Chapter 1
General introduction and scope of the thesis
Chapter 1

INTRODUCTION

The high disease burden related to atrial fibrillation (AF) worldwide is well acknowledged. AF increases the risk of stroke and mortality but effective stroke prevention can help to improve patient outcomes and therewith decrease the economic burden of this disease. Cost-effectiveness studies are often the starting point to provide market access for new drugs. This was also the case for the newer stroke prevention drugs, the non-vitamin K oral antagonists (NOACs). General cost-effectiveness studies are indispensable but often do not cover the full scope of treatment and do not focus on specific subgroups. High-impact variables, both on patient outcomes as well as on health care costs, need to be recognized and considered to optimize stroke prevention to show the true value of stroke prevention treatment. The aim of this thesis is to bring together the most important aspects that are relevant to stroke prevention in nonvalvular atrial fibrillation. Both clinical aspects as well as health economic considerations are discussed relating to disease detection, treatment and specific subgroups that would need a tailored approach. This thesis captures the aspects that are relevant from both a patient perspective as well as an economical and societal perspective. The thesis is divided into two parts. Part A of this thesis describes AF screening, stroke prevention strategies and aspects related to AF treatment. Part B of this thesis focuses on specific AF subpopulations. The following paragraphs provide a framework to introduce AF and the impact on both the patients’ wellbeing and the health care expenditures.

Atrial fibrillation - disease burden

Nonvalvular AF is the most common cardiac arrhythmia. Overall prevalence is estimated at 3% in adults 20 years and over, with a prevalence increasing with age.(1,2) Prevalence of AF in The Netherlands has been determined in a population-based prospective cohort (Rotterdam study), with an AF prevalence of 5.5% in the population aged 55 years or older.(3) The prevalence ranged from 0.7% in the 55-59 years age group and increased up to 17.8% in people aged 85 years and over. The lifetime risk to develop AF at the age of 55 years was 22–24% (women and men, respectively).(3) In the Framingham Heart Study, the lifetime risk was estimated at 23-26% in people aged 40 years or older.(4) During the 50 years observation period of the Framingham Heart Study there was a trend of increasing incidence and prevalence of AF, which could be due to better surveillance. Other studies demonstrated an increase in age-adjusted AF and suggest this to be a reflection of co-morbidities and cardiovascular risk.(1) AF is seen as a growing worldwide epidemic and there were an estimated 33.5 million individuals with AF in 2010. The burden of disease, measured in disability-adjusted life years (DALYs), increased with 19% from 1990-2010.(5) The prevalence of AF risk factors has also increased, however the
associated risk with AF changed little over time.(6) The occurrence of stroke and death in AF patients is decreasing in developed countries but from a global perspective this decline was not observed. The Global Burden of Disease (GBD) Study showed a 2-fold increase in mortality from 1990-2010. The increased AF burden could be linked to risk factors on a global level that were independent of age. There is an ongoing shift toward non-communicable disease in developing countries which could highly contribute to a rise in the global AF burden in the future.

**Stroke**

Patients with AF have a 5-fold increased risk of stroke.(7) Studies showed that AF was unknown in around 30% of the patients admitted with an ischaemic stroke.(7)(8) A systematic review concluded that the AF detection rate after stroke and transient ischemic attack was 24% with sequential cardiac monitoring.(9) The global burden of ischaemic stroke increased significantly between 1990-2010 with 37%, although incidence significantly decreased with 13% in high-income countries. The age-standardized mortality rate for ischaemic stroke did not change during this period, but the absolute number of people is increasing. Most of the burden comes from low-income and middle-income countries. Stroke is disabling in around one-third of the stroke patients and severe stroke affects a patient life-long.(10,11) The quality of life in stroke survivors is low and stroke could lead to a dependency for informal care. AF poses a significant burden of health care expenditures, with the major cost drivers being stroke, hospitalizations and loss of productivity.(5) Stroke is one of the most costly cardiovascular events. Prevention of stroke and/or stroke recurrence in AF patients can be established with the appropriate stroke prevention strategy. Anticoagulation can reduce the stroke risk by up to two-third and it is shown to be a cost-effective treatment option.(12,13)

**Atrial fibrillation – symptomatic state and disease detection**

Atrial fibrillation can be both symptomatic and asymptomatic. AF is asymptomatic in a considerable percentage of the AF patients and could therefore remain undetected in daily practice.(14,15) Since AF prevalence increases with age, it is recommended in the European Society of Cardiology guideline to screen all patients 65 years and over for a cardiac arrhythmia. Screening can be performed opportunistic where the health-care professional would screen for AF during a consultation that was scheduled for another reason. Another option is systematic screening where a bigger population is targeted based on specific criteria. Population based screening is often defined by a specific age-category and targeted systematic screening is more based on multiple risk factors.(16) Early detection of AF can help identify patients that are eligible for stroke prevention irrespective of the occurrence of symptoms. In general, screening programmes are not
always shown to be worth the investment relative to the benefits. One of the reasons is the high upfront costs that are associated with systematic, population-based screening. Early detection of AF can help identify patients that are eligible for stroke prevention irrespective of the occurrence of symptoms and therewith would reduce high future costs associated with stroke. Even a single screening session could be worth the investment if sufficient patients would be detected and therewith a high number of AF-related events could be prevented.

AF is classified severe and disabling in around 30% of the patients. Symptoms can be very limiting up to the point where normal daily activity is no longer possible.(17) This patient group would be eligible for acute restoration of the sinus rhythm, often carried out as electrical cardioversion. A direct-current electric shock is then used to restore the normal sinus rhythm. Cardioversion carries an inherent risk of stroke and anticoagulation is therefore crucial for a safe procedure.(2). Antiarrhythmic drugs such as amiodarone, dronedarone, sotalol and flecainide can be used for long-term antiarrhythmic treatment to reduce AF-related symptoms.(2)

**Atrial fibrillation treatment - focus on anticoagulation**

Drug treatment for AF has been established for many years and consists of rate and/or rhythm control and oral anticoagulation to reduce the risk of stroke. Specially focusing on oral anticoagulants, the vitamin K oral antagonist anticoagulants (VKAs) were the standard of care for many years. VKAs show a good efficacy in reducing stroke and mortality in AF. However, these drugs have several disadvantages including periodic monitoring of blood anticoagulation and drug-drug and drug-food interactions. From a patient perspective, the main disadvantage of VKAs is the need for frequent International Normalized Ratio (INR) monitoring. The INR is used to determine the VKA dose. The INR should be within the range of 2.0-3.0, a lower INR decreases the stroke prevention benefit and an INR >3 increases the risk of bleeding.(18) The time within this therapeutic range (TTR) predicts stroke and bleeding outcomes in AF populations.(19)

The first new generation oral anticoagulant entered the market in 2008 and three other new drugs followed quickly after. This new drug class was called the new oral anticoagulants which evolved into the non-vitamin K antagonist oral anticoagulant (NOACs) or direct oral anticoagulants (DOACs). The main advantage over VKAs is a fixed daily dose with no necessity to monitor anticoagulation and fewer drug-drug interactions. The NOACs are at least as effective as VKAs and even show superiority on specific outcomes. The NOACs took on a prominent place in AF stroke treatment and are the preferred drug in most guidelines. Clinicians were a bit reluctant in prescribing NOACs at first but this drug class is now the most prescribed anticoagulant.(20,21,22)
NOACs have a higher overall value compared to warfarin when also taking into account rank-weighted patient factors that affect patients. (23)

Apixaban, edoxaban and rivaroxaban are direct activating factor X (factor Xa) inhibitors, dabigatran is a direct inhibitor of thrombin. The four major trials that lead to the registration of the NOACs for stroke prevention in AF were the RE-LY (dabigatran), ROCKET-AF (rivaroxaban), ARISTOTLE (apixaban) and ENGAGE-AF TIMI 48 trial (edoxaban). (24-27) The trials included a total of 42,411 participants that received a NOAC and 29,272 participants that received warfarin. The separate trials were underpowered to detect a significant effect in specific subgroups or on secondary endpoint, for example all-cause mortality was only significant for apixaban and low-dose edoxaban. A NOAC class level effect in specific subgroups or secondary-endpoint with a lower prevalence can be supported by a meta-analysis on a drug class level. NOACs reduced stroke or systemic embolism (SE) by 19% compared with warfarin and reduced all-cause mortality by 10%. (28) The rivaroxaban and edoxaban trial included patients with a relatively high stroke risk (CHADS\(_2\) of 3.5 and 2.8), which could lead to a bias in the effect size of stroke reduction. Intracranial hemorrhage was substantially lower for NOACs (RR 0.48, 95% confidence interval [CI] 0.39-0.59) but gastrointestinal bleeding was increased with 25%. The relative risk reduction in major bleeding was greater when the TTR for warfarin was <66%. Low dose NOACs, dabigatran 110 mg twice daily and edoxaban 30 mg once daily, showed a similar overall reduction in stroke and SE compared to warfarin, a favorable bleeding profile but a 28% higher risk for ischemic stroke. (28) There was a statistical heterogeneity across the trials with respect to major bleeding and gastrointestinal bleeding, which could be a sign of differences across trials or between drugs. Also, the meta-analysis used a study level approach with leads to a combination of NOACs with a different mode of action (Xa inhibition and direct thrombin inhibition). A meta-analysis doesn’t directly compare the relative advantages and disadvantages of each agent nor does it demonstrate that the different agents are equivalent in terms of safety and efficacy. In an indirect comparison analysis, apixaban, dabigatran and rivaroxaban showed some differences in relation to efficacy and bleeding, although the effect on stroke or SE was comparable for all NOACs for both primary and secondary prevention. (29)

**Treatment aspects - NOAC dosing and adherence**

NOACs have a direct, predictable therapeutic effect allowing a fixed-dose regimen. The correct prescribed dose of the NOACs is determined by several patient characteristics and also concomitant medication use. Prescribing the correct NOAC dose warrants careful consideration of the prevailing dose criteria that differ per NOAC. The key to correct prescribing of NOACs in AF patients is incorporating all patient-specific characteristics into the decision making.
Medication adherence is deemed as an important contributor to treatment success. Medication adherence is key in treatment efficacy and crucial to warrant optimal stroke prevention. Since there is no routine monitoring of NOACs, treatment adherence is an important item to warrant correct use of the anticoagulant. (30) Medication adherence is a broad term that defines to which extent a patient’s drug-taking behavior corresponds to the prescribed dosing regimen. (31) Non-adherence in AF patients may lead to a significant disease burden and increased healthcare costs due to a decreased stroke preventive effect. (32,33) Non-adherence consists of non-compliance and non-persistence, where persistence refers to the act of continuing the treatment for the prescribed duration. In order to prevent non-adherence, it is important to understand which variables are related to non-adherence.

**Challenges in AF treatment**

The management of AF could induce challenges when dealing with other comorbidities that are often present in this patient population. AF is associated with valvular heart disease, heart failure, hypertension, diabetes mellitus, and ischemic heart diseases. (34) Almost 30% of patients with AF have coexisting coronary artery disease (CAD). (2,35) Anticoagulants are prescribed to AF patients to reduce the risk of stroke or systemic embolism. However, there is still a risk of the patient developing coronary artery disease. This specific patient group is eligible for both anticoagulation and (dual) antiplatelet therapy (DAPT). (2,36) This dual strategy causes some challenges in finding the optimal combination of drugs.

**Health economic evaluations**

NOACs can improve clinical outcomes and therewith have the potential to improve the patients’ quality of life. A health benefit could translate into lower health care costs, which can be evaluated with different health economic evaluation methodologies. Cost-utility or cost-effectiveness analyses are useful tools to explore the balance between health effects and costs. A general underlying assumption is that the intervention under evaluation has an effect on life expectancy, quality of life (QoL) or both. Health economic evaluations can determine if a therapy or intervention would be cost-effective or even cost-saving. Health outcomes are calculated as life-years or quality-adjusted life years (QALYs) and costs can be direct health care costs or direct plus indirect health care costs. The effect on life expectancy and/or QoL can be seen as the utility: the value of the effect. A QALY is a combined measure that incorporates life years and QoL and it is therefore the measurable value of a utility. A societal perspective is standard for health economic evaluations performed in the Netherlands. This perspective includes direct health care costs of the events but also costs of productivity losses and informal care costs.
if appropriate. Cost-effectiveness analyses can be used to evaluate the use of NOACs in AF patients in different settings and specific populations. A modelling approach can be used to simulate a potential cohort of AF patients and therewith determining the costs and health effects compared to another treatment, here specifically VKAs, in the setting under evaluation. In this thesis there are several health economic evaluations included that compare NOACs to other treatment options, examples are an evaluation of an AF screening setting and an evaluation comparing anticoagulants around cardioversion.

OUTLINE THESIS

Part A: Screening, Stroke Prevention, Atrial Fibrillation Treatment Aspects

In Chapter 2, single time point AF screening was evaluated from a health-economic perspective. AF screening was combined with the seasonal flu vaccination program in the Netherlands. The AF screening evaluation was performed with a single lead ECG device with automated arrhythmia detection and manual confirmation using the ECG strip from the device. Chapter 3 and 4 focus on AF in Africa. Chapter 3 is a systematic review that aimed to describe the incidence of AF in Africa, more specifically focusing on Sub-Saharan Africa. The epidemiology of AF and related risk factors is summarized based on studies that were conducted within the region. Chapter 4 is a cost-effectiveness study that evaluates the potential of AF screening in Sub-Saharan Africa. The evaluation is based on data specific for an African population, Nigeria is used as a case country. A theoretical single-screening session carried out in healthcare clinics is evaluated and a price threshold analysis for the NOACs is also incorporated. Chapter 5 describes a hospital-based real-world drug prescription study based on in-hospital initiation of NOACs. The study evaluates the appropriateness of the dose based on dosing criteria of the different NOACs. In Chapter 6 we dive a bit more in the stroke patient treatment pathway and look at NOAC drug adherence in AF patients. This study was based on data from drug prescription databases from both the Netherlands and Sweden. Chapter 7 is a costing study that retrospectively compares health care costs and also specifically the cardiology related costs in patients that initiated dabigatran or acenocoumarol, a VKA that is widely used in the Netherlands. The combination of antiplatelet therapy and anticoagulation is challenging.

Part B- Focus on Specific AF Subpopulations

Chapter 8 is a review that focuses on combining antiplatelet therapy and oral anticoagulation in patients with AF that undergo a coronary intervention. Chapter 9 describes a retrospective cohort study on new onset of AF in critically ill patients that
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are admitted to the Intensive Care Unit. The study describes mortality in this specific population and evaluates the initiated treatment strategies for stroke prevention. Bridging anticoagulation of VKAs for a procedure is a clinical dilemma. A model was developed to aid clinical decision making. The results of this evaluation of bridging anticoagulation are described in Chapter 10. Elective electrical cardioversion is a procedure that can be carried in symptomatic AF patients to restore the sinus rhythm. In Chapter 11, the use of rivaroxaban is compared to VKAs in a cardioversion setting where anticoagulation is used to reduce the embolic risk during the procedure. The health economic evaluation assesses the cost-effectiveness of rivaroxaban versus VKAs in this specific setting from a societal perspective. In Chapter 12, all findings are summarized and discussed also incorporating newer insights and putting recommendations into perspective.
REFERENCES


Chapter 1


General introduction


