Balancing risks and benefits in the optimization of oral antithrombotic therapy

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1

General introduction and outline of the thesis

GENERAL INTRODUCTION

Thrombosis is an everyday issue for cardiologists and is responsible for disabling and life-threatening conditions such as myocardial infarction and thrombo-embolic stroke. These conditions require the use of antithrombotic agents, both for its treatment, as well as for preventive measures.

However, antithrombotic agents are also associated with safety issues and adverse events, which increases the risk of non-compliance and undertreatment. For example, gastrointestinal side effects such as dyspepsia are associated with aspirin discontinuation, and the perceived risk of bleeding is one of the major determinants of underuse of oral anticoagulation in the elderly with atrial fibrillation.[1-7] These examples demonstrate that efficacy of antithrombotic therapy may be hampered by associated safety issues. Improved insights into patients at risk of bleeding may facilitate daily decision making and could reduce the issue of undertreatment in the elderly.

On the other hand, efficacy of antithrombotic medication may be influenced by concomitant medication and comorbidities. For example, the concomitant use of proton pump inhibitors (PPIs) has been implicated to result in impaired efficacy of clopidogrel in patients with acute coronary syndromes through a CYP-mediated mechanism.[8-12] In addition, patients with multiple co-existing diseases will use more drugs, increasing the risk of inhibiting or potentiating interactions. Apart from drug-drug interactions, patients with more comorbidity are more fragile, with impaired adaption mechanisms. This is an additional reason why fragile patients may have a differential response in terms of efficacy and/or safety to oral anticoagulants. These issues are especially important in patients with atrial fibrillation, which is a disease of the elderly.

Finally, special interest is warranted for patients with recurrent events, despite antithrombotic treatment. For example, in specific cases of acute coronary syndrome (ACS), the benefit of a long-term combination of both antiplatelet and anticoagulant therapy may outweigh the associated increased risk of bleeding.[13,14]

In this thesis, issues with regard to the efficacy and safety of oral antithrombotic therapy will be addressed, both in the treatment and prevention of arterial thrombosis and thrombotic complications of atrial fibrillation.

In the general introduction, the formation of thrombi will be highlighted, as well as the antithrombotic options. In the outline of this thesis, the different research questions will be addressed into more detail.

Pathogenesis of thrombosis in acute coronary syndromes and atrial fibrillation

Thrombosis formation depends on the interaction of thrombocytes, coagulation factors, and also red blood cells. Numerous conditions are known to increase the risk of thrombosis. Over one and a half century ago, Rudolph Virchow postulated that all these conditions can be classified among three key mechanisms: endothelial dysfunction/damage, abnormal blood flow (e.g. stasis), and hypercoagulability.[15]

The pathogenesis of an acute coronary syndrome involves the rupture of an atherosclerotic plaque of the coronary artery (endothelial damage). Due to this plaque rupture, the blood becomes exposed to the subendothelial layer containing various thrombo-active substrates, resulting in vasoconstriction of the blood vessel, platelet recruitment at the site of injury (primary hemostasis) as well as activation of the coagulation cascade (secondary hemostasis). Total occlusion of the coronary artery will result in an ST-elevation myocardial infarction indicating transmural ischemia, after which myocardial infarction will ensue. This demonstrates the importance of early reperfusion therapy in ST-elevation myocardial infarction. In contrast, if some perfusion is still present, this would result in a non-ST elevation acute coronary syndrome representing subendocardial myocardial ischemia, which not necessarily results in myocardial infarction.[16]

In atrial fibrillation, the development of a thrombus is multifactorial and involves all three aspects of Virchow's triad.[17] Due to functionally ineffective contractions of the atria, blood flow in the left atrium and left atrial appendage is altered. Moreover, structural defects in the atrial (appendage) walls have been documented, as well as increased levels of activated coagulation factors. These abnormalities observed in atrial fibrillation result in a prothrombotic state which can result in thrombo-embolic events such as ischemic stroke or a non-cerebral systemic embolism.

Thrombus formation

The formation of thrombi involves the activation of two different mechanisms: platelet aggregation (i.e. thrombocytes) and activation of the coagulation cascade (Figure 1).[18]

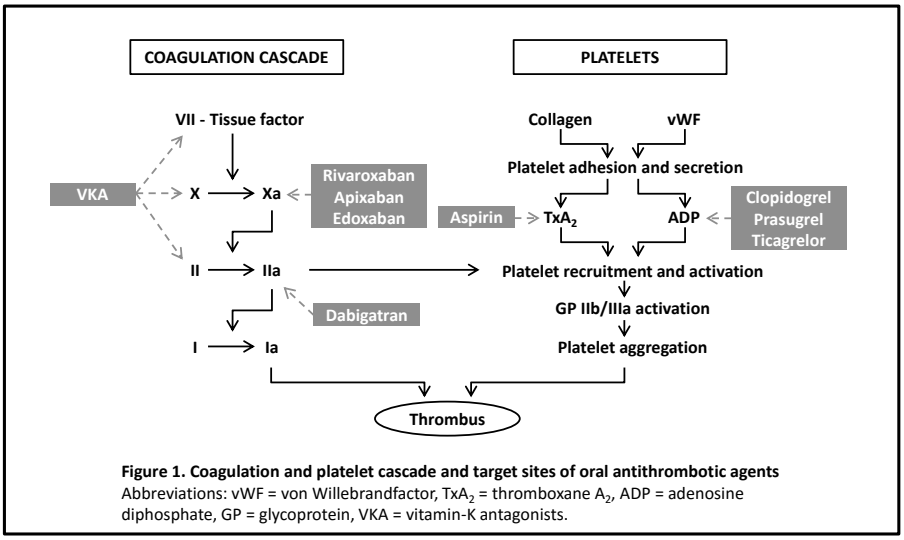

Figure 1. Coagulation and platelet cascade and target sites of oral antithrombotic agents
Abbreviations: vWF = von Willebrandfactor, TxA_2 = thromboxane A_2, ADP = adenosine diphosphate, GP = glycoprotein, VKA = vitamin-K antagonists.

Platelets

Under normal conditions, thrombocytes are in a nonreactive state and do not adhere to the endothelium or aggregate.[19] In case the endothelium is disrupted, collagen and Von Willebrand factor become exposed. These substrates anchor platelets to the subendothelium by bonding to receptors present on platelets (collagen: GPVI, GPIa-IIa; Von Willebrand factor: GPIb-IX-V), triggering the adhesion of platelets to the damaged endothelium.[20-22] The exposed matrix from the vessel wall, as well as thrombin generated from activation of the coagulation cascade, initiate the activation of the thrombocytes. The activation of platelets induces a shape change of the glycoprotein IIb/IIIa (GpIIb/IIIa) receptor distributed on the membrane of the platelet. The expression of the activated GpIIb/IIIa can serve as a receptor for adhesive ligands (e.g. Von Willebrand factor, fibrinogen) initiating platelet-platelet connection

or platelet aggregation. Finally, platelet activation initiates the recruitment of other platelets by initiating an increased production of thromboxane, a platelet agonist, as well as the secretion of various granules present in the platelets. These granules contain other platelet agonists such as adenosine diphosphate (ADP), platelet derived growth factor (involved in vessel repair) but also coagulation factors (factor I, V and XIII).

Coagulation cascade

The other mechanism involved in the formation of a thrombus involves the activation of the coagulation cascade.[21,22] This results in the production of thrombin (factor IIa), which is the most potent platelet activator and is also responsible for the cleavage of fibrinogen to fibrin (factor I and Ia, respectively). Fibrin binds to the glycoprotein (Gp) IIb/IIIa receptor of activated platelets connecting platelets thereby reinforcing the platelet plug. Tissue factor (TF) is the main initiator of the coagulation cascade and expressed within the vessel wall. Following vascular injury, coagulation factor VII/VIIa, present in the blood plasma, becomes exposed to tissue factor, which forms a complex initiating the coagulation cascade. The TF/FVIIa complex induces the formation of factor Xa which converts prothrombin into thrombin.

Mode of action of oral antithrombotics

In this thesis we mainly focus on efficacy and safety issues of oral antithrombotic agents. Hence, parenteral agents, such as fibrinolytics, glycoprotein IIb/IIIa receptor antagonists and (low-molecular weight) heparins, will be discussed only briefly in Chapter 4. Oral antithrombotics can be categorized in two groups: antiplatelet agents and anticoagulants.

Antiplatelet agents

Antiplatelet drugs inhibit the activation and/or aggregation of thrombocytes.[23,24] In the current field of cardiology, the most important oral antiplatelet agents are aspirin and thienopyridines such as clopidogrel, prasugrel and ticagrelor. Aspirin, or acetylsalicylic acid, irreversibly inhibits the formation of thromboxane by blocking the cyclooxygenase-1 (COX-1) pathway in circulating platelets.[23] Consequently, upon

activation by different stimuli, platelets affected by aspirin are hampered in their ability to recruit other platelets. Thienopyridines inhibit both activation of platelets (ADP-dependent) and subsequent aggregation by blocking or modifying the platelet P2Y12 receptor.[24] Despite this inhibition, platelets can still be activated by other stimuli and excrete ADP from their granules, but the P2Y12 receptors of platelets are inhibited by thienopyridines and the occupied receptors will thus not be stimulated, preventing further activation through the ADP-dependent pathway.

Anticoagulants

The second group of antithrombotics involve oral anticoagulants which either reduce the production or inhibit the activity of clotting factors.[25] Although novel oral anticoagulants have emerged in the last decade, vitamin K antagonists (VKA) have traditionally been the only form of oral anticoagulation therapy. The working mechanism of VKAs involves the inhibition of vitamin K epoxide reductase.[26] Although patients on VKA anticoagulation continue to manufacture the vitamin-K dependent coagulation factors (pro-coagulant factors: II, VII, IX, and X; anticoagulant factors: protein C and S) their function is impaired, and they are referred to as 'proteins induced by vitamin K absence/antagonism' (PIVKA).[27] As such, there is a shortage of effective coagulation factors in case of VKA treatment. Importantly, despite the anticoagulant effect of VKAs on the long-term, an increased coagulation status can be observed in the early phase due to the relative short half-life of protein C and S. To ensure optimal efficacy and safety, VKAs need careful monitoring using the International Normalized Ratio (INR).[26]

Recently, other forms of oral anticoagulants have entered the market. The working mechanism of these drugs does not involve vitamin-K and they are therefore referred to as non-VKA oral anticoagulants (NOAC). Instead, rather than targeting the production of coagulation factors these drugs directly inhibit the activity of factor Xa (apixaban, rivaroxaban and edoxaban) or thrombin (factor IIa; dabigatran).[28]

Safety and efficacy of oral antithrombotic drugs

Although platelet activation and the coagulation cascade are intertwined, their treatment differs according to the disease. Although VKA monotherapy proved effective in acute coronary syndromes, aspirin is the cornerstone in treatment given its safety profile and logistics (no INR measurement).[29] On the other hand, aspirin monotherapy, as well as in conjunction with clopidogrel, is inferior to oral anticoagulation in atrial fibrillation.[6,30-32] This results in a different approach of antithrombotic treatment for myocardial infarction when compared to atrial fibrillation.

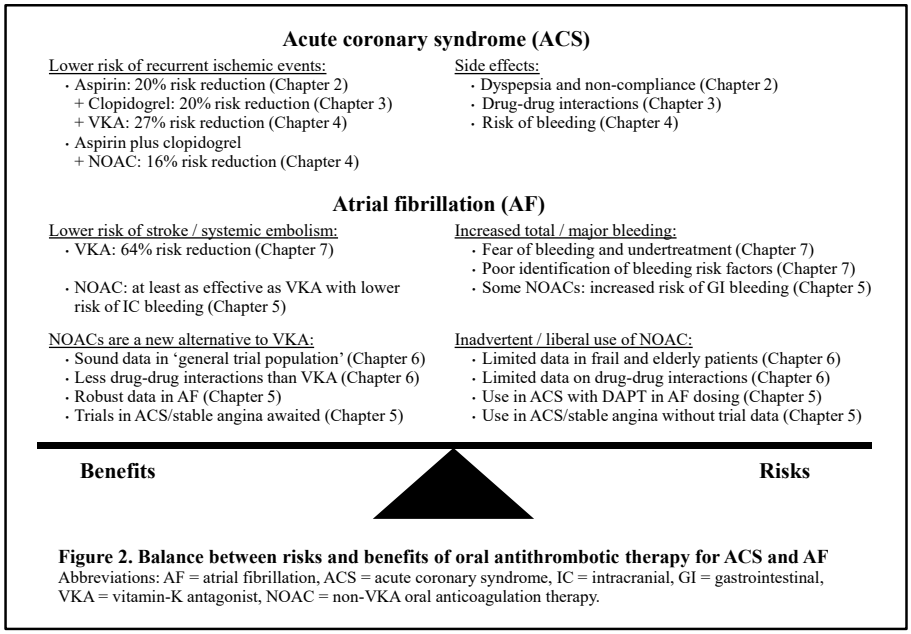

Figure 2. Balance between risks and benefits of oral antithrombotic therapy for ACS and AF
Abbreviations: AF = atrial fibrillation, ACS = acute coronary syndrome, IC = intracranial, GI = gastrointestinal, VKA = vitamin-K antagonist, NOAC = non-VKA oral anticoagulation therapy.

Prevention of acute coronary syndromes

Given the central role of platelets in an acute coronary syndrome, antiplatelet therapy is the key player in prevention of recurrent events. The efficacy and safety of aspirin has been assessed in numerous randomized controlled trials. In a meta-analysis of 16 long-term secondary prevention trials among over 17,000 patients with a previous vascular event, aspirin yielded an absolute risk reduction of coronary events from 5.3% to 4.3% per year during a 2.5 year follow-up period, which is equivalent to a 20% relative risk reduction.[33]

In primary prevention, the relative risk reduction was comparable, but given the very low event rates (~0.20% per year for non-fatal myocardial infarction), absolute benefits are minimal.[33] As for safety, in patients at high risk of atherothrombotic events, long-term treatment with aspirin approximately doubles the risk of major bleeding.[23,33,34] The majority of this risk increase was due to gastrointestinal bleeding complications. This well-known side-effect of aspirin is due to its inhibition of the COX enzyme, resulting not only in inhibition of the platelet agonist thromboxane, but also in impairment of the production of prostaglandin E2, which has protective properties of the stomach by producing a protective mucous layer.[35] In addition to this systemic gastrotoxicity, aspirin also has a more local, direct harmful effect to the stomach due to its ability to easily transfer through the gastroprotective mucous layer and enter and damage the underlying epithelial cells.[36-38] Hence, aspirin increases the risk of gastric ulcus formation and gastrointestinal bleeding, but also dyspepsia.[33,39-42] Although the latter is not a direct life threatening condition, it increases the risk of non-compliance to aspirin treatment resulting in a loss of efficacy.[43,44] This will be discussed in Chapter 2.

Thienopyridines are also important in the prevention of acute coronary syndromes. Although the current guidelines recommend the newer and more potent prasugrel and ticagrelor following an ACS, clopidogrel is worldwide still commonly used in the setting of secondary prevention following a myocardial infarction.[45,46] Clopidogrel has been studied both as monotherapy (vs. aspirin) and as adjunctive to aspirin (vs. placebo). As for monotherapy in the secondary prevention of vascular events, clopidogrel was comparable with regard to both efficacy as well as safety outcomes when compared to aspirin.[47] In the setting of dual antiplatelet therapy following an ACS, the addition of clopidogrel to aspirin reduced the rate of ischemic events from 11.4% to 9.3%, which represents a 20% relative risk reduction.[48] As to be expected was the combination of aspirin with clopidogrel associated with an increased risk of major bleeding when compared to aspirin monotherapy (2.7% vs. 3.7%), albeit that the trade-off (ischemic vs. bleeding) was in favor of double antiplatelet therapy with clopidogrel. As such, guidelines recommend the use of dual antiplatelet therapy for 12 months following an ACS.[45,46]

Notably, the addition of clopidogrel resulted in an increase in gastrointestinal bleeding complications (0.7% vs 1.3%), and the risk of those bleeding complications was dependent of the aspirin dose.[48,49] Given this observation, current guidelines recommend to prophylactically add a proton pump inhibitor in case of dual antiplatelet therapy, which is known to provide a 66% relative risk reduction in gastrointestinal bleedings in patients with dual aspirin and clopidogrel.[45,46,50] Notably, the Food and Drug Administration, as well as the European Medical Association issued warnings on a reduced efficacy of clopidogrel in case of PPI coadministration, which is the topic of Chapter 3.[51-53] This efficacy issue can result in discontinuation of the PPI by physicians, or may lead to a switch to different antitrombotic agents, which may affect safety.

Unfortunately, recurrent ischemic events still occur in about 10% of patients in the first year following an acute coronary syndrome, despite dual antiplatelet therapy.[48] Given the knowledge that VKA monotherapy was effective in reducing the risk of myocardial infarction, the addition of an anticoagulant to antiplatelet therapy in selected high risk patients could be of additional value. This will be addressed in Chapter 4.

Prevention of thrombo-embolic stroke in atrial fibrillation

Several trials studied the effects of aspirin in stroke prevention in AF and a meta-analysis indicated a 22% relative risk reduction of stroke and systemic embolism for aspirin.[28] Moreover, the addition of clopidogrel to aspirin further reduced the risk of stroke. However, every additional ischemic event prevented was at the cost of one major bleed.[32] Notably, oral anticoagulants proved to be much more effective than antiplatelet therapy. A meta-analysis of six trials comprising nearly 3000 patients randomized to either dose-adjusted warfarin or placebo/no treatment demonstrated a 64% relative risk reduction for stroke.[28] Importantly, also in elderly patients, the number needed to treat versus the number needed to harm favoured treatment with oral anticoagulants over placebo.

Also in comparison to aspirin, treatment with warfarin had a better risk-benefit profile, as it was not associated with higher rates of bleeding, and more effective in a large trial concerning elderly patients.[31] VKA therapy also proved more effective

when compared to aspirin used in combination with clopidogrel, without signs of safety concerns.[54]

In the last decade, an alternative to warfarin has become available. As of to date, four different NOACs have been approved for use in clinical practice: apixaban, dabigatran, edoxaban and rivaroxaban.[55] Importantly, NOACs do not require regular INR monitoring making them an interesting alternative to VKA treatment. Four large randomized trials concerning over 70,000 patients have demonstrated that this new class of drugs results in efficacy outcomes that are at least similar to those realized with VKAs with superiority for apixaban and dabigatran 150mg bid (relative risk reductions 21% and 34% respectively).[55-59] Importantly, all NOACs reduce the rate of intracranial hemorrhage with about 50%, and rates of major bleeding were significantly lower for apixaban, dabigatran 110mg bid and edoxaban (relative risk reductions 31%, 20% and 20%, respectively).[56-59] The flipside of the coin concerned an increased risk of gastrointestinal bleeding for dabigatran 150mg bid, edoxaban and rivaroxaban (relative risk increase 50%, 23% and 30%, respectively). Although this is a serious concern which requires attention, the reported rates in atrial fibrillation should be put in the context of the overall safety profile. This in contrast to the situation of ACS, in which the combination with dual antiplatelet therapy seemed associated with more harm than benefit (Chapter 5). Although current guidelines recommend to consider oral anticoagulation in patients with a CHA_2DS_2-VASc score of 1 or higher, appreciation of the associated number needed to treat and number needed to harm is warranted.[60,61] Moreover, it is important to realize whether trial data can be inferred to the general population, which is less selected than a study population. In that context, and with a growing population of elderly patient with atrial fibrillation with extensive comorbidity and associated drugs, we should question whether these patients could have a differential response to oral anticoagulation therapy. This issue is addressed in Chapter 6. Finally, the prediction of bleeding requires optimization, not only in the population as a whole, but especially in the elderly. In the abovementioned context, it is very well possible that risk factors for bleeding in the elderly differ from those in the young. Therefore we sought to assess the performance of the classical risk models for bleeding in the elderly. Insights into these issues may provide the prescribing physician more information to make a bal-

anced decision, and to potentially reduce the rate of undertreatment in the elderly. This issue will be discussed in Chapter 7.

Outline of the thesis

Aspirin is associated with gastrointestinal complaints affecting compliance and thus efficacy. In **Chapter 2**, we performed a large cohort study comparing the prevalence of gastrointestinal symptoms between patients using plain aspirin and effervescent calcium carbasalate.

Following the concerns of several medical agencies, **Chapter 3** addresses the impact of concomitant therapy of a proton pump inhibitor on the antiplatelet effect of clopidogrel in terms of efficacy. In this systematic review, both the effects on laboratory (platelet reactivity) and clinical outcomes are assessed.

About 10% of patients suffer from a recurrent thrombotic event while on adequate antiplatelet therapy. In this context, **Chapter 4** provides an overview of the treatment options with regard to anticoagulation therapy in patients with high platelet reactivity, i.e. patients in whom dual antiplatelet therapy has been proven ineffective. This chapter also touches upon the antithrombotic challenges with regard to efficacy and bleeding risk in case a patients suffers from both coronary artery disease and atrial fibrillation.

Chapter 5 concerns a commentary to a meta-analysis on the impact of treatment with a non-VKA oral anticoagulant on gastrointestinal bleeding. In this chapter, we provide a critical appraisal of the methodology and we address to the importance of balancing all risks and benefits of antithrombotic therapy.

Given that patients using more drugs are generally more fragile, these patients could have a differential response to anticoagulation therapy. In the post-hoc analysis of the ARISTOTLE trial depicted in **Chapter 6** we studied whether the number of concomitant drugs used is associated with the extent of comorbidity and the risk of adverse outcome, both ischemic as well as bleeding events in patients with atrial fibrillation. Moreover, we assessed the impact of the number of concomitant drugs on the effects of apixaban therapy on efficacy and safety when compared to warfarin.

Given that undertreatment in the elderly is common due to a perceived risk of bleeding, **Chapter 7** aims to provide insight in the discriminatory ability of three cur-

rently used bleeding risk stratification models in the very elderly patients (≥80 years) using a vitamin K antagonist in the setting of stroke prevention in atrial fibrillation. In addition to assessing and comparing the bleeding risk models, we also focused on the identification of bleeding risk factors in this specific cohort of very elderly patients.

Chapter 8 summarized the main findings and conclusions of all studies presented in this thesis. This chapter is concluded by an epilogue in which the clinical implications of the main findings are discussed.

Chapter 9 provides a Dutch translation of the summary and epilogue.

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Part 1

Acute coronary syndrome:
risks and benefits of oral antithrombotic therapy

2

Gastrointestinal symptoms in low-dose aspirin users: a comparison between plain and buffered aspirin

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ABSTRACT

Background: Aspirin is associated with gastrointestinal side effects such as gastric ulcers, gastric bleeding and dyspepsia. High-dose effervescent calcium carbasalate (ECC), a buffered formulation of aspirin, is associated with reduced gastric toxicity compared with plain aspirin in healthy volunteers, but at lower cardiovascular doses no beneficial effects were observed.

Aim: To compare the prevalence of self-reported gastrointestinal symptoms between low-dose plain aspirin and ECC.

Methods: A total of 51,869 questionnaires were sent to a representative sample of the Dutch adult general population in December 2008. Questions about demographics, gastrointestinal symptoms in general and specific symptoms, comorbidity, and medication use including bioequivalent doses of ECC (100 mg) and plain aspirin (80 mg) were stated. We investigated the prevalence of self-reported gastrointestinal symptoms on ECC compared with plain aspirin using univariate and multivariate logistic regression analyses.

Results: A total of 16,715 questionnaires (32%) were returned and eligible for analysis. Of these, 911 (5%) respondents reported the use of plain aspirin, 633 (4%) ECC and 15,171 reported using neither form of aspirin (no aspirin). The prevalence of self-reported gastrointestinal symptoms in general was higher in respondents using ECC (27.5%) compared with plain aspirin (26.3%), but did not differ significantly with either univariate (OR 1.06, 95%CI 0.84-1.33), or multivariate analysis (aOR 1.08, 95%CI 0.83-1.41). Also, none of the specific types of symptoms differed between the two aspirin formulations.

Conclusions: In this large cohort representative of the general Dutch population, low-dose ECC is not associated with a reduction in self-reported gastrointestinal symptoms compared with plain aspirin.

INTRODUCTION

Optimal antithrombotic therapy has proven to be essential in secondary prevention in cardiovascular disease. In this, aspirin has a pivotal role and is associated with a relative reduction of approximately 25% in recurrent cardiovascular events.[1] However, gastric toxicity is a well-known side effect of aspirin presenting as gastric or duodenal ulcers, bleeding and dyspepsia.[1-7] Of these, dyspepsia is most often reported (in 20-40% of chronic aspirin users)[4,7,8] and is associated with reduced aspirin compliance (9,10), increased healthcare costs[11] and reduced health-related quality of life.[12]

To reduce gastrointestinal damage, different formulations of aspirin have been developed. These formulations either delay the release of aspirin beyond the stomach (enteric-coated aspirin), facilitate the transit of aspirin across the gastric mucous layer (PL2200), or increase solubility of aspirin supposedly resulting in lower irritating concentrations on the gastric mucosa (effervescent calcium carbasalate (ECC)). The gastric toxicity of different formulations was mainly studied in high dosages and showed clear benefit over plain aspirin with respect to gastric ulcer formation when studied in healthy volunteers.[13-18] However, when investigating its clinical effect in patients on (low-dose) chronic antiplatelet therapy, no clear beneficial effect on gastrointestinal side effects was noticeable.[19-22]

In the Netherlands, a total of 1,290,000 patients use low-dose aspirin of which 41% are prescribed ECC.[23] No data have been published comparing the effects of ECC and plain aspirin on gastrointestinal symptoms. In this population-based cohort of respondents using low-dose aspirin we studied and compared the prevalence of gastrointestinal symptoms between those using ECC and plain aspirin. We also studied whether respondents using different formulations may present with different types of gastrointestinal symptoms.

METHODS

Study population

We sent 51,869 questionnaires by surface mail to a representative sample of the Dutch population in December 2008. Invited subjects were aged 18 years and above, and randomly selected from municipal databases of five different municipalities selected on their geographical location in the Netherlands, in order to gather a representative sample of the Dutch population. We included returned questionnaires until 31 March 2009. We excluded returned questionnaires with missing elements that were part of the primary outcome measure. We also excluded returned questionnaires in which all baseline characteristics were missing or when the medication was unreadable or if the used aspirin formulation was not reported. The complete cohort has been described previously.[24] The current sample size consisted of those respondents reporting the use of either low-dose plain aspirin or ECC.

The Medical Ethical Committee of the Radboud University Nijmegen assessed the research proposal of this study and concluded that it could be waived for ethical review, as questionnaires were returned and stored anonymously, and (non-)responders would not be contacted again. For this reason, we did not obtain written informed consent.

Questionnaire

The questionnaire has been used before and was specifically designed for collection of demographic information, gastrointestinal symptoms, and medication use (25,26). Participants were asked whether they suffer from gastrointestinal symptoms in general and about the presence of 26 gastrointestinal symptoms such as nausea, early satiety and bloating. Severity of gastrointestinal symptoms was assessed on a seven-point Likert scale (0 = absent, 1 = almost absent, 2 = mild, 3 = moderate, 4 = moderately severe, 5 = severe, 6 = very severe) over the preceding four weeks.[27] A symptom was considered to be present if the participants scored ≥ 2 on the Likert scale.

Outcomes

Our primary outcome was the presence of gastrointestinal symptoms, which was assessed with the question: 'Do you experience gastrointestinal complaints?' and had to be answered with either 'yes' or 'no'. Secondary outcomes were duration of the primary endpoint and the individual gastrointestinal symptoms among responders who reported the presence of gastrointestinal complaints. The primary and secondary outcomes were compared between respondents reporting the use of low-dose plain aspirin (80 mg) and those using ECC (100 mg).

Statistical analysis

Statistical analyses were performed with SPSS statistical software, version 16.0 (SPSS, Inc., Chicago, Illinois, USA). Frequency tables were provided describing respondents' baseline characteristics. Pearson's chi squared test was used to compare categorical variables. Continuous variables were compared with the Student T-test or the Mann-Whitney U method whenever appropriate. Univariate and multivariate associations for gastrointestinal endpoints in respondents using plain aspirin or ECC were analysed using logistic regression. Two-sided p-values of <0.05 were considered statistically significant. Covariates were included in the multivariate analysis if they significantly differed between respondents using ECC versus plain aspirin. In addition, those covariates associated with gastrointestinal symptoms at a level of $p<0.1$ in univariate analysis were included in multivariate analysis. Using forward selection, a covariate was allowed into the multivariate model if it influenced the model with a likelihood ratio significance level of $p<0.05$, and was removed again if its significance level exceeded $p=0.1$ during any of the following steps. The type of formulation used (ECC versus plain aspirin) was forced into the model.

With respect to the duration of symptoms and the analyses of the individual symptoms, only participants reporting the presence of the primary outcome were selected. The duration of symptoms was compared using the Mann-Whitney U method. The individual symptoms were divided into upper and lower gastrointestinal symptoms and figures were provided describing their frequencies. The sum of the individual symptoms present was categorised according to the number of symptoms present and frequencies were provided.

RESULTS

A total of 18,317 (35%) questionnaires were returned, of which 742 unopened for various reasons (Fig. 1). After applying our predetermined exclusion criteria a total of 16,715 questionnaires were included in our analyses. In total, 911 persons (5.4%) reported plain aspirin use, 633 ECC (3.8%) and 15,171 reported not using any form of aspirin (90.8%). Nearly all baseline characteristics differed between participants with and without aspirin (Online Supplementary Table 1). When comparing plain aspirin and ECC, participants using ECC were older, reported more comorbidity and were using more concomitant medication (Table 1).

The self-reported prevalence of gastrointestinal symptoms of no aspirin, plain aspirin, and ECC were 25.6%, 26.3%, and 27.5%, respectively. We observed no difference between plain aspirin and ECC for self-reported gastrointestinal symptoms (ECC: OR 1.06, 95% CI 0.84-1.33). Also after adjustment with multivariate regression

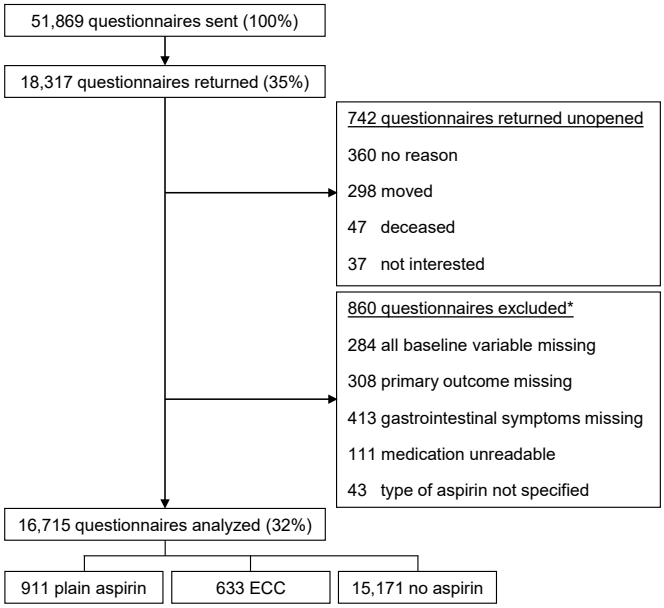


Figure 1: Flow chart
** Some respondents fulfilled more than 1 exclusion criterion*

Table 1: Baseline characteristics

	Plain aspirin	Effervescent calcium carbasalate	P-value
	N = 911	N = 633	
Mean age (±SD) (years)	59.7 (15.2)	64.7 (11.3)	<0.01
Male (%)	494 (56)	377 (61)	0.09
Smoking (%)	160 (18)	116 (19)	0.74
BMI (±SD) (kg/m^2)	26.3 (4.6)	27.0 (4.9)	<0.01
Comorbidity (%)			
Diabetes mellitus	108 (12)	106 (17)	<0.01
Rheumatoid arthritis	53 (6)	54 (9)	0.04
Asthma / COPD	62 (7)	69 (11)	<0.01
Coeliac disease	16 (2)	9 (1)	0.61
IBD	27 (3)	18 (3)	0.89
Medication use (%)			
PPI	191 (21)	188 (30)	<0.01
H2RA	24 (3)	14 (2)	0.60
Antacids	79 (9)	50 (8)	0.59
Paracetamol	474 (52)	276 (44)	<0.01
NSAIDs	274 (30)	186 (29)	0.77
Clopidogrel	17 (2)	36 (6)	<0.01
Dipyridamole	43 (5)	69 (11)	<0.01
Beta blockers	351 (39)	301 (48)	<0.01
ACE inhibitors	175 (19)	189 (30)	<0.01
Angiotensin-receptor antagonist	103 (11)	83 (13)	0.28
Calcium antagonist	128 (14)	105 (17)	0.17
Diuretics	185 (20)	155 (25)	0.051
Statins	396 (44)	373 (59)	<0.01
Systemic corticosteroids	15 (2)	11 (2)	0.89
Oral glucose lowering agents	85 (9)	70 (11)	0.27
Antidepressants	47 (5)	40 (6)	0.33
History (%)			
Peptic ulcer disease	69 (8)	76 (12)	<0.01
Peptic ulcer bleeding	26 (3)	15 (2)	0.56

SD = standard deviation, BMI = body mass index, kg/m^2 = kilogram per square meter, COPD = chronic obstructive pulmonary disease, IBD = inflammatory bowel disease, PPI = proton pump inhibitor, H2RA = H2-receptor antagonist, NSAID = non-steroid anti-inflammatory drugs, ACE = angiotensin converting enzyme.

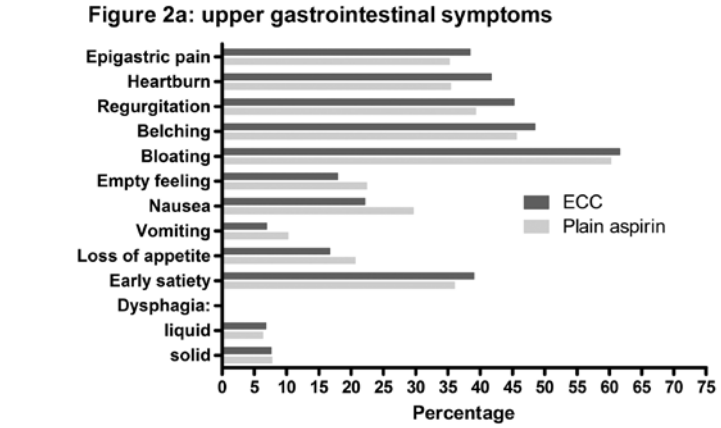
for multiple possible confounders there was no significant difference between plain aspirin and ECC for the presence of gastrointestinal symptoms (ECC: aOR 1.08, 95% CI 0.83-1.41, Table 2). Among those reporting gastrointestinal symptoms, respondents using ECC had a significantly longer history of symptoms (10 years, IQR 4-20) compared with participants using plain aspirin (7 years, IQR 3-16, p=0.04).

Table 2: Multivariate logistic regression model for reporting gastrointestinal symptoms with effervescent calcium carbasalate entered into the model

	aOR	95% CI	P-value
Age (per year increase)	0.98	0.97-0.99	<0.01
Male gender	0.71	0.55-0.92	0.01
Comorbidity			
Asthma / COPD	1.54	1.01-2.36	0.046
IBD	2.01	1.00-4.04	0.050
Medication use			
PPI	3.96	2.96-5.30	<0.01
H2RA	4.39	2.01-9.57	<0.01
Antacids	2.90	1.90-4.44	<0.01
Paracetamol	1.42	1.09-1.86	<0.01
Effervescent calcium carbasalate	**1.08**	**0.83-1.41**	**0.57**
History			
Peptic ulcer disease	2.39	1.60-3.58	<0.01

aOR = adjusted odds ratio, CI = confidence interval, COPD = chronic obstructive pulmonary disease, IBD = inflammatory bowel disease, PPI = proton pump inhibitor, H2RA = H2-receptor antagonist.

In respondents reporting the presence of gastrointestinal symptoms and using either plain aspirin or ECC the presence of no more than one individual upper gastrointestinal symptom was reported by 26.9% while five or more symptoms were reported present by 32.3%. The most frequently reported upper gastrointestinal symptoms were bloating (61%), belching (47%) and regurgitation (42%)(Fig. 2a). With respect to lower gastrointestinal symptoms, 23.0% reported no more than one symptom, while 39.0% experienced the presence of 5 or more symptoms. Flatulence (70%) and borborygmi (56%) were the most frequently reported lower gastrointestinal symptoms (Fig. 2b). No significant differences between plain aspirin and ECC were present for any of the upper or lower gastrointestinal symptoms.



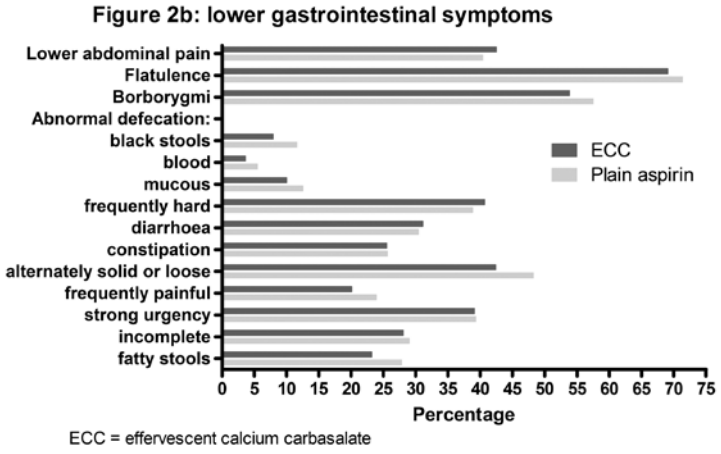


Figure 2: Type and prevalence of specific upper (a) and lower (b) gastrointestinal symptoms in patients experiencing gastrointestinal symptoms categorised by aspirin formulation

DISCUSSION

We aimed to compare the prevalence of self-reported gastrointestinal symptoms between respondents using plain aspirin and those who were prescribed ECC. We observed that in respondents using any form of low-dose aspirin the prevalence of gastrointestinal symptoms was 27%. The use of ECC is not associated with less gastrointestinal symptoms compared with plain aspirin. The most reported upper

gastrointestinal symptoms were bloating, belching, and regurgitation, whereas flatulence and borborygmi were reported most for lower gastrointestinal symptoms. No differences in the type of symptoms between users of ECC and plain aspirin were observed.

The prevalence of gastrointestinal symptoms in our study cohort is in line with previously reported data of aspirin users.[4,7,8] Interestingly, the prevalence of gastrointestinal symptoms in our non-aspirin using population is comparable with those who use aspirin. The selection of our study population could have contributed to this finding. Low-dose aspirin is generally a long-term treatment, i.e. for the remainder of the patients' life span. For our study we selected all low-dose aspirin users from a large cohort of randomly selected participants returning the questionnaire. As a result of this study design the odds that aspirin treatment was recently initiated for our participants are minimal. Those patients who suffered from gastrointestinal symptoms during (the initiation of) aspirin treatment were likely to receive co-treatment with a proton pump inhibitor, H2-receptor antagonist or antacid or were even switched to other antiplatelet agents. Consequently, our cohort may consist of a selected population of respondents in whom aspirin is relatively well tolerated. This hypothesis is supported by the more frequent use of gastroprotective agents in low-dose aspirin users compared with our non-aspirin using population (e.g. proton pump inhibitor use: 25% vs 9%). Irrespectively, our data indicate that ECC is of no beneficial value for gastrointestinal symptoms among our population of long-term aspirin users.

So far, only two studies have been conducted to investigate endoscopically proven gastric mucosal damage in users of ECC and plain aspirin. In a randomised cross-over trial, ECC significantly reduced endoscopically observed gastric erosions and ulcers compared with the bioequivalent dose of plain aspirin.[13] However, this study assessed healthy volunteers, investigated very high doses of aspirin (650 mg three times a day) and only studied the short-term effects. More recently, the effects of low-dose ECC and plain aspirin were compared in patients using long-term aspirin for cardiovascular prevention.[19] In this large retrospective cohort study, the authors concluded that the incidence rates of endoscopically proven peptic ulcers were not significantly different between the two groups.

This is the first study comparing the effects of ECC with plain aspirin for gastrointestinal symptoms. Moreover, in order to obtain a representative sample, persons were randomly selected through databases of local authorities without stringent inclusion and exclusion criteria. We do acknowledge some limitations in our study. First, due to our study design, response bias could be a potential limitation. Due to concealment we were unable to contact non-responders and compare their characteristics with responders. To minimise the effect of response bias all participants were invited with a personalised invitational letter and were asked explicitly to participate irrespective of experiencing gastrointestinal symptoms. Seventy-five percent of all respondents indeed did not report the presence of gastrointestinal symptoms. Secondly, we did not study the duration of low-dose aspirin use or the effect of gastrointestinal symptoms on aspirin compliance. Finally, we observed important differences in baseline characteristics between the two aspirin formulations, all to the detriment of those participants using ECC. This could be an indication that physicians are more likely to prescribe plain aspirin to the relatively healthy subjects and preferentially prescribe ECC to the older and more fragile patients. In order to adjust for this possible bias we performed multivariate analysis. Nonetheless, this observation suggesting confounding by indication should be noted and calls for a study with random allocation of aspirin formulation.

We observed that low-dose ECC is not associated with a reduction in gastrointestinal symptoms compared with plain aspirin. This absence of a beneficial effect of ECC over plain aspirin is in analogy to a previous study indicating that low-dose ECC is not associated with a reduction in the prevalence of gastric ulcer complications. Notably, the costs of ECC are significantly higher compared with plain aspirin (€1.55 vs. €0.79/month in the Netherlands).[28] With 530,000 ECC users in the Netherlands, these additive costs comprise nearly 5 million euro annually. In view of the lack of a beneficial clinical effect and the higher costs of ECC, we feel that plain aspirin is the first drug of choice. If gastrointestinal symptoms occur, we advise to prescribe a relatively cheap proton pump inhibitor with proven beneficial effects.[29-31] Only if this does not reduce the symptoms, might one consider ECC as an alternative to plain aspirin.

In conclusion, the prevalence of gastrointestinal symptoms among aspirin users in the Dutch community is 27% with no difference between effervescent calcium carbasalate and plain aspirin in overall prevalence and type of symptoms reported.

FUNDING

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3

Concomitant Use of Clopidogrel and Proton Pump Inhibitors: Impact on Platelet Function and Clinical Outcome – A Systematic Review –

Heart 2013;99:520-527

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SUMMARY

Background Clopidogrel as adjunct to aspirin has improved outcomes after acute coronary syndromes (ACS), but laboratory studies suggest a reduced antiplatelet effect when proton pump inhibitors (PPIs) are co-administered. Despite corroborating data from retrospective studies, new clinical data fuel the controversy on this issue.

Purpose Systematic review on the impact of the addition of PPIs to clopidogrel both on platelet function and cardiovascular outcome.

Data sources PubMed, Web-of-Science, Cochrane Database, and reference lists of related articles.

Study selection Published articles on controlled studies addressing the addition of PPIs to clopidogrel. Platelet function studies describe patients as well as healthy volunteers. Clinical studies concern patients using clopidogrel for ACS or due to stent implantation for stable coronary disease.

Data extraction Two investigators independently reviewed the identified articles for eligibility, one author extracted the data.

Data synthesis In 70% (7/10) of the laboratory studies examining healthy volunteers on clopidogrel, addition of PPIs resulted in a significant reduction in platelet inhibition. For patients this was observed in 11/18 (61%) studies. The 33 clinical studies showed significant heterogeneity in observed outcomes, with risk ratios for major adverse cardiovascular events varying from 0.64 to 4.58 in case of PPI use, which was randomly allocated in only two studies. Consequently, imbalances between prognosticators at baseline and PPI prescription bias markedly contributed to the variability in results.

Conclusions Despite indications of reduced antiplatelet activity *ex vivo* in case of PPI administration in clopidogrel users, data on the clinical consequences are controversial. With the accumulating evidence from better designed, prospective clinical studies an adverse impact of PPI use on clinical outcome in patients on clopidogrel cannot be substantiated. The present review challenges the validity of conclusions based upon quantitative analyses of predominantly non-randomized data.

INTRODUCTION

Optimal antithrombotic therapy has proven to be essential in secondary prevention after an acute coronary syndrome (ACS).[1] Aspirin is associated with a relative reduction of 25% on recurrent events.[1] Addition of clopidogrel has resulted in a further 20% reduction and the combination is therefore widely implemented.[2] In patients who use antiplatelet agents gastrointestinal complications are well-known side effects, which are reduced by proton pump inhibitors (PPIs).[3] Therefore, current guidelines advise to prescribe a PPI in high risk patients.[4]

However, the FDA and EMA published warnings for co-therapy of clopidogrel with PPIs which, initially, were primarily based on laboratory and retrospective cohort studies.[5-7] The former reported reduced *ex vivo* inhibition of platelet aggregation, indicative of a pharmacological interaction between (certain) PPIs and clopidogrel.[8-10] Retrospective studies that reported adverse clinical outcome in case of co-therapy seemed to corroborate the laboratory findings.[11,12]

From a pharmacological point of view, interference with clopidogrel metabolism seems plausible and could affect clinical efficacy. Transformation of clopidogrel into its active metabolite requires the liver's enzyme cytochrome P450 2C19 (CYP2C19).[13] PPIs also act through this enzyme, thereby reducing the enzymes' bio-availability.[14]

With regard to clopidogrel metabolism in healthy individuals, carriers of a reduced-function allele of CYP2C19 had 30% lower levels of the active clopidogrel metabolite and a 25% relative reduction in platelet inhibition *ex vivo*.[15] This suggests that CYP2C19 could affect pharmacodynamics of clopidogrel in patients as well.

A clinical effect of CYP2C19 polymorphisms has been shown among patients using clopidogrel: carriers with a loss of function CYP2C19 allele had a 53% increased risk for myocardial infarction, stroke, or cardiovascular death as compared with non-carriers.[15] Notably, these results were not adjusted for the patients' baseline cardiovascular risk profile and their demographic characteristics. In view of the above, addition of a PPI might have adverse impact on clinical outcome in patients using clopidogrel.[16]

In follow-up on the first retrospective clinical studies, several new prospective studies have been published that questioned the potentially reduced clinical efficacy of clopidogrel in case of PPI co-administration.[17,18]

Clopidogrel is most commonly prescribed in case of coronary heart disease, i.e. in the clinical setting of an acute coronary syndrome or after a percutaneous coronary intervention for stable angina. For these indications this review describes the presently available laboratory and clinical data on this controversial issue.

METHODS

The methodology and report of the present review is based on the recommendations described in the PRISMA statement.[19]

Study selection

Eligible studies were identified by searching the following electronic databases: PubMed, Web-of-Science, Cochrane Database. In these databases we combined the search terms "clopidogrel" and "proton pump inhibitors". The last search was performed on June 12th 2012. In addition we scrutinized the reference lists of the eligible articles, and the reviews, letters, or editorials on this subject.

After removing duplicates, we excluded scientific meeting abstracts. Second, articles reporting no original study data (e.g. reviews) were excluded. We only included studies written in European language. There were no restrictions with respect to publication date or with regard to the type of PPI studied. Third, studies were excluded if there was no control group that consisted of clopidogrel users without adjunctive use of a PPI. Fourth, studies without data on platelet function test results and/or cardiovascular clinical outcomes were excluded.

Platelet function studies

Patients as well as healthy volunteers were considered. Cross-over trials were accepted only for studies investigating healthy volunteers and only when a wash-out period of at least 10 days was used. In patient studies, we only included studies

when clopidogrel was administered in the setting of ACS (with or without coronary intervention) or after stent implantation for stable coronary disease. A cross-over design was not accepted given the effect of time on platelet function after ACS and/or stent implantation. We excluded studies that only reported relative reductions between groups. In case of reported relative reductions, at least in one of the groups an absolute measure of platelet function should be reported. No selection in type of platelet function test used was made.

Clinical outcome studies

Patients using clopidogrel in the setting of ACS (with or without coronary intervention) or after stent implantation for stable coronary disease were considered, studies with other indications for clopidogrel were excluded. We excluded studies that only reported relative reductions between groups. In case of reported relative reductions, at least in one of the groups absolute numbers/proportions should be available.

Endpoints

For the laboratory studies we reviewed the results of reported platelet function tests. The endpoints for the clinical studies consisted of all-cause mortality, myocardial infarction (MI) and major adverse cardiac events (MACE) as defined by the authors of the original articles, which are outlined in the online supplementary materials. We reported the outcome measures (i.e. relative risk, odds ratio, hazard ratio) as reported by the author.

Quality assessment and data collection

We assessed the methodological validity of each included study using criteria for minimization of bias. In detail, we determined the investigated populations, the possibility of exclusion bias, measurement of exposure, definition and measurement of the outcome, blinding, length of follow-up, loss to follow-up and control for confounders. In addition, for case-control studies we assessed matching and the definition of cases and controls. No scales that numerically summarized the components were used.

Two investigators (JJF and MGHvO) independently performed the study selection. One investigator (JJF) then extracted study characteristics and data from the included studies using a prespecified data collection form and assessed the study quality. These data were validated by a second author (MGHvO). In case of discrepancies, a third independent adjudicator (GEC) was asked. Reviewers were not blinded to the author, institution or journal.

Statistics

With regard to the comparison of the laboratory studies, outcome parameters cannot be pooled, given the wide variety of laboratory parameters that were used as endpoints. Therefore, we decided to review and describe the changes in platelet inhibition observed and not to perform summarized quantitative comparisons.

For the clinical trials, we assessed the risk of publication bias across studies by visually evaluating a funnel plot. Notably, there were only two randomized trials among the clinical studies and outcome data showed marked between-study heterogeneity: all-cause death I^2 83%, $p<0.001$; myocardial infarction I^2 96%, $p<0.001$; MACE I^2 83%, $p<0.001$ (RevMan version 5.0 Copenhagen, 2008). As the terms and conditions for a sound meta-analysis were not met, an approach of systematic review was adopted. Finally we performed separate analyses for certain individual PPIs for the endpoint MACE.

RESULTS

We identified a total of 838 hits with the search terms “clopidogrel” and “proton pump inhibitors”.

After adjustment for duplicates 577 unique records remained. After applying the exclusion criteria 59 records remained (figure 1). Of these records one reported data both on laboratory and clinical endpoints,[20] and one record addressed data both for healthy volunteers and for patients.[21]

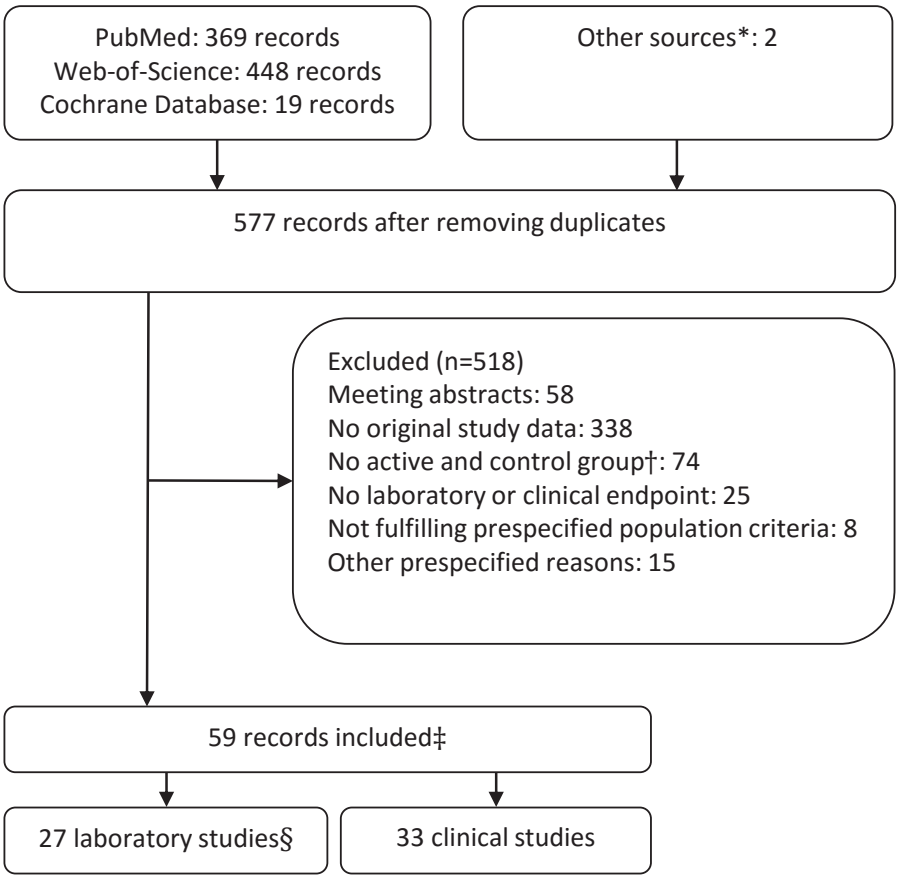

Figure 1. Flowchart of the study selection process.
*Records derived by scrutinizing the reference lists of the eligible articles, and reviews, letters, or editorials on this subject.
†Active group is defined as clopidogrel with PPI, control group is defined as clopidogrel without PPI.
‡One record reported both laboratory and clinical endpoints.
§One laboratory study reported data regarding both healthy volunteers and patients.

Laboratory studies

The study characteristics are outlined in the online supplementary materials both for studies on healthy volunteers (online supplementary table 1) and patients (online supplementary table 2). Of the studies investigating healthy volunteers, 90% (9/10) were randomized studies.[10,21-28] With regard to the 18 studies investigating patients, 61% (11/18) were of observational design.[8,29-38] Only 28% (5/18) had random allocation of a PPI.[9,21,39-41]

Clinical studies

The study characteristics are outlined in online supplementary table 3. Of the in total 33 clinical studies, in only two studies the use of a PPI was randomized.[42,43] Seven studies were prospective registries.[44-50] There were three post-hoc analyses on clinical data prospectively collected in the setting of a trial that randomized for stent treatment or for antithrombotic therapy.[20,51,52] Nineteen were retrospective cohort studies,[12,53-70] and two were case-control studies.[11,71]

Outcomes

Laboratory studies

With regard to the studies investigating healthy volunteers, the main results are summarized in table 1 (more detailed description in online supplementary table 4). In 70% (7/10) of the studies, addition of PPIs to clopidogrel resulted in a significantly reduced platelet inhibition in at least one platelet function test.[10,21,22,24,25,27,72]

The results of the 18 patient studies show that 11 (61%) reported a significantly reduced inhibition of platelet aggregation in at least one platelet function test when PPIs were co-administered.[8,9,20,30-32,34,36,37,40,73] Considering the five studies with random allocation of a PPI only two reported a significant difference (table 1 and more detailed description in online supplementary table 5).[9,40]

Table 1 Summary of the Results of the Laboratory Studies

Population	Design	Number of studies	Total subjects (analyzed)	Adverse impact of PPIs on at least one platelet function test
Healthy volunteers	Randomized controlled trial	9	473 (441)	6/9 (67%)
	Prospective study	1	21 (21)	1/1 (100%)
	Total	***10***	***494 (462)***	***7/10 (70%)***
Patients	Randomized controlled trial	5	505 (489)	2/5 (40%)
	Post-hoc analyses	2	131 (131)	2/2 (100%)
	Observational	11	4815(4815)	7/11 (64%)
	Total	***18***	***5451 (5435)***	***11/18 (61%)***

PPI, proton pump inhibitor.

Table 2 Study Outcome of Clinical Studies

Design	Trial/Author	Number of patients (analyzed)	PPIs used	Results for MI*	Results for all-cause mortality*	Results for MACE*
RCT	**COGENT, 2010**[42]	3873 (n=3761)	O	HR 0.92 (95% CI 0.44-1.90)	RR 1.00 (95% CI 0.29-3.47)	HR 0.99 (95% CI 0.68-1.44)
	Wu, 2011[43]	665	P	n.r.	RR 1.03 (95% CI 0.66-1.60)	n.r.
Prospective data collection	**Gaglia, 2010**[44]	820	P, O, L, R, E	n.r.	RR 2.63 (95% CI 1.17-5.94)	aHR 1.8 (95% CI 1.1-2.7)
	Zairis, 2010[45]	588	O	HR 1.0 (95% CI 0.5-1.9)	HR 1.1 (95%CI 0.4-2.7)§	HR 1.1 (95% CI 0.6-1.8)
	Tentzeris, 2010[46]	1210	P, O, L, R, E	PSaHR 1.27 (95% CI 0.29-5.70)†	PSaHR 0.78 (95% CI 0.34-1.76)	PSaHR 1.08 (95% CI 0.53-2.22)
	Rossini, 2011[47]	1346	P, O, L	n.r.	aOR 0.97 (95% CI 0.28-3.31)	aOR 1.54 (95% CI 0.60-4.02)
	Harjai, 2011[48]	2653	O, E, others not specified	PSaHR 1.04 (95% CI 0.64-1.69)	PSaHR 0.95 (95% CI 0.56-1.63)	PSaHR 0.89 (95% CI 0.63-1.27)
	Simon, 2011[49]	3670	P, O, L, R, E	n.r.	aHR 0.97 (95% CI 0.88-1.05)	aHR 0.99 (95% CI 0.92-1.07)
	Chitose, 2012[50]	630	n.r.	RR 0.79 (95% CI 0.083-7.54)	RR 1.90 (95% CI 0.51-6.98)§	aHR 1.10 (95% CI 0.45-2.68)
Post-hoc analysis of prospective study	**O'Donoghue, 2009**[20]	6795	P, O, L, R, E	aHR 0.98 (95% CI 0.82-1.17)	aHR 0.68 (95% CI 0.47-0.96)	aHR 0.94 (95% CI 0.80-1.11)
	Burkard, 2011[51]	826 (801)	P, O, L, E	aHR 1.88 (1.05-3.37)	RR 1.24 (95% CI 0.65-2.38)§	RR 1.45 (95% CI 1.06-2.00)
	Goodman, 2012[52]	18,601	P, O, L, R, E	PSaHR 1.12 (95% CI 0.90-1.40)	PSaHR 1.50 (95% CI 1.22-1.83)	PSaHR 1.20 (95% CI 1.04-1.38)

Design	Trial/Author	Number of patients (analyzed)	PPIs used	Results for MI*	Results for all-cause mortality*	Results for MACE*
Retrospective studies	**Ho, 2009**[12]	8205	P, O, L, R	aOR 1.86 (95% CI 1.57-2.20)‡	aOR 0.91 (95% CI 0.80-1.05)	aOR 1.25 (95% CI 1.11-1.41)
	Gupta, 2010[53]	315	O, L, R	n.r.	aOR 1.20 (95% CI 0.53-2.70)	aOR 1.95 (95% CI 1.09-3.49)
	Rassen, 2009[54]	18,565	P, O, L, R, E	PSaRR 1.22 (95% CI 0.95-1.57)	PSaRR 1.20 (95% CI 0.84-1.70)	PSaRR 1.22 (95% CI 0.99-1.51)
	Wang, 2009[55]	1751	n.r.	OR 1.62 (95% CI 1.01-2.59)	n.r.	n.r.
	Ray, 2010[56]	20,596	P, O, L, R, E	n.r.	n.r.	HR 0.99 (95% CI 0.82-1.19)
	Sarafoff, 2010[57]	3338	P, O, L, R, E	aHR 1.3 (95% CI 0.8-2.3)	aHR 2.2 (95% CI 1.1-4.3)	n.r.
	Kreutz, 2010[58]	16,690	P, O, L, R, E	aHR 1.63 (95% CI 1.40-1.90)	aHR 1.10 (95% CI 0.51-2.40)§	aHR 1.51 (95% CI 1.39-1.64)
	Stockl, 2010[59]	2066	P, O, L, R, E	aHR 1.93 (95% CI 1.05-3.54)	n.r.	aHR 1.64 (95% CI 1.16-2.32)
	Evanchan, 2010[60]	5794	P, O, L, E	aOR 1.78 (95% CI 1.55-2.07)	n.r.	n.r.
	Charlot, 2010[61]	24,702	P, O, L, R, E	aHR 1.19 (95% CI 1.05-1.35)	aHR 1.75 (95% CI 1.53-1.99)	aHR 1.29 (95% CI 1.17-1.42)
	Gaspar, 2010[62]	876	O, L, R	n.r.	aOR 1.04 (95% CI 0.49-2.18)	aOR 1.1 (95% CI 0.64-1.9)
	Ortolani, 2011[63]	3896	P, O, L, R, E	aHR 3.99 (95% CI 2.29-6.93)‡	aHR 0.69 (95% CI 0.40-1.16)	aHR 1.83 (95% CI 1.39-2.45)
	Yasu, 2010[64]	302	R	n.r.	n.r.	HR 1.28 (95% CI 0.54-3.00)
	Hudzik, 2010[65]	38	O	OR 6.67 (95% CI 0.89-50.2)	No deaths occurred	OR 2.78 (95% CI 1.05-7.32)
	Hsiao, 2011[66]	9753	P, O, L, R, E	aHR 1.12 (0.72-1.73)‡	n.r.	n.r.
	Ulhaq, 2011[67]	188 (184)	n.r.	RR 4.58 (95% CI 1.03-20.3)	No deaths occurred	RR 4.58 (95% CI 1.03-20.3)
	Aihara, 2012[68]	1887	O, L, R	aHR 0.30 (95% CI 0.08-1.11)	aHR 0.74 (95% CI 0.39-1.42)	aHR 0.64 (95% CI 0.36-1.14)
	Lin, 2012[69]	37,099	P, O, L, R, E	PSaHR 1.02 (95% CI 0.95-1.08) ‡	n.r.	n.r.
	Ching, 2012[70]	3287	P, O, L, R, E	RR 1.77 (95% CI 0.81-3.86)	PSaHR 1.79 (95% CI 1.03-3.12)	PSaHR 1.70 (95% CI 1.20-2.41)
Case-control studies	**Juurlink, 2009**[11]	2791	P, O, L, R	aOR 1.27 (95% CI 1.03-1.57)	aOR 0.82 (95% CI 0.57-1.18)	n.r.
	Valkhoff, 2011[71]	23,655	P, O, L, R, E	OR 1.62 (95% CI 1.15-2.27)	n.r.	n.r.

*Outcomes represent the risk ratio for combined use of clopidogrel and proton pump inhibitors.
†Study reported acute coronary syndrome.
‡Study reported rehospitalization for acute coronary syndrome.
§Study reported cardiovascular death.
PPI, proton pump inhibitor; P, pantoprazole; O, omeprazole; L, lansoprazole; R, rabeprazole; E, esomeprazole; OR, odds ratio; RR, relative risk; HR, hazard ratio; a, adjusted; PS, propensity score; CI, confidence interval; n.r., not reported; RCT, randomized controlled trial.

Clinical studies

With regard to the baseline characteristics, it should be appreciated that there is a higher incidence of established prognosticators for adverse short- and long-term outcome among patients using PPIs, most prominent in the retrospective studies (online supplementary table 6).

The main results of the clinical studies are presented in table 2 (summarized description in online supplementary table 7). Mortality was reported in 23 studies. In total, 17 (74%) articles reported no risk difference for patients on PPIs .[11,12,42,43,45-51,53,54,58,62,63,68] In the other 6 studies the effect ranged from a reduced risk in one study (adjusted hazard ratio 0.68, 95% confidence interval (CI) 0.47-0.96),[20] to an increased risk in five studies, with a relative risk of up to 2.63 (95% CI 1.17-5.94).[44,52,57,61,70] The endpoint MI was reported in 25 studies of which 11 (44%) reported a significantly increased risk ratio for PPI users from 1.19 up to 4.58.[11,12,51,55,58-61,63,67,71] The other 14 reported no difference in outcome.[20,42,45,46,48,50,52,54,57,65,66,68-70] Of the 25 studies reporting MACE, twelve (48%) showed a significantly increased risk when PPIs were combined with clopidogrel,[12,44,51-53,58,59,61,63,65,67,70] with an effect that ranged from hazard ratios of 1.20 to 4.58. The other 13 studies showed no impact on outcome.[20,42,45-50,54,56,62,64,68]

When examining esomeprazole/omeprazole as specific PPIs of interest, the reported effect between studies showed marked heterogeneity for the endpoint MACE as well: (es)omeprazole I^2 70%, $p<0.01$. Regarding (es)omeprazole, an increased risk was present in 2/7 (29%) studies.[44,65] The other 5 studies reported no significant risk difference.[42,45,47-49] Of the four studies reporting data for pantoprazole (no significant heterogeneity; I^2 0%, p=0.69), one study (25%) reported an increased risk,[59] while the other three studies reported no significant difference.[44,47,49]

DISCUSSION

The findings of the present review are that the majority of laboratory studies suggests that the addition of certain PPIs reduces platelet inhibition *ex vivo* in clopidogrel users. The studies on clinical outcome are often not well designed, with signs of prescription bias and apparent imbalances in baseline characteristics that mainly account for the large variability in the observed outcomes. It is only by acknowledgement of these aspects that reports suggesting harm from PPIs with relative risk increases up to 50-150% can be understood. Considering the firmly and thoroughly established relative benefit of about 20% with addition of clopidogrel to aspirin,[2] we feel that the reported magnitudes of increased risk cannot (solely) be attributed to the use of PPIs in many of these studies. Notably, nearly all prospective registries, and, most importantly, the only two trials with random allocation of a PPI reported no detrimental clinical effect of PPIs among clopidogrel users.

Indisputably, in the (predominantly) randomized trials on healthy individuals using clopidogrel monotherapy, addition of certain PPIs has proven to reduce the inhibition of platelet aggregation as measured by multiple platelet function tests. This supports a pharmacological interaction *ex vivo* under physiological conditions.

In contrast, acute coronary disease differs from physiological conditions, and patients use both aspirin and clopidogrel. Patients with stable coronary disease who underwent revascularization and stenting use dual therapy as well. Although about 60% (11/18) of laboratory studies suggest reduced platelet inhibition in case of co-therapy with a PPI, these results should be interpreted with caution. Importantly, only 5 of the 18 studies on patients had random allocation of PPIs, two of which demonstrated impaired platelet inhibition. Notably, it has been suggested that PPIs may also adversely affect the platelet response to aspirin. This may form an additional reason for the observed reduced inhibition of platelet aggregation.[74] Finally, some methodological issues characteristic for laboratory studies remain.

First, it is uncertain to what extent reproducibility contributes to the observed results, despite observed relative differences in laboratory outcome parameters of about 10 to 30%. A difference in lab results may be numerically statistically significant, but it depends on the coefficient of variation of the respective test whether there is

a true difference between values. Second, issues with regard to the pharmacology of antiplatelet therapy have not been accounted for. It should be appreciated that the timing of the laboratory assessment in relation to the intake of the antiplatelet therapy is often not systematically reported.

Although it is tempting to assume that a pharmacological interaction under physiological conditions will also be present in the setting of an acute coronary syndrome, the laboratory findings in patients are less uniform, which also holds true for the quality of the studies. The warnings issued for the combined use of certain PPIs and clopidogrel by the FDA were predominantly based upon laboratory studies showing reduced platelet inhibition, and the hypothesis that this surrogate endpoint might result in adverse outcome. Although data from retrospective studies seemed to support these recommendations, emerging evidence from prospective controlled studies fuelled the controversy on this issue.

It should be appreciated that there is uncertainty with regard to the question whether, and if so, to what extent adverse laboratory findings translate into clinical outcome. Even if the platelet function test results for patients on PPIs would be correlated with prognosis, these laboratory parameters may merely be a marker of poor outcome, and not indicate causality. In analogy, the GRAVITAS trial studied the impact of a more intense antithrombotic therapy when platelet function tests indicated inadequate reduction of platelet activity, a strategy that did not result in better clinical outcomes.[75] To date, it is uncertain which, if any, test is (most) reliable in the prediction of incident events, and how large the laboratory effect should be to result in a meaningful clinical difference.

With regard to clinical outcomes, accumulating data from recently published clinical studies fuelled the controversy on the potential adverse impact of PPIs in clopidogrel users. Cardiovascular outcomes of the different studies show marked heterogeneity (statistically significant), in our opinion precluding a reliable meta-analysis. Moreover, in only two of the 33 controlled studies the PPI was randomly allocated. Consequently, in most studies imbalances were present with regard to well-established baseline predictors of adverse outcome, which were more frequent in PPI users. For example, in the study by Ho et al. the odds ratio for all-cause mortality was 1.24 (95% CI 1.10-1.40), but after adjustment it changed to an odds ratio of

0.91 (95% CI 0.80-1.05), indicating the importance of confounders in the observed results.[12]

Another explanation for the observed differences in outcome is indication/prescription bias. According to the latest guidelines, patients on dual antiplatelet therapy (i.e. aspirin and clopidogrel) are -by definition- at an increased gastrointestinal risk and should consequently receive gastroprotective therapy in the form of PPIs.[4] Interestingly, only 30 to 40% of patients were using PPIs. This low incidence of PPI prescription could be due to a delay in guidelines applied to practice.[76] It is plausible that physicians are more likely to withhold PPIs from the relatively healthy patients, and more preferentially prescribe them to patients with more comorbidity. Post-hoc analyses of the PLATO trial corroborate with this hypothesis and stated that PPI use should be interpreted more as a marker of, than as a cause of higher cardiovascular event rates.[52]

To minimize the impact of the abovementioned factors, randomized PPI allocation is of the utmost importance. In case of controlled studies without random allocation other aspects of the study design are of importance. During our process of testing the criteria to perform meta-analysis, exploratory analyses showed that the heterogeneity was primarily caused by the retrospective studies (data not shown). Figure 2 provides insight into the distribution of point estimates of the prospective studies; there is no significant heterogeneity. If pooled estimates for the relative risk

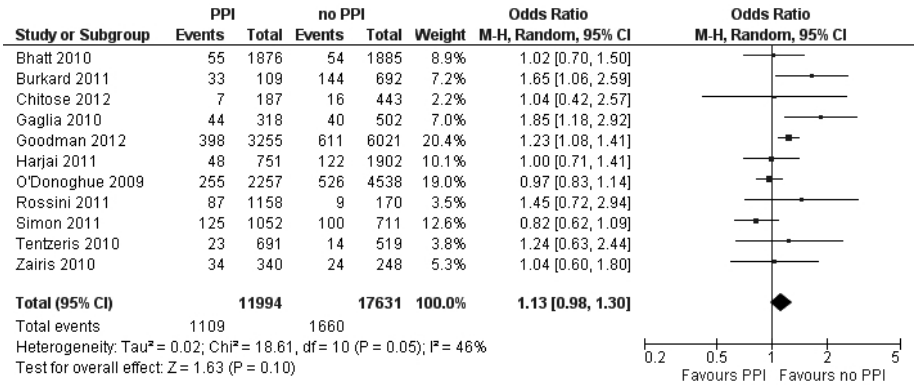

Figure 2. Forest plot of odds ratios of the prospective clinical studies of the endpoint MACE for patients using proton pump inhibitors (PPI) vs. those without concomitant PPI therapy. The squares represent risk ratios for the individual studies and the lines represent the 95% confidence intervals (CI). The pooled 95% confidence interval is visualized by a black diamond.

of PPIs were to be calculated, the prospective studies would result in an OR of 1.13 (95% CI 0.98-1.30), mutually exclusive from the 95% CI of the retrospective studies (OR 1.63, 95% CI 1.45-1.83).

The largest of the two studies with random allocation of a PPI, the COGENT trial, included 3873 patients, with a median follow-up of 106 days, and reported no significant difference in cardiovascular outcome for adjunctive use of omeprazole in clopidogrel users.[42] This result is especially interesting since omeprazole has most often been implicated with regard to warnings based upon laboratory findings and observational data on clinical outcome. Notably, if pooled estimates for (es)omeprazole and pantoprazole were to be calculated (online supplementary figure 1a and 1b, respectively), an adverse effect of PPIs on outcome would have been present only for pantoprazole (OR 1.54, 95% CI 1.13-2.09). This is one more indication that other factors are of more importance to the observed adverse clinical outcome than the observed pharmacological effect of the individual PPIs in the laboratory.

In summary, 40-50% of the studied records suggested adverse outcome in case of co-administration of PPIs for the endpoints MI and MACE, whereas for mortality this percentage was 22%. In view of the above mentioned methodological aspects, we feel that the many reports suggesting risk increases that are 'out of proportion' - i.e. more than the relative benefit of 20% that can be achieved with clopidogrel treatment [2,77,78] - should be interpreted with caution.

In view of the above, only well-designed, randomized trials powered to assess the impact on cardiac events can address the potential adverse impact of adjunctive PPI use in patients on clopidogrel. Until then, methodological flaws in laboratory studies, the fact that there is no one-to-one translation of impaired *ex vivo* platelet inhibition into adverse clinical outcome, and the marked heterogeneity observed in the clinical studies preclude a definite conclusion. Emerging evidence from the recent prospective studies strongly does not support the statement that the addition of PPIs in patients who use clopidogrel should be considered harmful. The suggestion that the potential adverse impact may not hold true for pantoprazole and should especially be considered in the event omeprazole is prescribed, is based upon pharmacological assumptions and laboratory measurements, but is contradicted by the available clinical evidence.

Limitations

As clopidogrel is predominantly prescribed in the setting of ACS or after coronary stent implantation for stable coronary disease, we defined our population accordingly. As a consequence, clopidogrel administration for other indications like stroke prevention were not included in our analyses. Notably, for these less frequent indications the lack of well-designed studies on the impact of PPIs holds true as well. With regard to the selection process of the reviewed studies, data presented in the form of an abstract only were not considered. However, the funnel plot did not indicate publication bias. It can be considered a limitation that we do not provide a summarized quantitative effect of the reported studies. As outlined before, we feel there are several arguments not to support the strategy of meta-analysis. In view of this, we addressed the question whether there are potential differences in effect between the various PPIs (pantoprazole vs. (es)omeprazole) only in the form of data review.

Conclusions and implications

In summary, there is clear *ex vivo* evidence of a pharmacological interaction between clopidogrel and PPIs in healthy individuals. In contrast, data for patients - who use both clopidogrel and aspirin - are less uniform.

As of to date, the available clinical evidence does not support the statement that PPI co-administration will adversely affect clinical outcome in patients treated with clopidogrel. These findings once again fuel the discussion with regard to the use of *ex vivo* data as a surrogate endpoint for clinical outcome. Moreover, it should be realized that summarized quantitative overviews on this subject are mainly driven by non-randomized, retrospective studies, with apparent differences in baseline characteristics and prescription bias.

These observations fuel the debate on this controversial issue and call for recommendations based upon well designed clinical trials.

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4

High platelet reactivity – the challenge of prolonged anticoagulation therapy after ACS

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SUMMARY

Despite dual antiplatelet therapy (DAPT), 1-year event rates after ACS vary from 9-12%. The development of novel oral anticoagulants (NOAC) without a need for monitoring has initiated renewed interest for prolonged adjunctive anticoagulation. Importantly, the cornerstone of treatment after ACS consists of long-term DAPT.

In that context, the NOACs have only been tested as *adjunctive* therapy. Of all new agents, only rivaroxaban –in a substantially lower dose than used for atrial fibrillation– has been demonstrated to improve outcome, albeit at the cost of bleeding. In selected cases, adjunctive therapy with dose-adjusted vitamin-K antagonists (INR 2.0-3.0) can be considered as well. These two strategies of prolonged anticoagulation can be considered in case of 'high platelet reactivity', i.e. in patients at high risk of recurrent thrombotic events despite DAPT.

Both during admission and after discharge for ACS, the use of NOACs in doses indicated for atrial fibrillation is strictly contra-indicated in patients on DAPT. In case of post-discharge anticoagulation therapy for atrial fibrillation, patients should preferably receive vitamin-K antagonists (INR 2.0-3.0), with discontinuation of one antiplatelet agent as soon as clinically justifiable.

Importantly, the impact of prolonged anticoagulation (low-dose rivaroxaban, vitamin-K antagonists) as adjunctive to DAPT after ACS has not been addressed with the most potent antiplatelet agents (prasugrel, ticagrelor) and merits further study.

Despite the potential indication of prolonged oral anticoagulation as adjunctive treatment, it remains to be established whether anticoagulation therapy could also be an *alternative* for either aspirin or thienopyridine treatment in selected ACS patients on DAPT.

INTRODUCTION

With new antiplatelet agents as adjunctive to long-term aspirin treatment, outcome after acute coronary syndromes has improved over the years.[1,2] As of to date, for the majority of patients aspirin and clopidogrel form the standard regimen, but more potent agents such as ticagrelor and prasugrel have been introduced as more efficacious alternatives for clopidogrel, especially in case of coronary interventions.[3-5]

Despite the use of long-term dual antiplatelet therapy after myocardial infarction[6,7], there is still a considerable rate of death, myocardial infarction and stroke of about 9-12% of patients at one year.[2-4] Moreover, the strategy of revascularization has changed over the years, in that the proportion of patients treated with a percutaneous coronary intervention (PCI) has increased. Stent thrombosis is an infrequent, but ominent complication, with mortality rates of up to 45%.[8-10] These findings call for further optimization of antithrombotic regimens, both during hospital admission, but also after discharge.

High platelet reactivity has been proposed as an indicator for adverse cardiac events, which could guide the choice of a more aggressive antithrombotic approach. So far, this approach cannot be substantiated by randomized evidence on clinical endpoints, and we feel that this strategy cannot be supported as regular clinical approach.[11-13]

In daily clinical practice, we are frequently faced with patients who experience recurrent thrombotic events despite dual antiplatelet therapy. In particular, this is a group of patients that merits further attention with regard to a more aggressive antithrombotic regimen.

In the formation of arterial thrombosis there is a strong interaction between the clotting cascade and circulating platelets.[14] In the acute phase of acute coronary syndromes, the impact of anticoagulation therapy has been extensively studied, and several new agents have been developed that have affected outcome.[15-21] Research with long-term treatment of anticoagulation has so far been primarily dominated by vitamin K antagonists. With the introduction of newer agents without need for monitoring, anticoagulation after discharge has become a more feasible option.

Given the need for more refined antithrombotic strategies in patients with thrombotic events despite dual antiplatelet therapy, we will shortly summarize the pathophysiology of clot formation and the clinical evidence of (long-term) anticoagulation therapy. In the context of the available data, we will address both the risks and benefits of potential treatment options that can be considered in patients in whom dual antiplatelet therapy has been proven clinically ineffective.

PATHOPHYSIOLOGICAL RATIONALE

The vast majority of acute coronary syndromes are caused by (sub) acute thrombosis in a coronary artery, resulting in a subtotal (non ST elevation acute coronary syndrome) or total (ST elevation acute coronary syndrome) occlusion. The precipitating pathophysiological event is often rupture of a plaque, with exposure of subendothelial matrix. In response, platelets adhere to the damaged vessel wall (adhesion) and secrete chemoattractive substances, involved in the process of platelet aggregation and the stimulation of the coagulation cascade.

Three key players in the process of coagulation are the tissue factor-factor VIIa complex, factor Xa and factor IIa (Figure 1). Thrombin (factor IIa) promotes the formation of a fibrin rich blood clot, but it is also a potent activator of platelet aggregation.[22] This demonstrates that coagulation and platelet aggregation are interrelated processes in the formation of a (sub)total occlusion.

Angiographic studies have confirmed this hypothesis, suggesting that anticoagulation therapy affects the risk of (re)occlusion on both the short- and the long-term.[23-26]

Therefore, several studies have been conducted based upon the rationale that anticoagulants such as (in)direct thrombin inhibitors, or Xa inhibitors could improve clinical outcome in acute coronary syndromes (ACS).

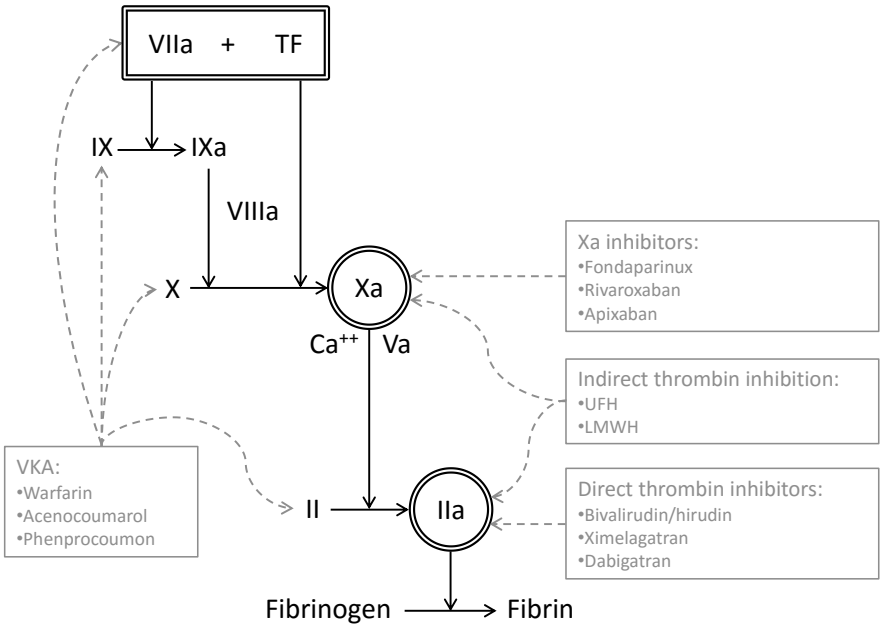

Figure 1: The coagulation cascade and the pharmacological interventions.
In response to plaque rupture or erosion, tissue factor (TF), forms a complex with coagulation factor VIIa. This complex initiates the formation of factor Xa.
Factor Xa is part of the prothrombinase-complex (Xa-Va-Ca^{++} complex), converting prothrombin (II) into thrombin (IIa). Thrombin on its turn converts fibrinogen into fibrin, the endproduct in the coagulation cascade.
The dotted arrows represent pharmacological interventions. Vitamin-K antagonists (VKA) inhibit the formation of factors II, VII, IX and X. Factor Xa can be inhibited directly (rivaroxaban, apixaban) or by potentiating the natural inhibitor antithrombin III (UFH, LMWH, fondaparinux). Factor IIa can also be inhibited directly (bivalirudin/hirudin, ximelagatran, dabigatran) or indirectly (UFH, LMWH).
UFH, unfractionated heparin; LMWH, low-molecular weight heparin.

ANTICOAGULATION THERAPY IN ACS : CLINICAL EVIDENCE

Indirect thrombin inhibition. The first randomized studies on the impact of anticoagulation therapy demonstrated that unfractionated heparin resulted in a ~ 30% risk reduction in myocardial infarction in patients treated with aspirin for unstable angina.[15] Subsequently, low molecular weight heparins (LWMH) were developed, which seem slightly more efficacious than unfractionated heparin (UFH).[16] They have a better bioavailability and more predictable effect, which obviates the need for monitoring.

For patients with ST elevation myocardial infarction (STEMI) treated with fibrinolysis similar observations hold true,[17] and it is suggested that reocclusion rates are lower with the use of LMWH.[27] The ease of longer administration (subcutaneous) and its more stable effect may both account for these observations.

After primary PCI the evidence for the routine use of heparin after the procedure is not very well established. It is often stated that thrombin inhibition can be discontinued after the procedure, with a few exceptions.[28] Still, routine periprocedural use of fondaparinux seemed less efficacious than unfractionated heparin in the setting of primary PCI, indirect evidence that routine anti-thrombin therapy seems indicated. [19]

Direct thrombin inhibition. Whereas UFH and LMWH both act on factors IIa and Xa, direct thrombin inhibitors only act on factor IIa, and are also able to inhibit clot-bound thrombin.[22] In patients with non ST elevation ACS, bivalirudin results in lower bleeding complications when compared to heparin alone, or the combination of UFH/LMWH with glycoprotein IIb/IIIa receptor blockers. This was observed without significant difference in efficacy. However, in the subgroup of patients without pretreatment with a thienopyridine bivalirudin seemed less efficacious, indirect evidence that this new drug may have a less intense antithrombotic effect.[20]

In patients treated with fibrinolytic therapy, bivalirudin resulted in a significant reduction in the combined endpoint of mortality and reinfarction at 30-days when compared to UFH.[29] For patients undergoing primary PCI again bleeding complications were markedly lower with the use of direct thrombin inhibition, mortality was lower and the composite of ischemic events was similar to the control arm of indirect thrombin inhibition with/without use of a GPIIb/IIIa receptor blocker.[21]

Xa-inhibition. Based on the hypothesis that interference in the earlier stages of coagulation, i.e. “higher in the coagulation cascade” (Figure 1), would require less potent drugs with potentially less bleeding complications factor Xa inhibitors have been developed. Fondaparinux is a synthetic pentasaccharide that selectively binds antithrombin and inhibits factor Xa.

In non ST elevation ACS it has improved 30-day outcome compared to enoxaparin, and the achieved clinical benefit was primarily realized through a reduction in

mortality. Notably, at hospital discharge (i.e. at the end of treatment), there was no difference in efficacy between fondaparinux and enoxaparin. The reduction in 30-day mortality was associated with a lower bleeding rate on fondaparinux as compared to enoxaparin.[18] These observations demonstrate that the choice of in-hospital anticoagulation, can affect outcome after discharge.

The fact that guiding cathether thrombosis was more often observed with this agent indirectly underscores its modest antithrombotic efficacy,[18,19] and shows that despite of this reduced antithrombotic potency outcome improved. Based on these cathlab observations, intravenous administration of an indirect or direct thrombin inhibitor is the preferred agent of choice in case of early PCI for non STEMI, and for similar reasons, Xa-inhibitors should not be given as anticoagulant shortly before/during primary PCI.

As adjunctive agent to fibrinolysis, the efficacy and safety of fondaparinux has unequivocally been demonstrated with use of streptokinase. In case of fibrin-specific agents, which require adjunctive thrombin inhibition, no randomized controlled evidence is available with Xa-inhibitors.

Oral Xa inhibitors have been the topic of interest for many years, providing the opportunity of a feasible form of extended anticoagulantion after discharge. Ximelagatran was the first drug that showed the potential of such a strategy, but due to an unacceptable incidence of liver toxicity this drug has not undergone further development. Notably, in this study patients used aspirin monotherapy (30). Recently, new oral Xa-inhibitors have been developed, and tested successfully in the field of atrial fibrillation: rivaroxaban and apixaban.[31,32]

Of these agents, rivaroxaban is the only agent that has also been proven efficacious in ACS in a phase III trial.[33,34] In contrast to the study with ximelagatran, the vast majority of patients was on dual antiplatelet therapy in the trials with the new agents.[33-35] It should be appreciated that the dose administered was markedly lower than the dose tested in atrial fibrillation (5 or 10 mg per day vs. 20 mg per day) and that the risk of bleeding was markedly increased.[33] Yet, these data show again that new adjunctive anticoagulation therapies have been developed that are efficacious in ACS (table 1).

Vitamin K antagonists. In contrast to all abovementioned agents which exert their action through inhibition of activated coagul ation factors, the oral vitamin K antagonists interfere with the production of factors II, VII, IX and X. For optimal efficacy in patients with a prothrombotic state (pulmonary embolism, venous thrombosis, ACS), vitamin K antagonists should be initiated in combination with another form of anticoagulation therapy to counteract the potential procoagulant effect early after initiation. The adjunctive form of anticoagulation can be discontinued when two subsequent INRs are in the target range.[22]

Importantly, vitamin K antagonists have been proven to be efficacious in ACS as monotherapy, with outcomes similar to those achieved on patients managed with aspirin. Most of the clinical experience and randomized trials on the impact of prolonged anticoagulation therapy after discharge as adjunct to aspirin is with vitamin K antagonists. There are robust data to demonstrate that the long-term combination of anticoagulation therapy and antiplatelet therapy results in better clinical outcome than aspirin alone, be it at the cost of more bleeding (table 1).[22,36] This especially holds true for patients after non ST ACS and STEMI patients not undergoing primary PCI.

Now that primary PCI has become the preferred reperfusion strategy, and management of non ST ACS has become more aggressively, dual platelet therapy has become the standard. Notably, even in the more modern era of revascularization with stenting, a strategy of aspirin and oral anticoagulation has been proven more efficacious than aspirin alone.[37] Yet, only indirect comparisons between aspirin and clopidogrel versus aspirin and vitamin K antagonists are available (38). Treatment with vitamin K antagonists is cumbersome, and the effect of therapy largely depends on an infrastructure to guarantee dose-adjusted, frequently monitored and individually tailored therapy. It should be appreciated that during the first 8 weeks after initiation of anticoagulation therapy, patients are less often in the therapeutic range than during long-term follow-up.[39] Moreover, intervention studies with aspirin and ticlopidine showed better outcome than an antithrombotic regimen of aspirin with long-term anticoagulation therapy.[40]

Table 1: Efficacious strategies of prolonged OAC treatment after ACS

Source	Patients at risk	Treatment	Control	Efficacy endpoint*		Safety endpoint**		NNT	NNH
				Treatment	Control	Treatment	Control		
Andreotti (36)	7836	VKA (INR 2-3) + ASA	ASA	9.4%	12.3%	2.6%	1.1%	33[†]	100[†]
ATLAS-ACS-2 (34)	15,526	Riva 2.5 bid + DAPT	DAPT	9.1%	10.7%	1.8%	0.6%	62	83
		Riva 5.0 bid + DAPT	DAPT	8.8%	10.7%	2.4%	0.6%	53	56

*Death, non-fatal myocardial infarction and/or stroke.
**Major bleeding.
[†]Numbers needed to treat and to harm were calculated based upon the duration of follow-up of the different studies.
ACS, acute coronary syndrome; ASA, acetylsalicylic acid; bid, bis in die (twice daily); DAPT, dual antiplatelet therapy; INR, international normalized ratio; NNT, number needed to treat; NNH, number needed to harm; OAC, oral anticoagulation; riva, rivaroxaban; VKA, vitamin K antagonist.

These aspects have largely contributed to the preference of dual antiplatelet therapy after ACS. Despite the proven efficacy, it should be appreciated that bleeding on dual antiplatelet therapy has also been related to mortality.[41]

ANTICOAGULATION THERAPY AND BLEEDING: THE FLIP SIDE

With the appreciation that bleeding is related to short- and long-term mortality (18,41), intensifying antithrombotic therapy may not necessarily result in better clinical outcome.

Even more complicating, the clinical factors that predict ischemic events are also associated with an increased risk of bleeding.[42,43] Therefore, the choice of adjunctive anticoagulation therapy to improve the net clinical benefit in patients with events while on dual antiplatelet therapy forms a clinical challenge.

Both patient factors (age, sex, prior history of bleeding, renal function etc),[44] concomitant medication and the choice of reperfusion strategy affect the options for adjunctive anticoagulation.

Renal function. In patients with poor creatinin clearance UFH is the drug of choice. Although labour-intensive, unfractionated heparin has the advantage that it can be discontinued and that protamine can be administered to counteract its effects. Fondaparinux has been tested in patients with a creatinin of up to 265 µmol and is a rather safe alternative, but no antidote exists.[6,7]

Concomitant medication. When glycoprotein IIb/IIIa blockers are administered, UFH dosing should be adjusted to reduce bleeding complications. In case of fibrinolysis, enoxaparin should be reduced to once daily dosing in case of a clearance < 30 ml/min.[6,7] Dosing of the newer agents like fondaparinux and bivalirudin is irrespective of patient characteristics and concomitant medication, which is likely to result in less administration errors. In case of non ST ACS or STEMI without reperfusion therapy, anticoagulation with fondaparinux is an attractive option given its excellent safety, and the reduced mortality compared to enoxaparin demonstrated in OASIS-5.[18,19]

Bivalirudin resulted in similar ischemic events but lower bleeding rates in non ST ACS when compared to indirect thrombin inhibition (ACUITY).[20]

Reperfusion therapy. In patients treated with fibrinolysis for STEMI, bivalirudin reduces ischemic events, but increases bleeding as compared to UFH.[29] Yet, in the setting of primary PCI bivalirudin is associated with lower bleeding rates and similar ischemic events as compared to UFH/LMWH with/without the use of glycoprotein IIb/IIIa receptor blockers.[21] Fondaparinux can be used with non-fibrin specific fibrinolysis, but is not recommended as pretreatment in the setting of a primary PCI.

These are only a series of examples of clinical decision making that affect efficacy and safety of the chosen antithrombotic regimen. As to the mechanism how bleeding results in worse outcome, various explanations have been proposed, varying from discontinuation of antithrombotic medication and subsequent events to the adverse impact of administration of blood transfusions and the statement that bleeding is merely a marker of a vulnerable patient.[44]

OPTIONS FOR PROLONGED ORAL ANTICOAGULATION THERAPY IN ACS

With the appreciation of the robust data on long-term adjunctive oral anticoagulation in patients using aspirin, and the recent ATLAS-2 trial,[34,36] it is clear that the mechanism behind recurrent events after discharge is not merely a process of platelet activity (table 1). This is underscored by the fact that coagulation activity is increased up to 6 months after the index event, which is correlated with the risk of recurrent events.[22]

Despite these correlations, evidence for causality is not present: there is no randomized evidence that a strategy of intensified antithrombotic therapy in patients with high platelet/coagulation activity improves outcome.[11,13,45] As of to date, selection of patients at high risk for recurrent events in whom antithrombotic should be optimized should primarily be based on clinical risk models.[46] Irrespective of these models, few clinicians will disagree that patients who experience a thrombotic event

despite dual antiplatelet therapy form a group of patients in whom antithrombotic therapy should be optimized .

During admission for ACS, recurrent events tend to cluster after cessation of anticoagulation therapy, often referred to as 'rebound phenomenon'.[47] In addition, about half of recurrent events occurs after discharge, despite (dual) antiplatelet therapy.[25]

Prolonged anticoagulation with vitamin K antagonists. Despite the disadvantages with regard to the rather complicated logistics to achieve dose-adjusted, frequently monitored, individually tailored anticoagulation, the risk-benefit ratio of this strategy merits appreciation. At the cost of 1 major bleeding, 3 myocardial infarctions can be prevented in patients on aspirin monotherapy (table 1).[36] These data compare fairly well with adjunctive therapy with clopidogrel in aspirin users, although direct comparisons are lacking.[48] Importantly, randomized trials on the impact of triple therapy (aspirin, clopidogrel, vitamin K antagonist) are lacking as well.

Yet, the observed risk-benefit ratio suggests that there might be room for improvement in case a thienopyridine is added to aspirin and a vitamin K antagonist, provided that dose-adjusted (INR 2.0-3.0) adjunctive treatment with vitamin K antagonists is optimally organized and monitored. Whether triple therapy confers a benefit in patients without an established indication for oral anticoagulation therapy, has never been addressed in a trial. Safety data on triple therapy after PCI and stenting in patients with an established indication for oral anticoagulation therapy suggests that the bleeding risk with this approach is considerably increased.[49]

Prolonged anticoagulation with NOACs. Various new agents have been tested in phase II trials (table 2).[30,35,50-52] Despite the successful data in atrial fibrillation studies, no phase III trials in ACS were initiated with oral thrombin inhibitors (dabigatran, ximelagatran). Of all NOACs, rivaroxaban is the only agent that has been proven effective in a phase III trial.[34] Importantly, in this study almost all patients (93%) used dual antiplatelet therapy, and the risk-benefit ratio of this strategy should be interpreted in this context. Dosing of the oral Xa-inhibitor seems crucial, and it should be realized that the doses used for atrial fibrillation are associated with unacceptable bleeding rates and a lack of efficacy in the setting of ACS.[33,50,51] In the case of rivaroxaban, 2.5

mg twice daily seems the strategy with the best trade off (table 1), which has recently been confirmed in the subgroup of STEMI patients on dual antiplatelet therapy.[53] In contrast to the evidence with oral vitamin K antagonists, the data on rivaroxaban reflects only one trial, with little information on how patients were managed with regard to revascularizations (PCI, CABG), bleeding and peri-operative care for non-cardiac indications.

Optimizing antiplatelet therapy. For both strategies of adjunctive oral anticoagulation it should be stressed that the available data reflect patients on aspirin monotherapy or dual antiplatelet therapy with clopidogrel. Information with the more potent agents such as prasugrel and ticagrelor is not available. We are of the opinion that in patients presenting with ACS while on dual therapy with aspirin and clopidogrel, optimization of antiplatelet therapy (prasugrel, ticagrelor) forms the cornerstone of treatment, especially if a coronary intervention is performed (3-5). Prasugrel deserves attention with regard to the risk of ICH and should be avoided in patients with a prior CVA and those > 75 years and < 60 kg.[7] If the clinician decides to treat a STEMI patient with fibrinolysis we strongly advise against addition of these new antiplatelet agents during fibrinolysis.

How to initiate oral anticoagulation therapy (figure 2). In patients with a high thrombotic risk on DAPT, without an established indication for oral anticoagulation therapy, vitamin K antagonists can be considered as adjunctive therapy. When vitamin K antagonists are initiated in a prothrombotic milieu (pulmonary embolism, deep venous thrombosis, myocardial infarction) concomitant anticoagulation is initially required[22] to counteract the potential procoagulant effect of vitamin K antagonists after the first few doses. This procoagulant effect can be minimized with use of a less aggressive dosing scheme. For example, in case of coumadin, initation of oral anticoagulation with a 3-day schedule of 4-4-2 mg (or 4-2-2) is to be preferred over 6-4-2 mg.

Given the fact that nowadays most patients are on dual antiplatelet therapy, extra attention is required with regard to the prevention of bleeding complications. Traditionally, UFH infusion or LWMH twice daily in therapeutic dose are the agents of choice. However, fondaparinux seems a very interesting alternative, not only given

the lower bleeding rate and superior efficacy as compared to these agents.[18,19] In contrast to most other anticoagulants, prolonged administration has been extensively studied (8 days/up to discharge). In addition, its dosing is irrespective of patient characteristics, and administration is only once daily.

Another strategy to reduce bleeding complications could be a dose-adjusted strategy of enoxaparin until the target INR has been reached twice. For example, patients with a creatinin clearance < 30 mL/min could be treated with once daily doses (1 mg/kg) and patients > 75 years with twice daily a reduced dose (0.75 mg/kg). It should be noted that this strategy is not evidence based, and has only been tested in case of fibrinolysis.[7]

However, in lack of sufficient studies addressing the issue of dual antiplatelet therapy with adjunctive anticoagulation, choices can only be made to the best of the phycian's knowledge. Prevention of bleeding and improving efficacy will more and more become a matter of individualized antithrombotic therapy, using adjusted doses or dosing intervals, based upon characteristics of the particular patient and without firm evidence from clinical trials.

With regard to the initiation of rivaroxaban, little information is available as to the initiation in the early phase after ACS. It seems rational to start these agents about 3-4 days after admission, at the time that the anticoagulants that were initiated in the acute phase have been discontinued. In ATLAS-2 rivaroxaban was started at a median of 4.7 days after the index event.[34]

Atrial fibrillation and ACS. The most challenging group of patients is formed by those with a strict indication for oral anticoagulation therapy. Although the introduction of new oral anticoagulants seems a major step forward in the treatment of atrial fibrillation, these agents are insufficiently tested in the acute setting of ACS, or in case of urgent or primary PCI. Moreover, data on how to manage patients in the setting of an elective PCI are scarce as well. We therefore recommend that in patients with atrial fibrillation who develop ACS these new agents are discontinued during hospital admission. As mentioned before, the doses used in the prevention of systemic embolism are high, and have been proven unsafe in combination with dual antiplatelet therapy for ACS.[33,35,50,51]

Importantly, the anticoagulant regimens used for ACS (UFH, LWMH, fondaparinux) are also effective in the treatment of deep venous thrombosis. Therefore, vitamin K antagonists and the new oral anticoagulants can be safely discontinued when patients are admitted for ACS.

With regard to the most safe strategy to recontinue oral anticoagulation while on dual antiplatelet therapy, fondaparinux followed by a vitamin K antagonist seems the preffered strategy. As stated, post-discharge dual antiplatelet therapy in combination with new oral anticoagulants in a dose to prevent systemic embolism should be avoided at any time. The impact of dual antiplatelet therapy with low dose rivaroxaban as antithrombotic strategy to prevent systemic embolism in patients with atrial fibrillation is uncertain.

Triple therapy after ACS (aspirin, thienopyridine, vitamin K antagonist) is associated with considerable bleeding rates, but the evidence is limited to observational data.[54-56] The first randomized trial on the adjunctive use of vitamin K antagonists in patients with dual antiplatelet therapy showed a markedly increased bleeding risk when compared to patients on vitamin K antagonists and clopidogrel.[49] Importantly, this trial was not powered for efficacy endpoints, and included only a minority of patients with ACS.[57] All patients had an established indication for oral anticoagulation.

Given the increased risk of bleeding on triple therapy, the guidelines recommend to discontinue aspirin as soon as possible, dependent on the type of stent placed after intervention.[58] If, for specific reasons, a novel oral anticoagulant for the prevention of systemic embolism is the agent of choice, this should not be combined with dual antiplatelet therapy, given the unacceptable bleeding risks demonstrated in the various phase II trials (table 2). It should be appreciated that little information is available with regard to the efficacy and safety of combined treatment with a NOAC and a single antiplatelet agent after ACS. In patients with atrial fibrillation, we therefore recommend prolonged anticoagulation with vitamin K antagonists in the first year after ACS. Then, based upon the patients clinical condition and the evidence available at that time, a renewed evaluation can be made.

Table 2: Clinical trials on prolonged treatment with novel oral anticoagulants after an ACS.

	Drug/Trial*	Year	N	Antiplatelet therapy	Intended treatment duration	Investigated dose	Major bleeding		Efficacy		Definition
							Placebo	NOAC	Placebo	NOAC	
Phase 2	**Ximelagatran** *ESTEEM (30)*	2003	1883	ASA	6 months	24 mg bid	0.9%	2.0%	16.0%	11.7%	All-cause death MI Rec ischemia
						36 mg bid		0.7%		13.5%	
						48 mg bid		3.2%		11.6%	
						60 mg bid		1.5%		12.7%	
	Apixaban *APPRAISE (50)*	2009	1715	DAPT	6 months	2.5 mg bid	0.8%	1.6%	8.7%	7.6%	CV death MI Stroke Severe rec ischemia
						10 mg qd		1.9%		6.0%	
						10 mg bid**	0.0%	2.9%	4.3%	2.8%	
						20 mg qd**		4.1%		3.2%	
	Rivaroxaban *ATLAS-ACS TIMI 46 (51)*	2009	761	ASA	6 months	5 mg/day	0.0%	0.0%	13.4%	7.8%	Death MI Stroke Severe rec ischemia (requiring revasc)
						10 mg/day		2.2%		8.2%	
						20 mg/day		0.0%		5.7%	
			2730	DAPT	6 months	5 mg/day	0.1%	0.7%	5.0%	5.8%	
						10 mg/day		1.5%		3.8%	
						15 mg/day		1.8%		6.2%	
						20 mg/day		1.8%		5.3%	
	Dabigatran *REDEEM (35)*	2011	1861	DAPT	6 months	50 mg bid	0.5%	0.8%	3.8%	4.6%	CV death MI Non-hemorrhagic stroke
						75 mg bid		0.3%		4.9%	
						110 mg bid		2.0%		3.0%	
						150 mg bid		1.2%		3.5%	
	Darexaban *RUBY-1 (52)*	2011	1279	DAPT	6 months	10 mg/day	0.3%	0.6%	4.4%	3.8%	Death MI Stroke Severe rec ischemia
						30 mg/day		1.6%		6.3%	
						60 mg/day		1.0%		6.9%	

	Drug/Trial*	Year	N	Antiplatelet therapy	Intended treatment duration	Investigated dose	Major bleeding		Efficacy		Definition
							Placebo	NOAC	Placebo	NOAC	
Phase 3	**Apixaban** *APPRAISE-2 (33)*	2011	7392	DAPT	Average 1.25 yrs	5 mg bid	1.1%	2.7%	7.9%	7.5%	CV death MI Ischemic stroke
	Rivaroxaban *ATLAS-ACS-2 TIMI 51 (35)*	2012	15,526	DAPT	31 months	2.5 mg bid	0.6%	1.8%	10.7%	9.1%	CV death MI Stroke
						5 mg bid		2.4%		8.8%	

*We performed a PubMed search using the search terms: "Acute Coronary Syndrome/Drug Therapy"; "Myocardial Infarction/Drug Therapy"; "Ximelagatran"; "Dabigatran"; "Rivaroxaban"; "Apixaban"; "Darexaban"; "Factor Xa"; "Factor IIa"; and used the filter "Clinical Trial". We identified 34 articles of which the abovementioned studies were the only trials comparing a novel oral anticoagulant with placebo in the setting of prolonged secondary prevention after ACS/myocardial infarction.
**Treatment arms of apixaban 10mg bid and 20mg qd were added during the trial and were discontinued prematurely due to excessive bleeding.
N, number of patients; APT, antiplatelet therapy; noac, novel oral anticoagulant; ACS, acute coronary syndrome; ASA, acetylsalicylic acid; DAPT, dual antiplatelet therapy; ISTH, international society on thrombosis and haemostasis; TIMI, thrombolysis in myocardial infarction; CV, cardiovascular; MI, myocardial infarction; yrs, years; qd, quaque die (once daily); bid, bis in die (twice daily); rec, recurrent; revasc, revascularization.

CONCLUSIONS AND IMPLICATIONS

The collective data on prolonged adjunctive anticoagulation suggests that interference with the coagulation system can improve outcome after ACS. The development of new oral anticoagulants without a need for monitoring has initiated a renewed interest for this strategy. Importantly, the cornerstone of antithrombotic treatment after ACS consists of optimal long-term dual antiplatelet therapy.

As of to date, the new oral anticoagulants have only been tested as *adjunctive* therapy. Of all the new agents, only rivaroxaban – in a substantially lower dose than used for atrial fibrillation – has been proven to improve outcome after ACS, albeit with an increased risk of bleeding. In selected cases, adjunctive therapy with dose-adjusted vitamin K antagonists can be considered as well. These two strategies of prolonged anticoagulation can be considered in patients with 'high platelet reactivity', i.e. patients at high risk of recurrent thrombotic events despite dual antiplatelet therapy (figure 2).

During admission for ACS, the higher doses of novel oral anticoagulants as indicated for atrial fibrillation should be avoided, given the unacceptably high bleeding rates. After discharge, patients on DAPT with atrial fibrillation should receive vitamin K antagonists (INR 2.0-3.0). After careful evaluation of the expected risks and benefits, one of the two antiplatelet agents should be discontinued as soon as clinically justifiable. Whereas monitoring and dose-adjustment have previously been considered drawbacks of oral vitamin K antagonist therapy to treat large groups of patients, it may be of value in selected patients who need careful monitoring of the risks and benefits of a rather aggressive antithrombotic regimen. Moreover, an antidote is available and clinical experience has been obtained in many thousands of patients, also in case of CABG, PCI and peri-procedural management of non-cardiac surgery and intervention.

In case of post-discharge use of a novel oral anticoagulant for atrial fibrillation, dual antiplatelet therapy is strictly contra-indicated in patients after ACS.

Notably, the accumulating evidence suggesting a role for prolonged adjunctive anticoagulation after ACS (low dose rivaroxaban, vitamin K antagonists) should be interpreted in the context that this strategy has not been addressed with the most potent antiplatelet agents (prasugrel, ticagrelor) and merits further study.

Despite the potential indication of prolonged oral anticoagulation as adjunctive treatment, it remains to be established whether anticoagulation therapy could serve as an *alternative* for either aspirin or thienopyridine treatment in selected cases and how the risk-benefit ratio of this regimen compares to dual antiplatelet therapy or triple therapy.

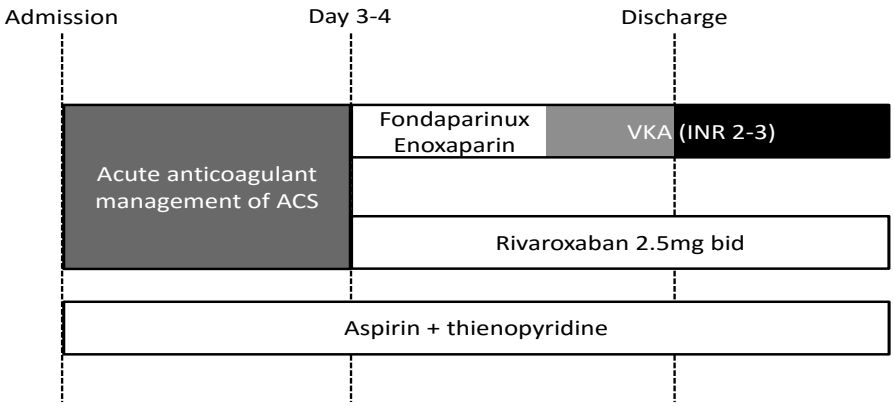

Figure 2: Potential options for prolonged adjunctive OAC
The initial antithrombotic management after admission for acute coronary syndromes depends on many factors, such as patient characteristics, concomitant medication and the choice of the revascularization/reperfusion strategy.
The cornerstone of antithrombotic treatment after ACS consists of long-term optimal dual antiplatelet therapy. In patients with a high thrombotic risk, or "high platelet activity", prolonged anticoagulation therapy can be considered. As initial strategy for anticoagulation unfractionated heparin, bivalirudin, enoxaparin or fondaparinux can be started.
Following the acute phase, potential options for prolonged OAC are vitamin K antagonists (VKA) and low dose rivaroxaban. Both bivalirudin and unfractionated heparin are less attractive agents for long-term in-hospital treatment. Given the potential procoagulant effect of VKAs when initiated in patients in a prothrombotic state, concomitant anticoagulation therapy (see figure) should be given until two subsequent INRs are within therapeutic range (22). No overlapping treatment is required for rivaroxaban (34).
Note that the dose of rivaroxaban is considerably lower (5 mg per day) than for the indication atrial fibrillation (15-20 mg per day). New oral anticoagulants with a dosing scheme as in atrial fibrillation should not be combined with dual antiplatelet therapy.
If VKAs are chosen, the expected benefit should be carefully weighed against the potential risk. In this context, dual antiplatelet therapy with a reduced target INR (2.0-2.5) can be considered, as alternative to a target INR of 2-3 (59).
ACS, acute coronary syndrome; bid, bis in die (twice daily); INR, international normalized ratio; OAC, oral anticoagulation; VKA, vitamin K antagonist.

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Part 2

Atrial fibrillation:
risks and benefits of oral antithrombotic therapy

5

Novel antithrombotic challenges: head, heart and guts

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Dear Sir,

We read with interest the article on the increased risk of gastrointestinal bleeding (GIB), associated with the use of the novel oral anticoagulants (NOAC).[1] We compliment the authors on their efforts to provide an up-to-date review on a very important issue. Despite the mortality rate (about 10%) associated with GIB, we sympathize with the authors' call for a better documentation of this safety endpoint: for the present analysis, only in 19 of 43 trials data on GIB were available.

Notably, the authors describe that non-major clinically relevant GIB was often not reported, and that, therefore, their observed increased risk for bleeding may even have been underestimated. Given the potential consequences for the perception of these new drugs in daily clinical practice, we call for a more cautious interpretation of the reported risk as outlined in this systematic review.

The inclusion of data from trials on acute coronary syndromes, reporting evidently increased bleeding rates, is questionable. As an adjunct to dual antiplatelet therapy, NOACs have been tested, but the doses represented in the present meta-analysis are not endorsed for use in daily clinical practice.[2] The only trial with data of an approved dose was not included in the meta-analysis as GIB was not reported in this study.[3] With regard to data from trials on atrial fibrillation, a substantial amount of available data on dabigatran is not incorporated in the analysis. Based upon data from RELY,[4] an 18,113 patients' randomized controlled trial (dabigatran 150 bid/dabigatran 110 bid/warfarin), dabigatran 110 mg has been approved in Europe, but not in the United States.[5] In analogy to apixaban, this lower dose of dabigatran did not result in an increased rate of GI bleeds: 1.12 %/year versus 1.02 %/year on warfarin (RR 1.10 95%CI 0.86-1.41).

Thus, not reporting data of an approved dose in Europe of a drug without an increased risk of GIB, and incorporating data for acute coronary syndromes on high doses that are not approved are two major points of concern.

We concur with the authors that it is important to assess numbers needed to harm, but we are more supportive of a careful evaluation of both the risk and the benefit, especially in the case of atrial fibrillation. Of note, with regard to efficacy, all NOACs for atrial fibrillation have proven to be non-inferior to vitamin K antagonists

for stroke prevention.[6] With regard to bleeding, all agents have similar or significantly lower overall bleeding rates.

An appealing advantage is that intracranial bleeding is significantly reduced by all the new drugs.[6] For example, when comparing dabigatran 150 mg bid with warfarin,[4] the reported absolute increase in GIB is 0.49%/year. However, the absolute reduction in intracranial hemorrhage is 0.44%/year. Given the much higher mortality rate (~60%) of intracranial hemorrhage,[7] this increase in GIB deserves to be put into perspective. This overall safety profile of dabigatran 150 mg bid compares favorably to the use of vitamin K antagonists, which is additional to the significant reduction in efficacy (trombo-embolic events).[4]

These calculations demonstrate that warnings on *individual* safety endpoints of drugs should always be put in the context of *overall* safety, and in relation to efficacy.

In summary, the reported increased risk of GIB with the use of NOACs deserves further study, be it restricted to the doses and indications that the drugs have been approved for. In line with this, we acknowledge the authors' statement that in future trials GIB events should be better reported. Finally, additional risk-benefit stratification for the individual patient is warranted and calls for meta-analyses with individual patient data, an intention for which the authors should be commended. In an era of research and efforts to stimulate personalized medicine, already available data constitute an invaluable source of information, which we should share to improve individual patient care.

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6

Polypharmacy and effects of apixaban versus warfarin in patients with atrial fibrillation: post hoc analysis of the ARISTOTLE trial

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ABSTRACT

Objective: In various clinical settings, polypharmacy has been associated with frailty and adverse outcome. Compared with warfarin, apixaban has a superior efficacy and safety profile in atrial fibrillation. However, patients with polypharmacy may have a differential response to anticoagulation therapy, due to extensive comorbidity and/or drug-drug interactions.

Design, Participants, Interventions, Main Outcome Measures: Patients in the ARISTOTLE trial (n=18,201) were divided into tertiles according to the number of medications used at baseline. We compared clinical outcomes and the treatment effects of apixaban versus warfarin (adjusted for age, sex, and country).

Results: Patients used a median of 6 drugs (interquartile range 5 to 9); polypharmacy (≥5 drugs) was seen in 76%. Greater numbers of concomitant medications were used in older patients and in women, and in patients in the United States. Number of comorbidities increased across tertiles of increasing number of medications (0-5; 6-8; ≥9 drugs), as did the proportions of patients with drugs that interact with warfarin or apixaban. Mortality significantly increased as number of medications increased. Across tertiles of increasing numbers of drugs, rates of stroke/systemic embolism (1.29; 1.48; 1.57 per 100 patient-years, respectively) and major bleeding (1.91; 2.46; 3.88 per 100 patient-years, respectively) increased. The relative risk reductions of stroke or systemic embolism for apixaban versus warfarin were consistent, regardless of the number of concomitant medications (interaction p-value=0.8). With regard to major bleeding, there was less reduction seen with apixaban versus warfarin with greater numbers of concomitant drugs (interaction p-value 0.017). Patients with interacting (potentiating) drugs for warfarin or apixaban had similar outcomes and consistent treatment effects of apixaban versus warfarin.

Conclusions: In ARISTOTLE, three quarters of patients have polypharmacy, and they constitute a population with a greater comorbidity, more interacting drugs, increased mortality, and higher rates of thrombo-embolic and bleeding complications. In terms of a potential differential response to anticoagulation therapy in patients with AF and polypharmacy, apixaban was more effective than warfarin and at least as safe.

Trial Registration: ClinicalTrials.gov (NCT00412984).

INTRODUCTION

In an era of increasing life expectancy, and with a growing population of survivors with various comorbidities, clinical decision making with regard to antithrombotic therapy for atrial fibrillation (AF) has become an even greater clinical challenge.[1] Despite the often well appreciated risk of stroke, oral anticoagulation is often not prescribed in the elderly, and undertreatment has been associated with adverse outcome.[2,3] However, physicians increasingly acknowledge that treatment decisions should probably be based on biological rather than chronological age.[4]

In a variety of populations, polypharmacy has been associated with multiple comorbidities and frailty.[5-10] Moreover, the risk of drug-drug interactions increases with the number of concomitant drugs. In addition, polypharmacy has been related to a higher risk of death and bleeding complications, also in patients with AF.[6-17] In this context, patients with polypharmacy may have a differential response to anticoagulation therapy.

With the introduction of apixaban, a safer alternative to warfarin has become available which has also proven to be of value in patients considered unsuitable for warfarin.[18,19] In a previous report we demonstrated that the benefits of apixaban versus warfarin were irrespective of age (<65 yrs vs 65-74 yrs vs ≥75 yrs). However, among the elderly there are patients with hardly any comorbidity, whereas there are also younger patients with significant comorbidity. On average, patients with AF use about four to six different medications,.[10,11,20] Given that polypharmacy is generally defined as the use of five or more concomitant medications, and thus represents an everyday issue, additional information on the impact of oral anticoagulation drugs in this specific subset of patients is of clinical importance.[21] Especially in the case of apixaban, information on the impact of potentiating drugs is limited, an issue that is specifically of interest in patients with many concomitant drugs.

In this context, we performed a post-hoc analysis of the ARISTOTLE trial (Apixaban for Reduction of Stroke and Other Thromboembolic Events in Atrial Fibrillation) to assess the association between the number of drugs used and the extent of comorbidity and adverse outcome.[19] In addition, we addressed the relative treatment effect of apixaban versus warfarin in relation to the number of concomitant medications.

METHODS

Patients

The study design and the main outcomes of the ARISTOTLE trial have been reported previously.[19,22] In brief, ARISTOTLE was a multicenter double-blind, double-dummy trial comparing apixaban with warfarin performed from 2006-2011. Patients with documented AF or atrial flutter were eligible for inclusion if one or more of the following risk factors for thromboembolism were present: symptomatic heart failure within 3 months prior to inclusion or left ventricular function ≤40%; hypertension requiring pharmacological treatment; age ≥75 years; diabetes mellitus; and prior stroke, transient ischemic attack (TIA), or systemic embolus. Exclusion criteria included clinically significant mitral stenosis, conditions other than AF requiring anticoagulation, required aspirin treatment in a dose >165 mg/day or used in combination with a thienopyridine, recent ischemic stroke, AF due to reversible causes, an increased bleeding risk considered to be a contraindication for oral anticoagulation, and severe renal insufficiency (i.e., serum creatinine >2.5 mg/dL or a calculated creatinine clearance <25 mL/min).

Patients were randomized to either apixaban 5 mg twice daily (n=9120) or a dose-adjusted regimen of warfarin (n=9081). The target international normalized ratio (INR) range was 2.0 to 3.0, using a blinded encrypted point of care device. In cases where two or more of the following three criteria were present at baseline, patients received apixaban in a dose of 2.5 mg twice daily or matching placebo: age ≥80 years, body weight ≤60 kilograms, serum creatinine ≥1.5 mg/dL. The study was approved by appropriate ethical committees at all sites and all patients provided written informed consent

Concomitant medications and comorbidity

To investigate the association between the number of concomitant medications and the extent of comorbidity, we assessed the number of drugs used for each patient. The study drug (apixaban or warfarin) and the matching placebo were counted as one drug. All medications were categorized according to the Anatomical Therapeutic

Chemical classification system.[23] Polypharmacy was defined as the use of five or more concomitant drugs.[21]

The use of drugs known to interact with apixaban or warfarin was assessed for each patient. For apixaban, we studied drugs known to inhibit both the cytochrome P450 3A4 (CYP3A4) enzyme as well as the P-glycoprotein (P-gp) as depicted by the Food and Drug Administration (FDA).[24] For warfarin, we studied the use of drugs known to inhibit or potentiate its anticoagulant effect with a high probability according to the American College of Chest Physicians guideline.[25]

All analyses performed were based upon the baseline medication burden; only for the anticoagulant we also studied premature permanent study drug discontinuation and for patients assigned to warfarin we calculated the time in therapeutic range (TTR) according to the Rosendaal method.[26]

Per protocol, the use of any concomitant medications during the trial was left to the discretion of the treating physician. The following concomitant medications were prohibited in combination with the study medication: potent inhibitors of CYP3A4 (e.g., azole antifungals, macrolide antibiotics, protease inhibitors, and nefazadone), aspirin in a daily dose >165 mg, other anticoagulant agents (e.g., unfractionated heparin, low molecular weight heparin, direct thrombin inhibitors, pentasaccharides), and glycoprotein IIb/IIIa inhibitors. If these agents were used during trial participation, study medication was to be (temporarily) interrupted and restarted as soon as the prohibited medication was discontinued. In addition, during the trial it was advised to cautiously use aspirin in combination with a thienopyridine, chronic daily use of a non-steroid anti-inflammatory agent, and cytotoxic or myelosuppressive therapy.

Clinical outcomes

We assessed outcomes in relation to the number of concomitant medications used at the time of randomization, during a median follow-up of 1.8 years (25th, 75th percentiles: 1.3, 2.3 years). The primary efficacy outcome was stroke (i.e., abrupt onset of focal neurological symptoms lasting at least 24 hours), or a systemic embolism (i.e., symptoms suggestive of an acute loss of blood flow to a non-cerebral artery, supported by evidence of embolism from surgical specimens, autopsy, angiography, or other objective testing).

Key secondary efficacy outcomes included assessment of the type of stroke (ischemic, hemorrhagic, unspecified) and all-cause death.

The primary safety endpoint was major bleeding according to the criteria set by the International Society on Thrombosis and Haemostasis (ISTH), which includes any clinically overt bleeding event accompanied by one or more of the following: a hemoglobin drop of 2 g/dL or more over a 24-hour period, a transfusion of 2 or more units of packed red blood cells, bleeding at a critical site (i.e., intracranial, intra-spinal, intraocular, intra-articular, pericardial, intramuscular with compartment syndrome, or retroperitoneal), or fatal bleeding.[27] Moreover, clinically relevant non-major bleeding events were monitored and were defined as all clinically overt bleeding not meeting the criteria of major bleeding though leading to either hospital admission, physician-guided medical or surgical treatment, or a change in antithrombotic therapy.

The combined endpoint of 'net benefit' was defined as the combination of death, stroke, systemic embolism, and major bleeding.

Statistical analysis

Based on the tertiles of the distribution of the number of concomitant medications used at baseline, patients were classified in three groups. Comorbidities, organized by organ system, were summarized for the three groups, as well as other baseline characteristics. A similar approach was followed for the different drug classes. Data were depicted as means and standard deviations for continuous variables and frequencies and percentages for categorical variables. One-way ANOVA and chi-square tests were used to compare groups. Efficacy, safety, and net benefit endpoints were compared among the three groups using rates per 100 patient-years of follow-up and adjusted hazard ratios with 95% confidence intervals. Adjusted hazard ratios were derived using Cox regression models adjusting for sex and age and country of randomization. In these models, age was considered non-linear and included as a restricted cubic spline. The randomized treatment effect was assessed within each group (0–5, 6–8, ≥9 medications) using a Cox regression model to estimate hazard ratios for apixaban versus warfarin along with 95% confidence intervals. The homogeneity of the randomized treatment effect across groups was tested by adding interaction terms to the Cox regression model.

The proportional hazard assumption was evaluated using scaled Schoenfeld residuals and no clinically relevant departure from the assumption was observed. All the analyses performed with SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Patient involvement

No patients were involved in designing the study, in assessing the burden of the intervention on patients, or in explicitly setting outcome measures; however, outcomes were chosen to reflect daily practice described in earlier studies.[28] Final study results of the ARISTOTLE trial were disseminated to study participants through their treating physicians.

RESULTS

Baseline characteristics and comorbidity

Table 1 depicts baseline characteristics of the study population, categorized in tertiles by the number of drugs. The randomized treatment was well balanced across tertiles and no relevant differences between apixaban and warfarin was observed for any of the drug categories across the tertiles (Online Supplementary Table 1).

Patients using more medications were older, more often female, and less often warfarin-naïve at study entry (Table 1). The $CHADS_2$ and HAS-BLED scores increased across tertiles of increasing number of concomitant medications. With increasing number of medications the associated comorbidity increased significantly (Table 1).

Table 1. Baseline Characteristics by Number of Medications Used

	Number of Medications			
Characteristic	**0-5 (N=6943)**	**6-8 (N=6502)**	**9 or more (N=4756)**	**p-value**
Age, mean (SD), yrs	68 (10)	69 (10)	71 (9)	<.0001
Male, no, (%)	4687 (67.5%)	4107 (63.2%)	2991 (62.9%)	<.0001
Weight, mean (SD), kg	81 (19)	84 (21)	89 (23)	<.0001
Body mass index, mean (SD), kg/m^2	28.2 (5.4)	29.5 (6.0)	30.7 (6.5)	<.0001
Prior use of Vitamin K antagonists for >30 days, no (%)	3555 (51.2%)	3656 (56.2%)	3190 (67.1%)	<.0001
Creatinine, mean (SD)	1.02 (0.24)	1.06 (0.28)	1.12 (0.32)	<.0001
Region of enrollment, no. (%)				<.0001
North America	736 (10.6%)	1353 (20.8%)	2385 (50.1%)	
Latin America	1809 (26.1%)	1306 (20.1%)	353 (7.4%)	
Europe	3128 (45.1%)	2811 (43.2%)	1404 (29.5%)	
Asia	1270 (18.3%)	1032 (15.9%)	614 (12.9%)	
HAS-BLED score, mean (SD)	1.45 (0.96)	1.77 (1.02)	2.25 (1.05)	<.0001
$CHADS_2$ score, mean (SD)	1.87 (1.02)	2.15 (1.08)	2.44 (1.17)	<.0001
$CHADS_2$ score, no (%)				
≤1	3093 (44.5%)	2057 (31.6%)	1033 (21.7%)	<.0001
2	2309 (33.3%)	2400 (36.9%)	1807 (38.0%)	
≥3	1541 (22.2%)	2045 (31.5%)	1916 (40.3%)	
Randomized group, no. (%)				0.1
Apixaban	3424 (49.3%)	3320 (51.1%)	2376 (50.0%)	
Warfarin	3519 (50.7%)	3182 (48.9%)	2380 (50.0%)	
Low dose apixaban/placebo (2.5 mg bid) received	253 (3.6%)	288 (4.4%)	290 (6.1%)	<.0001
Comorbidities organized by organ system, no. (%)				
Cardiovascular				
CAD	1795 (25.9%)	2184 (33.6%)	2063 (43.4%)	<.0001
Prior MI	564 (8.1%)	985 (15.2%)	1036 (21.8%)	<.0001
History of PCI/CABG	369 (5.3%)	815 (12.5%)	1292 (27.2%)	<.0001
Congestive Heart Failure within 3 Months	1931 (27.8%)	2194 (33.7%)	1416 (29.8%)	<.0001
At Least Moderate Valvular Heart Disease	926 (13.4%)	1192 (18.3%)	1116 (23.5%)	<.0001
Syncope in Last 5 years	258 (3.7%)	279 (4.3%)	322 (6.8%)	<.0001
Hypertension with Pharmacological Treatment	5844 (84.2%)	5762 (88.6%)	4310 (90.6%)	<.0001
PAD	193 (2.8%)	290 (4.5%)	401 (8.5%)	<.0001
Aortic Aneurysm	46 (0.7%)	84 (1.3%)	139 (3.0%)	<.0001
Neurological/Cerebrovascular				
Carotid Stenosis	54 (0.8%)	93 (1.4%)	190 (4.0%)	<.0001

Table 1. Baseline Characteristics by Number of Medications Used (continued)

	Number of Medications			
Characteristic	**0-5 (N=6943)**	**6-8 (N=6502)**	**9 or more (N=4756)**	**p-value**
TIA	302 (4.4%)	315 (4.8%)	337 (7.1%)	<.0001
Stroke	808 (11.6%)	750 (11.5%)	569 (12.0%)	0.8
Dementia	22 (0.4%)	29 (0.5%)	45 (1.0%)	<.0001
Epilepsy	22 (0.4%)	49 (0.8%)	41 (0.9%)	0.0006
Pulmonary				
COPD	435 (6.3%)	626 (9.7%)	889 (18.7%)	<.0001
Asthma	157 (2.3%)	250 (3.9%)	462 (9.7%)	<.0001
Sleep Apnea	145 (2.1%)	262 (4.0%)	606 (12.8%)	<.0001
Gastrointestinal				
Dyspepsia	374 (5.4%)	445 (6.9%)	556 (11.7%)	<.0001
GE Reflux Disease	315 (4.5%)	527 (8.1%)	1074 (22.6%)	<.0001
Peptic Ulcer Disease	383 (5.5%)	417 (6.4%)	406 (8.5%)	<.0001
GI Surgery	509 (7.3%)	606 (9.3%)	575 (12.1%)	<.0001
Chronic Liver Disease	190 (2.7%)	193 (3.0%)	121 (2.5%)	0.4
Endocrine				
Hypo/Hyperthyrodism	429 (6.2%)	733 (11.3%)	878 (18.5%)	<.0001
Diabetes	806 (11.6%)	1603 (24.7%)	2138 (45.0%)	<.0001
End organ Damage due to DM	75 (1.1%)	219 (3.4%)	459 (9.7%)	<.0001
Musculoskeletal				
Falls within 1 year	140 (2.3%)	215 (3.6%)	398 (8.8%)	<.0001
Previous Non-Traumatic Fracture	299 (4.3%)	339 (5.2%)	436 (9.2%)	<.0001
Osteoporosis	151 (2.2%)	298 (4.6%)	521 (11.0%)	<.0001
Renal				
Chronic Kidney Disease	434 (6.3%)	520 (8.0%)	553 (11.6%)	<.0001
Creatine Clearance < 50 mL/min	927 (13.4%)	1112 (17.2%)	970 (20.5%)	<.0001
Hematological				
History of Anemia	210 (3.0%)	359 (5.5%)	676 (14.2%)	<.0001
Thrombocytopenia (platelet at baseline < 150)	510 (7.6%)	467 (7.4%)	332 (7.2%)	0.8
Bleeding History	779 (11.2%)	1029 (15.8%)	1232 (25.9%)	<.0001
Number of organ systems affected (median, 25th-75th)	2, 1-3	2, 2-3	3, 2-4	<.0001

Subcategorization of all baseline characteristics per treatment allocation is presented in Online Supplementary Table 1.
Abbreviations: n = number of patients, sd = standard deviation, yrs = years, no = number, kg = kilogram, m = meter, CAD = coronary artery disease, MI = myocardial infarction, PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting, PAD = peripheral artery disease, TIA = transient ischemic attack, COPD = chronic obstructive pulmonary disease, GE = gastroesophageal, GI = gastrointestinal, DM = diabetes mellitus, mL = milliliter, min = minute.

Concomitant drugs - classification according to organ or system

The median number of medications used was 6 (25th, 75th percentiles: 5, 9) and polypharmacy was present in 13,932 (76.5%) patients (Online Supplementary Figure 1). There were marked regional differences in the number of medications used, with 53% (2385/4474) of patients enrolled in North America using 9 or more medications (United States 1980/3417 (58%); Canada 405/1057 (38%)), compared with 10–21% for the other regions (Table 1). Although 4 or more organ systems with comorbidity was higher in the U.S. (43.3% in the U.S. versus 20.5% in non-U.S. countries), the greater number of medications in the U.S. was observed regardless of the number of comorbidities.

Across tertiles of polypharmacy, the median number of represented drug classes increased from 2 (2, 3) for patients using 0–5 medications to 5 (4, 5) for patients using 9 or more medications.

Across the three studygroups, there were no relevant differences between apixaban and warfarin regarding the proportion of patients in each of the defined drug classes. For each of the respective drug classes the proportion of patients increased statistically significantly from the group with 0-5 drugs to the group with ≥9 concomitant drugs.

Across groups of increasing concomitant medication, the proportion of patients in the respective drug classes was higher in the U.S. than in the non-U.S. population (Online Supplementary Table 2 A, B). Despite this difference in prescription pattern, there was a clear association between the number of concomitant drugs at baseline and the number of comorbidities, both for the U.S. and the non-U.S. populations.

CLINICAL OUTCOMES ACCORDING TO THE NUMBER OF CONCOMITANT MEDICATIONS

Efficacy outcomes

With regard to the primary efficacy endpoint (stroke and systemic embolism), patients using more concomitant medications were at higher risk, with an increase in event rates from 1.29 for patients using 0–5 medications to 1.57 per 100 patient-years for

Table 2. Distribution of Drug Classes by Number of Medications Used

	Number of Medications			
Drug Class	**0-5 (N=6943)**	**6-8 (N=6502)**	**9 or more (N=4756)**	**p-value**
A. Alimentary tract and metabolism	962 (13.9%)	3045 (46.8%)	4094 (86.1%)	<.0001
B. Blood and blood forming organs [excluding apixaban/warfarin]	2282 (32.9%)	4322 (66.5%)	4116 (86.5%)	<.0001
C. Cardiovascular system	6460 (93.0%)	6468 (99.5%)	4737 (99.6%)	<.0001
D. Dermatologicals	34 (0.5%)	96 (1.5%)	346 (7.3%)	<.0001
G. Genito-urinary system and sex hormones	173 (2.5%)	510 (7.8%)	936 (19.7%)	<.0001
H. Systemic hormonal preparations, excluding sex hormones and insulins	181 (2.6%)	508 (7.8%)	852 (17.9%)	<.0001
J. Antiinfectives for systemic use	44 (0.6%)	161 (2.5%)	347 (7.3%)	<.0001
L. Antineoplastic and immunomodulating agents	14 (0.2%)	60 (0.9%)	152 (3.2%)	<.0001
M. Musculo-skeletal system	202 (2.9%)	688 (10.6%)	1350 (28.4%)	<.0001
N. Nervous system	523 (7.5%)	1448 (22.3%)	2376 (50.0%)	<.0001
P. Antiparasitic products, insecticides and repellents	0 (0.0%)	13 (0.2%)	46 (1.0%)	<.0001
R. Respiratory system	164 (2.4%)	600 (9.2%)	1336 (28.1%)	<.0001
S. Sensory organs	41 (0.6%)	115 (1.8%)	300 (6.3%)	<.0001
V. Various	126 (1.8%)	247 (3.8%)	630 (13.2%)	<.0001
Interacting drugs				
≥1 combined P-gp and weak-moderate-strong CYP3A4 inhibitor	1128 (16.2%)	1431 (22.0%)	1301 (27.4%)	<.0001
≥1 combined P-gp and weak-moderate-strong CYP3A4 inducer	12 (0.2%)	34 (0.5%)	47 (1.0%)	<.0001
≥1 highly probable VKA inhibiting drug	8 (0.1%)	19 (0.3%)	33 (0.7%)	<.0001
≥1 highly probable VKA potentiating drug	973 (14.0%)	1406 (21.6%)	1387 (29.2%)	<.0001
Use of ASA, NSAIDs and/or Prednisone	956 (13.8%)	2064 (31.7%)	2362 (49.7%)	<.0001

Abbreviations: n = number of patients, P-gp = P-glycoprotein, CYP = Cytochrome P450, VKA = vitamin K antagonist, ASA = acetylsalicylic acid, NSAID = non-steroidal anti-inflammatory drug.

patients using 9 or more medications (p<0.001; Table 3). For the secondary efficacy outcomes there was also a significant association with the number of concomitant medications, with a two-fold increased risk for all-cause death, when the highest tertile (≥9 medications) was compared with the lowest (0–5 medications) (p<0.001).

Safety outcomes

The risk of major bleeding for patients using 6–8 and 9 or more medications was significantly higher when compared with those using 0–5 medications (6–8 medications: adjusted HR 1.24, 95% CI 1.04 to 1.49; 9 or more drugs: adjusted HR 1.72, 95% CI 1.41 to 2.10; Table 3). When subdividing major bleeding according to the location, no significant difference across tertiles was observed for intracranial bleeding (p=0.73), while the event rate for gastrointestinal bleeding significantly increased with a higher number of concomitant medications.

Net benefit outcome

With regard to the combined endpoint stroke, systemic embolism, major bleeding, and all-cause death, event rates increased across tertiles (5.24, 6.59, and 8.92 per 100 patient-years for 0–5, 6–8, and 9 or more medications, respectively, p<0.001). This was associated with an adjusted hazard ratio of 1.84 (95% CI 1.631 to 2.071) for patients using 9 or more medications when compared with those using 0–5.

Other outcomes

With increasing numbers of medications, the risk of permanent study drug discontinuation increased significantly (discontinuation rates 14.3, 15.0, and 17.4 per 100 patient-years at risk for 0–5, 6–8 and 9 or more drugs, respectively, p<0.001) (Table 3). Poor INR control during follow-up (i.e., TTR below 66%) was highest in the patients using 0–5 concomitant medications and decreased across tertiles (53.2%, 50.2%, and 44.9% for 0–5, 6–8, and 9 or more respectively, p<0.001) (Table 3).

Table 3. Efficacy and Safety Outcomes by Number of Medications Used

	0-5 Meds	6-8 Meds		9 or more Meds		
Event	Rate (n)	Rate (n)	Adjusted Hazard Ratio* (95% CI)	Rate (n)	Adjusted Hazard Ratio* (95% CI)	p-value
Efficacy Outcomes						
Stroke/SE	1.29 (166)	1.48 (176)	1.270 (1.022 to 1.577)	1.57 (135)	1.539 (1.190 to 1.991)	0.0038
Ischemic or uncertain type of stroke	0.82 (106)	1.11 (132)	1.475 (1.136 to 1.915)	1.15 (99)	1.738 (1.275 to 2.369)	0.0010
All cause death	3.01 (396)	3.80 (462)	1.409 (1.229 to 1.616)	4.70 (414)	2.031 (1.735 to 2.377)	<.0001
Safety Outcomes						
Major bleeding	1.91 (224)	2.46 (267)	1.243 (1.036 to 1.491)	3.88 (298)	1.721 (1.414 to 2.095)	<.0001
Intracranial	0.54 (64)	0.55 (61)	1.025 (0.722 to 1.456)	0.62 (49)	1.153 (0.795 to 1.673)	0.7
Gastrointestinal	0.47 (56)	0.71 (78)	1.498 (1.062 to 2.111)	1.15 (90)	2.429 (1.740 to 3.391)	<.0001
Clinically relevant non-major bleeding	2.09 (243)	2.47 (267)	1.183 (0.994 to 1.408)	3.30 (252)	1.574 (1.319 to 1.877)	<.0001
Any bleeding	17.41 (1742)	21.40 (1908)	1.167 (1.092 to 1.247)	29.63 (1766)	1.452 (1.348 to 1.565)	<.0001
Net Benefit Outcomes						
Stroke/SE/major bleeding/all cause death	5.24 (665)	6.59 (769)	1.320 (1.187 to 1.468)	8.92 (743)	1.838 (1.631 to 2.071)	<.0001
Other Outcomes						
Permanent study drug discontinuation	14.32 (1699)	14.99 (1655)	1.053 (0.982 to 1.129)	17.44 (1372)	1.218 (1.123 to 1.322)	<.0001
Time in Therapeutic Range <66%[#]	53.2 (1823)	50.2 (1564)	0.887 (0.805 to 0.977)	44.9 (1044)	0.716 (0.644 to 0.795)	< .0001

Hazard ratios and p-value adjusted by country (strata), gender and age (spline)

* Hazard ratio vs. 0-5 meds

[#] Values reported are percentage (number of patients) and unadjusted odd ratios for patients randomized to warfarin.

Abbreviations: n = number of patients, CI = confidence interval, meds = medications, SE = systemic embolism.

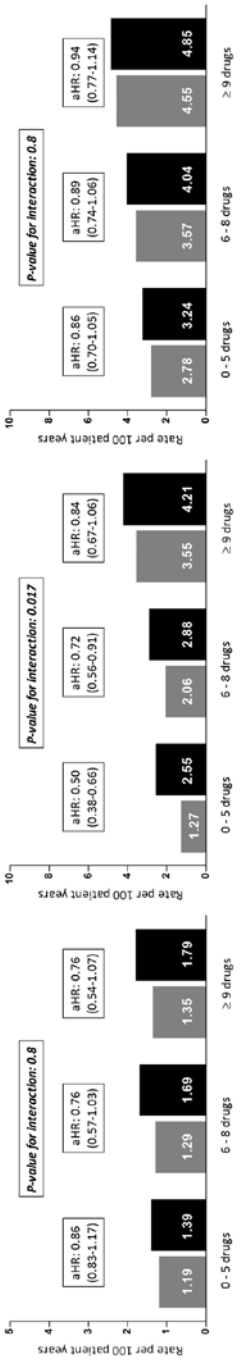

Figure 1.
Association between randomized treatment and the main outcomes by number of baseline medications.

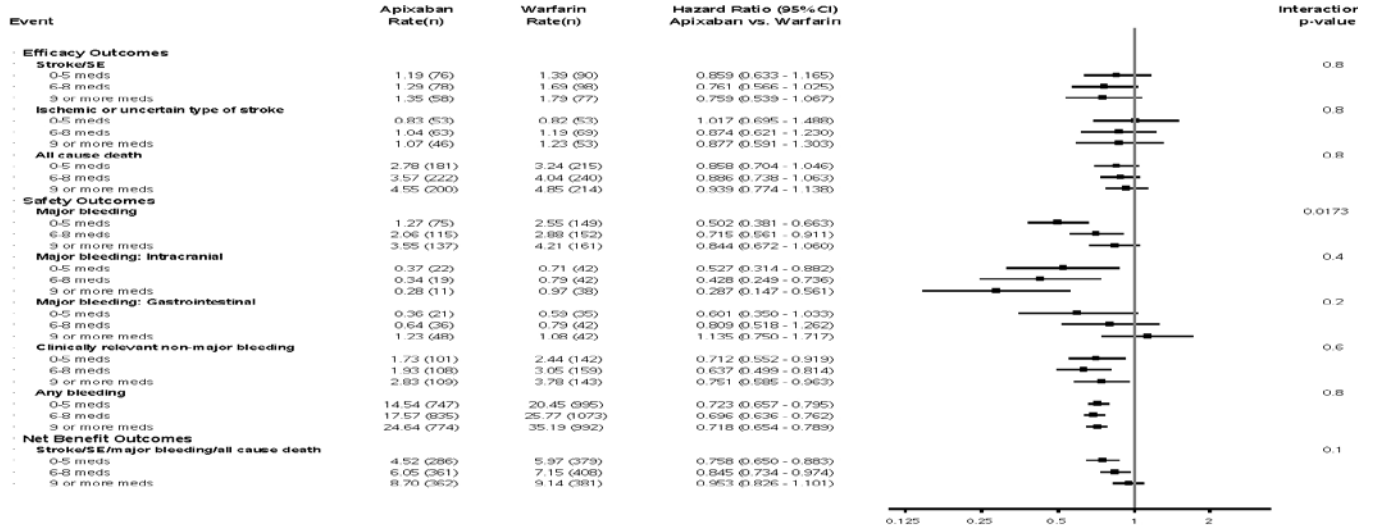

Figure 2.
Figure 2. Treatment comparisons for efficacy, safety and net benefit outcomes between apixaban and warfarin according to the number of baseline medications.

TREATMENT EFFECT

Figures 1 and 2 outline the treatment effect of apixaban when compared with warfarin for the different outcomes categorized by the number of medications used at baseline.

For the primary efficacy outcome, risk reductions of apixaban versus warfarin were consistent, irrespective of the number of medications used (p interaction=0.8), with lower event rates on apixaban for all tertiles. Also for the secondary efficacy outcomes, no significant interactions were observed.

With regard to major bleeding, relative risk reductions for apixaban versus warfarin decreased with increasing number of drugs (p interaction=0.017), corresponding with absolute reductions per 100 patient-years of 1.28 to 0.82 to 0.66 for the three respective categories (0–5, 6–8, and 9 or more drugs). For intracranial bleeding, the absolute benefit on apixaban showed a numeric increase across tertiles; this, in contrast to the numeric differences in major gastrointestinal bleeding observed between treatment groups. With regard to the combined outcome of stroke, systemic embolism, major bleeding and all-cause death, we observed no significant interaction between treatment groups (p=0.1) Rates of permanent study drug discontinuation were lower for apixaban in all tertiles (p interaction=0.4).

INTERACTING DRUGS

The proportion of patients using an interacting drug increased across tertiles, both for CYP3A4/P-gp inhibiting as warfarin potentiating drugs. At least one combined inhibitor of both the CYP3A4 enzyme and P-gp was used by 20.9% (1903/9120) of the apixaban users and 21.1% (1913/9081) of patients on warfarin used VKA potentiating drugs. As for the concomitant use of aspirin, NSAID and/or prednisone, proportions were 13.8%, 31.7%, and 49.7%, respectively (p<0.001).

Rates of major bleeding did not significantly differ between patients with or without combined CYP3A4 and P-gp inhibitors (2.59 vs 2.61 per 100 patient-years, respectively). Moreover, no significant interaction with the treatment allocation was observed (p=0.4). With regard to drugs known to potentiate warfarin, we also

Table 4: Major bleeding with apixaban or warfarin according to the use of interacting drugs

	Use of potentiating drug		No use of potentiating drug		
Interacting drugs	**Apixaban Rate (n)**	**Warfarin Rate (n)**	**Apixaban Rate (n)**	**Warfarin Rate (n)**	**P interaction**
≥ 1 combined P-gp and weak/ moderate/strong CYP3A4 inhibitor	2.27 (72)	2.91 (93)	2.10 (255)	3.14 (369)	0.4
≥ 1 Highly probable VKA potentiating drug	2.03 (62)	3.16 (96)	2.16 (265)	3.07 (366)	0.6

Abbreviations: n = number of patients, P-gp = P-glycoprotein, CYP = Cytochrome P450, VKA = vitamin K antagonist.

observed no difference in event rate of major bleeding (2.60 vs 2.61 per 100 patient-year for users and non-users, respectively).

DISCUSSION

In this post-hoc analysis of the ARISTOTLE trial, we observed that polypharmacy was present in three quarters of patients and that the number of concomitant medications is associated with increased comorbidity. Prescription patterns differed across regions, with approximately twice the number of concomitant medications in the U.S. vs non-U.S. populations. Adverse clinical outcome occurred more frequently in patients treated with a higher number of concomitant medications. The benefits of apixaban in reducing stroke were preserved, regardless of the number of medications taken. In terms of safety, while the rates of major bleeding were consistently lower with apixaban, the magnitude of benefit with apixaban decreased with the number of concomitant medications.

POLYPHARMACY AND ADVERSE OUTCOMES

AF is a disease of the elderly, who have a varying extent of comorbidity, and associated concomitant medication.[29] Previous studies have reported rates of polyphar-

macy in 40 to 64% of AF patients, with varying prescription patterns and inclusion and exclusion criteria.[9,10]

Various reports have demonstrated, for different clinical conditions, that polypharmacy is associated with increased comorbidity.[5-10] In addition, studies focusing on elderly populations have linked polypharmacy to adverse drug reactions, falls, disability, and frailty.[6-8] In this context, patients with polypharmacy may constitute a population with a differential response to oral anticoagulation.

Although differences in prescription thresholds may affect the classification of patients in individual cases, several reports have repeatedly demonstrated on a group level that polypharmacy is associated with comorbidity and adverse outcome, also in AF populations.[6-17] Our findings of higher risks of bleeding, stroke and all-cause mortality with increasing numbers of drugs are in line with these previous observations.

Notably, this higher risk of adverse outcomes should be placed in the context of the association between the number of medications and comorbidities present at baseline, indicating a more frail status of patients with polypharmacy. If we were to adjust for these baseline differences, it is likely that the risk of adverse outcomes related to the number of medications would diminish. However, it is not our objective to study the association between polypharmacy and adverse outcomes independent of the baseline difference. On the contrary, we studied the number of concomitant medications as a marker of comorbidity/frailty and adverse outcome.

As such, we performed adjustments limited to age, sex, and country of randomization. The latter is of special importance given the differences in prescription patterns between countries, independent of differences in comorbidity. It is striking that in the U.S., there is more use of polypharmacy, not explained by more comorbidity.

POLYPHARMACY AND TREATMENT EFFECT

Considering that patients with polypharmacy have a higher risk of adverse outcomes and multiple coexisting impairments, it is of special interest to study whether the main trial results of the ARISTOTLE study are consistent among patients using numerous concomitant medications. As far as the primary endpoint of stroke and systemic

embolism is concerned, there was an absolute risk reduction from 1.60% per year with warfarin to 1.27% per year with apixaban (21% relative risk reduction in the complete population that was consistent irrespective of the number of medications used).[19]

Overall, the use of apixaban was associated with an absolute risk reduction in major bleeding from 3.09% to 2.13% per year when compared with warfarin (relative risk reduction 31%).[19] However, we observed a statistically significant treatment interaction with relative risk reductions of apixaban varying from 50% (0–5 medications) to 28% (6–8 medications) and 16% (≥9 medications), respectively. Importantly, the risk reduction of intracranial bleeding did not diminish with an increasing number of concomitant medications. Therefore, the fact that the relative benefit of apixaban over warfarin appears to diminish across tertiles is due to other types of major bleeds. For example, with increasing numbers of medications, the numeric difference in gastrointestinal bleedings shifts from a benefit for apixaban (0–5 medications) to no apparent difference (≥9 medications) between both oral anticoagulants.

In the ROCKET AF trial, with overall similar rates of major bleeding for rivaroxaban and warfarin, there was also a treatment interaction for major bleeding, in that the hazard ratio for major bleeding in patients using fewer medications (0–4) was lower (adjusted HR 0.69, 95% CI 0.51 to 0.94) than observed in the entire study population (HR 1.04, 95% CI 0.90 to 1.20).[10] As for mortality, there was no difference in treatment effect of rivaroxaban in patients with polypharmacy. In ARISTOTLE, apixaban reduced the risk of mortality from 3.94% to 3.52% per year when compared with warfarin in the main study, a relative risk reduction of 11% that was consistent regardless of the number of concomitant medications.[19]

In ARISTOTLE as well as in ROCKET AF, patients with polypharmacy were older.[10] Nonetheless, the relative reduction of both apixaban and rivaroxaban on major bleeding proved to be consistent across the different age groups in previously reported post-hoc analyses.[30,31] Importantly, this implies that our findings cannot be inferred to the 'elderly patient' in general. In fact, our findings are irrespective of age and sex, and refer to the group of patients, both younger and older, with multiple comorbidities and medications.

Possible explanations for the attenuation of the observed safety benefit of apixaban with increasing concomitant drugs include effects of comorbidity and drug-drug interactions, or the play of chance. We demonstrated that various co-existing diseases (COPD, gastrointestinal disease, renal impairment) were more frequent with increasing numbers of concomitant drugs. Of interest, given the consistent risk reduction of apixaban for intracranial bleeding, the treatment interaction for major bleeding is related to other major bleeding. Risk factors for gastrointestinal bleeding complications (e.g., previous gastric ulcer, gastrointestinal surgery, dyspepsia, aspirin/prednisone/NSAID use) were more prevalent among patients with polypharmacy. In addition, other non-gastrointestinal risk factors for bleeding were also more often common in patients with more concomitant medications (e.g., older age, renal impairment, anemia, diabetes, and previous bleeding).[32]

Other aspects that may account for the decrease in benefit of apixaban in patients in the highest tertile are the higher rates of permanent study drug discontinuation and lower proportion of patients who were VKA-naïve.[33] The lower rates of patients on study medication may blunt the observed risk reduction of apixaban in this tertile. In addition, bleeding rates on warfarin are usually lower in patients with prior VKA experience. Finally, the better INR control in patients with ≥9 medications may have diminished bleeding rates on warfarin in this subgroup.[34,35]

As for drug-drug interactions, we specifically studied the impact of warfarin potentiating drugs and the combination of CYP3A4 and P-gp inhibitors, given the possibility of higher apixaban plasma concentrations with these agents. However, there was no evidence of differential treatment effect between apixaban and warfarin across tertiles of the number of concomitant drugs when accounting for warfarin potentiating or for apixaban potentiating drugs.

The abovementioned effects of non-vitamin K antagonist oral anticoagulants in patients with polypharmacy have also been studied in a pooled analysis of data in the setting of secondary prevention after a venous thromboembolism.[15] For major bleeding, there was no treatment interaction, when the safety of dabigatran versus warfarin was compared in patients with ≤3 or >3 concomitant medications. However, these patients are much younger and less fragile when compared to patients with AF.

Interestingly, also in the field of symptomatic venous thromboembolism the issue of a potential differential response to oral anticoagulation therapy in 'fragile' patients has been studied into more detail.[36] Of note, in this study, patients were considered to be 'fragile' if they were >75 years, had a low body weight (<50 kg), or had impaired renal function (creatinine clearance <50 mL/min). Although this certainly identifies patients at risk, incorporation of multiple comorbidities would allow for a more refined identification of frail patients within these specific subsets of patients.[37]

In summary, polypharmacy may be a marker of multi-morbidity and a predictor of adverse outcomes, and it may provide a first, general impression of a patients' frailty status. Future research on a differential response with oral anticoagulation therapy in patients with multi-morbidity may focus on incorporation of the key frailty criteria, for example the Fried criteria, which may help to identify a group of higher-risk patients that is often underrepresented in clinical trials.[38] This may be a group that deserves additional attention, as far as the generalizability of trial data is concerned, not only in the field of anticoagulation therapy, but also for other therapies.[39]

LIMITATIONS

There are several limitations of this study. First, this is a post-hoc analysis, though there was a prospective detailed analysis plan. Second, the analyses are based on baseline medication burden, without information on drug changes, reason and/or appropriateness of drug prescription. However, with polypharmacy that is often driven by chronic medical conditions, dramatic reductions in the number of drugs are not very likely. Third, although the number of drugs may not only be driven by the extent of comorbidity, but also by prescription patterns, we acknowledge that this may have affected classification on an individual level. However, on a group level the use of polypharmacy has repeatedly demonstrated to be a marker of the extent of comorbidity and associated with adverse outcome. The cut-off value of 5 or more drugs may be somewhat arbitrary, but has been used in many previous reports. Appreciating that three quarters of patients would qualify for polypharmacy according to this definition, our statistical approach was not arbitrary, but based on a common

approach of dividing our data into tertiles to allow exploration of polypharmacy across categories that are sufficiently large to avoid the hazard of small subgroups. With regard to generalizability, our findings may not apply to an unselected population with AF, given the selection that occurs when enrolling patients in clinical trials.

CONCLUSIONS

In this population with atrial fibrillation on oral anticoagulation therapy, polypharmacy (≥5 drugs) is observed in three quarters of patients. The extent of comorbidity increased with greater numbers of concomitant drugs, which was irrespective of regional prescription patterns. Mortality, stroke and major bleeding were also more frequent with increasing numbers of drugs. As for a potential differential response to anticoagulation therapy in this context, we observed that apixaban was superior to warfarin in terms of efficacy, regardless of the number of medications taken, whereas its magnitude of benefit on major bleeding decreased with higher numbers of concomitant medications. There were important differences in the comorbidity profile that could account for this, and it did not appear that warfarin or apixaban potentiating drugs (CYP3A4, P-gp inhibitors) explained this observed treatment interaction. In summary, apixaban is more effective than and at least as safe as warfarin in patients with AF, regardless of polypharmacy.

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Low performance of bleeding risk models in the very elderly with atrial fibrillation using vitamin K antagonists

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ABSTRACT

Background Anticipated bleeding complications contribute to underuse of oral anticoagulants, especially in elderly patients with atrial fibrillation (AF). Bleeding risk models could provide guidance, however, these were developed in the general AF-population.

Objective To study and compare the performance of the HAS-BLED, ATRIA and $HEMORR_2HAGES$ for major bleeding in very elderly AF-patients.

Methods Random sample (N=1,157) of VKA-anticoagulated AF-patients ≥80 years with prospective clinical follow-up from 2011-2014. Primary outcome was major bleeding (ISTH criteria).

Results Patients aged 84 years (median; 25^{th}-75^{th} 82-87) were classified as low risk in 25.2% (HAS-BLED), 59.6% (ATRIA) and 23.3% ($HEMORR_2HAGES$). Three year rates of major, clinically relevant and any bleeding were 6.7%, 28.3% and 42.3%, respectively. We observed a statistically significant association for all models with major bleeding, but discriminatory abilities were rather poor (C-statistics <0.60) without clear superiority for either of the three. Only two (anemia, antiplatelet therapy) of the various classical risk factors were associated with bleeding. An estimated risk-benefit profile indicated a favorable trade-off for oral anticoagulation in this specific cohort (NNT=22, NNH=91).

Conclusions In this large prospective cohort of very elderly AF patients, the currently used bleeding risk scores were all associated with major bleeding, but with poor predictive abilities. Guidance by use of the ATRIA model may inadvertently result in less attention for modifiable risk factors in this particular population. Appreciating the issues of undertreatment and the suggested favorable risk-benefit profile, future models with incorporation of elderly-

specific risk factors may provide more guidance in this growing population of AF patients.

INTRODUCTION

Stroke prevention among the elderly with atrial fibrillation (AF) remains a clinical challenge, as both the risk of stroke and bleeding increase with older age.[1] Despite randomized evidence of beneficial effects of oral anticoagulation (OAC), also demonstrated in patients aged 75 years or above, many physicians remain concerned about the bleeding risk; in the very elderly (≥80 years) undertreatment has been reported in up to 70% of patients.[2-4]

Appreciating the increasing life expectancy, risk stratification of bleeding in the specific subgroup of the very elderly has become a topic of increasing importance.[5] To assess the risk of major bleeding in the AF population as a whole, numerous risk stratification models have been introduced.[6] The HAS-BLED score has currently received most attention and has been implemented in the AF guidelines.[7-9] The ATRIA and HEMORR$_2$HAGES are two other models that have been studied extensively.[10,11] Although the respective bleeding scores have been associated with the risk of major bleeding, discriminatory ability of all the models is -at most- modest and differs across studies.[12-19]

All three models have been derived from the general AF population.[7,10,11] In these cohorts age was an acknowledged risk factor for bleeding, albeit with different cut-off values (>65 years HAS-BLED; ≥75 years ATRIA and HEMORR$_2$HAGES). In the very elderly the performance of the models is unknown and will depend on other variables than age, as all patients will be attributed the maximum score for age. Interestingly, the ATRIA and HEMORR$_2$HAGES scores have been derived in populations with a higher mean age, and might therefore better apply to the very elderly than the HAS-BLED score.[7,10,11]

In the abovementioned context, we sought to assess and compare the discriminatory ability of the three risk schemes on major bleeding in patients aged ≥80 years. We addressed this issue with data derived from the Nijmegen area Anticoagulation Registry (NAR), which was an initiative to prospectively collect data on VKA-users in the outpatient clinic to monitor treatment quality and patient outcomes.

METHODS

Study population

The anticoagulation clinic in the region Arnhem/Nijmegen, the Netherlands, provides services for about 18,000 patients using a VKA for various indications. In May 2011, a random sample of 5,000 VKA-users for AF was contacted by questionnaire to ask for participation in a quality control cohort with prospective data collection. The registry consists of the 3,162 patients (63%) who returned the questionnaire with written informed consent. Non-consenting patients were older (median age 77 vs 75 years) and more often female (55% vs 44%). For the current analysis we studied patients ≥80 years with non-valvular AF (no mechanical heart valve and/or clinically significant mitral valve stenosis).

Patient characteristics and bleeding risk scores

Demographic and clinical characteristics were collected from the patients' medical charts, the central database of the outpatient anticoagulation clinic as well as the data reported in the questionnaires. For each patient, the HAS-BLED, ATRIA and HEMORR$_2$HAGES risk scores were calculated according to the definitions as reported by each of the models, respectively (Online Supplementary Table 1).[7,10,11] For example, HAS-BLED uses a creatinine of >200 µmol/L (2.26 mg/dL) or chronic dialysis for abnormal renal function, HEMORR$_2$HAGES uses end-stage renal disease or a creatinine >221 µmol/L (2.5mg/dL) and ATRIA scores an estimated glomerular filtration rate of <30 ml/min or chronic dialysis.

To define subjects with a labile INR, the time in therapeutic range (TTR) was assessed.[20] In the Netherlands, the target INR range is usually set between 2.0-3.5. In general, we used the INR values of the 3 months prior to the study (Feb 2011–Apr 2011) to calculate the TTR. For patients who initiated VKA therapy within the last 6 months prior to study inclusion, we used INR values of the 4th until the 6th month after VKA initiation; this, because the first three months after initiation with VKA therapy is associated with suboptimal INR control. Genetic factors included in the HEMORR$_2$HAGES score were not available. Laboratory analyses (e.g. renal or liver function) were derived from the medical charts which were performed as part of

routine clinical practice. Due to our inclusion criteria, the risk factor ´age´ was present for all patients. Consequently, the minimum HAS-BLED and $HEMORR_2HAGES$ scores were 1, and the minimum ATRIA score was 2.

Follow-up and bleeding definitions

For all patients, clinical follow-up started at May 1st 2011 and ended at May 1st 2014.

The primary endpoint was major bleeding. Secondary outcome measures were non-major clinically relevant bleeding, any bleeding and stroke. Follow-up for major bleeding was performed until the earliest of: death; permanent VKA discontinuation; moving outside the region of outpatient anticoagulation clinic Arnhem/Nijmegen; or the end of the study period.

At each visit to the outpatient anticoagulation clinic, patients were interviewed by specialized nurses. Bleeding and/or ischemic events were reported in the electronic patient file. Follow-up information was obtained from the outpatient anticoagulation clinic as well as the hospital medical records. All reported bleeding events were reviewed by a physician, with predefined categorization of its severity.

Major bleeding was defined according to the 2005 International Society on Thrombosis and Haemostasis criteria: fatal bleeding; and/or symptomatic bleeding in a critical area or organ (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome); and/or bleeding causing a fall in hemoglobin level of ≥20 g/L (1.24 mmol/L), or leading to transfusion of ≥2 units of whole blood or red cells.[21]

A clinically relevant non-major bleeding was defined as a bleeding event not meeting the major bleeding criteria, and associated with medical intervention, unscheduled contact with a physician, or (temporary) change in anticoagulation therapy. Clinically relevant bleeding was defined as a major and/or a clinically relevant non-major bleed. All other bleeding events were classified as minor.

Statistical analyses

Every patient was appointed a bleeding risk score (Online Supplementary Table 1). Rates of major bleeding were reported for each of the risk scores of the three models. In addition, they were divided into previously reported risk categories (low,

intermediate, high).[12,16] Cohen's kappa was calculated to measure the agreement of this categorization between the respective three bleeding models.

To assess and compare the performance of the models, univariate associations between the patients' bleeding risk scores and the first occurrence of major bleeding were analyzed using Cox proportional hazard regression analysis for HAS-BLED, ATRIA and HEMORR$_2$HAGES, respectively. In addition to a continuous score, we also dichotomized the bleeding risk scores in analogy to previous publications.[16] To assess the calibration of the models we used the Hosmer-Lemeshow goodness-of-fit statistical method. The discriminatory ability of risk models was evaluated by constructing Receiver Operating Characteristics (ROC) curves and the C-statistic was calculated for the different bleeding scores. To compare the performance of the different bleeding risk models, the net reclassification improvement (NRI) was calculated.[22] The NRI can be used to quantify how well one model reclassifies patients into low or high risk groups (either appropriately, or inappropriately) when compared to another model.

In order to identify risk factors for major bleeding we adopted the following approach. First, we performed multivariate Cox regression analyses, for each of the respective bleeding models separately, starting with the full set of items that comprise the HAS-BLED, ATRIA or HEMORR$_2$HAGES models, respectively. Independent risk factors were identified by a backward stepwise selection algorithm based on likelihood-ratio tests (p-out=0.10; p-in=0.05). The variables that remained in the multivariate model were considered as potentially valuable items for estimation of bleeding risk in the elderly. In addition to these, we chose to include gender, diabetes, polypharmacy and the use of selective serotonin reuptake inhibitors (SSRIs) given their reported impact in (some or more) publications on bleeding risk in the elderly.[24-26,29]

Statistical analyses were performed with PASW Statistical software, version 18 (PASW, Inc., Chicago, Illinois, USA).

RESULTS

Cohort description and clinical follow-up

The present study population consists of 1,157 out of the total of 3,162 patients in the registry (excluded: <80 years, mechanical heart valves, clinically significant mitral valve stenosis).

Median age was 84 years (IQR 82-87) with the eldest patient being 101 years. Patients were predominantly female, the mean BMI was 25.6 kg/m^2 and the most frequently prescribed VKA was acenocoumarol (90%). Polypharmacy was present in 79.3% of patients, and SSRIs were used in 3.4%.

Table 1 shows baseline characteristics, categorized by the occurrence of major bleeding. Most patients were categorized as low risk by the ATRIA risk model (59.6%) and as intermediate risk by the HAS-BLED (38.9%) and HEMORR$_2$HAGES (51.9%). The agreement between the categories of the three models was low to moderate (Cohen's kappa coefficient for all <0.50). A total of 210 patients (18.2%) were categorized as low risk by all three of the models, and 124 patients (10.7%) were categorized as high risk. This was associated with major bleeding in 4.3% and 6.5% of the patients, respectively. Figure 1 presents the percentage of patients with one or more major bleeding categorized for the different risk scores and categories (low, intermediate, high).

Table 1. Baseline characteristics organized by major bleeding

	All (n=1157)	No major bleed (n=1080)	Major bleed (n=77)
Demographics			
Median age, years (IQR)	84 (82-87)	84 (82-87)	84 (82-87)
Age 80-84 years	*610 (52.7%)*	*569 (52.7%)*	*41 (53.2%)*
Age 85-89 years	*415 (35.9%)*	*387 (35.8%)*	*28 (36.4%)*
Age ≥90 years	*132 (11.4%)*	*124 (11.5%)*	*8 (10.4%)*
Male gender	493 (42.6%)	455 (42.1%)	38 (49.4%)
Median months on VKA (IQR)	37 (13-80)	37 (13-81)	35 (13-75)
Alcohol abuse[#]	157 (13.6%)	146 (13.5%)	11 (14.3%)
Medical history			
Hypertension	761 (65.8%)	712 (65.9%)	49 (63.6%)
Hypertension (uncontrolled)	161 (13.9%)	153 (14.2%)	8 (10.4%)

Table 1. Baseline characteristics organized by major bleeding (continued)

	All (n=1157)	No major bleed (n=1080)	Major bleed (n=77)
Previous stroke or TIA	256 (22.1%)	236 (21.9%)	20 (26.0%)
Left ventricular ejection fraction <40%	113 (9.8%)	106 (9.8%)	7 (9.1%)
Coronary artery disease	308 (26.6%)	286 (26.5%)	22 (28.6%)
Diabetes mellitus	297 (25.7%)	281 (26.0%)	16 (20.8%)
Previous bleeding*	252 (21.8%)	233 (21.6%)	19 (24.7%)
Recent or active malignancy	61 (5.3%)	56 (5.2%)	5 (6.5%)
History of falls	195 (16.9%)	182 (16.9%)	13 (16.9%)
Laboratory analyses			
Anemia†	308 (26.6%)	278 (25.7%)	30 (39.0%)
Renal dysfunction‡	100 (8.6%)	91 (8.4%)	9 (11.7%)
Liver dysfunction§	2 (0.2%)	2 (0.2%)	0 (0.0%)
Thrombocytopenia¶	102 (8.8%)	92 (8.5%)	10 (13.0%)
Time in therapeutic range < 60%	234 (20.2%)	218 (20.2%)	16 (20.8%)
Concomitant medication			
Antiplatelet agent	48 (4.1%)	41 (3.8%)	7 (9.1%)
NSAID	24 (2.1%)	22 (2.0%)	2 (2.6%)
Risk models			
Median $CHADS_2$ score (IQR)	2 (2-3)	2 (2-3)	3 (2-3)
Median CHA_2DS_2-VASc score (IQR)	4 (4-5)	4 (4-5)	4 (4-6)
HAS-BLED score			
Mean ± sd	2.23±0.99	2.22±0.98	2.48±1.03
Median (IQR)	2 (1-3)	2 (1-3)	2 (2-3)
ATRIA score			
Mean ± sd	3.93±1.79	3.90±1.77	4.40±1.98
Median (IQR)	3 (3-5)	3 (3-5)	4 (3-6)
$HEMORR_2HAGES$ score			
Mean ± sd	2.63±1.36	2.61±1.36	2.96±1.46
Median (IQR)	2 (2-3)	2 (2-3)	3 (2-4)

Results are presented as median (interquartile range) or mean±standard deviation for continuous data and as number of patients (%) for non-continuous data. #Defined as ≥8 units of per week; *defined as previous clinically relevant bleeding; †defined as hemoglobin < 8.1 mmol/L (males) or <7.5 mmol/L (females); ‡defined as estimated glomerular filtration rate <30ml/min or dialysis dependent; §defined as chronic hepatic disease or biochemical evidence of significant hepatic derangement (i.e. bilirubin>2ULN in association with ALAT/ASAT/ALP/GGT >3ULN); ¶defined as a trombocyte count of $<150x10^9$/L. Abbreviations: n= number of patients at risk; VKA = vitamin-K antagonist; TIA = transient ischemic attack; NSAID = non-steroid anti-inflammatory drug; IQR = interquartile range; sd = standard deviation.

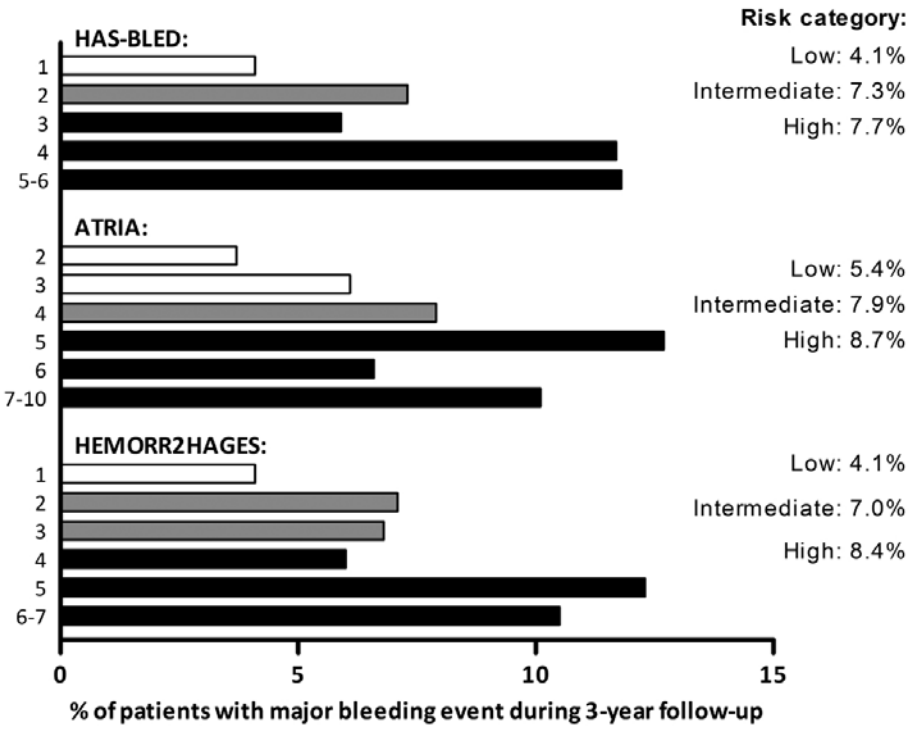

Figure 1: Major bleeding rates during the 3-year follow-up period in relation to the respective bleeding risk scores, and stratified by risk category.

Legend Figure 1: White bars represent low risk categories, grey bars represent intermediate risk categories, black bars represent high risk categories for the respective models. Categorization was performed as previously described.[12,16]

Follow-up

Mean follow-up was 30±10 months. A total of 735 (63.5%) completed the three year follow-up period, 367 patients (31.7%) deceased and 55 patients (4.8%) moved outside of the region or discontinued VKA treatment (e.g. perceived high bleeding risk; switch to NOAC).

After three years, major, clinically relevant and any bleeding occurred in 6.7%, 28.3% and 42.3% of patients, respectively. Overall, 80 major bleeds occurred in 77 patients, 448 clinically relevant bleeds were registered in 328 patients and any bleeding event was observed 807 times in 489 patients. Major bleeding events occurred

most often in the gastrointestinal tract (23/80 events), followed by intracranial bleeding (22/80) (Online Supplementary Table 2).
The median time with an INR in therapeutic range was 81% (IQR 74-87%).

Performance of the bleeding models

The continuous scores of all three models were significantly associated with major bleeding; for the dichotomized categories, there was no association between HAS-BLED and major bleeding (Table 2). For clinically relevant bleeding, there only was a significant association with the $HEMORR_2HAGES$ score. Any bleeding was associated with both the ATRIA and $HEMORR_2HAGES$ models.

The calibration of the bleeding risk models was adequate for all three bleeding endpoints (Hosmer-Lemeshow Goodness-of-Fit significance level >0.05). The discriminatory ability, measured by the receiver operating characteristic (ROC) analyses, was weak for all risk models for major bleeding (C-statistics <0.60) (Table 3). For clinically relevant and any bleeding, the performance of all models was also weak (C-statistic <0.55).

With use of NRI analyses, there were no significant differences between models in the classification of major bleeding (Table 4, Online Supplementary Tables 3-5). The same was observed for clinically relevant bleeding. For any bleeding, the predictive ability of ATRIA was significantly higher when compared to the HAS-BLED model (NRI 8.51%, p=0.009).

Table 2. Univariate analyses of the association of the risk models with bleeding

	Major bleeding HR (95% CI)	CR bleeding HR (95% CI)	Any bleeding HR (95% CI)
HAS-BLED cont	1.30 (1.05-1.61)	1.03 (0.93-1.15)	1.03 (0.94-1.12)
HAS-BLED dich	1.32 (0.84-2.08)	0.94 (0.74-1.18)	0.98 (0.82-1.18)
ATRIA cont	1.19 (1.06-1.33)	1.05 (0.99-1.12)	1.07 (1.02-1.12)
ATRIA dich	1.76 (1.13-2.75)	1.22 (0.98-1.52)	1.37 (1.14-1.63)
$HEMORR_2HAGES$ cont	1.22 (1.05-1.42)	1.11 (1.03-1.20)	1.09 (1.02-1.16)
$HEMORR_2HAGES$ dich	2.02 (1.07-3.83)	1.26 (0.97-1.65)	1.19 (0.96-1.47)

For the continuous models, hazard ratios were calculated per 1 unit of increase. For the dichotomous models, the low risk was used as the comparator and risk groups were defined as: HAS-BLED: low 0-2; high ≥3 points; ATRIA: low 0-3; high ≥4 points; $HEMORR_2HAGES$: low 0-1; high ≥2 points.
Abbreviations: HR = hazard ratio; CI = confidence interval; CR = clinically relevant; cont = continuous; dich = dichotomous.

Table 3. ROC analyses of the risk models with bleeding

	Major bleeding		CR bleeding		Any bleeding	
	C-statistic	95% CI	C-statistic	95% CI	C-statistic	95% CI
HAS-BLED	0.57	0.50-0.63	0.50	0.47-0.54	0.51	0.47-0.54
ATRIA	0.58	0.51-0.64	0.52	0.49-0.56	0.53	0.50-0.57
$HEMORR_2HAGES$	0.57	0.50-0.63	0.53	0.50-0.57	0.53	0.50-0.57

Bleeding risk models with scores as continuous variables.
Abbreviations: ROC = receiver operator characteristic; CR = clinically relevant; CI = confidence interval.

Table 4. Net reclassification improvement analyses

	Major bleeding			CR bleeding			Any bleeding		
	NRI	SE	P	NRI	SE	P	NRI	SE	P
HAS-BLED vs ATRIA	-0.0632	0.071	0.894	-0.0564	0.036	0.119	-0.0851	0.033	0.009
HAS-BLED vs $HEMORR_2HAGES$	-0.0360	0.078	0.460	-0.0561	0.043	0.194	-0.0372	0.038	0.334
$HEMORR_2HAGES$ vs ATRIA	-0.0272	0.069	0.395	-0.0003	0.039	0.994	-0.0479	0.035	0.178

Bleeding risk models analyzed with dichotomized scores.[16]
Abbreviations: CR = clinically relevant; NRI = net reclassification improvement; SE = standard error; vs = versus.

Identification of risk factors for bleeding

Multivariate Cox regression analysis was performed on HAS-BLED, ATRIA and $HEMORR_2HAGES$ separately, and resulted in the following variables that remained in the model after a backward stepwise approach: 1) Of the items in the HAS-BLED model we identified “bleeding predisposition” (=history of major bleeding and/or anemia) and “drugs” (=NSAIDs and/or antiplatelet therapy) 2) Of the variables in the ATRIA model “anemia” was the only identified variable 3) Of the various elements in $HEMORR_2HAGES$ “anemia” and “reduced platelet count/function” (=thrombocytopenia and/or antiplatelet therapy) were identified.

Additional analyses showed that “anemia” and “drugs” were the variables of choice, after which we combined these with predefined potential new risk factors for the elderly (gender, diabetes, polypharmacy, use of SSRIs). Starting with this full model, applying a backward stepwise approach, neither of the new variables remained in the model.

As for age, there was no association with major bleeding, neither studied as a continuous variable, nor as a dichotomous variable.

Estimated risk-benefit

In our VKA anticoagulated cohort rates for major bleeding and ischemic stroke or TIAs were 2.8 and 2.3 per 100 patient-years, respectively (Figure 2). Estimated event rates without VKA and associated NNT and NNH indicate that for every major bleeding caused by VKA treatment a total of four ischemic strokes or TIAs can be prevented, which is also true for patients categorized as high risk of bleeding according to current guidelines (i.e. those with HAS-BLED≥3).

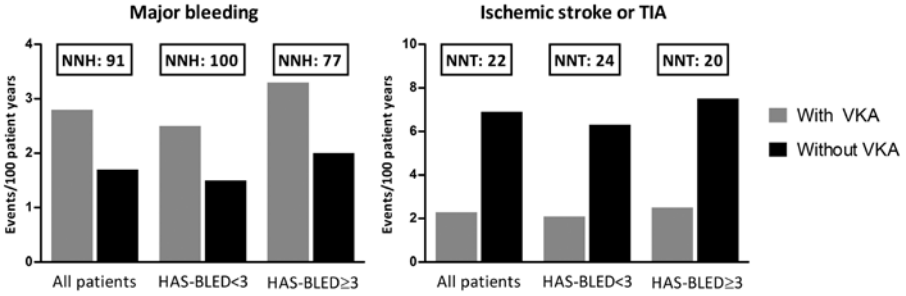

Figure 2: Estimated benefit and harm of VKA therapy in the very elderly

Legend Figure 2: Observed rates for bleeding and ischemic events were calculated by dividing the number of patients with one or more events by the total years at risk. Event rates without VKA treatment were estimated with use of the reported relative risks for VKA versus placebo from the cumulative evidence of published trials[2] (stroke: relative risk 0.36; major bleeding: relative risk 1.66). Based upon the estimated event rates without VKA treatment and the observed rates in our cohort of VKA users, we calculated the number needed to harm (NNH) and treat (NNT).

Abbreviations: VKA = vitamin K antagonist; TIA = transient ischemic attack; NNH = number needed to harm; NNT = number needed to treat.

DISCUSSION

To our knowledge this is the first prospective registry of the very elderly with AF that addresses the performance of currently available bleeding risk models in this specific group of VKA users. Despite a significant association between the continuous scores of all models with major bleeding, we demonstrated that their discriminatory ability was poor, without clear superiority for either of the models. The reported statistically significant superior performance of ATRIA for any bleeding when compared to the HAS-BLED score (significant NRI) should be interpreted with caution given the aforementioned context of poor clinical performance. Despite poor discriminative ability, the bleeding risk models serve as an important tool in clinical practice to identify and follow-up patients who have modifiable risk factors. In that context, the identification of almost 60% of patients as low risk using the ATRIA model seems of practical concern.

Importantly, for all three of the respective bleeding risk models, we observed that the vast majority of the incorporated risk factors was not independently associated with major bleeding; this underscores the need for identification of elderly-specific risk factors .

Lack of performance of bleeding risk models

Not only in the elderly, but also in the general AF population, a search for a model with good performance for major bleeding remains a clinical and statistical challenge. As for the latter, the development of a model with an acceptable positive predictive value is hampered by the infrequent occurrence of major bleeding. From a clinical perspective, the respective derivation cohorts used to develop the currently available models may not be representative of the truly elderly population. In that context, the higher mean age in the derivation cohorts of HEMORR$_2$HAGES and ATRIA (80 and 75 years, respectively) has been suggested as argument to prefer these models over HAS-BLED (65 years), but our data do not corroborate with these recommendations.[7,10,11,23]

Apart from the abovementioned aspects, other aspects such as non-uniformity in the definitions of risk variables are important factors that may complicate the identi-

fication of bleeding risk factors. In the case of anemia, for example, two of the three risk models apply a similar definition, whereas in HAS-BLED a combination is made of anemia and previous bleeding.[7,10,11] As such, the fact that bleeding predisposition in HAS-BLED is associated with major bleeding seems to imply that a history of previous bleeding may be of importance, whereas in fact -in our population- the association is driven by anemia only.

As for a history of bleeding, ATRIA and HEMORR$_2$HAGES use the same definition, referring to any bleeding, whereas HAS-BLED scores admissions for major bleeding.[7,10,11] Irrespective of either definition for a history of bleeding, we did not observe an association with future major bleeding (exploratory analyses). Similar problems regarding uniformity of definitions are true for the use of drugs/antiplatelet agents and renal function (Online Supplementary Table 1).

Apart from these methodological issues, it should be appreciated that the very elderly patient will always be appointed the maximum score for age; hence, the discriminative ability of the risk models will depend on the other variables in the model. As such, the suboptimal performance of all three models in our cohort is explained by the fact that we observed that most of the 'classical' bleeding risk factors that are incorporated in the risk models are not associated with major bleeding. This suggests that the risk factors for bleeding in the elderly may not be the same as observed in the general AF population.

Bleeding risk factors in the elderly

For all three respective models, we observed an independent association between anemia/bleeding predisposition and major bleeding during follow-up. In addition, for HAS-BLED the use of 'high risk drugs' (antiplatelet agents or NSAIDs; Online Supplementary Table 1) and for HEMORR$_2$HAGES a 'reduced platelet count/function' (antiplatelet agents or thrombocytopenia; Online Supplementary Table 1) were also factors related to major bleeding.

Only a limited number of studies has focused on the identification of bleeding risk factors in the elderly AF patient specifically.[24-31] As of to date, in only two other reports anemia was found to be a risk factor for bleeding.[24,25] One study in patients ≥75 years (n=208) identified the use of SSRIs as a risk factor.[24] The other study is by

far the largest registry addressing risk factors for bleeding (over 26,000 patients), in which diabetes, female gender and the use of antiplatelet therapy were the other risk variables.[25] Unfortunately, though intended as the first bleeding model for the elderly, its discriminative ability was modest, and the definition of 'elderly' was set at 65 years, which can be considered rather young for AF patients.[25]

A third study, also in patients ≥75 years (n=199), reported that polypharmacy and variability in the INR were risk factors for major bleeding.[26] Finally, in the largest cohort on patients ≥75 years (n=4130), renal impairment was the only risk factor for bleeding.[27]

Only two studies described bleeding risk factors in octogenarians.[28,29] Neither identified anemia or antiplatelet therapy as predictors of bleeding. In contrast, active cancer, previous bleeding and a history of falls were found as independent predictors of major bleeding in the EPICA study (n=4093).[28] Whereas age was not found to be related to bleeding, data from another cohort (n=798) identified age (>85 years) and diabetes mellitus as risk factors.[29] In our study age was not associated with bleeding, neither as a continuous, nor as a dichotomous variable.

These contrasting data underscore the clinical challenge of bleeding prediction in general, but specifically in the elderly. Based on the available previous reports, we decided to study the impact of gender, diabetes, polypharmacy and the use of SSRIs as potential new risk factors for bleeding. As for the classical bleeding risk models, anemia and the use of drugs were the two variables of interest. Multivariable analysis studying the impact of the abovementioned potential new risk variables did not result in a new contributing risk factor.

In summary, the majority of risk factors for bleeding represented in the current models, is found not to be associated with bleeding in the very elderly. This observation, in combination with reports that risk factors may differ between younger and older patients,[27] underscores the need for additional studies with specific focus on bleeding in populations of elderly patients.

Implications

Appreciating the consequences of undertreatment in the elderly AF patient, and the lack of performance of the current bleeding risk models, there are several implications for both future research and clinical practice.[32]

Future studies on risk factors for bleeding should ideally have a design that accounts for the aforementioned issues. This includes a sufficiently sized, representative cohort of elderly patients with uniform definitions of both risk and outcome variables. This holds especially true for the definition of bleeding as an endpoint, but the definition of a history of bleeding as a baseline risk factor shows great variability as well. In our analysis, we opted for the ISTH definition of the endpoint bleeding, but use of the BARC definition would not have altered our findings.[21,33] Importantly, to gain further insight into risk stratification of a rather infrequent event like major bleeding, we largely depend on quantitative and qualitative reviews, which are only possible if the abovementioned methodological issues have been accounted for.

Apart from more uniform study designs, future studies should anticipate that most risk factors derived from general AF populations do not apply to a very elderly population; therefore, it should be considered to study other, elderly-specific characteristics as potential risk factors, such as (the number/risk of) falls, cognitive function, polypharmacy and one might consider to pay more attention to other non-cardiovascular comorbidities as represented in the Charlson comorbidity index.[34] Moreover, endpoints other than mortality, stroke and bleeding could be of value, such as the impact of bleeding on (instrumental) daily activities. Importantly, the fact that elderly patients experience major bleeding in case of a cutaneous localization (Online Supplementary Table 2), which is infrequently the case in younger populations, is yet another indication that the very elderly should be considered as a unique population by itself: not only risk factors for bleeding may vary, also the impact of a bleeding may vary from younger populations.

As of yet, it remains a clinical challenge to identify subjects at high risk of bleeding, given the rather low frequency of major bleeding. Alternatively, identification of low risk patients seems feasible. Our data indicate that in the absence of other risk factors than age, a truly low risk group of about 25% of patients can be identified with 3-year rates of major bleeding of 4.1% (HAS-BLED=1), 3.7% (ATRIA=2) and 4.1%

(HEMORR$_2$HAGES=1), respectively. According to stratification by the models, 60% of patients would be considered low risk according to ATRIA, as compared to 25% and 23% for HAS-BLED and HEMORR$_2$HAGES respectively. This categorization is likely to result into less attention for lower risk individuals when using the ATRIA model. Especially in case of electronically based patient management systems, this could be a potential failing of the ATRIA model as this may result in a higher proportion of patients classified as 'low risk' and, as such, may cause less awareness for modification of the reversible risk factors.

Although identification of a truly low-risk subgroup seems feasible (no other risk factors than age), the majority of patients will present with risk factors, and specific tools for guidance are lacking. This is further complicated by the fact that several variables incorporated in the current bleeding risk models are also known risk factors for stroke.[8,9] In anticipation of future initiatives, and appreciating the rate of undertreatment and its adverse consequences, some form of guidance is warranted for the daily management of this growing population of the elderly.[32]

Based upon the observed event rates in the present cohort we estimate that, in general, the benefits of VKA therapy exceed the detrimental effects in an elderly AF population (Figure 2: NNH 91; NNT 22). To provide more objective guidance, new initiatives on bleeding risk factors in the very elderly are eagerly awaited, as well as additional safety data for the non-vitamin K oral anticoagulants.[35,36]

LIMITATIONS

A first limitation of our study refers to selection and generalizibility. About one-third of patients did not consent to participate and unfortunately, ethical considerations prohibited us from collecting other information than age and gender. Moreover, about a third of patients deceased before the end of follow-up. Their baseline profile was markedly different from survivors (history of falls, diabetes, anemia, thrombocytopenia). This, and the shorter time at risk of an event may have influenced our identification of risk factors for bleeding and/or the magnitude of the observed

associations. In addition, even though the rate of VKA discontinuation was low, this may have affected our findings.

Second, autopsy was not performed systematically and major bleeding in terms of deaths caused by (intracranial) bleeding could therefore have been missed. With regard to the net clinical benefit estimation, it should be considered that this calculation is based upon data from studies performed decades ago. Given the improved INR control (TTR) nowadays, associated with better efficacy and a lower bleeding risk of VKA treatment, the risk-benefit profile could even be more favorable than currently estimated.[37,38]

CONCLUSIONS

In this three year follow-up study of a large real-world cohort of very elderly AF patients, the currently available bleeding risk models did not provide clinically relevant discriminatory ability, despite statistically significant associations between the bleeding scores with major bleeding. Notably, apart from anemia and the use of antiplatelet agents none of the risk factors incorporated in the models derived in the general population was associated with major bleeding in this aged population.

Patients without other risk factors than age are at truly low risk of bleeding; for other patients, caution is warranted for the threshold to categorize patients as low-risk as this may inadvertently result in less attention for modifiable risk factors. Appreciating the issue of undertreatment, and the suggested favorable risk-benefit profile of oral anticoagulation in our cohort, tools that provide guidance in the potential harm and benefit in this specific population are eagerly awaited in this era of increasing life expectancy.

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8

Summary and epilogue

SUMMARY

In the general introduction of Chapter 1, background information is provided on the pathogenesis of an atherothrombotic event, the therapeutic options and its limitations. The remaining part addresses the scope of the current thesis with the different study questions.

Chapter 2 describes the occurrence of gastrointestinal symptoms with different formulas of low-dose aspirin. In the 1980s, aspirin proved to be essential in the secondary prevention of cardiovascular disease and is now prescribed to over 1 million patients in the Netherlands. Unfortunately, aspirin has gastrotoxic properties, both locally and systemically, which can manifest as gastric ulcer formation, gastric bleeding and is also associated with dyspepsia which affects compliance to aspirin. To reduce local gastric toxicity a buffered form of aspirin (effervescent calcium carbasalate) has been developed. To compare the prevalence of self-reported gastrointestinal symptoms between plain and buffered aspirin, we used data of a large population based cohort study on gastrointestinal symptoms (n=18,317). In this cohort, 1544 participants used low-dose aspirin, which was used in plain form by 911 patients, whereas the buffered formulation was used by 633 subjects. We demonstrated that gastrointestinal symptoms were frequently reported (≈27%) with no difference between both groups. Also with regard to specific upper and lower gastrointestinal symptoms, no differences were observed between groups. Hence, our data indicate that as far as gastrointestinal symptoms are concerned, buffered aspirin has no additional value over plain aspirin. To optimize compliance to aspirin we feel that the addition of a proton pump inhibitor seems a better alternative, given that proton pump inhibitors have demonstrated to effectively reduce gastrointestinal symptoms.

Although proton pump inhibitors (PPIs) increase safety of aspirin, concerns have been raised that they might decrease the efficacy of clopidogrel. In Chapter 3, we performed a systematic review to study the impact of the addition of PPIs on platelet function and clinical cardiovascular outcome. At present, the European Society of Cardiology (ESC) guidelines recommend aspirin and clopidogrel as standard treatment after a percutaneous coronary intervention for stable angina. Notably, although

a recent guideline update states that in patients with an acute coronary syndrome (ACS) more potent agents like ticagrelor and prasugrel are to be preferred, many ACS patients are still treated with clopidogrel as adjunctive to aspirin. In this context, the warnings issued by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2009 are still of interest. Co-therapy with a proton pump inhibitor (PPI) was reported to potentially reduce the antiplatelet effect of clopidogrel as both these drugs act on the cytochrome P450 2C19 iso-enzyme, thereby reducing the transformation of clopidogrel to its active metabolite. These reports were initially based on laboratory and retrospective cohort studies. In follow-up of these first reports, several prospective studies have been conducted that challenged the retrospective data. With regard to the laboratory studies, 10 studies were identified that involved healthy volunteers and 18 included cardiovascular patients. In both settings the co-administration of a PPI resulted in a significant reduction of platelet inhibition of clopidogrel in the majority of the ex vivo studies (7/10 in healthy volunteers; 11/18 in patients). The impact of conjunctive use of PPIs on clinical outcome was investigated in 33 studies concerning over 200 thousand patients. Importantly, most of these studies were of retrospective design (21/33) with signs of prescription bias and imbalances in baseline characteristics. In addition, there was significant heterogeneity in observed outcomes, with risk ratios varying from 0.68 to 4.58. Notably, taken into consideration the established 20% relative benefit of the addition of clopidogrel to aspirin treatment, it should be acknowledged that the reports of a relative risk increase exceeding 50% cannot solely be attributed to the use of PPI co-treatment. More importantly, only 48% of the studies reported an increased risk for major adverse cardiovascular events (MACE) in case of concomitant PPI use. Moreover, of the two studies in which the PPI was randomly allocated, none showed signs of adverse outcome in case of PPI use. Hence, despite indications of reduced antiplatelet activity in laboratory studies, the available reports on clinical outcome do not uniformly support the statement that PPI co-treatment adversely affects the beneficial properties of clopidogrel.

Nonetheless, despite the use of dual antiplatelet therapy (aspirin plus clopidogrel) following a myocardial infarction, recurrent events occur in about 10% of the patients within one year. In daily practice, this is a group that merits further attention

with regard to the antithrombotic regimen. In Chapter 4, we address the value of prolonged anticoagulation therapy in patients in whom dual antiplatelet therapy has been proven clinically ineffective. Vitamin K antagonists (VKAs) have proven efficacious in ACS as monotherapy, with outcomes similar to aspirin. As adjunct to aspirin, there is robust data indicating that long-term VKA therapy improves outcome after an ACS in patients with sinus rhythm. In a meta-analysis of 7,836 patients, the allocation of a VKA (INR 2.0-3.0) added to aspirin therapy reduced the risk of death, non-fatal myocardial infarction and/or stroke from 12.3% to 9.4%. Notably, this was at the cost of an increase in major bleeding from 1.1% towards 2.6%.

The development of the non-VKA oral anticoagulants (NOAC), without the need for monitoring, has renewed the interest for prolonged anticoagulation therapy. Importantly, these drugs have only been studied as adjunctive to dual antiplatelet therapy, which remains the cornerstone in the treatment of ACS. Of the NOACs, only rivaroxaban, used in very low doses, has demonstrated to improve clinical outcome. However, given the significant increase in bleeding risk, it should be used only in selected patients at very high risk of recurrent ischemic events.

The most challenging population concerns patients with a strict indication for oral anticoagulation therapy who develop an ACS. Given the scarcity of data of NOACs in the acute setting, we feel that NOACs should be discontinued during hospital admission in this specific group of patients. Following discharge, a NOAC used in a dose for atrial fibrillation should not be combined with dual antiplatelet therapy given the unacceptable high bleeding risk demonstrated in various phase II and III trials. Given these safety concerns, we recommend prolonged anticoagulation with VKAs in the first year following ACS. In case the indication for dual antiplatelet therapy has ended, physicians can reconsider switching the VKA to a NOAC.

The bleeding risk of NOACs is also the subject of Chapter 5. This chapter concerns a critical appraisal of a meta-analysis describing a 45% increased risk of gastrointestinal bleeding associated with the use of NOACs prescribed for various indications. In this commentary, we call for a more cautious interpretation of the reported risk. First, the meta-analysis included studies in which the NOAC was used for secondary prevention of ACS in which placebo was the comparator. Importantly, in these studies the NOAC was used in doses used for stroke prevention in atrial fibrillation,

which have not been endorsed by current guidelines given the known high bleeding rates. Secondly, with regard to trials on AF, a substantial amount of data without an increased gastrointestinal bleeding risk was not incorporated in the meta-analysis. Finally, we call for a more careful evaluation of both the risks and benefits, such as the reduced risk of intracranial bleeding with NOAC therapy.

One of the NOACs that demonstrated to be safer and more effective than warfarin when used for stroke prevention in AF is apixaban. However, this drug was studied in a general AF population, and there are suggestions that patients with polypharmacy (i.e. ≥5 drugs) are older and more frail and could have a differential response to anticoagulation therapy. In this context, we performed a post-hoc analysis of the ARISTOTLE trial in which apixaban was compared to warfarin in 18,201 patients with AF (Chapter 6). We demonstrated that patients using more drugs constitute a population with greater comorbidity, increased risk of mortality and were at higher risk of ischemic and bleeding complications. With regard to efficacy, the superiority of apixaban when compared to warfarin for stroke (21% risk reduction) and mortality (11% risk reduction) observed in the complete population were irrespective of the number of concomitant drugs used. Notably, although apixaban demonstrated a 31% risk reduction on major bleeding in the main trial, we observed a statistically significant treatment interaction with relative risk reductions of apixaban varying from 50% (0-5 drugs) to 28% (6-8 drugs) and 16% (≥9 drugs). Interestingly, it did not appear that the use of warfarin or apixaban potentiating drugs explained this observed treatment effect. These findings indicate that observations on efficacy and safety in general populations can differ in high risk populations, such as the elderly with various comorbidities.

Despite evidence of beneficial effects of oral anticoagulation therapy in the very elderly, physicians remain concerned about the bleeding risk and undertreatment of these patients is common. Various bleeding risk models have been developed to assess the bleeding risk of which HAS-BLED, ATRIA and HEMORR$_2$HAGES are mostly used. However, these models were developed in general populations and their performance in the very elderly is unknown. In Chapter 7 we assessed and compared the discriminatory ability of three acknowledged bleeding risk models on major bleeding in the very elderly AF patients using a vitamin K antagonist. During a 3-year follow-up

period, major bleeding occurred in 6.7% of this specific population (rate: 2.8%/year). Despite a significant association of all three models with major bleeding, the discriminatory abilities were rather poor (C-statistics < 0.60), without a clear superiority for any of the models. Notably, apart from anemia and the use of non-steroidal anti-inflammatory drugs (NSAIDs) or antiplatelet agents none of the 'classical' risk factors incorporated in the models derived in the general population was associated with major bleeding in this aged population. To provide some guidance with regard to clinical decision making, we calculated an estimated risk-benefit and demonstrated that, in general, the benefits of VKA therapy exceed the detrimental effects in this growing population of the very elderly. To provide more objective guidance, new initiatives on bleeding risk factors in the very elderly are eagerly awaited, which should focus on elderly specific risk factors.

EPILOGUE

This thesis focused on the balance between safety and efficacy of oral antithrombotic therapy in the field of cardiology. This topic was studied in antiplatelet agents, such as aspirin and clopidogrel, as well as oral anticoagulants, which can be categorized as vitamin K antagonists (VKAs) and non-VKA oral antagonists (NOACs).

An optimal balance between safety and efficacy is essential. A reduced efficacy can cause thrombosis which can result in a more intensive antithrombotic treatment, thereby increasing the risk of bleeding complications. On the other hand, a perceived high bleeding risk can result in a reduced compliance and undertreatment, which demonstrates that the safety of an antithrombotic agent affects the effectiveness of a drug.

This thesis describes the abovementioned interaction between safety and efficacy in the treatment and prevention of stable and unstable coronary artery disease as well as the treatment of atrial fibrillation.

ACUTE CORONARY SYNDROME

Efficacy

The prevention of an acute coronary syndrome (ACS) has changed extensively in the last decades. After aspirin became available, followed by clopidogrel, newer antiplatelet agents have emerged which proved to be even more effective in the prevention of ACS. In addition, more and more studies focused on the value of adding an (oral) anticoagulant as adjunct to the antiplatelet agents. These developments have improved the treatment of an ACS and significantly reduced the risk for recurrent events. Unfortunately, with the arrival of the antiplatelet agents, new problems have emerged.

Given the substantial number of patients with a recurrent thrombotic event despite dual antiplatelet therapy, the term ‘resistance’ to aspirin and clopidogrel has been introduced. It is uncertain to what extent this can be contributed to a suboptimal efficacy of the antiplatelet agents. This topic has been given much attention

in the recent past in which the results of ex vivo platelet function tests were used as surrogate for efficacy in vivo. An important example is the supposed interaction between clopidogrel and proton pump inhibitors, resulting in a reduced production of the active metabolite of clopidogrel, which is discussed in this thesis. Notably, the initial warnings of the Food and Drug Administration (FDA) and European Medicines Agency (EMA) were based only on ex vivo studies and clinical studies with a retrospective design. On the one hand did the ex vivo results indicate a clear interaction given the higher platelet reactivity in case of PPI coadministration, albeit that this was most pronounced in healthy volunteers with no history of an ACS. On the other hand did the data of prospective (randomized) studies not suggest an effect on clinical outcomes in case of clopidogrel and PPI coadministration.

This discrepancy between platelet function tests and clinical outcome has also been described in two large trials (GRAVITAS; ARCTIC) in which patients with an ex vivo increased platelet reactivity were randomized to more intensive antiplatelet therapy, or the continuation of the current treatment. These studies concluded that, although a more intensive approach significantly reduced platelet reactivity, it did not affect clinical outcome.

These findings in large randomized studies demonstrate the limitations of retrospective studies, which is the result of prescription bias and reduced quality of the collected data. Although the warnings of the FDA and EMA can be advocated in terms of efficacy, these warnings could potentially result in changes in prescription patterns, such as discontinuation of the PPI or switching to another P2Y12 inhibitor such as ticlopidine, which affects safety issues such as gastrointestinal bleeding and bone marrow suppression.

Although a certain part of the recurrent events can be attributed to ‘resistance’ to antiplatelet therapy, it should be noted that inhibition of only the thrombocytes in the treatment and prevention of an ACS does not suffice. Several older studies clearly indicated that VKA monotherapy is effective in the setting of acute and chronic coronary disease. However, no studies were performed to further investigate the potential value of oral anticoagulation as adjunct to dual antiplatelet therapy, although VKAs also proved their potential when added to aspirin monotherapy. As of to date, no large randomized studies have investigated the potential of adding VKA to

dual antiplatelet therapy in patients with sinus rhythm and this combination is based upon expert opinion and applied only in selected cases. Interestingly, several phase II studies with NOACs in patients with dual antiplatelet therapy have been performed. The only completed phase III trial concerns the prescription of triple therapy with a very low dose of rivaroxaban, which significantly lowered the risk of ischemic events at the cost of a markedly increased bleeding risk. These data underscore the value of (adjunctive) anticoagulation therapy in reducing the risk of thrombotic events following an ACS.

Implications for future research. The large variety in possible devices to determine the platelet reactivity as well as the lack of definite normal values for the treatment of the individual patient are striking. Moreover, there is limited uniformity between studies with regard to the timing of the measurement in relation to the intake of the antithrombotic agent or the onset of symptoms. Finally, given the coefficient of variation of the various laboratory tests, a minimum of three measurements should be performed to provide a reliable result. Future research should incorporate these aspects in the design of the study.

Besides these methodological aspects impeding the detection of a possible relation, the hypothesis that recurrent events are the result of 'resistance' is subject to critique. First, the term 'resistance' does not take into account the normal course of an ACS, nor the possibility of a new plaque rupture with (sub)total thrombotic occlusion. Attributing this to a failure of the antithrombotic agent does not take into account the multifactorial character of a complex disease such as an ACS. Moreover, no large and well designed studies demonstrated that platelet reactivity measured with laboratory devices independently predicts clinical outcome. There appears to be a relation between an increased risk profile (diabetes, renal impairment, age) and platelet reactivity in ACS. These observations deserve more attention in future research to get a better understanding of the value of platelet function tests and to investigate its role in future patient tailored medicine based on platelet function tests.

As for future studies on the addition of anticoagulants, the challenge would be to define an optimal dose and duration for adjunctive therapy, as well as the possibility

to discontinue one of the antiplatelet agents. This concept should be placed in the context of the balance between the thrombotic risk and safety aspects.

In summary, although mechanistic studies can provide insight in the potential working mechanisms of antiplatelet agents, it should be appreciated that there is uncertainty with regard to the question whether laboratory findings translate into clinical practice. Given the fact that activation of platelets and the coagulation cascade are intertwined and the proven efficacy of VKAs in patients with an ACS, we feel that renewed interest in the potential role for anticoagulation therapy in ACS is important, especially with the availability of the NOACs with their attractive safety profile.

Safety

With the improved efficacy of antithrombotic treatment, the risk of safety issues such as bleeding is also increased. Given the toxic effect of aspirin on the stomach, most research focused on the dose and formulation of this agent, and less attention was given to other antiplatelet agents.

As far as the dosing is concerned, randomized studies demonstrated an increased risk of gastro-intestinal complications in case of higher dosing. However, this concerned doses higher than those recommended in the setting of ACS. Retrospective data of ACS patients treated with lower doses of aspirin (75-325 mg) indicated that also in ACS the dosing of aspirin is related to bleeding complications.

With regard to the formulation of aspirin, various studies have been conducted to investigate a potential role in the reduction of gastro-toxicity, of which enteric coated aspirin and effervescent calcium carbasalate are two examples. Effervescent calcium carbasalate better dissolves in the stomach and it does not transfer through the protective mucus layer as easily as compared to plain aspirin, which would theoretically lower the local gastro-toxicity of this agent. Although effervescent calcium carbasalate was associated with a reduced risk of gastrointestinal ulcers, this was studied in healthy volunteers using very high daily doses. In contrast, in a large retrospective study performed in patients using low doses of aspirin, no differences between formulations on gastric ulcers was observed. Another possible advantage of these aspirin formulations could be a reduced risk of dyspepsia, which could

potentially reduce compliance thereby indirectly reducing the efficacy. In this thesis, we demonstrate no advantage of effervescent calcium carbasalate when compared to plain aspirin with regard to the risk of dyspepsia. However, this latter is associated with higher costs, which even exceed those of the combination of plain aspirin with the addition of a PPI. Given the knowledge of previous studies demonstrating a significant protective effect of PPIs on dyspepsia, we recommend to use a PPI in case a patient suffers from aspirin related dyspepsia. In addition, patients using aspirin who are at increased risk of gastrointestinal bleeding could also be prescribed a PPI. This risk can be assessed by the presence or absence of various clinical variables, such as a history of gastric ulcers or gastric bleeding, age, the use of two antiplatelet agents, or the concurrent use of an oral anticoagulant.

Implications for future research. The registration of the dose of aspirin has become standard in most of the large clinical trials. However, a systematic registration of gastrointestinal symptoms is lacking, despite its high occurrence and clinical importance. Notably, also the occurrence of gastrointestinal bleeding complications is not systematically reported. In an era in which consideration of the balance between risks and benefits is gaining importance, prospective registration of these safety aspects is essential. Moreover, with the introduction of new antithrombotic agents, the registration of the use of a PPI is important to provide insight in the gastrointestinal risk profile when comparing two antithrombotic regimens. In this context, the COMPASS trial is a major step forward. This study with a factorial design, not only compares the treatment of a NOAC with aspirin, but also studies the value of adding a PPI to these drugs.

Efficacy and safety: the balance

Now that the development of more potent antiplatelet agents has taken off, it is important to pay attention to the accurate balance between efficacy and safety. In addition to the risk of gastro-intestinal bleeding, the overall bleeding risk should also be assessed. For ACS the CRUSADE risk model has been developed, and ACS guidelines also refer to the HAS-BLED bleeding risk model. Notably, the HAS-BLED has been developed and validated in AF populations without ACS, in which the predictive ability already proved poor.

The risk of future thrombotic events can be determined using the TIMI risk score or the GRACE model, the latter of which is used by most European physicians. Both the GRACE as well as the CRUSADE models have been extensively validated with acceptable predictive abilities in patients without AF.

Implications for future research. Although a first step towards risk-stratified treatment has been made, data on the integration of information of both models and the potential treatment options is scarce. In this light, it is important that a consensus is formed about an acceptable number needed to harm (NNH) in relation to a provided number needed to treat (NNT). These questions could guide the trade-off between dual antiplatelet therapy with aspirin and clopidogrel versus one of the more potent antiplatelet agents (ticagrelor, prasugrel), but also for the adjunctive therapy with an anticoagulant as an intensified treatment option in the secondary prevention of an ACS. Especially for patients with sinus rhythm, the need exists for comparative research between the CRUSADE and the HAS-BLED score.

For AF patients, there often exists a life-long indication for oral anticoagulation, which is complicated by the fact that in case of an ACS these patients also require dual antiplatelet therapy. A recently published randomized controlled trial concerning patients with an indication for a VKA who underwent a percutaneous coronary intervention were randomized to clopidogrel alone or in combination with aspirin both as adjunct to a VKA. This study indicated that the omission of aspirin resulted in less bleeding complications without signs of reduced efficacy. Studies with a similar design are also ongoing with NOAC therapy instead of a VKA, in which the combination of one antiplatelet agent and one anticoagulant seem to be the future standard. However, triple therapy with oral prolonged anticoagulation as well as the period of dual antiplatelet therapy are also being studied. Given the fact that dual antiplatelet therapy with a very low dose of rivaroxaban resulted in more bleeding in the ATLAS-ACS-2 trial, but was also associated with significant increased efficacy, the trade-off in terms of NNT and NNH needs to be determined for these new regimens. It should be appreciated that this is more complex in AF patients, as they require a NOAC dose much higher than used for ACS.

ATRIAL FIBRILLATION

Efficacy

As mentioned before, stroke prevention in AF consists of anticoagulation with a VKA or a NOAC, and there is no longer an indication for aspirin in this setting. Even treatment with dual antiplatelet therapy is significantly inferior to the observed 60-70% risk reduction of anticoagulation therapy. Despite this impressive data on efficacy, oral anticoagulation is often withheld. One of the arguments concerns the question whether the trial data also apply to the 'older' and 'fragile elderly' patients. The data of the BAFTA trial, which studied a general population of patients aged 75 years or above, clearly demonstrated that VKA treatment is more effective than aspirin, without an increase in the risk of bleeding. Also with the NOACs, the available data indicate that the results with regard to efficacy also apply to the elderly patient.

In the current era of increasing life expectancy, but with an increasing extent of comorbidities, the question emerges about the trade-off between the NNT and NNH in this population. To provide more insight into this topic, we initiated a registry in collaboration with the INR Anticoagulation Clinic Arnhem-Nijmegen which focused on quality and patient satisfaction of VKA anticoagulated patients. In our cohort of patients aged 80 years or older, the balance between NNT and NNH seems te be in favor of VKA treatment. As for the NOACs, our data did not indicate a reduced effect in case of more comorbidity, which underscores the importance of treatment of the fragile elderly, also in the light of the reports on the risk of undertreatment.

Implication for future research. Although the populations studied in the recent AF trials are representative of the average outpatient clinic patient, they do not reflect all patients who are treated by the general physician. Especially patients with cognitive disorders, mobility dysfunction and for example patients with severe renal disorders are not represented in these trials and the subset of patients with extensive comorbidities would be rather low. For patients with these characteristics, future research is warranted, which should also include data on compliance, given its importance with regard to NOAC treatment.

Also patients with a recurrent stroke or TIA are a specific patient population that deserves more attention. For this group, measurements of the anticoagulation

activity could be incorporated in clinical practice to further enhance patient tailored medicine.

Safety

As described above, aspirin is not a safer alternative to oral anticoagulation therapy and the efficacy is significantly lower, findings which also hold true for the elderly. Another subset of patients whom are frequently prescribed aspirin are patients who are unwilling or have a contra-indication to take VKA. Also in this specific cohort, findings from a randomized study indicate that aspirin is not safer when compared to the oral anticoagulant apixaban, which is one of the NOACs.

In patients without a contra-indication for VKAs, NOACs are an at least as safe alternative with regard to major bleeding. Notably, for all NOACs an almost 50% risk reduction for intracranial bleeding was demonstrated, however, this advantage should be placed in the context of a higher risk of gastro-intestinal bleeding or other major bleeds for most of the NOACs.

Also with regard to safety the question emerges if the data from the NOAC trials apply for the 'older' and 'fragile elderly' patients. Patients with various comorbidities not only have an increased risk for the use of (potentially) interacting drugs, their general physical health is impaired as well as the adaptation mechanisms of the body. In this context, it is very well possible that the 'fragile elderly' are prone to a differential response to anticoagulation therapy when compared to younger patients. With regard to the elderly in general, safety outcomes of dabigatran 150 mg bid differ between the elderly and younger patients in which the elderly allocated to dabigatran are at higher risk of bleeding when compared to those receiving warfarin. For the other NOACs, no age-related differences with regard to safety were observed.

As for the safety of patients with various comorbidities, studies on both VKA as well as NOAC therapy are scarce. In our population of AF patients aged 80 years or above, we studied whether risk factors identified in general AF populations are associated with bleeding in the elderly. Interestingly, only a minority of these classical risk factors were associated with bleeding in this elderly population. Nonetheless, the trade-off in terms of NNT versus NNH was clearly in favor of treatment with an oral anticoagulant, which implies that the assumption of the advantage of not treating a

patient with oral anticoagulation based upon a perceived high bleeding risk could not be substantiated in our cohort.

Studies conducted to investigate a potential differential response to NOACs in terms of safety in patients with a greater number of comorbidities used polypharmacy as a tool to categorize these patients. It was shown that polypharmacy was not only related to mortality and stroke, but was also associated with an increased bleeding risk. While the rates were consistently lower with apixaban, the magnitude of benefit with apixaban decreased with the number of concomitant drugs. Taken into account that the safety benefit of apixaban did not significantly differ between chronologically younger and older patients, it can be concluded that observations made in the 'older' patients cannot simply be inferred to the 'fragile elderly'.

Implications for future research. The findings of the abovementioned retrospective analyses suggest that the safety of anticoagulation is related to the extent of comorbidity, the number of concomitant drugs, and the combination of these factors. Future large studies with emphasis placed on the biological age instead of chronological age are awaited, especially given the increasing life-expectancy and age dependent incidence of AF. The HAS-BLED model can be of some use in the risk stratification in general AF populations, however, the discriminative ability has proven to be very poor. As such, healthcare providers should be cautious with omitting anticoagulation therapy to a patient based only on a high HAS-BLED score. Alternatives for the HAS-BLED model have been proposed by several research groups in view of the improvements that can be made in the prediction of bleeding. Recently, the ABC-model has been proposed which combines clinical factors with age and biomarkers. Although this model seemed a better alternative when compared to other models, the accuracy is still not optimal and deserves further optimization.

The fact that the risk factors incorporated in the HAS-BLED model are not associated with bleeding in the elderly gives the impression that there is a need for 'elderly-specific' risk models. Examples of risk factors could be polypharmacy, cognitive function, but perhaps also easy to perform geriatric tests that could help in the assessment of a patient's biological age.

Finally, the question emerges if risk factors for bleeding differ between patients using a VKA or a NOAC. Although both concern oral anticoagulants, there are distinc-

tive differences with regard to the working mechanism, elimination and interacting drugs which calls for a renewed inventory of risk factors. Moreover, it could be of potential value to adjust the dose of NOACs based upon the anticoagulation activity measured with laboratory tests. Improved insight in factors associated with bleeding could give guidance to physicians, thereby reducing undertreatment and optimize the balance between safety and efficacy.

Efficacy and safety: the balance

With the addition of the NOACs as a treatment option, the landscape of antithrombotic therapy in AF has evolved and new questions have emerged. Although in general the NOACs improved safety, there is a need for the calculation of the risks versus the benefits, especially in view of the increased risk of gastrointestinal bleeding. Although the CHA_2DS_2-VASc model has been associated with ischemic events in both VKA and NOACs, research on the value of the HAS-BLED model in patients using a NOAC limited.

Implications for future research. In view of the above, it is important that a consensus is formed about an acceptable number needed to harm in relation to a provided number needed to treat. This consensus can be applied to the comparison between VKA versus a NOAC, but future research is likely to focus more on 'patient tailored' medicine. This could include risk-benefit models for all of the NOACs when compared to a VKA. However, the need will be especially high for the development of a bleeding risk model with good predicitive ability which could guide healthcare providers with decision making in daily clinical practice.

All in all, the field of anticoagulation is moving forward and given the wide selection of options of drugs, further refinement of the treatment of atrial fibrillation seems possible with the currently available options, especially if the balance between safety and efficacy is given special notice.

9

Samenvatting en epiloog

SAMENVATTING

In de algemene introductie in Hoofdstuk 1 wordt basale achtergrond informatie gegeven met betrekking tot de pathogenese van een atherotrombotische gebeurtenis, de therapeutische mogelijkheden en tekortkomingen. In het overige deel wordt de uiteenzetting van het proefschrift weergegeven met de verschillende studievragen.

Hoofdstuk 2 beschrijft het voorkomen van gastro-intestinale symptomen bij verschillende formules van aspirine. In de jaren 80 van de vorige eeuw is aangetoond dat aspirine essentieel is bij de secundaire preventie van cardiovasculaire ziekten en momenteel wordt het door meer dan 1 miljoen Nederlanders gebruikt. Helaas is aspirine geassocieerd met gastro-toxische bijwerkingen, zowel lokaal als systemisch, wat zich kan manifesteren als maagulcera, maagbloedingen, alsook dyspepsie hetgeen de therapietrouw van aspirine negatief kan beïnvloeden. Om lokale effecten van aspirine op de maag te reduceren is er een gebufferde vorm van aspirine ontwikkeld (calcium carbasalaat). Om de prevalentie van zelf gerapporteerde gastro-intestinale symptomen te vergelijken tussen 'gewone' aspirine en de gebufferde variant, hebben we gebruik gemaakt van een grote cohort studie naar gastro-intestinale symptomen (n=18.317). In dit cohort gebruikten 1544 deelnemers een lage dosering aspirine, waarvan 911 'gewone' aspirine gebruikten en 633 deelnemers de gebufferde variant. Onze studie toonde aan dat gastro-intestinale symptomen frequent voorkomen (~27%) zonder een verschil tussen de twee groepen. Ook met betrekking tot symptomen die de bovenste dan wel het onderste deel van het maag-darm systeem betreft zien we geen voordeel van de gebufferde aspirine in vergelijking met 'gewone' aspirine. Om de therapietrouw te optimaliseren is toevoeging van een protonpompremmer ons inziens een beter alternatief, aangezien het gebruik hiervan wel heeft aangetoond gastro-intestinale symptomen te verminderen.

Alhoewel protonpompremmers de veiligheid van aspirine verbeteren, zijn er aanwijzingen dat het gebruik hiervan de effectiviteit van clopidogrel kan verminderen. In hoofdstuk 3 hebben wij een systematisch review uitgevoerd om de impact van het toevoegen van een protonpompremmer op plaatjesfunctie en klinische cardiovasculaire uitkomsten te onderzoeken. De huidige European Society of Cardiology (ESC) richtlijn adviseert om aspirine en clopidogrel als standaard therapie te gebruiken na

een dotterprocedure bij stabiele angina pectoris. Alhoewel een recente update van de richtlijnen aangeeft dat bij patiënten met een acuut coronair syndroom (ACS) de voorkeur wordt gegeven aan potentere medicamenten als ticagrelor en prasugrel, worden veel patiënten nog steeds met clopidogrel als aanvulling op aspirine behandeld. In deze context zijn de waarschuwingen van de Food and Drug Administration (FDA) en European Medicines Agency (EMA) uit 2009 nog steeds actueel. Gelijktijdig gebruik van een protonpompremmer zou mogelijk het effect van clopidogrel op de trombocytenaggregatieremming verminderen doordat deze beide medicamenten van invloed zijn op het iso-enzym 2C19 van cytochroom P450. Hierdoor zou de transformatie van clopidogrel naar zijn actieve metaboliet worden verminderd. Deze waarschuwingen waren initieel gebaseerd op laboratorium studies en retrospectieve klinische studies. In navolging van deze studies zijn er verscheidene prospectieve onderzoeken verricht die niet in overeenstemming waren met de retrospectieve studies. Met betrekking tot de laboratorium studies zijn er 10 studies geïdentificeerd die gezonde vrijwilligers includeerden en 18 studies waarbij cardiovasculaire patiënten werden onderzocht. In het merendeel van beide van deze studieopzetten bleek dat het gebruik van een protonpompremmer resulteerde in een significante reductie van de plaatjesremming van clopidogrel (7/10 bij gezonde vrijwilligers; 11/18 bij patiënten). Het effect van gelijktijdig gebruik van een protonpompremmer met betrekking tot klinische uitkomsten is onderzocht in 33 studies hetgeen in totaal meer dan 200.000 patiënten betrof. Van belang is dat de meeste van deze studies (21/33) een retrospectieve opzet hadden met aanwijzingen voor voorschrijfbias en verschillen in baseline karakteristieken tussen patiënten met en zonder een protonpompremmer. Bovendien was er sprake van een significante heterogeniteit in de geobserveerde uitkomsten, met relatieve risico's variërend van 0.68 tot 4.58. Beseffende dat clopidogrel geassocieerd is met een 20% relatieve risicoreductie op ischemische complicaties na toevoeging aan aspirine, kan een verhoogd risico van meer dan 50% niet alleen toegeschreven worden aan een verminderd effect van clopidogrel door gelijktijdig gebruik van een protonpompremmer. Tevens was er slechts in 48% van de studies sprake van een verhoogd risico op majeure cardiovasculaire events bij patiënten die een protonpompremmer gebruikten en werd er in geen van de gerandomiseerde studies een nadelig effect geobserveerd bij patiënten

waarbij een protonpompremmer werd toegewezen. Samenvattend kan worden gesteld dat alhoewel er aanwijzingen zijn voor een verminderd effect van clopidogrel in laboratorium studies wordt dit effect niet uniform bevestigd in klinische studies.

Ongeveer 10% van de patiënten met een myocardinfarct zal binnen een jaar opnieuw een infarct doormaken ondanks het gebruik van duale antiplaatjestherapie. Dit betreft een populatie die meer aandacht verdient met betrekking tot antitrombotische behandeling. In Hoofdstuk 4 beschrijven we de waarde van behandeling met langdurige antistolling bij patiënten waarbij duale antiplaatjestherapie ineffectief is gebleken. Behandeling met vitamine-K antagonisten (VKA) is bewezen effectief bij ACS als monotherapie, met vergelijkbare uitkomsten als aspirine. Ook als toevoeging aan aspirine is duidelijk vastgesteld dat langdurige behandeling met een VKA de klinische uitkomsten verbeterd na een ACS bij patiënten in sinusritme. In een meta-analyse van 7.836 patiënten resulteerde randomisatie naar een VKA als toevoeging aan aspirine in een reductie van dood, niet fataal myocard infarct en/of een beroerte van 12,3% naar 9,4%. Hierbij was wel sprake van een toename in majeure bloedingen van 1.1% naar 2.6%.

De ontwikkeling van de non-VKA orale anticoagulantia (NOAC) waarbij er geen monitoring benodigd is, heeft de rol van verlengde antistolling nieuw leven ingeblazen. Hierbij is het van belang om te realiseren dat deze groep medicijnen alleen is onderzocht als toevoeging aan duale antiplaatjestherapie, hetgeen tot op heden de hoeksteen blijft in de behandeling van ACS. Van de NOACs is alleen bij een zeer lage dosering van rivaroxaban aangetoond dat het klinische uitkomsten verbetert. Echter, gezien de significante toename van het bloedingsrisico dient deze therapie alleen in uitzonderlijke gevallen bij patiënten met een hoog risico op recidief ischemische events te worden toegepast.

De meest uitdagende patiëntengroep betreft diegene met een strikte indicatie voor orale antistolling die tevens een ACS ontwikkelt. Gezien het gebrek aan studies van NOACs in de acute setting van een ACS, adviseren wij om de NOAC te stoppen tijdens de opname in het ziekenhuis bij deze specifieke patiëntenpopulatie. Na ontslag uit het ziekenhuis dient er geen NOAC gebruikt te worden in een AF dosering in combinatie met duale antiplaatjestherapie gezien het onacceptabel hoge bloedingsrisico hetgeen is aangetoond in meerdere fase II en III trials. In het kader van

deze veiligheidsaspecten raden wij aan om in het eerste jaar na een ACS een VKA te gebruiken. Indien de indicatie van duale antiplaatjestherapie is vervallen kan het gebruik van een NOAC heroverwogen worden.

Het verhoogde bloedingrisico van NOACs is tevens het onderwerp van Hoofdstuk 5. Dit hoofdstuk betreft een kritische kanttekening op een meta-analyse waarin een 45% verhoogd risico op gastro-intestinale bloedingen wordt beschreven bij het gebruik van een NOAC voor verschillende indicaties. In dit commentaar vragen wij om een meer voorzichtige interpretatie van het gerapporteerde risico. Ten eerste zijn in deze meta-analyse ook studies geïncludeerd waarbij NOACs zijn gebruikt als secundaire preventie na een ACS waarbij placebo werd gebruikt als controle. Van belang bij deze studies is dat de NOACs hierbij ook in AF doseringen zijn gebruikt, hetgeen niet door de huidige richtlijnen wordt aanbevolen gezien het bekende hoge bloedingsrisico. Ten tweede is er een substantieel deel van de data waarbij NOACs niet geassocieerd waren met een verhoogd risico op gastro-intestinale bloedingen buiten beschouwing gelaten in deze meta-analyse. Ten slotte roepen wij op tot een voorzichtigere interpretatie van data waarbij zowel de risico's alsook de voordelen worden afgewogen, zoals bijvoorbeeld het verlaagde risico op intracraniële bloedingen bij behandeling met NOACs.

Eén van de NOACs waarbij is aangetoond dat het zowel veiliger als meer effectief is als warfarine ter preventie van trombo-embolische events bij AF, is apixaban. Echter is dit medicijn alleen onderzocht in een algemene AF populatie en er zijn aanwijzingen dat patiënten met polyfarmacie (i.e. ≥5 medicijnen) ouder en zieker zijn en dat er sprake kan zijn van een andere respons op antistolling bij deze populatie. Met deze kennis hebben wij een post-hoc analyse uitgevoerd van de ARISTOTLE trial waarin apixaban is vergeleken met warfarine bij 18.201 patiënten met AF (Hoofdstuk 6). Wij toonden aan dat patiënten die meer medicijnen gebruikten een groep vormen waarbij comorbiditeit frequenter voorkomt, dat ze een hoger risico op overlijden hebben en dat er een hoger risico bestaat op ischemische en bloedingscomplicaties. Met betrekking tot de effectiviteit bleek dat de superioriteit van apixaban vergeleken met warfarine met betrekking tot beroertes (21% risico reductie) en overlijden (11% risico reductie) geobserveerd in de algehele trial populatie, niet significant verschilde tussen patiënten met veel of weinig medicijnen. Echter, alhoewel apixaban geassocieerd

is met een risico reductie van 31% voor majeure bloedingen in de gehele populatie, observeerden we een statistisch significante verschil in behandelingseffect tussen de twee anticoagulantia met relatieve risico's voor apixaban, variërende van 50% (0-5 medicijnen) naar 28% (6-8 medicijnen) en 16% (≥9 medicijnen). De interactie leek niet verklaard te kunnen worden door het gebruik van interacterende medicijnen. Onze bevindingen suggereren dat observaties met betrekking tot effectiviteit en veiligheid van antistolling in algemene populaties kunnen verschillen van hoog risico groepen zoals de ouderen met veel co morbiditeit.

Ondanks het bewijs dat antistolling ook in het voordeel is bij de ouderen, blijven artsen bezorgd om het bloedingsrisico bij deze groep en is onderbehandeling een frequent voorkomend probleem. Verschillende modellen zijn ontworpen om het bloedingsrisico van patiënten in te kunnen schatten. Hiervan worden de HAS-BLED, ATRIA en HEMORR$_2$HAGES momenteel het meest toegepast. Echter zijn deze modellen ontwikkeld in algemene AF populaties en is het onbekend of deze modellen ook goed kunnen discrimineren binnen de oudere patiënten. In Hoofdstuk 7 hebben wij het discriminerend vermogen van de drie modellen onderzocht en tevens met elkaar vergeleken in een zeer oude populatie van patiënten met AF die een VKA gebruikten. Gedurende een 3-jarige vervolgperiode kwam een majeure bloeding voor bij 6,7% van de populatie (rate 2,8%/jaar). Ondanks een significante associatie met majeure bloedingen voor alle drie de modellen bleek het discriminerende vermogen in alle modellen zeer matig (C-statistic < 0,60) zonder superioriteit voor één van de modellen. Een belangrijke bevinding was dat behoudens anemie en het gebruik van trombocytenaggregatieremmers, geen van de 'klassieke' risicofactoren behorende bij de modellen geassocieerd was met majeure bloedingen in deze oudere patiëntengroep. Om enige richting te geven aan de klinische beslisvorming hebben wij een geschatte risk-benefit berekend waaruit bleek dat de voordelen van VKA behandeling in het algemeen groter waren dan het nadeel bij deze groeiende groep van ouderen. Om meer objectieve adviezen te kunnen geven zijn nieuwe initiatieven nodig om risicofactoren voor bloeden bij de ouderen te identificeren, waarbij de nadruk dient te liggen op ouder-specifieke risicofactoren.

EPILOOG

Dit proefschrift heeft zich gericht op de balans tussen veiligheid en effectiviteit met betrekking tot orale antitrombotica in de cardiologie. Hierbij is aandacht besteed aan trombocytenaggregatieremmers, zoals aspirine en clopidogrel, alsook orale anticoagulantia, namelijk vitamine K antagonisten (VKA) en non-VKA orale anticoagulantia (NOAC).

Een goede balans tussen veiligheid en effectiviteit is van essentieel belang. Een verminderde effectiviteit kan resulteren in trombose met als gevolg een intensivering van de antitrombotische therapie waarbij het risico op bijvoorbeeld bloedingen wordt verhoogd. Anderszins kan de perceptie van een verhoogd bloedingrisico leiden tot angst en hierdoor een verminderde compliantie of een terughoudendheid in het voorschrijfgedrag. Hieruit blijkt dat de veiligheid van een antitromboticum ook weer invloed kan hebben op de gerealiseerde effectiviteit.

In dit proefschrift zijn bovengenoemde wisselwerkingen aan bod gekomen bij de behandeling en preventie van stabiel en acuut coronair lijden, als ook bij de behandeling van atriumfibrilleren (AF).

ACUUT CORONAIR SYNDROOM

Effectiviteit

De preventie van een acuut coronair syndroom (ACS) heeft in de laatste decennia een vogelvlucht genomen. Na de komst van aspirine, gevolgd door clopidogrel, zijn er sinds enige tijd nieuwere trombocytenaggregatieremmers beschikbaar gekomen waarbij er is aangetoond dat deze middelen een nog betere bescherming tegen acute coronaire syndromen bieden. Bovendien zijn er steeds meer onderzoeken gaande naar de waarde van (orale) antistolling als toevoeging aan deze trombocytenaggregatieremmers. Door deze ontwikkelingen is de behandeling na een ACSverbeterd en is het risico op een recidief in het algemeen sterk verlaagd. Helaas zijn er met de komst van de trombocytenaggregatieremmers ook nieuwe problemen ontstaan.

Met betrekking tot de effectiviteit van aspirine en clopidogrel is het begrip 'resistentie' geïntroduceerd, gebaseerd op het feit dat ondanks duale antiplaatjestherapie er in een substantieel deel van de patiënten terugkerende events worden waargenomen. De vraag is in hoeverre dit gerelateerd is aan suboptimale werking van trombocytenaggregatieremmers. Hier is de laatste jaren veel aandacht aan besteed, waarbij de uitslagen van ex vivo plaatjesfunctietesten veelal werden toegepast als surrogaat voor een in vivo verminderd effect. Een belangrijk voorbeeld hiervan is de in dit proefschrift bediscussieerde mogelijke interactie tussen clopidogrel en protonpomp remmers (PPIs) met als gevolg een verminderde productie van het actieve substraat van clopidogrel. De initiële waarschuwingen van de FDA en EMA waren louter gebaseerd op ex vivo studies en retrospectieve klinische studies. Enerzijds bleken er ex vivo duidelijke aanwijzingen te bestaan voor een interactie gezien de verhoogde reactiviteit van de trombocyten bij PPI gebruik, weliswaar voornamelijk geconstateerd in populaties van gezonden, en patiënten zonder ACS. Anderzijds bleek er in de prospectieve (gerandomiseerde) studies geen duidelijke verminderde effectiviteit op klinische eindpunten bij de combinatie clopidogrel met een PPI te bestaan.

Deze discrepantie tussen plaatjesfunctietesten en klinische gevolgen is ook eerder geobjectiveerd bij twee grote studies (GRAVITAS; ARCTIC) waarbij patiënten met een verhoogde plaatjesreactiviteit werden gerandomiseerd naar wel of geen intensievere behandeling met trombocytenaggregatieremmers. Uit deze studies bleek dat intensivering van de trombocytenaggregatietherapie wél de ex vivo plaatjesreactiviteit verminderde, maar niet resulteerde in een klinische verbetering in vergelijking met patiënten die geen intensievere therapie ondergingen.

Deze bevindingen in grote gerandomiseerde studies demonstreren de beperking van observaties uit retrospectieve studies, o.a. als gevolg van bias in het voorschrijfgedrag en minder optimale datacollectie. Hoewel deels begrijpelijk vanuit het oogpunt van effectiviteit, heeft de waarschuwing van de FDA en EMA ook geleid tot veranderingen in medicatie, zoals het stoppen van PPIs, of switchen naar bijvoorbeeld ticlopidine met daarmee verhoogde kans op gastro-intestinale en beenmerg problemen.

Hoewel door sommigen terugkerende events worden toegeschreven aan 'resistentie' voor antiplaatjestherapie, is de gedachte dat alleen bloedplaatjesremming afdoende is voor de behandeling en preventie van een ACS mogelijk te eenzijdig. Ondanks dat meerdere oudere studies overtuigend hebben aangetoond dat vitamine K antagonisten als monotherapie effectief zijn bij acuut en chronisch coronairlijden, heeft het onderzoek naar het nut van orale anticoagulantia bij ACS lange tijd stil gestaan. Dit ondanks een meta-analyse die een gunstig effect liet zien van de toevoeging van VKAs aan aspirine. Voor patiënten in sinusritme bestaan er geen grote gerandomiseerde studies waarbij het effect van VKAs is onderzocht als toevoeging aan dubbele antiplaatjestherapie en wordt dit slechts op theoretische gronden in geselecteerde gevallen toegepast. Wel bestaan er sinds enkele jaren verschillende fase II studies voor de NOACs. De enige afgeronde fase III studie betreft triple therapie met een zeer lage dosering rivaroxaban, waarbij de effectiviteit significant verbetert ten koste van een sterk verhoogd bloedingrisico. Deze data onderschrijven dat ook in het huidige tijdperk (adjuvante) antistollingstherapie invloed heeft op de trombotische uitkomstmaten na een ACS.

Implicaties voor toekomstig onderzoek. Opvallend is dat er een grote verscheidenheid van mogelijke devices bestaat om de plaatjesactiviteit te bepalen en dat er geen duidelijke naar het individu te vertalen normaalwaarden te formuleren zijn. Ook bestaat er geringe uniformiteit in het protocol met betrekking tot het tijdstip van de bepalingen na medicatie inname, dan wel ten opzichte van het tijdstip van start klachten. Tenslotte is de variatie coëfficiënt van verschillende methodes dusdanig dat minimaal 3 bepalingen nodig zouden zijn voor een betrouwbare meting. Voor eventueel toekomstig onderzoek dienen deze aspecten meegenomen te worden in het studie design.

Los van methodologische aspecten die het scherp krijgen van een mogelijke relatie bemoeilijken, is de primaire hypothese dat het krijgen van een nieuw event voor een groot deel samenhangt met 'resistentie' aan kritiek onderhevig. Ten eerste wordt hiermee voorbij gegaan aan het natuurlijk beloop na een acuut coronair syndroom, en het feit van altijd mogelijke hernieuwde plaque ruptuur met eventuele (sub)totale trombotische occlusie. De gedachte dat het optreden hiervan falen van een antitromboticum weergeeft doet geen recht aan het multifactoriële karakter van

een complex ziektebeeld als een acuut coronair syndroom. Bovendien is de mate van plaatjesactiviteit gemeten met een device nog nooit als onafhankelijke voorspeller van uitkomst naar voren gekomen in grote, goed ontworpen studies. Er lijkt een samenhang te bestaan tussen een verhoogd klinisch risicoprofiel (diabetes, verminderde nierfunctie, leeftijd) en de mate van plaatjesreativiteit tijdens een acuut coronair syndroom. Bovengenoemde overwegingen verdienen nader onderzoek, om tot een beter inzicht te komen, en de mogelijkheid te onderzoeken of er een toekomstige rol weggelegd is voor een individueel getrieërde behandeling middels een plaatjesactiviteit device.

Met betrekking tot toekomstige studies naar het effect van anticoagulantia, zal de uitdaging liggen in het bepalen van de juiste dosering en duur van de adjuvante antistolling, en het al dan niet vroegtijdig stoppen van één van beide antiplaatjesmiddelen. Dit alles in de context van een individueel bepaalde afweging op basis van het geschatte trombotisch risico en de kans op bloedingen.

Samengevat kunnen we stellen dat mechanistische studies inzicht kunnen geven in potentiële werkingsmechanismes, maar dat er in de toekomst terughoudend moet worden omgegaan met het gebruik van ex vivo maten zoals plaatjesreactiviteit als surrogaat voor in vivo werking van deze middelen. In het kader van genoemde verwevenheid van bloedplaatjes en stollingsfactoren bij het ontstaan van een ACS, en de reeds jarenlange bekende effectiviteit van VKAs bij coronairlijden, lijkt hernieuwde aandacht voor de rol van anticoagulantia gerechtvaardigd, zeker na de introductie van de veiliger imponerende NOACs.

Veiligheid

Met de verbeterde effectiviteit van de huidige behandeling met antitrombotica is ook de aandacht voor een verhoogd bloedingrisico toegenomen. Gezien de etsende werking van aspirine op de maagwand, heeft het meeste onderzoek zich in eerste instantie gericht op de dosis en vorm van dit medicament, en niet zozeer op de andere antiplaatjes middelen.

Met betrekking tot de dosis is uit gerandomiseerd onderzoek gebleken dat hogere doseringen gepaard gaan met meer gastro-intestinale complicaties. Echter, het betrof hier doseringen hoger dan gebruikelijk bij een ACS. Retrospectief onderzoek bij

ACS patiënten behandeld in lagere doseringen (75-325 mg) dan deze studies liet zien dat ook bij ACS de dosis aspirine gerelateerd kan worden aan de kans op bloedingen.

Met betrekking tot de vorm waarin aspirine wordt ingenomen is ook het nodige onderzoek verricht. Voorbeelden hiervan zijn enteric coated aspirine en carbasalaatcalcium. De laatste zou door betere oplosbaarheid en verminderde toelaatbaarheid door de beschermende mucuslaag van de maag, geassocieerd zijn met minder directe schadelijke werking op de maag. Alhoewel er aanwijzingen zijn dat deze vorm van aspirine geassocieerd is met minder gastro-intestinale ulcera, is dit onderzocht in gezonde proefpersonen waarbij er zeer hoge doseringen werden gebruikt. Bovendien is er in een groot retrospectieve cohort studie geen voordeel aangetoond indien het in de lage dosering bij patiënten werd toegepast. Een ander mogelijk voordeel van dergelijke aspirine-preparaten zou een verbetering zijn van andere veiligheidsaspecten zoals dyspepsie, hetgeen een negatief effect kan hebben op de compliantie, wat indirect de effectiviteit beïnvloedt. In het huidige proefschrift blijkt er geen voordeel van deze vorm van aspirine op het optreden van dyspepsie. Echter, deze gebufferde vorm van aspirine gaat wel gepaard met verhoogde kosten, hetgeen zelfs de kosten van een combinatie van aspirine met een PPI overschrijdt. Gezien deze bevindingen en de kennis van voorgaande studies waarin is aangetoond dat PPIs wel een positief effect hebben op het reduceren van dyspeptische klachten zien wij geen meerwaarde in carbasalaatcalcium en dient er in geval van klachten overwogen te worden om te starten met een PPI. Tevens dient volgens de huidige richtlijnen een PPI gestart te worden bij patiënten met een verhoogd risico op gastro-intestinale bloedingen die een trombocytenaggregatieremmer gebruiken. Dit risico kan worden ingeschat door het nagaan van verscheidene klinische factoren zoals een voorgeschiedenis van een maagulcus of -bloeding, de leeftijd, het gebruik van twee trombocytenaggregatieremmers en het gelijktijdig gebruik van anticoagulantia.

Implicaties voor toekomstig onderzoek. Over de jaren is het inmiddels bijna standaard gebruik geworden om de gebruikte dosis van aspirine tijdens de grote trials te registreren. Met betrekking tot gastro-intestinale klachten blijkt er in een groot aantal studies nog geen systematische rapportage plaats te vinden van deze toch vaak optredende relevante bijwerkingen. Zelfs het rapporteren van een gastro-intestinale bloeding is in recente studies met nieuwe antitrombotica niet altijd vanzelfsprekend.

In een tijdperk waarin afweging van risico's en voordelen steeds belangrijker wordt, is prospectieve registratie van deze cruciale events onontbeerlijk. Bovendien is het bij de introductie van nieuwe antitrombotische medicatie van belang het concomitante gebruik van PPIs in de studies nauwgezet bij te houden, om een correcte inschatting van het gerapporteerde gastro-intestinale risico te kunnen bepalen wanneer twee antitrombotica worden vergeleken. In deze context is het initiatief van de COMPASS studie een belangrijke stap voorwaarts, waarbij in een factorial design, naast het effect van een NOAC ten opzichte van aspirine ook de vraag wordt beantwoord of additionele behandeling met een PPI van waarde is.

Effectiviteit en veiligheid: de balans

Nu de ontwikkeling van nog sterkere trombocytenaggregatieremmers een enorme vlucht heeft genomen, is het zaak nog meer attent te zijn op de juiste balans tussen effectiviteit en veiligheid. Naast gastro-intestinale bloedingcomplicaties is het ook van belang om het algehele risico op bloedingen in te schatten. Bij ACS is hiervoor het CRUSADE risico model ontwikkeld, en wordt in de guidelines nogal eens gerefereerd naar het HAS-BLED risicomodel. Het is belangrijk te vermelden dat dit laatste model primair gevalideerd is op patiënten met atriumfibrilleren, zonder ACS, en dat de predictieve waarde in die setting reeds beperkt is.

Het risico op toekomstige trombotische events kan worden ingeschat met behulp van de TIMI risk score, of het in Europa veelal gebruikte GRACE risicomodel. Zowel het GRACE model als de CRUSADE zijn uitgebreid gevalideerd, met acceptabele predictieve waardes, waarbij het patiënten betrof zonder atriumfibrilleren.

Implicaties voor toekomstig onderzoek. Hoewel de eerste stap richting risk-stratified treatment is gemaakt, is er nog weinig data waar het gaat om de integratie van informatie uit beide modellen, en potentiële behandelingskeuzes. Belangrijk hierbij is tot een vorm van consensus te komen over het te accepteren number needed to harm, gegeven een bepaald number needed to treat. Deze vragen kunnen gelden voor de juiste trade off tussen duale antiplaatjestherapie met aspirine en clopidogrel versus een sterker antiplaatjesmiddel (ticagrelor, prasugrel), maar kunnen ook de toevoeging betreffen van orale anticoagulantia aan duale antiplaatjestherapie als intensievere vorm van secundaire coronaire preventie. Juist voor patiënten in

sinusritme bestaat er behoefte aan vergelijkend onderzoek tussen de waarde van de CRUSADE score ten opzichte van de regelmatig geadviseerde HAS-BLED score.

Voor patiënten met atriumfibrilleren geldt dat er vaak een indicatie voor levenslange orale antistolling bestaat, en wordt bij een ACS de situatie precair gezien de huidige consensus dat er ook duale antiplaatjestherapie dient te worden voorgeschreven. Bij patiënten met een indicatie voor een VKA die een dotter procedure ondergingen, heeft een recente gerandomiseerde studie aangetoond dat gebruik van clopidogrel met weglaten van de aspirine resulteerde in minder bloedingen, zonder dat er aanwijzingen waren voor een verminderde effectiviteit. Ook voor NOACs zijn er verschillende studies gestart bij patiënten met een ACS, waarbij de combinatie van 1 trombocytenaggregatieremmer en 1 anticoagulans de toekomst lijken te hebben. Echter, triple therapie met langdurige orale antistolling en wisselende periodes van adjuvante duale antiplaatjestherapie worden ook bestudeerd. Gegeven het feit dat in de ATLAS-ACS-2 studie duale antiplaatjes therapie met een zeer lage dosis rivaroxaban evident meer bloedingen gaf, maar ook significant effect op de effectiviteit liet zien, valt te bezien hoe de NNT en NNH er voor de te testen nieuwe regimes uit komen te zien. Wetende dat bij atriumfibrilleren de dosis van een NOAC vele malen hoger ligt dan in de huidige studie bij sinusritme, maakt dit de situatie in deze laatste categorie patiënten extra complex.

ATRIUMFIBRILLEREN

Effectiviteit

Zoals beschreven bestaat de behandeling van patiënten met atriumfibrilleren uit antistolling in de vorm van een VKA of een NOAC, en is er geen plaats meer voor aspirine. Zelfs duale antiplaatjes therapie komt qua reductie van trombo-embolieën niet in de buurt van de 60-70% reductie behaald met orale antistolling.

Ondanks deze indrukwekkende effectiviteitsdata wordt orale antistolling nogal eens niet gegeven. Eén van de argumenten is dat getwijfeld wordt in hoeverre data uit studies ook naar ‘de oudere’, en de ‘fragiele oudere’ te vertalen is. In de BAFTA studie is overtuigend aangetoond in een huisartsen populatie van 75 jaar en ouder

dat een VKA evident effectiever is dan aspirine, en niet tot meer bloedingen leidt. Ook met NOACs is uit de beschikbare data naar voren gekomen dat de gevonden resultaten qua effectiviteit kunnen worden doorvertaald naar de oudere patiënt.

In het huidige tijdperk van vergrijzing, waarin patiënten gemiddeld langer leven, maar wel met meer comorbiditeit, rijst de vraag in hoeverre hier de verhouding NNT en NNH gunstig ligt. Hiertoe maakten wij een eerste aanzet door een kwaliteit en patienttevredenheids project met de Trombosedienst Arnhem-Nijmegen op te starten. In het door ons beschreven cohort van 80 'plussers lijkt de verhouding NNT en NNH voordelig te liggen. Voor NOACs konden wij bij toenemende comorbiditeit geen vermindering van de effectiviteit waarnemen, wat het belang onderstreept van behandeling van de fragiele oudere, en de rapportages over de nadelen van onderbehandeling onderschrijft.

Implicaties voor toekomstig onderzoek. Hoewel de recente studies met atriumfibrilleren een behoorlijk goede weerspiegeling zijn van de 'gemiddelde patiënt' op de polikliniek, is dit mogelijk niet het geval voor alle patiënten die de huisartsenpraktijk bezoeken. Met name patiënten met cognitieve stoornissen, mobiliteitsproblemen en bijvoorbeeld ernstige nierfunctiestoornissen zijn niet vertegenwoordigd in de grote gerandomiseerde studies, en het percentage patiënten met uitgebreide comorbiditeit zal ook relatief laag liggen. Voor patiënten met deze kenmerken is aanvullend onderzoek gewenst, waarbij ook compliance data bij het gebruik van NOACs van belang zijn.

Daarnaast vormen patiënten met een recidief CVA/TIAs onder NOAC gebruik een groep van aandacht, bij wie mogelijk zelfs metingen van de antistollingsactiviteit geïncorporeerd zouden kunnen worden om tot nog betere, op het individu toegespitste behandelingen te komen.

Veiligheid

Zoals beschreven, vormt aspirine geen veiliger alternatief voor orale antistolling, ook niet bij ouderen, en is de effectiviteit duidelijk minder. Een andere groep patiënten met atriumfibrilleren die nogal eens met aspirine werd behandeld bestaat uit mensen die geen VKA willen, danwel een contra-indicatie hebben voor een VKA. Ook in deze

specifieke setting blijkt uit gerandomiseerd onderzoek dat aspirine niet veiliger is dan orale antistolling, dit maal in de vorm van de NOAC apixaban.

Bij patiënten zonder contra-indicaties voor een VKA, vormen de NOACs een alternatief dat minstens net zo veilig is, als het de majeure bloedingen betreft. Voor alle NOACs geldt een bijna 50% reductie in de kans op intracraniële bloedingen, echter bij een aantal van de NOACs gaat deze winst teniet door een grotere kans op gastrointestinale bloedingen en/of andere grote bloedingen.

Ook qua veiligheid rijst de vraag of de resultaten behaald met NOACs vertaald kunnen worden naar 'de oudere', dan wel 'de fragiele oudere'. Zeker voor de patiënt met multipele comorbiditeiten geldt dat er niet alleen sprake is van het gebruik van verschillende (potentieel) interacterende medicijnen, maar dat ook de algehele fysieke conditie minder is, en regelmechanismen minder (snelle) adaptie vertonen. In deze context is het heel wel mogelijk dat 'fragiele ouderen' een andere respons op antistolling medicatie vertonen dan vitale ouderen, of jongeren.

Met betrekking tot de oudere in het algemeen, is het zo dat qua veiligheid de resultaten beschreven in de gehele studiepopulatie niet zonder meer vertaald kunnen worden naar 'de oudere', als het om dabigatran 150 mg gaat. Patiënten ouder dan 75 jaar hebben duidelijk nadeel bij gebruik van dabigatran, als het om het veiligheidsaspecten gaat. Bij de overige NOACs zijn de veiligheidsconclusies van ouderen en jongeren ten opzichte van VKA niet verschillend.

Als het gaat om de veiligheid bij patiënten met multipele bijkomende aandoeningen, is zowel het onderzoek naar VKAs als naar NOACs nog schaars. In onze 80-plus populatie analyseerden wij in hoeverre risicofactoren voor bloeden op VKAs zoals die zijn gevonden in de algemene populatie met atriumfibrilleren ook golden bij de 80-plusser. Het bleek dat slechts weinig van de klassieke risicofactoren ook bij ouderen een associatie vertoonden met bloeden. Desalniettemin kwam de NNT vs NNH verhouding dusdanig te liggen, dat het niet behandelen op basis van een verwacht hoog bloedingrisico in dit cohort niet onderbouwd kon worden.

De studies naar NOACs die een mogelijk verschil in veiligheid bestudeerden bij patiënten met uitgebreidere comorbiditeit deden dit via het al dan niet bekend zijn met polyfarmacie. Polyfarmacie is niet alleen gekoppeld aan mortaliteit en de kans op een ischemische beroerte, maar gaat ook gepaard met een verhoogd bloedin-

grisico. Hieruit bleek dat de mate van het voordeel qua bloedingreductie behaald met apixaban afnam in relatie tot een toenemend aantal medicamenten. Dit dient afgezet te worden tegen het feit dat bij de oudere in het algemeen de reductie in bloedingen ten opzichte van VKAs vergelijkbaar was ten opzichte van de reductie bij jongeren. Deze observaties laten zien dat resultaten voor 'de oudere' niet zonder meer te vertalen zijn naar 'de fragiele oudere'.

Implicaties voor toekomstig onderzoek. De indicaties uit bovenstaande retrospectieve analyses doen vermoeden dat de veiligheid van antistolling gerelateerd is aan de mate van comorbiditeit, het aantal concomitante medicijnen en de combinatie van deze invloeden. Grootschaliger onderzoek met meer nadruk op de 'biologische oudere' dan op de 'chronologisch oudere' is gewenst, zeker in het licht van de toegenomen levensverwachting, en de leeftijdsafhankelijke incidentie van atriumfibrilleren.

Het HAS-BLED model in de algehele populatie met atriumfibrilleren is mogelijk een nog geaccepteerde vorm van risicostratificatie; echter, het discriminerend vermogen van dit model is in de meerderheid van de literatuur zeer matig gebleken. Voorschrijvers dienen voorzichtig te zijn met het onthouden van antistolling enkel en alleen op basis van een hoge HAS-BLED score. Verschillende research groepen hebben alternatieven voor de HAS-BLED geponeerd, omdat juist qua predictie van bloedingen nog de nodige winst te behalen valt. Een recent gepubliceerd model, het ABC-model genaamd, combineert klinische factoren met leeftijd en biomarkers, en heeft een betere, doch nog steeds niet optimale diagnostische accuratesse.

Het feit dat bij ouderen bijna geen van de variabelen in het HAS-BLED model gerelateerd is aan de kans op een bloeding doet vermoeden dat er behoefte is aan meer 'op de oudere toegespitste' risicomodellen. Hierbij valt te denken aan een rol voor polyfarmacie, cognitieve functie, maar wellicht ook makkelijk uit te voeren geriatrische onderzoeken die de biologische leeftijd van de patiënt proberen in te schatten.

Tot slot rijst de vraag of risicofactoren voor een bloeding bij het gebruik van een VKA wel overeenkomen met de factoren bij NOAC gebruik. Hoewel het in beide gevallen orale antistolling betreft, zijn er duidelijke verschillen qua werkingsmechanisme, eliminatie en interacterende medicijnen waardoor een nieuwe inventarisatie

gerechtvaardigd lijkt. Ook is de vraag actueel in hoeverre in geselecteerde gevallen dosisaanpassing zou kunnen plaatsvinden op basis van metingen van de antistollingsactiviteit. Beter inzicht in de factoren die gepaard gaan met een bloeding, kan door het bieden van meer houvast voor voorschrijvers onderbehandeling reduceren en zorgen voor een betere balans tussen effectiviteit en veiligheid.

Effectiviteit en veiligheid: de balans

Nu de ontwikkeling van NOACs heeft geleid tot een zich langzaam aan veranderend landschap qua antitrombotische behandeling van atriumfibrilleren, worden nieuwe vragen relevant. Hoewel door de bank genomen de behandeling met NOACs veiliger is geworden, bestaat er behoefte aan een risk-benefit bepaling, zeker gezien de bij een aantal NOACs gekende verhoging van het risico op gastro-intestinale bloedingen. Daar waar de CHA_2DS_2-VASc score zowel op VKA als op NOACs gerelateerd is met ischemische events, is dit voor de HAS-BLED score nog niet goed onderzocht als het gaat om de predictie van bloedingen op NOACs.

Implicaties voor toekomstig onderzoek. Belangrijk hierbij is tot een vorm van consensus te komen over het te accepteren number needed to harm, gegeven een bepaald number needed to treat. Deze beslissingen kunnen gaan over de vraag VKA versus NOAC, maar toekomstig onderzoek zal mogelijk ook meer gericht zijn op 'patient tailored' medicine. Hierbij valt te denken aan risk-benefit modellen voor ieder van de verschillende NOACs, in vergelijking tot VKAs. De meeste vraag blijft bestaan naar een risico model voor bloedingen dat tot een betere klinische inschatting leidt.

Samengevat is er op het gebied van antistolling een duidelijke stap voorwaarts gemaakt, en is er een dusdanig breed palet aan keuzes dat verdere verfijning van de behandeling van atriumfibrilleren mogelijk lijkt met de reeds beschikbare medicamenten, wanneer deze met meer kennis over effectiviteit en veiligheid in specifieke doelgroepen kunnen worden voorgeschreven.

10

Dankwoord

Curriculum Vitae

List of publications

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CURRICULUM VITAE

Jeroen Jaspers Focks werd op 13 maart 1983 geboren te Alkmaar en is als jongste van het gezin opgegroeid in Zutphen. In 2001 behaalde hij zijn VWO diploma aan het Baudartius College te Zutphen, waarna hij startte met de opleiding geneeskunde aan de Radboud Universiteit te Nijmegen. Tijdens zijn co-schappen ontstond zijn interesse voor de cardiologie. In 2008 begon hij zijn wetenschappelijke stage bij de afdeling cardiologie van het Radboudumc waarna hij in datzelfde jaar na het behalen van zijn arts-diploma startte met zijn promotieonderzoek onder leiding van prof. Freek W.A. Verheugt en dr. Marc A. Brouwer. Enige tijd later is ook prof. Menko-Jan de Boer als promotor betrokken geraakt bij het onderzoek. In het kader van dit onderzoek heeft Jeroen nauw samengewerkt met meerdere ziekenhuizen en onderzoeksinstellingen, de INR Trombosedienst en is hij ook betrokken bij NVVC Connect AF. Op 1 april 2016 is Jeroen gestart met zijn opleiding tot cardioloog in het Radboudumc en momenteel is hij werkzaam op de afdeling Interne Geneeskunde in het Rijnstate ziekenhuis te Arnhem.

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