Randomized database studies:

A combination of the strengths of observational studies and randomized clinical trials?

Georgio Mosis

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Gerandomiseerde database studies:
Een combinatie van de sterke punten uit observationele studies en gerandomiseerde klinische studies?

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Georgio Mosis
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Promotiecommissie

Promotoren
Prof. Dr. J. van der Lei
Prof. Dr. B.H. Ch. Stricker

Overige leden
Prof. Dr. B. Koes
Prof. Dr J.D.F. Habbema
Prof. Dr. A. Hasman

Co-promotor
Dr. M.C.J.M. Sturkenboom

Dedicated to Da Aguma Saka Labi Paansu and Ma Alime Paansu

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Chapter 1

Scope of the thesis

Introduction

Before a drug is allowed into clinical practice, randomized clinical trial (RCT) have been conducted in order to demonstrate efficacy and safety. The RCT method uses random treatment allocation to achieve comparable study groups and is further characterized by strict patient inclusion criteria, and strict follow-up schemes of the study groups.[2,3]

Once a drug enters the market, the drug is prescribed to a large number of heterogeneous patients who have concomitant diseases and drug use. As a result, unknown side effects may emerge (*e.g.*, rare side effects, side effects due to interactions or comorbidity). In addition, the effectiveness of the drug in clinical practice is not the same as the efficacy of the drug in clinical studies, mostly because usage patterns can be quite different. Postmarketing surveillance is the field that studies the beneficial and negative effects of drugs after they have been marketed.

In post-marketing studies, both experimental and observational methods can be applied to study drug safety and effectiveness. Both methods have advantages and disadvantages. We will first briefly discuss these methods.

Experimental Methods

Pragmatic or naturalistic trials are suggested as a possible solution to the low generalisability of pre-marketing RCTs. In a pragmatic trial treatment is assigned randomly but patient inclusion is more liberal (less strict inclusion criteria) and the treatment modalities are not organized as strictly as in RCTs (corresponding with regular patient care).[5] Therefore the results of pragmatic trials show effectiveness rather than efficacy and better reflect routine care practice. However, pragmatic trials often fail (or are not even considered as a possible alternative) because the implementation is time consuming and disrupts daily care processes or is ethically difficult.[6,7]

Observational methods

Observational post-marketing studies typically are based on data that are collected for other purposes such as claims data or electronic medical records. With the advent of electronic medical records, the volume of data available

to the researcher has increased; Examples are the general practice research data bases that emerged in several countries. Typically, analytic observational studies on drug effects in these databases rely on cohort and case-control designs.

Observational databases allow researchers to study large heterogeneous populations, various outcomes and treatments applied under daily practice circumstances.[8] Results from these studies, however, are often the subject of criticism due to the absence of randomization.[9,10,11] Without randomization, there is no guarantee that the treatment groups are comparable for all observed and unobserved prognostic factors and the results could therefore be subject to confounding by indication.

Confounding by indication occurs when a treatment is administered based on patient factors that are related to the prognosis of the patient or clinical endpoints.[12] Methods or techniques to rule out this form of bias completely in studies based on historic data are lacking.

Researchers engaged in post-marketing surveillance argued that an ideal design should comprise both the strengths of the experimental methods (*i.e.* randomised treatment allocation) and that of the observational methods (routine care follow-up provided by general practice databases). The challenge to develop a strategy that combines these strengths has resulted in a number of appealing research strategies and techniques:

1. *Cross-design synthesis* – a strategy of meta-analyses that combines studies with different study designs. Conventional meta-analyses combine results from complementary RCTs that cover different portion of patient populations in order to approximate the total patient population.[13] Cross-design synthesis combines the assessment, adjustment, and combination of treatment effects obtained in RCTs and observational studies.[14] An important drawbacks of cross-design synthesis is that several parts of the process require subjective judgments.[15]
2. *Randomised database studies* – a prospective study in which the Electronic Patient Record (EPR) is used to identify eligible cases, randomly assign treatment, and record the naturalistic follow-up of the treatment.[16] The outcome is assessed with information that is routinely collected and recorded in the EPR. Here, the claim is that randomised database studies would facilitate the assessment of drug effectiveness in large populations in real life practice by simultaneously using the strengths of experimental and observational methods. Although the advantage of this research strategy has been recognized, the method has only been described as a theoretical possibility – practical experience (*e.g.*, actual implementation) is not yet available.

General practice research database

In an environment where general practice research databases as data resource for observational studies are extensively used, the idea of randomized database studies is appealing. These general practice research databases are collections of EPRs used in general practices. In countries where general practitioners (GPs) have a gatekeeper's role in the healthcare system, this has led to population-based databases. A general practice research database typically contains information on patient identification, demographics, duration of observation, prescriptions, diagnoses, reason for encounter, referrals, laboratory findings and other notes. Well-known general practice research databases exist in several European countries, for example in the United Kingdom (*GPRD* and *Mediplus*), Italy (*Health Search* and *Pedianet*), or the Netherlands (*IPCI* and *LINH*).[17]

Integrated Primary Care Database (IPCI)

In the early 1990s, the department of Medical Informatics of the Erasmus University Medical Center in Rotterdam initiated the development of a general practice research database, the Integrated Primary Care Information (IPCI) database. The main objective of the IPCI databases was to achieve longitudinal medical information on large populations that can be used for post-marketing drug research. The development of the IPCI database is described in more details elsewhere.[18]

Since the development of the IPCI database, it has been used in many post-marketing observational studies on a variety of issues ranging from drug safety, incidence and prevalence of disease, to drug effectiveness.[19-24] Despite the successful use of the IPCI database for drug safety studies, studies concerning the effectiveness of treatments are difficult to conduct due to confounding issues. In an attempt to address these limitations, we wanted to explore the potential of the randomized database study in the IPCI database.

Objective of the thesis

The main objective of this thesis is to further explore the randomised database study and test its feasibility and validity in the IPCI database project.

As an application, we aimed to compare the gastrointestinal tolerability of celecoxib and diclofenac in patients diagnosed with osteoarthritis and subsequently treated.

The first part of this thesis, Chapters 2 through 4, is proof of concept. The presence of preferential prescribing (*channelling*) of selective COX-2 inhibitors to a specific patient population was demonstrated. In the presence of strong channelling it is difficult to draw conclusions of a potential increased risk that was shown in a study that assessed the association between gastrointestinal bleeding or ulcers and use of selective COX-2 inhibitors, it was deemed difficult to assess the gastrointestinal tolerability of COX-2 inhibitors without randomisation.
In the second part of this thesis, Chapters 5 through 7 we describe the exploration, implementation and evaluation of a randomised database study (to compare the gastrointestinal tolerability of celecoxib and diclofenac) in the IPCI database.

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Chapter 2

Part I

Channelling of COX-2 selective non-steroidal anti-inflammatory drugs

Georgio Mosis
Theo Stijnen
Jordi Castellsague
Jeanne P Dieleman
Johan van der Lei
Bruno HCh Stricker
Miriam CJM Sturkenboom

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Abstract

Purpose: To assess use and channelling of COX-2 selective inhibitors (coxibs) over time and to estimate the percentage of coxib users with cardiovascular contraindications.

Methods: The study population comprised all coxib and non-selective non-steroidal anti-inflammatory drugs (nNSAIDs) users in the Integrated Primary Care Information project between the period January 2000 and December 2004. The prevalence of risk factors for NSAID-related upper gastrointestinal ulcer complications, cardiovascular disease, and cerebro-vascular disease at the start of treatment was compared between users of coxibs and users of nNSAIDs.

Results: The study population included 72,841 users of nNSAIDs and 10,739 users of coxibs. The baseline prevalence of risk factors for NSAID-related gastrointestinal complications was higher in users of coxibs than nNSAIDs (OR 1.18, 95% CI 1.10–1.26). Similarly the prevalence of prior cardiovascular disease was higher in users of coxibs than in users of nNSAIDs (OR 1.35, 95% CI 1.28–1.43). Channelling of coxibs to patients with NSAID-related gastrointestinal risk factors declined after 2001 but increased again in 2004, while the channelling of coxibs to patients with cardiovascular disease remained constant. Less than 15% of all coxib users had history of ischemic coronary or cerebro-vascular disease. Among coxib users with increased risk for NSAID-related gastrointestinal disorders, 27% had history of ischemic coronary or cerebro-vascular disease.

Conclusion: This study shows that coxibs were preferentially prescribed to patients with risk factors for NSAID-related gastrointestinal disorders and/or cardiovascular diseases. Only a quarter of coxib users with increased risk for NSAID-related gastrointestinal complications had cardiovascular conditions compatible with recent European safety contraindications for coxibs.

Introduction

Non-selective non-steroidal anti-inflammatory drugs (nNSAIDs) are commonly used in the treatment of arthritis, pain and stiffness, but are associated with a 2 to 3 fold increase in the risk of upper gastrointestinal (UGI) complications such as bleeding, ulcers and perforation[1,2] due to the inhibition of cyclo-oxygenase (COX)-1. COX-2 selective inhibitors (coxibs) are efficacious pain relievers and reduce the risk of serious gastrointestinal (UGI) complication as compared to nNSAIDs.[3,4,5]

Based on evidence from clinical trials and cost-effectiveness analyses, the Dutch General Practice guidelines (2003) (in line with international guidelines), recommend that coxibs should be used only in persons with an increased risk of NSAID-related GI complications.[6,7,8]

The cardiovascular safety profile of rofecoxib has been discussed since the VIGOR (VIoxx Gastrointestinal Outcomes Research study) trial was published in 2000.[3] In 2002, the Food and Drug Administration (FDA) required a change in the package insert advising that caution should be exerted when Vioxx is used in patients with a medical history of ischemic disease. The drug was removed from the market in September 2004 because of cardiovascular safety problems.[9] In February 2005, the European Medicine Agency (EMEA) contraindicated the use of any coxibs in patients with ischemic heart disease or stroke, and the use of etoricixb in patients with r hypertension.[10] An Advisory Committee recommended to the FDA in February 2005 to issue a black box warning regarding the risk of heart attack and stroke for all coxibs. Due to the discussion about cardiovascular safety, the new contraindications and the clustering of GI risk and cardiovascular conditions, physicians may be confused to whom to prescribe coxibs.

Only few studies are available on the use of coxibs in the general population and all of them are relate to North-America.[11,12] In addition, little or no information is available on the concurrent prevalence of NSAID-related GI risk and cardiovascular disease in coxib users.

Evidence of channelling of coxibs to persons with NSAID-related GI risk factors is consistently described in all observational studies that aimed to study the gastrointestinal and/or cardiovascular effects of coxibs as compared to nNSAIDs, both in Canada[13] as well as in the USA.[13-17] In a UK study on GI outcomes, it was shown that coxibs are prescribed to patients with a greater disease severity, more co-morbid conditions and higher prevalence of gastrointestinal risk factors.[18] The concurrent existence of cardiovascular disease risk and GI disease risk was not described.

In view of the limited information on use and channelling of coxibs in Europe, the recent safety restrictions and the current confusion among physicians to whom to prescribe coxibs we aimed to describe the extent of coxib use in the first 5 years of marketing, to assess patterns of channelling of coxibs between 2000 and 2004, and to assess the percentage of coxib users with and without concurrent risk factors for NSAID-related GI complications and cardiovascular disease.

Methods

Setting

We conducted a population-based study in the Integrated Primary Care Information (IPCI) database. The IPCI database is a general practice research database in the Netherlands that comprises the complete electronic medical records of more than 500,000 patients. Details of the database have been published elsewhere.[19] In brief, the database contains anonymous data on patients' demographics, signs and symptoms, physical evaluation and findings, diagnoses, prescriptions, referrals, laboratory examinations and summaries of discharge letters. There is a complete record of all drug prescriptions, their indication, and dosage regimen. To maximize completeness of the data, GPs participating in the IPCI project are not allowed to maintain a system of paper-based records besides the electronic medical records. The IPCI system complies with the European Union guideline on the use of medical data for research and has been proven valid for pharmaco-epidemiological research.[19] The Scientific and Ethical Advisory Board of the IPCI project approved this study.

The source population for description of drug use comprised all subjects registered in the IPCI database during the study period (January 2000–December 2004). Each subject was followed from registration with the GP or start of the study period until the earliest of death, transferring out, or end of study period. The population for assessment of channeling and prevalence of concurrent risk factors for NSAID-related GI complications and cardiovascular disease comprised all persons with at least 12 months of valid database history.

Drug use was categorized in use of non-selective NSAIDs (all M01A except for COX-2 preferential drugs and COX-2 selective drugs) and use of coxibs (rofecoxib, celecoxib, etoricoxib, valdecoxib). In the assessment of channeling, the diclofenac+misoprostol (in a fixed combination) and COX-2 preferential

drugs (meloxicam, nabumetone) were excluded from the non-selective NSAIDs class.

Patient characteristics

The first time a person had an nNSAID or coxib prescription during the study period we assessed age, gender and the prevalence or history of the following diseases and conditions 12 months prior to the prescription: gastrointestinal co-morbidity (peptic ulcer disease, gastrointestinal hemorrhage, gastritis, duodenitis, dyspepsia and abdominal pain), cardiovascular co-morbidity (ischemic heart disease, chronic heart failure, hypertension, hyperlipidemia), stroke, and diabetes mellitus. Prior use of systemic corticosteroids, antiacids, Histamine2 (H2)-receptor antagonists, proton pump inhibitors (PPIs), other ulcer healing drugs, and cardiovascular drugs (positive inotropics, diuretics, ß-blockers, angiotensin-converting enzyme (ACE) inhibitors plus angiotensin II receptor blockers, vasodilators, anticoagulants, lipid-lowering drugs) issued in the 6-months period prior to the prescription of the nNSAID or coxib.
As overall measure of NSAID-related GI risk, the cumulative number of generally recognized risk factors for NSAID-related upper GI ulcer complications was calculated (age >65 years, use of systemic corticosteroids, use of anticoagulants or acetylsalicylic acid, and a history of peptic ulcer or gastrointestinal bleeding).
Patients were considered to have cardiovascular disease (contraindications) if they had a history of stroke, heart failure or ischemic heart disease.

Statistical analysis

Use of nNSAIDs and coxibs was described in terms of users per 1000 person-years of follow-up.
Logistic regression was used for assessment of channeling; in these analyses the odds of patient characteristics were separately compared between users of coxibs and users of nNSAIDs, while adjusting for age and gender. Therefore the observational unit in the logistic regression was a prescription of either a coxib (outcome 1) or an nNSAID (outcome 0). About 8% of the prescriptions were re-prescriptions in the same patient. The dependence of prescriptions within the same patient was accounted for by using earlier use of a coxib or nNSAID as predictor variable in the logistic regression. To look at patient characteristics as determinant for use of coxibs while adjusting for prescribing preference within a GP practice, in addition to age and gender, we used logistic regression with practice as a random effect, using PROC NLMIXED in SAS. Calendar year stratified analyses were conducted to verify trends

in channeling over time. All analyses were performed with SPSS version 11 (Chicago, IL) and SAS Release 8.2 (version 8.2 Cary, North Carolina).

Results

In the source population of more than 470,000 subjects during 2000–2004, use of non-selective NSAIDs decreased from 161 to 131 users per 1000 person years between 2000 and 2004. Meanwhile, use of coxibs increased from 0 to 32 users per 1000 person years (Figure 1).

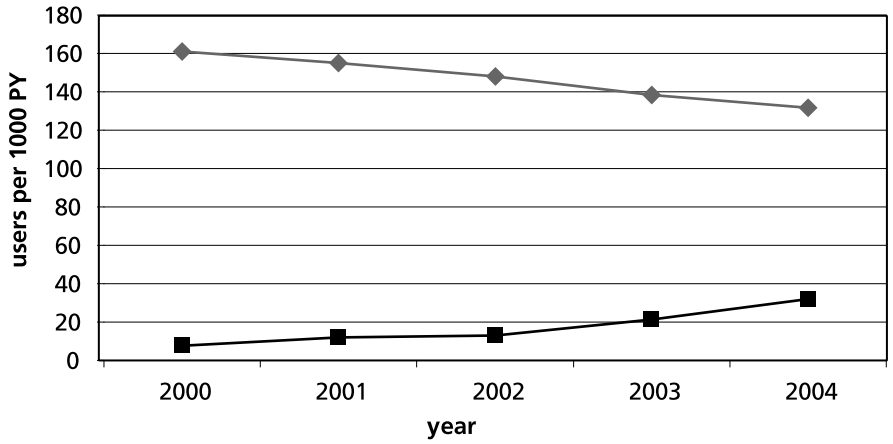

Figure 1: Use of non-selective NSAIDs (upper) and coxibs (lower) between 2000 and 2004. The X-axis represent the year of observation and the Y-axis represent the number of NSAID users per 1000 persons years of observation.

The subpopulation for assessment of channelling comprised 77,177 patients. Non-selective NSAIDs were used by 72,841 persons, and coxibs by 10,739. 6,403 patients had more than one prescription for a study drug and therefore entered more than once in the study. The mean percentage of coxib prescriptions over the total number of NSAIDs per practice increased from 6% in 2000 to 28% in 2004; 10% of the practices never prescribed coxibs during the study period.

Patients starting coxibs were more likely to be female (65.7% versus 56.8%) and older than those starting non-selective NSAIDs (mean ± SD, 58.3±17.0 years versus 46.1±17.7 years) (Table 1). Coxib users also had received NSAIDs (31.5 % versus 10.7%) and acid suppressive drugs (16.6% versus 6.8%) more frequently than non-selective NSAID users in the 6 months prior (Table 1). Use of cardiovascular drugs was 2.5 fold higher in coxib than nNSAID users.

The differences in prior or concomitant drug diminished substantially after adjustment for age, gender, and practice, but remained statistically different (Table 1). In line with the observed differences in drug use, the prevalence/ history of gastrointestinal, cardiovascular, cerebro-vascular diseases, and diabetes mellitus, were all higher in coxib users than in NSAID users (Table 1). Patients with ischemic heart disease or history of stroke were 32% and 23% more likely to receive a coxib, respectively. The most important determinants for prescription of a coxib were use of NSAIDs in the 6 months prior (OR 3.23, 95% CI 3.07–3.41), use of acid suppressive drugs (OR 2.01, 95% CI 1.89–2.15) and a history of GI disorders (OR 1.82, 95% CI 1.72–1.92).

Aggregation of risk factors showed that an increasing number of risk factors for NSAID-related GI complications increased the probability of receiving a coxib (Table 1). The extent of channelling of coxibs related to risk factors for NSAID-related GI complications decreased from being 40% more likely to receive a coxib if at least one GI risk factor was present to no increased probability in 2003 (Figure 2). Patients with cardiovascular disease were 20% to 30% more likely to receive a coxib than patients without cardiovascular disease, and this pattern did not change over time (Figure 3). In absence of gastrointestinal disease, cardiovascular disease remained an independent risk factor for receiving coxibs (Table 1).

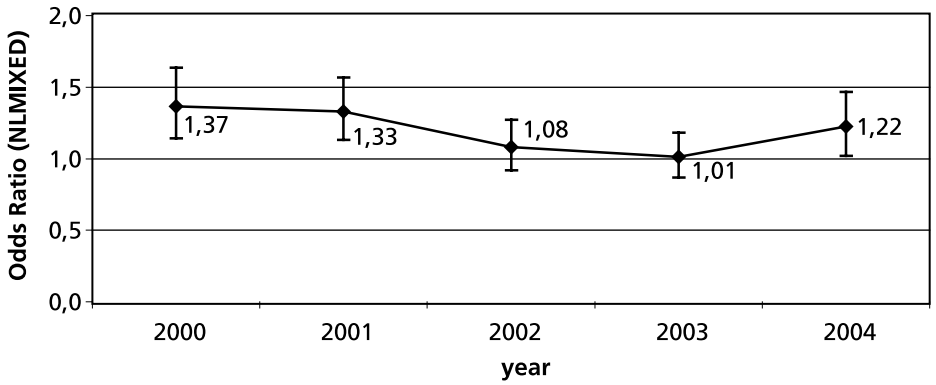

Figure 2: Probability of receiving coxibs for persons with at least one risk factor for NSAID-related gastrointestinal complications compared to patient without these risk factors (odds ratio adjusted for practice, age and gender). The X-axis represent the year of observation and the Y-axis represent the odds ratio.

About 45% of coxib users had one or more baseline risk factors for NSAID-related upper gastrointestinal complications, while these were present in 20.2 % of nNSAIDs users. Overall, less than 15% of coxib users would have had a cardiovascular contraindication, when we applied the February

2005 safety restrictions to the study period. Among the persons with at least one risk factor for NSAID-related GI complications, 27% had also a contraindicated cardiovascular condition.

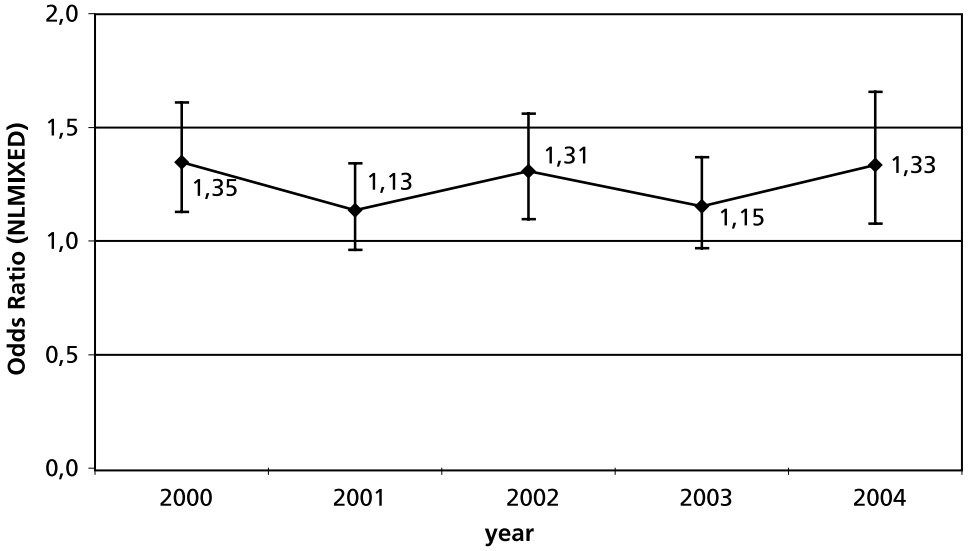

Figure 3: Probability of receiving coxibs for persons with cardiovascular disease compared to patients without cardiovascular disease (Odds Ratio adjusted for practice, age and gender). The X-axis represents the year of observation and the Y-axis represent the odds ratio.

Table 1: Patient characteristic of coxib and non-selective NSAID users and the association between use of coxibs and aggregated gastrointestinal risk factors, medication and cardiovascular disease.

	Coxib (n= 10739)	%	NSAID (n= 72841)	%	$OR_{age\ and\ gender}$ Population average OR			$OR_{NLMIXED\ age\ and\ gender}$ Practice adjusted OR		
						95%	CI		95%	CI
Female (%)	7054	65.7	41354	56.8	1.36	1.30 -	1.42	1.47	1.41 -	1.54
Mean age (SD)	58.3	17.0	46.10	17.7						
Age categories N (%)										
0–20	158	1.5	5612	7.7						
21–40	1559	14.5	23560	32.3						
41–60	4117	38.3	28067	38.5						
61–80	3904	36.4	13446	18.5						
80+	1001	9.3	2156	3.0						
Indication										
Osteoarthritis	1130	10.5	932	1.3	Ref.					
Rheumatoid arthritis	165	1.5	333	0.5	10.75	9.78	11.80	0.94	0.79	1.12
Other Musculoskeletal disorders	5435	50.6	31311	43.0	4.39	3.63	5.31	0.41	0.38	0.43
Other indications	682	6.4	10776	14.8	1.54	1.47	1.61	0.15	0.14	0.17
Unknown	3327	31.0	29489	40.5	0.56	0.52	0.61	0.19	0.17	0.21
NSAID use in 6 months prior (%)	3381	31.5	7805	10.7	3.02	2.88 -	3.18	3.23	3.07 -	3.41
acid suppressive agents and ulcers healing drugs (%)	1786	16.6	4973	6.8	1.97	1.85 -	2.09	2.01	1.89 -	2.15
Antiacids	91	0.9	436	0.6	1.11	0.88 -	1.40	1.17	0.91 -	1.50
H2 receptor antagonist	488	4.5	1782	2.5	1.40	1.26 -	1.56	1.52	1.36 -	1.70
PPIs	1271	11.8	2982	4.1	2.26	2.11 -	2.43	2.21	2.05 -	2.39
Other Ulcer healing drugs	54	0.5	144	0.2	2.04	1.47 -	2.83	2.14	1.51 -	3.04
Cardiovascular drugs (%)	3727	34.7	12674	17.4	1.28	1.22 -	1.35	1.28	1.21 -	1.35
Acetylsalicylic acid	515	4.8	1678	2.3	1.08	0.97 -	1.20	1.17	1.05 -	1.31
B-blocker	1399	13.0	5064	7.0	1.18	1.10 -	1.26	1.17	1.09 -	1.26

	Coxib (n= 10739)	%	NSAID (n= 72841)	%	OR age and gender Population average OR			OR NLMIXED age and gender Practice adjusted OR		
						95%	CI		95%	CI
Positive inotropics	148	1.4	429	0.6	0.90	0.75 -	1.10	1.02	0.98 -	1.06
Diuretics	1281	11.9	3697	5.1	1.14	1.06 -	1.22	1.17	1.08 -	1.26
ACE inhibitors	1304	12.1	3936	5.4	1.32	1.23 -	1.42	1.32	1.23 -	1.42
Other anti-hypertensive drugs	1063	9.9	3083	4.2	1.24	1.15 -	1.34	1.19	1.09 -	1.29
Anti-platelet drugs and anticoagulants	1294	12.1	3871	5.3	1.18	1.10 -	1.27	1.21	1.12 -	1.31
Lipid lowering drugs	887	8.3	2958	4.1	1.37	1.26 -	1.48	1.30	1.19 -	1.41
Other drugs (%)										
oral corticosteroids	543	5.1	1681	2.3	1.53	1.38 -	1.69	1.69	1.51 -	1.88
Prevalence of GI-co-morbidity (%)	2574	24.0	9379	12.9	1.92	1.83 -	2.02	1.82	1.72 -	1.92
Peptic ulcer	255	2.4	712	1.0	1.96	1.68 -	2.27	1.60	1.46	1.75
Gastrointestinal bleeding	102	1.0	243	0.3	2.03	1.59 -	2.59	1.72	1.33 -	2.22
Gastritis and duodenitis	1479	13.8	4789	6.1	2.11	1.98 -	2.25	1.86	1.74 -	2.00
Other disorders of stomach and duodenum	1773	16.5	6695	9.2	1.82	1.72 -	1.93	1.75	1.64 -	1.86
Prevalence of cardiovascular co-morbidity (%)	3733	34.8	12835	17.6	1.39	1.32 -	1.46	1.35	1.28 -	1.43
Ischemic heart disease	939	8.7	2628	3.6	1.34	1.24 -	1.46	1.32	1.21 -	1.44
Heart failure	433	4.0	901	1.2	1.32	1.16 -	1.49	1.25	1.09 -	1.42
Hypertension	1972	18.4	6616	9.1	1.32	1.24 -	1.40	1.27	1.20 -	1.36
Hyperlipidemia	1129	10.5	3850	5.3	1.38	1.28 -	1.48	1.29	1.20 -	1.40
Prevalence of other disease (%)										
Diabetes	853	7.9	2747	3.8	1.38	1.27 -	1.50	1.33	1.22 -	1.45
Cerebro-vascular disease	489	4.6	1442	2.0	1.21	1.09 -	1.35	1.23	1.10 -	1.39
Gastrointestinal risk factors										
0	5920	55.1	57839	79.4						
1	3476	32.4	11717	16.1	1.12	1.05-	1.20	1.09	1.02-	1.17
2+	1343	12.5	3285	4.5	1.29	1.18-	1.41	1.31	1.19-	1.44

	Coxib (n= 10739)	%	NSAID (n= 72841)	%	OR age and gender Population average OR			OR NLMIXED age and gender Practice adjusted OR		
						95%	CI		95%	CI
Combined gastrointestinal (GI)* and cardiovascular (CV)** risk factors (%)										
No GI and No CV risk factors	5654	52.7	56802	78.0						
At least one GI and one CV risk factor	1297	12.1	3379	4.6	1.36	1.24-	1.49	1.47	1.34-	1.60
No GI and at least one CV risk factor	266	2.5	1037	1.4	1.87	1.62-	2.15	2.68	2.58-	2.78
At least one GI risk factor and no CV risk factor	3522	32.8	11623	16.0	1.16	1.08-	1.24	3.02	2.89-	3.15

* Gastrointestinal risk factors comprised age>65, use of systematic corticosteroids, use of anticoagulants or acetylsalicylic acid and a history of peptic ulcer or gastro-intestinal bleeding.
** Cardiovascular risk factors comprised a history of stroke, heart failure, ischemic heart disease.

Discussion

This study showed that coxib use gradually increased at the expense of non-selective NSAID use during the first 5 years of marketing in the Netherlands. In line with the diffusion of coxib use, channelling related to the presence of a risk factor for NSAID-related GI complications decreased until 2004.

We estimated that 85% of all coxib users and 75% of persons with increased risk of NSAID-related GI complications have no history of contra-indicated cardiovascular disease and would be remain eligible for a coxib prescription. In view of the debates about the cardiovascular safety of coxibs, it is noteworthy that persons with cardiovascular disease (even in absence of GI risk) were more likely to receive a coxib.[20] Also, despite channelling to persons with GI risk factors, most coxib users are persons without risk factors for NSAID-related GI disorders. Our findings are in line with studies in the UK and USA, which have shown that coxibs are mostly prescribed to persons without increased risk of NSAID-related GI disorders.[18,21]

Our data on channelling of coxibs are in line with group differences in observational studies that compared gastrointestinal or cardiovascular safety between coxibs and NSAIDs.[13-18] Solomon and MacDonald showed that coxib users in the US and in UK also had a higher prevalence of GI risk factors.[18,21] Cohort studies (US and Canada) that compared cardiovascular outcomes between coxibs and nNSAIDs showed that coxib users had more cardiovascular co-medication and co-morbidity, higher prior use of NSAIDs, and more prescriptions at baseline,[13-17] which is in line with our data.

The differences between the population average and the practice adjusted odds ratios indicate that some, but not all of the observed overall channelling is due to patient characteristics. This observation is consistent with studies in Medicare[21,22] showing that first time selective COX-2 inhibitor prescribing is dependent on both gastrointestinal risk factors and physicians' preference in the first 2 years of the availability. Our data also showed an impact of physicians' preference in relation to the other determinants, although the impact was less substantial in the period of 5 years of observation.

Our study has some limitations that should be considered when reviewing the results. First, we conducted a cohort study in which a patient could contribute multiple times to the study cohort if he/she uses different NSAIDs during the study period. The number of persons entering twice was around 8%. Sensitivity analyses in which patients were included only once only had a minor effect on the results and did not change the conclusion. Second, the IPCI database did not contain enough coxibs users to enable us to analyse

individual coxibs. As a result, we combined the individual coxibs into one group. Lastly, there could be dependency in the data regarding general practices that preferentially prescribe a certain NSAID. Even though we attempt to adjust for this phenomenon with non-linear mixed model, it is no guarantee that the results are partly because of residual confounding.
In conclusion, this study showed that the use of coxibs have increased substantially between 2000 and 2004. The baseline prevalence of these factors was about 50% among users of coxibs and 20% among users of nNSAIDs. Only a quarter of coxib users with increased risk for NSAID-related GI complications had cardiovascular conditions compatible with recent European safety contraindications for coxibs.

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Chapter 3

NSAIDs and the risk of ulcers and upper gastrointestinal bleeding: A nested case-control study

Abstract

Objective: To compare the gastro-intestinal safety between selective COX-2 inhibitors (coxibs) and the one pill combination of diclofenac and misoprostol

Methods: Within the Integrated Primary Care Information (IPCI) general practice database, we conducted a nested case control study in a cohort of new NSAIDs users, 65 years and older, in the period between November 1999 and December 2004. Cases were all persons with a validated diagnosis of an upper gastrointestinal (GI) bleeding or a peptic ulcer, and at least one year of valid history prior to cohort entry. Each case was matched on calendar time, age, and gender to all available controls at the date of the GI event. The risk of GI bleeding or peptic ulcer among current users of coxibs was compared to that of current users of the one pill combination of diclofenac and misoprostol.

Results: We identified 217 cases of gastrointestinal bleedings and peptic ulcers during the study period. We observed an increased risk of gastrointestinal bleeding and ulcers for current use of coxibs (OR 2.92, 95%CI: 1.11–7.65) as compared to the one pill combination of diclofenac and misoprostol.

Conclusion: Our data show that the risk of gastrointestinal ulcers and bleedings is increased during use of coxibs compared to use of the one-pill combination of diclofenac and misoprostol.

Introduction

Data from two landmark clinical trials in patients with rheumatological disease have demonstrated that COX-2 selective inhibitors (coxibs) reduce the risk of gastrointestinal bleedings and ulcers as compared to non-selective non-steroidal anti-inflammatory drugs (nNSAIDs).[1,2] Other randomised studies have confirmed these findings.[3-5] Based on cost-effectiveness analyses, international guidelines recommend the use of coxibs in persons at increased risk of NSAID-related complications[6-8] and as a result coxibs are channelled to this population.[9,10]

An alternative treatment strategy to reduce the risk of NSAID-related gastrointestinal complication is the use NSAID with gastro-protective agents such as misoprostol, proton pump inhibitors, and histamine-2 (H2)-receptor antagonists.

Evidence from a randomised clinical trial showed that celecoxib was not inferior to diclofenac in combination with omeprazole regarding recurrent ulcer bleedings in patients at high risk of this condition.[11] Other randomized studies on the comparison between coxibs and non-selective NSAIDs with gastro-protective agents are not available as far as we know. Several observational studies data compared the gastrointestinal safety of coxibs and non-selective NSAIDs[10,12-14] but no studies have directly compared coxibs to the one pill combination of diclofenac and misoprostol.

The objective of this nested case-control study was to investigate whether the risk of upper gastro-intestinal bleedings and peptic ulcers is comparable between use of coxibs and use of diclofenac plus misoprostol in a population that is eligible for gastro-protection during use of NSAIDs.

Methods

Setting

This study was conducted in the Integrated Primary Care Information (IPCI) database. The IPCI database has been described elsewhere.[15] In brief, IPCI is a longitudinal general practice research database that contains data from computer-based patient records of a selected group of general practitioners (GPs) throughout the Netherlands. As of December 2004 there are more than 150 GPs who have provided data to the database. The database contains information on about 500,000 patients with an age and gender distribution comparable to the Dutch population. The database contains anonymized

plus demographic information (age, sex, GP registration information), notes, prescriptions, physician-linked indications for therapy, physical findings, and laboratory values which are directly entered into the computer by the GP. The International Classification of Primary Care (ICPC) is the coding system for patient complaints and diagnoses, but diagnoses and complaints can also be entered as free text. Prescription data such as product name, quantity dispensed, dosage regimens, strength, indication and Anatomical Therapeutic Chemical (ATC) codes are entered directly into the computer by the GPs. The system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological research.[15] The Scientific Advisory Board of the IPCI database approved this study.

Study population

A nested case control study was conducted in a cohort of new NSAID users who were 65 years or older during the period November 1999 and December 2004. All subjects were followed from the first NSAID prescription, until the end of the study period, death or occurrence of the outcome, whichever came first.

Once entered in the study cohort, patients could contribute to multiple episodes of NSAID use, if they switched or restarted therapy. NSAIDs were categorized in non-selective NSAIDs, the one pill combination of diclofenac and misoprostol, and coxibs. Contribution to an exposure category ended at the end of the prescription, or at the start of a new NSAID of a different category, or at the occurrence of a study outcome (whichever was earliest). When two or more NSAIDs categories overlapped, they were assigned to a combination category.

Case definition

The primary outcome was defined as an upper GI bleeding or a symptomatic peptic ulcer. All potential cases were manually validated by two medical doctors to exclude false positive records and to assess the earliest date of onset of each of the events (index date). Cases were classified as definite or possible cases based on the availability of endoscopic conformation. At the date of case occurrence we sampled all available controls who were in the cohort and who could be matched to the case on age (year of birth), year of first NSAID use during the study period, gender, and index date.

Exposure definition

From the prescription records we obtained all prescriptions for NSAIDs and classified exposure prior to the index date in mutually exclusive groups of current (still using or stopped 30 days before), past (stopped 31–180 days before the index date) and remote use (stopped more than 180 days prior to the index date). Groups were made for non-selective NSAIDs (nNSAIDs) (diclofenac, ibuprofen, naproxen and others), the one pill combination of diclofenac and misoprostol (Arthrotec) and coxibs (rofecoxib, celecoxib, etericoxib and other coxibs).

Co-variates

We considered the following conditions as potential confounders for the association between upper GI bleeding and peptic ulcers and the use of NSAIDs: smoking, prior ischemic cardiovascular events (angina, myocardial infarction, stroke), hypertension, diabetes mellitus, heart failure, prior gastrointestinal events (perforation, ulcers or bleedings), prior gastritis or duodenitis and the indication for NSAID use (osteoarthritis, rheumatoid arthritis, other musculoskeletal disorders, pain, or other indications).
Concomitant drug use was assessed up to one week prior to the index date to avoid protophathic bias and included: cardiovascular drug use (diuretics, digoxin, ACE inhibitors, calcium channel blockers (CCB), Beta-blockers and lipid lowering drugs), aspirin, systemic corticosteroids, selective serotonin reuptake inhibitors (SSRI), antibiotics, estrogens, gastro-protective drugs (proton pump inhibitors (PPIs), Histamine (H)2-receptor antagonists), antacids and anti-thrombotic agents.

Statistical Analysis

The association between GI bleedings and peptic ulcers and the co-variates was assessed through conditional logistic regression analysis. All covariates that were associated with the outcome ($p<0.05$) were considered as potential confounders and were used in the multivariate regression models.
For the principal analyses we compared current use of coxibs with current use of the one pill combination of diclofenac and misoprostol. Several sensitivity analyses were conducted by varying the reference group to remote use of NSAIDs, or use of NSAID plus PPIs and by restriction of the analyses to definite cases of gastrointestinal bleedings and ulcers. All analyses were conducted by using SPSS version 11 (Chicago, IL).

Results

A total of 27321 persons contributed to 1594 person-years of current coxib use, 6515 person-years of nNSAID use and 907 person-years of diclofenac plus misoprostol use.

In the study cohort we observed 217 cases of upper GI bleeding and peptic ulcers after entry. Compared to the controls, cases more frequently used diuretics (OR 1.76, 95%CI 1.28–2.44), ACE inhibitors (OR 1.69, 95%CI 1.18–2.43), SSRIs (OR 2.38 95%CI 1.19–4.78), antibiotics (OR 3.59 95%CI 1.82–7.06), and anti-thrombotic agents (OR 2.32 95%CI 1.66–3.23). Cases also more often were smokers, more often had chronic obstructive lung disease, cardiovascular co-morbidity, and more frequently had a history of gastrointestinal events (Table 1). To evaluate the association between covariates and exposure we looked at this association among the controls. Current coxib users more often had a history of stroke, gastritis and duodenitis, and hypertension compared to users of the one pill combination of diclofenac and misoprostol. Coxib users also more frequently used PPIs (Table 2).

In the primary analyses, none of the potential confounding factors influenced the point estimate between current use of coxibs and the one pill combination of diclofenac and misoprostol. Current use of coxibs was associated with a 2.9 fold increased risk of GI bleedings and peptic ulcers (OR 2.92 95%CI 1.11–7.65) as compared to use of the one pill combination of diclofenac and misoprostol. The risk was even higher in the group of patients who used both a non-selective NSAIDs and a coxib (OR 8.4 95%CI 2.0–35.1) (Table 3).

Table 1: Characteristics of cases and controls and association with ulcers and GI bleeding.

	Controls (n=9862)		Cases (n=217)		OR	95%CI	
Males	2771	28.1	80	36.9	–	–	
Age (mean, sd)	74.9	(6.0)	78.3	(7.6)			
Smokers	1918	20.2%	56	25.8%	1.71	1.24	2.36
Chronic obstructive lung disease	1023	10.4%	33	15.2%	1.57	1.07	2.31
Diabetes Mellitus	1240	12.6%	31	14.3%	1.11	0.75	1.65
History of Perforation ulcers and bleedings	360	3.7%	13	6.0%	1.56	0.88	2.80
History gastritis/duodenitis	1898	19.2%	51	23.5%	1.39	1.00	1.93
Cardiovascular events							
Angina	1217	12.3%	44	20.3%	1.70	1.20	2.41
History of myocardial infarction	545	5.5%	12	50.5%	0.93	0.51	1.69
History of Stroke	725	7.4%	30	13.8%	1.54	1.02	2.34
Hypertension	3762	38.1%	79	36.4%	0.97	0.73	1.29
Peripheral arterial disease	491	5.0%	24	11.1%	2.17	1.83	3.39
Arrhythmia	675	6.8%	29	13.4%	1.73	1.14	2.61
Heart failure	680	6.9%	28	12.9%	1.40	0.92	2.15
Indication							
Arthritis	873	8.9%	22	10.1%	ref	ref	ref
Rheumatoid arthritis	132	1.3%	3	1.4%	0.91	0.26	3.16
Other musculoskeletal disorders	4871	49.4%	83	38.2%	0.74	0.45	1.20
Other indications	1090	11.1%	35	16.1%	1.35	0.77	2.36
Not recorded	2896	29.4%	74	34.1%	1.10	0.67	1.81
Cardiovascular drugs							
Diuretics	1564	15.9%	58	26.7%	1.76	1.28	2.44
Digoxin	242	2.5%	13	6.0%	1.83	0.998	3.37
ACE-I	1091	11.1%	39	18.0%	1.69	1.18	2.43
CCBs	894	9.1%	27	12.4%	1.35	0.89	2.06
B-Blockers	1598	16.2%	41	18.9%	1.20	0.84	1.71
Lipid lowering drugs	929	9.4%	21	9.7%	1.29	0.81	2.06
Aspirin	786	8.0%	27	12.4%	1.50	0.98	2.27
Corticosteroids	200	2.0%	6	2.8%	1.13	0.48	2.71
SSRIs	193	2.0%	9	4.1%	2.38	1.19	4.78
Antibiotics	141	1.4%	10	4.6%	3.59	1.82	7.06
Proton pump inhibitors	714	7.2%	17	7.8%	1.13	0.68	1.87
H2 receptor antagonist	286	2.9%	7	3.2%	1.11	0.51	2.41
Anti-thrombotic agents	1066	10.8%	51	23.5%	2.32	1.66	3.23

Table 2: Characteristics of the controls currently exposed to coxibs and NSAIDs.

	Current Coxib (n=325)		Current diclofenac +misoprostol (n=231)		Current nNSAID (n=1260)	
	n	%	n	%	n	%
Gender (male %)	53**	16.3	50*	21.6	354	28.1
Smokers	66	20.3	36	15.6	210	16.7
Chronic obstructive lung disease	32	9.8	33*	14.3	119	9.4
Diabetes Mellitus	43	13.2	27	11.7	166	13.2
History of perforation ulcer bleedings	13	4.0	11	4.8	35	2.8
History of gastritis or duodenitis	72*	10.2	51*	22.1	203	16.1
Cardio vascular events						
Angina	42	12.9	24	10.4	142	11.3
History of myocardial infarction	18	5.5	12	5.2	57	4.5
History of stroke	39*	12.0	14	6.1	99	7.9
Hypertension	156**	48.0	91	39.4	476	37.8
Peripheral arterial disease	7	2.2	11	4.8	51	4.0
Arrhythmia	26	8.0	15	6.5	70	5.6
Heart failure	33	6.9	22	9.5	100	7.9
Indication						
Arthritis	53	16.3	26	11.3	154	12.2
Rheumatoid arthritis	10	3.1	8	3.5	27	2.1
Other musculoskeletal disorders	137	42.2	104	45.0	541	42.9
Other pain	33	10.2	30	13.0	109	8.7
Other indications	92	28.3	63	27.3	429	34.0
Cardiovascular drugs						
Diuretics	68	20.9	41	17.7	245	19.4
Digoxin	6	1.8	3	1.3	31	2.5
ACE inhibitors	48	14.8	34	14.7	160	12.7
CCB	40	12.3	25	10.8	137	10.9
Beta-Blockers	47	14.5	35	15.2	218	17.3
Lipid lowering drugs	26	8.0	20	8.7	111	8.8
Aspirin	30	9.2	19	8.2	117	9.3
Corticosteroids	13	4.0	12*	5.2	27	2.1
SSRI	5	1.5	7	3.0	25	2.0
Antibiotics	2	0.6	3	1.3	24	1.9
Gastro-protective agents						
PPI	42*	12.9	23	10.0	111	8.8
H2 receptor antagonist	18	5.5	10	4.3	46	3.7
Antiacids	4	1.2	2	0.9	9	0.7

* p<0.05, ** p<0.001 – Current diclofenac+misoprostol as reference group.

Table 3: Risk of gastrointestinal bleeding and ulcers with current, past and remote use of nNSAID, coxibs an combinations of coxibs and nNSAID.

	Case (n=217)	Control (n=9862)	OR crude	95.0% CI	
Current diclofenac +misoprostol	6 (2.8%)	231 (2.3%)	Ref.		
Current coxib	22 (10.1%)	325 (3.3%)	2.92	1.11	7.65
Current NSAID	54 (24.9%)	1260 (65.8%)	1.95	0.81	4.66
Current coxib + NSAID	4 (1.8%)	20 (0.2%)	8.4	2.0	35.1
Past coxib	4 (1.8%)	252 (2.6%)	0.8	0.2	2.9
Past NSAID	20 (9.2%)	1256 (12.7%)	0.77	0.29	2.01
Past coxib + NSAID	0	26 (0.3%)	–	–	–
Remote use NSAID	107 (49.3%)	6492 (65.8%)	0.83	0.34	2.01

Compared to the one pill combination in normal dosages we observed a positive dose response for the association between coxibs and upper GI bleeding or ulcers. Use of coxibs in dosages less than twice the defined daily dose the odds ration was 3.64 95%CI 1.02–13.05, and in current coxibs users with dosages more than 2 DDDs the odds ratio was 6.7 95%CI 1.6–28.2. The risk of gastrointestinal bleeding and ulcers was also increased in current NSAID users with a DDD greater than 2 (OR_{adj} 7.96 95%CI 2.28–27.75) and in users of a combination of coxibs and NSAIDs (Table 4). In these analyses we adjusted for rhythm disturbances and the use of anti-thrombotic agents.

Table 4: Effect of defined daily dosage (DDD) equivalent on gastrointestinal bleedings and ulcers.

	Cases (n=217)	Controls (n=9862)	OR crude	OR_{adj}*	95% CI	
Current diclofenac+ misoprostol <= 2 DDD	3 (1.4%)	194 (2.0%)	Ref.	Ref.		
Current diclofenac+ misoprostol >2 DDD	3 (1.4%)	37 (0.4%)	5.0	4.9	0.9	26.3
Current coxibs <=2 (DDD)	16 (7.4%)	259 (2.6%)	3.9	3.64	1.02	13.05
Current coxibs >2 (DDD)	6 (2.8%)	66 (0.7%)	7.3	6.7	1.6	28.2
Current nNSAID<=2 (DDD	35 (16.1%)	1102 (11.2%)	2.32	2.30	0.69	7.60
Current nNSAID >2 (DDD)	19 (8.8%)	158 (1.6%)	8.11	7.96	2.28	27.75
Current coxibs+ NSAID	4 (1.8%)	20 (0.2%)	13.0	13.9	2.7	71.2
Past or remote use of any NSAID or coxib	131 (60.4%)-	8026 (81.4%)	1.26	1.23	0.38	3.98

*Adjusted for rhythm disturbances and use of anti-thrombotic agents.

Analyses focused to assess whether concomitant use of PPIs or H2-receptor antagonists showed that the increased risk of GI bleeding and peptic ulcers in current users of coxibs was restricted to those who did not use gastro-protective agents (OR 3.00 95%CI 1.13–7.07) (Table 5).
Restriction of the cases to the definite cases (n=129) increased the association between current use of coxibs and the occurrence of upper gastro-intestinal events (OR 5.73, 95% CI 1.53–21.46).

Table 5: Risks of gastrointestinal bleeding and ulcers in current use of coxibs and nNSAID in combination with proton pomp inhibitors (PPI) or H2 receptor antagonist (H2RA)

	Cases (n=217)	Controls (n=9862)	OR-crude*	95.0% CI	
Current diclofenac+misoprostol	6 (2.8%)	231 (2.3%)	Ref.		
Current coxib + PPI and/or H2RA	3 (1.4%)	59 (0.6%)	2.4	0.6	10.2
Current coxib without PPI and H2RA	19 (8.8%)	266 (2.7%)	3.00	1.13	7.97
Current NSAID + PPI and/or H2RA	3 (1.4%)	155 (1.6%)	0.969	0.2	4.0
Current NSAID without PPI and H2RA	51 (23.5%)	1105 (11.2%)	2.08	0.87	5.00
Current coxib + NSAID	4 (1.38%)	20 (0.2%)	8.30	2.0	34.7
Past or remote use of any NSAID or coxib	131 (60.4%)	8026 (81.4%)	0.81	0.34	1.92

* No confounding factors.

Discussion

Our data show evidence that the risk of gastrointestinal bleeding and ulcers is higher during current use of coxibs as compared to current use of the one pill combination of diclofenac and misoprostol. We also observed a dose response relation both for coxibs users as well as for nNSAID use. Among the current coxibs users we observed an increased risk of gastrointestinal bleeding and ulcer only in those who did not concomitantly use gastro-protective agents.
Other observational studies suggested a protective effect for gastrointestinal disorders in coxib users compared to non-selective NSAIDs.[12-14,6] Layton *et al.* found a relative reduction (29%) in the incidence rate of symptomatic GI events, and no difference in the incidence rate of upper GI conditions (perforations/bleeding) for rofecoxib and celecoxib compared with meloxicam.[12,13] Goldstein *et al.* concluded that celecoxib use is associated with a significantly decreased risk of upper GI symptoms compared to nNSAIDs use.[14] Mamdani *et al.* compared patients aged 66 years and older who started taking nNSAIDs, diclofenac plus misoprostol, rofecoxib or celecoxib with a randomly selected control cohort not exposed to NSAIDs and found a lower

short term risk of upper GI bleeding for coxibs.[16] Relative to celecoxib, this study showed significantly higher risks of upper gastrointestinal bleeding for non-selective NSAIDs (4.4 (2.3 to 8.5)), diclofenac plus misoprostol (3.2 (1.6 to 6.5)), and rofecoxib (1.9 (1.2 to 2.8)).

These studies, however, demonstrated selective prescribing of coxibs to patients with greater disease severity, more co-morbid conditions and higher prevalence of gastrointestinal risk factors. Such channelling effects may easily confound the comparison of gastrointestinal safety of coxibs in naturalistic settings.[17,18]

Our observation may also be confounded due to unrecognised risks, such as incomplete medical history information, undetected or underreported risk factors. The physicians' preference for coxibs could also be an important factor to whether a patient is treated with a coxibs or an NSAID (plus a gastro-protective drug).[19,20] We assumed that this channelling phenomenon would be less apparent if we compared coxibs use with the alternative treatment option of NSAID with a gastro-protective agent. Still, we observed that patients treated with coxibs had greater disease severity, more co-morbid conditions and higher prevalence of gastrointestinal risk factors compared to the one pill combination of diclofenac and misoprostol (Table 1). Our study may have suffered from other additional limitations. The exposure to NSAIDs was assessed based on prescription records and we could not adjust for use of over the counter NSAID. This misclassification could be differential since we observed an increased risk and NSAIDs that are available over-the-counter increase the risk of gastrointestinal disorders.

We studied gastrointestinal bleeding and ulcers in a population of 27321 patients, but unfortunately, due to low numbers, we were not able to study the different coxibs separately and could not provide any information on the gastro-intestinal safety profile of the different coxibs.

Based on our results and in view of the new knowledge on the potential of cardiovascular side effects in users of coxibs, we would suggest that the one pill combination of diclofenac and misoprostol should be considered as the drug of first choice, especially in high risk patients.

In conclusion, our data show that the risk of gastrointestinal ulcers and bleedings is increased in current users of coxibs compared to diclofenac plus misoprostol. The increased risk reduces if coxibs are combined with proton pump inhibitors

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Chapter 4

Gastrointestinal Intolerability during use of Diclofenac: A pilot study to estimate the sample size for a randomised database study

Background

Celecoxib (a selective COX-2 inhibitor) and diclofenac (a non-selective NSAID) are officially licensed for the treatment of osteoarthritis.[1] Due to the channeling of selective COX-2 inhibitors to patients with a history of gastrointestinal and cardiovascular risk factors,[2] it is difficult to compare gastrointestinal tolerability of these NSAIDs without randomization.

We therefore aimed to assess gastrointestinal tolerability of celecoxib and diclofenac in daily practice with the randomised database study design.[3] Before we conducted the randomised database study, we assessed the frequency of the primary study outcome, treatment discontinuation due to gastrointestinal intolerability, in a retrospective cohort study with data from the Integrated Primary Care Information (IPCI) database. We hereby applied patient selection criteria and conducted follow-up as we planned to do in the RDS. The aim of pilot study was to assess the number of eligible subjects and occurrence of gastrointestinal intolerability during use of diclofenac, to better estimate the sample size required for the RDS.

Methods

Source population

The source population comprised all patients who are registered with one of the general practitioners (GPs) who contribute information to the IPCI database in the Netherlands. IPCI is a longitudinal observational database that contains data from EPRs of a selected group of GPs throughout the Netherlands.[4] Collaborating practices are comparable to other GPs regarding age and gender. Practices have been supplying data for varying periods of time and the current IPCI database contains information on over 500,000 patients.

The IPCI database contains identification information (age, sex, patient identification, GP registration information), notes, prescriptions, indications for therapy, physical findings, and laboratory values which are directly entered into the computer by the GP. Downloads are made on a monthly basis and the information is sent to the gatekeeper who anonymized all information before further access is provided. The International Classification of Primary Care (ICPC) is the coding system for patient complaints and diagnoses, but diagnoses and complaints can also be entered as free text. Prescription data such as product name, quantity dispensed, dosage regimens, strength, and indication are entered into the computer. The National Database of drugs, maintained by the Royal Dutch Association for the Advancement of Pharmacy, enables the coding of prescriptions, according to the Anatomical Therapeutic Chemical (ATC) classification scheme recommended by the WHO. The system complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological research.[5-9]

Study population

Patient selection for the pilot study was in line with that proposed for the RDS. In the RDS, special designed software is installed in the information system of the participating GPs. At installation of the software, a selection module identified all potential eligible patients by means of an automated search in the historic medical data. Since the pre-selection of possible candidates occurred at one moment in time, we acted as if the module was installed on January 1st 2000 in the IPCI database. Patients were pre-selected if they: were registered for at least 6 months with their GP, were at least 18 years of age, and had a diagnosis of osteoarthritis. The diagnosis of osteoarthritis was searched through coded diagnoses (ICPC codes: L84, L89, L90, L91) and text strings including 'osteoarthritis', 'joint' and 'pain'. The text string selections were manually validated to reduce false positively selected patients.
In the population of pre-selected patients (study population), we identified the first NSAID prescription and the first diclofenac prescription during the study period (January 2000 to December 2002). The date of the first NSAID prescription was considered the index date.

Exclusion criteria

At the index date we assessed the frequency of the following exclusion criteria: current treatment with NSAIDs (prescription in the last three months), current treatment with a gastro-protective agent (proton pump inhibitors (PPIs), Histamine (H)2-recepter antagonists or misoprostol), or contra-indication.
Patients were followed from the index date for a maximum of 6 and 12 months. Follow-up was censored upon the earliest of the following dates: end of NSAID treatment; death; pregnancy; occurrence of study outcome; transferring out of the practice.

Primary outcome

The primary outcome was defined as gastrointestinal intolerability leading to at least one of the following measures: switching to any other type of NSAID/ selective COX-2 inhibitor because of gastro-intestinal complaints; stopping of NSAID treatment because of gastro-intestinal complaints; endoscopy, or Helicobacter Pylori investigation; addition of gastro-protective drug (proton pump inhibitors (PPI), H2-receptor antagonist or misoprostol).
Patients were considered to have stopped if there was a gap of at least 6 months without a repeat prescription. All EPRs were evaluated to classify switching on termination of NSAID treatment, referrals for endoscopy or starting with gastro-protective medication as being related to gastrointestinal intolerability.

Analysis

The incidence rate of the overall primary outcome and the specific types of outcomes were estimated by dividing the number of cases by the amount of accumulated exposure time. The duration of the diclofenac treatment was estimated from the prescription records as the legend duration (number of units prescribed divided by the number of units per day). Consecutive prescriptions were corrected for overlap. All analyses were conducted using SPSS version 11 (Chicago, IL).

Results

The source population of patients who were 18 years or older, actively registered at January 1st 2000 with at least 6 months of valid database history, comprised 163,767 subjects from 57 practices. In this source population, we identified a total of 6191 patients diagnosed with osteoarthritis, 4974 patients (80.3%) with coded diagnosis of osteoarthritis and 1217 from validated free text hits.

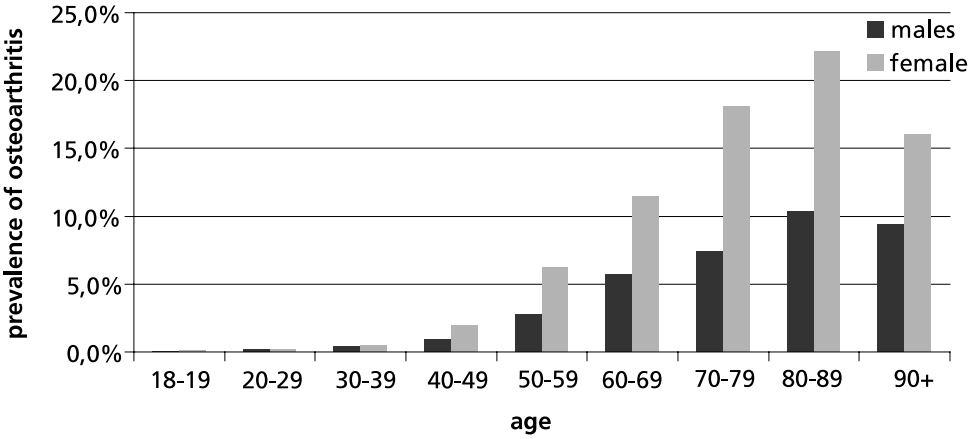

Figure 1: Prevalence of osteoarthritis by age and gender at January 1st 2000 in the IPCI population.

Figure 1 shows the prevalence of osteoarthritis by age and gender. The prevalence increased with age and was higher among females. The overall consultation rate of the selected patients diagnosed with osteoarthritis was 9.5 contacts per patient per year but varied largely by age (Figure 2). In total, 5987 subjects had more than one year of follow-up. The median follow-up period was 1035 days (range: 275–1070 days). In 2000, 5691 (95%) out of

the 5987 subjects with at least one year of follow-up after January 1st, 2000 contacted the GP at least once a year.

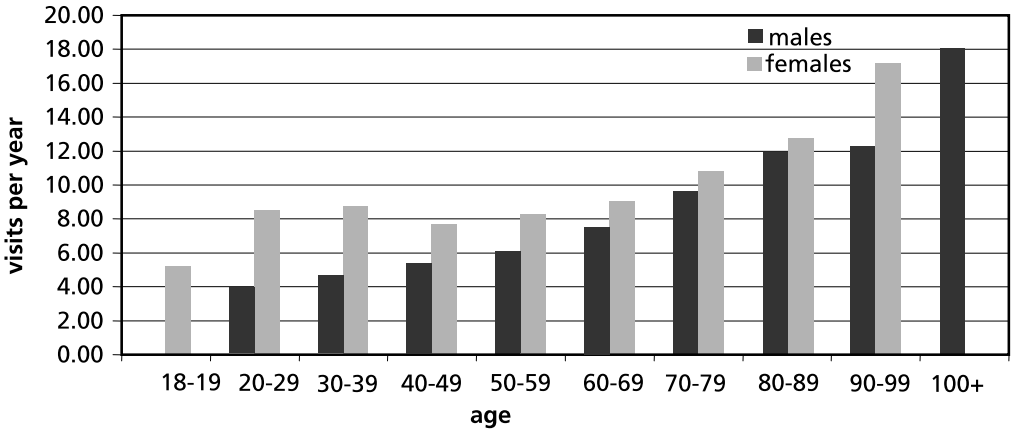

Figure 2: Contact rate of patients diagnosed with osteoarthritis by age.

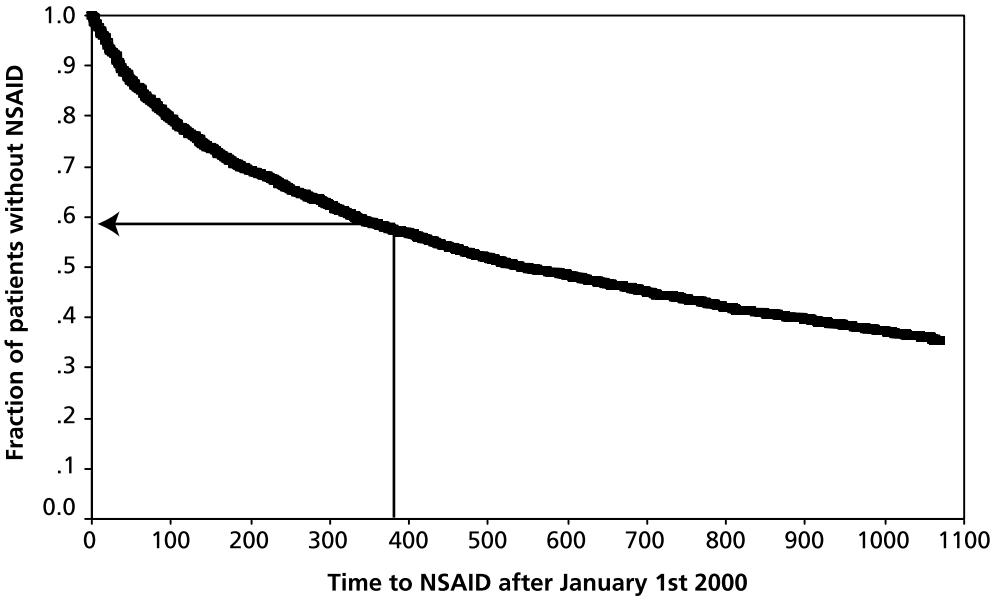

Figure 3: Time to first NSAID.

Figure 3 shows the time to receiving the first NSAID prescription after the index date. After one year, about 40% of subjects had received at least one NSAID prescription. A total of 3663 patients (59.1%) received an NSAID during follow-up. The most frequently prescribed first NSAID was diclofenac, followed by ibuprofen, naproxen and rofecoxib. In total, 1150 patients received a diclofenac prescription during the follow-up period.

Figure 4 and Figure 5 show reasons for exclusion for the study population that received all kinds of NSAIDs prescriptions and only diclofenac prescriptions, respectively. About 30% of patients starting with an NSAID were excluded. For the patients starting with diclofenac, more than a third (35.7%) was excluded. The most frequent reasons for exclusion were recent use of NSAIDs and the use of gastro-protective agents.

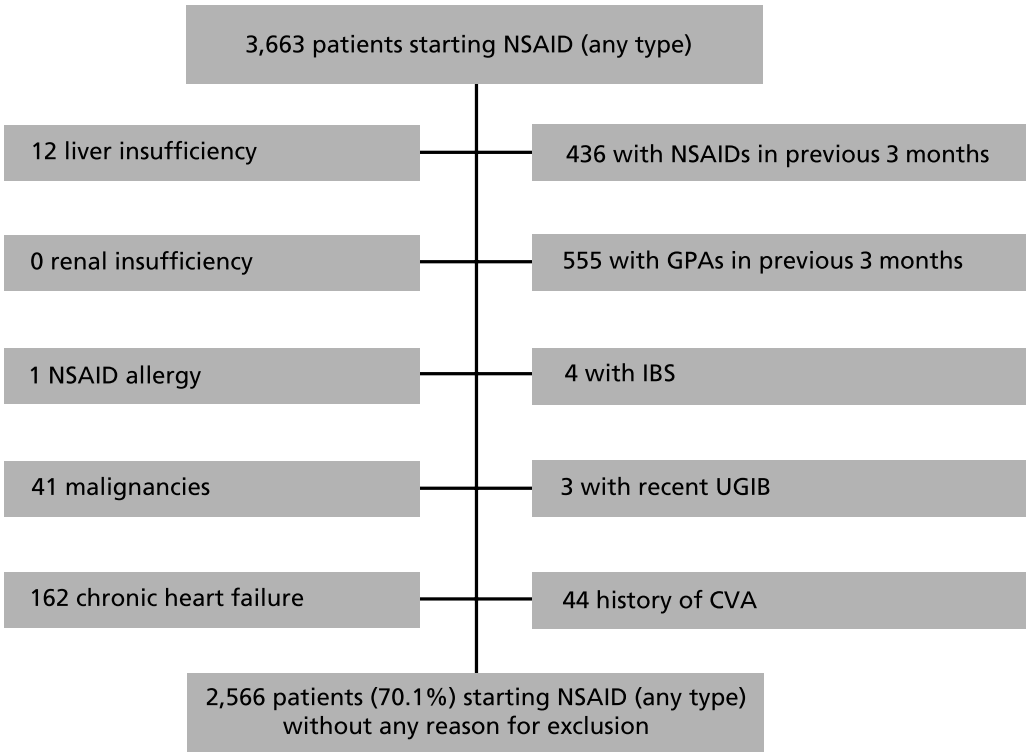

Figure 4: Reasons for exclusion (according to the RDS protocol) among patients diagnosed with osteoarthritis and treated with a first NSAID after January 1st 2000.

The majority of diclofenac users were female (71.7%) and about 20% of patients used diclofenac directly for osteoarthritis. In the 6 months prior to starting the diclofenac treatment, 3.6% of the patients used oral steroids and 4.9% used aspirin. During this period, the median duration of diclofenac use was 13 days while the risk of gastro-intestinal intolerability was 17.0% (95% CI 12.5–21.5). The incidence rate per 100 person-days exposure of the primary outcome was 0.25 (68 events in 26970 exposure days). In patients treated with diclofenac directly for osteoarthritis, the risk for gastrointestinal intolerability was 20.7% (95% CI 12.6–29.3) while the incidence rate was 0.27 (22 events in 8278 exposure days). In the 12 months follow-up period the risk of gastrointestinal intolerability was 23.7% (95%CI: 17.3–30.0%).

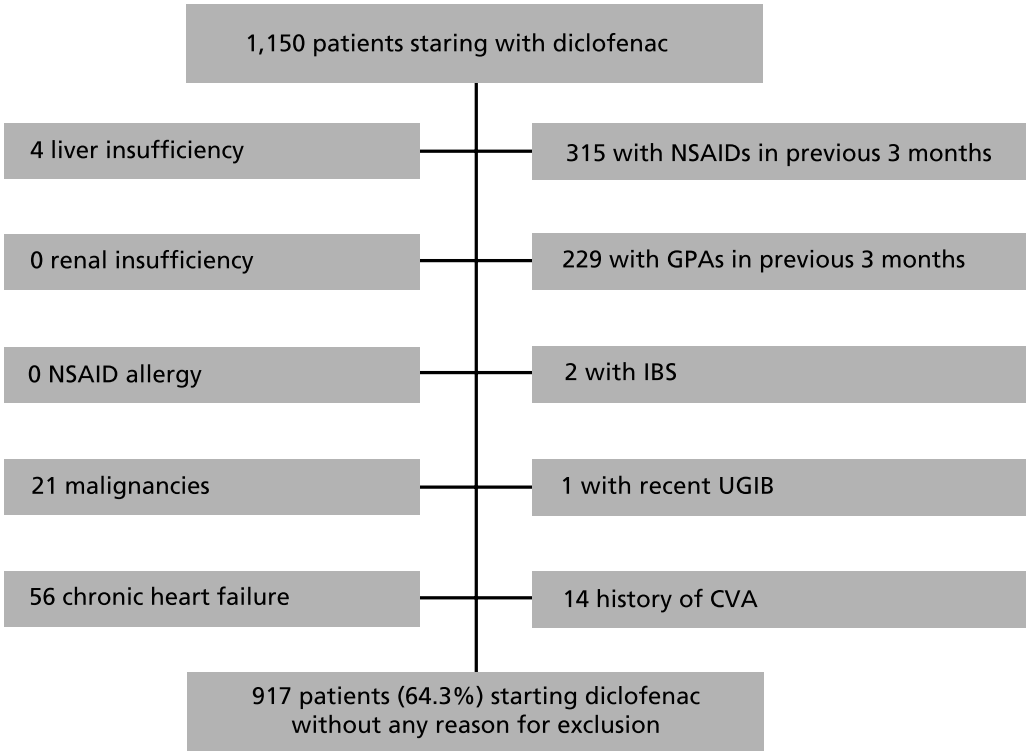

Figure 5: Reasons for exclusion (according to the study protocol) among patients diagnosed with osteoarthritis and treated with diclofenac after January 1st 2000.

Discussion

Our data have shown that the prevalence and the characteristics of patients diagnosed with osteoarthritis in the IPCI database are consistent with the literature.[10,11] The risk of the primary outcome during use was about 20%, which is consistent with data from other studies.[12,13]

We required that the minimal detectable rate ratio was 0.70. With an incidence rate of 0.25 cases per 100 person days of exposure, we would need 58,800 exposure days to observe 147 events. We observed 26,970 days of diclofenac exposure in a period of 6 months follow-up. That means that for the RDS we would require about 2117 subjects ((58,800/26,970)*971) in each treatment arm.

In potential, there are enough patients diagnosed with osteoarthritis in the IPCI database to conduct the trial. However, there are some issues that need to be taken into consideration when deciding to conduct the trial in the IPCI database.

About one third of eligible patients who start treatment with a diclofenac treatment are excluded mainly due to previous use of NSAIDs and gastro-protective agents. We recommended not loosening the criteria, even though we may loose one third of potential patients. It would be difficult to determine if the outcome was due to the "old" or the "new" NSAID prescription in patients who recently switched from another NSAID the trial treatment the trial. Allowing patients who previously used an NSAID or a gastro-protective agent could also distort the results of the trial because, patients who use gastro-protective agents have a lower risk of the outcome.[14,15]

Within one year of follow-up, 95% of selected patients see their GP at least once. The visit rate, nevertheless, was higher for elderly persons. To allow younger persons to be included as well, we recommended continuing the recruitment for at least one year.

The treatment duration with diclofenac was very low and the adherence was around 50%. Also, the number of days of follow-up that were covered with diclofenac was very low. We therefore recommended conducting rate analyses since this reduces underestimation of the relative risk (the majority of follow-up time is non-exposure time).

The majority of patients (about 80%) diagnosed with osteoarthritis received diclofenac not directly for osteoarthritis. We initially proposed to allow other indications in the trial as well, but that would indicate that off-label use of NSAIDs (especially celecoxib) would be allowed in our randomised database study. Since celecoxib was only licensed for osteoarthritis and osteoarthritis related complaints, we had to limit the indication for NSAIDs use to these indications. We recommended allowing the inclusion of newly diagnosed (incident) patients with osteoarthritis to increase the chance of recruiting enough patients.

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Part II

Randomised studies in general practice: How to integrate the electronic patient record

Chapter 5

Georgio Mosis
Bart Koes
Jeanne P Dieleman
Bruno HCh. Stricker
Johan van der Lei
Miriam CJM Sturkenboom

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Abstract

The "randomised database study" strategy was first proposed in 1997, with the aim to combine the generalisability of observational database studies based on electronic patient records and the validity of randomised clinical trials (RCTs). The key feature was to randomly assign treatments and to use routine care data, as available in the observational database for patient identification and follow-up. To our knowledge, however, the idea of the randomised database study has not been implemented yet.

The conduct of a randomised study in an observational database requires adjustments to the methods of medical information processing in the general practice. We developed a software system that facilitates the conduct of a randomised clinical trial with observational databases based on electronic patient records. It identifies eligible subjects and presents them one by one to the physician once their electronic patient record is accessed. The general practitioner can start an interactive recruitment process and after completion, the computer randomises the patients. Follow-up is documented by normal routine care in the electronic patient record.

Although the randomised database study has many methodological advantages, it has never been tested. Our software system is meant as a tool to implement and facilitate evaluation of the randomised database approach.

Introduction

The randomised controlled trial (RCT) is considered as the gold standard in clinical research. The main objective of a RCT is to evaluate whether an intervention is efficacious.[1] This evaluation is usually performed by randomisation, blinding, intensive patient monitoring, and strict management according to Good Clinical Practice (GCP) guidelines and protocols. Although these conditions facilitate the measurements of treatment effects, they limit generalisation of the results to other populations and settings.

Observational studies usually have a greater generalisability because they cover treatment patterns in normal care.[2] Yet, the absence of randomisation in the treatment allocation often hampers sound comparison between treatments. Hence, observational studies are considered unsuitable for the evaluation of effectiveness of treatments.[3,4]

General practitioners (GPs) are faced with the problem to apply evidence from studies that are conducted in strictly controlled settings to patients in normal care.[5,6] Ideally, for them, evidence of treatment effectiveness should be obtained in routine care, in pragmatic randomised trials with patients normally seen by GPs.[7] Although RCT in general practice may have better applicability to the primary care setting, there are many difficulties in conducting them.[8-10] Frequently reported problems are lack of time, recruitment of investigators and patients, obtaining informed consent, randomisation, and data collection. However, most of the randomised studies in general practice use conventional methods for patient selection, recruitment, and data collection.

A new approach that could facilitate RCTs in general practice is the *randomised database study* that was proposed by Sacristan and colleagues in 1997.[11] This approach is based on the good experience with observational databases based on electronic patient records (EPRs) in the conduct of observational outcomes studies. An observational database is this context, contains data on regular patient care, which is collected for other purposes than research. Sarcristan argues that inclusion of a randomisation module in the EPR would allow assessment of drug effectiveness in a large population.[12] The EPR would further function as a source for patient selection, and data collection during a naturalistic follow-up, like in observational studies. Although researchers recognized the advantages of the randomised database studies, to our knowledge it has not been implemented.

The conduct of a randomised database study requires adjustments or additions to the regular medical information processing with the EPR system. The objective of this paper is to describe additions to the method of information

processing with an EPR system that facilitate the conduct of a randomised database study.

Method

The proposed adjustments in the data processing methods are meant to facilitate the conduct of a randomised study in the normal care process and are possible after installation of additional software in the EPR system. The RCT procedures and the proposed additions to the EPR system are described in Table 1.

Table 1: Integration of the electronic patient record into randomized clinical trial procedures.

Randomized trial procedure	Integrated task of the electronic patient record
Patient selection	The physician's patient database is used to identify and flag all eligible subjects
Patient recruitment	Additional software in the EPR may aid by reminding, and data preprocessing.
Informed consent	Documentation of consent and reason for refusal of patients
Randomization	Recruited patients are automatically randomized by a randomization module in the EPR
Data collection during follow-up	Routine patient care data are used for outcome assessment

Setting

The setting of this study is an ongoing longitudinal general practice research database, the Integrated Primary Care Information database (IPCI). This database is described in more details elsewhere and has been used extensively for observational epidemiological and drug outcomes studies.[13] In brief, the IPCI research database contains ELIAS EPRs of over 500.000 patients from 150 physicians throughout the Netherlands. The database comprises patient demographic information (date of birth, sex, anonymous patient identification, insurance, date of registration and transferring out, date of death), medical notes, diagnoses both as codes and as free text, prescriptions, and indications for therapy, physical findings, referrals, hospitalisations and laboratory values. The method we describe allows for a randomised study in the setting of the IPCI database.

Patient selection

The first procedure in the conduct of a RCT is the identification and selection of potential patients (Table 1). The physicians or investigators usually do not systematically search for eligible patients and recruitment may be organized by asking consecutively presenting patients. Included patients are generally not compared with non-included eligible patients (since these are not identified), therefore, little can be said about the generalisability of the data.[14,15]

In our approach, the EPR database is used to select potential patients. With tailored software, the researchers may build queries to select eligible patients in the individual EPR systems. This method standardizes the selection procedure across research sites. An additional advantage is that all eligible subjects in the complete source population are identified and marked. Availability of demographic and medical information on all eligible subjects in the database allows for detailed comparison of included and non-included patients and a better estimate of external validity.

Patient recruitment

The second procedure in a randomised study is patient recruitment. GCP guidelines require a signed informed consent if a patient is randomised to treatment, even if these treatments are already licensed for marketing. Physicians often fail to recruit a sufficient sample due to waning enthusiasm and the time needed to complete the recruitment procedure.[16,17] Providing information and asking for participation is probably one of the major hurdles in recruitment, and little can be done to reduce the recruitment time. Due to lack of time and disruption of normal care, physicians perceive it as difficult to ask their patients to participate and to address all their questions during a normal consultation.[18]

We developed an interactive software module with a reminder and data pre-processing function to facilitate the recruitment process. As soon as the EPR of a selected patient is opened, the physician is informed about eligibility of the patient and is given the option to start the recruitment procedure. The software also enables researchers to monitor inclusion and the reasons for exclusion.

Randomisation

In conventional multi-center clinical trials, randomisation usually occurs at one coordinating center. However, while centralized randomisation is often used, decentralized remote accesses, via web or telephone are increasingly employed.

With the EPR software, randomisation is conducted automatically in the EPR system after recruitment is finalized. The incorporated randomisation scheme should be unpredictable to avoid anticipation of treatment assignment by the GP, especially if the trial is not blinded.

Data collection and patient assessment

Data collection in standard RCTs is often done by means of paper based case report forms and standardized questionnaires. Errors and incompleteness are monitored and corrected as far as possible by a clinical research organization. Even though this method ensures complete and accurate data, it is labor intensive.

Since all the important clinical findings and baseline characteristics are usually documented in the EPR, it can be used as the primary information source for baseline information and clinical outcome assessment.

Case study

We implemented a randomised database study to compare gastrointestinal tolerability of diclofenac and celecoxib in patients diagnosed with osteoarthritis. Project specific software has been built and implemented in the EPR systems of the participating GPs. The local EPR databases were used to select patients older than 18 years of age who were diagnosed with osteoarthritis. The patient selection was based on historical data in coded and free text format. Researchers reduce false positive hits by manually validating selections based on free text information. The software was installed in the EPR system of 42 GPs and it selected 7127 possible candidates. These patients were the source population from which the study population later emerged. An electronic reminder was placed in the EPRs of selected patients to enable immediate recognition by the GP upon visits. If a patient diagnosed with osteoarthritis required a non-steroidal anti-inflammatory drug treatment during that regular visit, the GP could start the interactive recruitment procedure that was facilitated by the software module. The GP could verify the inclusion criteria and exclusion criteria (*i.e.* contraindication) and the software documented the inclusion or reason for exclusion in the EPR system. As a result, we could quantify the number of patients who refused to participate, those excluded because of exclusion criteria and the number of patients 'missed' by the GPs.

Immediately after written informed consent was obtained, the patient was allocated to diclofenac or to celecoxib by the randomisation software. The data that was recorded with the EPR during the naturalistic course of the

treatment was sent to the central observational database (IPCI). This database was used to assess outcomes as done in other observational studies.

Discussion

In this paper, we proposed a method to include the electronic patient record in the conduct of a RCT and described the software for the practical implementation of a randomised database study. The major advantages of this method are first the potential reduction of resources to conduct a study and secondly the availability of detailed information about the external validity since medical and demographic information of included and non-included patients are available.

Although the idea is attractive, the randomised database study is not without limitations or prerequisites. The successful implementation depends on the possibilities to interfere with the existing EPR system and the mode of information processing during normal practice.

In order to minimize disruption of the normal consultation routines we inserted an electronic reminder system to alert the GPs about eligible patients, but subsequent steps had to be started by the GP. Although this leaves some freedom to the GP, it may also lead to non-inclusion and therefore selection bias. Because we had demographic and medical information on the entire source population it is always possible to estimate the magnitude of selection.

By national regulation, the GPs' and at least the patients' identity is confidential in observational databases that are used for medical research.[19] However, for the randomised database study named informed consent is required.[20] The requirement to keep the level of privacy in line with national regulations increase the complexity of communication between the researchers, the research database organization, and the physicians. We used an extra identification number on top of the anonymous IPCI number to avoid the possibility that the patient name was directly linked to the existing database number, which would lead to the possibility to have access to non-anonymized medical information in subsequent studies.

The randomised database study approach is a clinical trial under the terms of the GCP guidelines. As a result, the principles of the GCP need to be followed which might reduce the possible resource savings. For example, if a patient is found to be eligible during a consultation extra time is necessary to explain the study and obtain informed consent. However the need for this extra time

cannot readily be anticipated and scheduled, which will create problems during busy consultations.

With the randomised database study, it is difficult to adhere to the GCP requirements regarding documentation since the EPR, rather than a case report form is the primary data collection tool.[20] GCP requires that source information cannot be altered. . An EPR can be changed retrospectively, which could go unnoticed if time stamping does not occur accurately. Therefore, the EPR may not be considered as a source document and a time-stamped printed version of the medical record in the database should be used instead.

Investigator recruitment is a major obstacle in the conduct of RCT in general practice. GPs recognize the need to improve evidence-based medicine in primary care, but their lack of participation in clinical trials is also evident.[21-23] GPs report the lack of support staff for research to be a major barrier to participate in RCTs. However, use of a clinical research nurse requires a change in the study strategy. It would not be cost-efficient to recruit patients only when they present themselves at normal visits. Preferably, they should be called in actively. Although the proposed software may facilitate the conduct of a randomised study in general practice, it cannot remove all obstacles, and participation will always increase the workload. Sufficient patient recruitment may therefore remain a problem even with the proposed methods.

In summary, this paper describes our approach to actually implement the randomised database study. With adjustments and additions in the methods of information processing with the EPR the selection, recruitment, randomisation and data collection procedure of the RCT can be integrated in the normal care process. Our case study proved that it is possible. However, now that it is possible to facilitate the 'randomised database study' it should be evaluated on its validity and performance.

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Chapter 6

A technical infrastructure to conduct randomised database studies facilitated by a general practice research database

Georgio Mosis
Albert E Vlug
Mees Mosseveld
Jeanne P Dieleman
Bruno HCh Stricker
Johan van der Lei
Miriam CJM Sturkenboom

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Abstract

General practice research databases are increasingly used to study intended and unintended effects of treatments. However, confounding by indication remains a major problem. The randomized database study methodology has been proposed as a method to combine the strengths of observational database (generalisability) and the strength of the randomized clinical trial (RCT) design (randomization).

We developed an infrastructure that enables the execution of randomized database studies with treatment randomization facilitated by a general practice research database. The requirements posed by the methodology of randomized database studies were facilitated by software components.

Our assessment showed that it is technically possible to conduct randomized trials in general practice according to the randomized database design. The infrastructure facilitated the conduct of randomized database studies in general practice but some practical difficulties and methodological issues remain. The technical infrastructure seems to be both promising and potentially feasible to facilitate future randomized database studies, although the methodology needs to be evaluated in more detail.

Background

An increasing number of general practitioners (GPs) replace traditional paper-based patient records with electronic patient records (EPRs). A typical EPR contains information about patient identification, demographics, type of visits, prescriptions, diagnoses, reasons for visits, referrals, laboratory findings and other notes. In the Netherlands, for example, more than 90% of the GPs have replaced their paper records with the EPRs.[1] In automated general practices, the EPR facilitates many processes such as patient care, management, billing, planning of care processes, and education.[2]

Researchers have recognized the potential value of data collected with the EPR, and this realization has resulted in a number of so-called *general practice research databases.* These general practice research databases contain longitudinal data from the EPRs. In countries where the GP has a gatekeeper role in the healthcare system (*e.g.* the Netherlands, or United Kingdom), these databases contain almost complete medical data. Examples are the General Practice Research Database,[3] Mediplus UK[4] and Integrated Primary Care Information database.[5]

Pharmaco-epidemiology is an example of a research area that takes advantage of the availability of general practice research databases since the databases contain information on the population, drug use and mild and severe outcomes. However, a major issue in the conduct of observational studies, especially concerning intended drug effects, is confounding by indication*.[6] Such confounding occurs when the physicians' selection of a treatment is related to the severity of the underlying disease or to the prognosis of the patient.[7]

In the randomized clinical trials (RCT) design, confounding is dealt with by random allocation of treatments.[8] Even though the RCT design is considered the gold standard in asserting treatment effects, it has some limitations. RCTs are often conducted in controlled environments with selected and limited patient groups. One of the key challenges in the interpretation of RCT results, therefore, is to determine whether the study results also apply to other settings and populations. The term 'generalisability' is used to describe the degree to which the results can be generalized to other settings and populations.[9] For example, a RCT conducted in a hospital environment controlled by a strict protocol with a specific patient population may not be generalisable to the general practice population.

*Confounding by indication is a term used when a variable is a risk factor for a disease among non-exposed persons and is associated with exposure of interest in the population from which the cases derive, without being an intermediate step in the causal pathway between the exposure and the disease.

Due to the lack of generalisability of RCTs to primary care settings, there has been a request for large simple trials or pragmatic trials that provide measures of treatment effectiveness (rather than efficacy) in this setting.[10] In pragmatic RCTs, the patient sample is more heterogeneous and the evaluation and follow-up criteria are similar to those used in clinical practice. Compared to conventional RCTs, pragmatic RCTs are conducted with fewer restrictions, and enable researchers to use study designs and data that are representative of the natural patient care setting.[11]

A number of researchers have argued that combining the strengths of observational studies in databases (generalisability) and the strength of the pragmatic RCT design (randomization) will result in a new method of research: *randomized database studies.*[13] A randomized database study is described as a study in which the EPR is used to select eligible study candidates, to randomize patients and to collect data on the course of the treatment.

Researchers use data collected during daily care to assess the outcome, as is done in pharmaco-epidemiological studies with general practice research databases. In a randomized database study, however, the randomization procedure needs to be incorporated in the daily care workflow, preferably when the treatment is prescribed.

Although the advantages of this approach have been recognized,[13] no research has been conducted to further develop the randomized database study approach. In this paper, we describe our attempt to develop an infrastructure that enables the execution of randomized database studies with treatment randomization in the context of a general practice research database.

We first briefly describe the changes that have to be made to the EPR in order to generate data for a general practice research database. We subsequently describe the additional system requirements posed by the randomized database study. Finally, we describe the different additional software components we built to enable the execution of randomized database studies.

Methods

From the EPR to a general practice research database

Physicians in primary care mainly use the EPR to document patient treatment. Researchers using data from the EPR have concluded that data in the EPR are not always suitable for their needs,[5] as the data requirements for research and clinical care are not always congruent. For example, researchers report that EPRs often contain in detail the actions performed by the physician, but

often not the underlying rationale;[14,15] physicians often use the EPR to record "*what was done*" rather than "*why it was done*".
In the early 1990's, we were involved in the development of a general practice research database based on EPRs used in general practice, the Integrated Primary Care Information (IPCI) database.[5] When we developed the IPCI database, we analyzed the requirements of the researchers and built additional software to address the limitations of routinely recorded data when utilizing such data for research purposes.

Requirement for observational research with the IPCI database

Researchers intended to use the IPCI database primarily for pharmaco-epidemiological research; the database should be the data source to test hypotheses about both adverse and beneficial effects of drugs. To enable investigators to conduct this type of research, we formulated the following requirements:

1. Researchers should have access to all medical data on the patients. Since GPs may record data in the EPR and on paper, we required that the GPs record all medical data in the electronic records. The general practices that supply data to the IPCI database should be paperless to ensure that all relevant events are recorded in the EPR.
2. Researchers should be able to follow treatments over time including changes in treatment. Therefore, GPs should record the indication for each prescription and switches to other treatments.
3. Researchers should not have to obtain informed consent from each individual patient for each study to avoid selective participation. The Dutch law stipulates that patient data can be used for research without the patient's consent only if the data are anonymized.[16] Therefore, we required the data in the IPCI database to be anonymous. This means that the identity of both the physicians and patients should be concealed to the researchers.
4. Researchers anticipated that it would be impossible to predict all data requirements for future studies. For some studies, the data might be incomplete. We therefore required the ability to obtain additional data from the GP.

Changes in the information processing with the EPR

In addition to the requirement that practices work paperless, three types of changes had to be made in the (information processing with the) EPR to enable the development of the IPCI database: changes in the *data* recorded

by the GP, changes in the *communication* with the EPR, and finally changes in the *organization* of the database.
Changes in the *data* recorded by the GP involved adding software to link prescriptions to indications. When the GP prescribes a treatment, the software asks the GP additional data about the indications and therapy changes.
We added *communication* software that ensures the anonymity of the patient data and assigns a unique patient identification number that would allow researchers to follow the patient over time. The GP is the only person who is able to translate that identification number to the potential identity. After the patient has been anonymized, the communication software sends all data to the gatekeeper. The gatekeeper is a person responsible for the anonymity of the GPs. Finally, the data is stored in the central IPCI database.
The *organization* of the IPCI database uses a board of supervisors, which has the responsibility to ensure the maintenance of the anonymity of patients and GPs. In addition, the board of supervisors has to approve each study proposal and researchers' request to collect additional data. After the board of supervisors has approved a study, all individual GPs are informed about the study. The technical infrastructure of the IPCI project allows individual GPs to withdraw data on patients or specific data elements for studies.[5] Patients are informed of the existence of the IPCI project by leaflets and posters in the office of the participating GPs.
Currently, the IPCI database contains information from EPRs of about 150 general practitioners (GPs) covering more than 500,000 patients and provides data for studies with various epidemiological study designs *e.g.* case-control design, cohort design, and cross sectional design.[17-22] Conducting a study with the randomized database study method, however, was not possible in the IPCI database.

Towards randomized database studies with the IPCI database

To enable researchers to conduct randomized database studies, we first analyzed the requirements posed by randomized database studies. Second, we built additional software to solve the shortcomings of the GP information system with respect to the conduct of randomized database studies.

Requirements for a randomized database study

We analyzed the procedures in the conduct of RCTs in general in order to integrate them with the daily care process. Four essential steps were distinguished in the conduct of randomized trials that would apply to the randomized database study as well (Figure 1):

a. Patient selection
b. Patient recruitment
c. Randomization of treatment
d. Follow-up of patients

Patient selection comprises the identification of patients who are eligible for participation in a specific trial. Completeness of identification of eligible patients is necessary to be able to assess whether the included group is representative for the total eligible population.[23] There may be large differences between the included patients and the total eligible population, for example, if the included patients are healthier or if there is a large overrepresentation of one gender. In conventional randomized studies, the selection methods are often are not standardized and there is no information about the non-included persons, which severely limits the possibility to evaluate generalizibility.[23]
Patient recruitment in randomized trials involves the assessment of inclusion and exclusion criteria and obtaining informed consent from the patient. Researchers and recruiters are required to adhere to the Good Clinical Practice (GCP) guidelines.[24] GCP is an international ethical and scientific standard for designing, conducting, performing, analyzing, and reporting clinical trials. One of the most important ethical principles of GCP is *informed consent* from participating patients: the recruiter should fully inform the patient about the study before the patient gives written consent to participate. In addition, the patients should have enough time to reflect before consent is given.
In randomized database studies, patients may be recruited during routine care visits.[13] The constraints of the GP in recruiting patients during regular visits (*i.e.* time or disruption of the daily care process), however, needs to be addressed. The procedure itself should not be a disproportional disruption of the normal interaction between the GP and the patient.
Randomization in randomized database studies comprises the random allocation of treatment on a patient level. Randomization of treatments in a multi-center trial is often done centrally or by a local randomization procedure (*i.e.* envelopes, random number generator). To minimize disruption of the normal care process, the randomization procedure should preferentially be integrated in the workflow of the normal prescription routine.
Patient *follow-up* in randomized trials are scheduled return visits to assess outcome parameters. Data are usually collected on case report forms. In the randomized database study, researchers use daily care data as recorded in the EPR to assess outcomes. This requirement poses two problems related to the GCP guidelines and the quality of the data. First, the GCP guidelines

require that the documentation of follow-up is accurate, complete, legible, and time-stamped and available for auditing. Second, study data derived from the source documents should be consistent with the source documents. If there are inconsistencies, the researchers should document and be able to explain them. There is a theoretical possibility that data in the EPR can be changed retrospectively, which could go unnoticed if time stamping does not occur accurately. An audit trail of the EPR, therefore, is an essential feature to comply with the GCP documentation guidelines.

Outcome assessment in the randomized database study approach will be done from the EPR data, but the quality and completeness of the data might not be optimal for all types of outcomes. For that reason, researchers required the possibility to collect data from the patient as well. At the same time, the researchers should maintain the level of confidentiality required by use of the IPCI database.

Data on adverse drug reactions need to be collected according to regular spontaneous reporting schemes. Sudden unexpected serious adverse reactions and serious reactions have to be reported within 24 hours to the research center and the Netherlands Pharmaco-vigilance center in line with the newest European guidelines.[25]

Results

Changes in infrastructure to enable randomized database studies

We aimed to integrate the randomized database study with the daily care process in general practice by means of adding software to the general practice information system. The software consisted of different modules corresponding with the four essential steps in randomized studies: selection, recruitment, randomization, and follow-up of the patients.

Selection Module

After installation of the software, the information system of the GP activated the selection module. The selection module contained the query that identifies potential patients for a specific study based on data that was already available in the general practice information system (*e.g.* diagnosis, demographics, or laboratory findings). The query may contain coded and free text searches but the latter required manual validation of the results to reduce the false positively selected patients prior to having them marked for recruitment. After the selection of potential patients, the selection module generated a

reminder with a special message in the EPR of the selected patients. Whenever the GP opened the patient's EPR, the message reminded the GP that the patient had been selected as a potential subject for a study.

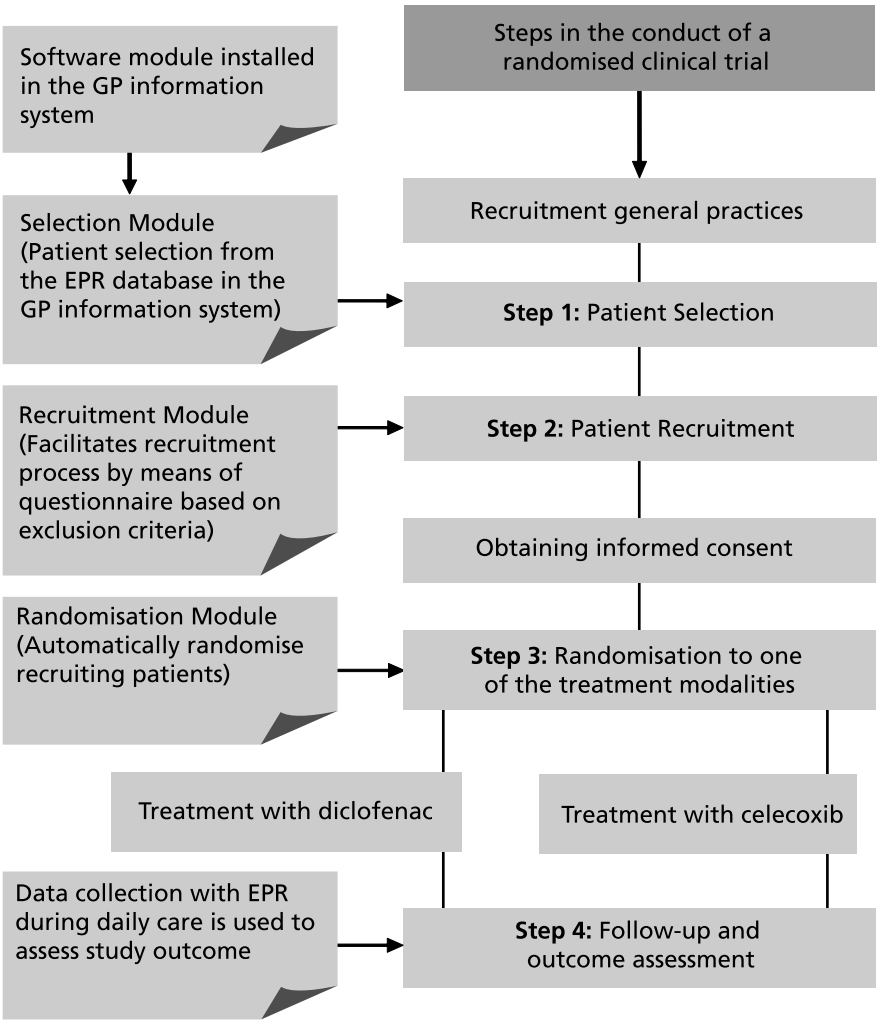

Figure 1: Steps in a randomised clinical trial and the software modules built to integrate the steps with the workflow of general practices working with an electronic patient record.

Recruitment Module

GPs were confronted with reminders in the EPRs of the selected patients whenever the patients´ EPR was opened. To minimize interference of the regular workflow, the GP had to start the recruitment module themselves whenever the patient was eligible for recruitment.

The recruitment module required completion of an automated questionnaire based on the inclusion and exclusion criteria that were formulated in the study protocol. Patients who fulfilled the inclusion criteria, needed to give written informed consent before the GP could finalize the recruitment step. If the patient asked for time to reflect, the recruitment module enabled the GP to postpone the decision to include the patient in the study and to continue later in time from that point on. The recruitment module also stored an electronic version of the patients' informed consent for the research database. Once a patient was included or excluded, the software removed the reminder from the EPR. The user interface of the recruitment module was the same as the interface of the general practice information system.

Randomization Module

After finalization of the recruitment step, the randomization module allocated the patient to one of the treatment options. The software presented the results of the randomization procedure to the GP and verified if the randomized treatment was actually prescribed. The recruitment module also assured equal allocation to the alternative treatments within a practice.[26]

Follow-up Module

We used the IPCI infrastructure to collect patient data but added a follow-up module that allowed researchers to collect data directly from the patients while maintaining the anonymity of the patients and the GPs. This was achieved by producing a new study number for each individual patient. This number differed from the patient number in the GP information system and the patient identification number in the IPCI database. Researchers used this study number to collect data from patients by means of patient questionnaires, to communicate with the GP about the patient and to link the information with the IPCI database. To comply with the GCP documentation requirement, we retained a time-stamped printed version of the EPR and the patient questionnaires as source document.

Application

To test the feasibility and validity of a randomized database study, we compared the gastro-intestinal tolerability of celecoxib and diclofenac in patients diagnosed with osteoarthritis. Both celecoxib and diclofenac are non-steroidal anti-inflammatory drugs (NSAIDs) licensed, marketed and reimbursed for the treatment of osteoarthritis. Due to preferential prescribing (*i.e.* channeling) of celecoxib to patients with gastro-intestinal and cardiovascular co-morbidity

in general practice,[27] it was considered difficult to assess this study question in an observational study with a general practice research database. All patients diagnosed with osteoarthritis who needed an NSAID for osteoarthritis during routine GP visits, were eligible for entry in the study. During the recruitment, patients could be excluded if they were treated with an NSAID in the last three months or if they had any contraindication. After recruitment, patients were automatically randomized to diclofenac or celecoxib but the GP decided the dosage and treatment regimen. In the naturalistic follow-up, we focused on changes in NSAID treatment indicative of gastrointestinal intolerability (*e.g.*, discontinuation of drug or adding gastro-protective agents).

We recruited 42 GPs and implemented the software in their information system. We used the local EPR database in the general practice information system to select patients older than 18 years of age who were diagnosed with osteoarthritis. The selection module selected 7127 patients who met the selection criteria; for these patients, the selection module generated a reminder in the EPR.

During a median patient-recruitment period of 188 days (range 26–261 days), the GPs had contact with 4586 of the 7127 selected patients. When the GP accessed the EPR of these patients, the selection module displayed the message reminding the GP that these patients were selected for the randomized database study. The GPs prescribed NSAIDs to 1245 of the 4586 patients. However, only 170 received the NSAID directly for osteoarthritis – these patients were potentially eligible patients for the study.

The objective of the recruitment module was to facilitate the recruitment procedure and it also documented the reasons for non-inclusion. Of the 170 potentially eligible patients, 42 (24.7%) patients meet one of the exclusion criteria. Another 12 patients (7.1%) refused to participate. In 55 (32.4%) cases, the GP stated that he or she was not the principal healthcare provider treating the patient at the moment the patient was eligible for recruitment and therefore could not include the patient. In 30 cases (17.6%), the GP stated he or she was too busy to start the informed consent procedure. Finally, in 11 cases (6.5%) the GP forgot to start the recruitment procedure. The remaining 20 cases (11.8%) were included in the study and randomized to the treatment arms by the randomization module. By retrieving the EPRs of the included patients, we monitored the naturalistic course of their treatment. In addition, to study generalisability, the EPRs of the entire selected population were retrieved.

Due to low number of eligible patients, the recruitment was less than our initial expectations and we planned to terminate the study. Events overtook us

when other researchers reported an increased risk for cardiovascular adverse events in patients treated with high dosage of celecoxib and we therefore terminated the study at that time.[28]

Discussion

In this paper, we describe our attempt to build an infrastructure to enable researchers to conduct a randomized database study in the IPCI general practice research database.

Our assessment shows that it is technically possible to conduct a randomized database study in a general practice research database and randomized clinical trials in the future. The shortcomings of the existing GP information systems that are the basis for the IPCI database, were solved by software modules that corresponded with the essential steps in the conduct of randomized database studies namely patient selection, recruitment, randomization, and follow-up. Although the software facilitates the conduct of a randomized database study, some practical and methodological problems remain.

Regarding practical issues, the number of eligible patients was less than expected. Patient recruitment depended on the visit-rate of the selected patients, and whether they required an NSAID treatment for osteoarthritis. In our study, we observed that more than a third of the selected patients did not visit the GP during the patient-recruitment period and almost half of the patients did not require an NSAID treatment. In addition, many patients received an NSAID treatment for other indications than osteoarthritis.

The pressure on daily care in general practice is reflected by the fact that the participating GPs were not always the principal healthcare providers treating the patient, or that they reported to be too busy, or they simply forgot to recruit the patient. These general practices related issues were the leading cause of non-inclusion (56.5%). Although we facilitated the recruitment procedure, it remains a disruption of the workflow of normal practice and it does require extra time, which may have limited the performance.[29]

It is difficult to judge how the performance of the recruitment strategy in our randomized database study (11.8%) compares to other studies, due to the lack of data about their source populations. In one study comparing multiple patient recruitment approaches in a RCT conducted in primary care, the researchers reported that only 1.4% of all enrolled patients were recruited directly by the physicians.[30] In this study direct physician recruitment was discontinued. Even though we cannot compare the percentages of this

study with our data directly, we conclude that our recruitment strategy was effective, but leaves room for improvement; alternative patient recruitment strategies should be considered in future studies.

Several methodological issues remain regarding the implementation of the randomized database study design itself. The purpose of the whole endeavor was to circumvent confounding by indication while keeping the naturalistic follow-up procedure and outcome assessments. The gain obtained with removal of confounding may go at the expense of introducing a form of selection and information bias, which are absent in observational studies in the same research database. For example, due to time constraints, hesitance to recruit, or other issues, GPs may not recruit consecutive patients.[31] As a result, only a selected population will enter the study, which may limit the generalisability of the results.

Although we were able to verify patient-recruitment (information on eligible but non-included patients is available in the IPCI database and in the randomized database study software log), selective recruitment may limit both the sample size and the possibility to extrapolate the results to other populations.[32] In addition, a naturalistic randomized database study is an open-labeled study (*i.e.* the GP and the patients are aware of the study question and the intervention). Due to this feature, information bias may occur if the follow-up and outcomes are recorded differently for the different study drugs.[33]

Conclusion

In conclusion, we described an infrastructure that facilitates randomized database studies in the IPCI database. Technically, it is feasible to conduct studies in automated general practice according to the randomized database study design. The infrastructure built to conduct randomized database studies in general practice research databases, however, showed some practical difficulties in the conduct of such a study and some issues that could jeopardize the validity of the methodology. Randomized database studies seem to be both promising and potentially feasible for future studies; the methodological issues, however, need to be evaluated in more detail.

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Chapter 7

Evaluation of a randomized database study in general practice: Patient recruitment and quality of data

Georgio Mosis
Jeanne P Dieleman
Bruno HCh Stricker
Johan van der Lei
Miriam CJM Sturkenboom

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Abstract

Objective: To describe the implementation and practicalities of a randomised database study.

Method: An open label randomised database study was conducted in the Integrated Primary Care Information (IPCI) general practice research database. Software was inserted in the general practitioners information system to allow for automated patient identification, recruitment, and randomisation. As an application, we compared gastrointestinal tolerability in persons who needed an NSAID for osteoarthritis and were randomised to either diclofenac or celecoxib. The exposures and outcomes were obtained from the electronic patient records in the IPCI database. To assess accuracy of exposure and outcome measures, we also collected information by self-administrated patient questionnaires. Reasons and characteristics of non-included eligible subjects were assessed to describe selection processes. Physicians were interviewed to evaluate the RDS and to identify the major obstacles.

Results: 42 GPs collaborated, and 7127 prevalent osteoarthritis patients were identified. Among these subjects, 170 were eligible for recruitment (received an NSAID for osteoarthritis), 20 (11.8%) were randomized 54 (31.8%) were not recruited because of exclusion criteria 96 (56.5%) of the eligible patients were not recruited because the physician was too busy, or the patient was treated by another healthcare provider. Concordance between IPCI data and questionnaires for the outcome was good (Kappa 0.7; sd 0.14). Evaluation of the study with physicians showed that they appreciated the software but recruitment during routine visits was too time-consuming in particular since informed consent needed to be obtained.

Conclusion: Although a randomised database study is feasible from a technical and practical perspective, patient recruitment and time remain the major obstacles. This leads to selective inclusion, but the conduct of a RDS in a population-based database allows for quantification of this bias.

Background

Post-marketing observational studies are necessary to study safety and effectiveness of new drug treatments due to the limitations of randomised clinical trials (*i.e.* limited sample size (only frequent adverse effects are detected) and lack of generalisability due to: stringent in- and exclusion criteria and protocol-driven assessment).[1] These observational studies are usually conducted with claims or medical record databases, since they reflect real life practice, contain many patients and allow for flexibility in study design.[2] However, they suffer from potential confounding by indication due to the lack of randomisation and channelling of drugs to patients with prognostic differences.[3]

The randomised database study (RDS) was proposed as a solution to the poor generalisability of randomised clinical trials (RCTs) and the confounding problem in observational studies.[4] In a RDS, the electronic patients records (EPRs) are used to identify possible candidates, to randomise treatments, and to collect data on the natural course of the treatment and outcomes.

To our knowledge, the RDS design has only been described but has not been further developed and explored. Our question was whether the RDS would overcome the limitations of a standard RCT (effectiveness vs. efficacy, better generalisability) and the standard observational study (confounding by indication). To test this we conducted a RDS with the aim to compare gastrointestinal tolerability of celecoxib and diclofenac in patients diagnosed with osteoarthritis who required a non-steroidal anti-inflammatory drug (NSAID) for this condition. Due to premature termination of the study, we could not test whether celecoxib and diclofenac differed in gastrointestinal tolerability. The goal of this study is therefore to evaluate the implementation and conduct of a RDS with a special focus on patient recruitment, quality of outcome and exposure data, good clinical practice obligations and the GP's opinion.

Methods

Design

A randomized database study was conducted among general practitioners who provide ongoing electronic patient record (EPR) data to the Integrated Primary Care Information (IPCI) database. The EPR data were used for exposure and outcome assessment, Identification and randomization software was added to the GP's information system to optimize time and recruitment.

Setting

The IPCI database has been described in detail elsewhere.[5] In brief, IPCI is a general practice research database containing longitudinal data of more than 500,000 patients registered with around 150 general practitioners (GPs).

In the Dutch health care system, patients are registered with a GP who acts as a gatekeeper of medical care and information. The EPRs contain data on patient demographics, symptoms (using codes and free text), diagnoses (codes and free text), clinical findings, referrals, laboratory findings, prescriptions and hospitalisations. Summaries of the hospital discharge letters or information from specialists is entered in a free text format and hard copies can be provided upon request. Information on drug prescription comprises product name, quantity, strength, indication, prescribed daily dose, the Anatomical Therapeutic Chemical classification (ATC) code, and the indication. To maximize completeness of the data, GPs who participate in the IPCI project are not allowed to use paper-based records. The IPCI project complies with European Union guidelines on the use of medical data for medical research and the database has been proven valid for pharmaco-epidemiological studies on drug safety, and effectiveness.[5-8]

Application

We aimed to study the gastro-intestinal tolerability of celecoxib and diclofenac in patients diagnosed with osteoarthritis who required an NSAID for their osteoarthritis, with the RDS design. This application was chosen since a previous study had shown strong channelling of celecoxib to patients at higher risk of gastrointestinal and cardiovascular problems. An observational comparison would have suffered from strong confounding by indication.

The eligible study population comprised all patients 18 years and older, who were diagnosed with osteoarthritis and needed an NSAID for osteoarthritis. Patients were excluded if they had contraindications for the study drugs, were chronically using NSAIDs or used proton pump inhibitors or H2 receptor

antagonists. The study needed to include 4234 subjects (2117 in each arm) to show a reduction in the occurrence of gastrointestinal outcomes by celecoxib.
Patients were actively (with questionnaires) followed for a maximum of six months and passively (through the IPCI database) during and after 6 months. Patients were randomised to either celecoxib or diclofenac. The dose and duration of treatment was left to the decision of the GP, to reflect real life practice. The primary outcome was defined as gastrointestinal intolerability leading to randomised treatment discontinuation; the addition of a proton pump inhibitor or H2 receptor antagonist; referral for endoscopy or referral for *Helicobacter Pylori* assessment. The outcomes were obtained from diagnosis, referral and prescription records in the IPCI database. To assess the accuracy of the exposure and outcome data, a self-administered questionnaire was supposed to complete 4 times (baseline and each week during the first month). In addition, the occurrence of adverse effects were solicited by asking the patients whether they experienced nausea, diarrhoea, flatulence, stomach pain/heartburn, headache, sleepiness, or skin rash.
Data on adverse drug reactions and sudden unexpected serious adverse reactions needed to be reported by the GP to the Dutch Pharmaco-vigilance Center on separate forms consistent with the Good Clinical Practice guidelines.[12]
The Medical Ethics Committee of the Erasmus University Medical Center and the Scientific and Ethical Advisory Group of the IPCI project approved the study.

Randomized database study infrastructure and software architecture

The IPCI infrastructure was expanded to allow the conduct of a RDS, while taking into account Good Clinical Practice (GCP) guideline requirements.[12] Additional software incorporated in the general practice information systems to identify eligible candidates, to facilitate patient recruitment and to automatically randomise recruited patients.
Upon installation of the software in the general practice information systems of the participating GPs, patients diagnosed with osteoarthritis were automatically selected as possible candidates. An electronic reminder was added to the EPRs of the possible candidates. Each time the EPR of a possible candidate was opened the message was displayed and if the patient required an NSAID treatment for osteoarthritis at that time the GP could initiate the recruitment procedure. Newly diagnosed patients with osteoarthritis (incident cases), could not be pre-selected by the software and for these patients, the GP had to remember study eligibility for these patients.

During the recruitment phase, the software guided GPs through the exclusion criteria. Finally, the patients had to provide written informed consent before they could be randomised. The additional study specific software documented the recruitment process for each possible candidate and stored the reasons for non-inclusion. Each time the GP did not start the recruitment procedure for a possible candidate, the software asked the GP to motivate the reason for non-inclusion after closing the visit. The GP could choose between pre-specified answers such as *'the patient had no indication for an NSAID treatment', 'I was too busy', 'forgot to start the recruitment procedure',* or the GP could specify the reason in free text.
Recruited patients who consented to participate were randomised immediately in the GP's office by the software to either celecoxib or diclofenac (dose and duration was not fixed). Since both drugs are licensed for osteoarthritis and reimbursed a regular prescription was printed that had to be filled in the pharmacy.

Evaluation of the randomised database study

To evaluate the implementation of the RDS itself we

1. described patient recruitment and selection processes in recruitment;
2. compared information on exposure to celecoxib, diclofenac between the electronic patient record and the questionnaire;
3. compared information on gastrointestinal outcomes between the electronic patient record and the questionnaire;
4. assessed GP's opinion about the RDS. Since the study was stopped prematurely we could not answer the study question whether celecoxib and diclofenac differed in gastrointestinal tolerability.

To evaluate recruitment and selective in- exclusion, patients were considered eligible to be included when they received an NSAID treatment for osteoarthritis during a visit at the GP office. Patients were not considered to be eligible for inclusion if they received a prescription after a telephone contact or at a home visit. Reasons for non-inclusion were categorized as follows:

a. Practice-related issues; GP listed the reason for non-inclusion as " *I was too busy"* or, " *I forgot to recruit the patient",* or the GP who was treating the patient did not collaborate with the study.

b. Patient-related issues; patient met exclusion criteria or refused to participate.

Selection (bias) in the inclusion procedure was assessed by comparing baseline characteristics between patients who were included and patients who were not included because of physician related issues.
Agreement between the EPR and the patient questionnaires was assessed by means of Kappa statistics for exposure to study drugs and outcomes.[14]
To evaluate GP's experience with the RDS, GPs underwent a semi-structured interview at the closing-visit of the study. We asked the GPs to reflect on their general thought of the RDS methodology, the issues encountered during the study and suggestions to improve the method. The interview focused mainly on feasibility, methodology and topic of the study.

Table 1: The total number of participating general practitioners, the number of pre-selected osteoarthritis patients per practice, the duration of participation in the study per GP and the included patients.

General practice number	Number of participating GPs within a practice*	Identified possible candidates	Duration of participation of the GP ** (in days)	Possible candidates included	Incident cases***
1	4	370	152	1	1
2	1	177	183	1	2
3****	2	1423	261	0	0
4	1	156	259	0	0
5	2	368	237	1	3
6	3	376	224	1	0
7	1	193	223	2	0
8	1	132	222	0	0
9	2	216	36	0	0
10	1	147	203	1	1
11	1	172	202	0	1
12	2	212	198	3	5
13	3	289	196	0	0
14	1	302	188	1	0
15	1	192	183	0	0
16	1	200	138	0	0
17	2	150	132	0	0
18	1	53	132	0	0
19	3	336	131	0	0
20	1	294	127	0	0
21	1	230	32	0	0

General practice number	Number of participating GPs within a practice*	Identified possible candidates	Duration of participation of the GP ** (in days)	Possible candidates included	Incident cases***
22	1	144	126	1	0
23	1	182	119	0	0
24	1	295	113	0	1
25	1	180	112	0	1
26	3	338	112	0	0
Total	42	7127	Median=188	20	15

* In group practices, different GPs may start on different points in time.
** In case of group practices, we reported the longest duration.
*** The General practitioners could also included newly diagnosed patients that were not selected by the software during installation of the RDS software.
**** Group practices where not all the GPs participated while the total number of possible candidates were selected.

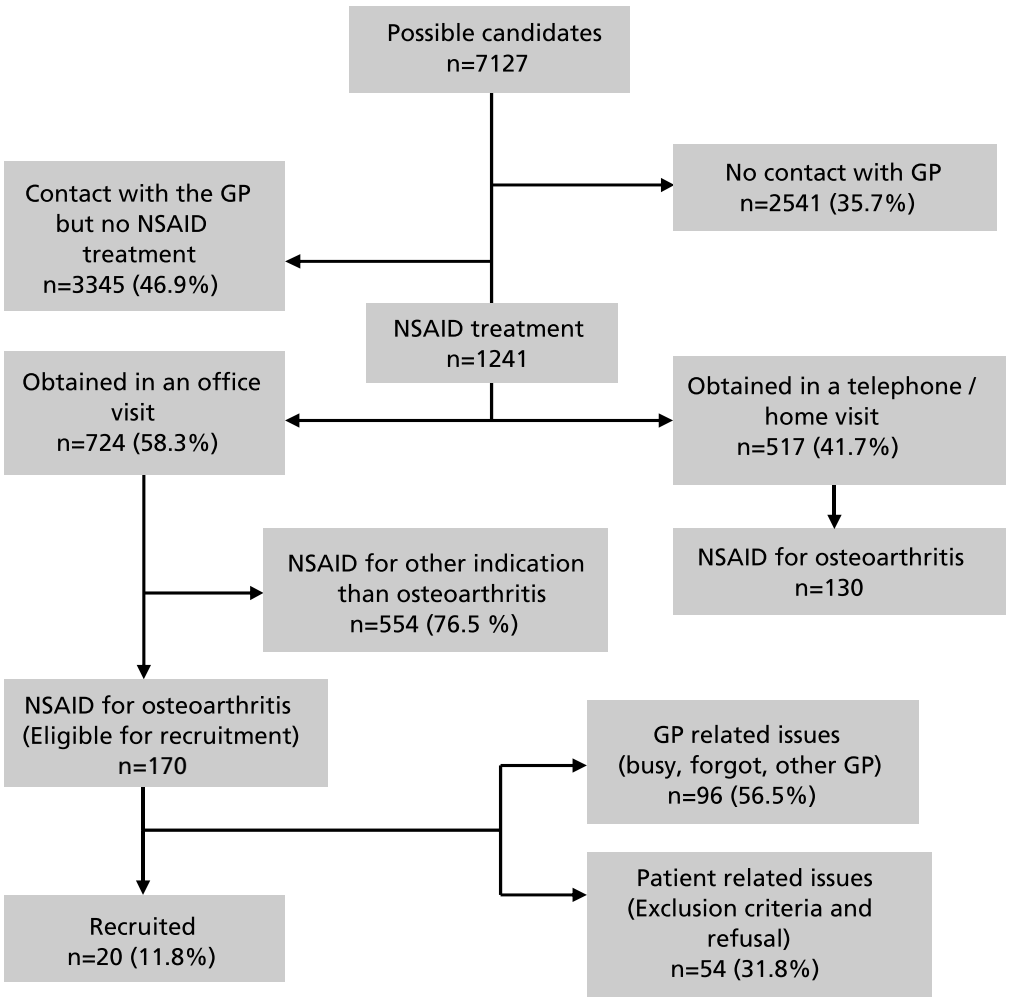
Results

Patient inclusion started on January 1, 2004 and was prematurely ended on December 17, 2004. Patient recruitment was slow and was not expected to improve. Recruitment of general practitioners was therefore stopped in September 2004 and patient recruitment was planned to stop on December 31, 2004. The study was however, terminated on December 17, 2004 when Pfizer announced an increased cardiovascular risk during use of celecoxib in the APC trial.[13]

Forty-two GPs (belonging to 26 practices) participated (Table 1). Together they covered a population of 141,395 patients. The median duration of participation per GP was 188 days (range 32–261 days). A total of 7127 patients were identified and flagged as possible candidates for recruitment (on average 170 per GP).

More than a third of the pre-identified candidates (n=2541, 35.7%), did not have any contact with the GP during the study period, 46.9% (n=3345) contacted the GP but did not receive an NSAID (Figure 1). A total of 1241 (17.4%) subjects received an NSAID prescription, 517 of them were not eligible for recruitment with the RDS software because they received an NSAID during a telephone (with assistant) or home visit. Of the 724 patients who received the NSAID during an office visit, 554 received the NSAID for another indication than osteoarthritis (Figure 1). Hence, during the follow-up period, 170 (2.4%) of the 7127 possible candidates were eligible for recruitment. Twenty of the eligible candidates (11.8%) were randomised, 96 (56.6%) could

not be recruited because of practice-related issues. In 55 of these 96 cases, the patient received the NSAID from a healthcare provider in the general practice who was not participating in the study. In 30 cases (17.6%), the GP reported to be too busy to start the recruitment procedure, and in 11 cases (6.5%), the GP reported to have forgotten to recruit the patient.



Figures 1: Flow diagram of possible study candidates in the randomized database study. Possible candidates were osteoarthritis patients that were automatically pre-selected by the specific study software.

Fifty-four out of the 170 eligible patients (31.8%) were not recruited because of patient-related issues. 25 of these 54 patients were excluded because they were either current or chronic NSAID users, 13 patients had a contraindication, 12 patients refused to participate, and 4 patients (2.3%) were excluded because they were not eligible according to the GP.

During the follow-up period, 94 patients were newly diagnosed with osteoarthritis in the practices that participated in the study. Of these patients, 26 (27.7%) received an NSAID prescription during a GP-visit and therefore were eligible for recruitment; fifteen (57.7%) of these patients were recruited.
Of the thirty five patients 20 received celecoxib and 15 diclofenac. Baseline characteristics were comparable between the two study arms. Comparisons of included prevalent OA patients with OA patients who were not included because of practice issues showed that the included patients were younger (mean age 60.2, sd 13.3 vs. 66.7, sd 11.1, p= 0.04) and had more contacts with their GPs (mean 30.9, sd 3.8 vs 14.8, sd 2.9, p= 0.01).

Data quality

The 35 included and randomised patients returned 83% of the questionnaires to the study center. Agreement between the EPR and the patients' questionnaires regarding baseline exposure (drug name, dosage, and treatment regimen) was complete (Kappa 1.0). Data on outcomes, however, showed some differences between the EPR and the questionnaires but the agreement was good[16] (Kappa 0.7; SD 0.14) (Table 2). Ten patients reported to have stopped or changed the treatment before the prescription ended. The same information was reported in seven of the corresponding EPRs. The three cases in which there was no agreement between the EPR and the questionnaire regarded patients who stopped the treatment without consulting the GP. None of these patients stopped treatment because of gastrointestinal intolerability.

Table 2: Changes in baseline exposure indicative of study outcome (treatment change during the follow up period) from the electronic patient records and the patients' questionnaires.

		Patients' questionnaires Exposure status during follow-up		Total
		No changes	Changes/Stop	
Electronic Patient Record*	No changes	24	3	27
	Changes/Stop	1	7	8
Total		25	10	35

*Kappa statistic: 0.7 (SD 0.14).

GP perception

The majority of the participating GPs appreciated the developed RDS methodology. The automated selection, recruitment and randomisation procedures were the most appealing aspect of the methodology.

The main general criticism on the study was the lack of suitable patients. More specific problems were the high number of false positive reminders and difficulty to recruit patients during routine visits. On average two messages per day were seen but the patients often came for other reasons than osteoarthritis. The necessity to inform the patient and ask for consent disrupted the normal workflow, especially since this had not been planned in the day schedule.
Suggestions to improve the RDS methodology comprised use of the GPs' assistant in the recruitment process, to recruit patients outside office hours, and help of a research assistant.

Discussion

This RDS was not able to answer the study question whether celecoxib or diclofenac differed in gastrointestinal tolerability. Despite the premature ending of the study it has shown that a RDS is feasible and it has provided insight in the actual conduct, obstacles and possibilities of the design. Despite the recognized ease of participation and automated identification, recruitment and randomization procedures, practice organization and time constraints remained the bottleneck in this study. We chose for the consultation as place of recruitment because it was considered the most naturalistic approach to enroll patients who acutely require an NSAID for osteoarthritis. The main problem was the time required to obtain informed consent, which is mandatory according to GCP even if both treatments are licensed and marketed for the indication.[12] A second problem was topic related; most patients were not eligible for recruitment since they received an NSAID for another primary indication. Since our study was not a registration trial we did not allow off-label use. Another study specific problem was the fact that most patients obtained their NSAID through request of a repeat prescription during telephone or home consultation. Our software was not built to include patients outside of the office and written consent could not be obtained during a telephone visit.
By using the RDS methodology in an existing population-based general practice research database, it was possible to track and quantify recruitment. This allows for inspection of selective patient participation and recruitment which is an important limitation of regular trials.[17,18]
We did not require completion of case report forms because this is known to be time consuming and the source documentation was assumed to be

available in the EPRs. We assessed whether the quality of data in the EPR was good but we also acknowledge that this depends on the type of outcome. Quality of data in the EPR is likely to be better when the outcome is more severe. In our small study concordance was good between EPR data and the patient questionnaire on the outcomes.

After evaluation of the trial and interviews with the GPs, we concluded that it is technically feasible to conduct a randomized database study. There is a potential to benefit from the strength of the RCT design (randomization) and the observational study (generalisability). A major hurdle in our randomized database study was patient recruitment (during routine consultations). Alternative patient recruitment approaches need to be investigated to improve the feasibility of randomized database studies. The potential of the randomized database study, however, is clear and there should be more research to increase the performance.

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Summary

In 1997 Sacristan and colleagues posed the idea of randomised database studies as a possible solution for the weaknesses of observational studies (confounding) and randomised clinical trials (generalisability) in the evaluation of drug effects.
The randomised database study (RDS) was proposed as a study with the following characteristics: computerized selection of potentially eligible candidates, randomization of patients to one of the treatment arms, and naturalistic follow-up of patients with routine care data in general practice databases (as in observational studies). Because of the naturalistic follow-up, results from a RDS would be better generalisable to the general population and would not suffer from confounding because of the random treatment assignment. The potential benefits of the RDS can be easily recognized, however to our knowledge this research methodology has only been described and has not been tested. We further developed the RDS methodology and tested its feasibility in the Integrated Primary Care Information (IPCI) general practice research database.

Application of a randomised database study in the IPCI database

To test the feasibility of the randomised database study we aimed to compare the gastrointestinal tolerability of celecoxib and diclofenac in patients diagnosed with osteoarthritis. Celecoxib and diclofenac are non-steroidal anti-inflammatory drugs (NSAIDs) licensed, marketed and reimbursed for the treatment of osteoarthritis. Diclofenac is a non-selective NSAID that is commonly used for the treatment of arthritis, pain and stiffness. Due to the inhibition of cyclo-oxygenase-1 (COX)-1, use of diclofenac is associated with a 2- to 3-fold increased risk of upper gastrointestinal complications such as bleeding, ulcers and perforation. Celecoxib is a COX-2 selective inhibitor (coxib) with efficacy comparable to non-selective NSAIDs but with a significantly lower risk of endoscopically confirmed gastro-intestinal lesions and a tendency to less serious upper gastrointestinal events. The comparison of gastrointestinal tolerability of these drugs was chosen as test case since we hypothesized that an observational comparison would not be feasible due to channelling of coxibs to patients at higher risk of upper gastrointestinal complaints and therefore confounding by indication. The existence of channelling, confounding by indication was first evaluated in observational studies and subsequently the RDS was designed, developed and tested.

Proof of concept studies

In **Chapter 2** we conducted a retrospective cohort study in the IPCI general practice research database. It was demonstrated that coxibs with comparison to non-selective NSAIDs are preferentially prescribed to patients with more risk factors for NSAID-related gastrointestinal disorders. That phenomenon is known as channelling (bias). We observed that coxib users more frequently had one or more risk factors for NSAID-related gastro-intestinal disorders (OR 1.18, 95% CI 1.10–1.26). In addition coxib users more often had cardiovascular disease (independent of gastrointestinal risk) (OR 1.35 95% CI 1.28–1.43). This channelling phenomenon was present from the moment of launch until the moment of data drawdown (end of 2004). Due to the channelling of coxibs, it was considered difficult to compare the gastrointestinal tolerability of celecoxib and diclofenac without randomised assignment of treatment.

To illustrate the weakness of observational studies on (beneficial) treatment effects, we studied whether coxibs lowered the risk of upper gastrointestinal bleedings or ulcers compared to the one pill combination of diclofenac and misoprostol. The one pill combination of diclofenac and misoprostol is an alternative NSAID regimen, which is also indicated in patients with an increased risk of NSAID-related gastrointestinal disorders due to the gastro-protective effects of misoprostol. **Chapter 3** shows that use of coxibs increases the risk of gastrointestinal bleeding or ulcers as compared to the one pill combination of diclofenac and misoprostol. Despite the fact that both coxibs and the one pill combination of diclofenac and misoprostol are indicated for the high GI-risk population, we could not exclude that our findings were due to residual confounding by indication. We adjusted for all measurable risk factors that affected the point estimate, but only random treatment assignment may deal with measurable and immeasurable differences in risk factor patterns. We therefore proposed to conduct a randomised database study in the IPCI database.

We conducted a pilot study **(Chapter 4)** to assess the sample size required for the randomised database study. The minimal detectable rate ratio was set at 0.70, α at 0.05 and the power at 80%. Given the event rate, required events and the mean treatment duration it was estimated that about 2117 subjects in each treatment arm would generate the required persontime and events.

Randomised database study

Chapter 5 and 6 describe the development, concept and implementation of the randomised database studies in the IPCI general practice research database. We used the general practitioners' information system with electronic patient

records as a tool to identify possible candidates (pre-selection), to facilitate the recruitment process and to randomise treatments. The IPCI database with the electronic medical records of the same patients was used to collect data on patient follow-up. Since we anticipated that the outcome data in the electronic medical records could be incomplete, patient questionnaires were administered as concomitant data collection method to assess the quality of data in the electronic medical record.

In **Chapter 6**, we further describe the changes to the IPCI infrastructure that were required for the conduct of the RDS. All pre-selected patients automatically received a study number, which could be linked to the IPCI identifier. This study number enabled us to follow the patients from the day of selection until the end of the study. As a result we could track whether pre-selected patients visited the GP, reasons for non-inclusion, the outcome of the randomisation procedure and eventually study outcomes. We concluded that it was technically feasible to conduct a randomised database study in the IPCI general practice research database.

We conducted an evaluation study to describe the issues we encountered and interviewed GPs to obtain their perception of the randomised database study methodology (**Chapter 7**). In the study period between January and September 2004, we recruited 42 general practitioners, in these practices 7127 patients were considered eligible for inclusion. During the follow-up period (terminated early in December 2004 because of slow recruitment and uncertainty about cardiovascular safety of celecoxib), more than a third (35.7%) of the possible candidates did not have any contact with the GPs and almost half (46.7%) of the patients who contacted the GP did not require NSAID treatment. This was important because we only considered patients to be eligible if they received an NSAID treatment for osteoarthritis during a regular visit with their GP. Patients who were treated with an NSAID often received it for another indication than osteoarthritis or they received the NSAID during a telephone contact or home visit. In total, 170 patients were eligible for recruitment of which twenty (n=20) were recruited. Most of the other eligible patients (88.3%) could not be recruited because of practice-related issues (n=96.) (*i.e.* GP prescribing the NSAID was too busy, or GP was not the principle healthcare provider) and patient related issues (n=56) (*i.e.* exclusion criteria, refusal to participate and GPs exclusion based on their own opinion).

From the interviews with the participating GPs we learned that almost all of them appreciated the methodology. The GPs reported that the automated procedures were the most appealing aspect of the study. The most important

weakness of the RDS was reported to be timing of recruitment which was during regular visits. The recruitment procedure disrupted the normal workflow.
Our assessment of the quality of information showed that the EPR is an excellent tool to obtain information on prescriptions and outcomes that lead to a GP visit. The EPR was incomplete on reasons for stopping treatment.

Discussion and Recommendations

The main objective of this thesis was to implement and test the randomised database study, which conceptually should bridge the gap between observational studies and randomized clinical trials.

Randomized trials

The randomised controlled trial (RCT) is considered as the gold standard in clinical research. The main objective of a RCT is to evaluate whether an intervention is efficacious.[1] This evaluation is usually performed by randomisation, blinding, intensive patient monitoring, and strict management according to Good Clinical Practice (GCP) guidelines and protocols. Although these conditions facilitate the measurement of treatment effects, they limit generalisation of the results to other populations and settings. Evidence in respiratory research has demonstrated that RCTs include <10% of the eligible population for treatment who present to physicians' offices[2] (Table 1). These data underline the importance of the selection problem. However in most clinical trials the selection process is unknown since the source population is usually not quantified.

Table 1: Number of asthma patients remaining in clinical trials after stepwise introduction of selection criteria for an asthma RCT according to WHO criteria[2].

	Number	Percentage
Clinical asthma (seeking primary medical care)	334	100.0
FEV1 50–85% of predicted	124	37.1
Reversibility 12% with ß-agonist use	50	15.0
No co-morbidity	32	9.6
Pack-years smoked <10	18	5.4
Regular use of ICS	15	4.5
Symptomatic asthma (eligible for asthma RCT)	11	3.3

General practitioners (GPs) are faced with the problem of applying evidence on drug efficacy from studies that are conducted in strictly controlled

settings with a very homogeneous patient group to the heterogeneous and uncontrolled situation of their normal care.[3,4] Ideally, for them, evidence of treatment effectiveness should be obtained in routine care, in pragmatic or naturalistic randomised trials with patients normally seen by GPs.[5]

Although trials in general practice may have better applicability to the primary care setting, there are many difficulties in conducting them.[6-8] Frequently reported problems are lack of time, recruitment of investigators and patients, obtaining informed consent, randomisation, and data collection. Most of the randomised studies in general practice still use conventional methods for patient selection, recruitment, and data collection. Our belief was that making use of the automated patient record potentially could facilitate the process of patient selection and data collection.

Observational studies

Postmarketing observational studies are necessary to study safety and effectiveness of new drug treatments due to the limitations of randomised clinical trials (*i.e.* limited sample size – only frequent adverse effects are detected) and lack of generalisability due to stringent in- and exclusion criteria and protocol-driven assessment.[9,10] These observational studies are usually conducted with claims or medical record databases; they reflect real life practice, contain many patients, and allow for flexibility in study design. Observational studies on drug effects usually have a greater generalisability because they cover treatment patterns in normal care.[9] Yet, the absence of randomisation in the treatment allocation often troubles sound comparison of effects between treatments. Although observational studies have been pivotal in the assessment of adverse drug reactions, they are considered as less suitable for the evaluation of effectiveness of treatments.[11,12] In most instances the occurrence of an adverse drug reactions is not related to the severity or indication of the drug, whereas the intended benefit of the drug is highly associated with the indication or severity.[13]

Randomised database study

A new approach that could facilitate trials in general practice is the *randomised database study* that was proposed by Sacristan and colleagues in 1997.[14,15] This approach is based on experience with observational databases based on electronic patient records (EPRs) in the conduct of observational outcomes studies. Sacristan argues that inclusion of a randomisation module in the EPR would allow assessment of drug effectiveness in a large population.[14,15]

The EPR would further function as a source for patient selection, and data collection during a naturalistic follow-up, like in observational studies. The conduct of a randomised database study requires adjustments or additions to the regular medical information processing with the EPR system and the purpose of this thesis was to describe these and test the RDS design.

Main findings

In the initial part of this thesis, proof of concept was given by demonstrating that channelling occurs with the prescription of selective COX-II inhibitors (coxibs) in comparison to non-selective NSAIDs. Patients who received coxibs had a significantly higher prevalence of risk factors for NSAID-related gastrointestinal disorders and a higher prevalence of cardiovascular diseases/ conditions; this was independent of the practice the patient belonged to. Although the extent of channelling changed slightly during the study period, channelling remained significant.

As a second proof of concept study to underline the need for a RDS, a case control study was conducted in a cohort of NSAID or coxib users to assess whether use of coxibs was associated with a lower or comparable risk of upper gastrointestinal ulcers and bleedings in comparison to the one pill combination of diclofenac and misoprostol (Arthrotec®). This drug is an alternative NSAID regimen, which is indicated in patients with an increased risk of NSAID-related gastrointestinal disorders due to the gastroprotective effects of misoprostol. This comparator was chosen to reduce the risk of confounding by indication. Coxibs increased the risk of gastrointestinal bleeding and ulcers as compared to the one pill combination of diclofenac and misoprostol. Despite the fact that both coxibs and the one pill combination of diclofenac and misoprostol are indicated for the high GI-risk population, we could not exclude that our findings were due to residual confounding by indication.

The remaining of the thesis is dedicated to the exploration, implementation and evaluation of the RDS method. The main finding is that the RDS method is technically feasible; we could implement a randomized database study in an existing general practice research database. The recruitment process, however, needs to be changed. The methodology is appealing to both the general practitioners and researchers. The following advantages were observed:

1. Easy access to a large heterogeneous population reflecting the general population;
2. Automated patient selection, randomisation and data collection with the EPR, which reduced time investment and loss to follow-up;

3. Elimination of confounding by randomly assigning treatments;
4. The ability to study the source population from which the study population emerges and to quantify selective recruitment and participation.

Access to the source population from which the study population emerges gives the unique opportunity to study issues that could affect the generalisability of the study results.[15] For example, we could exactly track reasons for non-inclusion, we could study whether the participating population differed in characteristics from the non-participating population, and we could evaluate whether outcome occurrence was different in the included and non-included population. The fact that the complete medical records are collected for all patient in the practice – included in the trial or not – enables such a detailed analysis. In addition we could study whether participation in the study changed the behaviour of the GPs (Hawthorne effect).[5]

Despite the recognized advantages, conducting the RDS revealed unforeseen problems; these problems will be described below.

A RDS is considered to be an interventional study since treatment assignment is randomised. Therefore, researchers should follow the principles of the Good Clinical Practice (GCP). Adherence to these guidelines proved to be a significant hurdle that required time and effort on the part of the GP. For example, GPs have to obtain written informed consent from every individual patient. Although in absolute terms GP workload was reduced in comparison to a conventional trial it became clear that a naturalistic trial always remains time consuming. Moreover, the naturalistic trial does disrupt the normal flow of the practice. In the RDS described in this thesis, we only recruited patients during regular visits – randomization had to be done at the time a patient required new NSAID treatment. Most of the problems we encountered were related to the fact that the moment of inclusion was at the time GP decided to prescribe a NSAID. At that point in time, typically at the end of the consultation, randomization should occur and patients had to be recruited. The recruitment process itself was time consuming and could not be planned in advance – the burden of the recruitment process was the factor limiting inclusion. One of the most important lessons learnt was that, in a future RDS, recruitment should be organized differently. Options suggested by the GPs included to specifically invite potentially eligible patients outside of routine consultation hours, or to block a double consultation for potentially eligible patients.

Blinding is a feature that is not a part of the current RDS methodology. The open study character may result in bias if outcomes are recorded differently per treatment arm. Our data showed that GPs had the tendency to record more data on patients treated with celecoxib compared to patients treated with diclofenac. Therefore blinding assessment of the outcome should be considered in future RDS.

We also have encountered unforeseen logistical issues that had a significant impact on the study. In the RDS we conducted, patients could only be recruited during visits at the GP's office since they had to provide written consent. However a large percentage of the eligible patients received the NSAID prescription, which would allow them to be included in the study, during a telephone consultation. Especially for chronic diseases, telephone consultations are a frequent alternative to face-to-face encounters. Future studies with similar designs should therefore include recruitment options for patients who receive the inclusion qualifying medication through telephone consultations.

Most patients diagnosed with osteoarthritis, received NSAIDs for another indication than osteoarthritis. According to the Good Clinical Practice guidelines, these patients could not be included since off-label use (even if such off-label use is widely applied in clinical practice) cannot be promoted in a non-registration trial.[19]

GCP requires that source information cannot be altered or otherwise that all changes in source documents are signed off. Data in the EPR system, which we considered to be the source documents, can be changed retrospectively and therefore the EPR itself can not be considered the source document in all instances. We used a time-stamped versions of the medical records in the database to comply with GCP guidelines. It should be discussed with competent regulatory bodies whether this solution will stand up in case of dispute.

In conclusion, the RDS design is an elegant alternative to the resource intensive randomised clinical trials conducted in general practice. The RDS methodology does combine the strengths of the RCT design and that of observational studies. On the other hand, it also combines the weaknesses of both the RCT design and observational studies. The adherence to the ethical requirements posed by the GCP guidelines, for example, may reduce the avowed benefits in terms of the resource savings. Physician and patient recruitment is an issue in the conduct of a RDS, as well as blinding and potential selection.

Recommendations

We formulated a few recommendations to improve future randomized database studies.

1. The research topic in a randomized database study should be of immediate interest for the GPs and reflect a clinical important question with genuine equipoise about the differential benefit of one or the other treatment.[19] If some of the participating GPs have prior believes that one of the treatments is superior, it may result in lack of compliance or information bias in the data collection procedure.
2. RDS protocols should be easy to follow and have a robust outcome. Soft outcomes might not lead to a GP encounter and therefore may go unnoticed. To avoid differential misclassification in outcomes, researchers should consider collecting data also directly from patients.
3. To render a randomized database study feasible with large numbers patient, recruitment should be organized outside the regular visit.

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Samenvatting

In 1997 lanceerden Sacristan en collegae het idee van gerandomiseerde database studies (RDS) voor onderzoek naar effecten van geneesmiddelen. Een RDS zou de oplossing zijn voor de confounding problematiek in observationale studies naar geneesmiddel effecten die vaak uit worden gevoerd in databases van geautomiseerde patienten dossiers en het gebrek aan generaliseerbaarheid van gerandomiseerde klinische trials.
Een RDS werd gepresenteerd als een studie met de volgende karakteristieken: automatische selectie en randomisatie van mogelijke participanten, en een naturalistische follow-up door middel van data die is verzameld in de elektronische medische dossiers (EMDs) van de participanten. De analyse van een dergelijke studie kan vervolgens worden uitgevoerd met gegevens die uit de database worden gehaald (zoals bijvoorbeeld IPCI). Omdat het hier om een naturalistische follow-up betreft, zullen de resultaten uit een RDS waarschijnlijk beter generaliseerbaar zijn en de randomisatie van behandelingen zou het confounding probleem oplossen. Ondanks de potentiële voordelen van de RDS zijn er geen publicaties bekend van studies die op deze manier zijn uitgevoerd. Wij hebben daarom de RDS methodologie verder ontwikkeld en de haalbaarheid getoetst in de IPCI onderzoeksdatabase.

RDS in de IPCI database

Om de haalbaarheid van de RDS methodologie te toetsen hebben we een sponsor gevonden die geinteresseerd was in de vergelijking van gastrointestinale verdraagzaamheid tussen celecoxib en diclofenac bij patiënten met artrose. Celecoxib en diclofenac zijn geregistreerde niet steroidale ontstekingsremmende geneesmiddelen (NSAIDs) die werken via remming van cyclo-oxygenase (COX) en zijn geïndiceerd voor onder andere de behandeling van artrose. Diclofenac behoort tot de groep COX niet selectieve NSAIDs en wordt behalve voor artrose ook voorgeschreven aan patiënten met pijn en stijfheid (in de gewrichten). Doordat diclofenac niet selectief is voor COX-2 maar ook COX-1 remt, verhoogt het de kans op gastrointestinale klachten zoals bloedingen, ulcers en perforaties. Celecoxib behoort tot de categorie NSAIDs die selectief COX-2 remmen (coxibs) en heeft een vergelijkbare effectiviteit als de niet selectieve NSAIDs, maar een lagere kans op endoscopische vastgestelde gastrointestinale klachten. De vergelijking van de gastrointestinale klachten van deze twee types NSAIDs werd in de RDS gekozen als test case.
We hadden verwacht dat we deze vergelijking middels observationele studies niet goed zouden kunnen doen omdat COX-2 remmers selectief worden voorgeschreven en aangeraden aan patiënten met een hoger risico

op gastrointestinale klachten. Dit wordt ook wel "channelling" genoemd. Channeling is een belangrijke oorzaak van confounding. Om deze aanname te onderbouwen hebben we channelling van COX-2 remmers in kaart gebracht, een observationele vergelijking van geneesmiddel effecten gedaan middels een geneste case controle studie uitgevoerd. Uiteindelijk hebben we een RDS studie opgezet.

'Bewijs van concept' studies

Hoofdstuk 2 is een beschrijving van een cohort studie waarin coxib gebruikers worden vergeleken met niet-selectieve NSAIDs gebruikers. Deze studie laat zien dat coxibs selectief worden voorgeschreven aan patiënten die intrinsiek een hoger risico op gastrointestinale klachten hebben. De analyse laat ook zien dat coxib gebruikers meer cardiovasculaire co-morbiditeit hebben (onafhankelijk van de gastro-intestinale risico) (OR 1.35 95% BI 1.28–1.43). De channelling trad op vanaf het moment van marketing van coxibs en bleef aanwezig tot aan het moment van deze studie (eind 2004). Vanwege de channeling is het dus moeilijk om de gastrointestinale verdraagzaamheid van celecoxib te vergelijken met diclofenac zonder de participanten te randomiseren, hoewel statistisch geadjusteerd kan worden voor meetbare verschillen tussen patienten, kan confouding van niet meetbare factoren nooit uitgesloten worden.

Om het probleem van observationele studies verder te illustreren, hebben we een studie uitgevoerd waarin werd gekeken of coxibs het risico op gastrointestinale bloedingen of ulcers verlaagt ten opzichte van de vaste combinatie van diclofenac en misoprostol. Deze combinatie is een alternatieve behandelstrategie voor patiënten met een verhoogd risico op NSAID gerelateerde gastrointestinale klachten. **Hoofdstuk 3** laat zien dat het gebruik van coxibs geassocieerd was met een verhoogd risico op gastrointestinale bloedingen en ulcers in vergelijking tot de combinatie van diclofenac en misoprostol. Wij kunnen in deze studie echter niet uitsluiten dat de resultaten vertekend zijn door residuele confounding ondanks het feit dat beide behandelstrategieën voor patiënten met een verhoogde risico bedoeld is. Er is gecorrigeerd voor alle meetbare risicofactoren die de geschatte risico zou kunnen beïnvloeden, maar alleen randomisatie van de participanten garandeert vergelijkbare risicopatronen van deze twee populaties. We hebben daarom een RDS in de IPCI database voorgesteld.

Hoofdstuk 4 beschrijft een pilot studie die werd uitgevoerd het minimale aantal RDS participanten vast te stellen. De minimale detecteerbare ratio was gezet op 0.70, de α op 0.05 en de power op 80%. Gegeven de ratio van de

uitkomst, het aantal events en de gemiddelde behandelduur is er geschat dat er 2117 participanten per behandelarm nodig waren om de persoonstijd en events te genereren.

Gerandomiseerde database studie

In **hoofdstuk 5** en **6** worden concepten en de implementatie van de RDS in de IPCI onderzoeksdatabase beschreven. We hebben de EMDs in de huisartsinformatiesystemen gebruikt om potentiële kandidaten te selecteren, om het rekruteringsproces te ondersteunen en om de participanten te randomiseren. De EMDs, die later in de IPCI database worden geïntegreerd, werden ook gebruikt om de gerekruteerde patiënten te volgen. Omdat we hadden geanticipeerd dat de EMDs niet altijd volledig zouden zijn, hebben we ook via de participanten door middel van vragenlijsten data verzameld. Met deze data konden we de kwaliteit van de data in de EMDs vaststellen.

In **hoofdstuk 6** worden de veranderingen beschreven die nodig waren om de IPCI infrastructuur geschikt te maken voor een RDS. Alle geselecteerde patiënten (potentiële kandidaten) kregen een studienummer, die werd gekoppeld met het IPCI- studienummer. Op deze manier waren wij in staat om de patiënten te volgen vanaf de dag van de selectie tot het einde van de studie. Deze koppeling maakte het ook mogelijk te verifiëren wanneer de geselecteerde patiënten hun huisarts hebben bezocht, waarom ze niet in de studie zitten, de uitkomst van de randomisatie en de eventuele studie uitkomst. Deze infrastructuur liet zien dat het technisch mogelijk was om een RDS uit te voeren in de IPCI onderzoeksdatabase.

In de evaluatie studie (**Hoofdstuk 7**) beschrijven we de praktische issues en feedback van huisartsen over de RDS. In de studie periode tussen januari en september 2004 hebben we 42 huisartsen gerekruteerd met een totale populatie van 7127 potentiële artrose patiënten. Gedurende de follow-up hadden meer dan een derde (35.7%) van deze potentiële kandidaten echter geen contact met hun huisarts en bijna de helft (46.7%) van de patiënten die wel contact met hun huisarts hadden, werden niet met een NSAID behandeld. Dit was belangrijk omdat de potentiële participanten alleen gerecruteerd konden worden op het moment dat ze tijdens een reguliere huisartsbezoek een NSAID behandeling kregen voor artrose. Het kwam ook vaak voor dat deze artrose patiënten wel een NSAID behandeling kregen maar voor een andere indicatie dan artrose, of ze kregen een herhaal recept via een telefonisch contact met de huisarts(assistent). In totaal waren 170 patiënten geschikt voor inclusie waarvan 20 zijn gerekruteerd voor de studie. De meeste geschikte patiënten (88.3%) werden niet gerekruteerd vanwege praktijk

gerelateerde issues (zoals drukte van de huisarts of vervangend huisarts die de behandeling voorschreef) en patiënten gerelateerde issues (zoals exclusie criteria of weigering om mee te doen, of uitsluiting door de huisarts).
Uit de interviews met de deelnemende huisartsen bleek dat de meeste huisartsen enthousiast waren over de methodologie. Vooral de geautomatiseerde procedures vonden de meeste huisartsen aantrekkelijk. Als zwak punt van de RDS methodologie werd de rekruteringsstrategie genoemd. Dit vooral omdat de rekrutering gedurende normale visites moest plaats vinden en dit verstoorde de workflow van de praktijk.
Het EMD blijkt ook een goed instrument te zijn om data over prescripties en uitkomsten te verzamelen, met als kanttekening dat de studie-uitkomst moet leiden tot huisarts bezoek. Het EMD was bijvoorbeeld niet altijd compleet als het ging om de rede van stoppen met de medicatie.

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One love,

Georgio

Curriculum Vitae

Georgio Mosis was born on February 9, 1976 in Paramaribo, Surinam. He started his undergraduate education at Lyceum II (Surinam), and emigrated with his family to the Netherlands in 1992. He continued his undergraduate education at the Johan de Witt College in Scheveningen, the Netherlands.
Between 1995–1996 he studied Biomedical Science at the Rotterdam School of Professional Education.
In 1996 he started studying Medical Informatics at the Academic Medical Center of the University of Amsterdam, which he completed in September 2000. In the last year of his education at the University of Amsterdam he was selected to participate in the Top Stage Master Class/ International Partnership in Health Informatics project.
He started the research reported in this thesis in June 2001, at the department of Medical Informatics and the department of Epidemiology & Biostatistics at the Erasmus University Medical Center in Rotterdam. In 2002, he obtained the degree of Master of Science in Clinical Epidemiology at the Netherlands Institute for Health Sciences.
As of May 2005, he works as a research scientist at Philips Research Laboratories (NatLab) in Eindhoven, The Netherlands.