

A series of drug safety warnings have recently been made by drug authorities relating to adverse effects of rosiglitazone and pioglitazone on cardiovascular diseases and bladder cancer. The changes to the patterns of rosiglitazone and pioglitazone utilisation in Australia following the timing of these various health authority warnings such as the Australian Therapeutic Good Administration (TGA), European Medicines Agency (EMA) press releases or U.S. Food and Drug Administration (FDA) is unknown. This study investigated the utilisation patterns of rosiglitazone and pioglitazone in Australia before and after warnings of major drug authorities.

Methods

We evaluated rosiglitazone and pioglitazone dispensing using the Pharmaceutical Benefit Scheme (PBS) subsidised drug dispensing data for the Australian population from February 2004 to July 2012. The World Health Organisation Anatomic Therapeutic Chemical (ATC)/Defined Daily Dose (DDD) system was used to compare the drug utilisation patterns following the announcements of EMA, FDA, and TGA safety warnings, which first occurred in May 2007. The DDD/1000population/day were examined in a series of time-series regression analysis with the drug safety warnings specified as interventions.

Results

Rosiglitazone utilisation increased steadily from 2004 until reaching a peak at 1.96/1000population/day in January 2007. Then rosiglitazone use decreased significantly

after the initial EMA press release and FDA warning on cardiovascular risk in May 2007 (with a 15.04% average monthly decline, p-value<0.001), however use did not significantly decrease after the TGA warning or subsequent EMA and FDA warning. Pioglitazone utilisation proceeded rosiglitazone in September 2008 and remained above 1.5/1000/day during 2009–2010. However, pioglitazone utilisation has slightly declined after the FDA, EMA, and TGA warnings related to bladder cancer.

Conclusions

Drug safety warnings were associated with a decrease in rosiglitazone and pioglitazone utilisation in Australia. Rosiglitazone began to decline prior to TGA warnings in December 2007, which suggests that Australian prescribers may have acted in response to scientific evidence or international safety warnings (EMA, FDA), prior to the response of the TGA. Minor effects were observed after bladder cancer warnings on pioglitazone utilisation.

Background

Thiazolidinediones (TZDs) were approved for type 2 diabetes mellitus treatment based on efficacy studies, which showed a decrease in HbA1c, by 0.8–1.5% and improved insulin sensitivity (Aronoff et al. 2000; Phillips et al. 2001). Both TZDs, rosiglitazone and pioglitazone, were listed on the Australian Pharmaceutical Benefit Scheme (PBS) as subsidised second line therapy with either metformin or a sulfonylurea in November 2003 and later extended to triple oral therapy with metformin and a sulfonylurea and in combination with insulin.

In May 2007, a meta-analysis by Nissen and Wolski found a small increased risk in myocardial infarction and a borderline increase in cardiovascular death in patients treated with rosiglitazone (Nissen et al. 2007); however, another ongoing clinical trial evaluating cardiovascular outcomes of rosiglitazone showed cardiovascular events associated with rosiglitazone (Home et al. 2007) to be inconclusive. Because cardiovascular disease can be a lethal complication in patients with diabetes mellitus, several studies have tried to establish the adverse cardiovascular effect associated with rosiglitazone treatment (Gerrits et al. 2007; Bilik et al. 2010).

Since then, drug regulatory authorities have investigated these cardiovascular effects and issued several warnings on the use of rosiglitazone (Weatherby et al. 2002; FDA 2010).

The Australian regulatory authority, the Therapeutic Goods Administration (TGA) is responsible for ensuring the safety of medical products within Australia. The TGA distributes safety information to healthcare professionals through the “Safety Advisory” on the TGA’s website, similar to that of the U.S. Food and Drug Administration (FDA) drug safety communication and European Medicines Agency (EMA) press releases.

Since late 2008, the PBS steadily limited the subsidisation of rosiglitazone use in combination with insulin and triple oral therapy. On 1 July 2011, the PBS restricted prescription of rosiglitazone by requiring prior telephone approval.

While the meta-analysis raised a concern around the cardiovascular risk of rosiglitazone, a study of pioglitazone showed that in comparison it was a safe alternative with an insignificant increase in mortality, myocardial infarction and stroke (Lincoff et al. 2007). Pioglitazone also reduced the risk of hospitalisation for acute myocardial infarction in patients with type 2 diabetes in comparison with rosiglitazone (Lincoff et al. 2007; Erdmann et al. 2010). In June 2011, a French study suggested an increased risk of bladder cancer in patients who were treated with pioglitazone for more than one year leading to a temporary withdrawal of pioglitazone by the French Agency. Another study in the US also indicated a possible increase in bladder cancer risk in patients on pioglitazone for more than 2 years, compared with diabetes patients who were not receiving pioglitazone (Lewis et al. 2011; Mamtani et al. 2012). The TGA, as well as FDA and EMA, announced safety warnings outlining a possible risk of bladder cancer related to pioglitazone use in June–July 2011; however, there have been no further updates on this issue.

The increasing risk of cardiovascular disease with rosiglitazone led to a decrease in the utilisation patterns, in the US (Starner et al. 2008; Cohen et al. 2010) and some countries in Europe (Stewart et al. 2009; Ruiter et al. 2012). It is expected that after the bladder cancer warnings, pioglitazone will follow a similar utilisation trend to that of rosiglitazone. However, it is plausible that pioglitazone use may have slightly changed as a result of prescribers weighing up the benefit in blood sugar control and prevention of cardiovascular events versus the possible increased risk of bladder cancer, which has a very low incidence (3 cases per 1000 pioglitazone users) (Lewis et al. 2011; Mamtani et al. 2012). The dispensing patterns of rosiglitazone and pioglitazone following the emerging cardiovascular event and safety warnings have not been described in Australia, although it

is hypothesised that the trends will follow that of the US and Europe. This study aims to describe the patterns of rosiglitazone and pioglitazone use, and investigate the influential factors on changes of utilisation in Australia, with special focus on the safety warnings by TGA, FDA and EMA.

Methods

Data sources

Drug utilisation among populations over time can be examined using the World Health Organization Anatomic Therapeutic Chemical (ATC)/Defined Daily Dose (DDD) system. Data on monthly dispensing were obtained from the PBS database, a national administrative scheme which records drugs subsidised by the Government for Australian citizens. The PBS database captures all subsidised drug formulations, cost and amount of dispensing and period of drug dispensed by pharmacists for patients used at home. Drug dispensed data on the PBS database were used in research studied and shown to represent trends of drug utilisation in Australia (Hollingworth et al. 2010; Islam et al. 2014). Rosiglitazone and pioglitazone are listed as subsidised drugs for all Australians therefore a complete record of dispensed medicines was obtained. Denominator populations from Centrelink and the Australian Bureau of Statistics were used to calculate the DDD per 1000 population per day (the proportion of the population receiving a DDD of this drug per day). All the data for this study were aggregated, routinely collected and publically available via government sources, therefore ethics approval was not required.

Australian drug safety warnings for rosiglitazone and pioglitazone were acquired from safety alerts and safety information for health professionals on the TGA website. We accessed the EMA's safety announcements, called "press releases", and the FDA drug safety communication from their official websites. Since mid-2007, major drug authorities have issued safety warnings related to rosiglitazone and pioglitazone. The first TGA announcement which highlighted the increased risk of ischemic heart disease associated with rosiglitazone was issued in December 2007 (TGA1), followed by a second warning to avoid using rosiglitazone in patients with ischemic heart disease in September 2010 (TGA2). The FDA had three announcements related to cardiovascular risk of rosiglitazone; firstly, a safety alert in May 2007 (FDA1), a label update on heart-related risks in August 2007 (FDA2), and then restrictions on rosiglitazone use in September 2010 (FDA3). There

were four EMA press releases on risk of ischemic heart disease in May 2007 (EMA1), October 2007 (EMA2), January 2008 (EMA3) and September 2010 (EMA4). While the TGA and FDA still allowed rosiglitazone on the market, the EMA suspended all medical products containing rosiglitazone across Europe in September 2010.

For pioglitazone, the FDA issued a warning on a possible increased risk of bladder cancer in patients who used pioglitazone for longer than one year in June 2011, followed by the same warnings in the EMA press release and the TGA safety advisory in July 2011.

Whilst there were other plausible types of information sent to prescribers with regards to the drug safety, it is recognised that the warnings from the FDA, EMA and TGA have a large influence on drug safety communication. For example, the pharmaceutical companies marketing these medicines did not implement changes to the Product Information until after the TGA announcement. In Australia, medical media picked up this side effect once it came out from the FDA as well as medical associations issued the FDA warning on their articles.

Analyses

Monthly dispensing data of rosiglitazone and pioglitazone from January 2004 to July 2012 were converted to DDD/1000population/day. Descriptive trends in rosiglitazone and pioglitazone utilisation were examined in the time series of DDD/1000pop/day. The auto-regressive, integrated, moving average model (ARIMA) integrates the temporal size and direction dependency (autocorrelation) inherent in time-series data to better characterise changes in data over a period of time (Box GEP 1975). Autocorrelation functions (ACF) and partial autocorrelation functions (PACF) was used to obtain the best fitted model for analysis as well as the Bayesian Information Criteria. The percentage change in DDD/1000pop/day was used to remove the month to month trend component of the time series before fitting into ARIMA models. The separate and combined effects of the announcement of the EMA, FDA, and TGA warnings on trends in rosiglitazone and pioglitazone utilisation were also investigated by fitting into ARIMA models. Impacts of drug safety warnings (interventions) on the subsequent observations were then investigated using the ARIMA model as a step-function (having a permanent and immediate impact on any subsequent trends). All statistical analyses were performed with a 5% statistical significance level using STATA 12.1 (StataCorp, College Station, TX).

Results

A total of 1,686,087 rosiglitazone prescriptions and 2,405,881 pioglitazone prescriptions were dispensed during January 2004–July 2012. We calculated the monthly utilisation (DDD/1000population/day) using Australian population data, which was in the range of 20.1 million in 2004 to 22.9 million in 2012. As shown in Figure 3, the rosiglitazone utilisation increased steadily from 2004 and reached the peak in January 2007 with a defined daily dose of 1.96 per 1000 people per day. However, in May 2007, the trend of rosiglitazone utilisation started decreasing and remaining lower than 0.50 DDD/1000pop/day in May 2009 and 0.15 DDD/1000pop/day in July 2011. Pioglitazone utilisation has exceeded rosiglitazone use since September 2008 and remained stable during 2009–2010 (1.5–1.7 DDD/1000pop/day). Nevertheless, the trend of pioglitazone utilisation appeared to decrease in September 2011.

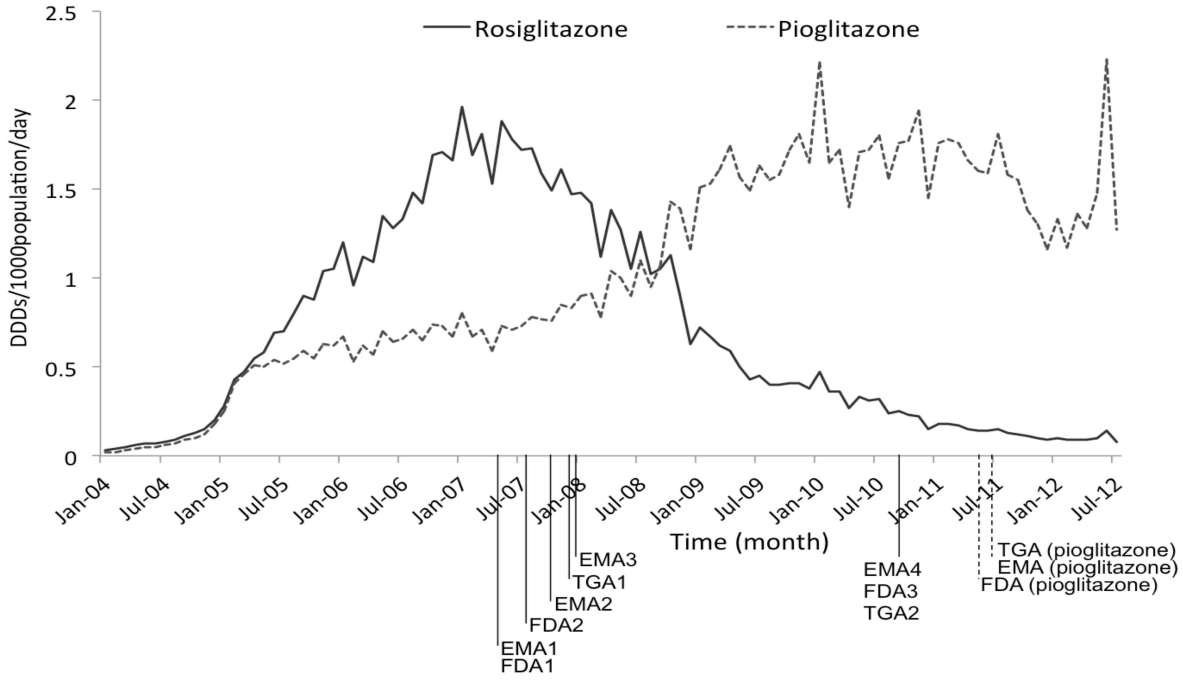


Figure 3. Utilisation of rosiglitazone and pioglitazone by the Australian population between 2004–2012.

The drop-down lines indicate months of drug safety warnings issued.

Rosiglitazone warnings

EMA1 Reminded the risk of rosiglitazone in patients with cardiac failure and other cardiac disorders including myocardial infarction.

FDA1 Advised to evaluate the antidiabetic treatment options other than rosiglitazone in patients who have underlying heart disease and high risk of heart attack.

FDA2 Adds box warnings for heart-related risks of rosiglitazone.

EMA2 Suggested that rosiglitazone should only be used after careful evaluation of ischemic heart disease.

TGA1 Advised that rosiglitazone should not be prescribed for patients with known ischemic heart disease or at high risk for ischemic heart disease.

EMA3 Suggested that rosiglitazone must not be used in patients with an acute coronary disease.

EMA4 Recommended suspension of all rosiglitazone-containing products.

FDA3 Restricts access to rosiglitazone due to an elevated risk of cardiovascular events.

TGA3 Reinforced that rosiglitazone should not be used in patients with known ischemic heart disease.

Pioglitazone warnings

FDA Announced the warnings on a possibly increased risk of bladder cancer in patients who used rosiglitazone for longer than one year.

TGA Advised the prescribers that use of pioglitazone for more than a year may be associated with an increased risk of bladder cancer.

EMA Recommends new contraindications and warnings for pioglitazone to reduce small increased risk of bladder cancer.

There are no seasonal autocorrelation detected for both rosiglitazone and pioglitazone utilisations. Based on visual inspection of PACF and ACF plots, an ARIMA (1,0,2) model best characterised for rosiglitazone data and pioglitazone data was best characterised as an ARIMA (1,0,1). Findings from ARIMA models indicated that the utilisation of rosiglitazone decreased significantly after the EMA1 and FDA1 warnings by 15.04%. This decline was seen after the intervention in June 2007 compared to before the warnings ($p<0.001$) (Table 6). Additionally, the utilisation of rosiglitazone also significantly decreased following warnings from FDA2, EMA2, TGA1, and EMA3. However, after adjustment for FDA2, EMA2, TGA1, and EMA3 for preceding warnings, effects were attenuated and were no longer statistically significant (Table 6). Later warnings relating to EMA4, FDA3, and TGA2 were not significantly associated with decreases in rosiglitazone use (Table 6).

Table 6. Effects of drug warnings on the utilisation of rosiglitazone and pioglitazone

Drug authorities	Month-year	Warnings	Adjusted for	Coefficient[a]	95%CI[b]	p-value
Rosiglitazone: ARIMA (1,0,2) model						
EMA1_FDA1	May 2007	Ischemic heart		-15.04	[-21.86, -8.22]	**<0.001**
FDA2	Aug 2007	Label update	EMA1_FDA1	-2.61	[-40.41, 35.20]	0.893

		heart related				
EMA2	Oct 2007	Ischemic heart	EMA1_FDA1, FDA2	1.94	[-95.49, 99.36]	0.969
TGA1	Dec 2007	Ischemic heart	EMA1_FDA1, FDA2, EMA2	-5.25	[-38.01, 27.51]	0.837
EMA3	Jan 2008	Ischemic heart	EMA1_FDA1, FDA2, EMA2, TGA1	-0.39	[-80.06, 79.28]	0.992
FDA3, TGA2, EMA4	Sep 2010	EU suspended, US restriction	EMA1_FDA, FDA2, EMA2, TGA1, EMA3	1.25	[-8.99, 11.49]	0.811
Pioglitazone: ARIMA (1,0,1) model						
FDA	June 2011	Bladder cancer		-5.76	[-13.91, 2.39]	0.166
EMA, TGA	July 2011	Bladder cancer		-6.57	[-14.80, 1.65]	0.117

[a]Coefficient=Percentage change in magnitude and direction after the intervention; [b]CI=confidence interval; TGA=Therapeutic Good Administration; EMA=European Medicines Agency; FDA=U.S. Food and Drug Administration; EU=European Union; US=United States of America

For pioglitazone, although we can see a decline after the FDA, TGA, and EMA warnings on bladder cancer in June–July 2011, there is no statistically significant effect on subsequent pioglitazone use after fitting this into ARIMA model (Table 6).

Discussion

The changes of rosiglitazone and pioglitazone utilisation were observed between 2004 and 2012 in Australia. It is always difficult to attribute cause to utilisation trends, however it is likely that increased marketing of TZDs may have contributed to the increasing trend of rosiglitazone during 2004–2006 or that fewer alternatives to metformin, sulfonylurea, and insulin were available at this time. Our results show a decreasing trend in rosiglitazone utilisation in the period after the drug authorities' warnings in 2007–2008. Although the numbers of rosiglitazone prescriptions in Australia are relatively low in comparison to the UK, and North America, the overall trends are consistent with those shown in Europe and North America (Starner et al. 2008; Stewart et al. 2009; Shah et al. 2010; Ruiter et al. 2012). There are two possible explanations for the dip seen in April 2007. It might be a

seasonal trend as the same fluctuation was noted in March–April 2006; however, this was not sensitive enough to be detected by the ARIMA model. Secondly, the dip is an artifact of the data, this is actually the utilisation on its way up which is demonstrated by the higher use again in May 2007.

The sharply decreasing utilisation trend is significantly attributable to the safety alert from meta-analysis study and the initial warnings from the EMA and FDA in May 2007. For the reason that the FDA issued the cardiovascular alert of rosiglitazone on the same day as publication by Nissen et al. (Nissen et al. 2007), we could not distinguish the effects between the authority warnings and the publication. Furthermore, the effects of these warnings and associated literature are likely to be cumulative rather than a discrete effect on the following utilisation. Several restrictions in rosiglitazone subsidies from the PBS during October 2008–February 2009 were also examined; however, these impacts are not significant after adjustment for previous warnings. As a result of the consecutive series of cardiovascular warnings on rosiglitazone since 2007 and the limited access on PBS, the numbers of rosiglitazone prescriptions have remained lower than 5,000 per month since 2010.

Australian utilisation of pioglitazone was less than half of rosiglitazone during 2005–2007 and the increasing trend in use was moderate compared to the Netherlands and the US (Cohen et al. 2010; Ruiter et al. 2012). From 2008–2010, when peak levels were reached, the increase in pioglitazone nearly mirrors the decline in rosiglitazone. The findings suggest that prescribers might have replaced rosiglitazone with the same drug class pioglitazone (Starner et al. 2008; Hurren et al. 2011), due to the reported cardiovascular benefits of pioglitazone, and no clinical outcome associated with an increase risk of ischemic heart disease that was seen with rosiglitazone (Gerrits et al. 2007; Erdmann et al. 2010). While the decreasing trend of pioglitazone was observed in the US and Europe in 2008 (Hurren et al. 2011; Ruiter et al. 2012), Australian pioglitazone utilisation plateaued until 2011. The delay in decreasing trend compared to that of other countries may be attribute to limited availability of second-line and third-line therapy alternatives such as sitagliptin (was not PBS subsidised until August 2008) or exenatide (was not PBS subsidised until August 2010). The US and UK data (Hurren et al. 2011; Leal et al. 2013) show that the number of other new drugs, which were available in their markets since 2007 such as sitagliptin and exenatide, increased after the cardiovascular alerts of TZD. Nevertheless, Figure 3 shows the decline in the utilisation of pioglitazone after July 2011.

This decreasing trend may have been caused by more alternative treatments on the PBS or the safety concern of increased risk of bladder cancer in long-term users of pioglitazone. Although, this decline was of a lesser magnitude than for rosiglitazone, prescribers may consider the risk/benefit ratio, where the benefits of pioglitazone in lowering blood sugar outweigh the possible risk of bladder cancer (Kostapanos et al. 2012). However, more data points following this bladder cancer risk might be needed to examine the true effect of this warning.

Since TGA safety warnings are considered by the Australian Department of Health and Aging to be first-line alerts to healthcare providers, we would expect to see a significant effect on these utilisations. However, the fact that a) the decline in rosiglitazone use occurred prior to the first TGA warning, and b) after we adjusted for the preceding EMA, FDA warnings, we could not see a significant effect of the TGA warning on utilisation trends suggests that Australian prescribers were aware of the international warnings as well as the safety information from the literature. This might be associated with the way that information was delivered, since Australian warnings were delayed, less frequently communicated, and accessed compared to the FDA and European warnings (Buckley et al. 2011). Australian practitioners may receive safety information from medical articles or media that referred to the US or European warnings. A further qualitative study is being conduct to gain the insight into sources of drug safety information among Australian prescribers.

Since time series model prediction is based on the pattern of drug use in the past confounding influences on data may be difficult to disentangle. Although trends can be impacted by temporal changes in drug supply or the way data are recorded, we did not find those problems during study period. Furthermore, the Australia PBS data is aggregated data collected for administrative purposes, which does not link utilisation to the prescribing data in clinical settings. Therefore, clinical reasons for the decrease in dispensing cannot be fully investigated, nor primary non-compliance in patients be established.

The strength of this study is that it captures almost all prescriptions dispensed over 2004–2012 in total Australian population (private prescriptions represent a very small percentage of all prescriptions). This is achieved because rosiglitazone and pioglitazone are ‘high’ cost

drugs that are government subsidised in Australia. This allowed us to investigate the patterns of population based thiazolidinedione utilisation.

Conclusions

The utilisation of rosiglitazone significantly decreased following the authorities' safety warnings on ischemic heart disease. The pattern of rosiglitazone utilisation started declining significantly prior to the TGA warning in December 2007; therefore it appears that Australian prescribers were alerted by the literature and international warnings such as EMA and FDA. In contrast, pioglitazone utilisation increased during the rosiglitazone warning period during 2007–2010. In comparison to the US and Europe, the decline in the trend of pioglitazone use maybe due to a lack of second and third line therapies in Australia. Despite concerns surrounding the possible risk of bladder cancer with long term use of pioglitazone, this study showed weaker effects of safety warnings on bladder cancer and pioglitazone utilisation. A number of publications have studied the effect of authorities' warnings in the US and Europe to improve their warning systems (Esterly et al. 2011; Sen et al. 2011; Ruiter et al. 2012). This is one of the first studies to date that has investigated utilisation patterns in relation to drug safety warnings in Australia and suggests that TGA warnings may not affect prescribing in cases such as this where prescribers may be attuned to particular medicine safety issues described in earlier international warnings or literature. Further research is needed to understand how and when prescribers obtain drug safety information in Australia. This is particularly pertinent as Australia and New Zealand look to combine their drug safety warning systems.

5. Additional analyses

Sensitivity analyses of rosiglitazone and pioglitazone utilisation were performed using segmented regression modelling.

5.1 Sensitivity analysis of rosiglitazone utilisation

The segmented regression model was fitted to a least squared regression line for each segment of DDD/1000population/day of rosiglitazone before and after the EMA and FDA warning in June 2007. Parameter estimates, standard errors and p-values from segmented regression models predicting the DDD of rosiglitazone have been included in Table 7.

The times series regression equation for this analysis is

$$\hat{y}_t = \beta_0 + \beta_1 \times \text{Time} + \beta_2 \times \text{Intervention} + \beta_3 \times \text{Time\_post\_intervention} + e_t$$

; $\hat{y}_t$ is the independent outcome variable (DDD/1000population/day). Time is the number of months, starting from February 2004 as 1, and then increasing by 1 for every month. Intervention is a variable with the value 0 for the segment before the FDA_EMA warning and 1 for the segment after the FDA_EMA warning. Time_post_intervention is the number of months after the EMA_FDA warning, starting from June 2007, with the value 0 for the segment before the warning. e_t is the random variation at time t not explained by the model.

The coefficient β_0 estimates the baseline level of the rates at which DDD/1000pop/day of rosiglitazone was at the beginning of the observation; β_1 estimates the base rate trend before the EMA_FDA warning; β_2 estimates the change in rate level after the EMA_FDA warning. It is the measurement of rate change from the last time point before the warning to the first time point after the warning; β_3 estimates the change in rate slope after the warning.

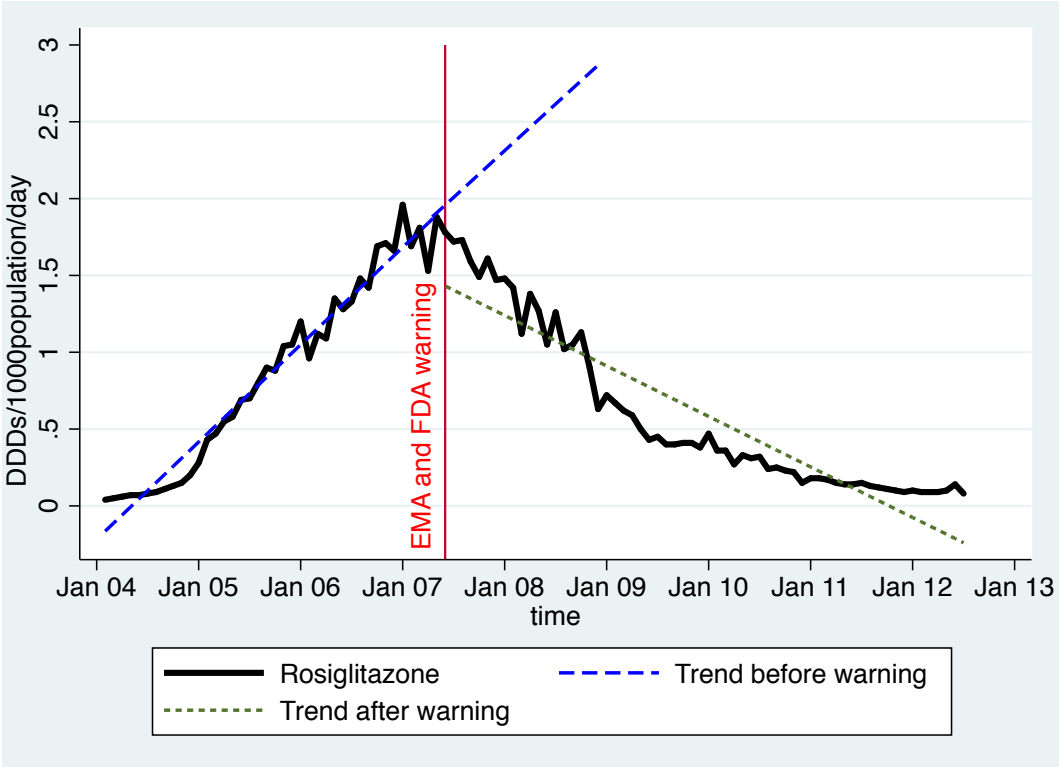


Figure 4. Monthly daily drug dose of rosiglitazone per 1000 population per day in the PBS database from February 2004 to July 2012

The results indicated that before the EMA_FDA warning, there was a significant month-to-month increase in the trend of rosiglitazone by 0.053 DDD/1000pop/day (p-value for pre-intervention trend <0.001). Right after the warning in June 2007, there was a slight decrease in the DDD of rosiglitazone from the month before (β_2=0.1, from 1.88 in May 2007 to 1.78 in June 2007) but this decrease was not significant.

There was a significant decrease in the month-to-month trend of rosiglitazone by 0.027 DDD/1000pop/day after the EMA and FDA warning (p-value for post-intervention trend <0.001). The visual inspection of Figure 4 and results of segmented regression modelling suggested that the post-intervention trend was in a different direction to the pre-intervention trend. The effect of the warning in June 2007 resulted in a decrease of rosiglitazone dispensing. For example, at 12 months after the warning, the utilisation of rosiglitazone was 1.05 DDD/1000pop/day while the predicted utilisation calculated from the baseline trend (β_1) was 2.579 DDD/1000pop/day.

Table 7. Parameters from segmented regression model of DDD/1000population/day of rosiglitazone in the PBS database

	Coefficient	Standard error	t-statistic	p-value
Intercept (β_0)	-0.2 7	0.041	-5.27	<0.001
Baseline trend (β_1)	0.0528	0.002	26.77	<0.001
Level change after warning (β_2)	-0.100	0.016	-0.11	0.99
Trend change after warning (β_3)	-0.0274	0.002	-16.62	<0.001

5.2 Sensitivity analysis of pioglitazone utilisation

Firstly, the spike of pioglitazone utilisation in June 2012 was balanced by using the mean difference of the point before (May 2012) and the point after (July 2012). In this study, two

models of segmented regressing modelling were performed as sensitivity analyses: two-segmented regression and three-segmented regression models.

In two-segmented regressing model, the pioglitazone utilisation was divided into two segments before and after the FDA warning in June 2011. Subsequently, a least squared regressing line to each segment was fitted into the model.

The two-segmented regression equation for this analysis is

$$\hat{y}_t = \beta_0 + \beta_1 \times \text{Time} + \beta_2 \times \text{Intervention} + \beta_3 \times \text{Time\_post\_intervention} + e_t$$

; $\hat{y}_t$ is the independent outcome variable (DDD/1000population/day). Time is the number of months, starting from February 2004 as 1, and then increasing by 1 for every month. Intervention is a variable with the value 0 for the segment before the FDA warning and 1 for the segment after the FDA warning. Time_post_intervention is the number of months after the FDA warning, starting from July 2011, with the value 0 for the segment before the warning. e_t is the random variation at time t not explained by the model.

The coefficient β_0 estimates the baseline level of the rates at which DDD/1000pop/day of pioglitazone was at the beginning of the observation; β_1 estimates the base rate trend before the FDA warning; β_2 estimates the change in rate level after the FDA warning. It is the measurement of rate change from the last time point before the warning to the first time point after the warning; β_3 estimates the change in rate slope after the warning.

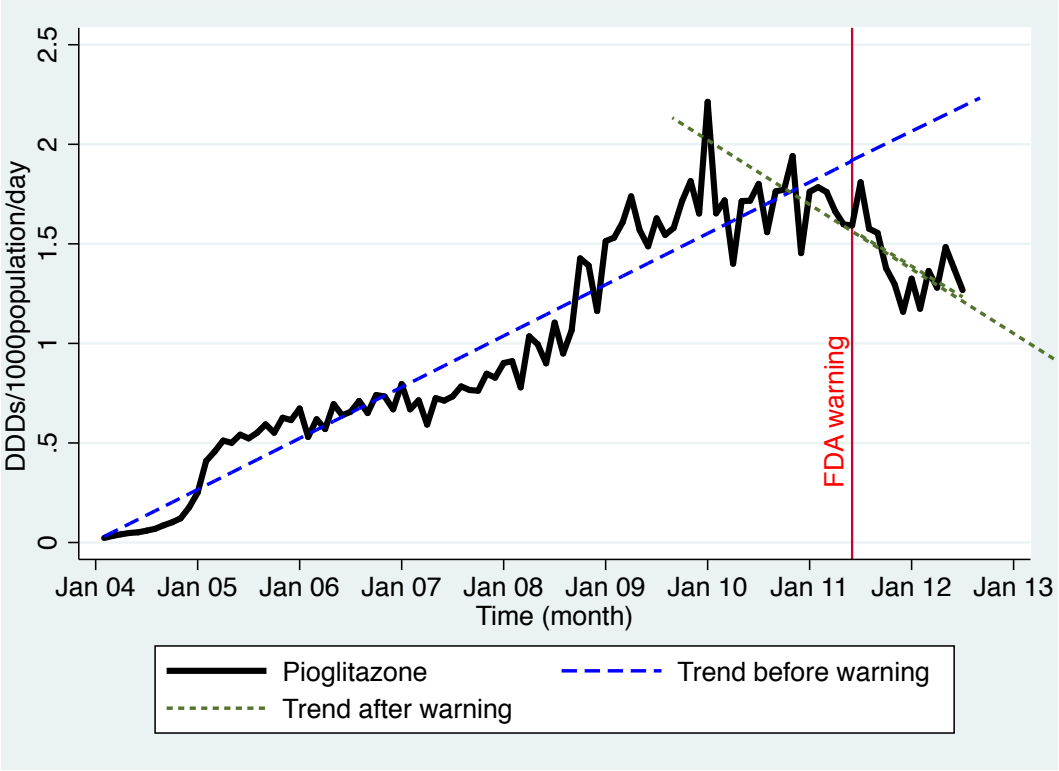


Figure 5. Monthly daily drug dose of pioglitazone per 1000 population per day and predicted lines of segments before and after the FDA warning in the PBS database from February 2004 to July 2012

Figure 5 depicts the pioglitazone utilisation in the PBS database and the predicted trends of segments before and after the warning based on the least square regression. The results indicated that before the FDA warning, there was a significant month-to-month increase in the trend of pioglitazone by 0.021 DDD/1000population/day (p-value for pre-intervention trend <0.001). There was a slight increase in the pioglitazone utilisation from the month before the FDA warning but this increase was not significant (Table 8).

The change in trends of the two predicted lines in Figure 5 suggested a significant impact by the warning on the trend of pioglitazone utilisation. There was a decrease in the month-to-month trend of pioglitazone by 0.026 DDD/1000population/day after the FDA warning; however, this decrease was not statistically significant (p-value for post-intervention trend 0.054).

Table 8. Parameters from two-segmented regression model of DDD/1000population/day of pioglitazone in the PBS database

	Coefficient	Standard error	t-statistic	p-value

Intercept (β_0)	0.009	0.026	0.34	0.732
Baseline trend (β_1)	0.021	0.001	30.86	<0.001
Level change after warning (β_2)	-0.100	0.016	-0.11	0.99
Trend change after warning (β_3)	-0.026	0.012	-2.15	0.054

Although slopes of segments before and after the warning are different in the two-segmented regression model, a plateau was observed from January 2010 to June 2011 (before the warning). Therefore, the three-segmented regression model was fitted by dividing the period before the warning into two segments: the segment between February 2004 - December 2009 and the segment between January 2010 - June 2011. Figure 6 depicts the pioglitazone utilisation in the PBS database and three predicted lines from the three-segmented regression model.

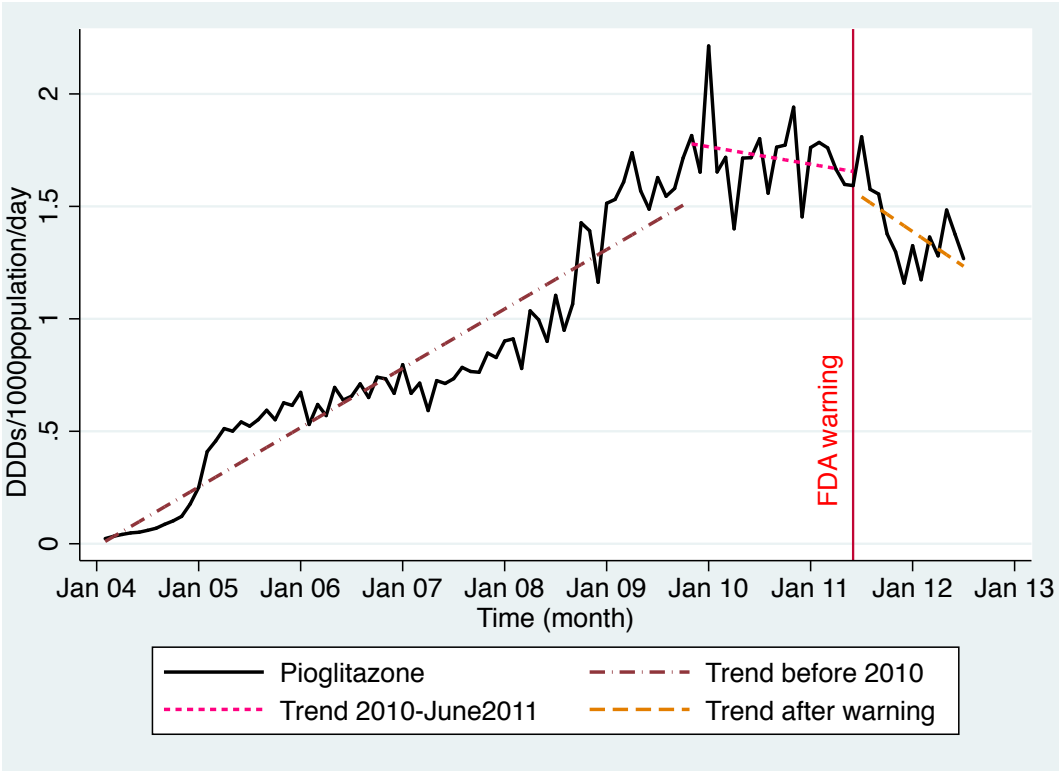


Figure 6. Monthly daily drug dose of pioglitazone per 1000 population per day and predicted lines of three segments in the PBS database from February 2004 to July 2012

The visual inspection of Figure 6 and results from the three-segmented regression model (Table 9) suggested a slight decrease of month-to-month pioglitazone utilisation by 0.006 DDD/1000population/day from January 2010 - June 2011, although this decrease is not statistically significant (p-value 0.347).

There was a month-to-month decrease in the post-intervention trend by 0.026 DDD/1000population/day but this decrease was not statistically significant. In comparison to the segment (January 2010 - June 2011) before the warning, the impact of the FDA warning resulted in a more decrease in the trend of pioglitazone utilisation.

Table 9. Parameters from two-segmented regression model of DDD/1000population/day of pioglitazone in the PBS database

	Coefficient	**Standard error**	**t-statistic**	**p-value**
Intercept (β_0)	-0.012	0.027	-0.43	0.671
Baseline trend (β_1) (February 2004 - December 2009)	0.022	0.001	24.25	<0.001
Level change (β_2) from December 2009 to January 2010	0.35	0.016	1.23	0.709
Trend (β_3) (December 2009-January 2010)	-0.006	0.007	-0.97	0.347
Level change after warning (β_4)	0.217	0.020	0.98	0.199
Trend after warning (β_5)	-0.026	0.012	-2.15	0.054

6. Chapter conclusion

This chapter described the utilisation of rosiglitazone and pioglitazone in the national PBS database and the impact of warnings issued by the TGA, FDA, and EMA on the patterns of drug use. The first warning issued by the TGA on the risk of cardiovascular events of rosiglitazone (in December 2007) was 6 months behind the warnings from the FDA and EMA (in May 2007). There were two safety communications on cardiac events related to rosiglitazone by the TGA, which seemed to be less frequent compared to the FDA and EMA communications (Buckley et al. 2011). The prevalence of dispensing rosiglitazone was highest in early 2007 when the first warnings from the FDA and EMA came out. The results in this chapter suggest that a decrease in dispensing trend of rosiglitazone was significantly associated with the warnings issued by the FDA and EMA. The impact of the TGA warning in December 2007 insignificantly changed the amplitude of the declining trend of rosiglitazone following previous warnings from the FDA and EMA. Findings from this study imply that prescribers stopped using rosiglitazone but how prescribers changed the management in patients taking rosiglitazone cannot be examined in this PBS database.

Conversely to the decrease in rosiglitazone use following the cardiovascular warning, the prevalence of dispensing pioglitazone continuously increased and reached its plateau in late 2009. Since there was no evidence on an increased risk of myocardial infarction related to pioglitazone, prescribers may have switched from rosiglitazone to pioglitazone. In chapter 4, changes in antidiabetic prescriptions following warnings on rosiglitazone will be investigated using the AsteRx clinical data.

The TGA warning on the bladder cancer risk related to pioglitazone was issued in the same period as other major regulatory warnings. However, there was no significant change to the pattern of pioglitazone use following these warnings. Further investigation into why different impacts of warnings on changes in patterns of rosiglitazone and pioglitazone were observed will be conducted using a combined interview and survey study in Chapter 6.

Chapter 4. The impact of thiazolidinedione warnings on the prescribing of drugs in the AsteRx database

1. Synopsis

The previous chapter investigated the impact of adverse events warnings on the national dispensing trends of rosiglitazone and pioglitazone. In this chapter, the AsteRx data provides further details on changes of prescribing rosiglitazone and pioglitazone following their warnings. Using the AsteRx data the prescribing trend of rosiglitazone significantly decreased after the warnings from the FDA and EMA in May 2007 similar to the dispensing trend seen in the PBS database. There were increases in the number of switches from rosiglitazone to pioglitazone and pioglitazone initiations after the cardiovascular warnings of rosiglitazone. The trend in the prescribing of pioglitazone insignificantly changed after the bladder cancer warning in June–July 2011. This is likely to be due to the availability of the new antidiabetic drug, dipeptidyl peptidase-4 inhibitors.

2. Chapter aims

The chapter aims to evaluate the impact of warnings from the TGA, FDA and EMA on the changes in prescribing details of patients using thiazolidinediones in the AsteRx database.

3. Submitted Manuscript entitled “Impact of regulatory warnings on the prescribing rosiglitazone and pioglitazone in Australia”

The manuscript entitled “Impact of regulatory warnings on the prescribing rosiglitazone and pioglitazone in Australia” is submitted to Research in Social & Administrative Pharmacy 2014.

The co-authors contributed to the manuscript as follows: PhD candidate, Suvimol Niyomnaitham, designed the study under the supervision of Dr Alesha Smith, Dr Adam La Caze, and Dr Karen Whitfield. The PhD candidate performed all data collection and data analysis. Suvimol Niyomnaitham took the lead role in manuscript preparation and writing. All co-authors revised the manuscript for intellectual content and approved the final manuscript.

Impact of regulatory warnings on the prescribing rosiglitazone and pioglitazone in Australia

Suvimol Niyomnaitham[1,2], Adam La Caze[1], Karen Whitfield[1], and Alesha J. Smith[1, 3]

[1]School of Pharmacy, University of Queensland, [2]Faculty of Medicine Siriraj Hospital, Mahidol University, [3]School of Pharmacy, University of Otago

Running Head: Prescribing changes after safety warnings

Corresponding author:

Suvimol Niyomnaitham
Address: School of Pharmacy, University of Queensland, 20 Cornwall Street, Woolloongabba, 4102, QLD, Australia

Telephone number: +61 40 617 8866, Fax number: +61 7 3346 1917

Keywords Drug safety warning, Rosiglitazone, Pioglitazone

Take-home' messages

- Australian prescribers were aware of international authorities' warnings.
- Prescribing of rosiglitazone decreased immediately after the warnings on the risk of myocardial infarction.
- Pioglitazone was a popular choice when switching from rosiglitazone during late 2007–2009.

Conflict of Interest statement

No sources of funding were involved in this study. The authors declare that they have no competing interests.

Word count: 2855 words

Presentation: The abstract of this study was presented on the National Medicines Symposium 2014, Brisbane, Australia, May 21–23, 2014.

ABSTRACT

Purpose

This study describes Australian prescribing patterns of rosiglitazone, following the warnings regarding myocardial infarction in 2007, and pioglitazone, following the warnings on the risk of bladder cancer in 2011.

Methods

Rosiglitazone and pioglitazone were described using the AsteRx database as proportions of total antidiabetic prescriptions from January 2005–April 2012. The database contains prescribing and other clinical details collected from 100 practices in Australia. Changes in prescribing trends after warnings from the Australian Therapeutic Goods Administration (TGA), US Food and Drug Administration (FDA), and European Medicines Agency (EMA) were investigated using the auto-regressive, integrated, moving average (ARIMA) model.

Results

The trend of rosiglitazone significantly declined after the warnings from FDA and EMA in May 2007 (p=0.001) using the ARIMA model. Within one year from May 2007, rosiglitazone fell from 7.2% to 3.1% of total antidiabetic prescriptions. The TGA warning in December 2007 had no significant effect on the declining trend of rosiglitazone prescribing after adjustment for the previous FDA and EMA warnings. Pioglitazone was the most popular switching choice from rosiglitazone after May 2007. That explained the upward trend of pioglitazone until its decline was observed in 2009. Warnings on the risk of bladder cancer in June–July 2011 did not have any significant effect on the ongoing decline of pioglitazone prescriptions.

Conclusions

Prescribing of rosiglitazone significantly decreased due to a series of warnings on cardiac risk. The 2011 warnings regarding the risk of bladder cancer were not significantly associated with changes in the pioglitazone prescribing.

Introduction

Recently, drug authorities issued several warnings on thiazolidinediones (TZDs) related to their risks on cardiovascular disease and bladder cancer. Rosiglitazone and pioglitazone

belong to the TZD drug class. Their efficacy in increasing insulin sensitivity helps improve glycemic control (e.g. HbA1c) in patients with type 2 diabetes (Bolen et al. 2007). However, long-term outcomes of TZDs were not known. In November 2003, TZDs were first listed on the Pharmaceutical Benefit Scheme (PBS), a national subsidised program for Australian citizens, for dual oral therapy with metformin or a sulfonylurea. Subsequently, the TZDs listing was extended to include in combination with insulin. Rosiglitazone was subsidised for triple oral therapy with metformin and a sulfonylurea in 2005 (PBAC 2007).

During 2005-2006, studies suggested an increased risk of macular oedema and proximal fractures related to TZDs (Colucciello 2005; Bonds et al. 2006). However, the emerging risk of myocardial infarction among rosiglitazone users from a meta-analysis in May 2007 raised the public awareness of potential harms of rosiglitazone treatment (Nissen et al. 2007). Evidence for an increased risk of myocardial infarction in patients taking rosiglitazone was inconclusive from two large clinical studies (Gerstein et al. 2006; Kahn et al. 2006) and an interim analysis of cardiovascular outcomes of rosiglitazone (Home et al. 2007). Major drug authorities promptly responded to the evidence of an increased risk of myocardial ischemia of rosiglitazone. Firstly, the FDA announced a safety concern on the same day as the meta-analysis was published on 21 May 2007 and then placed a Box warning on rosiglitazone in August 2007. In September 2010, the FDA restricted rosiglitazone via a registration program (Beermann et al. 2005; Berger et al. 2009; Bennett et al. 2010). The EMA issued three press releases on the cardiac risk related to rosiglitazone in May 2007, October 2007 and January 2008, followed by the suspension of all rosiglitazone products in September 2010 (Bhatt et al. 2006; Bhatia et al. 2008; Bhatt et al. 2010; Boisvert 2010).

The Therapeutic Goods Administration (TGA) is a regulatory authority in Australia responsible for the safety of medicines. The TGA communicates new drug safety information to healthcare professionals by publishing ‘Alerts’ (as required) and every two months a ‘Medicines safety update’ on their website, similar to that of the US Food and Drug Administration (FDA) drug safety communication and the European Medicines Agency (EMA) press release. The TGA issued its first official warning on the myocardial infarction risk of rosiglitazone in December 2007 (Gaarder et al. 1961). The TGA’s second warning released in September 2010 recommended avoiding rosiglitazone use in patients with cardiac conditions (TGA 2011). Although the EMA had suspended rosiglitazone

across Europe, the FDA and TGA still allowed rosiglitazone marketing in the US and Australia.

In November 2008, rosiglitazone was no longer PBS subsidised for treatment in combination with insulin and triple oral therapy, as a result of the increased risk of congestive heart failure and myocardial infarction (2005; Cobitz et al. 2008). Subsequently, the PBS required telephone approval for rosiglitazone prescriptions from 1 July 2011.

Studies suggest that pioglitazone is a safer alternative without evidence of an increase in myocardial infarction, stroke and mortality (Dormandy et al. 2005; Lipscombe et al. 2007). However, findings from a French study in 2011 showed an increased risk of bladder cancer related to long term treatment of pioglitazone which led to a temporary suspension of pioglitazone in France and Germany (Gaspar et al. 2010). A retrospective study from the US supported a possible risk of bladder cancer in patients using pioglitazone for more than two years compared to those who were not taking pioglitazone (Lewis et al. 2011). Safety warnings from the FDA in June 2011 and the EMA and TGA in July 2011 outlined the possible risk of developing bladder cancer when used more than 1 year (2005; 2007; Gaspar et al. 2010).

Declining trends of thiazolidinedione utilisation after the safety warnings were found in a previous study using the national dispensing data (Niyomnaitham et al. 2014). To date there has not been an analysis of changes in thiazolidinedione use focusing on patient-level data, such as that provided by the AsteRx database. To better understand the impact of drug safety warnings, we conducted a retrospective analysis investigating the changes to the prescribing of antidiabetic drugs in patients using rosiglitazone and pioglitazone after the safety warnings.

Aims

The goals of this study are to investigate the use of rosiglitazone and pioglitazone over the period 2005–2012 using the AsteRx clinical database and to describe the change in prescribing patterns after drug safety warnings.

Materials and methods

Data sources

The AsteRx database contains clinical data from more than 100 medical practices in all states of Australia since 2003. De-identified demographic data of over half a million patients and six hundred doctors are collected. There are a total of seven million prescriptions including prescribing date, chemical name, strength, quantity, and drug code (WHO Anatomical Therapeutic Chemical Classification (ATC) system codes and Australian Pharmaceutical Benefits Scheme (PBS) item codes). PBS codes are unique for each drug formulation and strength and are used for dispensing and government reimbursement in Australia. Diagnoses, consultations, and laboratory results are recorded in plain text (Gilard et al. 2008).

1. Rosiglitazone and pioglitazone utilisation

All antidiabetic prescriptions from 1 January 2005–30 April 2012 were extracted from the AsteRx database using ATC drug codes and PBS drug codes. ATC codes of oral antidiabetic drugs (biguanides, sulfonamides, alpha glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors (DPP-4), thiazolidinediones, and combinations of oral antidiabetic drugs) including insulin and analogues were used to extract and identify classes of antidiabetic drugs. Each antidiabetic drug in a multiple anti-diabetes regimen contributed to each antidiabetic prescription where the premixed formulation, for example, Avandamet (rosiglitazone combined with metformin) was counted twice – one in rosiglitazone and one in metformin. We also used PBS codes to confirm the completeness of antidiabetic data capture.

2. Discontinuation among patients using TZD

All patients who were prescribed rosiglitazone or pioglitazone from January 2005–April 2012 were identified using ATC codes and PBS codes. We only included patients who had at least two prescriptions of any kind of antidiabetic drug to confirm that the patients had diabetes. The use of the diagnostic data recorded as plain text entries into AsteRx was explored, but this data was found to be unreliable.

All prescriptions of diabetes medicines after the first TZD prescription of each patient were investigated until the earliest of the following: a) 30 April 2012; b) termination of patient's medical record; or c) discontinuation of the TZD treatment.

Dates at which patients discontinued their TZD were divided into: i) date of discontinuation of TZD in the treatment regimen without addition of any antidiabetic agent to an existing regimen after 60 days of the end of last TZD supply date ("stop" TZD date); ii) date of replacement of TZD by another antidiabetic agent in an existing regimen within 60 days of the end of last TZD supply date ("switch" TZD date). An antidiabetic agent that was prescribed to replace TZD in an existing regimen was defined as the "switching choice".

Drug safety warnings (interventions)

Drug safety warnings in Australia were obtained from the TGA website under 'Safety alerts' and 'Safety information for health professionals' (Almadi et al. 2011). The safety announcement called 'Press release' from the EMA and the FDA drug safety communication were acquired from their official websites (Angiolillo et al. 2007; Almadi et al. 2011). In this study, we assessed the effects of the first safety announcements from each of the regulatory authorities on cardiac risk of rosiglitazone in May 2007 (EMA and FDA) and December 2007 (TGA).

The effects of warnings on an increased bladder cancer risk related to long-term use of pioglitazone were investigated after June 2011 (FDA) and July 2011 (EMA and TGA).

Analyses

1. Changes in rosiglitazone and pioglitazone prescriptions

Numbers of prescriptions for each antidiabetic drug were converted to a percentage of total monthly antidiabetic prescriptions. The combined formulation of rosiglitazone and metformin was attributed to thiazolidinedione drug class and rosiglitazone prescriptions. To investigate the prescribing trend, the percentage of rosiglitazone and pioglitazone prescriptions were assessed using the time series analysis called auto-regressive, integrated, moving average model (ARIMA). The ARIMA model has been used to investigate the impact of health care interventions on trends of drug use (Ferrand et al. 2011; Langley et al. 2011; Ruiter et al. 2012). The ARIMA (*p,d,q*) model is an applied time-series model developed by Box-Jenkins (Griffiths et al. 2000) to forecast future observations that occur at equal intervals and determine the effect of an intervention in time series data. *p* refers to accumulated effect of the preceding data and *q* is the most recent random shock carried over from one period to the next. *d* indicates number of

differences to achieve stationary of the trend. Firstly, the integration process is differenced (*d*) to make stationary data. Then autocorrelation functions (ACF) and partial autocorrelation functions (PACF) were plotted and visually observed to obtain the appropriate model (*p, q*) for analysis (McDowall 1980). The best fitted model for analysis was obtained using the Bayesian Information Criteria (Schwarz 1978). The coefficient (ω) represents the effect of warnings from the EMA, FDA, and TGA, which were tested for statistical significance on subsequent prescribing trends and were assumed as an abrupt and permanent effect in this study (McDowall 1980; Griffiths et al. 2000).

2. Discontinuation among patients using TZD

The proportion of patients who discontinued (stop/switch) rosiglitazone before and after: May 2007 (first EMA and FDA warnings on myocardial ischemia) and December 2007 (the first TGA warning) were investigated. The rate of discontinuations per patient using rosiglitazone during periods before/after warnings or incidence rate ratio (IRR) was analysed using Poisson regression (Cameron et al. 2013). We also limited the comparison period to two years before and after the warnings to further investigate the chance of discontinuation. STATA 12.1 (StataCorp, College Station, TX) was used to perform all statistical analyses with a 5% significance level.

Results

Diabetes diagnoses and prescriptions were examined in the AsteRx database to estimate diabetes prevalence. Among patients who were active in the AsteRx database (had at least one prescription of any medicines), 6.19% had a diabetes diagnosis or antidiabetic prescription. There was a total of 101,874 prescriptions for all antidiabetic drugs among 29,125 patients from 1 January 2005–30 April 2012. Figure 4 shows the percentage of each antidiabetic drug class that was prescribed in the AsteRx database. A biguanide (metformin) was the most commonly prescribed antidiabetic drug class during the study period, followed by sulfonamide and insulin. Overall use of thiazolidinediones peaked at 12.26% in May 2007 after that the number of prescriptions gradually decreased to 1.76% in December 2011. After DPP-4 became available in August 2008 and DPP-4 plus metformin in 2009, the combination of these DPP-4 prescriptions surpassed thiazolidinediones in May 2010.

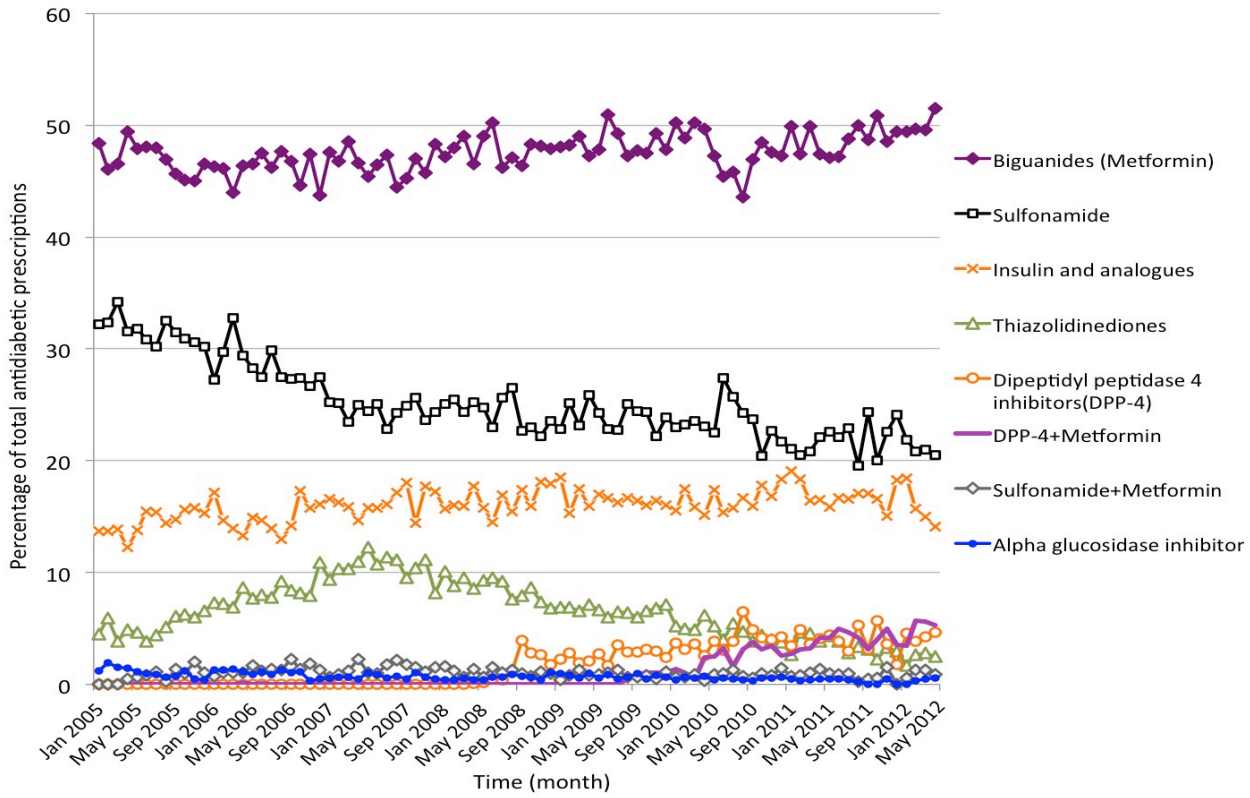


Figure 7. Percentage of each antidiabetic drug in the AsteRx database from January 2005–April 2012

The market share of rosiglitazone (including both rosiglitazone and rosiglitazone+metformin) progressively increased and reached its peak in May 2007 with a 9.28% share of total antidiabetic prescriptions. After May 2007, the use of rosiglitazone declined substantially until the end of 2008 where prescriptions made up less than 2% of all antidiabetic prescriptions. Pioglitazone rose over 3% during 2008 and overtook rosiglitazone prescriptions in September 2008. Pioglitazone started decreasing in October 2008 and remained steady at approximately 2% of total use at the end of study period (Figure 5).

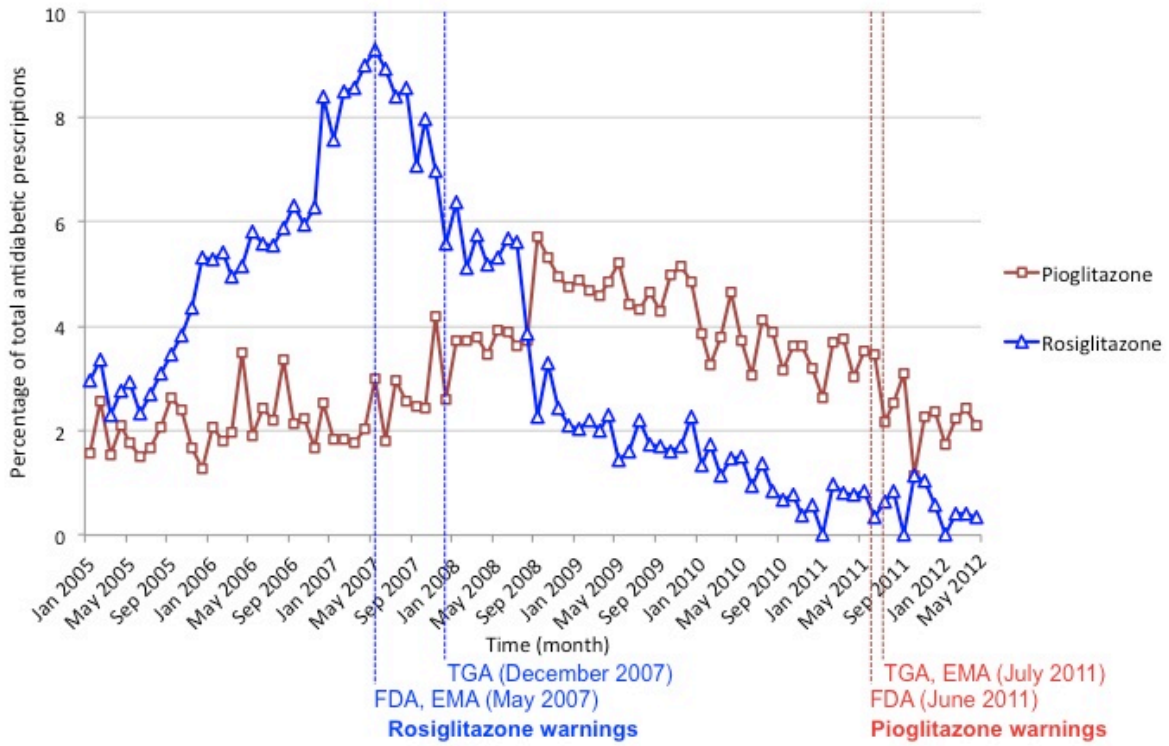


Figure 8. Percentage of rosiglitazone and pioglitazone from January 2005–April 2012 in the AsteRx database. The dashed lines indicate released months of safety warnings.

There were no seasonal autocorrelation detected for rosiglitazone or pioglitazone prescriptions in this database. Both rosiglitazone and pioglitazone data were stationary after one difference (*d* =1). The visual observation of PACF and ACF plots suggested an ARIMA (1,1,0) model to best characterize the rosiglitazone data and ARIMA (0,1,1) for pioglitazone data. The monthly percentage of rosiglitazone prescriptions was fitted into the ARIMA (1,1,0) model to investigate the effects of 1) the FDA and EMA warnings in May 2007 and 2) TGA in December 2007 (Table 10). The proportion of rosiglitazone prescriptions decreased significantly after the FDA and EMA warnings (p=0.001). The declining trend of rosiglitazone was not significantly associated with the TGA warning (p=0.062). Although the p-value was significant in the ARIMA model after adjusting for the previous EMA and FDA warnings, the positive number of adjusted coefficient (ω=0.37) indicates the upward trend of the rosiglitazone from the TGA warning. Therefore, the TGA warning was also not significantly associated with the subsequent trend of rosiglitazone prescriptions after adjusting for the EMA and FDA warnings. For pioglitazone, a decline was observed after the FDA, EMA, and TGA warnings related to the risk of bladder cancer; however, this was not significant according to the ARIMA model.

Table 10. Effects of drug warnings on the trend of rosiglitazone and pioglitazone prescriptions in ARIMA models

Drug authorities	Month-year	Warnings	Adjusted for	Coefficient [a] (ω)	95%CI[b]	p-value[c]
Rosiglitazone *ARIMA (1,1,0)*						
EMA, FDA	May 2007	Myocardial infarction	-	-0.37	[-0.60, -0.15]	**0.001**
TGA	December 2007	Myocardial infarction	-	-0.19	[-0.40, 0.01]	0.062
			EMA, FDA	0.37	[0.09, 0.65]	**0.010**
Pioglitazone *ARIMA (0,1,1)*						
FDA	June 2011	Bladder cancer	-	-0.13	[-0.32, 0.06]	0.191
EMA, TGA	July 2011	Bladder cancer	-	-0.10	[-0.32, 0.12]	0.374

[a] Coefficient **(ω)** =Coefficients were transformed to percentage change in magnitude and direction after the intervention; [b]CI=confidence interval; [c]Statistical significance at p-value<0.05 is presented in bold; TGA=Therapeutic Good Administration; EMA=European Medicines Agency; FDA=US Food and Drug Administration

We examined other factors that might have impacted on the trend of rosiglitazone and pioglitazone prescriptions. After adjustment for the first warning from the FDA and EMA, the PBS's subsidy change and restriction in November 2008 and 2011 had insignificant associations with the decreasing trend of rosiglitazone. The introduction of DPP4 in late 2008 was also not significantly associated with either rosiglitazone or pioglitazone prescriptions in the ARIMA models.

Nine hundred and seven patients were prescribed rosiglitazone before May 2007 and twelve hundred and ninety five patients after May 2007. Approximately 20% of patients had evidence of rosiglitazone discontinuation (termination of rosiglitazone before the ending of their prescribing records) with 17.97% switching to another antidiabetic drug before the warning in May 2007 (Table 11). It is estimated that 35% of patients discontinued rosiglitazone after May 2007. The rate of rosiglitazone discontinuation (both switching and stopping) after May 2007 was 7.33 [95%CI 6.46–8.33] times the rate before

the FDA and EMA warnings in May 2007. When the comparison period is limited to two years before and after May 2007, the rate of rosiglitazone discontinuation during June 2007–May 2009 is 5.70 [95%CI 4.79–6.79] times the incidence rate during June 2005–May 2007.

Table 11. Number of patients who discontinued rosiglitazone before and after the FDA and EMA warnings in May 2007

Discontinuation	January 2005–May 2007	June 2007–April 2012
Switch	163 (17.97%)	414 (31.97%)
Stop	19 (2.09%)	44 (3.4%)
Total patients	907	1295

For those who switched from rosiglitazone to another antidiabetic drug before May 2007, insulin was the most common switching choice (27%) along with 25% metformin, 24% sulfonamide, and 18% pioglitazone. After May 2007, the most common switching choice was pioglitazone (32%), followed by 24% metformin, 19% insulin, and 16% sulfonamide. Moreover, pioglitazone accounted for 47% of all switching choices in 2008 and 21% in 2009. Many patients (n=150) discontinued rosiglitazone during June 2007–December 2007, the period between the first EMA/FDA warnings and the TGA warning.

Discussion

In the AsteRx database, the diabetes prevalence (6.19%) was slightly higher than the Australian Health Survey 2011-2012, in which 4.6% of the Australian population self-reported diabetes mellitus (Gladding et al. 2010). TZDs reached its highest share of overall antidiabetic prescriptions in 2007, which was considerably delayed compared to North America or Europe (between 2005–2006) (Starner et al. 2008; Stewart et al. 2009; Ruiter et al. 2012). Right at the peak of rosiglitazone use in May 2007, the FDA and EMA announced the warnings related to a meta-analysis study by Nissen on the risk of myocardial infarction and death (Nissen et al. 2007). A sharp decline of rosiglitazone was immediately observed after May 2007 and the change was statistically significant after fitting into the ARIMA model. This decreasing pattern is consistent with the overall rosiglitazone dispensing in the Australian PBS database as well as prescribing trends in

the US and Europe (Starner et al. 2008; Stewart et al. 2009; Ruiter et al. 2012; Niyomnaitham et al. 2014). The change in drug choice is more likely to be from an accumulation of events as opposed to a distinct singular effect from regulatory warnings. It is not possible to distinguish whether this decline was from discussion in the medical literature or initial safety warnings from the FDA and EMA.

There was a 40% drop in rosiglitazone use during June 2007–December 2007 following two FDA warnings, two EMA warnings and many publications on the risk of myocardial ischemia (Lipscombe et al. 2007; Nissen et al. 2007; Singh et al. 2007). Consequently, the interrupted time series analysis suggested that the TGA warning in December 2007 did not have a further significant effect on the ongoing decline of rosiglitazone after adjustment for the previous EMA and FDA warnings. These findings indicate that Australian prescribers responded to the safety information from the literature and/or international warnings prior to the local TGA warning. There are many communication pathways for drug safety information including warnings, the literature, medical articles, or the media. The insight into sources of drug safety information is being conducted among Australian prescribers in a study linked to this project.

The discontinuation rate of rosiglitazone after May 2007 was significantly higher than before the warnings. A sensitivity analysis of 2-year periods before and after the warnings also shows a higher discontinuation rate of rosiglitazone after the warnings on the risk of myocardial infarction. Pioglitazone was the most popular antidiabetic alternative among patients who switched from rosiglitazone after May 2007. In 2008 when pioglitazone surpassed rosiglitazone prescriptions, almost half of those prescribed pioglitazone was as a switched drug choice. Pioglitazone rose more than 200% from June 2007 to September 2008 as a result of studies that showed no clinical evidence of myocardial infarction associated with pioglitazone (Dormandy et al. 2005; Lincoff et al. 2007). However, the use of pioglitazone was not sustained following the increased use of DPP4 in 2010 (Figure 4 and 5). Studies in the US and UK showed a decline in pioglitazone prescriptions and an increase in prescriptions for new antidiabetic drugs such as sitagliptin and exenatide after the warnings in 2007. This difference is not surprising as there was no alternative third-line drug for diabetes treatment in Australia until sitagliptin was first listed on the PBS in August 2008.

Figure 5 shows that the trend of pioglitazone prescribing started dropping at the end of 2009. When we fitted pioglitazone prescriptions into the ARIMA model, the warnings on bladder cancer in 2011 did not change the magnitude of the declining pioglitazone. It is likely that due to a low incident rate of bladder cancer (3 cases per 1000 pioglitazone users) compared to the risk of cardiovascular disease, prescribers did not immediately stop prescribing pioglitazone as seen with rosiglitazone. They may consider that the benefits in glycemic control of pioglitazone outweigh the possible risk of bladder cancer. Changes in pioglitazone prescriptions may be observed if prescribing data was analysed after the end of the current study period (May 2012).

Although the number of patients in the AsteRx database is a small proportion of Australians, the prescribing patterns of rosiglitazone and pioglitazone were comparable to the PBS dispensing trends indicating generalisability to the overall Australian population (Niyomnaitham et al. 2014). The AsteRx database allowed us to describe the changes in prescribing and antidiabetic preferences among Australian prescribers.

Conclusions

Our findings suggest that Australian prescribers discontinued rosiglitazone following warnings from the FDA and EMA on the risk of myocardial infarction. The TGA warning in December 2007 did not significantly add to the effect of the declining trend of rosiglitazone. Pioglitazone was the preferred choice for switching from rosiglitazone after May 2007. Differences were observed between the impact of cardiac warnings on rosiglitazone and bladder cancer warnings on pioglitazone, with the warnings related to the possible risk of bladder cancer in 2011 having no impact on the trend of pioglitazone prescriptions. A future qualitative study is designed to determine sources of drug safety information among Australian prescribers.

ABBREVIATIONS

TGA = Therapeutic good administration; EMA = European medicines agency; FDA = US food and drug administration; TZD = Thiazolidinedione; PBS = Pharmaceutical benefit scheme; ATC = Anatomical Therapeutic Chemical Classification; DPP-4 = Dipeptidyl peptidase-4 inhibitors; ARIMA = Auto-regressive, integrated, moving average; ACF = Autocorrelation functions; PACF = Partial autocorrelation functions; IRR = Incidence rate ratio; CI = Confidence interval; US = United States; UK = United Kingdom

AUTHORS' CONTRIBUTIONS

SN, AC, KW, and AS contributed to design the study and method. SN was responsible for the data collection, statistical analysis and result interpretation. All authors contributed to manuscript writing and all revisions of the manuscript. All authors approved the final manuscript.

4. Chapter conclusion

There are very few studies in Australia that have examined the trends of drug use at patient level data in relation to the PBS data, especially compared the impacts of regulatory warnings between these databases. Figure 9 depicts the dispensing trends of thiazolidinediones in the PBS database and the prescribing trends in the AsteRx database. From visual observation of slope and statistical results from ARIMA model, the trends of rosiglitazone and pioglitazone use in these two database are comparable therefore the prescribing trends in the AsteRx represents the national trends of these two drugs well.

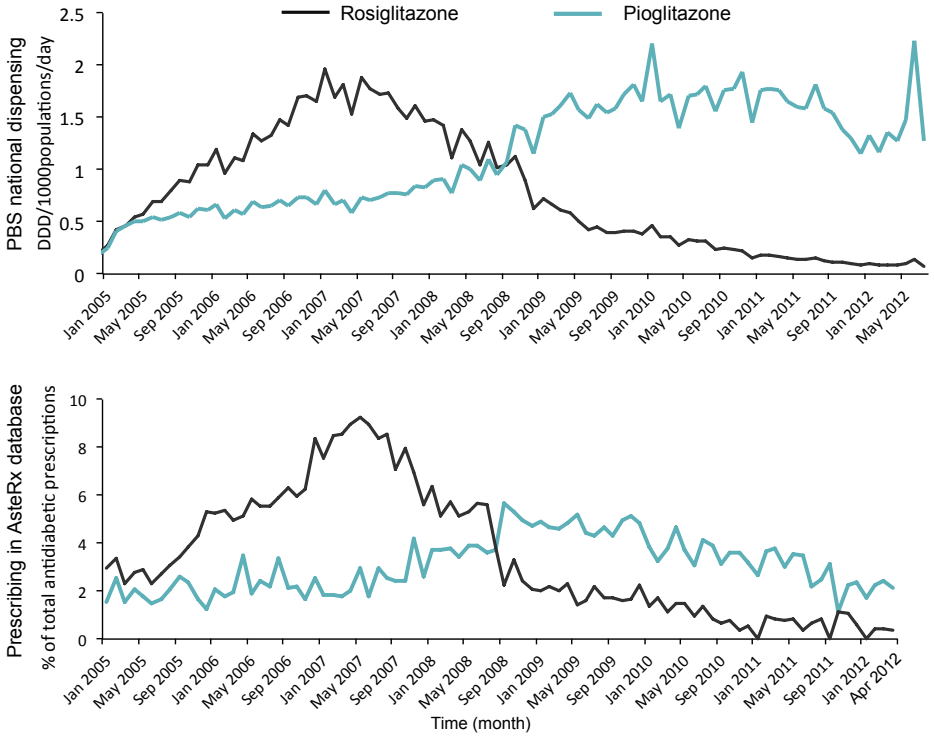


Figure 9. Trends in utilisation of rosiglitazone and pioglitazone in the PBS (above) and prescribing rosiglitazone and pioglitazone in the AsteRx (below)

A decrease of rosiglitazone use was associated with the warnings issued by the key international regulators who announced the cardiovascular concern prior to the TGA. Since a decline of prescribing rosiglitazone in late 2007, pioglitazone had increased and surpassed the rosiglitazone in 2009. Pioglitazone had no evidence of increased myocardial events that had been confirmed by well-recognise medical associations and regulators during cardiac concern with rosiglitazone. These may explain the rise in pioglitazone initiations and switches from rosiglitazone to pioglitazone. To gain a greater insight into the impact of drug safety warnings on clinical practice, information on the sources of drug safety information among prescribers are needed. How prescribers receive and respond to warnings will help us understand the differences in changes to the pattern of rosiglitazone and pioglitazone. Further study on the sources of drug safety information and prescribers' perspective toward rosiglitazone and pioglitazone will be assessed in chapter 6.

Chapter 5. Impact of drug interaction warnings on concomitant use of proton pump inhibitors and clopidogrel

1. Synopsis

The previous chapter investigated the impact of more conclusive warnings on the adverse events of thiazolidinediones. This chapter examines the complicated and conflicting case of the clopidogrel-PPI interaction for which clinical studies could not provide meaningful outcomes as shown in *in vitro* studies. Despite the warnings issued by the FDA and EMA on the possible cardiovascular events related to concomitant use of clopidogrel and proton pump inhibitors, the TGA took no action toward this interaction. The findings in this study suggested that there was a significant association between the international recommendations and the coprescribing of antisecretory agents among clopidogrel users in the AsteRx database. The recommended PPI—pantoprazole significantly increased following the EMA warning in May 2009. This is likely to be due to an increase in switches from PPIs of concern—omeprazole and esomeprazole to pantoprazole.

2. Overview

Gilard et al. (2006) demonstrated a reduction in measures of platelet aggregation when a PPI was co-administered with clopidogrel (Gilard et al. 2006). Studies investigated PPIs as a group and found a decrease in platelet response and active metabolites of clopidogrel. Subsequently, research studies indicated that the clopidogrel-PPI interaction might not be from the PPI drug class but rather through CYP2C19 enzyme activity, which plays an important role in converting clopidogrel to its pharmacologically active metabolite (Cuisset et al. 2009; Ho et al. 2009). Omeprazole is a potent inhibitor of CYP2C19 therefore it would attenuate the antiplatelet efficacy of clopidogrel. Pantoprazole has less effect on the CYP2C19 metabolic pathway, and therefore might be a better alternative for concomitant use with clopidogrel (Angiolillo et al. 2011). Most of data from pharmacodynamic studies supported this hypothesis; however, clinical trials have presented inconsistent results on cardiovascular outcomes (Kwok et al. 2011; Kwok et al. 2013).

The FDA and EMA issued several announcements on the proposed clopidogrel and PPI interaction with updated contents according to the research findings during 2009–2010.

The announcements and context have been extensively discussed in Chapter 2. A summary in a chronological order is listed below.

Release date: 26 January 2009

- FDA—"*Early Communication about an Ongoing Safety Review of Clopidogrel bisulfate (marketed as Plavix).*" The FDA pointed out its awareness of the clopidogrel-PPI interaction and a review was in progress. In the meantime, the FDA suggested healthcare professionals re-evaluate the necessity of PPI treatment in patients receiving clopidogrel and indicated that there was no evidence of changes in the antiplatelet activity of clopidogrel by H2RAs (FDA 2009).

Release date: 29 May 2009

- EMA—"*Public statement on possible interaction between clopidogrel and proton pump inhibitors.*" The EMA indicated the existent of an interaction and advised against using all members of the PPI class with clopidogrel. The product information for all clopidogrel-containing medicines was updated to discourage concomitant use of PPI with clopidogrel, unless absolutely needed (EMA 2009).

Release date: 17 November 2009

The clopidogrel manufacturer was asked by the FDA to update the safety information label indicating against the concomitant use of CYP2C19 inhibitory medicines (e.g. omeprazole) with clopidogrel (FDA 2009).

- FDA—Public Health Advisory: Updated Safety Information about a drug interaction between clopidogrel bisulfate (marketed as Plavix) and omeprazole (marketed as Prilosec and Prilosec OTC) (FDA 2009). Clopidogrel users were recommended to consult healthcare providers if they are currently taking or considering omeprazole. The update indicated the FDA believed that ranitidine, famotidine, and nizatidine did not interfere with the efficacy of clopidogrel.
- FDA—Information for Healthcare Professionals: Update to the labeling of Clopidogrel Bisulfate (marketed as Plavix) to alert healthcare professionals about a drug interaction with omeprazole (marketed as Prilosec and Prilosec OTC) (FDA 2009). Omeprazole and esomeprazole (a component of omeprazole) as CYP2C19 inhibitors should be avoided in combination with clopidogrel.

- FDA—Follow-up to the January 26, 2009, Early Communication about an Ongoing Safety Review of Clopidogrel Bisulfate (marketed as Plavix) and Omeprazole (marketed as Prilosec and Prilosec OTC) (FDA 2009).

Release date: 17 March 2010

- EMA—Public statement. Interaction between clopidogrel and proton-pump inhibitors. CHMP updates the warning for clopidogrel-containing medicines. The EMA changed from avoiding all PPIs to only omeprazole and esomeprazole in combination with clopidogrel due to the update evidence on CYP2C19 inhibitory activity.

Release date: 27 October 2010

- FDA—"*Reminder to avoid concomitant use of Plavix (clopidogrel) and omeprazole"* The FDA issued a reminder on the clopidogrel and omeprazole interaction. This time they emphasised the less potent CYP2C19 inhibitory effect of pantoprazole and recommended this as an alternative in patients with high risk of GI bleeding (FDA 2010).

In October 2011, the TGA updated the advisory statement 223 "*Ask your doctor or pharmacist before use if you are taking other medicines regularly*." on the label of proton pump inhibitors including omeprazole, pantoprazole, rabeprazole and lansoprazole. The required advisory statements for medicine labels update 6 stated "*TGA considers that it would be misleading if consumers are only warned about this particular interaction and not to other interactions and may assume that they do not need to check if they are not taking Clopidogrel. Therefore the TGA is of the opinion that the advisory statement 223 is sufficient in addressing the issue of all possible interactions between PPIs and Clopidogrel*." (TGA 2011) Therefore, there was no specific warning on the clopidogrel-PPI interaction from the TGA.

Because of the worldwide connection via media and online resources, it is likely that the safety communication released by the FDA and EMA, for two of the highest medicines by cost and number of prescriptions would be seen by Australian prescribers. However, the impact of these communications on prescribing patterns of concomitant use of clopidogrel and PPI were unknown and are difficult to predict due to the uncertainty of clinical evidence and no specific action from the TGA.

3. Chapter aims

This chapter investigates the changes in the coprescribing of antisecretory drugs in patients using clopidogrel in clinical practice after the warnings on the drug-drug interaction between clopidogrel and PPIs.

4. Submitted Manuscript entitled "Pattern of the concomitant use of antisecretory drugs with clopidogrel in Australia including changes after the international clopidogrel-PPI warnings"

The manuscript entitled "Impact of regulatory warnings on the prescribing rosiglitazone and pioglitazone in Australia" is submitted to Pharmacoepidemiology and drug safety, 2014.

The co-authors contributed to the manuscript as follows: PhD candidate, Suvimol Niyomnaitham, designed the study under the supervision of Dr Alesha Smith and Dr Adam La Caze. The PhD candidate performed all data collection and data analysis. Suvimol Niyomnaitham took the lead role in manuscript preparation and writing. All co-authors revised the manuscript for intellectual content and approved the final manuscript.

Pattern of the concomitant use of antisecretory drugs with clopidogrel in Australia including changes after the international clopidogrel-PPI warnings

Suvimol Niyomnaitham[1,2], Adam La Caze[1], Alesha Smith[1,3]

[1]School of Pharmacy, University of Queensland, Australia, [2]Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand, [3]School of Pharmacy, University of Otago, New Zealand

ABSTRACT

Background

Antisecretory agents consisting of proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H2RA) are often coprescribed with clopidogrel to reduce the risk of gastrointestinal bleeding. Several pharmacodynamic studies demonstrated that PPIs, specifically omeprazole and esomeprazole, reduced the efficacy of clopidogrel by inhibiting metabolic enzyme CYP2C19 and suggested pantoprazole and H2RA as alternatives. Due to a lack of consistent cardiovascular outcomes from clinical studies, no definite warning was announced from Australian Therapeutic Goods Administration (TGA). On the other hand, the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) recommended avoiding omeprazole and esomeprazole concomitant with clopidogrel and suggesting pantoprazole and H2RA as an alternative.

Objective

We examined the patterns of coprescribing of antisecretory drugs in patients using clopidogrel. The changes of coprescribing patterns before/after the international warnings on the drug-drug interaction between clopidogrel and PPIs were also investigated.

Methods

The prescribing of antisecretory medicines within 30 days of clopidogrel prescribing was identified during January2006–December2011 in the AsteRx database. AsteRx is a de-identified clinical database that collects data from more than a hundred of primary

practices in Australia. Monthly trends of coprescribing clopidogrel with PPIs and H2RA were examined. The impacts of three safety warnings by the EMA in May 2009 and March 2010 and by the FDA in November 2009 were analysed using the interrupted time-series analysis called autoregressive integrated moving average (ARIMA) model. Number of switches and initiations of coprescribing antisecretory agents with clopidogrel before and after warnings were also investigated.

Results

There were a total of 7,757 coprescriptions of antisecretory agents with clopidogrel during 2006–2011. Approximately 90% of those were the coprescribing of proton pump inhibitors. Esomeprazole was the most frequent PPI to be coprescribed with clopidogrel, followed by pantoprazole and omeprazole. The coprescription of omeprazole with clopidogrel decreased from 2006. No significant change in esomeprazole coprescribing after the regulatory warnings were observed in the ARIMA model. The proportion of pantoprazole coprescribing significantly increased after the EMA warning in May 2009 (p=0.011). There was no significant change in H2RA coprescribing.

After the warning in May 2009, 42% switched from omeprazole to pantoprazole compared to 22% before the warning. There was a significant increase in switches from esomeprazole to pantoprazole after May 2009 (p=0.003). There was a total of 815 antisecretory initiations in clopidogrel users after May 2009 and pantoprazole was the most frequently initiated antisecretory agent in patients taking clopidogrel (35.09%), compared to 24.95% before the warning in May 2009.

Conclusions

It appears that after the warnings on clopidogrel-PPI interaction, esomeprazole was continually the most coprescribed antisecretory drug with clopidogrel. However, pantoprazole coprescribing significantly increased after the safety warnings in 2009. This increasing trend could be explained by the switches from omeprazole and esomeprazole to pantoprazole, the suggested alternative PPI.

Introduction

Clopidogrel and proton pump inhibitors (PPIs) have been in the top 5 list of high-cost drugs on the Australia Pharmaceutical Benefits Scheme (PBS), a national subsidised formulary

(PBS 2010) for the past decade. PPIs and histamine 2 receptor antagonists (H2RAs) are antisecretory agents that are often prescribed prophylactically to prevent gastrointestinal complications in patients taking clopidogrel (Lev et al. 2007; Schafer et al. 2010). *In vitro* studies demonstrated that PPIs attenuate the antiplatelet efficacy of clopidogrel and provide evidence that CYP2C19 enzyme activity might contribute to this clopidogrel-PPI interaction (Gilard et al. 2008; Cuisset et al. 2009). A potent CYP2C19 inhibitor such as omeprazole and its S-isomer, esomeprazole may interfere with the effectiveness of clopidogrel in preventing cardiovascular events but not pantoprazole, as pantoprazole has less effect on CYP2C19. However, the clinical relevance of this interaction remains unclear, and clinical trials have not provided consistent evidence in relation to the effect of PPI-clopidogrel coprescription on cardiovascular outcomes (Bhatt et al. 2010; Kwok et al. 2013).

Regulatory authorities are responsible for ensuring the safety and efficacy of marketed medicines by taking prompt action towards any emerging risks. The degree of regulatory response depends on evidence and severity of the risk whether it be a market withdrawal or updated safety information. Additionally, a regulatory warning containing safety information and recommendations will be issued to healthcare providers. In Australia, the Therapeutic Goods Administration (TGA) assesses the risk of marketing drugs and updates to their product information. The TGA informs healthcare professionals through an 'Alert' on the TGA website or subscribed email. The 'Medical safety update' is published every two months on the TGA website and in the *Australian Prescriber*. The effectiveness of the safety warning process in Australia has been under question and led to the public recommendation for regulatory reforms such as more transparency and improving communication (TGA 2011).

In Europe, the European Medicines Agency (EMA) collaborates with a network of expertise across the European Union to evaluate and take timely action to the possible hazard of medical products. 'Public statement' and 'Press Release' containing safety warnings are publicly announced (EMA). Similarly, the United States Food and Drug Administration (FDA) works closely with manufactures to analyse the risks of concerned drugs. A safety communication is issued by the FDA to alert healthcare professionals to a new risk and also includes a recommendation on related treatment (FDA).

Given global access to medicines and the importance of timely communication on new safety concerns, drug safety regulation has an international focus. Medicine use in Australia is influenced not only by the local drug authority, but also key international drug regulatory bodies such as the FDA and EMA. The EMA released its first warning in May 2009 and recommending against the combination of all PPIs with clopidogrel. Later in March 2010, the recommendation was changed to avoid only omeprazole and esomeprazole in patients taking clopidogrel (EMA 2010). In November 2009, the FDA updated the label for clopidogrel recommending to avoid using clopidogrel with omeprazole and esomeprazole (FDA 2009). Both the FDA and EMA emphasised that there was no sufficient evidence on other PPIs and most H2RAs (ranitidine, famotidine, nizatidine) on the anti-clotting function of clopidogrel. On the other hand, in Australia, the TGA refrained from the safety labelling change or the safety communication on the clopidogrel-PPI interaction.

The impacts of warnings issued by the EMA and FDA on patterns of drug use have been examined in several studies (Dorsey et al. 2010; Dusetzina et al. 2012; Ruiter et al. 2012). The observed prescribing trends do not always follow the recommendation but depend on many factors such as the certainty of evidence and tendency to prescribe highly advertised drugs (Dusetzina et al. 2012). Studies in the UK show a significant increase in the omeprazole substitution rate with another PPIs (except esomeprazole), or a H2RA after their warning came out (Thomas et al. 2013). Previous studies have shown the influences of the major international warnings on the changes of local drug trends (Leal et al. 2013; Kashour et al. 2014; Niyomnaitham et al. 2014). Although there is no local regulatory warning on the concomitant use of clopidogrel and PPI, it is thought that Australian prescribers might be aware of the warnings from the FDA and EMA. This study investigated the patterns of coprescribing antisecretory agents with clopidogrel and changes following the warnings issued by the FDA and EMA.

Methods

Data collection

1. Coprescribing antisecretory agents with clopidogrel

All prescriptions of clopidogrel, PPIs, and H2RA from January 2005–December 2011 were identified from the AsteRx database. AsteRx has collected medical data from >100 primary

practices located all over Australia since 2003. There are a total of seven million prescriptions from half a million patients recorded in a de-identified manner. Details of prescriptions include prescribing date, chemical name, strength, quantity, and drug codes. Drugs of interests were extracted using a combination of chemical name, the WHO Anatomical Therapeutic Chemical Classification (ATC) system, and Australian Pharmaceutical Benefits Scheme (PBS) item codes for the completeness of data capture. The PBS codes are used for dispensing purposes from the government reimbursement formulary. Other information such as diagnoses, consultations, laboratory results are recorded in plain text.

Omeprazole, esomeprazole, rabeprazole, lansoprazole, and pantoprazole were the PPIs included in the analyses. Ranitidine, famotidine, and nizatidine were grouped into H2RAs in this study. The coprescribing of PPIs and H2RAs with clopidogrel was defined as PPIs and H2RAs prescribed within 30 days before and after a clopidogrel prescription.

2. Switches and initiations of coprescribed antisecretory agents

Switches were counted every time that the coprescribed antisecretory agent with clopidogrel was not the same as the previous agent within individual patients. In this study, the number of switches from omeprazole to another PPI or an H2RA and number of switches from esomeprazole to another PPI or an H2RA were examined.

Initiations were identified when an antisecretory agent was first coprescribed with clopidogrel in patients who did not have any previous record of a coprescribed antisecretory agent during the study period.

Analyses

1. Impacts of warnings on coprescribing trends

The percentages of the monthly coprescribing of each PPI and H2RA were calculated thorough the study period. Monthly data on the coprescribing of PPIs and H2RA with clopidogrel were depicted and fitted into the time series analysis called auto-regressive, integrated, moving average (ARIMA) model. The impacts of the warnings from the EMA and FDA on coprescribing trends were analysed using the ARIMA model. Three safety warnings—the first warning by the EMA in May 2009 (EMA1), the second warning by the EMA in March 2010 (EMA2), and the warning by the FDA in November 2009—were

investigated as interventions in the ARIMA model. The ARIMA model has been used to investigate the trend of time-series data and the impact of health care interventions on trends of drug use (Ferrand et al. 2011; Langley et al. 2011; Ruiter et al. 2012). The ARIMA (*p,d,q*) model is an applied time-series model developed by Box-Jenkins (Box 1976; Griffiths et al. 2000) to forecast future observations that occur at equal time intervals and determine the effect of an intervention in time series data. Firstly, the integration process is differenced (*d*) to make stationary data. Dickey-Fuller test was also used to confirm the stationary data (Dickey 1979). Autoregressive model of order *p* explains the accumulated effect of the preceding data and moving average model of order *q* indicates the most recent random shock carries over from one period to the next. The appropriate model (*p, q*) is obtained from the visibility to the plots of autocorrelation functions (ACF) and partial autocorrelation functions (PACF) of time-series values (McDowall 1980). The best fitted model for analysis was also examined using the Bayesian Information Criteria (Schwarz 1978). An abrupt and permanent effect from the warnings by the EMA and FDA on subsequent prescribing trends was assumed and represented by coefficient (ω) (McDowall 1980; Griffiths et al. 2000).

2. Switches and initiations before and after the warnings

The rate of switching from omeprazole/esomeprazole to another antisecretory agent before and after the warning in May 2009 was analysed using Poisson regression (Cameron et al. 2013). The rates of each antisecretory initiation before and after the warning in May 2009 were also investigated using the same statistical analysis. STATA 12.1 (StataCorp, College Station, TX) was used to perform all statistical analyses with a 5% significance level.

Results

Out of 8,100 patients who were prescribed clopidogrel, 3,499 patients (43% of clopidogrel users) were coprescribed at least one antisecretory drug between January 2006 and December 2011. A total of 7,757 coprescriptions of antisecretory agents were included in the analyses. Figure 7 displays the percentage that each PPI and H2RA contributes to the total co-prescriptions in each month. Esomeprazole was the most frequent antisecretory coprescribed with clopidogrel, followed by pantoprazole, omeprazole, rabeprazole, H2RAs, and lansoprazole, respectively during the study period. Omeprazole

coprescriptions continuously decreased from 2006 until the end of study period. H2RA coprescriptions were approximately less than 10% of all antisecretory coprescriptions. The dashed lines in Figure 10 represent the months of warnings that were investigated as interventions in the ARIMA model.

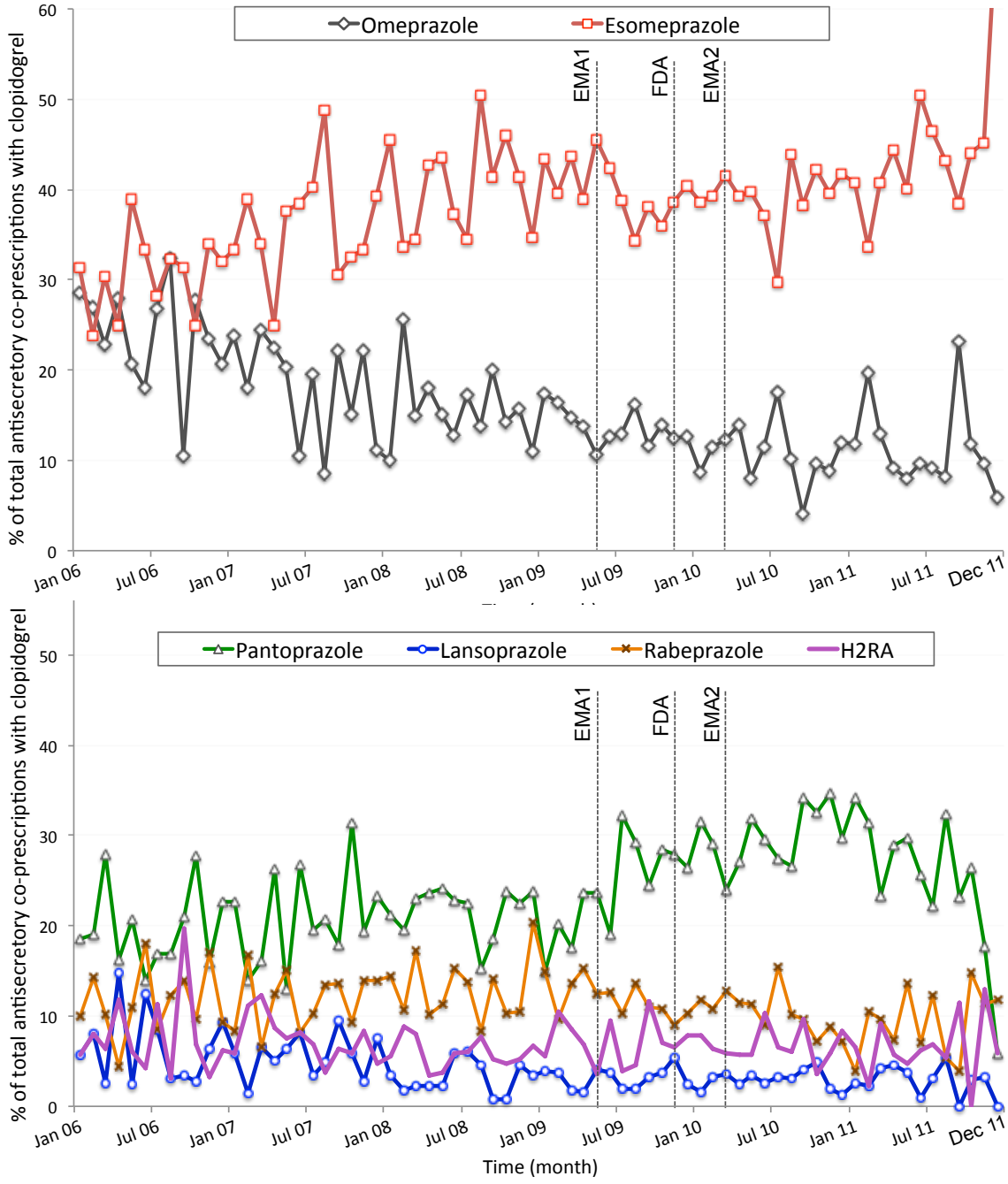


Figure 10. Percentage of each coprescribed antisecretory drug with clopidogrel in the AsteRx database from January 2006–December 2011.

Dashed lines indicate the warnings issued by regulatory authorities. H2RA: histamine 2 receptor antagonist, EMA1: First warning by the European Medicines Agency, EMA2: Second warning by the European Medicines Agency, FDA: Food and Drug Administration

There were no seasonal autocorrelation detected for the patterns of coprescribing antisecretory agents with clopidogrel in the AsteRx database. All prescribing data are stationary from the Dickey-fuller test. The visual observation of PACF and ACF plots suggested an ARIMA (1,0,1) model to best characterise all coprescribing data.

Table 12 describes the coefficients and significant changes (p-value) of the subsequent trends of omeprazole, esomeprazole, pantoprazole and H2RAs in the ARIMA model. The increased trend of pantoprazole coprescribing was significantly associated with the first warning by the EMA (EMA1), the FDA warning, and the second warning by the EMA (EMA2). After adjustment for the previous warnings, the increased trend of pantoprazole coprescribing was not significantly associated with the FDA warning (adjusted coefficient 2.840, 95%CI [-2.70,8.38], p=0.315) nor with the EMA2 (adjusted coefficient 1.657, 95%CI [-1.58,4.89], p=0.315). A continuing decrease in the trend of omeprazole coprescribing was observed; however, no significant change was associated with the EMA1 or FDA after fitting into the ARIMA model. Only the more specific EMA warning on avoiding omeprazole and esomeprazole in March 2010 (EMA2) was significantly associated with a decline in omeprazole coprescribing (p<0.0001). There was no significant change in esomeprazole coprescribing after the warnings; moreover, esomeprazole was the antisecretory drug which had the highest proportion of coprescribing with clopidogrel after the warnings. EMA2 coincided with a significant decline in the trend of coprescribing H2RAs. No significant associations between warnings and the coprescribing of lansoprazole or rabeprazole were observed in the ARIMA model.

Table 12. Impacts of authority warnings on the trends of coprescribing antisecretory drugs with clopidogrel in ARIMA models

Warnings by authorities	Month-year	Adjusted for	Coefficient[a] (ω)	95%CI[b]	p-value[c]
Omeprazole *ARIMA(1,0,1)*					
EMA1	May 2009	-	0.460	[-5.42, 6.34]	0.878
FDA	Nov 2009	-	-1.208	[-3.41, 0.99]	0.282
EMA2	Mar 2010	-	-3.104	[-4.75, -1.46]	**<0.0001**
		EMA1, FDA	-2.948	[-4.64, -1.25]	**0.001**

Esomeprazole *ARIMA(1,0,1)*					
EMA1	May 2009	-	0.594	[-6.88, 8.07]	0.594
FDA	Nov 2009	-	1.680	[-5.85, 9.21]	0.662
EMA2	Mar 2010	-	-1.391	[-8.63, 5.85]	0.707
		EMA1, FDA	-1.652	[-8.68, 5.38]	0.645
Pantoprazole *ARIMA(1,0,1)*					
EMA1	May 2009	-	2.769	[0.64, 4.89]	**0.011**
FDA	Nov 2009	-	3.153	[0.51, 5.80]	**0.019**
		EMA1	2.840	[-2.70, 8.38]	0.315
EMA2	Mar 2010	-	3.030	[0.372, 5.69]	**0.025**
		EMA1, FDA	1.657	[-1.58, 4.89]	0.315
H2RA *ARIMA(1,0,1)*					
EMA1	May 2009	-	-1.053	[-11.07, 8.96]	0.837
FDA	Nov 2009	-	-1.441	[-7.04, 4.16]	0.614
EMA2	Mar 2010	-	-3.223	[-5.34, -1.11]	**0.003**
		EMA1, FDA	-3.030	[-7.78, 1.72]	0.211

[a]Coefficient **(ω):** Coefficients were changes in magnitude and direction after the intervention, [b]CI: confidence interval, [c]Statistical significance at *p* value <0.05 is presented in bold., H2RA: histamine 2 receptor antagonist, EMA1: First warning by the European Medicines Agency, EMA2: Second warning by the European Medicines Agency, FDA: Food and Drug Administration

The number of switches from omeprazole and esomeprazole coprescriptions to other antisecretory agents before and after the warning in May 2009 are displayed in Table 13 and 11, respectively. Out of 141 switches from coprescribed omeprazole before the warning, 24.82% switched to pantoprazole. There was a significant increase in the rate of switches from omeprazole to pantoprazole after the warning with an incidence rate ratio (IRR) of 1.708 (95%CI [1.08,2.70], p=0.022). Although there was an observed decline in switching from omeprazole to esomeprazole from 44% to 34% after the warning, there was no statistical significance suggested by the Poisson regression (p=0.226).

Table 13. Number of switched coprescriptions from omeprazole to other antisecretory drugs

Warning Period	Esomeprazole	Pantoprazole	Lansoprazole	Rabeprazole	H2RA	Total switches
Before (Jan06–May09)	62 (43.97%)	35 (24.82%)	4 (2.84%)	25 (17.73%)	15 (10.64%)	141
After (Jun09–Dec11)	31 (33.69%)	39 (42.39%)	0	11 (11.96%)	11 (11.96%)	92
IRR, 95%CI p-value	0.766, [0.50,1.18] p=0.226	**1.708, [1.08,2.70]** **p=0.022**	7.588, [0,∞] p=0.994	0.674, [0.33,1.37] p=0.276	1.124, [0.52,2.45] p=0.769	

IRR: Incidence rate ratio, CI: confidence interval, Statistical significance at p-value<0.05 is presented in bold, H2RA: histamine 2 receptor antagonist

An increase in switching from esomeprazole to pantoprazole was shown from 41% before the warning to 53% but this increase was not significant in the Poisson regression. A significant decline in the rate of switching from esomeprazole to omeprazole was detected after the warning with an IRR of 0.454 (p=0.012). There were no significant changes in the rates of switching to lansoprazole, rabeprazole, and H2RA between periods before and after May 2009 (Table 14).

Table 14. Number of switched coprescriptions from esomeprazole to other antisecretory drugs

Warning Period	Omeprazole	Pantoprazole	Lansoprazole	Rabeprazole	H2RA	Total switches
Before (Jan06–May09)	25 (17.24%)	59 (40.69%)	3 (2.07%)	18 (12.41%)	40 (27.59%)	145
After (Jun09–Dec11)	17 (7.86%)	116 (53.46%)	8 (3.69%)	25 (11.52%)	51 (23.51%)	217
IRR, 95%CI p-value	**0.454, [0.24,0.84]** **p=0.012**	1.314, [0.96,1.79] p=0.088	1.782, [0.47,6.72] p=0.394	0.928, [0.51,1.70] p=0.809	0.852, [0.52,2.45] p=0.448	

IRR: Incidence rate ratio, CI: confidence interval, Statistical significance at p-value <0.05 is presented in bold, H2RA: histamine 2 receptor antagonist

For the initiations, esomeprazole was the most commonly initiated antisecretory agent in patients taking clopidogrel with 32.04% of total initiations before the warning. After May 2009, pantoprazole became the most initiated antisecretory medicine at 35.09%, compared to 24.95% before the warning (Table 15). After the warning in May 2009, a significant increase in the rate of pantoprazole initiations was suggested with an IRR of

1.419 (p<0.0001). Whereas there were significant decreases in the rates of omeprazole, lansoprazole and rabeprazole initiations after this warning (p=0.001, p=0.049, and p=0.009, respectively).

Table 15. Number of coprescribed antisecretory initiations before and after the warning in May 2009

Warning Period	Omeprazole	Esomeprazole	Pantoprazole	Lansoprazole	Rabeprazole	H2RA	Total initiations
Before (Jan06–May09)	200 (18.52%)	346 (32.04%)	268 (24.95%)	44 (4.07%)	157 (14.54%)	65 (5.02%)	1080
After (Jun09–Dec11)	102 (12.52%)	267 (32.76%)	286 (35.09%)	20 (2.45%)	83 (10.18%)	57 (6.99%)	815
IRR 95%CI p-value	**0.676, [0.53,0.86] p=0.001**	1.023, [0.87,1.20] p=0.784	**1.419, [1.20,1.68] p<0.0001**	**0.589, [0.35,0.99] p=0.049**	**0.701, [0.54,0.91] p=0.009**	1.162, [0.81,1.66] p 0.408	

IRR: Incidence rate ratio, CI: confidence interval, Statistical significance at p-value<0.05 is presented in bold., H2RA: histamine 2 receptor antagonist

Discussion

Esomeprazole was the leading antisecretory drug coprescribed with clopidogrel throughout the study period. Although the regulatory warnings and publications suggested the same possible CYP2C19 inhibitory effect of esomeprazole on the antiplatelet activity of clopidogrel as of omeprazole, they had no impact on the trend of coprescribing esomeprazole. There are several influential factors on prescribing decisions. Esomeprazole was the highest PPI used in Australia due to the influence of new drug marketing strategies. Studies show that medical research, training activities or conferences endorsed by pharmaceutical companies may lead to an associated subconscious bias in decision-making process by attending clinicians (Jones et al. 2001; Hansen et al. 2005; Fugh-Berman et al. 2006; Brody 2009; Sah et al. 2013). Advertising and sale representatives were also influential on the switching within drug class (Hansen et al. 2005) and prescribing decisions (Vancelik et al. 2007). A previous study shows that omeprazole use has decreased once it was no longer under patent with far less marketing activities (Hollingworth et al. 2010). For coprescribing omeprazole, a decreased trend was

observed during the study period. Our analysis found that the significant decline in the coprescribing of omeprazole was concurrent with the specific warning on avoiding omeprazole and esomeprazole issued by the EMA in March 2010. Table 13 and 14 show that the switching between omeprazole and esomeprazole occurred less after the warning while switching from omeprazole and esomeprazole to another PPI was more frequent. These changes were similar to the rates of switching to an alternative PPI in European studies (Sanchez Ruiz-Gordoa et al. 2011; Thomas et al. 2013). However, there was no significant change to the coprescribing of H2RAs compatible with the recommendations issued by regulatory bodies. Moreover, coprescribing of H2RAs decreased following these warnings.

Results from the ARIMA model demonstrated that a significant increase was observed in the trend of coprescribed pantoprazole following the release of the first warning on the clopidogrel-PPI interaction by the EMA in patients taking clopidogrel. During the May 2009 warning, published evidence on the potential interaction of clopidogrel and omeprazole/CYP2C19 inhibitors suggested that pantoprazole had less of an effect on clopidogrel's antiplatelet function (Gilard et al. 2008; Sibbing et al. 2009; Siller-Matula et al. 2009). Prescribers may have been triggered by the EMA warning in May 2009 and changed their practice to coprescribe pantoprazole in patients who needed a PPI. In later announcements by the FDA in November 2009 and the EMA in March 2010, pantoprazole was specified as an alternative PPI to omeprazole and esomeprazole therefore the trend in coprescribing pantoprazole continuously increased following these warnings. Physicians seemed to switch from omeprazole and esomeprazole to pantoprazole after the warning in May 2009. These may explain why a subsequent increase in the trend of coprescribing pantoprazole was shown.

Although a clinically meaningful impact of the clopidogrel-PPI interaction on cardiovascular outcomes has not been established, the evidence of in vitro studies suggested an impaired effectiveness of antiplatelet activity of clopidogrel. The FDA and EMA had updated labelling for PPIs and clopidogrel and issued several warnings including a reminder on the interaction between omeprazole and clopidogrel by the FDA in October 2010. However, the TGA has not issued any recommendations on prescribing these drugs. Presumably the thresholds of changing the label or issuing a warning are different between the TGA and these two international authorities as shown in less frequent warnings on other adverse events (Buckley et al. 2011; Alves et al. 2014). The TGA may consider this interaction has

insufficient supporting evidence and decided that it is not significant enough to inform the public. Despite the absence of TGA's warning, our results implied that prescribers changed their coprescribing of PPI and clopidogrel after the warnings released by key international authorities. A proportion of Australian prescribers may be aware of this interaction but not sure how to apply it to their practice.

Part of the TGA's responsibility includes ensuring the safe use of medicines and communicating emerging risks to health care providers and patients. The importance of efficient drug safety communication was highlighted in recent literature (Dusetzina et al. 2012; Edwards et al. 2012). This communication should provide evidence supporting the risk and the clinical implication appropriate for safe medical treatment. However, practitioners' compliance with regulatory warnings has not always successfully been achieved (Yu et al. 2010). Rather, it depends on several components. Firstly, the existence of the evidence is important on the potential impact on prescribers' decision. The clinical relevance of the clopidogrel-PPI interaction remains unclear therefore it appears that the impact of EMA and FDA warnings has not affected the prescribing of esomeprazole and H2RAs in Australia. The content of warnings must be summarised and focused directly on the risk and management, including alternative treatment options to receive a targeted and widespread response (Dusetzina et al. 2012). The EMA and FDA warnings did suggest pantoprazole and H2RAs as alternative treatment if an antisecretory drug is necessary in patients taking clopidogrel. The FDA's strategy in reinforcing their risk communications over time through a reminder seems to increase the uptake and adherence to the recommendation (Dusetzina et al. 2012). Lastly, the recommendations need to be distributed and promoted through other prescribing support systems. For example, the National Prescribing Service (NPS) MedicineWise and Medicare locals in Australia can help distribute the safety communication and provide educational programs to health professionals in their network.

Limitations

The time-series analysis ARIMA model incorporates the past values and directions over a period of time to better describe the trend of data and investigates the impact of the intervention on this trend (Piening et al. 2012). However confounding effects on data were assumed to be similar both before and after the intervention periods.

Since the information regarding this interaction was updated multiple times and different sources provided conflicting data, it is impossible to know what specific sources of information prescribers were relying on to make their decisions. This research is not able to disentangle the impact of research publications from warnings or between different warnings on prescribing decisions.

The trends of prescribing data in the AsteRx database has been shown to be similar to the national dispensing trends in previous studies (Niyomnaitham et al. 2014). There were no changes in drug listings or major prescribing criteria that we are aware of during the study period. The diagnoses in the AsteRx were recorded as free text therefore it was difficult to fully examine the clinical reason for switching to another PPI or H2RA. Therefore factors that influenced prescribing changes of PPIs and clopidogrel in Australia would need a further investigation.

Conclusions

Results from this study show that international warnings are associated with the changes in the coprescribing of PPIs with clopidogrel in Australian practices. Although there was no significant change in esomeprazole, a significant increase in pantoprazole and a decline in omeprazole were consistent with the recommendations from the FDA and EMA. As there was a lack of information from the TGA and conflicting clinical evidence on the clopidogrel-PPI interaction, prescribers may have difficulties in managing patients with an indication for clopidogrel and a PPI. An effective system to communicate risk and safety of drug needs to be established in order to ensure public safety and help practitioners translate the information into their practice.

AUTHORS' CONTRIBUTIONS

SN, AC, and AS were responsible for developing the study and method. SN performed the data collection, statistical analysis and result interpretation. All authors contributed to manuscript writing and all revisions of the manuscript. All authors read and approved the final manuscript.

5. Chapter conclusion

A common combination of proton pump inhibitors and clopidogrel led to the drug-drug interaction in which CYP2C19 inhibitory effects of PPIs may attenuate the effectiveness in preventing the cardiovascular event of clopidogrel. Due to conflicting outcomes from clinical studies, the TGA refrained from any specific warning on the clopidogrel-PPI interaction. The key international regulatory agencies such as the FDA and EMA issued warnings on concomitant use of clopidogrel and potential CYP2C19 inhibitors, omeprazole and esomeprazole. With supporting information from literature and experts' opinion in cardiology and gastroenterology, the FDA and EMA suggested pantoprazole as an alternative PPI for patients taking clopidogrel.

Results from this chapter show the changes in the coprescribing of antisecretory agents with clopidogrel in Australian practice even though there was no specific warning from the TGA. A significant increase in pantoprazole and a decline in omeprazole corresponded to the warnings issued by international authorities whereas there was no change to prescribing esomeprazole among clopidogrel users. It is difficult to determine whether these significant changes in Australian practice were influenced by the international warnings or the literature. Moreover, the continuation of esomeprazole in combination with clopidogrel may be due to the lack of a local warning of regarding the interaction.

In the next chapter we will gain further qualitative data to complement the prescribing data presented in this chapter. We assessed prescribers' perception of the interaction between clopidogrel and PPIs. Sources of information on this interaction and their influence on prescribing decision were also examined among Australian prescribers.

Chapter 6. Prescribers' perspective on drug safety warning

1. Synopsis

In chapters 3–5, quantitative analyses were undertaken on the impact of drug safety warnings on patterns of drug use in Australia. The combined qualitative and quantitative methods in this chapter examines prescribers' perspective on current drug authority warnings and their impact on practice using two case studies of thiazolidinediones and clopidogrel-PPI interaction. Findings were obtained from interviews and an electronic survey of general practitioners (GPs) in Australia. The findings suggest that direct communication with GPs has not been achieved through regulatory communication. Although the majority of respondents were aware of cardiovascular events related to rosiglitazone, there was low awareness of the risk of bladder cancer associated with pioglitazone. Despite no communication on the possible risk of proton pump inhibitors (PPIs) on the antiplatelet effect of clopidogrel by the Australian authority, half of the respondents knew about this interaction and of those 69% changed their prescribing. Results from this chapter help to explain the small changes in pioglitazone use and the coprescribing of PPIs with clopidogrel from the previous studies. Going forward, the TGA may need to review their actions on new safety information and whether a prescribing decision needs to be changed to ensure the safety use of medicines. Cooperation with risk communication experts may improve the communication with health professionals and meet their expectation to be a reliable source of information for clinical practice (Lofstedt 2010).

2. Introduction

Unexpected adverse effects of marketed drugs, for example, the increasing number of heart attacks and stroke events related to rofecoxib treatment since the first spontaneous report, require a prompt response from all parties to prevent further public harm (Strom 2006). Previous studies show that an effective system of safety communication has positive impacts on health outcomes such as fewer adverse events (Lofstedt 2005; Lofstedt 2008). Social mechanisms that involve many influential stakeholders including pharmaceutical industry, government agencies, academia, and the media may affect perceptions, acceptance and eventually decisions regarding a response to emerging risk

(Fischhoff 2009). Actions of these stakeholders can amplify or attenuate the risk and explain why certain risks have received more attention than others (Poortinga et al. 2003).

As discussed in previous chapters, the Therapeutic Goods Administration (TGA) is a regulatory authority in Australia responsible for evaluating the risks and benefits of medical products (TGA 2014). Briefly, the TGA plays an important role in requesting updated product information and releasing safety communication of marketed products. These communications contain new safety information and recommendations for using the concerned drugs. The main TGA communications are 'Alerts' published on the TGA' website, 'TGA-SAFETYINFO' email subscription, and 'Medicine Safety Update' articles published every two months on the TGA's website and Australian Prescriber (TGA).

Besides the safety warning from the TGA, other medical organizations are also involved in distributing safety information and promoting efficient drug use. The National Prescribing Service (NPS) provides up-to-date drug information through NPS MedicineWise in the Australian Prescriber (NPS 2014). Medical associations such as the Royal Australian College of General Practitioners, the Heart Foundation and the Endocrine Society of Australia also provide updated safety information according to the drug of interest. Other available sources of drug safety information are the Australian Medicines Handbook, Therapeutic Guidelines, and MIMS (monthly index of medical specialties). Previous research indicated changes in the use of medicines in Australia to be associated with the warnings issued by key international regulators such as the FDA and EMA (Niyomnaitham et al. 2014).

In the past few years, the TGA's regulatory roles have been reviewed and recommended for reform. The reform issues include improving the understanding of the TGA's role as a regulator, improving the public's confidence in regulatory decisions, and providing increased access to information used to evaluate medical products. The public have also called for further transparency around risk communication, specifically, strategies to promote and distribute safety information to healthcare providers and consumers as well as mechanisms for improving timely communication of alerts and recalls (TGA 2011).

Understanding how prescribers perceive and act on current drug safety warnings is valuable in planning for improved drug safety communication. Whilst aggregated prescribing data allows an investigation into the association between warnings and

patterns of drug use, influences from other confounders cannot be distinguished (Chapters 3–5). There is limited work on how Australian prescribers obtain safety information. The qualitative study in this chapter assessed the sources of drug safety information among prescribers and the level of awareness regarding emerging risks. Prescribers characteristics such as specialties, years of experience, or practice settings were also examined since they had been associated with the response to the warnings in previous research (Wagner et al. 2006; Piening et al. 2012; Sanderson et al. 2013).

Two recent drug safety warnings on the adverse events of thiazolidinediones and the drug interaction between clopidogrel and proton pump inhibitors (as presented in Chapter 2) are used as case studies to assess the impact of different contexts of warnings and certainty of risks on clinical decisions.

Interview and survey methods are used to acquire Australian prescribers' perception of current drug warnings and their opinions towards two recent warnings.

3. Aims

This study aims to ascertain Australian prescribers' perspective regarding drug safety warnings. The specific objectives are:

- To determine sources of drug safety information among general practitioners
- To obtain participants' opinions on local drug safety warnings
- To examine the awareness and response towards two recent drug warnings
- To identify the impact of regulatory warnings and other factors on prescribing decisions using two recent drug warnings

4. Methods

The study was approved by the School of Pharmacy Ethics Committee, the University of Queensland in accordance with the National Health and Medical Research Council's guidelines, approval number 2013/16 and 2013/17 (Appendix 2, 3).

Study design

Firstly, semi-structured interviews to elicit prescribers' views regarding drug safety warnings were conducted. The data gathered from these interviews were then used to develop an online survey. The online survey was piloted with health professionals before the main data collection phase.

4.1.1 Semi-structured interview

The primary aim of the semi-structured interviews was to gather interviewees' opinions and experience regarding the current safety warnings and two case studies and inform the development of a survey. We conducted semi-structured interviews with a convenient sample of general practitioners (GPs), cardiologists, and drug regulatory personnel. Informed consent was obtained from all participants (Appendix 4). The interviews were undertaken by a single researcher (SN) for consistency until theme saturation was reached.

TGA

The interviewee participated in a telephone interview and was asked about the TGA's roles and actions in response to emerging safety issues and differences from other international drug authorities. The strategies regarding the distribution of safety communication to target audiences and the measurements used for evaluating the effectiveness of the TGA's warnings were also included in the interview questions (Appendix 5).

Physicians

Face-to-face interviews with GPs and specialists contained two sections, both with open-ended questions (Appendix 6). Section one, elicited participants' opinion on the drug warning system in Australia, sources of drug safety information, and the influence of each source of information on their practice.

The questions on participants' knowledge of two recent safety issues and recommendations regarding the use of concerned drugs were included in section two. In the case where the interviewees knew about these safety issues, they were asked to explain how these warnings affected their prescribing decision.

Recruitment for the interview

An invitation email was sent to TGA officers who were involved in the safety regulation of marketed drugs for an interview. A convenience sample of ten practitioners working in Brisbane were recruited to take part in a face-to-face interview with the researcher at their workplace over a 2-month period during October–November 2013. The practice managers of the practice sites were contacted to distribute an email inviting practitioners to participant in the interview.

The interviews took approximately 20–30 minutes. Permission to record the interview using a voice recorder for transcribing later was obtained prior to the interview. The transcripts were labelled with a specific identification code and no identifying information was collected.

The principle investigator undertook a basic thematic analysis of results from the interviews. The data collected from these interviews were used to construct an online survey to elicit GP's perceptions of drug safety warnings. The data gathered from the TGA interview and section one of the prescribers interview were used to construct the selection/answer choices of drug safety information and dissemination methods of the TGA's safety communication in the main survey. Information acquired from section two of the prescribers interview was used to develop answer choices for each case study. For example, the treatment options after the safety concern of the clopidogrel-PPI interaction was released and the prescribing decisions in response to the adverse cardiovascular events of rosiglitazone.

4.1.2 Online survey

Before the survey was distributed to the larger group of participants, it was piloted on GPs (approximately 10 in total). Recruitment was done during December 2013–January 2014. A survey feedback section was included to ensure ease of completion and understanding. The survey was then modified to improve the robustness and feasibility for this study according to the feedback from the pilot study. The final survey was made available online through a web-based survey provider, Survey Monkey (SurveyMonkey® 2014).

The survey included multiple-choice questions and was estimated to take 10–15min to complete. The survey was divided into 5 parts. Part one elicited demographic information: years of practicing medicine, medical specialty, and practice settings. Part two was designed to assess sources of drug safety information and opinions of the TGA's safety

communication. Part three to five contained questions on the awareness and prescribing responses to the clopidogrel-PPI interaction, the cardiac events of rosiglitazone, and the bladder cancer risk of pioglitazone, respectively (Appendix 7).

Recruitment of GPs for the online survey

Each email and advertisement was sent between February–August 2014 contained participant information and a link to the survey on SurveyMonkey. The consent form on the first page of the survey included a data confidentiality statement, procedure and contact details. Participation in this study was voluntary. All data were collected and stored anonymously and confidentially.

The response rates from previous studies varied from 4% to 60% among GPs (or family physicians) (Watkins et al. 2003; Krantz et al. 2007; Berg et al. 2008; Karpel et al. 2009). A recent survey study has a response rate of 16.1% with GPs in NSW (Garg et al. 2014).

A number of strategies were employed to recruit GPs. General practitioners were recruited through two Medicare Locals: Metro North Brisbane and Greater Metro South Brisbane, which includes 1,112 and 954 general practitioners, respectively (PHIDU 2014). Both Medicare Locals advertised the survey through their upcoming Newsletter. Following poor recruitment, a further two Medical Locals were enlisted to advertise the survey to their members (Townsville-Mackay and West Moreton-Oxley). Medicare Locals who agreed to participate were asked to advertise the survey in their newsletters and repeat in their following issues until the survey closed in August 2014. An example of the survey advertisement placed in the Medicare Local newsletter is shown in Appendix 8. A number of practices around Brisbane were also invited via phone calls or a visit by the researchers at practice sites.

Analysis plan

Results were collected and reported in an aggregated form to evaluate overall practitioner perception towards drug safety warnings. Data were analysed using statistical software STATA 12 (Statacorp, College Station, TX). Descriptive analyses were used. Chi-square tests and Fisher's test were used to assess the associations between baseline characteristics and a binary variable.

5. Results

Interviews

Of the ten invites, six face-to-face interviews were completed (response rate, 60%). The interviewees comprised of two specialists, three GPs, and one TGA officer (job title not released to protect confidentiality). Both specialists were aware of international warnings from the case studies because they subscribed to email lists from an international medical association (e.g. American Heart Association) and Medscape (Medical News), which always include new warnings from the FDA. Five interviewees did not receive direct information from the TGA either by using the TGA's website or subscribing to TGA emails. Two GPs interviewed typically heard about the TGA's warnings from reading the Australian Prescriber (paper version) and the NPS MedicineWise website. Hospital or medical practices of the interview participants did not have any internal drug safety communication system in place.

The TGA officer believed that the regulatory process of the TGA and its regulatory actions were not different from other international regulatory bodies. The TGA's decision may be influenced by the key international regulators' opinions and vice versa. The TGA officer also confirmed that the TGA does not conduct new research regarding a new risk nor does it investigate the effectiveness of drug safety warnings and their impact on changes to prescribing. It was noted that the TGA is obligated to notify consumers and practitioners on the safety of products and tries to cooperate with the NPS, medical societies, and Medicare locals to distribute safety information. The TGA considers these dissemination methods to be more widespread compared with the TGA's website or email.

Web-based Survey

Demographics of participants

Thirty GPs completed the survey during the study period. 43.3% (13/30) were experienced GPs who had been practicing for more than 20 years, 20% 15–19 years, 3.3% (1/30) 10–14 year, and 33.3% less than 10 years of experience. 67% practiced in a private hospital/clinic, 30% in community medical centre, and 13% public hospital.

Drug safety warnings

Using the list compiled from the interviews, participants were asked to rank the sources of drug safety information they used for the drug safety warnings. Ten GPs (33%) ranked the TGA as the first source of drug safety warnings, followed by the NPS MedicineWise and the Australian Prescriber (Figure 11). Medical Association and medical research publications were ranked as number four and five, respectively. Other sources of drug information that participants suggested were MIMs, Australian Medicines Handbook and Therapeutic Guidelines.

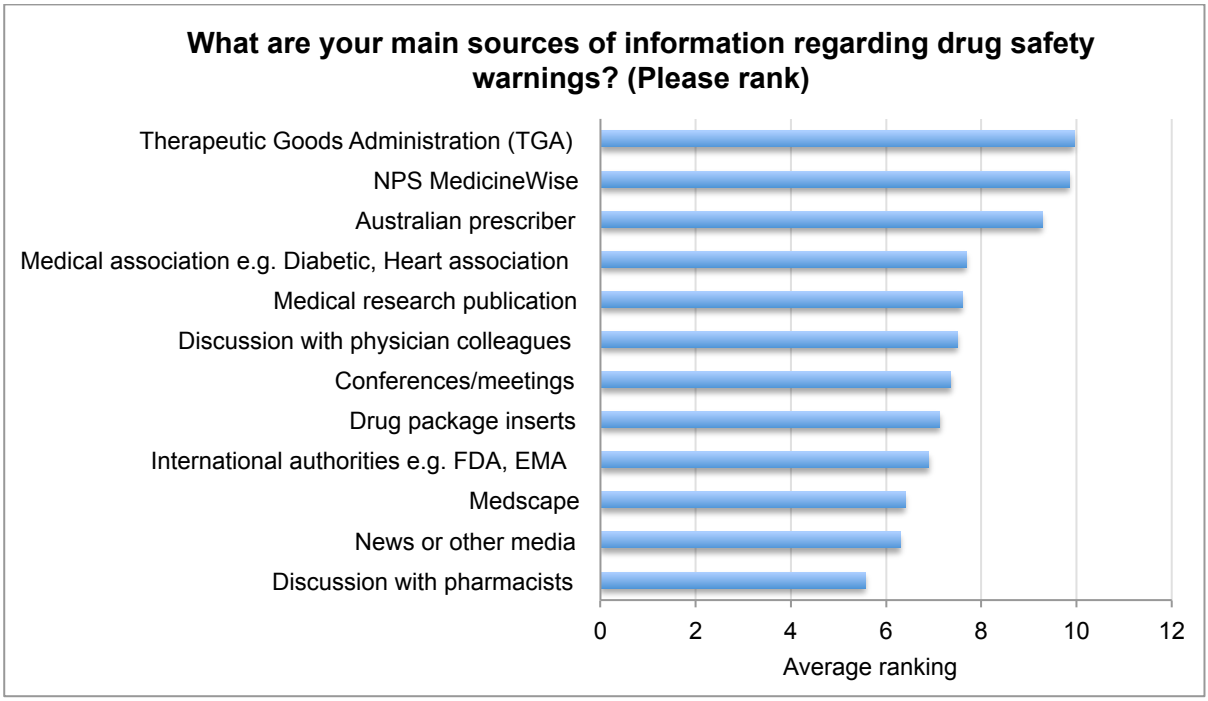


Figure 11. Sources of information regarding drug safety warnings and their ranking from highest to lowest scores.

Twenty (66.7%) of respondents did not directly receive the drug safety information through the primary communication methods provided by the TGA such as TGA's website and email subscription. Of those who received information from the TGA, three participants obtained this from the TGA website, seven participants received this from the Medicine Safety Update published in Australian Prescriber and two participants received both the Australian Prescriber and the TGA subscribed email. Receiving the TGA safety information was associated with higher years of practice (>=15 years) (Fisher's test, p-value 0.031). Of the ten participants who received drug safety information from the TGA, 80% think the information provided by the TGA is adequate for their practice and 60% think the TGA's warning is more timely than the FDA and EMA. The respondents understanding of the TGA's role varied as shown in Figure 12.

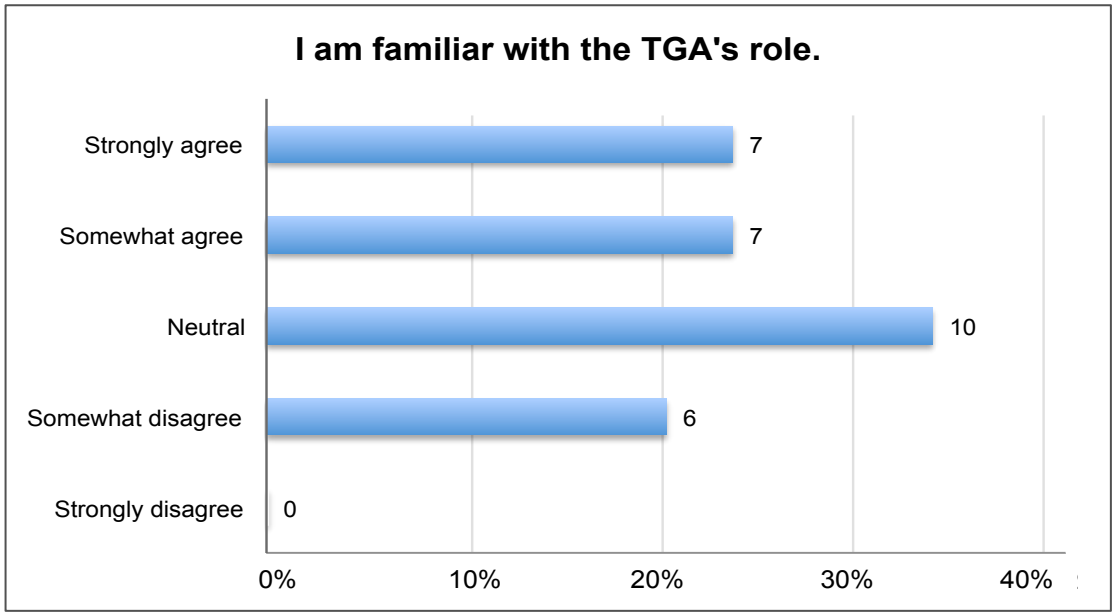


Figure 12. Level of familiarity with the TGA's role

Adverse events of thiazolidinediones

Majority of participants (90%) were aware of the cardiovascular risk associated with rosiglitazone and all of those who indicated that they had changed their practice in relation to rosiglitazone, 33.3% reported they would switch their patient from rosiglitazone to other antidiabetic drug class while 18.5% would switch to pioglitazone (same drug class as rosiglitazone).

Twelve respondents (40%) were aware of the increased risk of bladder cancer associated with long-term use of pioglitazone among participants. Of those who knew, 41.7% made no prescribing changes in patients using pioglitazone after the safety warnings whereas a quarter would discontinue pioglitazone even if the patient had no history of bladder cancer (Table 16).

Table 16. Responses of general practitioners on the management of patients who were using pioglitazone

Management in patients who were using pioglitazone	Response count (%)
Made no changes	5 (41.7%)
Continued pioglitazone with bladder cancer screening	0 (0.0%)

Discontinued pioglitazone in patients with high risk of bladder cancer	2 (16.7%)
Discontinued pioglitazone in all patients	3 (25.0%)
Switched to another antidiabetic drug class	1 (8.3%)
Other (please specify):	1 (8.3%) Monitoring information

Drug interaction between clopidogrel and proton pump inhibitors

About half the respondents (53.3%) were aware of the interaction between clopidogrel and proton pump inhibitors. Participants were able to choose more than one source of information regarding this drug interaction. Seven respondents answered that the TGA was their source of information on this interaction while other answers were NPS MedicineWise(6), medical research publication(5), and the media(5). Among the GPs who were aware of this interaction, most of them (75%) indicated that they changed their prescribing behaviour in response. Half of them would prescribe a PPI with a weak inhibitor effect on CYP2C19 and two respondents (12.5%) indicated they would prescribe a histamine 2 receptor antagonists (Table 17).

Table 17. Responses on the management of patients who were coprescribed clopidogrel and a PPI

Management in patients who were coprescribed clopidogrel and a PPI	**Response count (%)**
Made no changes	3 (18.8%)
Prescribed PPI with dosage adjustment	2 (12.5%)
Prescribed PPI with a weak inhibitory effect on CYP2C19 (e.g. pantoprazole)	7 (43.8%)
Prescribed histamine 2 receptor antagonists (e.g. ranitidine) instead of PPI	2 (12.5%)

Stopped prescribing all proton pump inhibitors	0
Other (please specify)	4 (25.0%)

If a new initiation of a PPI is needed, 75% would choose pantoprazole and 83.1% would not initiate omeprazole or esomeprazole in patients taking clopidogrel.

There was no association between outcomes and years of practice or practice settings based on analyses using Fisher's exact test.

Comments from respondents suggested that there are different preferences for sources of drug safety information among prescribers. Instead of tracking down every source of information, one reliable or 'one-stop service' may be needed. Some examples of open-ended responses from the survey are quoted below:

"*Unless information is put in MIMs or published in Medical Journal Australia then it is unlikely to become widely and rapidly known*"

"*Too many cooks, and lots of assumption that one or more will have warned us at the coalface. It has reached the stage where it seems I am obliged to actively track down every possible source, just in case they have some info I might not have heard. We need a "one-stop-shop*", *so we aren't tossing away the newsletters with the other superfluous junk mail*."

"*Perhaps if the various groups—NPS, Australian Prescriber, TGA etc—were singing from the same song sheet simultaneously*?"

"Should know more about it"

6. Discussion

The majority of the interviewees were familiar with the TGA and its role in issuing drug safety warning; however, they did not receive direct communication from the TGA (e.g. TGA's website, TGA subscripted email list, or TGA published article in medical journal). One of possible reasons is that there were other available sources of drug information in which each practitioner assessed on a regular basis. For instance, specialists subscribed

to the newsletter of their medical associations to receive not only drug information but also updated guidelines that are essential for their practice.

The timing of receiving a warning and responding to this new safety information was difficult to determine based on the data extracted from the interviews. This was due to the different sources of drug safety information used by different healthcare practitioners. It appears that it may take at least a year for general practitioners who only receive safety updates from the Australian prescriber handbook or e-therapeutic guidelines to know about this new safety information and subsequently change their practices.

Another issue raised from the interviewees' responses was a lack of an established system to circulate emerging drug safety information or drug warnings in hospitals and practice sites. Establishing such system could be a potential area for the TGA to enhance safety communication. This would need to be done in conjunction with healthcare facilities to ensure the distribution of safety drug information reached all healthcare professional.

The TGA, NPS MedicineWise, and Australian Prescriber were the main sources of drug safety information among general practitioners surveyed. However, the findings suggest that current methods to disseminate drug safety warnings used by the TGA, which consists of 'Alert' or 'Medical safety Update' via the TGA website and email subscription, are not widely read by GPs. One third of respondents directly received or accessed information provided by the TGA from a secondary source and only a few respondents accessed the TGA website or subscribed to the TGA's safety information email list.

Studies in chapters 3–5 indicated that the changes in patterns of Australian dispensing and prescribing data were associated with the warnings issued by key international regulators such as the FDA and EMA. However, these international agencies were not ranked as highly as local sources of drug safety information in this survey. Prescribers may receive overseas safety warnings from NPS MedicineWise or medical associations who usually publish reviews of evidence regarding emerging risks and updated warnings (NPS 2009; GESA 2010). In 2010, NPS MedicineWise and the Gastroenterological Society of Australia published articles on the interaction between clopidogrel and proton pump inhibitors (PPIs) on their websites while no action was taken from the TGA. NPS articles provided the recommendations that were often suggested by the FDA and well-

recognised medical associations, for example, the American Heart Association on the preferable PPI in clopidogrel users.

The high awareness of cardiovascular events associated with rosiglitazone treatment was expected because the evidence was compelling and many actions had been taken by the TGA and PBS. The survey indicated that most practitioners would switch their patients from rosiglitazone to another antidiabetic medicine, which correlates with the sharp decline in the patterns of dispensing and prescribing rosiglitazone seen in the PBS and AsteRx data. This may help explain why there was an 18.5% switching rate from rosiglitazone to pioglitazone in the prescribing data right after the warnings on rosiglitazone.

Although the TGA issued a warning on the bladder cancer risk related to long-term pioglitazone use, only 40% of respondents knew about this issue. Besides the small awareness among respondents, only 58% indicated that they would make a change to pioglitazone management. The low awareness of safety warnings issued by the regulatory agencies have been shown in the ‘Dear Doctor letter’ containing warnings of malaise in infants after the administration of certain brands of vitamin D in France and many other cases that led to market withdrawal of medicines (van Grootheest et al. 2002; Theophile et al. 2011). The insignificant change of pioglitazone use shown in the dispensing data (Chapter 3–4) following the TGA warning may be associated with the small awareness of its safety alert. Other explanations for this limited change are the lower incidence of the risk and a new availability of dipeptidyl peptidase-4 inhibitors during the release of the bladder cancer warning.

Surprisingly, GPs were aware of the clopidogrel-PPI interaction from the TGA despite the fact that the TGA had not issued any specific warnings on this. This finding could demonstrate that GPs might pick up this information via other sources but inaccurately attribute it to the TGA, or that they were providing what they thought were “socially acceptable” answers. Even though the TGA had no action toward this interaction, 53% of respondents knew about it. Moreover, most of the survey responses regarding the changes in management of coprescribing a PPI correspond with recommendations from key international regulators and international guidelines. This was also seen with the significant increase in the coprescribing of pantoprazole in the AsteRx database. Pantoprazole was the preferred PPI from the survey and the majority of respondents would not initiate omeprazole or esomeprazole. The preferences of prescribers observed

in this study are consistent with the increase in the coprescribing of pantoprazole with clopidogrel in the AsteRx database. In chapter 5, although the switching rates from omeprazole and esomeprazole to pantoprazole increased following the EMA warning, the overall trend of esomeprazole did not change. Moreover, esomeprazole was still the highest coprescribed PPI with clopidogrel.

The findings and comments from both interview and survey parts suggested that there was considerable diversity in the source of drug safety information among participants. This could lead to difficulty in predicting changes in clinical practice after an emerging adverse event. Prescribers sometimes feel a burdensome responsibility to track the latest information; or in making a decision based on the various recommendations, which may vary between sources. Whereas some practitioners did not know about these new risks until it was published in the routine drug manual. The educational programmes from the TGA and the Quality Use of Medicines Policy could help provide guidelines for managing emerging drug safety information for practitioners and patients.

Limitations in this study

Although an electronic survey has the advantage of being issued immediately to a large population with minimal budget, low-response rates are a well-known limitation (Sturkenboom et al. 1994). Meta-analyses show both monetary and non-monetary incentives were associated with increased survey response rates among physicians (Kellerman et al. 2001; Edwards et al. 2009; James et al. 2011; Pit et al. 2014), but such incentives were not possible in this study. Shorter questionnaires, pre-notification by phone, up to 3 reminders with a copy of questionnaires may also improve response rates (Jepson et al. 2005; Cook et al. 2009; Edwards et al. 2009; Pit et al. 2014). The Medicare locals agreed to advertise the surveys on 2–5 follow-up newsletters (one placed the advertisement in 5 editions, 2 placed it in 3 editions, and 2 placed it in 2 editions). The length of questionnaires was kept less than 15 minutes and 20 multiple-choice questions. Studies show that physicians increasingly receive requests to participant in research, especially in the modern era of social media, our passive approach and lack of incentive therefore encountered the above problems (Moore et al. 1999; Cook et al. 2009).

The low response rate observed in this study mean it is open to survey bias including a lack of validity and generalisability (Groves et al. 2008). Healthcare professionals who paid

attention to the newsletter may be better at keeping up-to-date with new information and tend to know about these warnings. Moreover, practitioners who failed to respond may be distinct from those who participated in the survey. Like all survey-based and interview studies, our questionnaire may suffer from recall bias. As seen in answers in obtaining the risk of clopidogrel-PPI interaction from the TGA therefore questions addressing choice of prescribing decision may or may not reflect actual practices in the last few years (Delgado-Rodriguez et al. 2004).

7. Conclusions

This survey provides information on the sources of drug safety information used by general practitioners in Australia. Prescribers considered the TGA as the main source of new drug safety information. NPS MedicineWise and Australian Prescriber are well-recognised source among practitioners where they may come across overseas recommendations or emerging issues such as the clopidogrel-PPI interaction.

The level of awareness of the case studies differed. The issuing of warnings by the TGA does not necessary result in a higher awareness or a change in prescribing decision, as was the case with pioglitazone after the release of the TGA's warning on bladder cancer. Other factors that may influence prescribers' decision such as certainty of the evidence, promoting strategy, and an available treatment alternative were discussed in previous chapters.

Combining quantitative and qualitative approaches can improve the robustness of research finding and answer different types of questions (Creswell 2008; Lobe 2008). The strengths of a quantitative approach (e.g. interrupted time-series analyses) are the impact size of drug safety warnings on overall patterns of concerned drug use and also generalisation of findings from the survey study.

The combined interview and survey study provides insight into how prescribers obtain safety information and how respondents changed their prescribing behaviour. The survey findings offer a possible link between the period of change in prescribing patterns and sources of drug safety information used when making decisions as well as the explanation as to why changes were observed in certain drugs but not others. Results from the interrupted time-series analyses and the survey were largely consistent. Levels of

awareness and tendency to change prescribing between rosiglitazone and pioglitazone are relevant to the differences in trends of these two drugs following their warnings. Survey participants who were aware of the clopigorel-PPI interaction chose pantoprazole as the coprescribed PPI choice, which can help explain the incline in the coprescribing of pantoprazole in the AsteRx database. Very little research has used this mixed method approach to show the impact of drug safety warnings in Australia or for pharmacoepidemiology studies. Combining a quantitative and qualitative approach in this thesis helps reflect the current situation of drug safety warnings and their impact on practice.

Chapter 7. Summary and future direction

1. Background of the study

This research examined the impact of drug safety warnings on the trend of overall drug use in Australia. Dispensing and prescribing data from the time-series analysis were interpreted together with the findings from the survey study to assess prescribers' sources of drug safety information and decisions in response to drug safety warnings. Prompt identification of and response to drug safety signals is a matter of international importance. Drug safety warnings issued by key international drug authorities such as the FDA and EMA have an influence on medicine use in Australia as well as those from the TGA (Dean et al. 2007).

2. Findings in this study

The impacts of warnings from the FDA, EMA, and TGA on the trends in utilisation of rosiglitazone and pioglitazone in the PBS national dispensing data from January 2004–July 2012 were investigated using the ARIMA model. Using the prescribing data in the AsteRx database, the impact of these warnings was further examined, looking for specific changes to patterns of prescribing for rosiglitazone and pioglitazone from January 2005–May 2012. The switching rates and switching choice from rosiglitazone to other antidiabetic drugs in the AsteRx data before and after the warnings were analysed. The coprescribing patterns of proton pump inhibitors among clopidogrel users were examined using the AsteRx database to assess the impacts of various warnings issued by the major regulators. These following findings incorporate results in the PBS, and AsteRx data with the survey study.

2.1 Impacts of myocardial infarction warnings on the use of rosiglitazone

Rosiglitazone utilisation reached its highest peak in January 2007 at 1.96DDD/1000population/day and stayed at 1.88DDD/1000population/day in May 2007. The first warning from the FDA and EMA in May 2007 was significantly associated with decline in rosiglitazone utilisation at the decreased rate of 15.04% per month (coefficient -15.04, $p<0.001$). The rosiglitazone utilisation had fallen to 1.49DDD/1000population/day by December 2007; however, the first TGA warning in December 2007 was not

significantly associated with the decreasing trend of rosiglitazone after adjustment for the previous FDA and EMA warnings.

Similar to the PBS dispensing data, a significant decline of prescribing rosiglitazone was found immediately after the FDA and EMA warning in May 2007 in the AsteRx database (p=0.001) but was not associated with the TGA warning in December 2007. These findings suggested that international warnings influenced local rosiglitazone use. Although the findings from the survey study did not rank the EMA and FDA as main sources of drug safety information, prescribers may be alerted by publications or other sources that often include international warnings such as medical associations and Medscape. The survey findings also mirror the impacts found in the time-series analysis, with a high awareness of ischemic heart events relating to rosiglitazone use and subsequent changes made in the management of patients taking rosiglitazone.

The cardiovascular warnings of rosiglitazone in May 2007 also influenced the use of pioglitazone in both the PBS and AsteRx databases, where an increasing trend was seen. Pioglitazone was the most popular antidiabetic alternative for patients who switched from rosiglitazone after May 2007 in the AsteRx database. Additionally, the survey indicated that most practitioners would switch their patients from rosiglitazone to another antidiabetic medicine and one third of those would switch to pioglitazone. In 2008 when pioglitazone use surpassed rosiglitazone, almost half of those prescribed pioglitazone had switched from rosiglitazone.

The 200% rise of pioglitazone from June 2007 to September 2008 may have resulted from the lack of clinical evidence around myocardial infarction associated with pioglitazone use and no alternative third-line drug for diabetes treatment. However, the use of pioglitazone was not sustained following the introduction of sitagliptin to the PBS in August 2008 (Dormandy et al. 2005; Lincoff et al. 2007; PBS 2008). This trend in Australian pioglitazone use following the rosiglitazone warning is different from US and European studies that showed a decline in pioglitazone prescriptions and an increase in prescriptions for other available antidiabetic drugs such as sitagliptin and exenatide after the warnings in 2007 (Hurren et al. 2011; Ruiter et al. 2012; Leal et al. 2013).

2.2 Impacts of warnings about the risk of bladder cancer related to pioglitazone

Since 2010, the use of pioglitazone gradually decreased in both PBS and AsteRx data, with 4.7% of total antidiabetic drugs in April 2010 to 3.4% in May 2011. Although a small decline in the dispensing and prescribing of pioglitazone were observed after the warnings issued by the local and international regulatory bodies on bladder cancer in June–July 2011, this decline was not significant in the ARIMA model. In the AsteRx database, prescribers did not immediately stop prescribing pioglitazone after the warnings came out as seen with rosiglitazone. This insignificant decline of pioglitazone could be explained by the findings from the survey study which indicated there was a low awareness of the bladder cancer risk related to pioglitazone treatment and only 58% of those who were aware of the risk would change the management in patients taking pioglitazone. Another explanation could be due to the low incident rate of bladder cancer (3 cases per 1000 pioglitazone users) compared to the high prevalence of ischemic heart disease, therefore prescribers may have been likely to consider that the benefits in glycaemic control of pioglitazone outweighed the possible risk of bladder cancer (Mamtani et al. 2012).

2.3 Impacts of drug interaction warnings on the concomitant use of clopidogrel and proton pump inhibitors

Approximately 90% of antisecretory agents coprescribed in clopidogrel users were PPIs during 2006–2011. Following the May 2009 EMA warning, to avoid omeprazole and suggesting pantoprazole as alternative PPI, the proportion of pantoprazole coprescribing significantly increased ($p=0.011$). A significant decrease in the coprescribing of omeprazole was not observed until after the second warning from the EMA in March 2010. The effects of warnings did not change the overall trend in the coprescribing of esomeprazole during the study period, which continued to be the leading coprescribed PPI choice in patients who were taking clopidogrel. There were significant increases in switching rates from esomeprazole and omeprazole to pantoprazole as well as an increased prevalence of pantoprazole initiations after May 2009. Despite the absence of local regulatory action, changes to the coprescribed proton pump inhibitors were seen in Australian data. In the survey study, half of respondents were aware of this interaction and most of them changed antisecretory agents from omeprazole and esomeprazole to pantoprazole in patients taking clopidogrel. An incline in the coprescribing of pantoprazole

after the overseas warning was likely to be from prescribers' increased awareness of the reduced antiplatelet effect of clopidogrel when used concomitantly with CYP2C19 inhibitors and the subsequent response of choosing pantoprazole over omeprazole or esomeprazole. Survey respondents suggested that they received safety information on the clopidogrel/PPI interaction from NPS Medicinewise, medical associations and the media that commonly reviewed the new evidence and provided or presented the recommendation not only from local but also key international authorities such as the FDA and EMA.

3. Key points from the findings

- Regulatory warnings regarding two case studies were very different from three regulatory authorities. This suggests that we lack a uniform framework for assessing evidence and providing the recommendations for healthcare professionals and patients.
- Local dispensing and prescribing is influenced by many factors, including international drug warnings as seen by the significant decline in the use of rosiglitazone following the FDA and EMA warnings and the changes in the coprescribing of proton pump inhibitors with clopidogrel. Local systems such as available treatment choices in the national subsidised list are also important for changes to local trends (Hurren et al. 2011; Ruiter et al. 2012; Leal et al. 2013).
- Local prescribers vary in how they receive information about drug safety. The research literature as well as local and international warnings may not be directly accessed by practitioners but rather through articles or newsletters distributed by secondary sources or local organisations. Moreover, very few have a specific approach or strategy for receiving safety information.

4. Possible future work

4.1 Improving the framework for assessing and communicating drug safety

The variability in response to safety signals from different regulatory bodies seen in the case studies described in this thesis illustrates the opportunity for future work on how

safety signals should be identified, assessed and communicated to healthcare professionals.

Although several scales have been developed to assess the quality of studies on drug effects, most are not specific for evaluating pharmacoepidemiology studies (Loke et al. 2007; Cornelius et al. 2009). Unlike randomised control trials, these studies reflect the use of drugs in real-life situations and are often confounded by many factors (e.g. confounding by indication) (Hermann et al. 2012).

A well-established conceptual framework to assess the contribution of studies to the available evidence on an emerging safety issue is needed at either a national level or an international level. National regulatory agencies should come together to set up a guideline for appropriately assessing the quality and significance of evidence as a means to generate standard responses and recommendations.

The benefits of this assessment framework are not only to improve the quality of regulatory decision making on an emerging safety events but also to facilitate the transparency and consistency of the regulatory process.

Given that evidence regarding drug safety is often complex and emerges over time, to what degree should regulatory bodies provide prescribing guidance when the evidence is unclear. Currently, each national authority body has adopted different methods in response to this problem. The FDA often starts with the early communication stating ‘safety issues are under review’ and issues reminders as the evidence emerges (Lester et al. 2013), whereas others may take no specific actions. The optimal mixture of guidance and evidence needs to be further assessed.

4.2 Evaluation of the impact of safety warnings

After the establishment of a framework for providing the recommendations regarding the use of the drug concerned, the effectiveness of a drug safety warning system should be evaluated. The evaluations will provide an understanding of the impact of warnings on utilisation patterns of products and help ensure that these warnings are suitable for the target prescribers and patients.

The analyses of utilisation data will help inform the current situation and provide data on whether changes have occurred as expected. If prescribing continued in an unsafe manner, further regulatory actions such as repeated warnings, increased restriction, or withdrawal may be needed (Smalley et al. 2000). These evaluations could also help identify the obstacles of the current system, which should be considered in the TGA's strategies to reform safety communication.

The assessment of a larger scale public expectation for drug safety warnings would guide the regulatory body in constructing a framework of safety communication. Firstly, the preference of methods and dissemination of safety communication may vary among health services (e.g. primary and secondary care), healthcare settings (e.g. urban and remote area) and different specialties. As this study did not concentrate on the methods of distribution, it would help improve the efficiency of safety communication by examining the preference of distribution methods such as a paper-based mail or electronic materials (e.g. email and website). Secondly, the contents required by different types of healthcare providers (e.g. physicians, nurses, pharmacists) and patients need to be assessed in order to receive an appropriate response from each target group.

The impact of drug safety warnings on the use of drugs at a community level would differ from secondary or tertiary healthcare settings, especially when government subsidisation differs between States and/or hospitals. Appropriate study designs are needed to investigate the impact of safety warnings on drug use in hospital settings and also to provide a causal relationship between clinical reasons and changes in prescribing choice.

5. Conclusions

Evaluations of the impact of drug safety warnings on overall drug utilisation in Australia and prescribing data in the AsteRx database suggest an association between local drug use/prescribing decisions and international warnings. This study used a mixed method approach to assess the relationship between the level of awareness to safety warnings and the changes to dispensing and prescribing data. Whilst there was a small response rate in the survey study, the integrated results from changes of drug use in databases and perception from prescribers provide an overall understanding of impact of drug safety warning in Australia. Reminders of risk over time and the provision of treatment recommendations are associated with clear changes on drug utilisation. Apart from the

regulatory warnings, the influential factors on prescribing decisions are certainty of evidence, prevalence/incidence of adverse events, and treatment options.

The combined approach taken in this project provides a basic guideline for investigating the impacts of drug safety warnings in Australia. The findings of this research provide an overview of current drug safety warnings and also suggest the potential areas for improvement to the local drug warning system.

References

"AFSSAPS. Available from: http://ansm.sante.fr/var/ansm_site/storage/original/application/3b70d267800de891b8f204f0376b7538.pdf. (accessed May 30, 2012)."

"Australian Bureau of Statistics. Available from: http://www.abs.gov.au/. (accessed July 20, 2012)."

"Australian Goverment Department of Health and Ageing. About PBS. Available from: http://pbs.gov.au/info/about-the-pbs (accessed November 30, 2011)."

"Australian Government Department of Health and Ageing. March 2008 PBAC Outcomes — Positive Recommendations made by the PBAC-November 2008. Available from: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/2008-11/positive-recommendations (accessed May 30, 2012)."

"BJCardio editorial staff. EMEA warns of possible interaction between clopidogrel and PPIs. ." Br J Cardiol 2009;16:163-6

"Centrelink. Department of Human Services. Australian Government. Available from: http://www.humanservices.gov.au/. (accessed July 20, 2012)."

"Centrelink. Department of Human Services. Australian Government. http://www.humanservices.gov.au/. (accessed July 20, 2012).".

"European Medicines Agency. European Medicines Agency recommends suspension of Avandia, Avandamet and Avaglim. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/09/news_detail_001119.jsp&mid=WC0b01ac058004d5c1&jsenabled=true. (accessed May 30, 2012)."

"European Medicines Agency. News and events. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/landing/news_and_events.jsp&mid=. (accessed May 30, 2012)."

"European Medicines Agency. News, press release and public statement archive. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/landing/news_search_landing_page.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1. (accessed on Nov 12, 2012)."

"European Medicines Agency. Press release on January 24, 2008. Available from: http://www.emea.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500015420.pdf. (accessed May 15, 2012)."

"European Medicines Agency. Press release on May 23, 2007. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500013467.pdf. (accessed May 15, 2011)."

"European Medicines Agency. Press release on October 18, 2007. Available from: http://www.emea.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500011009.pdf. (accessed May 15, 2011)."

"European Medicines Agency. Press release. European Medicines Agency recommends new contraindications and warnings for pioglitazone to reduce small increassed risk of bladder cancer. Available from:

http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/07/WC500109176.pdf. (accessed May 30, 2012)."

"FDA Drug Safety Communication: Update to ongoing safety review of Actos (pioglitazone) and increased risk of bladder cancer. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm259150.htm. (accessed Dec 20, 2012)."

"FDA Drug Safety Communication. FDA Issues Safety Alert on Avandia. Available from: http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134225.htm. (accessed Dec 20, 2012)."

"FDA significant restricts access to the diabetes drug Avandia. Available from: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm226956.htm. (accessed Dec 20, 2012)."

"FDA. Advisory Committee. Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM218493.pdf. (accessed May 30, 2012)."

"FDA. Avandia label. Available from: http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM143413.pdf. (accessed Dec 20, 2012)."

"FDA. Briefing Information for the July 13-14, 2010 Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee. Available from: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm218491.htm. (accessed Dec 20, 2012)."

"FDA. Drug Safety Communication. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm199082.htm. (accessed Dec 20, 2012)."

"FDA. Postmarket Drug Safety Information for Patients and Providers. Available from: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm143349.htm. (accessed Dec 20, 2012)."

"Food and Drug Administation. Drug Safety Communications. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm199082.htm. (accessed May 30, 2012)."

"Harrison's Principles of Internal Medicine, 18th Edition (Harrison's Online, Chapter 237, Ischemic Heart Disease, 2008)."

"Liamputtong, P. (2013). Qualitative research methods. South Melbourne, Vic: Oxford University Press.".

"PBS Latest News. Changes to listings for ROSIGLITAZONE MALEATE (Avandia®) and ROSIGLITAZONE MALEATE with METFORMIN HYDROCHLORIDE (Avandamet®)-1 November 2008. Available from: http://www.pbs.gov.au/info/news/2008/11/List-amndmnts-avandia-avandamet (accessed May 10, 2012)."

"Pharmaceutical benefit scheme medicine listing. Department of Health and Ageing. Australian Government. Available from: http://www.pbs.gov.au/browse/medicine-listing. (accessed December 20, 2012)."

"Pharmaceutical Benefits Advisory Committee. Positive Recommendations made by the PBAC — March 2011. Canberra: Australian Government Department of Health and Ageing, 2011. Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/pbacrec-mar11-positive (accessed May 26, 2012)."

"TGA. Australian Adverse Drug Reactions Bulletin, Vol 26, No 6. Available from: http://www.tga.gov.au/hp/aadrb-0712.htm. (accessed Dec 20, 2012)."

"TGA. Pioglitazone and risk of bladder cancer. Safety advisory. Available from: http://www.tga.gov.au/safety/alerts-medicine-pioglitazone-110718.htm. (accessed Dec 12, 2012)."

"TGA. Safety information. Available from: http://www.tga.gov.au/hp/information-safety.htm. (accessed Dec 12, 2012)."

"TGA. Safety information. Rosiglitazone (Avandia/Avandamet). Advisory statement. Available from: http://www.tga.gov.au/safety/alerts-medicine-rosiglitazone-100924.htm. (accessed Nov 20, 2012)."

"Therapeutic Goods Administralion. About the TGA. Available from: http://www.tga.gov.au/about/committees-acsom.htm. (accessed May 30, 2012)."

"WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index. Available from: http://www.whocc.no/atc_ddd_index/. (accessed Nov 23, 2011)."

(2005). "Counterfeit drug warning." FDA Consum **39**(4): 5.

(2005). "Roche issues drug interaction warning." AIDS Alert **20**(4): 48.

(2007). "FDA, Bristol-Myers Squibb issue warning on hepatitis B drug." AIDS Read **17**(10): 478-510.

Abraham, N. S., M. A. Hlatky, E. M. Antman, D. L. Bhatt, D. J. Bjorkman, C. B. Clark, C. D. Furberg, D. A. Johnson, C. J. Kahi, L. Laine, K. W. Mahaffey, E. M. Quigley, J. Scheiman, L. S. Sperling and G. F. Tomaselli (2010). "ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use." Am J Gastroenterol **105**(12): 2533-2549.

ABS. (2012, 5 August 2013). "Australian Bureau of Statistics. 4364.0.55.005 - Australian Health Survey: Biomedical Results for Chronic Diseases, 2011-12." Retrieved 10 January 2014, from http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/9769589F9E465EE6CA257BBB00121648?opendocument.

Ahmad, S. R. (2003). "Adverse drug event monitoring at the Food and Drug Administration." J Gen Intern Med **18**(1): 57-60.

Aihara, H., A. Sato, N. Takeyasu, H. Nishina, T. Hoshi, D. Akiyama, Y. Kakefuda, H. Watabe and K. Aonuma (2012). "Effect of individual proton pump inhibitors on cardiovascular events in patients treated with clopidogrel following coronary stenting:: Results From the Ibaraki Cardiac Assessment Study Registry." Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions.

Ali, T. and R. F. Harty (2009). "Stress-induced ulcer bleeding in critically ill patients." Gastroenterol Clin North Am **38**(2): 245-265.

Ali, T., D. N. Roberts and W. M. Tierney (2009). "Long-term safety concerns with proton pump inhibitors." Am J Med **122**(10): 896-903.

Almadi, M. A., A. Barkun and J. Brophy (2011). "Antiplatelet and anticoagulant therapy in patients with gastrointestinal bleeding: an 86-year-old woman with peptic ulcer disease." JAMA : the journal of the American Medical Association **306**(21): 2367-2374.

Alves, C., F. B. Marques and A. F. Macedo (2014). "Drug-safety alerts issued by regulatory authorities: usefulness of meta-analysis in predicting risks earlier." Eur J Clin Pharmacol **70**(6): 745-756.

Andersen, M., U. Bergman, N. K. Choi, T. Gerhard, C. Huang, J. Jalbert, M. Kimura, T. Kimura, K. Kubota, E. C. Lai, N. Ooba, B. J. Park, N. Pratt, E. E. Roughead, T. Sato, S. Setoguchi, J. Y. Shin, A. Sundstrom and Y. H. Yang (2013). "The Asian Pharmacoepidemiology Network (AsPEN): promoting multi-national collaboration for pharmacoepidemiologic research in Asia." Pharmacoepidemiol Drug Saf **22**(7): 700-704.

Angiolillo, D. J., A. Fernandez-Ortiz, E. Bernardo, F. Alfonso, C. Macaya, T. A. Bass and M. A. Costa (2007). "Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives." J Am Coll Cardiol **49**(14): 1505-1516.

Angiolillo, D. J., C. M. Gibson, S. Cheng, C. Ollier, O. Nicolas, L. Bergougnan, L. Perrin, F. P. LaCreta, F. Hurbin and M. Dubar (2011). "Differential effects of omeprazole and pantoprazole on the pharmacodynamics and pharmacokinetics of clopidogrel in healthy subjects: randomized, placebo-controlled, crossover comparison studies." Clinical pharmacology and therapeutics **89**(1): 65-74.

Armstrong, D. (2006). "How the New England Journal missed warning signs on Vioxx: medical weekly waited years to report flaws in article that praised pain drug; Merck seen as "punching bag"." Wall St J (East Ed): A1, A10.

Aroney, C. N., P. Aylward, D. P. Chew, N. Huang, A. M. Kelly, H. White and M. Wilson (2008). "2007 addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes 2006." Med J Aust **188**(5): 302-303.

Aronoff, S., S. Rosenblatt, S. Braithwaite, J. W. Egan, A. L. Mathisen and R. L. Schneider (2000). "Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. The Pioglitazone 001 Study Group." Diabetes Care **23**(11): 1605-1611.

AsteRx. (2012). "About us." Retrieved 10 January 2013, from http://asterx.com/who.html.

Awtry, E. H. and J. Loscalzo (2000). "Aspirin." Circulation **101**(10): 1206-1218.

Bach, L. A., E. I. Ekinci, D. Engler, C. Gilfillan, P. S. Hamblin, R. J. MacIsaac, G. Soldatos, C. Steele, G. M. Ward and S. Wyatt (2014). "The high burden of inpatient diabetes mellitus: the Melbourne Public Hospitals Diabetes Inpatient Audit." Med J Aust **201**(6): 334-338.

Baigent, C., L. Blackwell, R. Collins, J. Emberson, J. Godwin, R. Peto, J. Buring, C. Hennekens, P. Kearney, T. Meade, C. Patrono, M. C. Roncaglioni and A. Zanchetti (2009). "Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials." Lancet **373**(9678): 1849-1860.

Barkun, A. N., M. Bardou, E. J. Kuipers, J. Sung, R. H. Hunt, M. Martel and P. Sinclair (2010). "International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding." Ann Intern Med **152**(2): 101-113.

BEACH. (2012). "BEACH. DATA VARIABLES COLLECTED." Retrieved 10 January 2014, from http://sydney.edu.au/medicine/fmrc/beach/about/data-variables/index.php.

BEACH. (2012, 5 Jul 2012). "The University of Sydney. Family medicine reserach centre. BETTERING THE EVALUATION AND CARE OF HEALTH (BEACH)." Retrieved 10 January 2014, from http://sydney.edu.au/medicine/fmrc/beach/index.php.

Beardon, P. H., M. M. McGilchrist, A. D. McKendrick, D. G. McDevitt and T. M. MacDonald (1993). "Primary non-compliance with prescribed medication in primary care." BMJ **307**(6908): 846-848.

Beermann, B., J. Liliemark and K. Johansson (2005). "[More information on drug package inserts and counseling replace the warning triangle]." Lakartidningen **102**(24-25): 1918, 1921.

Benbow, A., M. Stewart and G. Yeoman (2001). "Thiazolidinediones for type 2 diabetes. All glitazones may exacerbate heart failure." BMJ **322**(7280): 236.

Bennett, C. L., O. S. Adegboro, E. A. Calhoun and D. Raisch (2010). "Beyond the black box: drug- and device-associated hypersensitivity events." Drug Healthc Patient Saf **2**: 1-5.

Berg, M. J., R. A. Gross, L. S. Haskins, W. M. Zingaro and K. J. Tomaszewski (2008). "Generic substitution in the treatment of epilepsy: patient and physician perceptions." Epilepsy Behav **13**(4): 693-699.

Berger, J. S., D. L. Bhatt, C. P. Cannon, Z. Chen, L. Jiang, J. B. Jones, S. R. Mehta, M. S. Sabatine, S. R. Steinhubl, E. J. Topol and P. B. Berger (2009). "The relative efficacy and safety of clopidogrel in women and men a sex-specific collaborative meta-analysis." Journal of the American College of Cardiology **54**(21): 1935-1945.

Berlin, J. A., S. C. Glasser and S. S. Ellenberg (2008). "Adverse event detection in drug development: recommendations and obligations beyond phase 3." Am J Public Health **98**(8): 1366-1371.

Bhatia, S. K., A. J. Rezac, B. Vitiello, M. A. Sitorius, B. A. Buehler and C. J. Kratochvil (2008). "Antidepressant prescribing practices for the treatment of children and adolescents." J Child Adolesc Psychopharmacol **18**(1): 70-80.

Bhatt, D. L., B. L. Cryer, C. F. Contant, M. Cohen, A. Lanas, T. J. Schnitzer, T. L. Shook, P. Lapuerta, M. A. Goldsmith, L. Laine, B. M. Scirica, S. A. Murphy and C. P. Cannon (2010). "Clopidogrel with or without omeprazole in coronary artery disease." N Engl J Med **363**(20): 1909-1917.

Bhatt, D. L., K. A. Fox, W. Hacke, P. B. Berger, H. R. Black, W. E. Boden, P. Cacoub, E. A. Cohen, M. A. Creager, J. D. Easton, M. D. Flather, S. M. Haffner, C. W. Hamm, G. J. Hankey, S. C. Johnston, K. H. Mak, J. L. Mas, G. Montalescot, T. A. Pearson,

P. G. Steg, S. R. Steinhubl, M. A. Weber, D. M. Brennan, L. Fabry-Ribaudo, J. Booth and E. J. Topol (2006). "Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events." N Engl J Med **354**(16): 1706-1717.

Bhurke, S. M., B. C. Martin, C. Li, A. M. Franks, Z. Bursac and Q. Said (2012). "Effect of the clopidogrel-proton pump inhibitor drug interaction on adverse cardiovascular events in patients with acute coronary syndrome." Pharmacotherapy **32**(9): 809-818.

Bilik, D., L. N. McEwen, M. B. Brown, J. V. Selby, A. J. Karter, D. G. Marrero, V. C. Hsiao, C. W. Tseng, C. M. Mangione, N. L. Lasser, J. C. Crosson and W. H. Herman (2010). "Thiazolidinediones, cardiovascular disease and cardiovascular mortality: translating research into action for diabetes (TRIAD)." Pharmacoepidemiology and drug safety **19**(7): 715-721.

Blume, H., F. Donath, A. Warnke and B. S. Schug (2006). "Pharmacokinetic drug interaction profiles of proton pump inhibitors." Drug Saf **29**(9): 769-784.

Boisvert, C. M. (2010). "Negative treatment effects: is it time for a black box warning?" Am Psychol **65**(7): 680-681.

Bolen, S., L. Feldman, J. Vassy, L. Wilson, H. C. Yeh, S. Marinopoulos, C. Wiley, E. Selvin, R. Wilson, E. B. Bass and F. L. Brancati (2007). "Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus." Ann Intern Med **147**(6): 386-399.

Bonds, D. E., J. C. Larson, A. V. Schwartz, E. S. Strotmeyer, J. Robbins, B. L. Rodriguez, K. C. Johnson and K. L. Margolis (2006). "Risk of fracture in women with type 2 diabetes: the Women's Health Initiative Observational Study." J Clin Endocrinol Metab **91**(9): 3404-3410.

Bonevski, B., P. Magin, G. Horton, M. Foster and A. Girgis (2011). "Response rates in GP surveys - trialling two recruitment strategies." Aust Fam Physician **40**(6): 427-430.

Bonython, B. B. A. a. W. (2014). "The TGA - a watchdog with dentures?" The TGA - a watchdog with dentures? http://blogs.crikey.com.au/croakey/2014/03/25/the-tga-a-watchdog-with-dentures/.

Bouder, F. (2011). Benefit/risk communication by the European Medicines Agency: a study of

influential stakeholders' expectations and attitudes Department of Technology and Society Studies, Maastricht

University, the Netherlands.

Bowling, A. (2005). "Mode of questionnaire administration can have serious effects on data quality." J Public Health (Oxf) **27**(3): 281-291.

Box GEP, T. G. (1975). "Intervention analysis with applications to economic and environmental problems." Journal of the American Statistical Association **70**: 70–74.

Box, G. E. P. a. J., G.M. (1976). Time Series Analysis: Forecasting and Control., San Francisco: Holden Day.

Brandt, J. T., C. D. Payne, S. D. Wiviott, G. Weerakkody, N. A. Farid, D. S. Small, J. A. Jakubowski, H. Naganuma and K. J. Winters (2007). "A comparison of prasugrel and clopidogrel loading doses on platelet function: magnitude of platelet inhibition is related to active metabolite formation." Am Heart J **153**(1): 66 e69-16.

Bresalier, R. S., R. S. Sandler, H. Quan, J. A. Bolognese, B. Oxenius, K. Horgan, C. Lines, R. Riddell, D. Morton, A. Lanas, M. A. Konstam and J. A. Baron (2005). "Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial." N Engl J Med **352**(11): 1092-1102.

Brody, H. (2009). "Pharmaceutical industry financial support for medical education: benefit, or undue influence?" J Law Med Ethics **37**(3): 451-460, 396.

Buckley, N. A. and S. Rossi (2011). "Bringing greater transparency to "black box" warnings." Clin Toxicol (Phila) **49**(6): 448-451.

Busch, S. H., R. G. Frank, D. L. Leslie, A. Martin, R. A. Rosenheck, E. G. Martin and C. L. Barry (2010). "Antidepressants and suicide risk: how did specific information in FDA safety warnings affect treatment patterns?" Psychiatr Serv **61**(1): 11-16.

Cameron, A. C. and P. K. Trivedi (2013). Regression analysis of count data, Cambridge university press.

Cayla, G., J. S. Hulot, S. A. O'Connor, A. Pathak, S. A. Scott, Y. Gruel, J. Silvain, J. B. Vignalou, Y. Huerre, A. de la Briolle, F. Allanic, F. Beygui, O. Barthelemy, G. Montalescot and J. P. Collet (2011). "Clinical, angiographic, and genetic factors associated with early coronary stent thrombosis." JAMA : the journal of the American Medical Association **306**(16): 1765-1774.

Ceilley, R. and A. Eisenthal (2009). "The unintended effects of a boxed warning." J Clin Aesthet Dermatol **2**(9): 33-39.

Centrelink. (2014). "Australian Government. Department of Human Services. Centrelink." from http://www.humanservices.gov.au/customer/dhs/centrelink.

Charlot, M., O. Ahlehoff, M. L. Norgaard, C. H. Jorgensen, R. Sorensen, S. Z. Abildstrom, P. R. Hansen, J. K. Madsen, L. Kober, C. Torp-Pedersen and G. Gislason (2010). "Proton-pump inhibitors are associated with increased cardiovascular risk independent of clopidogrel use: a nationwide cohort study." Ann Intern Med **153**(6): 378-386.

Chen, M., J. F. Wei, Y. N. Xu, X. J. Liu and D. J. Huang (2011). "A Meta-Analysis of Impact of Proton Pump Inhibitors on Antiplatelet Effect of Clopidogrel." Cardiovasc Ther.

Chen, Z. M., L. X. Jiang, Y. P. Chen, J. X. Xie, H. C. Pan, R. Peto, R. Collins and L. S. Liu (2005). "Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial." Lancet **366**(9497): 1607-1621.

Chevarley, F. M. (2010). "Average Outpatient Out-of-Pocket Prescription Drug Costs for the Top Five Prescription Drugs for Adults Age 65 and over: 2005 and 2006. Statistical Brief # 288. July 2010. Agency for Healthcare Research and Quality, Rockville, MD.", from http://www.meps.ahrq.gov/mepsweb/data_files/publications/st285/stat285.pdf.

Chew, D. P., C. N. Aroney, P. E. Aylward, A. M. Kelly, H. D. White, P. A. Tideman, J. Waddell, L. Azadi, A. J. Wilson and L. A. Ruta (2011). "2011 Addendum to the National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand Guidelines for the management of acute coronary syndromes (ACS) 2006." Heart Lung Circ **20**(8): 487-502.

Cluxton, R. J., Jr., Z. Li, P. C. Heaton, S. R. Weiss, I. H. Zuckerman, C. J. Moomaw, V. D. Hsu and E. M. Rodriguez (2005). "Impact of regulatory labeling for troglitazone and

rosiglitazone on hepatic enzyme monitoring compliance: findings from the state of Ohio medicaid program." Pharmacoepidemiol Drug Saf **14**(1): 1-9.

Cobitz, A., A. Zambanini, M. Sowell, M. Heise, B. Louridas, S. McMorn, M. Semigran and G. Koch (2008). "A retrospective evaluation of congestive heart failure and myocardial ischemia events in 14,237 patients with type 2 diabetes mellitus enrolled in 42 short-term, double-blind, randomized clinical studies with rosiglitazone." Pharmacoepidemiol Drug Saf **17**(8): 769-781.

Cohen, A., A. Rabbani, N. Shah and G. C. Alexander (2010). "Changes in glitazone use among office-based physicians in the U.S., 2003-2009." Diabetes Care **33**(4): 823-825.

Collaboration., A. T. (2002). "Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients." BMJ **324**(7329): 71-86.

Collet, J. P., J. S. Hulot, A. Pena, E. Villard, J. B. Esteve, J. Silvain, L. Payot, D. Brugier, G. Cayla, F. Beygui, G. Bensimon, C. Funck-Brentano and G. Montalescot (2009). "Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study." Lancet **373**(9660): 309-317.

Colucciello, M. (2005). "Vision loss due to macular edema induced by rosiglitazone treatment of diabetes mellitus." Arch Ophthalmol **123**(9): 1273-1275.

Committee, C. S. (1996). "A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE)." Lancet **348**(9038): 1329-1339.

Cook, D. M., R. K. Gurugubelli and L. A. Bero (2009). "Risk management policy and black-box warnings: a qualitative analysis of US FDA proceedings." Drug Saf **32**(11): 1057-1066.

Cook, J. V., H. O. Dickinson and M. P. Eccles (2009). "Response rates in postal surveys of healthcare professionals between 1996 and 2005: an observational study." BMC Health Serv Res **9**: 160.

Cooke, G., L. Valenti, P. Glasziou and H. Britt (2013). "Common general practice presentations and publication frequency." Aust Fam Physician **42**(1-2): 65-68.

Cornelius, V. R., M. J. Perrio, S. A. Shakir and L. A. Smith (2009). "Systematic reviews of adverse effects of drug interventions: a survey of their conduct and reporting quality." Pharmacoepidemiol Drug Saf **18**(12): 1223-1231.

Creswell, J. W. (2008). "Research design: Qualitative, quantitative, and mixed methods approaches. Thousand

Oaks, CA and London: Sage Publications. ."

Cuisset, T., C. Frere, J. Quilici, R. Poyet, B. Gaborit, L. Bali, O. Brissy, P. E. Morange, M. C. Alessi and J. L. Bonnet (2009). "Comparison of omeprazole and pantoprazole influence on a high 150-mg clopidogrel maintenance dose the PACA (Proton Pump Inhibitors And Clopidogrel Association) prospective randomized study." J Am Coll Cardiol **54**(13): 1149-1153.

de Vries, C. S., P. B. van den Berg and L. T. de Jong-van den Berg (1998). "Oral contraceptive use before and after the latest pill scare in The Netherlands. Changes in oral contraceptive use and how users change." Contraception **57**(4): 247-249.

Dean, A. J., A. Hendy and T. McGuire (2007). "Antidepressants in children and adolescents--changes in utilisation after safety warnings." Pharmacoepidemiol Drug Saf **16**(9): 1048-1053.

Dechanont, S., S. Maphanta, B. Butthum and C. Kongkaew (2014). "Hospital admissions/visits associated with drug-drug interactions: a systematic review and meta-analysis." Pharmacoepidemiol Drug Saf **23**(5): 489-497.

Defreyn, G., C. Gachet, P. Savi, F. Driot, J. P. Cazenave and J. P. Maffrand (1991). "Ticlopidine and clopidogrel (SR 25990C) selectively neutralize ADP inhibition of PGE1-activated platelet adenylate cyclase in rats and rabbits." Thromb Haemost **65**(2): 186-190.

Delgado-Rodriguez, M. and J. Llorca (2004). "Bias." J Epidemiol Community Health **58**(8): 635-641.

Dial, S., K. Alrasadi, C. Manoukian, A. Huang and D. Menzies (2004). "Risk of Clostridium difficile diarrhea among hospital inpatients prescribed proton pump inhibitors: cohort and case-control studies." CMAJ **171**(1): 33-38.

Diamant, M. and R. J. Heine (2003). "Thiazolidinediones in type 2 diabetes mellitus: current clinical evidence." Drugs **63**(13): 1373-1405.

Diamond, G. A., L. Bax and S. Kaul (2007). "Uncertain effects of rosiglitazone on the risk for myocardial infarction and cardiovascular death." Ann Intern Med **147**(8): 578-581.

Dickey, E. B., and Fuller, W.A. (1979). ""Distribution of the Estimators for Autoregressive Time Series with Unit Root," " Journal of the American Statistical Association **74**: 427-431.

Diener, H. C., J. Bogousslavsky, L. M. Brass, C. Cimminiello, L. Csiba, M. Kaste, D. Leys, J. Matias-Guiu and H. J. Rupprecht (2004). "Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial." Lancet **364**(9431): 331-337.

Dormandy, J. A., B. Charbonnel, D. J. Eckland, E. Erdmann, M. Massi-Benedetti, I. K. Moules, A. M. Skene, M. H. Tan, P. J. Lefebvre, G. D. Murray, E. Standl, R. G. Wilcox, L. Wilhelmsen, J. Betteridge, K. Birkeland, A. Golay, R. J. Heine, L. Koranyi, M. Laakso, M. Mokan, A. Norkus, V. Pirags, T. Podar, A. Scheen, W. Scherbaum, G. Schernthaner, O. Schmitz, J. Skrha, U. Smith and J. Taton (2005). "Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial." Lancet **366**(9493): 1279-1289.

Dorsey, E. R., A. Rabbani, S. A. Gallagher, R. M. Conti and G. C. Alexander (2010). "Impact of FDA black box advisory on antipsychotic medication use." Arch Intern Med **170**(1): 96-103.

Dunn SP, M. T., Brennan DM, Campbell CL, Charnigo RJ, Smyth SS, Berger PB, Steinhubl SR, Topol EJ. (2008). "Baseline proton pump inhibitor use is associated with increased cardiovascular events with and without the use of clopidogrel in the CREDO trial." Circulation 2008;118(A:3999):P815.

Dunn, S. P., S. R. Steinhubl, D. Bauer, R. J. Charnigo, P. B. Berger and E. J. Topol (2013). "Impact of proton pump inhibitor therapy on the efficacy of clopidogrel in the CAPRIE and CREDO trials." J Am Heart Assoc **2**(1): e004564.

Dusetzina, S. B., A. S. Higashi, E. R. Dorsey, R. Conti, H. A. Huskamp, S. Zhu, C. F. Garfield and G. C. Alexander (2012). "Impact of FDA drug risk communications on health care utilization and health behaviors: a systematic review." Med Care **50**(6): 466-478.

DVA. "Health care and support services." Retrieved 10 January 2014, from http://www.dva.gov.au/BENEFITSANDSERVICES/HEALTH/Pages/index.aspx.

DVA. "Repatriation Pharmaceutical Benefits Scheme." Retrieved 10 January 2014, from http://www.dva.gov.au/service_providers/doctors/Pages/rpbs.aspx.

DVA (2011). Australian Government Department of Veterans' Aff airs. Treatment population statistics. Quarterly report - March 2011. Canberra.

Edwards, B. and S. Chakraborty (2012). "Risk Communication and the Pharmaceutical Industry: what is the reality?" Drug Saf **35**(11): 1027-1040.

Edwards, P. J., I. Roberts, M. J. Clarke, C. Diguiseppi, R. Wentz, I. Kwan, R. Cooper, L. M. Felix and S. Pratap (2009). "Methods to increase response to postal and electronic questionnaires." Cochrane Database Syst Rev(3): MR000008.

Ehrenstein, V., R. K. Hernandez, S. P. Ulrichsen, J. Rungby, T. L. Lash, A. H. Riis, L. Li, H. T. Sorensen and S. S. Jick (2013). "Rosiglitazone use and post-discontinuation glycaemic control in two European countries, 2000-2010." BMJ Open **3**(9): e003424.

Eikelboom, J. W., J. Hirsh, F. A. Spencer, T. P. Baglin and J. I. Weitz (2012). "Antiplatelet drugs: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines." Chest **141**(2 Suppl): e89S-119S.

EMA. "European Medicines Agency. About us." Retrieved 30 May 2013, from http://www.ema.europa.eu/ema/.

EMA. "European Medicines Agency. European public assessment reports." Retrieved 10 January 2014, from http://www.ema.europa.eu/ema/.

EMA. "European Medicines Agency. European public assessment reports." Retrieved 10 September 2014, from http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124.

EMA. "News, press release and public statement archive." Retrieved 10 January 2014, from http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/landing/news_search_landing_page.jsp&mid=WC0b01ac058004d5c1.

EMA. (2005, 16 December 2006). "European Medicines Agency. Guideline on risk management systems for medical products for human use. Incorporated into: Volume 9A of the rules governing medicinal products in the European Union. Guidelines on pharma-covigilance for medicinal products for human use. Part I-3: requirements for risk management systems [online]." Retrieved 10 January 2013, from http://ec.europa.eu/health/files/pharmacos/docs/doc2005/12-05/draft_of_volume_9a_12_2005_en.pdf.

EMA. (2007). "PRESS RELEASE. EMEA statement on recent publication on cardiac safety of rosiglitazone

(Avandia, Avandamet, Avaglim)." from http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500013467.pdf.

EMA. (2007). "PRESS RELEASE. European Medicines Agency confirms positive benefit-risk balance for

rosiglitazone and pioglitazone. 18 October 2007." from http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500011009.pdf.

EMA. (2008). "Press release. EMEA recommends new warnings and contraindications for rosiglitazone.", from http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2009/11/news_detail_000385.jsp&mid=WC0b01ac058004d5c1.

EMA. (2009). "European Medicines Agency. Transparency." Retrieved 10 September 2014, from http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000526.jsp&mid=WC0b01ac0580789730.

EMA. (2009). "Public statement on possible interaction between clopidogrel and proton pump inhibitors. 29 May 2009." Retrieved 10 January 2013, from http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2009/11/news_detail_000194.jsp&mid=WC0b01ac058004d5c1.

EMA. (2010). "Assessment report for AVANDIA. 03 December 2010." from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000268/WC500100757.pdf.

EMA. (2010). "Public statement. Interaction between clopidogrel and proton-pump inhibitors. CHMP updates warning for clopidogrel-containing medicines. 17 March 2010. EMA/174948/2010. ." Retrieved 10 January 2013, from http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2010/03/WC500076346.pdf.

EMA. (2010, 16 December 2010). "Road map to 2015. The European Medicines Agency's contribution to science, medicines and health." Retrieved 10 September 2014, from http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/01/WC500101373.pdf.

EMA. (2011). "Press release. European Medicines Agency recommends new contraindications and warnings for pioglitazone to reduce small increased risk of bladder cancer. 21 July 2011.", from http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/07/WC500109176.pdf.

EMA. (2011). "Press release. Update on ongoing European review of pioglitazone-containing medicines. 9 June 2011." Retrieved 10 Janaury 2013, from http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/06/news_detail_001275.jsp&mid=WC0b01ac058004d5c1.

EMA. (2014). "European Medicines Agency. CHMP: Working parties and other groups." Retrieved 10 September 2014, from http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000102.jsp&mid=WC0b01ac058002d0ec.

Eom, C. S., C. Y. Jeon, J. W. Lim, E. G. Cho, S. M. Park and K. S. Lee (2011). "Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis." CMAJ **183**(3): 310-319.

Erdmann, E., R. Spanheimer and B. Charbonnel (2010). "Pioglitazone and the risk of cardiovascular events in patients with Type 2 diabetes receiving concomitant treatment with nitrates, renin-angiotensin system blockers, or insulin: results from the PROactive study (PROactive 20)." J Diabetes **2**(3): 212-220.

Esterly, J. S., E. Steadman and M. H. Scheetz (2011). "Impact of the FDA warning of potential ceftriaxone and calcium interactions on drug use policy in clinical practice." Int J Clin Pharm **33**(3): 537-542.

Evanchan, J., M. R. Donnally, P. Binkley and E. Mazzaferri (2010). "Recurrence of acute myocardial infarction in patients discharged on clopidogrel and a proton pump inhibitor after stent placement for acute myocardial infarction." Clin Cardiol **33**(3): 168-171.

Farid, N. A., C. D. Payne, C. S. Ernest, 2nd, Y. G. Li, K. J. Winters, D. E. Salazar and D. S. Small (2008). "Prasugrel, a new thienopyridine antiplatelet drug, weakly inhibits cytochrome P450 2B6 in humans." J Clin Pharmacol **48**(1): 53-59.

FDA. "Drug Safety Communications." Retrieved 10 January 2014, from http://www.fda.gov/Drugs/DrugSafety/ucm199082.htm.

FDA. "FDA Organization. About the Center for Drug Evaluation and Research. CDER Offices and Divisions." Retrieved 10 August 2014, from http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/default.htm.

FDA. "FDA. News & Events. Interactive Media." Retrieved 10 January 2014, from http://www.fda.gov/NewsEvents/InteractiveMedia/default.htm.

FDA. "U.S. Food and Drug Administration. MedWatch: The FDA safety information and adverse event reporting Program." Retrieved 10 January 2014, from http://www.fda.gov/Safety/MedWatch/default.htm.

FDA. "US Food and Drug Administration. Guidance for industry: development and use of risk minimization action plans [online]." Retrieved 10 January 2013, from http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126830.pdf.

FDA. (1999). "FDA. Drug Approval Package. Avandia (Rosiglitazone Maleate) Tablets. Company: SmithKline Beecham Pharmaceuticals. Application No.: 21-071. Approval Date: 5/25/1999." Retrieved 10 January 2014, from http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/21071_Avandia.cfm.

FDA. (2000, 21 March 2000). "FDA. News Release. Rezulin (troglitazone)." Retrieved 10 January 2014, from http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm173081.htm.

FDA. (2002, 20 August 2013). "Safey Alerts for Human Medical Products. Vioxx (rofecoxib) May 2002." Retrieved 10 January 2014, from

http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm154520.htm.

FDA. (2004, 21 August 2013). "Safety Alerts for Human Medicial Products. Vioxx(rofecoxib) Sep 2004." Retrieved 10 January 2014, from http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm166532.htm.

FDA. (2005, 22 December 2010). "FDA Organization. Drug Safety Oversight Board." Retrieved 10 August 2014, from http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm082129.htm.

FDA (2007). FDA Briefing Document: Division of Metabolism and Endocrine Products and Office of Surveillance and Epidemiology. Joint meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee.

FDA. (2007, 4 March 2014). "FDA. Advisory Committees. Risk Communication Advisory Committee." Retrieved 10 August 2014, from http://www.fda.gov/advisorycommittees/committeesmeetingmaterials/riskcommunicationadvisorycommittee/default.htm.

FDA. (2007, 20 April 2013). "FDA. News&Events. FDA Issues Safety Alert on Avandia. P07-88, 21 May 2007." Retrieved 10 August 2014, from http://www.fda.gov/newsevents/newsroom/pressannouncements/2007/ucm108917.htm.

FDA. (2007). "Food and Drug Administration Amendments Act of 2007." Retrieved 10 Janaury 2014, from http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/FullTextofFDAAALaw/default.htm.

FDA. (2007). "Information for Healthcare Professionals Rosiglitazone maleate (marketed as Avandia, Avandamet, and Avandaryl)." from http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm143406.htm - 2007_5.

FDA. (2009, 19 June 2009). "Detailed View: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER) -- May 2009." Retrieved 12 January 2014, from http://www.fda.gov/safety/medwatch/safetyinformation/ucm165166.htm.

FDA. (2009, 26 January 2009). "Early Communication about an Ongoing Safety Review of clopidogrel bisulfate (marketed as Plavix)." Retrieved 10 January 2013, from http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm079520.htm.

FDA. (2009). "FDA Drug Safety Communication: reduced effectiveness of Plavix (clopidogrel) in patients who are poor metabolizers of the drug." Retrieved 20 January 2012, from http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm203888.htm.

FDA. (2009). "Follow-Up to the January 26, 2009, Early Communication about an Ongoing Safety Review of Clopidogrel Bisulfate (marketed as Plavix) and Omeprazole

(marketed as Prilosec and Prilosec OTC), 17 November 2009." Retrieved 12 January 2014.

FDA. (2009, 15 August 2013). "Information for Healthcare Professionals: Update to the labeling of Clopidogrel Bisulfate (marketed as Plavix) to alert healthcare professionals about a drug interaction with omeprazole (marketed as Prilosec and Prilosec OTC). 17 November 2009." Retrieved 12 January 2014, from http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm190787.htm.

FDA. (2009). "Public Health Advisory: Updated Safety Information about a drug interaction between Clopidogrel Bisulfate (marketed as Plavix) and Omeprazole (marketed as Prilosec and Prilosec OTC)." Retrieved 12 January 2014, from http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm190825.htm.

FDA. (2010, 27 October 2010). "FDA reminder to avoid concomitant use of Plavix (clopidogrel) and omeprazole. 27 October 2010." Retrieved 10 January 2014.

FDA. (2010). "FDA significant restricts access to the diabetes drug Avandia." Retrieved 10 January 2013, from http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm226956.htm.

FDA (2010). "FDA. Advisory Committee. Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM218493.pdf. (accessed April 6, 2014).".

FDA. (2011). "FDA Drug Safety Communication: Update to ongoing safety review of Actos (pioglitazone) and increased risk of bladder cancer. 15 June 2011." Retrieved 10 Janaury 2013, from http://www.fda.gov/Drugs/DrugSafety/ucm259150.htm.

FDA. (2011, 22 April 2014). "FDA Transparency Initiative." Retrieved 10 August 2014, from http://www.fda.gov/AboutFDA/Transparency/TransparencyInitiative/default.htm.

FDA. (2012, 8 September 2014). "FDA Basics. How does FDA monitor safety after drugs are approved and marketed?" Retrieved 10 September 2014, from http://www.fda.gov/AboutFDA/Transparency/Basics/ucm305058.htm.

FDA. (2013, 25 November 2013). "FDA NEWS RELEASE. FDA requires removal of certain restrictions on the diabetes drug Avandia." Retrieved 10 August 2014, from http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm376516.htm.

FDA. (2013, 10 January 2014). "Plavix (clopidogrel bisulfate) tablet. Detailed View: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER)." Retrieved 10 January 2014.

FDA. (2014, 19 August 2014). "FDA Organization. About the Center for Drug Evaluation and Research." Retrieved 10 September 2014, from http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/default.htm.

Feldman, L., K. S. Williams, J. Coates and M. Knox (2011). "Awareness and utilization of a prescription monitoring program among physicians." J Pain Palliat Care Pharmacother **25**(4): 313-317.

Fernando, H., N. Bassler, J. Habersberger, L. J. Sheffield, R. Sharma, A. M. Dart, K. H. Peter and J. A. Shaw (2011). "Randomized double-blind placebo-controlled crossover study to determine the effects of esomeprazole on inhibition of platelet function by clopidogrel." J Thromb Haemost **9**(8): 1582-1589.

Ferrand, Y., C. M. Kelton, J. J. Guo, M. S. Levy and Y. Yu (2011). "Using time-series intervention analysis to understand U.S. Medicaid expenditures on antidepressant agents." Res Social Adm Pharm **7**(1): 64-80.

Ferreiro, J. L., M. Ueno, S. D. Tomasello, D. Capodanno, B. Desai, K. Dharmashankar, N. Seecheran, M. K. Kodali, A. Darlington, J. P. Pham, A. Tello-Montoliu, R. K. Charlton, T. A. Bass and D. J. Angiolillo (2011). "Pharmacodynamic evaluation of pantoprazole therapy on clopidogrel effects: results of a prospective, randomized, crossover study." Circ Cardiovasc Interv **4**(3): 273-279.

Fischhoff, B. (2009). Risk perception and communication. In:Oxford Textbook on Public Health, Fifth Edition.

Detels R, Beaglehole R, Lansang MA, Gulliford M.(Eds). Oxford University Press, Oxford, UK 941–952.

Flett, G., E. Gurney, L. McKessock and J. Reid (1998). "Impact of the October 1995 pill scare in Grampian." Br J Fam Plann **24**(1): 18-20.

Fowler, F. J., Jr., P. M. Gallagher, V. L. Stringfellow, A. M. Zaslavsky, J. W. Thompson and P. D. Cleary (2002). "Using telephone interviews to reduce nonresponse bias to mail surveys of health plan members." Med Care **40**(3): 190-200.

Freed, G. L., N. A. Spike, J. R. Sewell, L. M. Moran, H. Britt, L. Valenti and P. Brooks (2013). "Changes in longer consultations for children in general practice." J Paediatr Child Health **49**(4): 325-329.

Fugh-Berman, A., K. Alladin and J. Chow (2006). "Advertising in medical journals: should current practices change?" PLoS Med **3**(6): e130.

Funck-Brentano, C., J. Szymezak, O. Steichen, D. Ducint, M. Molimard, V. Remones, M. Azizi and P. Gaussem (2013). "Effects of rabeprazole on the antiplatelet effects and pharmacokinetics of clopidogrel in healthy volunteers." Arch Cardiovasc Dis **106**(12): 661-671.

Gaarder, A., J. Jonsen, S. Laland, A. Hellem and P. A. Owren (1961). "Adenosine diphosphate in red cells as a factor in the adhesiveness of human blood platelets." Nature **192**: 531-532.

Gadzhanova, S. V., E. E. Roughead and M. J. Bartlett (2013). "Improving cardiovascular disease management in Australia: NPS MedicineWise." Med J Aust **199**(3): 192-195.

Garcia Rodriguez, L. A., S. Johansson and L. Cea Soriano (2013). "Use of clopidogrel and proton pump inhibitors after a serious acute coronary event: risk of coronary events and peptic ulcer bleeding." Thromb Haemost **110**(5): 1014-1024.

Garcia Rodriguez, L. A. and S. Perez Gutthann (1998). "Use of the UK General Practice Research Database for pharmacoepidemiology." Br J Clin Pharmacol **45**(5): 419-425.

Garg, P., D. Lillystone, D. Dossetor, C. Kefford and S. Chong (2014). "An Exploratory Survey for Understanding Perceptions, Knowledge and Educational Needs of General Practitioners (GSs) Regarding Autistic Disorders in New South Wales (NSW), Australia." J Clin Diagn Res **8**(7): PC01-09.

Gaspar, A., S. Ribeiro, S. Nabais, S. Rocha, P. Azevedo, M. A. Pereira, A. Brandao, A. Salgado and A. Correia (2010). "Proton pump inhibitors in patients treated with aspirin and clopidogrel after acute coronary syndrome." Rev Port Cardiol **29**(10): 1511-1520.

Gerrits, C. M., M. Bhattacharya, S. Manthena, R. Baran, A. Perez and S. Kupfer (2007). "A comparison of pioglitazone and rosiglitazone for hospitalization for acute myocardial infarction in type 2 diabetes." Pharmacoepidemiology and drug safety **16**(10): 1065-1071.

Gerstein, H. C., S. Yusuf, J. Bosch, J. Pogue, P. Sheridan, N. Dinccag, M. Hanefeld, B. Hoogwerf, M. Laakso, V. Mohan, J. Shaw, B. Zinman and R. R. Holman (2006). "Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial." Lancet **368**(9541): 1096-1105.

GESA. (2010). "Gastroenterological Society of Australia. Medical News. Proton pump inhibitor and clopidogrel interaction: The case for watchful waiting." from http://www.gesa.org.au/news.asp?id=138.

Gilard, M., B. Arnaud, J. C. Cornily, G. Le Gal, K. Lacut, G. Le Calvez, J. Mansourati, D. Mottier, J. F. Abgrall and J. Boschat (2008). "Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study." J Am Coll Cardiol **51**(3): 256-260.

Gilard, M., B. Arnaud, G. Le Gal, J. F. Abgrall and J. Boschat (2006). "Influence of omeprazol on the antiplatelet action of clopidogrel associated to aspirin." J Thromb Haemost **4**(11): 2508-2509.

Gillen, D., A. A. Wirz and K. E. McColl (2004). "Helicobacter pylori eradication releases prolonged increased acid secretion following omeprazole treatment." Gastroenterology **126**(4): 980-988.

Gitlin, N., N. L. Julie, C. L. Spurr, K. N. Lim and H. M. Juarbe (1998). "Two cases of severe clinical and histologic hepatotoxicity associated with troglitazone." Ann Intern Med **129**(1): 36-38.

Giuliano, C., S. M. Wilhelm and P. B. Kale-Pradhan (2012). "Are proton pump inhibitors associated with the development of community-acquired pneumonia? A meta-analysis." Expert Rev Clin Pharmacol **5**(3): 337-344.

Gladding, P., L. Panattoni, M. Webster, L. Cho and S. Ellis (2010). "Clopidogrel pharmacogenomics: next steps: a clinical algorithm, gene-gene interactions, and an elusive outcomes trial." JACC Cardiovasc Interv **3**(10): 995-1000.

Goldberg, R. B., D. M. Kendall, M. A. Deeg, J. B. Buse, A. J. Zagar, J. A. Pinaire, M. H. Tan, M. A. Khan, A. T. Perez and S. J. Jacober (2005). "A comparison of lipid and

glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia." Diabetes Care **28**(7): 1547-1554.

Graham, D. J., C. R. Drinkard, D. Shatin, Y. Tsong and M. J. Burgess (2001). "Liver enzyme monitoring in patients treated with troglitazone." JAMA **286**(7): 831-833.

Graham, D. J., R. Ouellet-Hellstrom, T. E. MaCurdy, F. Ali, C. Sholley, C. Worrall and J. A. Kelman (2010). "Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone." JAMA **304**(4): 411-418.

Gray, S. L., A. Z. LaCroix, J. Larson, J. Robbins, J. A. Cauley, J. E. Manson and Z. Chen (2010). "Proton pump inhibitor use, hip fracture, and change in bone mineral density in postmenopausal women: results from the Women's Health Initiative." Arch Intern Med **170**(9): 765-771.

Grey, A., M. Bolland, G. Gamble, D. Wattie, A. Horne, J. Davidson and I. R. Reid (2007). "The peroxisome proliferator-activated receptor-gamma agonist rosiglitazone decreases bone formation and bone mineral density in healthy postmenopausal women: a randomized, controlled trial." J Clin Endocrinol Metab **92**(4): 1305-1310.

Griffiths, P., L. Vingoe, N. Hunt, J. Mounteney and R. Hartnoll (2000). "Drug information systems, early warning, and new drug trends: can drug monitoring systems become more sensitive to emerging trends in drug consumption?" Subst Use Misuse **35**(6-8): 811-844.

Groves, R. M. and E. Peytcheva (2008). "The impact of nonresponse rates on nonresponse bias a meta-analysis." Public opinion quarterly **72**(2): 167-189.

Guo, J. J., S. Curkendall, J. K. Jones, D. Fife, E. Goehring and D. She (2003). "Impact of cisapride label changes on codispensing of contraindicated medications." Pharmacoepidemiol Drug Saf **12**(4): 295-301.

Gupta, E., D. Bansal, J. Sotos and K. Olden (2010). "Risk of adverse clinical outcomes with concomitant use of clopidogrel and proton pump inhibitors following percutaneous coronary intervention." Dig Dis Sci **55**(7): 1964-1968.

Gurbel, P. A., K. P. Bliden, K. M. Hayes, J. A. Yoho, W. R. Herzog and U. S. Tantry (2005). "The relation of dosing to clopidogrel responsiveness and the incidence of high post-treatment platelet aggregation in patients undergoing coronary stenting." J Am Coll Cardiol **45**(9): 1392-1396.

Gurbel, P. A., K. P. Bliden, B. L. Hiatt and C. M. O'Connor (2003). "Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity." Circulation **107**(23): 2908-2913.

Habib, A. S. and T. J. Gan (2008). "The use of droperidol before and after the Food and Drug Administration black box warning: a survey of the members of the Society of Ambulatory Anesthesia." J Clin Anesth **20**(1): 35-39.

Hall, G. C., H. T. Smith, B. Curtis and A. D. McMahon (2011). "Changes and predictors for change to thiazolidinedione prescribing in UK primary care following the rosiglitazone safety warning." Int J Clin Pract **65**(5): 586-591.

Hampp, C., V. Borders-Hemphill, D. G. Moeny and D. K. Wysowski (2014). "Use of antidiabetic drugs in the U.S., 2003-2012." Diabetes Care **37**(5): 1367-1374.

Hansen, R. A., N. J. Shaheen and J. C. Schommer (2005). "Factors influencing the shift of patients from one proton pump inhibitor to another: the effect of direct-to-consumer advertising." Clin Ther **27**(9): 1478-1487.

Harjai, K. J., C. Shenoy, P. Orshaw, S. Usmani, J. Boura and R. H. Mehta (2011). "Clinical outcomes in patients with the concomitant use of clopidogrel and proton pump inhibitors after percutaneous coronary intervention: an analysis from the Guthrie Health Off-Label Stent (GHOST) investigators." Circ Cardiovasc Interv **4**(2): 162-170.

Hatlebakk, J. G. and A. Berstad (1996). "Pharmacokinetic optimisation in the treatment of gastro-oesophageal reflux disease." Clin Pharmacokinet **31**(5): 386-406.

Health_Canada. (2013). "Health Canada. Regulatory transparency and openness." Retrieved 11 August 2014, from http://www.hc-sc.gc.ca/home-accueil/rto-tor/index-eng.php.

Henschke, N., C. Harrison, D. McKay, C. Broderick, J. Latimer, H. Britt and C. G. Maher (2014). "Musculoskeletal conditions in children and adolescents managed in Australian primary care." BMC Musculoskelet Disord **15**: 164.

Herbst, A. L., H. Ulfelder and D. C. Poskanzer (1971). "Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women." N Engl J Med **284**(15): 878-881.

Hermann, R., P. Cnota and J. Maus (2012). "Minimum quality criteria are needed in the assessment and communication of unexpected drug safety findings of marketed products from randomized controlled trials." Br J Clin Pharmacol **74**(1): 207-208.

Ho, P. M., T. M. Maddox, L. Wang, S. D. Fihn, R. L. Jesse, E. D. Peterson and J. S. Rumsfeld (2009). "Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome." JAMA : the journal of the American Medical Association **301**(9): 937-944.

Hollingworth, S., E. L. Duncan and J. H. Martin (2010). "Marked increase in proton pump inhibitors use in Australia." Pharmacoepidemiol Drug Saf **19**(10): 1019-1024.

Holmes, M. V., P. Perel, T. Shah, A. D. Hingorani and J. P. Casas (2011). "CYP2C19 genotype, clopidogrel metabolism, platelet function, and cardiovascular events: a systematic review and meta-analysis." JAMA : the journal of the American Medical Association **306**(24): 2704-2714.

Home, P. D., S. J. Pocock, H. Beck-Nielsen, P. S. Curtis, R. Gomis, M. Hanefeld, N. P. Jones, M. Komajda and J. J. McMurray (2009). "Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial." Lancet **373**(9681): 2125-2135.

Home, P. D., S. J. Pocock, H. Beck-Nielsen, R. Gomis, M. Hanefeld, N. P. Jones, M. Komajda and J. J. McMurray (2007). "Rosiglitazone evaluated for cardiovascular outcomes--an interim analysis." N Engl J Med **357**(1): 28-38.

Hsu, P. I., K. H. Lai and C. P. Liu (2011). "Esomeprazole with clopidogrel reduces peptic ulcer recurrence, compared with clopidogrel alone, in patients with atherosclerosis." Gastroenterology **140**(3): 791-798.

Hulot, J. S., J. P. Collet, J. Silvain, A. Pena, A. Bellemain-Appaix, O. Barthelemy, G. Cayla, F. Beygui and G. Montalescot (2010). "Cardiovascular risk in clopidogrel-

treated patients according to cytochrome P450 2C19*2 loss-of-function allele or proton pump inhibitor coadministration: a systematic meta-analysis." J Am Coll Cardiol **56**(2): 134-143.

Hurren, K. M., T. N. Taylor and L. A. Jaber (2011). "Antidiabetic prescribing trends and predictors of thiazolidinedione discontinuation following the 2007 rosiglitazone safety alert." Diabetes Res Clin Pract **93**(1): 49-55.

ims. (2011). "Top 20 Global Products, 2011. Top 15 Global Products, 2008." Retrieved 10 January 2014, from http://www.imshealth.com/deployedfiles/imshealth/Global/Content/StaticFile/Top_Line_Data/Global_Top_15_Products.pdf, http://www.imshealth.com/deployedfiles/ims/Global/Content/Corporate/Press Room/Top-Line Market Data & Trends/Top_20_Global_Products.pdf.

Islam, M. M., K. M. Conigrave, C. A. Day, Y. Nguyen and P. S. Haber (2014). "Twenty-year trends in benzodiazepine dispensing in the Australian population." Intern Med J **44**(1): 57-64.

Iyer, S. V., R. Harpaz, P. LePendu, A. Bauer-Mehren and N. H. Shah (2014). "Mining clinical text for signals of adverse drug-drug interactions." J Am Med Inform Assoc **21**(2): 353-362.

James, K. M., J. Y. Ziegenfuss, J. C. Tilburt, A. M. Harris and T. J. Beebe (2011). "Getting physicians to respond: the impact of incentive type and timing on physician survey response rates." Health Serv Res **46**(1 Pt 1): 232-242.

Jepson, C., D. A. Asch, J. C. Hershey and P. A. Ubel (2005). "In a mailed physician survey, questionnaire length had a threshold effect on response rate." J Clin Epidemiol **58**(1): 103-105.

Johnston, V. J., H. Britt, Y. Pan and A. Mindel (2004). "The management of sexually transmitted infections by Australian general practitioners." Sex Transm Infect **80**(3): 212-215.

Johnstone, J., K. Nerenberg and M. Loeb (2010). "Meta-analysis: proton pump inhibitor use and the risk of community-acquired pneumonia." Aliment Pharmacol Ther **31**(11): 1165-1177.

Jones, M. I., S. M. Greenfield and C. P. Bradley (2001). "Prescribing new drugs: qualitative study of influences on consultants and general practitioners." BMJ **323**(7309): 378-381.

Juurlink, D. N., T. Gomes, D. T. Ko, P. E. Szmitko, P. C. Austin, J. V. Tu, D. A. Henry, A. Kopp and M. M. Mamdani (2009). "A population-based study of the drug interaction between proton pump inhibitors and clopidogrel." CMAJ **180**(7): 713-718.

Kahn, S. E., S. M. Haffner, M. A. Heise, W. H. Herman, R. R. Holman, N. P. Jones, B. G. Kravitz, J. M. Lachin, M. C. O'Neill, B. Zinman and G. Viberti (2006). "Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy." N Engl J Med **355**(23): 2427-2443.

Kahrilas, P. J., G. W. Falk, D. A. Johnson, C. Schmitt, D. W. Collins, J. Whipple, D. D'Amico, B. Hamelin and B. Joelsson (2000). "Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: a randomized controlled trial. The Esomeprazole Study Investigators." Aliment Pharmacol Ther **14**(10): 1249-1258.

Kalisch, L. M., G. E. Caughey, J. D. Barratt, E. N. Ramsay, G. Killer, A. L. Gilbert and E. E. Roughead (2012). "Prevalence of preventable medication-related hospitalizations in Australia: an opportunity to reduce harm." Int J Qual Health Care **24**(3): 239-249.

Karpel, J. P., J. I. Peters, A. M. Szema, B. Smith and P. J. Anderson (2009). "Differences in physicians' self-reported knowledge of, attitudes toward, and responses to the black box warning on long-acting beta-agonists." Ann Allergy Asthma Immunol **103**(4): 304-310.

Kashour, T., M. Al-Tannir and R. Bahamid (2014). "Changing prescription pattern of omeprazole among patients receiving clopidogrel." Int Heart J **55**(2): 93-95.

Kellerman, S. E. and J. Herold (2001). "Physician response to surveys. A review of the literature." Am J Prev Med **20**(1): 61-67.

Kim, K. A., P. W. Park, S. J. Hong and J. Y. Park (2008). "The effect of CYP2C19 polymorphism on the pharmacokinetics and pharmacodynamics of clopidogrel: a possible mechanism for clopidogrel resistance." Clinical pharmacology and therapeutics **84**(2): 236-242.

Kimura, T., Y. Matsushita, Y. H. Yang, N. K. Choi and B. J. Park (2011). "Pharmacovigilance systems and databases in Korea, Japan, and Taiwan." Pharmacoepidemiol Drug Saf **20**(12): 1237-1245.

Klinkenberg-Knol, E. C., H. P. Festen and S. G. Meuwissen (1995). "Pharmacological management of gastro-oesophageal reflux disease." Drugs **49**(5): 695-710.

Kongkaew, C., P. R. Noyce and D. M. Ashcroft (2008). "Hospital admissions associated with adverse drug reactions: a systematic review of prospective observational studies." Ann Pharmacother **42**(7): 1017-1025.

Kostapanos, M. S., M. S. Elisaf and D. P. Mikhailidis (2012). "Pioglitazone and cancer: angel or demon?" Curr Pharm Des.

Krantz, M. J., S. B. Rowan, J. Schmittner and B. Bucher Bartelson (2007). "Physician awareness of the cardiac effects of methadone: results of a national survey." J Addict Dis **26**(4): 79-85.

Kreutz, R. P., E. J. Stanek, R. Aubert, J. Yao, J. A. Breall, Z. Desta, T. C. Skaar, J. R. Teagarden, F. W. Frueh, R. S. Epstein and D. A. Flockhart (2010). "Impact of proton pump inhibitors on the effectiveness of clopidogrel after coronary stent placement: the clopidogrel Medco outcomes study." Pharmacotherapy **30**(8): 787-796.

Kushner, F. G., M. Hand, S. C. Smith, Jr., S. B. King, 3rd, J. L. Anderson, E. M. Antman, S. R. Bailey, E. R. Bates, J. C. Blankenship, D. E. Casey, Jr., L. A. Green, J. S. Hochman, A. K. Jacobs, H. M. Krumholz, D. A. Morrison, J. P. Ornato, D. L. Pearle, E. D. Peterson, M. A. Sloan, P. L. Whitlow and D. O. Williams (2009). "2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines." J Am Coll Cardiol **54**(23): 2205-2241.

Kushner, F. G., M. Hand, S. C. Smith, Jr., S. B. King, 3rd, J. L. Anderson, E. M. Antman, S. R. Bailey, E. R. Bates, J. C. Blankenship, D. E. Casey, Jr., L. A. Green, J. S.

Hochman, A. K. Jacobs, H. M. Krumholz, D. A. Morrison, J. P. Ornato, D. L. Pearle, E. D. Peterson, M. A. Sloan, P. L. Whitlow and D. O. Williams (2009). "2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (updating the 2005 Guideline and 2007 Focused Update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines." Circulation **120**(22): 2271-2306.

Kwok, C. S., V. Jeevanantham, B. Dawn and Y. K. Loke (2013). "No consistent evidence of differential cardiovascular risk amongst proton-pump inhibitors when used with clopidogrel: meta-analysis." Int J Cardiol **167**(3): 965-974.

Kwok, C. S. and Y. K. Loke (2010). "Meta-analysis: the effects of proton pump inhibitors on cardiovascular events and mortality in patients receiving clopidogrel." Aliment Pharmacol Ther **31**(8): 810-823.

Kwok, C. S. and Y. K. Loke (2011). "Effects of Proton Pump Inhibitors on Platelet Function in Patients Receiving Clopidogrel: A Systematic Review." Drug Saf.

Kwok, C. S., R. S. Nijjar and Y. K. Loke (2011). "Effects of proton pump inhibitors on adverse gastrointestinal events in patients receiving clopidogrel: systematic review and meta-analysis." Drug Saf **34**(1): 47-57.

Laheij, R. J., M. C. Sturkenboom, R. J. Hassing, J. Dieleman, B. H. Stricker and J. B. Jansen (2004). "Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs." JAMA **292**(16): 1955-1960.

Lanas, A., L. A. Garcia-Rodriguez, M. T. Arroyo, L. Bujanda, F. Gomollon, M. Forne, S. Aleman, D. Nicolas, F. Feu, A. Gonzalez-Perez, A. Borda, M. Castro, M. J. Poveda and J. Arenas (2007). "Effect of antisecretory drugs and nitrates on the risk of ulcer bleeding associated with nonsteroidal anti-inflammatory drugs, antiplatelet agents, and anticoagulants." Am J Gastroenterol **102**(3): 507-515.

Lancet (2010). "European Medicines Agency--more transparency needed." Lancet **375**(9728): 1753.

Langley, T. E., Y. Huang, A. McNeill, T. Coleman, L. Szatkowski and S. Lewis (2011). "Prescribing of smoking cessation medication in England since the introduction of varenicline." Addiction **106**(7): 1319-1324.

Leal, I., S. A. Romio, M. Schuemie, A. Oteri, M. Sturkenboom and G. Trifiro (2013). "Prescribing pattern of glucose lowering drugs in the United Kingdom in the last decade: a focus on the effects of safety warnings about rosiglitazone." Br J Clin Pharmacol **75**(3): 861-868.

Leonard, J., J. K. Marshall and P. Moayyedi (2007). "Systematic review of the risk of enteric infection in patients taking acid suppression." Am J Gastroenterol **102**(9): 2047-2056; quiz 2057.

Lester, J., G. A. Neyarapally, E. Lipowski, C. F. Graham, M. Hall and G. Dal Pan (2013). "Evaluation of FDA safety-related drug label changes in 2010." Pharmacoepidemiol Drug Saf **22**(3): 302-305.

Lev, E. I., R. S. Ramabadran, S. Guthikonda, R. Patel, A. Kleiman, J. F. Granada, T. DeLao and N. S. Kleiman (2007). "Effect of ranitidine on the antiplatelet effects of aspirin in healthy human subjects." Am J Cardiol **99**(1): 124-128.

Lewis, J. D., A. Ferrara, T. Peng, M. Hedderson, W. B. Bilker, C. P. Quesenberry, Jr., D. J. Vaughn, L. Nessel, J. Selby and B. L. Strom (2011). "Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study." Diabetes Care **34**(4): 916-922.

Lexchin, J. (2005). "Drug withdrawals from the Canadian market for safety reasons, 1963-2004." CMAJ **172**(6): 765-767.

Li, X. Q., T. B. Andersson, M. Ahlstrom and L. Weidolf (2004). "Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome P450 activities." Drug Metab Dispos **32**(8): 821-827.

Liazos, E., D. M. Broadbent, N. Beare and N. Kumar (2008). "Spontaneous resolution of diabetic macular oedema after discontinuation of thiazolidenediones." Diabet Med **25**(7): 860-862.

Liberopoulos, E. N., M. S. Elisaf, A. D. Tselepis, A. Archimandritis, D. Kiskinis, D. Cokkinos and D. P. Mikhailidis (2006). "Upper gastrointestinal haemorrhage complicating antiplatelet treatment with aspirin and/or clopidogrel: where we are now?" Platelets **17**(1): 1-6.

Lincoff, A. M., K. Wolski, S. J. Nicholls and S. E. Nissen (2007). "Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials." JAMA : the journal of the American Medical Association **298**(10): 1180-1188.

Lipscombe, L. L., T. Gomes, L. E. Levesque, J. E. Hux, D. N. Juurlink and D. A. Alter (2007). "Thiazolidinediones and cardiovascular outcomes in older patients with diabetes." JAMA **298**(22): 2634-2643.

Lobe, B. (2008). "Integration of Online Research Methods. Information Technology/Social Informatics collection. Faculty of Social Sciences Press.".

Lofstedt, R. (2010). "Risk communication: the Avandia case, a pilot study." Expert Rev Clin Pharmacol **3**(1): 31-41.

Lofstedt, R., F. Bouder and S. Chakraborty (2013). "Transparency and the Food and Drug Administration--a quantitative study." J Health Commun **18**(4): 391-396.

Lofstedt, R. E. (2005). "Risk Management in Post Trust Societies. Palgrave/Macmillan, Basingstoke, UK."

Lofstedt, R. E. (2008). "Academic analysis of the Institute of Medicine report: The Future of Drug Safety." Expert Rev Clin Pharmacol **1**(5): 617-625.

Loke, Y. K., D. Price and A. Herxheimer (2007). "Systematic reviews of adverse effects: framework for a structured approach." BMC Med Res Methodol **7**: 32.

Lunde PKM, A. M., Baksaas I (1987). Drug utilization—an instrument in drug research. In: Kewitz H, Roots I, Voight K, eds, Epidemiological Concepts in Clinical Pharmacology. Berlin: Springer-Verlag, 1987; pp. 57–72.

Lydersen, S. and P. Laake (2003). "Power comparison of two-sided exact tests for association in 2 x 2 contingency tables using standard, mid p and randomized test versions." Stat Med **22**(24): 3859-3871.

Magrini, N., T. Einarson, A. Vaccheri, P. McManus, N. Montanaro and U. Bergman (1997). "Use of lipid-lowering drugs from 1990 to 1994: an international comparison among

Australia, Finland, Italy (Emilia Romagna Region), Norway and Sweden." Eur J Clin Pharmacol **53**(3-4): 185-189.

Majumdar, S. R., L. M. Guirguis, E. L. Toth, R. Z. Lewanczuk, T. K. Lee and J. A. Johnson (2003). "Controlled trial of a multifaceted intervention for improving quality of care for rural patients with type 2 diabetes." Diabetes Care **26**(11): 3061-3066.

Maladie, C. N. d. A. (2011). Risque de cancer de la vessie chez les personnes diabétiques traitées par pioglitazone en France : une étude de cohorte sur les données du SNIIRAM et du PMSI. Paris, France, Saint Denis: Afssaps.

Malgarini, R. B. and G. Pimpinella (2000). "Thrombotic thrombocytopenic purpura induced by ticlopidine: the power of "dear health professional" letters." Ann Pharmacother **34**(3): 404-405.

Mamtani, R., K. Haynes, W. B. Bilker, D. J. Vaughn, B. L. Strom, K. Glanz and J. D. Lewis (2012). "Association between longer therapy with thiazolidinediones and risk of bladder cancer: a cohort study." J Natl Cancer Inst **104**(18): 1411-1421.

Matlock, A., N. Allan, B. Wills, C. Kang and J. B. Leikin (2011). "A continuing black hole? The FDA boxed warning: an appeal to improve its clinical utility." Clin Toxicol (Phila) **49**(6): 443-447.

McDowall, D. (1980). Interrupted Time Series Analysis, Los Angeles, EUA : Sage 1980.

McGee, R. G., A. C. Webster, T. E. Rogerson and J. C. Craig (2012). "Medical device regulation in Australia: safe and effective?" Med J Aust **196**(4): 256-260.

Meadows, M. (2002). "The FDA's drug review process: ensuring drugs are safe and effective." FDA Consum **36**(4): 19-24.

MedEffect™. "Health Canada. MedEffect™ Canada. Advisories, warnings and recalls." Retrieved 10 January 2014, from http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/index-eng.php.

Medicare. (8 April 2014). "The Department ofHealth. Medicare." Retrieved 10 September 2014, from http://www.health.gov.au/internet/main/publishing.nsf/Content/health-medicarebenefits-healthpro.

Medicare. "Pharmaceutical Benefits Schedule Item Reports." Retrieved 10 January 2014, from http://www.medicareaustralia.gov.au/statistics/pbs_item.shtml.

Mehta, S. R., S. Yusuf, R. J. Peters, M. E. Bertrand, B. S. Lewis, M. K. Natarajan, K. Malmberg, H. Rupprecht, F. Zhao, S. Chrolavicius, I. Copland and K. A. Fox (2001). "Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study." Lancet **358**(9281): 527-533.

MHRA. "MHRA. Safety warnings, alerts and recalls." Retrieved 10 Janaury 2014, from http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/index.htm.

Miguel, A., L. F. Azevedo, M. Araujo and A. C. Pereira (2012). "Frequency of adverse drug reactions in hospitalized patients: a systematic review and meta-analysis." Pharmacoepidemiology and drug safety **21**(11): 1139-1154.

Mol, P. G., A. H. Arnardottir, D. Motola, P. J. Vrijlandt, R. G. Duijnhoven, F. M. Haaijer-Ruskamp, P. A. de Graeff, P. Denig and S. M. Straus (2013). "Post-approval safety

issues with innovative drugs: a European cohort study." Drug Saf **36**(11): 1105-1115.

Mol, P. G., S. M. Straus, S. Piening, J. T. de Vries, P. A. de Graeff and F. M. Haaijer-Ruskamp (2010). "A decade of safety-related regulatory action in the Netherlands: a retrospective analysis of direct healthcare professional communications from 1999 to 2009." Drug Saf **33**(6): 463-474.

Moore, M., K. Post and H. Smith (1999). "'Bin bag' study: a survey of the research requests received by general practitioners and the primary health care team." Br J Gen Pract **49**(448): 905-906.

Moore, T. J. and C. D. Furberg (2014). "Development times, clinical testing, postmarket follow-up, and safety risks for the new drugs approved by the US food and drug administration: the class of 2008." JAMA Intern Med **174**(1): 90-95.

Morrato, E. H., B. Druss, D. M. Hartung, R. J. Valuck, R. Allen, E. Campagna and J. W. Newcomer (2010). "Metabolic testing rates in 3 state Medicaid programs after FDA warnings and ADA/APA recommendations for second-generation antipsychotic drugs." Arch Gen Psychiatry **67**(1): 17-24.

Morrato, E. H., A. M. Libby, H. D. Orton, F. V. Degruy, 3rd, D. A. Brent, R. Allen and R. J. Valuck (2008). "Frequency of provider contact after FDA advisory on risk of pediatric suicidality with SSRIs." Am J Psychiatry **165**(1): 42-50.

Mukherjee, D., S. E. Nissen and E. J. Topol (2001). "Risk of cardiovascular events associated with selective COX-2 inhibitors." JAMA **286**(8): 954-959.

Muller, I., F. Besta, C. Schulz, S. Massberg, A. Schonig and M. Gawaz (2003). "Prevalence of clopidogrel non-responders among patients with stable angina pectoris scheduled for elective coronary stent placement." Thromb Haemost **89**(5): 783-787.

Nathan, D. M., J. B. Buse, M. B. Davidson, R. J. Heine, R. R. Holman, R. Sherwin and B. Zinman (2006). "Management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes." Diabetologia **49**(8): 1711-1721.

Nesto, R. W., D. Bell, R. O. Bonow, V. Fonseca, S. M. Grundy, E. S. Horton, M. Le Winter, D. Porte, C. F. Semenkovich, S. Smith, L. H. Young and R. Kahn (2003). "Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. October 7, 2003." Circulation **108**(23): 2941-2948.

Neubauer, H., A. Engelhardt, J. C. Kruger, S. Lask, J. Borgel, A. Mugge and H. G. Endres (2010). "Pantoprazole does not influence the antiplatelet effect of clopidogrel-a whole blood aggregometry study after coronary stenting." J Cardiovasc Pharmacol **56**(1): 91-97.

Ng, F. H., K. F. Lam, S. Y. Wong, C. M. Chang, Y. K. Lau, W. C. Yuen, W. M. Chu and B. C. Wong (2008). "Upper gastrointestinal bleeding in patients with aspirin and clopidogrel co-therapy." Digestion **77**(3-4): 173-177.

Ng, F. H., P. Tunggal, W. M. Chu, K. F. Lam, A. Li, K. Chan, Y. K. Lau, C. Kng, K. K. Keung, A. Kwan and B. C. Wong (2011). "Esomeprazole Compared With

Famotidine in the Prevention of Upper Gastrointestinal Bleeding in Patients With Acute Coronary Syndrome or Myocardial Infarction." Am J Gastroenterol.

Ng, F. H., P. Tunggal, W. M. Chu, K. F. Lam, A. Li, K. Chan, Y. K. Lau, C. Kng, K. K. Keung, A. Kwan and B. C. Wong (2012). "Esomeprazole compared with famotidine in the prevention of upper gastrointestinal bleeding in patients with acute coronary syndrome or myocardial infarction." Am J Gastroenterol **107**(3): 389-396.

NHS (2012) "Prescribing Measures and their application."

NICE. (2003). "Glitazones in the treatment of type 2 diabetes (Review of TA9 and TA21). NICE technology appraisal guidance 63. August 2003." from http://www.nice.org.uk/guidance/ta63/resources/guidance-glitazones-in-the-treatment-of-type-2-diabetes-review-of-ta9-and-ta21-pdf.

NICE (2004). "National Institute for Clinical Excellence. Dyspepsia: management of dyspepsia in

adults in primary care. Clinical Guideline No. 17. 2004. Available from:

http://www.nice.org.uk/download.aspx?o=CG017NICEguideline (accessed 20

January 2012).".

NICE. (2011, August 2011). "National Institute for Health and Clinical Excellence. The management of type 2 diabetes. Type 2 diabetes (partially updated by CG87) (CG66)." Retrieved 10 Janaury 2014, from http://www.nice.org.uk/guidance/CG66.

Nissen, S. E. and K. Wolski (2007). "Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes." N Engl J Med **356**(24): 2457-2471.

Nissen, S. E. and K. Wolski (2010). "Rosiglitazone revisited: an updated meta-analysis of risk for myocardial infarction and cardiovascular mortality." Arch Intern Med **170**(14): 1191-1201.

Niyomnaitham, S., A. Page, A. La Caze, K. Whitfield and A. J. Smith (2014). "Utilisation trends of rosiglitazone and pioglitazone in Australia before and after safety warnings." BMC Health Serv Res **14**(1): 151.

Nkeng, L., A. M. Cloutier, C. Craig, J. Lelorier and Y. Moride (2012). "Impact of regulatory guidances and drug regulation on risk minimization interventions in drug safety: a systematic review." Drug Saf **35**(7): 535-546.

NPS. (2009). "NPS Medicinewise News. Proton pump inhibitors: step-down to symptom control. 4 May 2009." Retrieved 10 January 2014, from http://www.nps.org.au/publications/health-professional/prescribing-practice-review/2009/nps-prescribing-practice-review-45.

NPS. (2014). "NPS MedicineWise. About us." Retrieved 10 January 2014, from http://www.nps.org.au/about-us.

O'Donoghue, M. L., E. Braunwald, E. M. Antman, S. A. Murphy, E. R. Bates, Y. Rozenman, A. D. Michelson, R. W. Hautvast, P. N. Ver Lee, S. L. Close, L. Shen, J. L. Mega, M. S. Sabatine and S. D. Wiviott (2009). "Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials." Lancet **374**(9694): 989-997.

Ogawa, R. and H. Echizen (2010). "Drug-drug interaction profiles of proton pump inhibitors." Clin Pharmacokinet **49**(8): 509-533.

Ogilvie, B. W., P. Yerino, F. Kazmi, D. B. Buckley, A. Rostami-Hodjegan, B. L. Paris, P. Toren and A. Parkinson (2011). "The proton pump inhibitor, omeprazole, but not lansoprazole or pantoprazole, is a metabolism-dependent inhibitor of CYP2C19: implications for coadministration with clopidogrel." Drug Metab Dispos **39**(11): 2020-2033.

Olefsky, J. M. (2000). "Treatment of insulin resistance with peroxisome proliferator-activated receptor gamma agonists." J Clin Invest **106**(4): 467-472.

Olsen, A. K. and M. D. Whalen (2009). "Public perceptions of the pharmaceutical industry and drug safety: implications for the pharmacovigilance professional and the culture of safety." Drug Saf **32**(10): 805-810.

Paschall, S. and A. M. Kaunitz (2008). "Depo-Provera and skeletal health: a survey of Florida obstetrics and gynecologist physicians." Contraception **78**(5): 370-376.

Patrono, C., F. Andreotti, H. Arnesen, L. Badimon, C. Baigent, J. P. Collet, R. De Caterina, D. Gulba, K. Huber, S. Husted, S. D. Kristensen, J. Morais, F. J. Neumann, L. H. Rasmussen, A. Siegbahn, P. G. Steg, R. F. Storey, F. Van de Werf and F. Verheugt (2011). "Antiplatelet agents for the treatment and prevention of atherothrombosis." Eur Heart J **32**(23): 2922-2932.

Patrono, C., F. Andreotti, H. Arnesen, L. Badimon, C. Baigent, J. P. Collet, R. De Caterina, D. Gulba, K. Huber, S. Husted, S. D. Kristensen, J. Morais, F. J. Neumann, L. H. Rasmussen, A. Siegbahn, P. G. Steg, R. F. Storey, F. Van de Werf and F. Verheugt (2011). "Antiplatelet agents for the treatment and prevention of atherothrombosis." European heart journal **32**(23): 2922-2932.

Patrono, C., F. Bachmann, C. Baigent, C. Bode, R. De Caterina, B. Charbonnier, D. Fitzgerald, J. Hirsh, S. Husted, J. Kvasnicka, G. Montalescot, L. A. Garcia Rodriguez, F. Verheugt, J. Vermylen, L. Wallentin, S. G. Priori, M. A. Alonso Garcia, J. J. Blanc, A. Budaj, M. Cowie, V. Dean, J. Deckers, E. Fernandez Burgos, J. Lekakis, B. Lindahl, G. Mazzotta, J. Morais, A. Oto, O. A. Smiseth, R. Ferreira, P. G. Steg, F. Teixeira and R. Wilcox (2004). "Expert consensus document on the use of antiplatelet agents. The task force on the use of antiplatelet agents in patients with atherosclerotic cardiovascular disease of the European society of cardiology." Eur Heart J **25**(2): 166-181.

Patrono, C., C. Baigent, J. Hirsh and G. Roth (2008). "Antiplatelet drugs: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)." Chest **133**(6 Suppl): 199S-233S.

PBAC. (2007, 14 Mar 2008). "ROSIGLITAZONE MALEATE, tablet, 4 mg (base) and 8 mg Avandia; and ROSIGLITAZONE MALEATE with METFORMIN HYDROCHLORIDE, 2 mg (base) – 500 mg, 2 mg (base) – 1 g, 4 mg (base) – 500 mg and 4 mg (base) – 1 g, Avandamet , November 2007." from http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2007-11/pbac-psd-rosiglitazone-nov07.

PBS. "2. Prescribing Medicines – Information for PBS Prescribers." Retrieved 10 January 2014, from http://www.pbs.gov.au/info/healthpro/explanatory-notes/section1/Section_1_2_Explanatory_Notes.

PBS. "Browse the PBS. A02BC - Proton pump inhibitors." Retrieved 10 January 2014, from http://www.pbs.gov.au/browse/body-system?depth=4&codes=a02bc.

PBS. (2006, 27 October 2006). "Public Summary Document. Rosiglitazone Maleate with Metformin Hydrochloride, tablet, 2 mg (base)-500 mg, 2 mg (base)-1000mg, 4 mg (base)-500 mg, 4 mg (base)-1000mg, Avandamet®, July 2006." Retrieved 10 January 2014, from http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2006-07/rosiglitazone.

PBS. (2007, 29 February 2008). "Pioglitazone hydrochloride, tablet, 15 mg, 30 mg and 45 mg, Actos, November 2007." Retrieved 10 January 2014, from http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2007-11/pbac-psd-pioglitazone-nov07.

PBS. (2008). "PBS Latest News. Changes to listings for ROSIGLITAZONE MALEATE (Avandia®) and ROSIGLITAZONE MALEATE with METFORMIN HYDROCHLORIDE (Avandamet®)-1 November 2008." Retrieved 10 January 2014, from http://www.pbs.gov.au/info/news/2008/11/List-amndmnts-avandia-avandamet.

PBS. (2008, 4 July 2008). "Sitagliptin phosphate, tablets, 100 mg, 50 mg and 25 mg, Januvia, March 2008." Retrieved 10 Janaury 2014, from http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2008-03/pbac-psd-sitagliptin-phosphate-mar08.

PBS (2009). "Public Summary Document. Clopidogrel hydrogen sulfate, tablet, 75 mg (base), Iscover®, Plavix®, 2009. Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/E6B3E30135C68639CA257BF0001C1CFA/$File/Clopidogrel BMS & sanofi aventis PSD 9-2 2009-03 Final.pdf accessed 11 August 2014."

PBS (2010). "Australian Statistics on Medicines. Available from: http://www.pbs.gov.au/statistics/asm/2010/australian-statistics-on-medicine-2010.pdf accessed 10 January 2014.".

PBS. (2012). "About the PBS." from http://www.pbs.gov.au/info/about-the-pbs.

PBS. (2014). "Fees, Patient Contributions and Safety Net Thresholds." Retrieved 10 January 2014, from http://www.pbs.gov.au/info/healthpro/explanatory-notes/front/fee.

PBS. (2014). "A-Z medicine listing." Retrieved 10 January 2014, from http://www.pbs.gov.au/browse/medicine-listing.

Pereillo, J. M., M. Maftouh, A. Andrieu, M. F. Uzabiaga, O. Fedeli, P. Savi, M. Pascal, J. M. Herbert, J. P. Maffrand and C. Picard (2002). "Structure and stereochemistry of the active metabolite of clopidogrel." Drug Metab Dispos **30**(11): 1288-1295.

PHIDU. (2014). "Public Health Information Development Unit. The University of Adelaide. Social Health Atlas of Australia: Medicare Local." from http://www.adelaide.edu.au/phidu/maps-data/data/.

Phillips, L. S., G. Grunberger, E. Miller, R. Patwardhan, E. B. Rappaport and A. Salzman (2001). "Once- and twice-daily dosing with rosiglitazone improves glycemic control in patients with type 2 diabetes." Diabetes Care **24**(2): 308-315.

Phipps, S., K. E. Buckholdt, L. Fernandez, L. Wiener, M. J. Kupst, A. Madan-Swain, L. Mullins, R. Robert, O. J. Sahler, N. Vincent and R. B. Noll (2011). "Pediatric

oncologists' practices of prescribing selective serotonin reuptake inhibitors (SSRIs) for children and adolescents with cancer: A multi-site study." Pediatr Blood Cancer.

Piening, S., F. M. Haaijer-Ruskamp, J. T. de Vries, M. E. van der Elst, P. A. de Graeff, S. M. Straus and P. G. Mol (2012). "Impact of safety-related regulatory action on clinical practice: a systematic review." Drug Saf **35**(5): 373-385.

Pit, S. W., T. Vo and S. Pyakurel (2014). "The effectiveness of recruitment strategies on general practitioner's survey response rates - a systematic review." BMC Med Res Methodol **14**: 76.

PMDA. "Pharmaceuticals and Medical Devices Agency, Japan. safety Information." Retrieved 10 August 2014, from http://www.pmda.go.jp/english/service/safety_info.html.

Pongprasobchai, S., S. Kridkratoke and C. Nopmaneejumruslers (2009). "Proton pump inhibitors for the prevention of stress-related mucosal disease in critically-ill patients: a meta-analysis." J Med Assoc Thai **92**(5): 632-637.

Poortinga, W. and N. F. Pidgeon (2003). "Exploring the dimensionality of trust in risk regulation." Risk Anal **23**(5): 961-972.

Pratt, N., M. Andersen, U. Bergman, N. K. Choi, T. Gerhard, C. Huang, M. Kimura, T. Kimura, K. Kubota, E. C. Lai, N. Ooba, U. Osby, B. J. Park, T. Sato, J. Y. Shin, A. Sundstrom, Y. H. Yang and E. E. Roughead (2013). "Multi-country rapid adverse drug event assessment: the Asian Pharmacoepidemiology Network (AsPEN) antipsychotic and acute hyperglycaemia study." Pharmacoepidemiol Drug Saf **22**(9): 915-924.

Rassen, J. A., N. K. Choudhry, J. Avorn and S. Schneeweiss (2009). "Cardiovascular outcomes and mortality in patients using clopidogrel with proton pump inhibitors after percutaneous coronary intervention or acute coronary syndrome." Circulation **120**(23): 2322-2329.

Ratanawijitrasin, S. (2002). "World Health Organization. Effective Drug Regulation - A Multicountry Study and Annex 1; 2002." from http://apps.who.int/medicinedocs/pdf/s2300e/s2300e.pdf.

Ray, W. A., K. T. Murray, M. R. Griffin, C. P. Chung, W. E. Smalley, K. Hall, J. R. Daugherty, L. A. Kaltenbach and C. M. Stein (2010). "Outcomes with concurrent use of clopidogrel and proton-pump inhibitors: a cohort study." Ann Intern Med **152**(6): 337-345.

Ray, W. A. and C. M. Stein (2006). "Reform of drug regulation--beyond an independent drug-safety board." N Engl J Med **354**(2): 194-201.

Richardson, L. P., C. W. Lewis, M. Casey-Goldstein, E. McCauley and W. Katon (2007). "Pediatric primary care providers and adolescent depression: a qualitative study of barriers to treatment and the effect of the black box warning." J Adolesc Health **40**(5): 433-439.

Richter, J. E., P. J. Kahrilas, J. Johanson, P. Maton, J. R. Breiter, C. Hwang, V. Marino, B. Hamelin and J. G. Levine (2001). "Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial." Am J Gastroenterol **96**(3): 656-665.

Rodriguez, E. M., J. A. Staffa and D. J. Graham (2001). "The role of databases in drug postmarketing surveillance." Pharmacoepidemiol Drug Saf **10**(5): 407-410.

Rosen, C. J. (2007). "The rosiglitazone story--lessons from an FDA Advisory Committee meeting." N Engl J Med **357**(9): 844-846.

Roughead, E. E. (1999). "The nature and extent of drug-related hospitalisations in Australia." J Qual Clin Pract **19**(1): 19-22.

Roughead, E. E., A. L. Gilbert and J. G. Primrose (1999). "Improving drug use: a case study of events which led to changes in use of flucloxacillin in Australia." Soc Sci Med **48**(6): 845-853.

Roughead, E. E., R. Lopert and L. N. Sansom (2007). "Prices for innovative pharmaceutical products that provide health gain: a comparison between Australia and the United States." Value Health **10**(6): 514-520.

Ruiter, R., L. E. Visser, M. P. van Herk-Sukel, P. H. Geelhoed-Duijvestijn, S. D. Bie, S. M. Straus, P. G. Mol, S. A. Romio, R. M. Herings and B. H. Stricker (2012). "Prescribing of Rosiglitazone and Pioglitazone Following Safety Signals: Analysis of Trends in Dispensing Patterns in the Netherlands from 1998 to 2008." Drug Saf.

Ruiter, R., L. E. Visser, M. P. van Herk-Sukel, P. H. Geelhoed-Duijvestijn, S. de Bie, S. M. Straus, P. G. Mol, S. A. Romio, R. M. Herings and B. H. Stricker (2012). "Prescribing of rosiglitazone and pioglitazone following safety signals: analysis of trends in dispensing patterns in the Netherlands from 1998 to 2008." Drug Saf **35**(6): 471-480.

Runciman, W. B., E. E. Roughead, S. J. Semple and R. J. Adams (2003). "Adverse drug events and medication errors in Australia." Int J Qual Health Care **15 Suppl 1**: i49-59.

Ryan, E. H., Jr., D. P. Han, R. C. Ramsay, H. L. Cantrill, S. R. Bennett, S. Dev and D. F. Williams (2006). "Diabetic macular edema associated with glitazone use." Retina **26**(5): 562-570.

Sabatine, M. S., C. P. Cannon, C. M. Gibson, J. L. Lopez-Sendon, G. Montalescot, P. Theroux, M. J. Claeys, F. Cools, K. A. Hill, A. M. Skene, C. H. McCabe and E. Braunwald (2005). "Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation." N Engl J Med **352**(12): 1179-1189.

Sabesin, S. M. (1993). "Safety issues relating to long-term treatment with histamine H2-receptor antagonists." Aliment Pharmacol Ther **7 Suppl 2**: 35-40.

Sah, S. and A. Fugh-Berman (2013). "Physicians under the influence: social psychology and industry marketing strategies." J Law Med Ethics **41**(3): 665-672.

Sanchez Ruiz-Gordoa, M., J. M. Tenias Burillo, R. Ruiz Martin de la Torre and J. C. Valenzuela Gamez (2011). "Impact of pharmacotherapeutic warnings on the prescription of clopidogrel and proton pump inhibitors in hospitalised patients." Farm Hosp.

Sanderson, A., D. Zurakowski and J. Wolfe (2013). "Clinician Perspectives Regarding the Do-Not-Resuscitate Order." JAMA Pediatr.

Savi, P., J. M. Herbert, A. M. Pflieger, F. Dol, D. Delebassee, J. Combalbert, G. Defreyn and J. P. Maffrand (1992). "Importance of hepatic metabolism in the antiaggregating activity of the thienopyridine clopidogrel." Biochem Pharmacol **44**(3): 527-532.

Savi, P., M. C. Laplace and J. M. Herbert (1994). "Evidence for the existence of two different ADP-binding sites on rat platelets." Thromb Res **76**(2): 157-169.

Savi, P., P. Nurden, A. T. Nurden, S. Levy-Toledano and J. M. Herbert (1998). "Clopidogrel: a review of its mechanism of action." Platelets **9**(3-4): 251-255.

Savi, P., J. M. Pereillo, M. F. Uzabiaga, J. Combalbert, C. Picard, J. P. Maffrand, M. Pascal and J. M. Herbert (2000). "Identification and biological activity of the active metabolite of clopidogrel." Thromb Haemost **84**(5): 891-896.

Schafer, A., U. Flierl, S. Pfortsch, N. Seydelmann, J. Micka and J. Bauersachs (2010). "The H(2)-receptor antagonist ranitidine interferes with clopidogrel-mediated P2Y(12) inhibition in platelets." Pharmacol Res **62**(4): 352-356.

Schmidt, M., M. B. Johansen, D. J. Robertson, M. Maeng, A. Kaltoft, L. O. Jensen, H. H. Tilsted, H. E. Botker, H. T. Sorensen and J. A. Baron (2012). "Concomitant use of clopidogrel and proton pump inhibitors is not associated with major adverse cardiovascular events following coronary stent implantation." Aliment Pharmacol Ther **35**(1): 165-174.

Schwartz, A. V., D. E. Sellmeyer, E. Vittinghoff, L. Palermo, B. Lecka-Czernik, K. R. Feingold, E. S. Strotmeyer, H. E. Resnick, L. Carbone, B. A. Beamer, S. W. Park, N. E. Lane, T. B. Harris and S. R. Cummings (2006). "Thiazolidinedione use and bone loss in older diabetic adults." J Clin Endocrinol Metab **91**(9): 3349-3354.

Schwarz, G. (1978). "Estimating the Dimension of a Model." (2): 461-464.

Sen, E. F., K. M. Verhamme, M. Felisi, G. W. t Jong, C. Giaquinto, G. Picelli, A. Ceci and M. C. Sturkenboom (2011). "Effects of safety warnings on prescription rates of cough and cold medicines in children below 2 years of age." Br J Clin Pharmacol **71**(6): 943-950.

Shah, B. R., D. N. Juurlink, P. C. Austin and M. M. Mamdani (2008). "New use of rosiglitazone decreased following publication of a meta-analysis suggesting harm." Diabet Med **25**(7): 871-874.

Shah, N. D., V. M. Montori, H. M. Krumholz, K. Tu, G. C. Alexander and C. A. Jackevicius (2010). "Responding to an FDA warning--geographic variation in the use of rosiglitazone." N Engl J Med **363**(22): 2081-2084.

Shmulevich, E., M. Friger, H. Gilutz and A. N. Azab (2011). "Clopidogrel and proton pump inhibitors: is there a significant drug-drug interaction?" Can J Cardiovasc Nurs **21**(4): 27-36.

Shneker, B. F., J. S. Cios and J. O. Elliott (2009). "Suicidality, depression screening, and antiepileptic drugs: reaction to the FDA alert." Neurology **72**(11): 987-991.

Shrank, W. H., N. K. Choudhry, M. A. Fischer, J. Avorn, M. Powell, S. Schneeweiss, J. N. Liberman, T. Dollear, T. A. Brennan and M. A. Brookhart (2010). "The epidemiology of prescriptions abandoned at the pharmacy." Ann Intern Med **153**(10): 633-640.

Sibbing, D., T. Morath, J. Stegherr, S. Braun, W. Vogt, M. Hadamitzky, A. Schomig, A. Kastrati and N. von Beckerath (2009). "Impact of proton pump inhibitors on the antiplatelet effects of clopidogrel." Thromb Haemost **101**(4): 714-719.

Siller-Matula, J. M., B. Jilma, K. Schror, G. Christ and K. Huber (2010). "Effect of proton pump inhibitors on clinical outcome in patients treated with clopidogrel: a systematic review and meta-analysis." J Thromb Haemost **8**(12): 2624-2641.

Siller-Matula, J. M., A. O. Spiel, I. M. Lang, G. Kreiner, G. Christ and B. Jilma (2009). "Effects of pantoprazole and esomeprazole on platelet inhibition by clopidogrel." Am Heart J **157**(1): 148 e141-145.

Simon, T., P. G. Steg, M. Gilard, D. Blanchard, L. Bonello, M. Hanssen, H. Lardoux, P. Coste, T. Lefevre, E. Drouet, G. Mulak, V. Bataille, J. Ferrieres, C. Verstuyft and N. Danchin (2011). "Clinical events as a function of proton pump inhibitor use, clopidogrel use, and cytochrome P450 2C19 genotype in a large nationwide cohort of acute myocardial infarction: results from the French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) registry." Circulation **123**(5): 474-482.

Simon, T., C. Verstuyft, M. Mary-Krause, L. Quteineh, E. Drouet, N. Meneveau, P. G. Steg, J. Ferrieres, N. Danchin and L. Becquemont (2009). "Genetic determinants of response to clopidogrel and cardiovascular events." N Engl J Med **360**(4): 363-375.

Singh, G. and G. Triadafilopoulos (2005). "Appropriate choice of proton pump inhibitor therapy in the prevention and management of NSAID-related gastrointestinal damage." Int J Clin Pract **59**(10): 1210-1217.

Singh, S., Y. K. Loke and C. D. Furberg (2007). "Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis." JAMA **298**(10): 1189-1195.

Smalley, W., D. Shatin, D. K. Wysowski, J. Gurwitz, S. E. Andrade, M. Goodman, K. A. Chan, R. Platt, S. D. Schech and W. A. Ray (2000). "Contraindicated use of cisapride: impact of food and drug administration regulatory action." JAMA **284**(23): 3036-3039.

Smith, S. C., Jr., J. Allen, S. N. Blair, R. O. Bonow, L. M. Brass, G. C. Fonarow, S. M. Grundy, L. Hiratzka, D. Jones, H. M. Krumholz, L. Mosca, R. C. Pasternak, T. Pearson, M. A. Pfeffer and K. A. Taubert (2006). "AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute." Circulation **113**(19): 2363-2372.

Spiegelman, B. M. (1998). "PPAR-gamma: adipogenic regulator and thiazolidinedione receptor." Diabetes **47**(4): 507-514.

Squires, D. A. (2011). "The U.S. health system in perspective: a comparison of twelve industrialized nations." Issue Brief (Commonw Fund) **16**: 1-14.

Srba, J., V. Descikova and J. Vlcek (2012). "Adverse drug reactions: analysis of spontaneous reporting system in Europe in 2007-2009." Eur J Clin Pharmacol **68**(7): 1057-1063.

Stanton, L. A., G. M. Peterson, R. H. Rumble, G. M. Cooper and A. E. Polack (1994). "Drug-related admissions to an Australian hospital." J Clin Pharm Ther **19**(6): 341-347.

Starner, C. I., J. A. Schafer, A. H. Heaton and P. P. Gleason (2008). "Rosiglitazone and pioglitazone utilization from January 2007 through May 2008 associated with five risk-warning events." J Manag Care Pharm **14**(6): 523-531.

Statistics. (2012, 25 March 2014). "Australian Bureau of Statistics. Causes of Death, Austarlia, 2012." Retrieved 10 August 2014, from http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/3303.0main+features100012012.

Steinhubl, S. R., P. B. Berger, J. T. Mann, 3rd, E. T. Fry, A. DeLago, C. Wilmer and E. J. Topol (2002). "Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial." JAMA : the journal of the American Medical Association **288**(19): 2411-2420.

Stewart, K. A., B. M. Natzke, T. Williams, E. Granger, S. W. Casscells and T. W. Croghan (2009). "Temporal trends in anti-diabetes drug use in TRICARE following safety warnings in 2007 about rosiglitazone." Pharmacoepidemiology and drug safety **18**(11): 1048-1052.

Stockigt, J. R. (2007). "Barriers in the quest for quality drug information: salutary lessons from TGA-approved sources for thyroid-related medications." Med J Aust **186**(2): 76-79.

Stockl, K. M., L. Le, A. Zakharyan, A. S. Harada, B. K. Solow, J. E. Addiego and S. Ramsey (2010). "Risk of rehospitalization for patients using clopidogrel with a proton pump inhibitor." Arch Intern Med **170**(8): 704-710.

Stricker, B. H. and B. M. Psaty (2004). "Detection, verification, and quantification of adverse drug reactions." BMJ **329**(7456): 44-47.

Strom, B. L. (2005). Pharmacoepidemiology, John Wiley & Sons, Ltd.

Strom, B. L. (2006). "How the US drug safety system should be changed." JAMA **295**(17): 2072-2075.

Sturkenboom, M. C., L. T. de Jong-van den Berg, M. C. Cornel, B. H. Stricker and H. Wesseling (1994). "Communicating a drug alert. A case study on acitretin in The Netherlands." Eur J Clin Pharmacol **47**(2): 125-132.

SurveyMonkey®. (2014). from https://http://www.surveymonkey.com.

Suvarna, R. (2011). PML: Risk Communication in the EU, Safeguarding public health.

Sylvain Pichetti, C. S., Saskia van der Erf (2013). "The Diffusion of New Anti-diabetic drugs: an International Comparison." INSTITUT DE RECHERCHE ET DO CUMEN TA TION EN ÉCONOMIE DE LA SANTÉ.

Tett, S. E., I. Sketris, C. Cooke, S. V. van Zanten and N. Barozzi (2013). "Differences in utilisation of gastroprotective drugs between 2001 and 2005 in Australia and Nova Scotia, Canada." Pharmacoepidemiol Drug Saf **22**(7): 735-743.

TGA. "Medicines Safety Update." Retrieved 10 January 2014, from http://www.tga.gov.au/hp/msu.htm - .VA4JX2SSylg.

TGA. "Safety information. Alerts." Retrieved 10 January 2014, from http://www.tga.gov.au/safety/alerts.htm - .VAQr_WS1aCA.

TGA. (7 May 2014). "TGA structure." Retrieved 7 August 2014, from http://www.tga.gov.au/about/tga-structure.htm - .VAQqOWS1aCA.

TGA. (2007, 22 February 2011). "Australian Adverse Drug Reactions Bulletin, Vol 26, No 6, December 2007. Emerging cardiovascular concerns with rosiglitazone." Retrieved 10 Janaury 2014, from http://www.tga.gov.au/hp/aadrb-0712.htm - .U1jHJ-aSylg.

TGA. (2010, 16 February 2011). "TGA. Safety information. Alerts. Rosiglitazone (Avandia/Avandamet). Advisory statement. 24 September 2010." Retrieved 10

January 2014, from http://www.tga.gov.au/safety/alerts-medicine-rosiglitazone-100924.htm - .VCFs2iuSx9w.

TGA. (2011, April 2012). "Required Advisory Statements for Medicine Labels updates. TGA response to submissions. Version 3.0, April 2012." https://http://www.tga.gov.au/pdf/archive/consult-labelling-rasml-110218-response.pdf. Retrieved 10 January 2013.

TGA. (2011, 24 August 2011). "Safety information. Alerts. Pioglitazone and risk of bladder cancer. Safety advisory. 18 July 2011." Retrieved 10 January 2013, from http://www.tga.gov.au/safety/alerts-medicine-pioglitazone-110718.htm - .VCFOSSuSx9w.

TGA. (2011, 26 March 2014). "TGA reforms: A blueprint for TGA's future. 8 December 2011.", from http://www.tga.gov.au/archive/tga-reforms-blueprint.htm.

TGA. (2011). "Transparency review of the TGA." Retrieved 10 January 2014, from http://www.tga.gov.au/newsroom/review-tga-transparency-1101.htm - .VA4DeGSSx9w.

TGA. (2013, 4 June 2013). "About the Early Warning System." Retrieved 10 January 2014, from http://www.tga.gov.au/safety/ews-about.htm - .VAQsAmS1aCA.

TGA. (2013, 4 June 2013). "Therapeutic Goods Administration. Monitoring communications." Retrieved 10 January 2014.

TGA. (2014, 12 August 2014). "About the TGA. Advisory Committee on the Safety of Medicines (ACSOM)." Retrieved 14 August 2014, from http://www.tga.gov.au/about/committees-acsom.htm - .VBCag2SSx9w.

TGA. (2014). "Australian Government Department of Health. Therapeutic Goods Administration. The role of the TGA." Retrieved 6 August 2014, from http://www.tga.gov.au/hp/education-hp-role.htm - .VAQqqGS1aCA.

TGA (2014). "TGA. About the TGA. Available from: http://www.tga.gov.au/about/tga-who-we-are.htm - .U_F_2LxU4y4 (accessed on May 30, 2014).".

TGA_Alerts. "Safety information. Alerts." Retrieved 10 January 2014, from http://www.tga.gov.au/safety/alerts.htm - .VA4H0GSSylg.

TGA_reforms. (2012, 9 July 2014). "TGA reforms." Retrieved 10 August 2014, from http://www.tga.gov.au/about/tga-reforms.htm - .VAQqPGS1aCA.

Theophile, H., G. Miremont-Salame, P. Robinson, N. Moore, B. Begaud and F. Haramburu (2011). "Relevance of a "Dear Doctor letter" to alert healthcare providers to new recommendations for vitamin D administration." Eur J Clin Pharmacol **67**(7): 681-686.

Thomas, S. K., J. Hodson, G. McIlroy, A. Dhami and J. J. Coleman (2013). "The impact of direct healthcare professional communication on prescribing practice in the UK hospital setting: an interrupted time series analysis." Drug Saf **36**(7): 557-564.

Thompson, D. and G. Oster (1996). "Use of terfenadine and contraindicated drugs." JAMA **275**(17): 1339-1341.

Torguson R, C. C., Kaneshige K, Xue Z, Satler L, Kent K, Pichard A, Suddath W, Waksman R. "Does proton pump inhibitor use following percutaneous coronary intervention with drug-eluting stents impact clinical outcome?" Circulation 2009; 120: S968.

Trenk, D. (2009). "Proton pump inhibitors for prevention of bleeding episodes in cardiac patients with dual antiplatelet therapy - between Scylla and Charybdis?" Int J Clin Pharmacol Ther **47**(1): 1-10.

Tsai, Y. W., Y. W. Wen, W. F. Huang, P. F. Chen, K. N. Kuo and F. Y. Hsiao (2011). "Cardiovascular and gastrointestinal events of three antiplatelet therapies: clopidogrel, clopidogrel plus proton-pump inhibitors, and aspirin plus proton-pump inhibitors in patients with previous gastrointestinal bleeding." J Gastroenterol **46**(1): 39-45.

UKPDS (1998). "Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group." Lancet **352**(9131): 837-853.

Valuck, R. J., H. D. Orton and A. M. Libby (2009). "Antidepressant discontinuation and risk of suicide attempt: a retrospective, nested case-control study." J Clin Psychiatry **70**(8): 1069-1077.

van Boxel, O. S., M. G. van Oijen, M. P. Hagenaars, A. J. Smout and P. D. Siersema (2010). "Cardiovascular and gastrointestinal outcomes in clopidogrel users on proton pump inhibitors: results of a large Dutch cohort study." Am J Gastroenterol **105**(11): 2430-2436; quiz 2437.

van Grootheest, A. C. and I. R. Edwards (2002). "Labelling and 'Dear Doctor' letters: are they noncommittal?" Drug Saf **25**(15): 1051-1055.

Vancelik, S., N. E. Beyhun, H. Acemoglu and O. Calikoglu (2007). "Impact of pharmaceutical promotion on prescribing decisions of general practitioners in Eastern Turkey." BMC Public Health **7**: 122.

Vaughn, B. P., G. A. Doherty, S. Gautam, A. C. Moss and A. S. Cheifetz (2012). "Screening for tuberculosis and hepatitis B prior to the initiation of anti-tumor necrosis therapy." Inflamm Bowel Dis **18**(6): 1057-1063.

Wagner, A. K., K. A. Chan, I. Dashevsky, M. A. Raebel, S. E. Andrade, J. E. Lafata, R. L. Davis, J. H. Gurwitz, S. B. Soumerai and R. Platt (2006). "FDA drug prescribing warnings: is the black box half empty or half full?" Pharmacoepidemiology and drug safety **15**(6): 369-386.

Wagner, A. K., S. B. Soumerai, F. Zhang and D. Ross-Degnan (2002). "Segmented regression analysis of interrupted time series studies in medication use research." J Clin Pharm Ther **27**(4): 299-309.

Wahab, A. I., N. L. Pratt, L. M. Kalisch and E. E. Roughead (2014). "Comparing time to adverse drug reaction signals in a spontaneous reporting database and a claims database: a case study of rofecoxib-induced myocardial infarction and rosiglitazone-induced heart failure signals in Australia." Drug Saf **37**(1): 53-64.

Wahab, I. A., N. L. Pratt, L. M. Kalisch and E. E. Roughead (2013). "The detection of adverse events in randomized clinical trials: can we really say new medicines are safe?" Curr Drug Saf **8**(2): 104-113.

Watkins, C., I. Harvey, P. Carthy, L. Moore, E. Robinson and R. Brawn (2003). "Attitudes and behaviour of general practitioners and their prescribing costs: a national cross sectional survey." Qual Saf Health Care **12**(1): 29-34.

Wax, D., A. Doshi, S. Hossain, C. A. Bodian, M. Krol and D. L. Reich (2007). "Changing patterns of postoperative nausea and vomiting prophylaxis drug use in an academic anesthesia practice." J Clin Anesth **19**(5): 356-359.

Weatherby, L. B., B. L. Nordstrom, D. Fife and A. M. Walker (2002). "The impact of wording in "Dear doctor" letters and in black box labels." Clinical pharmacology and therapeutics **72**(6): 735-742.

Wedemeyer, R. S. and H. Blume (2014). "Pharmacokinetic drug interaction profiles of proton pump inhibitors: an update." Drug Saf **37**(4): 201-211.

Weiss, H. J. and L. M. Aledort (1967). "Impaired platelet-connective-tissue reaction in man after aspirin ingestion." Lancet **2**(7514): 495-497.

Welage, L. S. and R. R. Berardi (2000). "Evaluation of omeprazole, lansoprazole, pantoprazole, and rabeprazole in the treatment of acid-related diseases." J Am Pharm Assoc (Wash) **40**(1): 52-62; quiz 121-123.

Wertheimer, A. I. (1986). "The defined daily dose system (DDD) for drug utilization review." Hosp Pharm **21**(3): 233-234, 239-241, 258.

Wheeler, B. W., C. Metcalfe, D. Gunnell, P. Stephens and R. M. Martin (2009). "Population impact of regulatory activity restricting prescribing of COX-2 inhibitors: ecological study." Br J Clin Pharmacol **68**(5): 752-764.

WHO (2000). "Safety Monitoring of Medicinal Products: Guidelines for Setting Up and Running a Pharmacovigilance Centre, 2000.".

WHO (2003). "WHO International Working Group for Drug Statistics Methodology, WHO Collaborating Centre for Drug Statistics Methodology, WHO Collaborating Centre for Drug Utilization Research and Clinical Pharmacology. Introduction to Drug Utilization Research. Geneva: World Health Organization, 2003.".

WHO (2004). "Pharmacovigilance: Ensuring the Safe Use of Medicines - WHO Policy Perspectives on Medicines, No.009, October 2004.".

WHO. (2013, 19 December 2013). "ATC/DDD Index. A10BG Thiazolidinediones." Retrieved 10 January 2014, from http://www.whocc.no/atc_ddd_index/?code=A10BG.

WHO. (2013, 19 December 2013). "WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index." Retrieved 10 January 2014, from http://www.whocc.no/atc_ddd_index/.

Wijlaars, L. P., I. Nazareth and I. Petersen (2012). "Trends in depression and antidepressant prescribing in children and adolescents: a cohort study in The Health Improvement Network (THIN)." PLoS One **7**(3): e33181.

Wilhelm, S. M., R. G. Rjater and P. B. Kale-Pradhan (2013). "Perils and pitfalls of long-term effects of proton pump inhibitors." Expert Rev Clin Pharmacol **6**(4): 443-451.

Woosley, R. L. (2000). "Drug labeling revisions-guaranteed to fail?" JAMA **284**(23): 3047-3049.

Wright, K. B. (2005). "Researching Internet-Based Populations: Advantages and Disadvantages of Online Survey Research, Online Questionnaire Authoring Software Packages, and Web Survey Services. Journal of Computer-Mediated Communication, 10: 00. doi: 10.1111/j.1083-6101.2005.tb00259.x."

Xu, R. and Q. Wang (2014). "Automatic signal extraction, prioritizing and filtering approaches in detecting post-marketing cardiovascular events associated with targeted cancer drugs from the FDA Adverse Event Reporting System (FAERS)." J Biomed Inform **47**: 171-177.

Yang, Y. X., J. D. Lewis, S. Epstein and D. C. Metz (2006). "Long-term proton pump inhibitor therapy and risk of hip fracture." JAMA **296**(24): 2947-2953.

Yasuda, H., M. Yamada, S. Sawada, Y. Endo, K. Inoue, F. Asano, Y. Takeyama and M. Yoshiba (2009). "Upper gastrointestinal bleeding in patients receiving dual antiplatelet therapy after coronary stenting." Intern Med **48**(19): 1725-1730.

Yki-Jarvinen, H. (2004). "Thiazolidinediones." N Engl J Med **351**(11): 1106-1118.

Yu, D. T., D. L. Seger, K. E. Lasser, A. S. Karson, J. M. Fiskio, A. C. Seger and D. W. Bates (2010). "Impact of implementing alerts about medication black-box warnings in electronic health records." Pharmacoepidemiology and drug safety.

Yusuf, S., F. Zhao, S. R. Mehta, S. Chrolavicius, G. Tognoni and K. K. Fox (2001). "Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation." N Engl J Med **345**(7): 494-502.

Zahno, A., K. Brecht, M. Bodmer, D. Bur, D. A. Tsakiris and S. Krahenbuhl (2010). "Effects of drug interactions on biotransformation and antiplatelet effect of clopidogrel in vitro." Br J Pharmacol **161**(2): 393-404.

Zairis, M. N., G. Z. Tsiaousis, N. G. Patsourakos, A. T. Georgilas, C. F. Kontos, E. N. Adamopoulou, K. Vogiatzidis, S. K. Argyrakis, C. N. Fakiolas and S. G. Foussas (2010). "The impact of treatment with omeprazole on the effectiveness of clopidogrel drug therapy during the first year after successful coronary stenting." Can J Cardiol **26**(2): e54-57.

Zomerdijk, I. M., F. A. Sayed-Tabatabaei, G. Trifiro, S. C. Blackburn, M. C. Sturkenboom and S. M. Straus (2012). "Risk minimization activities of centrally authorized products in the EU: a descriptive study." Drug Saf **35**(4): 299-314.

Appendices

Niyomnaitham et al. BMC Health Services Research 2014, 14:151
http://www.biomedcentral.com/1472-6963/14/151

BMC Health Services Research

RESEARCH ARTICLE Open Access

Utilisation trends of rosiglitazone and pioglitazone in Australia before and after safety warnings

Suvimol Niyomnaitham[1,2*], Andrew Page[3], Adam La Caze[1], Karen Whitfield[1] and Alesha J Smith[1,4]

Abstract

Background: A series of drug safety warnings have recently been made by drug authorities relating to adverse effects of rosiglitazone and pioglitazone on cardiovascular diseases and bladder cancer. The changes to the patterns of rosiglitazone and pioglitazone utilisation in Australia following the timing of these various health authority warnings such as the Australian Therapeutic Good Administration (TGA), European Medicines Agency (EMA) press releases or U.S. Food and Drug Administration (FDA) is unknown. This study investigated the utilisation patterns of rosiglitazone and pioglitazone in Australia before and after warnings of major drug authorities.

Methods: We evaluated rosiglitazone and pioglitazone dispensing using the Pharmaceutical Benefit Scheme (PBS) subsidised drug dispensing data for the Australian population from February 2004 to July 2012. The World Health Organisation Anatomic Therapeutic Chemical (ATC)/Defined Daily Dose (DDD) system was used to compare the drug utilisation patterns following the announcements of EMA, FDA, and TGA safety warnings, which first occurred in May 2007. The DDD/1000population/day were examined in a series of time-series regression analysis with the drug safety warnings specified as interventions.

Results: Rosiglitazone utilisation increased steadily from 2004 until reaching a peak at 1.96/1000population/day in January 2007. Then rosiglitazone use decreased significantly after the initial EMA press release and FDA warning on cardiovascular risk in May 2007 (with a 15.04% average monthly decline, p-value <0.001), however use did not significantly decrease after the TGA warning or subsequent EMA and FDA warnings. Pioglitazone utilisation proceeded rosiglitazone in September 2008 and remained above 1.5/1000/day during 2009–2010. However, pioglitazone utilisation has slightly declined after the FDA, EMA, and TGA warnings related to bladder cancer.

Conclusions: Drug safety warnings were associated with a decrease in rosiglitazone and pioglitazone utilisation in Australia. Rosiglitazone began to decline prior to TGA warnings in December 2007, which suggests that Australian prescribers may have acted in response to scientific evidence or international safety warnings (EMA, FDA), prior to the response of the TGA. Minor effects were observed after bladder cancer warnings on pioglitazone utilisation.

Keywords: Rosiglitazone, Pioglitazone, Safety warnings

Background

Thiazolidinediones (TZDs) were approved for type 2 diabetes mellitus (DM) treatment based on efficacy studies, which showed a decrease in HbA1c, by 0.8-1.5% and improved insulin sensitivity [1,2]. Both TZDs, rosiglitazone and pioglitazone, were listed on the Australian Pharmaceutical Benefit Scheme (PBS) as subsidised second line therapy with either metformin or a sulfonylurea in November 2003 and later extended to triple oral therapy with metformin and a sulfonylurea and in combination with insulin [3].

In May 2007, a meta-analysis by Nissen and Wolski found a small increased risk in myocardial infarction and a borderline increase in cardiovascular death in patients treated with rosiglitazone [4]; however, another ongoing clinical trial evaluating cardiovascular outcomes of rosiglitazone showed cardiovascular events associated with rosiglitazone [5] to be inconclusive. Because cardiovascular disease can be a lethal complication in patients

* Correspondence: suvimol.niyomnaitham@uq.net.au
[1]School of Pharmacy, University of Queensland, 20 Cornwall Street, Woolloongabba, Australia
[2]Faculty of Medicine Siriraj Hospital, Mahidol University, Wanglang Road, 10700 Bangkok, Thailand
Full list of author information is available at the end of the article

with diabetes mellitus, several studies have tried to establish the adverse cardiovascular effect associated with rosiglitazone treatment [6,7].

Since then, drug regulatory authorities have investigated these cardiovascular effects [8] and issued several warnings on the use of rosiglitazone [9,10]. The Australian regulatory authority, the Therapeutic Goods Administration (TGA) is responsible for ensuring the safety of medical products within Australia [11]. The TGA distributes safety information to healthcare professionals through the "Safety Advisory" on the TGA's website, similar to that of the U.S. Food and Drug Administration (FDA) drug safety communication [12] and European Medicines Agency (EMA) press releases [13].

Since late 2008, PBS steadily limited the subsidisation of rosiglitazone use in combination with insulin and triple oral therapy [14]. On 1st July 2011, the PBS restricted prescription of rosiglitazone by requiring prior telephone approval [15].

While the meta-analysis raised a concern around the cardiovascular risk of rosiglitazone, a study of pioglitazone showed that in comparison it was a safe alternative with an insignificant increase in mortality, myocardial infarction and stroke [16]. Pioglitazone also reduced the risk of hospitalization for acute myocardial infarction in patients with type 2 diabetes in comparison with rosiglitazone [16,17]. In June 2011, a French study suggested an increased risk of bladder cancer in patients who were treated with pioglitazone for more than one year leading to a temporary withdrawal of pioglitazone by the French Agency [18]. Another study in the US also indicated a possible increase in bladder cancer risk in patients on pioglitazone for more than 2 years, compared with diabetes patients who were not receiving pioglitazone [19,20]. The TGA, as well as FDA and EMA, announced safety warnings outlining a possible risk of bladder cancer related to pioglitazone use in June-July 2011; however, there have been no further updates on this issue [21-23].

The increasing risk of cardiovascular disease with rosiglitazone led to a decrease in the utilisation patterns, in the US [24,25] and some countries in Europe [26,27]. It is expected that after the bladder cancer warnings, pioglitazone will follow a similar utilisation trend to that of rosiglitazone. However, it is plausible that pioglitazone use may have slightly changed as a result of prescribers weighing up the benefit in blood sugar control and prevention of cardiovascular events versus the possible increased risk of bladder cancer, which has a very low incidence (3 cases per 1000 pioglitazone users) [19,20]. The dispensing patterns of rosiglitazone and pioglitazone following the emerging cardiovascular event and safety warnings have not been described in Australia, although it is hypothesised that the trends will follow that of the US and Europe. This study aims to describe the patterns of rosiglitazone and pioglitazone use, and investigate the influential factors on changes of utilisation in Australia, with special focus on the safety warnings by TGA, FDA and EMA.

Methods

Data sources

Drug utilisation among populations over time can be examined using the World Health Organization Anatomic Therapeutic Chemical (ATC)/Defined Daily Dose (DDD) system [28]. Data on monthly dispensed medicines were obtained from the PBS database, a national administrative scheme which records drugs subsidised by the Government for Australian citizens. The PBS database captures all subsidized drug formulations, cost and amount of dispensing and period of drug dispensed by pharmacists for patients used at home [29]. Drug dispensed data on the PBS database were used in research studied and shown to represent trends of drug utilisation in Australia [30,31]. Rosiglitazone and pioglitazone are listed as subsidised drugs for all Australians therefore a complete record of dispensed medicines was obtained [3]. Denominator populations from Centrelink [32] and the Australian Bureau of Statistics [33] were used to calculate the DDD per 1000 population per day (the proportion of the population receiving a DDD of this drug per day). All the data for this study were aggregated, routinely collected data and publically available via government sources, therefore ethics approval was not required.

Australian drug safety warnings for rosiglitazone and pioglitazone were acquired from safety alerts and safety information for health professionals on the TGA website [34]. We accessed the EMA's safety announcements, called "press releases" [35], and the FDA drug safety communication [36] from their official websites. Since mid-2007, major drug authorities have issued safety warnings related to rosiglitazone and pioglitazone. The first TGA announcement which highlighted the increased risk of ischemic heart disease associated with rosiglitazone was issued in December 2007 (TGA1) [37], followed by a second warning to avoid using rosiglitazone in patients with ischemic heart disease in September 2010 (TGA2) [38]. The FDA had three announcements related to cardiovascular risk of rosiglitazone [39]; firstly, a safety alert in May 2007 (FDA1) [40], a label update on heart-related risks in August 2007 (FDA2) [41], and then restrictions on rosiglitazone use in September 2010 (FDA3) [42]. There were four EMA press releases on risk of ischemic heart disease in May 2007 (EMA1) [43], October 2007 (EMA2) [44], January 2008 (EMA3) [45] and September 2010 (EMA4) [46]. While the TGA and FDA still allowed rosiglitazone on the market, the EMA suspended all medical products containing rosiglitazone across Europe in September 2010 [46].

For pioglitazone, the FDA issued a warning on a possible increased risk of bladder cancer in patients who used pioglitazone for longer than one year in June 2011 [23], followed by the same warnings in the EMA press release [21] and the TGA safety advisory [22] in July 2011.

Whilst there were other plausible types of information sent to prescribers with regards to the drug safety, it is recognized that the warnings from the FDA, EMA and TGA have a large influence on drug safety communication. For example, the pharmaceutical companies marketing these medicines did not implement changes to the Product Information until after the TGA announcement. In Australia, medical media picked up this side effect once it came out from the FDA as well as medical associations issued the FDA warning on their articles.

Analyses

Monthly dispensing data of rosiglitazone and pioglitazone from January 2004 to July 2012 were converted to DDD/1000population/day. Descriptive trends in rosiglitazone and pioglitazone utilisation were examined in the time series of DDD/1000pop/day. The auto-regressive, integrated, moving average model (ARIMA) integrates the temporal size and direction dependency (autocorrelation) inherent in time-series data to better characterize changes in data over a period of time [47]. Autocorrelation functions (ACF) and partial autocorrelation functions (PACF) was used to obtain the best fitted model for analysis as well as the Bayesian Information Criteria. The percentage change in DDD/1000pop/day was used to remove the trend component of the time series before fitting into ARIMA models. The separate and combined effects of the announcement of the EMA, FDA, and TGA warnings on trends in rosiglitazone and pioglitazone utilisation were also investigated by fitting into ARIMA models. Impacts of drug safety warnings (interventions) on the subsequent observations were then investigated using the ARIMA model as a step-function (having a permanent and immediate impact on any subsequent trends). All statistical analyses were performed with a 5% statistical significance level using STATA 12.1 (StataCorp, College Station, TX).

Results

A total of 1,686,087 rosiglitazone prescriptions and 2,405,881 pioglitazone prescriptions were dispensed during January 2004-July 2012. We calculated the monthly utilisation (DDD/1000population/day) using Australian population data, which was in the range of 20.1 million in 2004–22.9 million in 2012. As shown in Figure 1, the rosiglitazone utilisation increased steadily from 2004 and reached the peak in January 2007 with a defined daily dose of 1.96 per 1000 people per day. However, in May 2007, the trend of rosiglitazone utilisation started decreasing and remaining lower than 0.50 DDD/1000pop/day in May 2009 and 0.15 DDD/1000pop/day in July 2011. Pioglitazone utlisation has exceeded rosiglitazone use since September 2008 and remained stable during 2009–2010 (1.5-1.7 DDD/1000pop/day). Nevertheless, the trend of pioglitazone utilisation appeared to decrease in September 2011.

There are no seasonal autocorrelation detected for both rosiglitazone and pioglitazone utilisations. Based on visual inspection of PACF and ACF plots, an ARIMA (1,0,2) model best characterised for rosiglitazone data and pioglitazone data was best characterised as an ARIMA (1,0,1). Findings from ARIMA models indicated that the utilisation of rosiglitazone decreased significantly after the EMA1 and FDA1 warnings with −15.04% per month (p-value <0.001) (Table 1). Additionally, the utilisation of rosiglitazone also significantly decreased following warnings from FDA2, EMA2, TGA1, and EMA3. However, after adjustment for FDA2, EMA2, TGA1, and EMA3 for preceding warnings, effects were attenuated and were no longer statistically significant (Table 1). Later warnings relating to EMA4, FDA3, and TGA2 were not significantly associated with decreases in rosiglitazone use (Table 1).

For pioglitazone, although we can see a decline after the FDA, TGA, and EMA warnings on bladder cancer in June-July 2011, there is no statistically significant effect on subsequent pioglitazone use after fitting this into ARIMA model (Table 1).

Discussion

The changes of rosiglitazone and pioglitazone utilisation were observed between 2004 and 2012 in Australia. It is always difficult to attribute cause to utilisation trends, however it is likely that increased marketing of TZDs may have contributed to the increasing trend of rosiglitazone during 2004–2006 or that fewer alternatives to metformin, sulfonylurea, and insulin were available at this time. Our results show a decreasing trend in rosiglitazone utilisation in the period after the drug authorities' warnings in 2007–2008. Although the numbers of rosiglitazone prescriptions in Australia are relatively low in comparison to the UK, and North America, the overall trends are consistent with those shown in Europe and North America [24,26,27,48]. There are two possible explanations for the dip seen in April 2007. It might be a seasonal trend as the same fluctuation was noted in March-April 2006; however, this was not sensitive enough to be detected by the ARIMA model. Secondly, the dip is an artifact of the data, this is actually the utilisation on its way up which is demonstrated by the higher use again in May 2007.

The sharply decreasing utilisation trend is significantly attributable to the safety alert from meta-analysis study

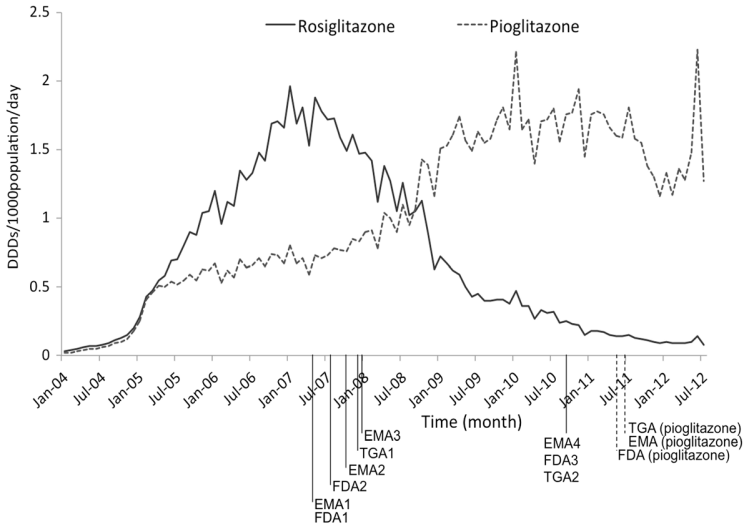


Figure 1 Utilisation of rosiglitazone and pioglitazone by the Australian population between 2004–2012. The drop-down lines indicate months of drug safety warnings issued. Notes: Rosiglitazone warnings: EMA1-Reminded the risk of rosiglitazone in patients with cardiac failure and other cardiac disorders including myocardial infarction. FDA1-Advised to evaluate the antidiabetic treatment options other than rosiglitazone in patients who have underlying heart disease and high risk of heart attack. FDA2-Adds box warnings for heart-related risks of rosiglitazone. EMA2-Suggested that rosiglitazone should only be used after careful evaluation of ischemic heart disease. TGA1-dvised that rosiglitazone should not be prescribed for patients with known ischemic heart disease or at high risk for ischemic heart disease. EMA3-Suggested that rosiglitazone must not be used in patients with an acute coronary disease. EMA4-Recommended suspension of all rosiglitazone-containing products. FDA3-Restricts access to rosiglitazone due to an elevated risk of cardiovascular events. TGA3-Reinforced that rosiglitazone should not be used in patients with known ischemic heart disease. Pioglitazone warnings: FDA-Announced the warnings on a possibly increased risk of bladder cancer in patients who used rosiglitazone for longer than one year. TGA-Advised the prescribers that use of pioglitazone for more than a year may be associated with an increased risk of bladder cancer. EMA-Recommends new contraindications and warnings for pioglitazone to reduce small increased risk of bladder cancer. TGA = Therapeutic Good Administration; EMA = European Medicines Agency; FDA = U.S. Food and Drug Administration.

and the initial warnings from the EMA and FDA in May 2007. For the reason that the FDA issued the cardiovascular alert of rosiglitazone on the same day as publication by Nissen et al. [4], we could not distinguish the effects between the authority warnings and the publication. Furthermore, the effects of these warnings and associated literature are likely to be cumulative rather than a discrete effect on the following utilisation. Several restrictions in rosiglitazone subsidies from the PBS during October 2008-Febraury 2009 were also examined; however,

Table 1 Effects of drug warnings on the utilisation of rosiglitazone and pioglitazone in Australia

Drug authorities	Time	Warnings	Adjusted for	Coefficient[a]	95% CI[b]	*p* value
Rosiglitazone: ARIMA (1,0,2) model						
EMA1_FDA1	May 2007	Ischemic heart	-	−15.04	[−21.86, −8.22]	**<0.001**[c]
FDA2	Aug 2007	Label update heart related	EMA1_FDA1	−2.61	[−40.41, 35.20]	0.893
EMA2	Oct 2007	Ischemic heart	EMA1_FDA1, FDA2	1.94	[−95.49, 99.36]	0.969
TGA1	Dec 2007	Ischemic heart	EMA1_FDA1, FDA2, EMA2	−5.25	[−38.01, 27.51]	0.837
EMA3	Jan 2008	Ischemic heart	EMA1_FDA1, FDA2, EMA2, TGA1	−0.39	[−80.06, 79.28]	0.992
FDA3, TGA2, EMA4	Sep 2010	EU suspended, US restriction	EMA1_FDA1, FDA2, EMA2, TGA1, EMA3	1.25	[−8.99, 11.49]	0.811
Pioglitazone: ARIMA (1,0,1) model						
FDA	June 2011	Bladder cancer	-	−5.76	[−13.91, 2.39]	0.166
EMA, TGA	July 2011	Bladder cancer	-	−6.57	[−14.80, 1.65]	0.117

[a]Coefficient = Percentage change in magnitude and direction after the intervention.
[b]CI = confidence interval.
[c]Statistical significance at *p* value <0.05.
TGA = Therapeutic Good Administration; EMA = European Medicines Agency; FDA = U.S. Food and Drug Administration; EU = European Union; US = United States of America.

these impacts are not significant after adjustment for previous warnings. As a result of the consecutive series of cardiovascular warnings on rosiglitazone since 2007 and the limited access on PBS, the numbers of rosiglitazone prescriptions have remained lower than 5,000 per month since 2010.

Australian utilisation of pioglitazone was less than half of rosiglitazone during 2005–2007 and the increasing trend in use was moderate compared to the Netherlands and the US [25,27]. From 2008–2010, when peak levels were reached, the increase in pioglitazone nearly mirrors the decline in rosiglitazone. The findings suggest that prescribers might have replaced rosiglitazone with the same drug class pioglitazone [24,49], due to the reported cardiovascular benefits of pioglitazone, and no clinical outcome associated with an increase risk of ischemic heart disease that was seen with rosiglitazone [7,17]. While the decreasing trend of pioglitazone was observed in the US and Europe in 2008 [27,49], Australian pioglitazone utilisation plateaued until 2011. The delay in decreasing trend compared to that of other countries may be attribute to limited availability of second-line and third-line therapy alternatives such as sitagliptin (was not PBS subsidised until August 2008) or exenatide (was not PBS subsidised until August 2010) [50]. The US and UK data [49,51] show that the number of other new drugs, which were available in their markets since 2007 such as sitagliptin and exenatide, increased after the cardiovascular alerts of TZD. Nevertheless, Figure 1 shows the decline in the utilisation of pioglitazone after July 2011. This decreasing trend may have been caused by more alternative treatments on the PBS or the safety concern of increased risk of bladder cancer in long-term users of pioglitazone. Although, this decline was of a lesser magnitude than for rosiglitazone, prescribers may consider the risk/benefit ratio, where the benefits of pioglitazone in lowering blood sugar outweigh the possible risk of bladder cancer [52]. However, more data points following this bladder cancer risk might be needed to examine the true effect of this warning.

Since TGA safety warnings are considered by the Australian Department of Health and Aging to be first-line alerts to Australian prescribers, we would expect to see a significant effect on these utilisations. However, the fact that a) the decline in rosiglitazone use occurred prior to the first TGA warning, and b) after we adjusted for the preceding EMA, FDA warnings, we could not see a significant effect of the TGA warning on utilisation trends suggests that Australian prescribers were aware of the international warnings as well as the safety information from the literature. This might be associated with the way that information was delivered, since Australian warnings were delayed, less frequently communicated, and accessed compared to the FDA and European warnings [38,53]. Australian prescribers may receive safety information from medical articles or media that referred to the US or European warnings. A further qualitative study is being conduct to gain the insight into sources of drug safety information among Australian prescribers.

Since time series model prediction is based on the pattern of drug use in the past confounding influences on data may be difficult to disentangle. Although trends can be impacted by temporal changes in drug supply or the way data are recorded, we did not find those problems during study period. Furthermore, the Australia PBS data is aggregated data collected for administrative purposes, which does not link utilisation to the prescribing data in clinical settings. Therefore, clinical reasons for the decrease in dispensing cannot be fully investigated, nor primary non-compliance in patients be established.

The strength of this study is that it captures almost all prescriptions dispensed over 2004–2012 in total Australian population (private prescriptions represent a very small percentage of all prescriptions). This is achieved because rosiglitazone and pioglitazone are 'high' cost drugs that are government subsidised in Australia. This allowed us to investigate the patterns of population based thiazolidinedione utilisation.

Conclusions

The utilisation of rosiglitazone significantly decreased following the authorities' safety warnings on ischemic heart disease. The pattern of rosiglitazone utilisation started declining significantly prior to the TGA warning in December 2007; therefore it appears that Australian prescribers were alerted by the literature and international warnings such as EMA and FDA. In contrast, pioglitazone utilisation increased during the rosiglitazone warning period during 2007–2010. In comparison to the US and Europe, the decline in pioglitazone trend was much more deferred due to no available second and third line therapies in Australia. Despite concerns surrounding the possible risk of bladder cancer with long term use of pioglitazone, this study showed weaker effects of safety warnings on bladder cancer and pioglitazone utilisation. A number of publications have studied the effect of authorities' warnings in the US and Europe to improve their warning systems [27,54,55]. This is one of the first studies to date that has investigated utilisation patterns in relation to drug safety warnings in Australia and suggests that TGA warnings may not affect prescribing in cases such as this where prescribers may be attuned to particular medicine safety issues described in earlier international warnings or literature. Further research is needed to understand how and when prescribers obtain drug safety information in Australia. This is particularly pertinent as Australia and New Zealand look to combine their drug safety warning systems.

Abbreviations
TGA: Therapeutic good administration; EMA: European medicines agency; FDA: U.S. food and drug administration; PBS: Pharmaceutical benefit scheme; DDD: Defined daily dose; TZD: Thiazolidinedione; DM: Diabetes mellitus; ARIMA: Auto-regressive, integrated, moving average model; ACF: Autocorrelation functions; PACF: Partial autocorrelation functions; CI: Confidence interval.

Competing interests
No sources of funding were involved in this study. The authors declare that they have no competing interests.

Authors' contributions
SN, AC, KW, and AS were responsible for developing the study and method. SN and AP participated in the data collection, statistical analysis and result interpretation. All authors contributed to manuscript writing and all revisions of the manuscript. All authors read and approved the final manuscript.

Acknowledgements
We would like to thank the Faculty of Medicine Siriraj Hospital and University of Queensland for the postgraduate scholarship.

Author details
[1]School of Pharmacy, University of Queensland, 20 Cornwall Street, Woolloongabba, Australia. [2]Faculty of Medicine Siriraj Hospital, Mahidol University, Wanglang Road, 10700 Bangkok, Thailand. [3]School of Science and Health, Campbelltown campus, University of Western Sydney, Richmond, NSW, Australia. [4]School of Pharmacy, University of Otago, Frederick Street, 9016 Dunedin, New Zealand.

Received: 12 November 2013 Accepted: 27 March 2014
Published: 4 April 2014

References

1. Phillips LS, Grunberger G, Miller E, Patwardhan R, Rappaport EB, Salzman A: **Once- and twice-daily dosing with rosiglitazone improves glycemic control in patients with type 2 diabetes.** *Diabetes Care* 2001, **24**(2):308–315.
2. Aronoff S, Rosenblatt S, Braithwaite S, Egan JW, Mathisen AL, Schneider RL: **Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose–response study. The Pioglitazone 001 Study Group.** *Diabetes Care* 2000, **23**(11):1605–1611.
3. **Pharmaceutical benefit scheme medicine listing. Department of Health and Ageing. Australian Government.** Available from: http://www.pbs.gov.au/browse/medicine-listing. (accessed December 20, 2012).
4. Nissen SE, Wolski K: **Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes.** *N Engl J Med* 2007, **356**(24):2457–2471.
5. Home PD, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJ: **Rosiglitazone evaluated for cardiovascular outcomes–an interim analysis.** *N Engl J Med* 2007, **357**(1):28–38.
6. Bilik D, McEwen LN, Brown MB, Selby JV, Karter AJ, Marrero DG, Hsiao VC, Tseng CW, Mangione CM, Lasser NL, Crosson JC, Herman WH: **Thiazolidinediones, cardiovascular disease and cardiovascular mortality: translating research into action for diabetes (TRIAD).** *Pharmacoepidemiol Drug Saf* 2010, **19**(7):715–721.
7. Gerrits CM, Bhattacharya M, Manthena S, Baran R, Perez A, Kupfer S: **A comparison of pioglitazone and rosiglitazone for hospitalization for acute myocardial infarction in type 2 diabetes.** *Pharmacoepidemiol Drug Saf* 2007, **16**(10):1065–1071.
8. FDA: **Briefing Information for the July 13–14, 2010 Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee. Available from**: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm218491.htm. (**accessed April 6, 2014**).
9. Weatherby LB, Nordstrom BL, Fife D, Walker AM: **The impact of wording in "Dear doctor" letters and in black box labels.** *Clin Pharmacol Ther* 2002, **72**(6):735–742.
10. FDA: **Advisory Committee. Available from**: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM218493.pdf. (**accessed April 6, 2014**).
11. **Therapeutic Goods Administralion. About the TGA. Available from**: http://www.tga.gov.au/about/committees-acsom.htm. (**accessed May 30, 2012**).
12. FDA: **Drug Safety Communication. Available from**: http://www.fda.gov/Drugs/DrugSafety/ucm199082.htm. (**accessed Dec 20, 2012**).
13. European Medicines Agency: **News, press release and public statement archive. Available from**: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/landing/news_search_landing_page.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1. (**accessed on Nov 12, 2012**).
14. **PBS Latest News. Changes to listings for ROSIGLITAZONE MALEATE (Avandia®) and ROSIGLITAZONE MALEATE with METFORMIN HYDROCHLORIDE (Avandamet®)-1 November 2008. Available from**: http://www.pbs.gov.au/info/news/2008/11/List-amndmnts-avandia-avandamet (**accessed May 10, 2012**).
15. *Pharmaceutical Benefits Advisory Committee. Positive Recommendations made by the PBAC — March 2011.* Canberra: Australian Government Department of Health and Ageing; 2011. **Available from**: http://www.pbs.gov.au/info/publication/factsheets/professional/new-listings-and-changes-1-july-2011 (**accessed April 6, 2014**).
16. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE: **Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials.** *JAMA* 2007, **298**(10):1180–1188.
17. Erdmann E, Spanheimer R, Charbonnel B: **Pioglitazone and the risk of cardiovascular events in patients with Type 2 diabetes receiving concomitant treatment with nitrates, renin-angiotensin system blockers, or insulin: results from the PROactive study (PROactive 20).** *J Diabetes* 2010, **2**(3):212–220.
18. **AFSSAPS. Available from**: http://ansm.sante.fr/var/ansm_site/storage/original/application/3b70d267800de891b8f204f0376b7538.pdf. (**accessed May 30, 2012**).
19. Lewis JD, Ferrara A, Peng T, Hedderson M, Bilker WB, Quesenberry CP Jr, Vaughn DJ, Nessel L, Selby J, Strom BL: **Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study.** *Diabetes Care* 2011, **34**(4):916–922.
20. Mamtani R, Haynes K, Bilker WB, Vaughn DJ, Strom BL, Glanz K, Lewis JD: **Association between longer therapy with thiazolidinediones and risk of bladder cancer: a cohort study.** *J Natl Cancer Inst* 2012, **104**(18):1411–1421.
21. European Medicines Agency: **Press release. European Medicines Agency recommends new contraindications and warnings for pioglitazone to reduce small increassed risk of bladder cancer. Available from**: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2011/07/WC500109176.pdf. (**accessed May 30, 2012**).
22. TGA: **Pioglitazone and risk of bladder cancer. Safety advisory. Available from**: http://www.tga.gov.au/safety/alerts-medicine-pioglitazone-110718.htm. (**accessed Dec 12, 2012**).
23. **FDA Drug Safety Communication: Update to ongoing safety review of Actos (pioglitazone) and increased risk of bladder cancer. Available from**: http://www.fda.gov/Drugs/DrugSafety/ucm259150.htm. (**accessed Dec 20, 2012**).
24. Starner CI, Schafer JA, Heaton AH, Gleason PP: **Rosiglitazone and pioglitazone utilization from January 2007 through May 2008 associated with five risk-warning events.** *J Manag Care Pharm* 2008, **14**(6):523–531.
25. Cohen A, Rabbani A, Shah N, Alexander GC: **Changes in glitazone use among office-based physicians in the U.S., 2003–2009.** *Diabetes Care* 2010, **33**(4):823–825.
26. Stewart KA, Natzke BM, Williams T, Granger E, Casscells SW, Croghan TW: **Temporal trends in anti-diabetes drug use in TRICARE following safety warnings in 2007 about rosiglitazone.** *Pharmacoepidemiol Drug Saf* 2009, **18**(11):1048–1052.
27. Ruiter R, Visser LE, van Herk-Sukel MP, Geelhoed-Duijvestijn PH, Bie SD, Straus SM, Mol PG, Romio SA, Herings RM, Stricker BH: **Prescribing of Rosiglitazone and Pioglitazone Following Safety Signals: Analysis of Trends in Dispensing Patterns in the Netherlands from 1998 to 2008.** *Drug Saf* 2012, **35**(6):471–480.
28. **WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index. Available from**: http://www.whocc.no/atc_ddd_index/. (**accessed Nov 23, 2011**).
29. **Australian Goverment Department of Health and Ageing. About PBS. Available from**: http://pbs.gov.au/info/about-the-pbs (**accessed November 30, 2011**).

30. Hollingworth S, Duncan EL, Martin JH: **Marked increase in proton pump inhibitors use in Australia.** *Pharmacoepidemiol Drug Saf* 2010, **19**(10):1019–1024.
31. Islam MM, Conigrave KM, Day CA, Nguyen Y, Haber PS: **Twenty-year trends in benzodiazepine dispensing in the Australian population.** *Intern Med J* 2014, **44**(1):57–64.
32. **Centrelink. Department of Human Services. Australian Government. Available from**: http://www.humanservices.gov.au/. (**accessed July 20, 2012**).
33. **Australian Bureau of Statistics. Available from**: http://www.abs.gov.au/. (**accessed July 20, 2012**).
34. TGA: **Safety information. Available from**: http://www.tga.gov.au/hp/information-safety.htm. (**accessed Dec 12, 2012**).
35. European Medicines Agency: **News and events. Available from**: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/landing/news_and_events.jsp&mid=. (**accessed May 30, 2012**).
36. Food and Drug Administation: **Drug Safety Communications. Available from**: http://www.fda.gov/Drugs/DrugSafety/ucm199082.htm. (**accessed May 30, 2012**).
37. TGA: **Australian Adverse Drug Reactions Bulletin, Vol 26, No 6. Available from**: http://www.tga.gov.au/hp/aadrb-0712.htm. (**accessed Dec 20, 2012**).
38. TGA: **Safety information. Rosiglitazone (Avandia/Avandamet). Advisory statement. Available from**: http://www.tga.gov.au/safety/alerts-medicine-rosiglitazone-100924.htm. (**accessed Nov 20, 2012**).
39. FDA: **Postmarket Drug Safety Information for Patients and Providers. Available from**: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm143349.htm. (**accessed Dec 20, 2012**).
40. **FDA Drug Safety Communication. FDA Issues Safety Alert on Avandia. Available from**: http://www.fda.gov/newsevents/newsroom/pressannouncements/2007/ucm108917.htm. (**accessed April 6, 2014**).
41. FDA: **Avandia label. Available from**: http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM143413.pdf. (**accessed Dec 20, 2012**).
42. **FDA significant restricts access to the diabetes drug Avandia. Available from**: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm226956.htm. (**accessed Dec 20, 2012**).
43. European Medicines Agency: **Press release on May 23, 2007. Available from**: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500013467.pdf. (**accessed May 15, 2011**).
44. European Medicines Agency: **Press release on October 18, 2007. Available from**: http://www.emea.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500011009.pdf. (**accessed May 15, 2011**).
45. European Medicines Agency: **Press release on January 24, 2008. Available from**: http://www.emea.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500015420.pdf. (**accessed May 15, 2012**).
46. European Medicines Agency: **European Medicines Agency recommends suspension of Avandia, Avandamet and Avaglim. Available from**: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/09/news_detail_001119.jsp&mid=WC0b01ac058004d5c1&jsenabled=true. (**accessed May 30, 2012**).
47. Box GEP TG: **Intervention analysis with applications to economic and environmental problems.** *J Am Stat Assoc* 1975, **70:**70–74.
48. Shah ND, Montori VM, Krumholz HM, Tu K, Alexander GC, Jackevicius CA: **Responding to an FDA warning–geographic variation in the use of rosiglitazone.** *N Engl J Med* 2010, **363**(22):2081–2084.
49. Hurren KM, Taylor TN, Jaber LA: **Antidiabetic prescribing trends and predictors of thiazolidinedione discontinuation following the 2007 rosiglitazone safety alert.** *Diabetes Res Clin Pract* 2011, **93**(1):49–55.
50. Australian Government Department of Health and Ageing: **March 2008 PBAC Outcomes — Positive Recommendations made by the PBAC-November 2008. Available from**: http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/2008-11/positive-recommendations (**accessed May 30, 2012**).
51. Leal I, Romio SA, Schuemie M, Oteri A, Sturkenboom M, Trifiro G: **Prescribing pattern of glucose lowering drugs in the United Kingdom in the last decade: a focus on the effects of safety warnings about rosiglitazone.** *Br J Clin Pharmacol* 2013, **75**(3):861–868.
52. Kostapanos MS, Elisaf MS, Mikhailidis DP: **Pioglitazone and cancer: angel or demon?** *Curr Pharm Des* 2012, **19**(27):4913–4929.
53. Buckley NA, Rossi S: **Bringing greater transparency to "black box" warnings.** *Clin Toxicol (Phila)* 2011, **49**(6):448–451.
54. Esterly JS, Steadman E, Scheetz MH: **Impact of the FDA warning of potential ceftriaxone and calcium interactions on drug use policy in clinical practice.** *Int J Clin Pharm* 2011, **33**(3):537–542.
55. Sen EF, Verhamme KM, Felisi M, t Jong GW, Giaquinto C, Picelli G, Ceci A, Sturkenboom MC: **Effects of safety warnings on prescription rates of cough and cold medicines in children below 2 years of age.** *Br J Clin Pharmacol* 2011, **71**(6):943–950.

doi:10.1186/1472-6963-14-151
Cite this article as: Niyomnaitham *et al.*: Utilisation trends of rosiglitazone and pioglitazone in Australia before and after safety warnings. *BMC Health Services Research* 2014 **14**:151.

THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

School of Pharmacy

4th October 2013

Ms Suvimol (Jess) Niyomnaitham
School of Pharmacy
The University of Queensland

Ethics Committee Approval – (2013/16)
'Prescriber perspectives towards the drug safety warning in Australia using the warnings on clopidogrel and thiazolidinediones as case studies"

Dear Jess,

I am pleased to advise that the School of Pharmacy Ethics Committee has given approval to your application for the interview component of the above project, pending some slight changes.

- The information and consent forms need to show that the School of Pharmacy Ethics Committee, is the body granting ethical approval.
- It also needs to be clear that should participants have any concerns about the study or the conduct of the study that these be referred to an independent person (usually the Ethics Committee Secretary) not the CI of the research.
- Before proceeding to the survey component please resubmit the full survey to the Ethics Committee in the School of Pharmacy for approval.

The Committee would like to wish you every success for the outcome of your project.

If you have any further queries please do not hesitate to contact me.

Yours sincerely,

Vanessa King
Secretary
School of Pharmacy
Ethics Committee

School of Pharmacy
Pharmacy Australia Centre of Excellence
The University of Queensland

20 Cornwall Street
Woolloongabba Qld 4102 Australia

T +61 7 3346 1900
F +61 7 3346 1999

E enquiries@pharmacy.uq.edu.au
W www.uq.edu.au/pharmacy

THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

School of Pharmacy

19th November 2013

Ms Suvimol (Jess) Niyomnaitham
School of Pharmacy
The University of Queensland

Ethics Committee Approval – Amendment (2013/17)
'Prescriber perspectives towards the drug safety warning in Australia using the warnings on clopidogrel and thiazolidinediones as case studies"

Dear Jess,

I am pleased to advise that the School of Pharmacy Ethics Committee has given approval to your amendment of the above project.

However, should any deviation from the approved research protocol occur please inform the Committee as it may be necessary to resubmit an amended protocol for ethical approval.

The Committee would like to wish you every success for the outcome of your project.

If you have any further queries please do not hesitate to contact me.

Yours sincerely,

Vanessa King
Secretary
School of Pharmacy
Ethics Committee

School of Pharmacy
Pharmacy Australia Centre of Excellence
The University of Queensland

20 Cornwall Street
Woolloongabba Qld 4102 Australia

T +61 7 3346 1900
F +61 7 3346 1999

E enquiries@pharmacy.uq.edu.au
W www.uq.edu.au/pharmacy

THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

Participant Information Sheet (Version 1, 9 September 2013)

Semi-structured interview: Prescriber perspectives towards the drug safety warning in Australia using the warnings on clopidogrel and thiazolidinediones as case studies

Principal Investigator: Suvimol Niyomnaitham
Co Investigators: Alesha Smith
Adam La Caze
Karen Whitfield

1. Your Consent

You are invited to participate in a semi-structured interview because you are prescribers and regulatory perssonel in Australia.

This participant information and consent form contains detailed information about the research project. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project before you decide whether or not to take part in it.

Please read this participant information sheet carefully. Feel free to ask questions about any of the information in the document.

Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate that you understand the information and that you give your consent to participate in the research project.

You will be given a copy of the participant information sheet and consent form to keep for your records.

2. Background and purpose

Changes in prescribing occurred following the release of regulatory safety warnings regarding the clopidogrel and proton pump inhibitor interaction and adverse effects of thiazolidinediones. Prescriber perspectives towards the drug warning system in Australia and prescribing decisions in response to these warnings will inform how these prescribing changes take place.

This study conducted by researchers at the University of Queensland aims to investigate prescribers' attitudes toward the current drug warning system in Australia and investigate prescribing decisions in response to emerging safety warnings.

3. Procedures

Participation involves a one-on-one interview with the principal researcher. The interview will last 15–20 minutes. You will be asked to respond to questions regarding sources of drug safety information, opinion on drug safety processes in Australia and prescribing decisions in response to drug safety information.

The interview will be recorded and later transcribed by the principal investigator. No identifying information will be recorded.

There are no right or wrong answers to any of the questions in the interview; it is your view and opinion that is important.

THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

4. Possible Benefits and Risks

Your experience will help us understand how prescribers respond to the drug warning system in Australia and provide information on the impact of drug warnings on prescribing decisions. These data may lead to improved communication and collaboration between drug authorities and prescribers.
It is not anticipated that any risks will be associated with participating in the project. No identifying information will be collected during the interview. You can stop the interview at any time.

5. Participation, Privacy, Confidentiality and Disclosure of Information

Participation is voluntary. If you decide to take part and later change your mind, you are free to withdraw from the study anytime without giving a reason.

The information collected from you will be stored in a locked filing cabinet in a locked office. Access will only be given to researchers involved in this project. The data will be stored for a period of 7 years and then will be destroyed.

All information collected as part of this research will be collected, stored and reported in non-identifiable manner (no names or other personal identifiers will be collected).

6. Results of the Project

The data from the study will be analysed by the research team at the University of Queensland and the aggregated results will be published in health care journals to inform other health care professionals and researchers. You may request a summary of the results from Dr Suvimol Niyomnaitham.

8. Further Information or Any Problems

If you have any concerns or questions about this study or the way it has been carried out, you should contact: Dr Suvimol Niyomnaitham at the University of Queensland, School of Pharmacy Phone: (07) 3346 1995 email: suvimol.niyomnaitham@uq.net.au

9. Other Issues

This study has been approved by the School of Pharmacy Ethics Committee in accordance with the National Health and Medical Research Council's guidelines. If you would like to speak to an officer of the University not involved in the study, you may contact the Ethics Officer on 3365 3924.

School of Pharmacy
Pharmacy Australia Centre of Excellence
The University of Queensland
20 Cornwall Street
Woolloongabba Qld 4102 Australia
T +61 7 3346 1900
F +61 7 3346 1999
E enquiries@pharmacy.uq.edu.au
W www.uq.edu.au/pharmacy

THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

PARTCIPANT CONSENT FORM

Semi-structured interview: Prescriber perspectives towards the drug safety warning in Australia using the warnings on clopidogrel and thiazolidinediones as case studies

- I confirm that I have read and understand the information sheet for the above study and have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
- I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my legal rights being affected.
- I understand that all my information and the data generated will be kept anonymous and confidential
- I agree to being interviewed
- I give consent for the researchers to record my voice in the interview
- I give consent for the researchers to the use anonymised quotes from my interview in reports or publications.

By signing this document I agree to participate in this project.

Full Name of Participant (printed):…….…….……

Signature of Participant:…….…… Date:……/……/…….

Full Name of Researcher (printed):…… ……...……..

Signature of Researcher:……..…….....….. Date:……./……/…..….

Dr Suvimol Niyomnaitham
School of Pharmacy
The University of Queensland, QLD, 4102
Ph: 0 7 3346 1995
E: suvimol.niyomnaitham@uq.net.au

Dr Alesha Smith
School of Pharmacy
The University of Queensland, QLD, 4102
Ph: 0 7 3346 1900
E: asmith@pharmacy.uq.edu.au

THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

Semi-structured interview: The impacts of the drug safety warnings on prescribing in Australia

Target participants: Therapeutical Goods Administration (TGA) personnel

Principal Investigator: Dr Suvimol Niyomnaitham

Co Investigators: Dr Alesha Smith, Dr Adam La Caze, and Dr Karen Whitfield School of Pharmacy, University of Queensland

Objective: This interview is aiming to assess the TGA's roles on emerging safety concerns in post-marketed drugs. It is hypothesised that regulatory safety warnings are one of the primary influences on the changes in prescribing behaviour.

Interview questions:

1. How does the TGA decide when a safety signal requires a warning?
2. How would you compare the TGA's approach to the US and European regulatory bodies? How do the international warnings such as FDA and EMA have any influence on TGA's warning?
3. What are strategies that TGA used for promoting drug safety warnings?
4. What is the relation between the TGA and the Pharmaceutical Benefit Scheme (PBS) regarding the emerging of safety signal of drugs listed in the PBS?
5. From the TGA aspect, currently, what is the most effective tool for drug safety communication between the TGA and Healthcare professionals?
6. What do you think is the primary influence on prescribing behaviour following a safety signal?
7. How does the TGA evaluate the effectiveness of drug safety warnings in Australia?
8. What do you think are the key challenges for the TGA in identifying a safety signal and in distributing a safety communication?

Dr Suvimol Niyomnaitham
School of Pharmacy
The University of Queensland, QLD, 4102
Phone: 0 7 3346 1995
E: suvimol.niyomnaitham@uq.net.au

Dr Alesha Smith
School of Pharmacy
The University of Queensland, QLD, 4102
Phone: 0 7 3346 1995
E: asmith@pharmacy.uq.edu.au

THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

Semi-structured interview: Prescribers perspective towards drug safety warnings in Australia

Target participants: General practitioners and specialists

Principal Investigator: Dr Suvimol Niyomnaitham

Co Investigators: Dr Alesha Smith, Dr Adam La Caze, and Dr Karen Whitfield School of Pharmacy, University of Queensland

Objective: This interview is aiming to assess the prescribers perspective towards current drug safety warnings and two recent drug safety warnings on thiazolidinediones and clopidogrel and proton pump inhibitor interaction

Interview questions:

Part One: Drug safety information on emerging concerns

1. What are your sources of drug safety information when there is a new side effect or contraindication of a post-marketed drug?
2. How do these safety information influence your practice?
3. How familiar are you with the process of drug safety warning from the Therapeutic Goods Administration (TGA)?
4. How do you usually find out about TGA drug safety warnings?
5. What are your opinions on how TGA communicate with you regarding the drug safety information in term of access to the safety warning and information for your practice?
6. Are you aware of warnings issued by overseas regulatory bodies such as European Medicine Agency (EMA) or the United States Food and Drug Administration (FDA)?

Part Two: Recent drug safety warnings

Adverse effects of rosiglitazone and pioglitazone

1. Are you aware of the cardiovascular risk of rosiglitazone and bladder cancer risk associate with pioglitazone?
2. How did you find out about these safety issues?

School of Pharmacy
Pharmacy Australia Centre of Excellence
The University of Queensland
20 Cornwall Street
Woolloongabba Qld 4102 Australia
T +61 7 3346 1900
F +61 7 3346 1999
E enquiries@pharmacy.uq.edu.au
W www.uq.edu.au/pharmacy

3. How did the safety warnings on these adverse effects influence your prescribing decision? Do you make a decision on prescribing these drugs by yourself or consult the specialists?
4. How did your decision on these adverse effects changed as the evidence or warnings have been updated over time?

Interaction between clopidogrel and proton pump inhibitors

5. Are you aware of the interaction between clopidogrel and proton pump inhibitors?
6. How did you find out about this safety issue?
7. How did the safety warnings on this interaction affect your prescribing practice? Do you make a decision on prescribing these drugs by yourself or consult the specialists?
8. Have your opinions on these warnings changed over time as the different evidence or warnings have come out?

Dr Suvimol Niyomnaitham
School of Pharmacy
The University of Queensland, QLD, 4102
Phone: 0 7 3346 1995
E: suvimol.niyomnaitham@uq.net.au

Dr Alesha Smith
School of Pharmacy
The University of Queensland, QLD, 4102
Phone: 0 7 3346 1995
E: asmith@pharmacy.uq.edu.au

THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

Participant Information Sheet

Survey study: Prescriber perspectives of drug safety warnings

Principal Investigator: Suvimol Niyomnaitham
Co Investigators: Alesha Smith, Adam La Caze, Karen Whitfield

What is the purpose of the study?
This study conducted by researchers at the University of Queensland aims to investigate prescribers' attitudes toward the current drug warning system in Australia and investigate prescribing decisions in response to emerging safety warnings.

Do I have to take part?
No. It is up to you to decide whether or not to take part. You are free to withdraw from the study at any time without giving a reason.

What will happen to me if I take part?
We would like you to fill in an online survey. This should take no more than 10-15 minutes to complete. The survey is available via https://www.surveymonkey.com/s/ImpactOfDrugWarning. By completing the survey, you consent to participate in this study.

What are the possible benefits of talking part?
Your experience will help us understand the impact of drug warning systems in Australia, which may lead to improved communication and collaboration between drug authorities and prescribers.

Will my taking part in the study be kept confidential?
Yes. All the information you provide in the survey will be anonymous and confidential. You will not be identified in any publications or documents arising from this study.

What if there is a problem or I have further questions?
If you have any concerns or questions about this study or the way it has been carried out, you should contact: Dr Suvimol Niyomnaitham at the University of Queensland, School of Pharmacy Phone: (07) 3346 1995 email: suvimol.niyomnaitham@uq.net.au

What will happen to the results of the research study?
The data from the study will be analysed by the research team at the University of Queensland and the aggregated results will be published in health care journals to inform other health care professionals and researchers. You may request a summary of the results from Dr Suvimol Niyomnaitham.

Who has reviewed the study?
This study has been approved by the School of Pharmacy Ethics Committee in accordance with the National Health and Medical Research Council's guidelines. If you would like to speak to an officer of the University not involved in the study, you may contact the Ethics Officer on 3365 3924.

Dr Suvimol Niyomnaitham
School of Pharmacy
The University of Queensland, QLD, 4102
Ph: 0 7 3346 1995
E: suvimol.niyomnaitham@uq.net.au

Dr Alesha Smith
School of Pharmacy
The University of Queensland, QLD, 4102
Ph: 0 7 3346 1900
E: alesha.smith@uq.edu.au

Prescriber perceptions of drug safety warnings

THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

Thank you for taking the time to complete this survey from the University of Queensland. This survey should take about 10 minutes.

The results from this research will be published in health care journals to inform other health care professionals and researchers. All responses will be aggregated and individual responses will remain confidential.

If you have any questions about the survey, please contact Dr. Suvimol Niyomnaitham at School of Pharmacy, the University of Queensland, Phone: 04 06178866 or email: suvimol.niyomnaitham@uq.net.au or Ethics Officer on 3365 3924.

Your participationis voluntary. By chicking the Next button below, you agree that you have read the participant information and consent to participate.

Prescriber perceptions of drug safety warnings

THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

Part I. Demographics

***1. How many years have you been practicing medicine (post-internship)?**

- ◯ <5
- ◯ 5-9
- ◯ 10-14
- ◯ 15-19
- ◯ >=20

***2. What is your medical specialty?**

- ☐ General practitioner
- ☐ Internal medicine
- ☐ Cardiology
- ☐ Gastroenterology
- ☐ Endocrinology
- ☐ Geriatrics
- ☐ Pharmacy
- ☐ Other (please specify)

3. Where do you practice? (can choose more than 1 place)

- ☐ ate hospital/clinic
- ☐ lic hospital
- ☐ nmunity medical centre
- ☐ Other (please specify)

Prescriber perceptions of drug safety warnings

Part II. Drug safety warnings

***4. What are your main sources of information regarding drug safety warnings? (Can choose more than one)**

☐	Therapeutic Goods Administration (TGA)	☐ N/A
☐	International authorities e.g. U.S. Food and Drug Agency (FDA), European Medicines Agency (EMA)	☐ N/A
☐	Medical research publication	☐ N/A
☐	Medical association e.g. Diabetic association, heart association, etc.	☐ N/A
☐	Medscape	☐ N/A
☐	Australian prescriber	☐ N/A
☐	NPS MedicineWise	☐ N/A
☐	Drug package inserts	☐ N/A
☐	Conferences/meetings	☐ N/A
☐	Discussion with physician colleagues	☐ N/A
☐	Discussion with pharmacists	☐ N/A
☐	News or other media	☐ N/A

5. Are there any other sources that you used other than specified in Question 4?

- ○ No
- ○ Yes, please specify

***6. Do you receive drug safety information from TGA?**

- ○ Yes
- ○ No

Prescriber perceptions of drug safety warnings

7. What is your main communication tool from the TGA for drug safety information? (can choose more than 1)

- [ ] TGA website
- [ ] A_SAFETYINFO subscribed email
- [ ] S feeds
- [ ] dicine Safety Update articles on the Australian Prescriber
- [ ] Other (please specify)

8. The emerging drug safety information provided by the TGA is adequate to make an informed decision for my practice.

Strongly disagree	Somewhat disagree	Neutral	Somewhat agree	Strongly agree
○	○	○	○	○

9. The TGA drug safety information is more timely than the U.S.FDA or the European Medicines Agency information.

Strongly disagree	Somewhat disagree	Neutral	Somewhat agree	Strongly agree
○	○	○	○	○

10. I am familiar with the TGA's role.

Strongly disagree	Somewhat disagree	Neutral	Somewhat agree	Strongly agree
○	○	○	○	○

Part III. Coprescribing of clopidogrel and proton pump inhibitors

During 2009-2010, many drug authorities issued warnings on the interaction between clopidogrel and proton pump inhibitors (PPIs) via enzyme CYP2C19, especially omeprazole and esomeprazole; indicating that, PPIs may reduce the antiplatelet effect of clopidogrel.

***11. Are you aware of ther interaction between clopidogrel and proton pump inhibitors?**

- ○ Yes
- ○ No

Prescriber perceptions of drug safety warnings

12. Which source did you rely on the most for the interaction between clopidogrel and proton pump inhibitors? (can choose more than 1)

- [ ] Therapeutic Goods Administration (TGA)
- [ ] International authorities e.g. U.S. Food and Drug Agency (FDA), European Medicines Agency (EMA)
- [ ] Medical research publication
- [ ] Medical association e.g. diabetic association, heart association
- [ ] Medscape
- [ ] Australian prescriber
- [ ] NPS MedicineWise
- [ ] Drug package inserts
- [ ] Conferences/meetings
- [ ] Discussion with physician colleagues
- [ ] Discussion with pharmacists
- [ ] News or other media
- [ ] Other (please specify)

***13. How did the drug safety warnings on the interaction between clopidogrel and proton pump inhibitors affect your management of patients who were taking clopidogrel? (can choose more than 1)**

- [ ] Made no changes
- [ ] Prescribed PPI with dosage adjustment
- [ ] Prescribed PPI with a weak inhibitory effect on CYP2C19 (e.g. pantoprazole)
- [ ] Prescribed histamine 2 receptor antagonists (e.g. ranitidine) instead of PPI
- [ ] Stopped prescribing all proton pump inhibitors
- [ ] Other (please specify)

Prescriber perceptions of drug safety warnings

14. What is your antisecretory drug of choice to prescribe in patients who are taking clopidogrel?

e.g. Discharge medication for a 65-year-old patient with history of upper GI who was hospitalised with ischemic heart disease.

- ◯ Omeprazole
- ◯ Pantoprazole
- ◯ Lansoprazole
- ◯ Esomeprazole
- ◯ Rabeprazole
- ◯ Histamine 2 receptor antagonist (e.g. ranitidine, famotidine, nizatidine)
- ◯ Other (please specify)

15. Would you initiate a new prescription of omeprazole or esomeprazole in patients taking clopidogrel?

- ◯ Yes
- ◯ No

Part IV. Rosiglitazone

During 2007-2010, several drug authorities issued safety warnings on the risk of cardiovascular disease associated with rosiglitazone.

***16. Are you aware of the cardiovascular risk associated with rosiglitazone?**

- ◯ Yes
- ◯ No

Prescriber perceptions of drug safety warnings

17. Which source did you rely on the most for the cardiovascular risk of rosiglitazone? (can choose more than 1)

- [ ] Therapeutic Goods Administration (TGA)
- [ ] International authorities e.g. U.S. Food and Drug Agency (FDA), European Medicines Agency (EMA)
- [ ] Medical research publication
- [ ] Medical association e.g. diabetic association, heart association
- [ ] Medscape
- [ ] Australian prescriber
- [ ] NPS MedicineWise
- [ ] Drug package inserts
- [ ] Conferences/meetings
- [ ] Discussion with physician colleagues
- [ ] Discussion with pharmacists
- [ ] News or other media
- [ ] Other (please specify)

18. How did the drug safety warnings on rosiglitazone affect your management of patients who were using rosiglitazone? (can choose more than 1)

- [ ] Made no changes
- [ ] Discontinued rosiglitazone in patients with high risk of cardiovascular disease
- [ ] Discontinued rosiglitazone in all patients
- [ ] Switched to pioglitazone
- [ ] Switched to other antidiabetic drug class
- [ ] Other (please specify)

Part V. Pioglitazone

In 2011, several drug authorities had announced that long-term use of pioglitazone might be associated with an increased risk of bladder cancer.

***19. Are you aware of an increased risk of bladder cancer associated with long-term pioglitazone use?**

- ○ Yes
- ○ No

Prescriber perceptions of drug safety warnings

20. Which source did you rely on the most for the bladder cancer risk of pioglitazone? (can choose more than 1)

- [ ] Therapeutic Goods Administration (TGA)
- [ ] International authorities e.g. U.S. Food and Drug Agency (FDA), European Medicines Agency (EMA)
- [ ] Medical research publication
- [ ] Medical association e.g. diabetic association, heart association
- [ ] Medscape
- [ ] Australian prescriber
- [ ] NPS MedicineWise
- [ ] Drug package inserts
- [ ] Conferences/meetings
- [ ] Discussion with physician colleagues
- [ ] Discussion with pharmacists
- [ ] ws or other media
- [ ] er (please specify)

21. How did the drug safety warnings on pioglitazone affect your management of patients who were using pioglitazone? (can choose more than 1)

- [ ] de no changes
- [ ] ntinue pioglitazone with bladder cancer screening
- [ ] Discontinue pioglitazone in patients with high risk of bladder cancer
- [ ] Discontinue pioglitazone in all patients
- [ ] Switched to other antidiabetic drug class
- [ ] Other (please specify)

Thank you for your participation.

22. Please let us know if you have any further comments about the Australian drug safety warning system.

GMSBML NEWS

medicare local
GREATER METRO SOUTH BRISBANE
Connecting health to meet local needs

Greater Metro South Brisbane Medicare Local | t 1300 467 265 | e engagewithus@gmsbml.org.au
w www.gmsbml.org.au www.facebook.com/sthbrisbanemedlocal www.twitter.com/sthbrismedlocal

2014 Issue 9

Evidence into Action – GMSBML's Commitment to General Practice

Greater Metro South Brisbane Medicare Local conducted an evaluation of the expectations of GPs and practice employees to gain an understanding of how GMSBML can improve their services to meet the future needs of General Practice in 2014/15.

GMSBML CEO Simon James said the Medicare Local is making a strong commitment to local health service providers to ensure that the organisation continues to deliver responsive services based on the identified priorities.

"Medicare Locals provide a vital link between our General Practices, allied health providers and the public and private hospital system. Fostering these relationships at the local level and knowing the needs and priorities for our community's health providers is fundamental to what we do.

"The more we learn about the unique needs of our diverse health provider community then the stronger the services GMSBML can provide," Mr James said.

One of GMSBML's highest rated programs is Positive Impact.

"It was no surprise that Positive Impact rated so well. The program recently celebrated its 2000th participant. That's over 2000 lives that have been changed due to the ongoing partnership between our General Practices and this Medicare Local," Mr James said.

Other services that ranked well include:

- Access to Allied Psychological Services (ATAPS)
- After Hours and
- Immunisation.

"We are committed to continue building on this strong foundation to deliver responsive services to our GPs and their practice teams," Mr James said.

Read the full Evidence into Action report here.

Contents

2000 Participants and Counting for Positive Impact

GMSBMLs Positive Impact Team

GMSBMLs Positive Impact program recently celebrated its 2000th participant. The program has quadrupled the number of participants in the last 12 months.

Positive Impact can support your patients who want help with weight loss but can't afford it or don't qualify for a care plan.

The service offers a free 6 or 12 month program that promotes sustainable lifestyle changes and is delivered over the phone by Phone Coaches (dietitians and nutritionists).

To find out how you can refer patients into the Positive Impact program visit http://www.gmsbml.org.au/Positive-Impact-Health-Professionals.php or phone our Positive Impact Team on 07 3390 2466.

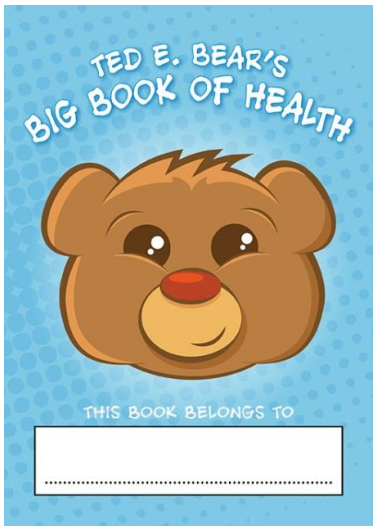
GMSBML's Bee Wise Immunise Bike Comp is back

GMSBML launched their popular 4-year-old bike competition for the second year running to coincide with World Immunisation Week on 24-30 April.

The 2014 theme is *Immunise for a healthy future: Know, Check, Protect.*

GMSBML continues to support practices to continue their great work in promoting flu vaccinations, school based programs and childhood immunisations.

If your practice would like to register for the bike competition or would like any support around immunisation please contact Carmel Vellacott and Jenny Pethoe on 1300 467 265 or immunisation@gmsbml.org.au.



Teddy Bear Hospital Helps to Educate Children

Building health literacy within our community is a key activity for GMSBML. To have the greatest chance of success we need to start this process as early as possible.

GMSBML are partnering with Griffith University medical students and Hope4Health to deliver the Teddy Bear Hospital to early primary school students. The first of three sessions kicks off on Monday 5 May. More than 100 year three students from Woodridge and Marsden State Schools will be treated to a fun and informative session talking about healthy eating, exercise, hygiene, dental health and visiting the doctor and dentist. To support this initiative GMSBML are developing age appropriate materials for the kids and resources to help schools continue to deliver the message to students. We hope to be able to offer this program to more schools in our service area next financial year.

REMINDER: Bonus payment for GP After Hours Providers

As reported in last fortnight's newsletter, as a result of the negotiations with the Medical Deputising Service, GMSBML is now in a position to share these savings with you in recognition of the contribution the participating practices have made to maintaining after hours service delivery during the 2013/14 year.

Bonus payments will be paid to practices upon receipt of the completed January – March After Hours reports (and any other outstanding reports) and a correctly rendered invoice, including GST being submitted.

There are still over 40 reports outstanding and will be required to be completed to receive the bonus payment.

For each report please ensure that:

- Your practice name is on your report. If you think you may have sent back your report without your practice's name, please contact us.
- The full report is returned. If you do not have any information to enter for some parts of the report, write nil in the space provided and return all pages.
- The report page regarding operating hours is returned.

For further information on the After Hours reporting requirements please contact our After Hours Service on 1300 467 265 or email afterhours@gmsbml.org.au.

GMSBML Supports Expansion of Healthy Start Program

Workshop participants at Multicultural Development Association (MDA)

For the past two years GMSBML have supported Hope4Health to deliver the Healthy Start program. Healthy Start provides easy to understand information on visiting a GP, medicine safety, healthy eating and hygiene as well as men's and women's health messages for recently settled refugees. Many of these people have lived for considerable periods of time in camps with limited health care. GMSBML is committed to ensuring they are supported in their navigation of the Australian health care system.

Healthy Start has recently expanded its team of facilitators from Griffith University to include students from Queensland University of Technology, University of Queensland and Bond University which will ensure the program is able to be delivered more widely and help more refugees. To fund this expansion Hope4Health have dedicated the funds raised by their annual dinner dance towards the Healthy Start program.

The Jazz Dinner Dance will be attended by over 350 doctors and medical students. Each year this black tie charity ball raises money to support a different health project.

This year and with your help, Hope4Health are hoping to raise even more funds for Healthy Start to enable the project to be maintained in Queensland as well as expand into other universities including Australian National University, University of Western Sydney and James Cook University. Visit hope4health.org.au to see the range of work they are involved in.

Put Saturday 13 September as a date claimer in your calendar and help support this program. Tickets are on sale soon.

PCEHR – GMSBML's First Allied Health Provider on Board

Greater Metro South Brisbane Medicare Local's eHealth team has signed up their first allied health provider to be fully compatible with and ready to use the Personally Controlled Electronic Health Record (PCEHR) system.

This is the first of many providers who are well on their way to being connected to the national system. The PCEHR provides many benefits to healthcare providers and their patients. The system allows timely access to patient information, such as medications, shared health summaries, event summaries, immunisations, discharge summaries and allergies.

The following allied health scenario demonstrates the benefits of the PCEHR:

A woman in her mid 40's presents to a dietician: The woman is a busy person, with many competing priorities. When asked by the dietician her current medications and previous medical history, the woman cannot remember correctly or accurately.

	No PCEHR	With a PCEHR
Medical history and current conditions	Disjointed, fragmented information is given.	The dietician can see: previous medical history and current health conditions, in around 10 seconds.
Current medical conditions	Some medications mentioned.	The current medications are known.
Allergies	None mentioned.	All allergies and adverse reactions listed clearly.

When the women goes to see her exercise physiologist:

	No PCEHR	With a PCEHR
Treatment	The session with the dietician is not recalled well and there is nothing about the dieticians appointment in the GP's faxed notes.	Exercise physiologist can see the diagnosis and treatment prescribed by the woman's dietician and GP.

If your Allied Health practice is interested in becoming connected to the PCEHR system, please contact Jenaya Wyatt on 1300 467 265 or email eHealth@gmsbml.org.au.

Health and Wellbeing Programs Assisting Hundreds

GMSBML has delivered 74 health and wellbeing sessions over the period of October 2013 to March 2014. The team has assisted a total of 226 participants to achieve and maintain a healthy lifestyle. Participants came along for a period of 6-10 weeks to learn new skills and recap on some old skills to make their day to day life more bearable when living with a long term health conditions or those at risk. The most common feedback received is that participants are so grateful they are able to meet with others who know what they are going through and can support each other to make lifestyle changes.

One of our past participants said;

"I thought prior to commencing the course that I had heard it all before and possibly had. However this program clarified much and has greatly assisted me to understand how I can help myself more. I thoroughly recommend it to others"

The Pain Self-Management Program group at the Browns Plains Library

For further information about the health and wellbeing programs visit http://www.gmsbml.org.au/Health-Professionals-Services-Health-and-Wellbeing-Group-Programs.php or contact Susan Tippett (stippett@gmsbml.org.au) or Michelle Nielsen (mnielsen@gmsbml.org.au) on 3290 3733.

Secure your spot at GMSBML's Popular Annual Forum

GMSBML are holding the second Healthy Communities Consultation Forum on 27 May 2014 at Brisbane Technology Park. If you have received an invitation please book your place as soon as possible as numbers are strictly limited.

Click here to register http://goo.gl/z5pZtv.

Please note as a private health professional you will be renumerated as per GMSBML's remuneration policy for your attendance at this event, however places are limited.

Yarning Sessions Identify Opportunities

As part of our Health Literacy Program GMSBML is delivering and supporting a number of initiatives focusing on Aboriginal and Torres Strait Islander communities.

Yarning sessions with Aboriginal and Torres Strait Islander communities were held in April in Beenleigh and Beaudesert. These were aimed at identifying what barriers community members were experiencing. These Yarning sessions provide the framework for GMSBML to engage with the Aboriginal and Torres Strait Islander Community at a local level. Further yarning sessions will be held in Brisbane South and the Bayside regions with local Elders and community members.

The yarning sessions held to date provided feedback which included the need of more culturally appropriate services, and more engagement and coordination of local services for their community. GMSBML aims to address some of these local issues by working with the community to focus on solutions.

Treasure Chest

Strive for 5 - Are you missing pages?

Some copies of *Strive for 5* have been found to have pages missing from the first part of the booklet. Pages in these faulty booklets start at Appendix 1, so some recipients may not be aware that they have only received half a booklet.

Your copy of *Strive for 5* can be checked against the online version for missing pages.

If you have a faulty copy please email editor@apna.asn.au.

Beenleigh yarning session, from top left to right Sophia Seve (Centacare), Estelle Congoa, Jo-Ann Nicol (both Queensland Health), Colleen Power (Pathways Foster Care Agencies), Natalie Pakoa, Jason Roe, Florence Williams, Jenni Beetson-Mortimer (all GMSBML), Kym Alexander (Beenleigh State Primary School)

GMSBML Events




Click on the below hyperlinks to view the event flyers and registration form.

6 May Healthy Ageing Nursing Workshop
At the completion of the workshop participants will be able to describe concepts of healthy ageing, understand the older population in general practice and identify the role of Practice Nurses to promote healthy ageing.

7 May Department of Human Services: Disabilities Focus Group
This is an opportunity to work with the Department of Human Services on improvements that can make processes more streamlined for General Practice.

14 May The Role of Physical Activity in the Prevention and Management of Chronic Disease
In partnership with Exercise is Medicine Australia. Presented by a local accredited exercise physiologist. The resources available to participants support the assessment, management and referral of patients.

16 May GMSBML Adolescent and Young Adult Health and Service Plan - Stakeholder Consultation
GMSBML are conducting workshops with key community stakeholders to understandthe issues and propose solutions to a range of barriers impacting adolescent and young adult (15-24) community members.

22 May Diabetes and the High Risk Foot
Come along to find out more about the new series of referral pathways in our region and refresh your skills in preventing, assessing and managing foot complications in your patients with diabetes.

27 May Perform CPR (HLTAID001) – Wynnum
Two hour practical course run by B.L.S First Aid Training.

17 June Primary Care Nurse Network Meeting
Come and join us for our next Primary Care Nurse Network meeting. It is a great opportunity to network, share and learn from each other.

July Allied Health Networking Meetings
Connect with local primary health care providers, promote your services to other health professionals, discuss local issues in a multidisciplinary setting and find out about new initiatives in the GMSBML region.

External Events

Wesley LifeForce Suicide Prevention Workshop
Two workshops designed to teach people how to identify the signs that someone may be at risk of suicide and appropriate action to take. **Thursday 22 May** for practice staff and **Saturday 24 May** for GPs and Nurses.

A Fresh Approach to FPS – Focused Psychological Strategies
Provides participants with skills in the provision of Focused Psychological Strategies, with a focus on those strategies specifically derived from Interpersonal Therapy (IPT). **Saturday 24 May** and **Saturday 31 May 2014**. For more information view the invitation.

Working with Refugees Training
A one day accredited training course to develop competency in working with refugees. Tuesday 3 June 2014. For more information view the invitation.

Australian Winter School Conference
A unique forum for people working in the alcohol and other drug sector to share experiences and update skills. Wednesday 23 to Friday 25 July 2014. For more information visit the website.

Please visit the Education and Events page on our website for a full list of events.

Online Education

By 2025, it is predicted that nearly 80% of Australian adults will be either overweight or obese. Are you managing a lot of patients struggling with excess weight? Consider taking part in ThinkGP's module – Weight management – evidence and practical strategies for a higher protein, low GI diet - examining the benefits of higher protein, low GI diets for encouraging patients to achieve weight management and meet nutritional requirements.

Brisbane SEAGP South East Alliance of General Practice

SEA-GP invites all members of General Practice & Allied Health practitioners to attend the:

Health Professionals Speed Dating Event

Date

Thursday 8th May 2014

Venue

Pacific Golf Club

430 Pine Mountain Road

Carindale, Qld 4152

Time

6.00pm Registration – 9.00pm Close

RSVP

Tuesday 6th May 2014

No Charge

Medical Students & Registrars in Training can accompany GP's in Practice to our Monthly Dinner Meetings

MAY DINNER MEETING

Speakers:

- *Dr Wendy Burton, Morningside General Practice – CHQHHS*
- *Dr Ken Stephenson, Cleveland Medical Centre-Musculoskeletal*
- *Dr Sue Scott, Cleveland Medical Centre – Pelvic Floor Urine Incontinence*
- *Lynne Blighton , The Fragile Puzzle – Services Provided by "The Fragile Puzzle"*
- *Gerda Muller , The Psych Professionals – Animal Assisted Therapy*
- *Dr Andrew Hadley , Bayside Urology – Urology*
- *Dr Michael Mastry , Moreton Bay Obstetrics & Gynaecology*
- *Dr Gill Van Iddekinge , Moreton Bay Obstetrics & Gynaecology*
- *Siona Hardy , Active Rehabilitation – Mars Clinic: Children's Continence Clinic*
- *Jason Crow , Active Rehabilitation – Men's Health Services*
- *Dr Alastair Macbeth , Bayside Obstetrics & Gynaecology – Business & our Services for GP's*
- *Nola Williams, Cleveland Medical Centre – Yellow Fever & Travel*

The evening will involve members of SEAGP and non-members to share aspects of their work, with particular focus on new services and innovations that might be of interest to other members, both GP & Allied Health.

Each presentation would last approximately 10 minutes, with movement and rotation between tables in a "Speed Dating" format.

This would be a great way to connect with other health professionals and hopefully open up better lines of communication for patient care.

RSVP: SEAGP FAX: 3330 2399 EMAIL: vjessen@seagp.org.au

Numbers are limited - so to make sure you don't miss out register below & email back by Tuesday 6th May 2014.

Practice: _____ ***Suburb:*** _____

Phone Number: _____ ***Mobile Number:*** _____ ***Fax Number:*** _____

	Name of Attendees	Email	Position	Special Dietary Requirements/ Allergies
1				
2				
3				
4				

For further information, contact Vivian Jessen by email: vjessen@seagp.org.au

medicare local
GREATER METRO SOUTH BRISBANE
Connecting health to meet local needs

Please pass on to all GPs and Health Professionals

NPS MEDICINEWISE PROFESSIONAL

GP PRACTICE VISIT

OLDER AND WISER -

Promoting Safe Use of Medicines in Older People

Older people are at greater risk of **medicines-related problems** due to co-morbidities, age-related changes and polypharmacy, with potentially undesirable consequences.

In partnership with NPS – MedicineWise, we are offering this program which provides a valuable opportunity to discuss **up-to-date, independent, practical** and **evidence-based** information about the safe use of medicines in older people.

This program will focus on:

- ***Explore treatment goals with your older patients***
- ***Identify triggers for reviewing your older patient's medicines***
- ***Recognise specific medicines-related problems in older patients and identify potential contributing medicines***
- ***Use a step-wise approach when stopping medicines***
- ***Document health decisions agreed with the patient and update regularly***

What's in it for me?

- **Access to unbiased evidence, information and resources**
- **Visits can be one on one or in a small group *at your practice at a time during the day that suits you or your practice***
- **Accredited RACGP QI & CPD and/or ACRRM PDP program points**
- **Recognised Quality Prescribing Initiative (QPI) activity within the Practice Incentives Program (PIP)**

To participate *if you have not already received a visit*, please provide your details:

or for more information please phone: 07 3864 7555 (*Bo Frederiksen* or *Joy Chen*)

Name: _____ Practice name: _____

Preferred time: _____ Preferred day of week: _____

Phone: _____

Practice Stamp

Post this page to:

Greater Metro South Brisbane Medicare Local
PO Box 6435, Upper Mt Gravatt QLD 4122

Or Fax to: (07) 3864-7599

Safe Use of Medicines in Older People

Australian Hearing GP Hearing Program

Maintaining patients' health and wellbeing through regular screening programs is a key goal of GP practices. At Australian Hearing we are committed to providing easily accessible hearing health screening programs as well as public education and awareness about hearing services across Australia. Your patient's hearing needs are our highest priority. Australian Hearing offer two hearing health screening programs for GP practices, both of which are free of charge:

1. Hearing screening for patients, where a claim for the service can be made under the MBS.
2. Hearing screening for patients which is not claimable under the MBS.

The program that would suit your practice depends upon the demographic make-up of your practice's patients. Australian Hearing Logan are happy to discuss your practice's requirements with you via 07 3387 6600.

Prescriber Perspectives of Drug Safety Warnings

The researcher team from the University of Queensland is conducting a survey study to assess the prescribers' **point of view** on the current drug safety warnings in Australia. Healthcare professionals are inviting to participate in a **short electronic survey** on recent emerging drug safety and sources of information. This should take no more than 10 minutes. All responses will be aggregated and individual responses will remain confidential. Your experience will help us understand the impact of drug warning systems, which could lead to improve communication and collaboration between drug authorities and prescribers.

THE UNIVERSITY OF QUEENSLAND
AUSTRALIA

Click the link: https://www.surveymonkey.com/s/PrescriberPerceptionDrugSafety

For further information contact Dr. Suvimol Niyomnaitham via suvimol.niyomnaitham@uq.net.au or phone 07 3346 1995.

Chronic Disease Self Management Post Graduate Qualification

This is a unique opportunity for nurses to complete a Post Graduate Qualification in Advising on Chronic Disease Self Management. At the completion of the program, successful students will have the skills and knowledge necessary to work as CDSM Advisors providing an integrated and collaborative healthcare approach enabling a wider network of support for self management of chronic diseases.

The first two days of training are Tuesday 27th and Wednesday 28th May. As a special offer to fill the remaining places, we are offering students a significant discount, reducing the cost of the program from $4250 to $2750.

Attached course pack includes registration information.

Resources for GPs in Managing Patients with Chronic Pain

NSW's Agency for Clinical Innovation (ACI) has developed a new website devoted to providing information to patients and practitioners on how to manage chronic pain. Early assessment and effective management of pain is essential to prevent its progression to chronic pain. Best evidence for effective management and prevention of chronic pain is to use an interdisciplinary bio-psychosocial approach to people in pain.

Tools and resources are available at the Pain Management Network website: http://www.aci.health.nsw.gov.au/chronic-pain/health-professionals.

New Resources: Better Living With Your Lung Disease

Lung Foundation Australia has produced a new range of resources in lung disease focusing on self-management titled Better Living With your Lung Disease (BLLD) - Health Professional's Kit. This kit is targeted towards GPs, practice nurses, domiciliary, community and tertiary healthcare providers.

This all-in-one package was developed to assist health professionals to promote self-management to their patients with lung disease. BLLD is a 10-part DVD series that enables patients to learn more about self-management and how to manage their disease and its symptoms. The kit also includes BLLD collateral such as brochures and posters suitable for a practice waiting room or centre. This information encourages patients to find out more about how they can improve their general wellbeing and quality of life.

How will BLLD benefit lung disease patients?

- Improved self-management skills
- Achieve their care plan goals
- Learn more about managing their disease, its symptoms and how they can live better with their lung disease
- Learn how to access supportive and palliative care services
- Will better inform carers and family members on what to expect

How can you help?

- Place the attached article in your weekly newsletter
- Add the Health Professional Kit to your website under resources or where suitable
- Distribute promotional material to GP practices in your area
- Display postures and brochures in your waiting room

The Health Professional Kit is available from our online shop for $65 + postage, please visit www.shop.lungfoundation.com.au.

Metro South Health

Introducing the

Central Referral Hub

For all new Metro South Health referrals from 5 May 2014:

Fax	**1300 364 248** This will need to be updated on your fax machine
Phone	**1300 364 155** If you have any questions or would like to talk to a clinical nurse or health practitioner
e-Referrals	Will be automatically redirected to the hub

Great state. Great opportunity.

Queensland Government

Hurry, Ending Soon: Complimentary Trial of BMJ Best Practice

British Medical Journal (BMJ) are offering general practices in the Greater Metro South Brisbane Medicare Local region a complimentary 30-day trial of their online clinical decision support tool, BMJ Best Practice. The tool combines the latest evidence, guidelines and expert advice into a single source to give busy clinicians an instant second opinion at the point of care.

To find out more or request a trial for your practice, please visit http://bestpractice.bmj.com/anztrial. Offer ends 15 May 2014.

Positions Vacant

Practice Manager, RN, Medical Receptionist Needed
A growing modern general practice is seeking a full-time/part-time medical receptionist/RN to manage a busy environment. Practice is bulk billing, open seven days a week and has Allied heath, pathology and skin clinic on site. For further details please send CV to wcmedicalcentre@gmail.com or phone 0400 025 649.

Visiting Allied health required
A growing modern general practice in logan area is seeking for following allied health: Dietitian, Diabetic nurse educator, Podiatrist, Physiotherapist (22 sqm room available), excercise physiologist and Psychologist. For further details please send CV to wcmedicalcentre@gmail.com or call 0400 025 649.

VR GP Wanted
Our well established practice (1983), requires a VR GP male/female, as sadly one of our team is relocating to the Gold Coast in March. If you would like to work in a friendly family atmosphere, with full RN support, accredited, private billing, fully computerised, and onsite pharmacy, pathology, please phone Kay or Carolyn at Shailer Medical on 3287 6699.

Doctor, Are You Looking For A Change?
Garden City Family Doctors located in the newly renovated Westfield Garden City is seeking GPs for weekend/evening work. This highly sort after location is open seven days bulk billing with provision of evening work. Car parking provided for doctors. We are offering flexible days and hours. Fully computerised Pracsoft/MD. We are a modern privately owned practice with an established patient database plus potential to establish your own! Come join our experienced team of Doctors/Nursing and Administration staff. Well supported by allied health, onsite pathology and pharmacy. Attractive remuneration. Phone Di on 0427 909 298.

Casual Medical Receptionist Wanted
For small bulk-billing General Practice at Norman Park. Initially to fill-in for two weeks in early June with further hours to be considered in the near future. Experience with Medical Director or similar NOT required. Please phone Fay or Margo for an interview between 8:30am and 12:30pm Monday to Friday on 3398 2457.

Doctor Required
Sunnybank Hills Family Practice is looking for a friendly Doctor to be part of our working family. We are located inside Sunnybank Hills Shopping town within a Priceline Pharmacy. We offer great remuneration and flexible working hour arrangement. With nurses and administration staff by your side. Feel free to contact Fabienne on 0415 961 089 I will be more than happy to help and show you around the practice.

Visiting Allied Health Professionals Wanted
Busy Medical Centre in Underwood and Nerang is seeking visiting Allied Health Professionals (Physio, Podiatry, Hearing, Clinical Psychologist) to join our team. Options include room rental or percentage of billings. Contact rajesh.sharma@qualitashealth.com.au or 0422 852 000.

Rooms Available at Bay Terrace Specialist Centre
Modern spacious consulting rooms available for sessional lease. Situated within a landmark heritage-listed building only a short stroll to the Wynnum waterfront. Including: reception services, furnished examination rooms, staff facilities, off-street parking, sterilsation facilties and Registered Nurse available. For further information phone 3893 1244 or email pauldollardental@bigpond.com.

Registered Nurse Required
Looking for a team focused, experienced Registered Nurse to join our friendly medical centre located in Alexandra Hills for approximately 16-20 hours per week. Medical centre experience is essential. Minimum two years. Become part of a team in a well-established centre with dedicated, experienced Doctors and longstanding, loyal patients. Hourly Rate is negotiable depending on experience. Contact Annette on 07 3824 3882.

Positions Vacant *continued*

Full-time / 2 x Part-time Cleveland GP
Opportunity available in the great lifestyle location of Cleveland on Brisbane Bayside for a VR preferably full-time GP looking to establish themselves in a friendly, innovative, non-corporate environment with full support from staff and nurses running diabetes, respiratory and weight loss clinics. Visit our website: www.clevelandmedical.com.au. Please email a CV and arrange a visit to the practice with Melinda: pm@clevelandmedical.com.au.

Capalaba Central Doctors seeking VR GPs
Bulk-billing medical centre located in busy shopping centre seeking full-time/part-time VR GPs. Fully computerised, full equipped room with full-time nurse. $150PH or high %. Choose your own hours. Contact Kylie White on 3808 3300 / 0450 738 401 / 0412 888 067 or ccd4157@yahoo.com.au.

GP Wanted!
Full-time or part-time VR GPs welcome. DWS doctors are invited to apply as well. Well-equipped medical centre, 15 mins south of Brisbane. Skin cancer work available. Up to 70 % of billings. Busy location, along Logan Road with excellent exposure. Position available from early June 2014. If interested, please contact Dr J KU at j_k_ku@hotmail.com or 0413 932 445.

Casual Endorsed Enrolled Nurse Required
Currently seeking Casual Practice Nurse to join our friendly team. Zedmed experience preferred but not essential. General Practice Treatment Room experience essential. Must be flexible and be available some weekends. Please forward resume to holmview@qmedical.net.au.

Casual Receptionist Required
Currently seeking a Casual Medical Receptionist to join our friendly team. Zedmed experience preferred but not essential. Must be available to work some weekends. Please forward resume to holmivew@qmedical.net.au.

VR GP Required
VR GP required for busy Southside privately owned, well established practice. New modern premises, fully computerised with full RN support. Psychologist, Dietitian and S & N Pathology on site. Come and join our experienced friendly team, please email bryantss@bigpond.net.au.

Registered Nurse Camp Hill
Registered Nurse required with minimum of three years experience for a large busy General Practice, Camp Hill Healthcare. Casual / part-time. Expressions of interest to camphillmedical@ozdoc.com.au.

Full-time/Part-time Doctor Required Slacks Creek Medical Centre
Replacing existing doctor in busy, well established practice. Doctor owned, accredited, fully computerised, not DWS. Conveniently located 20 minutes from Brisbane, 35 minutes form Gold Coast. Friendly experienced team including nurse and visiting allied health. Pathology and pharmacy next door. Excellent remuneration with initial guaranteed minimum. Contact Dr Stone on 0419 660 019, 3209 3911 or email mstone_77@Hotmail.com. Visit our website: slackscreekmedicalcentre.com.

RN Wanted
RN with PAP Smear training to offer clinic sessions. Times negotiable. Generous remuneration. Contact Karen or Robyn on 5547 0541 or info@pioneer-lv.com.au.

Wembley Rd Medical Centre Seeking VR GP
Newly renovated non-corporate bulk-billing medical centre located in Logan Central seeking full-time/part-time VR GP to work with our friendly team of four doctors. High number of patients, very high rate you will never refuse. Full-time nursing support. Choose your hours. We open from 8:30am to 11pm. 19AB exemption after 6pm, A0N positions available. AH period ideal for non-VR temporary residents. Contact Kylie White on 3808 3300, 0412 888 067 or email wembleyrd@outlook.com.au.

Contact Details

To submit articles or for further information please email: engagewithus@gmsbml.org.au
Deadline is 5pm Friday for inclusion in Wednesday publication.

Greater Metro South Brisbane Medicare Local
PO Box 6435, Upper Mt Gravatt QLD 4122 | **t** 07 3864 7555 or 1300 467 265 | **f** 07 3864 7599

Opening Hours: 8:00am – 5:00pm Monday to Friday ABN 53 151 707 765

www.facebook.com/sthbrisbanemedlocal www.twitter.com/sthbrismedlocal