European Primary Care Cardiovascular Society (EPCCS) consensus guidance on stroke prevention in atrial fibrillation (SPAF) in primary care

Hobbs FDR, FMedSci[1], Taylor CJ, MPH[2], Geersing GJ, MD, PhD[3], Rutten FH, MD, PhD[4], and Brouwer JR, PhD[5] on behalf of The European Primary Care Cardiovascular Society (EPCCS) SPAF working group

[1] Head, Nuffield Department of Primary Care Health Sciences, University of Oxford, UK, NIHR Senior Investigator, Director, NIHR School for Primary Care Research, and supported by NIHR BRC and CLAHRC; [2] NIHR Doctoral Research Fellow, Department of Primary Care Clinical Sciences, University of Birmingham, UK; [3] Senior Lecturer, and [4] Senior Research Fellow, Julius Center for Health Sciences and Primary Care, University of Utrecht, Netherlands, and [5] Medical Scientific Writer, Medcon International, Heemstede, Netherlands

Corresponding Author: richard.hobbs@phc.ox.ac.uk

Keywords: Atrial Fibrillation, Stroke Prevention, Stroke Risk, Bleeding Risk, Anticoagulation

Table of contents

Abstract

Background
Atrial fibrillation affects 1-2% of the general population and 10% of those over 75 and is responsible for around a quarter of all strokes. These strokes are largely preventable by the use of anticoagulation therapy, though many eligible patients are not treated appropriately. Recent clinical trials have added to the evidence base on stroke prevention and international clinical guidelines have been updated.

Design
Consensus practical recommendations from primary care physicians with an interest in vascular disease and vascular specialists.

Methods
Focussed all-day meeting, with presentation of summary evidence under each section of this guidance and review of European guidelines on stroke prevention in atrial fibrillation, generated a draft document, which then underwent 3 cycles of revision and debate before all panel members agreed with the consensus statements.

Results
Six areas were identified that included how to identify patients with atrial fibrillation, how to determine their stroke risk and whether to recommend modification of this risk, and what management options are available, with practical recommendations on maximising benefit and minimising risk if anticoagulation is recommended and the reasons why antiplatelet therapy is no longer recommended. The summary evidence is presented for each area and simple summary recommendations are highlighted, with areas of remaining uncertainty listed.

Conclusions
Atrial fibrillation related stroke is a very major public health priority for most health systems. This practical guidance can assist generalist community physicians to translate the large evidence base for this major cause of preventable stroke and implement this at a local level. The guidance is slightly more conservative guidance on who to treat.

Background

In 2012, the European Society of Cardiology (ESC) Committee for Practice Guidelines (CPG) published an update [1] of the 2010 ESC Guidelines for the management of atrial fibrillation (AF) [2]. The update includes evidence from major clinical trials of the recently introduced novel oral anticoagulants or 'NOACs'. Arguably the term NOAC may become obsolete over time as they become too established to be termed 'novel,' and alternatives such as DOAC (direct oral anticoagulants) exist, but for the purposes of this paper we use the term NOAC to avoid confusion.

Despite the addition of recent clinical outcome data and clinical experience, the European Primary Care Cardiovascular Society (EPCCS) felt that wider implementation of the available guidelines (ESC and others) in primary care settings would benefit from adding contextual changes or clarifications of the evidence to aid the uptake of guidance in primary care. The EPCCS therefore established a Stroke Prevention in Atrial Fibrillation (SPAF) working group to develop an evidence-guided pragmatic guide on SPAF in primary care. To a large extent, our recommendations overlap with those described by the ESC and other European guidelines, including the revised 2014 UK NICE guidelines [3]. However, we distinguish preferable (ideal practice, first choice approach) and optional (alternative approach) diagnostic and treatment strategies, as we are aware that facilities and resources vary considerably across primary care practices in Europe.

This document does not make use of the commonly used classification of recommendations and distinctive levels of evidence, since these may not be familiar to some GPs and, further, they are less effective in grading epidemiological or diagnostic studies than clinical trials. Instead, we have adopted the 'user-friendly' terminology used by the UK National Institute for Health and Care Excellence (NICE) for the strength of our recommendations – 'some recommendations can be made with more certainty than others'. The EPCCS Consensus Group made its recommendations based on 'the trade-off between the benefits and harms of any intervention, taking into account the quality of the underpinning evidence'. The wording used in our recommendations (see Box 1) denotes the certainty with which the recommendation is made (the strength of the recommendation). As promoted by NICE, there should be discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help clinician and patient to reach a fully informed decision.

To highlight the summary recommendations the writing committee chose to indicate where the position taken is clearly evidence-based (green), and where it is more inferred and consensus-based (blue). It is also specified when studies were carried out in primary care settings, and therefore the evidence is most relevant. The working group also explored possible weaknesses in the enormous evidence base that guides the SPAF guidelines, and identified unresolved issues where further research is needed.

Box 1: Strength of Recommendations

The following colour coding will be used throughout the document, to indicate the strength of the individual recommendations.

Interventions that should (or should not) be used – a 'strong' recommendation

'Offer' (and similar words such as 'refer' or 'advise') indicates confidence that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. Similar forms of words (for example, 'Do not offer...') are used when we are confident that an intervention will not be of benefit for most patients.

Interventions that could be used

'Consider' indicates confidence that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Terminology used with permission from NICE

1. Introduction

Atrial fibrillation (AF) is the commonest cardiac arrhythmia, with about 1-2% of the general population estimated to be affected [1, 2]. It is a particularly common disorder in the elderly, with over 5% over the age of 65 suffering from AF, and around 10% of people over the age of 75 [4-6]. As a consequence of the ageing population, the prevalence of AF is predicted to rise [7]. Data from the General Practice Research Database (GPRD), a large retrospective routine case notes database in the United Kingdom, have shown a steady increase in AF prevalence for men and women of different ages since the early 1990s [8]. American data predict that by 2050 prevalence will have doubled, assuming that the rate of increase in AF over the past decade does not continue to accelerate. If AF prevalence rates continue to augment at the current increase rate, prevalence is expected to triple [9-11]. In addition to an ageing population, rising prevalence has been attributed to better survival of patients following acute coronary events, and a greater awareness amongst healthcare professionals of the importance of diagnosing AF.

Clinical picture of patients with atrial fibrillation

Patients with AF may have symptoms such as palpitations, lack of energy, dizziness, chest discomfort and shortness of breath, which may impair quality of life [12]. The degree of these symptoms varies considerably, from patients who are completely asymptomatic to those who are quite disabled by the arrhythmia. The use of rate and rhythm control to improve symptoms is beyond the scope of this guideline, which will focus exclusively on stroke prevention.

It is important to note that, for many patients with AF, the condition is often asymptomatic - or associated with minor symptoms that are ignored or unrecognised by patients - therefore, if the arrhythmia is to be identified in all, some type of AF screening is needed.

Perhaps the most important consequence of AF is the risk of embolic stroke. Patients with AF are at an almost five-fold higher risk of stroke compared to age-matched individuals with normal sinus rhythm, as shown in the Framingham study [13], as well as at a twice as high risk of all-cause mortality and heart failure. About 20–25% of all ischaemic strokes are attributable to embolism as a result of AF [14]. Not only do patients with AF have more strokes, they also develop more recurrent strokes, both fatal and nonfatal [13]. In addition, strokes are likely to be more severe in patients with AF, than in patients who have a stroke not associated with AF, regardless of age [15]. Following a stroke, patients with AF are more likely to be left with long-term disability and may require long-term care [16, 17]. This disability is a major source of concern for patients and is associated with high costs for healthcare systems.

Types of atrial fibrillation

ESC guidelines distinguish various types of AF, mainly based on duration e.g. paroxysmal (usually ≤48 hours), persistent (≥7 days) and long-standing or permanent (> 1 year) [1, 2]. These classifications are somewhat arbitrary and their use in clinical practice might be limited. They may, however, be relevant to determine how to treat the arrhythmia itself, rather than the stroke risk associated with AF. The risk of stroke is considered similar for all types of AF [18].

AF is often associated with other underlying pathology, especially in the elderly. It is more common in people who have structural heart or lung disease, as well as cardiovascular risk factors such as hypertension. It may also be associated with other diseases, the most common being thyroid disease, or start suddenly following a viral infection. In younger patients, occasional episodes of AF may follow a significant challenge, such as endurance sports or acute alcohol excess. In 1 out of 6 people, there is no obvious precedent disease – sometimes referred to as 'lone AF'- which is more common in those under 65. In some cases, treating the underlying disease may resolve the AF; this is particularly true in patients with hyperthyroidism. Modifying cardiovascular risk factors may also be effective in preventing the onset of AF [19, 20].

It is also important to consider the distinction between valvular and non-valvular types of AF, since it affects management. In the ESC guidelines [1, 2] the term valvular AF is used to indicate that AF is related to rheumatic valvular disease (predominantly mitral stenosis) or prosthetic heart valves. The distinction is mostly a historical label, though, and definitions have been subject to change.
Nowadays, due to improved imaging techniques and better screening of patients, the vast majority (up to 95%) of patients diagnosed with AF have some degree of valvular disease [11]. Patients with clinically significant valvular disease or mechanical heart valve, whether AF is present or not, require anticoagulation with a Vitamin K antagonist and aiming for a higher INR target. This strategy is related to the high flow state with prosthetic or mechanical valves and different activation of the coagulation cascade. The only trial to date evaluating a NOAC in patients with mechanical heart valves was halted after 250 enrolled patients, since the NOAC, used in higher dosage than for NVAF, was associated with more strokes and more bleeds than the vitamin K antagonist [21].

Atrial flutter, a different type of atrial arrhythmia, is sometimes considered along with AF. Atrial flutter and AF represent distinct diagnoses, and flutter is often more amenable to curative rhythm control but the stroke risk is similar. Patients with atrial flutter are often referred for consideration of curative management, but in the meantime stroke risk should be considered and managed in the same way as AF.

In summary, all types of AF, with the exception of clinically significant valvular AF and mechanical heart valves, should be regarded as the same in terms of stroke risk. Defining the type of AF can provide a diagnostic label, which can be useful when considering rate or rhythm management, but stroke risk is similar. Importantly, re-establishing sinus rhythm will not remove the stroke risk [20, 22-24].

Burden of atrial fibrillation

AF has considerable impact on individuals and health systems. It is also associated with increased mortality, heart failure, and high rates of hospitalisation due to stroke. Admission and readmission rates are the most important factors driving healthcare expenditure [25-27]. Aside from it being a very costly event, patients fear stroke because of the high chance of resulting impairment. AF is very common; affecting 1-2 percent of the general population overall. As we get better at preventing strokes due to other factors such as hypertension and transient ischaemic attacks, the proportion of strokes attributable to AF is likely to increase. AF is therefore an important modifiable risk factor for stroke that should be appropriately managed in all patients.

The role of the general practitioner in stroke prevention in atrial fibrillation

AF often co-exists with other chronic diseases such as heart failure. These conditions may cause or exacerbate each other. Over extended periods of time AF may cause substantial cardiac remodelling that can impact on the management of both conditions. A recent epidemiological study showed that 5% of over 65 year-olds had AF, and at least three other chronic conditions [28]. This implies that the general practitioner can play a crucial, central role, since he or she is aware of and can manage different conditions.

More than any other specialist, the GP knows the whole situation of a patient, including the full medical background, social circumstances including family setting and psychosocial context. Generalist care improves patient outcomes and the GP has a pivotal position within many European healthcare systems. Informing GPs about recent advances in stroke prevention strategies is vital to ensure effective, high quality primary care for patients.

Practical recommendations

Based on current evidence and experience, we recommend the following in a primary care setting:

Interventions that should be used

- **AF is one of the most important causes of preventable stroke, is associated with more severe strokes, and is therefore a major health risk to modify in patients and an important disease target for health systems.**
- **AF meets all the Wilson-Jungner criteria for a condition worth screening for.**
- **All patients with AF, regardless of AF type, are at increased risk of stroke as they age or develop certain co-morbid conditions and therefore all AF patients should be offered assessment of their stroke risk (see section 3).**
- **Patients who are treated for AF and returned to sinus rhythm should be risk assessed as if they were still in AF and should remain on their stroke prevention therapy if it was indicated prior to rhythm control. If a decision is taken to stop anticoagulation in these patients it should be a specialist decision.**

2. How is Atrial Fibrillation Detected? Should we Screen for Atrial Fibrillation?

Rationale for opportunistic case-finding

Patients with AF may present with symptoms, and AF should be considered in anyone complaining of palpitations (fluttering or irregular heart beat), dizziness or fainting spells, chest discomfort, shortness of breath and/or reduced exercise tolerance. Also very non-specific symptoms like general malaise can be related to AF. Patients with certain co-morbidities are more likely to develop AF. As outlined in the ESC Guidelines, patients with hypertension, heart failure, valvular heart disease, coronary artery disease, thyroid dysfunction, obesity, diabetes mellitus, chronic obstructive pulmonary disease, sleep apnoea, and chronic renal disease, as well as more rare cardiac disorders such as cardiomyopathies, atrial septal defects and other congenital heart defects are more prone to developing AF [2].

However, not all patients with AF will have symptoms and may therefore be unaware they have an arrhythmia. The observation that even short episodes of silent AF (as measured with implanted devices and by Holter electrocardiograms (ECGs)) convey an increased risk of stroke [29, 30] offers the rationale for opportunistic screening.

The SAFE study found that opportunistic screening by pulse palpation in general practice detected a large number of patients with previously undiagnosed AF compared to usual care (1.64% per year by screening vs. 1.04% per year with care as usual), yielding a feasible number needed to screen of 169 [31]. Importantly, a recent analysis of the SAFE study suggests that stroke risk profiles of AF patients detected via opportunistic and systematic screening were similar. These data suggest that active screening for AF in patients of 65 years and older can identify patients eligible for anticoagulation treatment according to $CHADS_2$ criteria [32]. New technologies such as modified sphygmomanometers capable of detecting an irregular pulse may also improve pick up rates. The similarity in picking up AF with such a device as compared to pulse feeling in general practice is reassuring. However, it should be noted that to date, no randomised trial has provided direct evidence that such screen-detected AF patients have a similar prognosis to non-screen-detected AF cases [32]. Nevertheless, all currently available evidence, although still small in number, points towards a comparable prognosis for both groups.

Confirming the diagnosis in suspected atrial fibrillation

In patients with suspected AF, an ECG, preferably 12-lead ECG, can confirm the diagnosis. Loss of P-waves and completely irregular R-R distances are characteristic features of AF on ECG, however, ECG changes may be subtle so judgement by a competent ECG-reader is required to confidently diagnose AF [6]. Adequate interpretation of a single-lead ECG may be considered as convincing as a 12-lead ECG for detection or exclusion of AF [33].

For opportunistic screening to be effective, ECG should be performed shortly after an irregular pulse has been detected [34]. If the delay is too long, patients may be missed because they have gone back into sinus rhythm, or patients may lose the motivation to participate in screening and fail to have an ECG done. Here single-lead ECG devices have the advantage that they give immediate results; they provide information with only one lead, but for the duration of one minute, as compared with a 12 lead ECG that normally records 10 seconds.

There is debate about the significance of 'short' episodes of AF; how long should AF last for it to be considered a significant arrhythmia? There is a direct relationship between the burden of AF and stroke risk including in those with paroxysmal AF [29]. It is, however, as yet unclear whether a causal relationship between very short bouts of AF and stroke risk exists, since this can occur in young, otherwise well individuals who therefore have a low background risk of ischaemic stroke.

It is not clear how many and how long lasting bursts of AF must be to affect the structure of the atria of the heart which leads to high risk of thromboembolism. Conventionally, an ECG should contain a total of 30 seconds of AF to confirm the diagnosis, but this criterion is consensus not evidence-based and was developed for considering which patients to offer cardioversion or pacing to. Therefore, a standard 12 lead ECG of 10 seconds is perhaps sufficient in practice settings.

Practical recommendations

Based on current evidence and experiences, we recommend the following case finding efforts in a primary care setting:

Interventions that should be used

- **Opportunistic case finding should be carried out to timely detect AF in all patients over 65 years of age, and in anyone who receives routine cardiovascular follow-up:**
- **Pulse palpation, at least once a year could be incorporated in to already existing medical visits, for instance during an annual cardiac disease review, and/or at flu vaccinations or pharmacy visits.**
- **In case of a positive pulse palpation:**
- **12-lead ECG follow-up should be performed shortly after pulse assessment. 12-lead ECG follow-up should be done by a practitioner who is competent in ECG interpretation.**

Alternative approach

- Modified sphygmomanometers or other devices using single lead ECG registrations to detect an irregular pulse may be used instead

of pulse palpation, but only where they have been subject to independent validation with a 12 lead ECG.
- If not enough expertise is available in the primary care setting to confidently read a 12-lead ECG, it should be reviewed by a specialist. 12-lead ECG may also provide other useful information on cardiac functioning.

Additional work recommended in this area / gaps in the evidence:

- How much atrial fibrillation – length or frequency of AF runs – constitutes a sufficient stroke risk to warrant treatment should be established
- In the absence of prospective trials, more follow-up data from screened cohorts, such as the SAFE study [31, 32], would be useful to establish if over time stroke risk is similar or higher in screen detected patients as compared with AF cases identified through systematic screening.
- Trials of screening plus treatment versus routine care should be conducted to identify whether comprehensive care packages are more effective at reducing stroke outcomes.

3. How to Decide Whether to Treat Stroke Risk in Atrial Fibrillation?

Risk assessment for stroke prevention in atrial fibrillation

When giving antithrombotic agents to reduce stroke risk in AF, both thromboembolic risk and bleeding risk need to be considered. 'Whom not to treat?' is a question at least as important to ask as 'whom to treat?', since each form of antithrombotic therapy has an inherent, and possibly severe, bleeding risk.

The $CHADS_2$ score is a valuable tool that has been used for some time to assess stroke risk in patients with AF [35, 36](see table 1 for components of the $CHADS_2$ score). Low to moderate-risk patients ($CHADS_2$ score 0 or 1) were recommended not to receive anticoagulation, since the risk of bleeding was thought to exceed the risk of stroke. A $CHADS_2$ score of 2 or more was associated with high stroke risk and anticoagulation was likely to be beneficial. However, more recent data calls for refinement of that view. Even in the low-risk group, there is a 2-3 %/year incidence of stroke after AF has been diagnosed [37]. The large ACTIVE-W trial found a stroke rate of 2.2 %/year in moderate-risk ($CHADS_2$=1) AF patients, who were treated with acetyl salicylic acid (ASA) [38].

These observations highlighted the need for a more robust stroke risk score. The CHA_2DS_2-VASc score has since been developed, which includes additional risk factors and gives a maximum score of 9 compared to a maximum of 6 in the $CHADS_2$ score (*see table 1* for components of the CHA_2DS_2-VASc score). Age can contribute 2 points, rather than 1, if the patient is ≥75 years old. Vascular disease and female sex also add an extra point [1, 2] - the latter however only contributing a score if other stroke risk factors are present (i.e. if the only 'risk' factor is being female the CHA_2DS_2-VASc score is 0). This more refined risk calculation improves risk stratification of AF patients with a $CHADS_2$ score of 0 or 1.

When comparing the different risk levels based on the CHA_2DS_2-VASc score within $CHADS_2$=0 and $CHADS_2$=1, different annual stroke rates were seen for CHA_2DS_2-VASc scores 0-4 [39]. Within a $CHADS_2$ category, CHA_2DS_2-VASc annual event rates increased with each incremental CHA_2DS_2-VASc score, the lowest of which was lower than the overall event rate associated with the $CHADS_2$ score. Thus, refinement allows identification of patients at truly low risk; e.g. in a large Danish registry, among those with $CHADS_2$=0-1, those with CHA_2DS_2-VASc=0 showed a stroke/thromboembolism rate of 0.84 per 100 person-years (95%CI: 0.65-1.08), those with CHA_2DS_2-VASc=1 had a rate of 1.79, while patients with CHA_2DS_2-VASc=2 had 3.67, CHA_2DS_2-VASc=3 had 5.75 and CHA_2DS_2-VASc=4 had 8.18 per 100 person-years, after 1 year of follow-up. Individuals with a $CHADS_2$ score=0 were not all 'low risk', with one-year event rates ranging from 0.84 (CHA_2DS_2-VASc score=0), to 1.75 (CHA_2DS_2-VASc score=1), to 2.69 (CHA_2DS_2-VASc score=2), to 3.20 (CHA_2DS_2-VASc score=3). Persons with $CHADS_2$=1 had event rates of 1.93 per 100 person-years (CHA_2DS_2-VASc score=1), 4.05 (CHA_2DS_2-VASc score=2), to 5.81 (CHA_2DS_2-VASc score=3), and 8.18 per 100 person-years (CHA_2DS_2-VASc score=4) after 1 year of follow-up. [39]. So CHA_2DS_2-VASc risk stratification identifies patients at substantial risk who would not have been considered eligible for stroke prevention with anticoagulation according to the $CHADS_2$ score.
The improved risk stratification with CHA_2DS_2-VASc as opposed to $CHADS_2$ score has been validated in several studies [40-44], and

TABLE 1: $CHADS_2$ and CHA_2DS_2-VASc risk score components

Condition	$CHADS_2$ score	Points	CHA_2DS_2-VASc score	Points
Congestive heart failure (or Left ventricular systolic dysfunction)	C	1	C	1
Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)	H	1	H	1
Age ≥75 years	A	1	A_2	2
Diabetes Mellitus	D	1	D	1
Stroke or TIA or thromboembolism in history	S_2	2	S_2	2
Vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque)			V	1
Age 65–74 years			A	1
Sex category (i.e. female gender)			Sc	1

This table shows the components of the $CHADS_2$ (Gage et al., JAMA 2001 [36]) and CHA_2DS_2-VASc scores (Lip et al., Chest 2010 [41]) tools to assess stroke risk in patients with AF. These risk assessment tools help to determine who should and who should not receive anticoagulation. CHA_2DS_2-VASc improves risk stratification in patients with $CHADS_2$=0 or 1, and allows for identification of patients at truly low risk.

TABLE 2: Event rates per $CHADS_2$ and CHA_2DS_2-VASc category

Score/risk category	1 year's follow-up annual event rate	5 years' follow-up annual event rate	10 years' follow-up annual event rate
$CHADS_2$ score:			
0	1.67 (1.47 to 1.89)	1.28 (1.19 to 1.38)	1.24 (1.16 to 1.33)
1	4.75 (4.45 to 5.07)	3.70 (3.55 to 3.86)	3.56 (3.42 to 3.70)
2	7.34 (6.88 to 7.82)	5.58 (5.35 to 5.83)	5.40 (5.18 to 5.63)
3	15.47 (14.62 to 16.36)	10.29 (9.87 to 10.73)	9.89 (9.50 to 10.31)
4	21.55 (20.03 to 23.18)	14.00 (13.22 to 14.82)	13.70 (12.95 to 14.48)
5	19.71 (16.93 to 22.93)	12.98 (11.52 to 14.63)	12.57 (11.18 to 14.14)
6	22.36 (14.58 to 34.30)	16.75 (11.91 to 23.56)	17.17 (12.33 to 23.92)
$CHADS_2$ risk category:	**annual event rate**	**annual event rate**	**annual event rate**
Low risk (0)	1.67 (1.47 to 1.89)	1.28 (1.19 to 1.38)	1.24 (1.16 to 1.33)
Intermediate risk (1)	4.75 (4.45 to 5.07)	3.70 (3.55 to 3.86)	3.56 (3.42 to 3.70)
High risk (2-6)	12.27 (11.84 to 12.71)	8.30 (8.08 to 8.51)	7.97 (7.77 to 8.17)
CHA_2DS_2-VASc risk score			
0	0.78 (0.58 to 1.04)	0.69 (0.59 to 0.81)	0.66 (0.57 to 0.76)
1	2.01 (1.70 to 2.36)	1.51 (1.37 to 1.67)	1.45 (1.32 to 1.58)
2	3.71 (3.36 to 4.09)	3.01 (2.83 to 3.20)	2.92 (2.76 to 3.09)
3	5.92 (5.53 to 6.34)	4.41 (4.21 to 4.61)	4.28 (4.10 to 4.47)
4	9.27 (8.71 to 9.86)	6.69 (6.41 to 6.99)	6.46 (6.20 to 6.74)
5	15.26 (14.35 to 16.24)	10.42 (9.95 to 10.91)	9.97 (9.53 to 10.43)
6	19.74 (18.21 to 21.41)	12.85 (12.07 to 13.69)	12.52 (11.78 to 13.31)
7	21.50 (18.75 to 24.64)	13.92 (12.49 to 15.51)	13.96 (12.57 to 15.51)
8	22.38 (16.29 to 30.76)	14.07 (10.80 to 18.33)	14.10 (10.90 to 18.23)
9	23.64 (10.62 to 52.61)	16.08 (8.04 to 32.15)	15.89 (7.95 to 31.78)
CHA_2DS_2-VASc risk category:	**annual event rate**	**annual event rate**	**annual event rate**
Low risk (0)	0.78 (0.58 to 1.04)	0.69 (0.59 to 0.81)	0.66 (0.57 to 0.76)
Intermediate risk (1)	2.01 (1.70 to 2.36)	1.51 (1.37 to 1.67)	1.45 (1.32 to 1.58)
High risk (2-9)	8.82 (8.55 to 9.09)	6.01 (5.88 to 6.14)	5.72 (5.60 to 5.84)

Event rates (95%CI) of hospital admission and death due to thromboembolism (including peripheral artery embolism, ischaemic stroke and pulmonary embolism) per 100 person years, for each $CHADS_2$ and CHA_2DS_2-VASc category. Risk profiles are largely similar with different lengths of follow-up. Based on Olesen et al., BMJ 2011 [40].

TABLE 3: HAS-BLED risk score components

Clinical characteristic			Points
Hypertension	Uncontrolled, >160 mmHg systolic)	H	1
Abnormal renal and liver function (1 point each)	Dialysis, transplant, Cr >200 µmol/L, Cirrhosis, bilirubin >2x normal, AST/ALT/AP >3x normal)	A	1 or 2
Stroke history		S	1
Bleeding or predisposition to bleeding		B	1
Labile INR	Unstable/high INRs, time in therapeutic range < 60%)	L	1
Elderly	Age > 65	E	1
Drugs or alcohol (1 point each)	Antiplatelet agents, NSAIDs, ≥ 8 alcohol drinks/week	D	1 or 2

This table shows the components of the HAS-BLED score (Pisters et al, Chest 2010 [45], Camm et al., Eur H J 2010 [2]), used to assess bleeding risk.

CHA_2DS_2-VASc is the recommended score for assessment of stroke risk in the ESC guidelines [1]. Event rates of hospital admission and death due to thromboembolism (including peripheral artery embolism, ischaemic stroke and pulmonary embolism) for each $CHADS_2$ and CHA_2DS_2-VASc category are shown in table 2 *(see page 8)*.

Risk assessment for bleeding risks from anticoagulation

Bleeding is an important, potentially serious, side effect of anticoagulation and should be considered for all patients prior to treatment initiation.

Bleeding risk can be assessed with the HAS-BLED score, as introduced in the 2010 ESC Guidelines (see *table 3* for components of the HAS-BLED score)[2, 45]. The HAS-BLED score takes into account nine risk factors for bleeding that should be considered before starting antithrombotic treatment. The most important factor determining both stroke and bleeding risk appears to be age [1, 46-49], which justifies its double weight in the CHA_2DS_2-VASc score. Certain factors are potentially modifiable, such as hypertension and reduced renal function. Treating these co-morbidities thus likely lowers bleeding risk.
An observational retrospective study has confirmed increased bleeding rates in incremental HAS-BLED scores [46]. The HAS-BLED score has been validated in several studies and found to accurately predict bleeding risk in clinical trials evaluating NOACs [48, 50, 51], and in a 'real world' setting, in non-selected patients with AF receiving anticoagulant therapy [46, 47, 52]. *Table 4* shows the incidence of major bleeding per HAS-BLED category as seen in non-selected patients receiving anticoagulation. The HAS-BLED score has been found to be at least as good as older and more complicated bleeding risk scores such as ATRIA and $HEMORR_2HAGES$ in AF patients [46, 49-53], as well as in a non-AF population [54]. Due to its simplicity, the HAS-BLED score is the bleeding risk assessment tool of choice [1, 49].

HAS-BLED score can be useful to identify the patient at increased risk, and highlight the opportunities to lower bleeding risk through risk factor modification. However, the HAS-BLED score is NOT appropriate for guidance in decision-making about whether to anticoagulate or not.
It has been modelled that there will not be a combination of a CHA_2DS_2-VASc and HAS-BLED score at which the risk of bleeding outweighs the risk of anticoagulation (see table 5 for net clinical benefit of different combinations of CHA_2DS_2-VASc and HAS-BLED scores on different antithrombotic regimes)[46], implying that anticoagulation will always be dominant in terms of beneficial effect. HAS-BLED should therefore guide the patient and clinician to reduce modifiable bleeding risks (namely high blood pressure, liver and kidney function, INR control and use of interacting medications or alcohol) but not determine whether to offer anticoagulation or not – that decision is based on stroke risk estimation.

TABLE 4: Major bleeding event rates per HAS-BLED category

HAS-BLED score	Incidence (%/year) of major bleeding events
0	0
1	0.83
2	1.88
3	5.72
4	5.61
>5	16.48

Incidence of major bleedings per HAS-BLED category as seen in non-selected AF patients receiving anticoagulation. N=937 patients. Median follow-up was 952 (IQR: 785-1074) days. C-statistic as a quantitative variable: 0.71 and 0.68 as a dichotomised variable. (Roldan et al., Chest 2013 [52])

TABLE 5: Net clinical benefit (95% confidence interval) for combinations of CHA_2DS_2-Vasc and HAS-BLED scores on different antithrombotic regimes.

	Stroke Ischaemic		Haemorrhagic		VKA HAS-BLED score		ASA HAS-BLED score		VKA+ASA HAS-BLED score	
	N (%)	Person to years at risk	N (%)	Person to years at risk	Score ≤2	Score ≥3	Score ≤2	Score ≥3	Score ≤2	Score ≥3
$CHADS_2$										
Score 0	323 (1.0)	157279	184 (0.6)	157511	−0.02 (-0.09 to 0.06)	0.19 (-1.39 to 1.77)	−0.10 (-0.20 to −0.00)	0.37 (-0.74 to 1.48)	−0.25 (-0.48 to −0.03)	–
Score 1	1853 (3.9)	169755	436 (0.9)	170606	0.84 (0.70 to 0.99)	0.56 (0.16 to 0.95)	−0.26 (-0.44 to −0.07)	0.21 (-0.18 to 0.60)	0.46 (0.17 to 0.75)	0.6 (0.14 to 1.07)
Score 2–6	5034 (7.9)	180237	761 (1.2)	182250	1.95 (1.70 to 2.20)	2.68 (2.33 to 3.04)	0.21 (-0.14 to 0.55)	0.3 (-0.08 to 0.68)	1.67 (1.20 to 2.13)	2.31 (1.86 to 2.76)
CHA_2DS_2-VASc										
Low risk (score 0)	46 (0.4)	6020	32 (0.3)	66076	−0.11 (-0.20 to −0.03)	–	−0.00 (-0.09 to 0.08)	–	−0.03 (-0.21 to 0.15)	–
Intermediate risk (score 1)	170 (0.9)	86370	108 (0.6)	86474	−0.02 (-0.15 to 0.11)	0.25 (-0.86 to 1.36)	−0.02 (-0.15 to 0.11)	0.14 (-0.89 to 1.17)	−0.20 (-0.46 to 0.06)	–
High risk (score 2–9)	6994 (6.2)	354881	1241 (1.1)	357817	1.19 (1.07 to 1.32)	2.21 (1.93 to 2.50)	−0.04 (-0.22 to 0.14)	0.23 (-0.06 to 0.53)	0.81 (0.56 to 1.07)	1.97 (1.62 to 2.32)

Net clinical benefit was calculated as: (ischaemic stroke rate with no treatment – ischaemic stroke rate on treatment) – 1.5(intracranial haemorrhage rate on treatment – intracranial haemorrhage rate with no treatment), thus balancing ischaemic stroke risk agains intracranial haemorrhage. Values greater than zero favour treatment. These data show that in situations with both a high stroke risk (CHA_2DS_2-VASc >2) and a high bleeding risk (HAS-BLED>3) treatment with antithrombotics is beneficial. If less than 200 person-years in treatment in a cell the net clinical benefit was not calculated. ASA: acetylsalicylic acid; VKA: vitamin K antagonist.*
Adapted from: Olesen et al., Thrombosis and Haemostasis 2011 [46].

Falls are sometimes given as an argument not to anticoagulate a frail patient, yet evidence suggests that patients with low impact falls need to fall a great number of times before it actually increases the bleeding risk. Prospective research, which is more reliable than retrospective comparisons, has shown no additional bleeding risk for patients at high risk of falls who are anti-coagulated [55]. Moreover, patient preferences should not be ignored; some patients are willing to endure many bleeds if that means they can prevent a stroke and its consequences [56]. In general, it should be noted though that with an area under the curve below 70 [49, 52, 53], these risk scores remain less than perfect predictors of individual risk.

Practical recommendations

Based on current evidence and experiences, we recommend the following stroke and bleeding risk assessment strategy in primary care in patients who have been diagnosed with AF:

Stroke and bleeding risk interventions that should be used

- **CHA_2DS_2-VASc score is superior to $CHADS_2$ score for assessing stroke risk in AF, and should specifically be used to identify who should not receive anticoagulation.**
- **Alternatively, since $CHADS_2$ is simpler to use, patients' risk of stroke can be initially assessed using $CHADS_2$ but if their score is 1 or less, then a CHA_2DS_2-VASC score should be performed to identify those patients who do not require anticoagulation.**
- **Patients with a CHA_2DS_2-VASc score of 0 *should not* be offered antiplatelet or anticoagulation therapy.**
- **Patients with a CHA_2DS_2-VASc score of 2 or above *should* be offered anticoagulation. In patients with a CHA_2DS_2-VASc score of 1, *consider* anticoagulation and base any decision to treat or not treat on patient preference after balancing the benefits with risks of treatment.**
- **As a second step, HAS-BLED *should* be used to assess bleeding risk, with the aim of modifying this risk through addressing individual risk factors that can be altered.**
- **HAS-BLED *should not* be used to decide whether to offer anticoagulation in someone with a CHA_2DS_2-VASc score of 2 or above, but *consider* its use to balance the benefits of anticoagulation in patients with a CHA_2DS_2-VASc score of 1.**
- **On a regular basis, presumed once a year, the risk status of patients with AF should be re-evaluated depending on change in risk factors (change of age category, new hypertension, etc).**

These scoring tools are available on the EPCCS website at: www.epccs.eu

Alternative risk assessment approaches that may be used:

- A more pragmatic strong risk application might simply be to consider age, since women over 65 with AF and an additional risk factor qualify for anticoagulation according to CHA_2DS_2-VASc stroke risk stratification, and so do men over 75.
- People under 65 with no additional risk factor to their AF, in contrast, do not need anticoagulation.
- Risk assessment should also be done in patients younger than 65 years of age who have multiple risk factors.

Additional work recommended in this area / gaps in the evidence:

- Risk scores, for both stroke and bleeding risk, must continue to be assessed, validated and modified where necessary to ensure accurate predictive values are available to help clinicians to make informed decisions.
- More prospective data to quantify whether fall rates above a threshold increase bleeding risk are needed.

4. What are the Management Options to Treat Stroke Risk in Atrial Fibrillation?

What is the evidence for anticoagulation in patients with atrial fibrillation in primary care?

Different antithrombotic strategies to prevent stroke in AF have been

TABLE 6: Nature of primary events with warfarin or aspirin in an elderly community population with atrial fibrillation

	Warfarin n=488		Aspirin n=485		Warfarin vs. aspirin	
	n	risk per year	n	risk per year	RR (95%CI)	P
Stroke	21	1.6%	44	3.4%	0.46 (0.26-0.79)	0.003
By severity						
Fatal	13	1.0%	21	1.6%	0.59 (0.27-1.24)	0.14
Disabling-non fatal	8	0.6%	23	1.8%	0.33 (0.13-0.77)	0.005
Type of stroke						
Ischaemic	10	0.8%	32	2.5%	0.30 (0.13-0.63)	0.0004
Haemorrhagic	6	0.5%	5	0.4%	1.15 (0.29-4.77)	0.83
Unknown	5	0.4%	7	0.5%	0.69 (0.17-2.51)	0.53
Other intracranial haemorrhage	2	0.2%	1	0.1%	1.92 (0.10-113.3)	0.65
Systemic embolism	1	0.1%	3	0.2%	0.32 (0.01-3.99)	0.36
Total number of events	24	1.8%	48	3.8%	0.48 (0.28-0.80)	0.0027

The BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged) Study was a randomised controlled trial comparing warfarin (target INR: 2.0-3.0) with aspirin (75 mg/day) for stroke prevention in atrial fibrillation in a community population of over 75 years of age. Primary events are shown for both treatments, along with the relative risk (RR) for warfarin vs. aspirin. Taken from: Mant et al., Lancet 2007 [61].

investigated over time. Early studies suggested that antiplatelet agents were effective in reducing stroke risk with one meta-analysis showing acetyl salicylic acid (ASA) reduced the stroke rate by 22% [57], and addition of clopidogrel led to a risk reduction of 28% [58]. Vitamin K antagonists gave a further risk reduction of 43% [59, 60].
A meta-analysis that compared multiple trials that evaluated the efficacy of ASA or warfarin against placebo in SPAF, showed a much larger risk reduction with warfarin vs. placebo, than with ASA vs. placebo [57]. The number needed to treat (NNT) to prevent a stroke with warfarin as primary prevention was 37 and 12 in secondary prevention, while with ASA NNT for primary prevention was 125 and 26 in secondary prevention. In the meta-analysis of data of 2900 patients, 6 intracranial haemorrhages were observed with adjusted-dose warfarin, vs. 3 with control or placebo. 31 extracranial haemorrhages were seen on warfarin, as compared with 17 in controls, yielding a relative risk increase of 66% (95%CI: 18-235), and an absolute risk increase of 0.3%. A relative risk reduction for all-cause mortality of 26% (95%CI: 3-43) was observed, implying an absolute risk reduction of 1.6%. Given the rare nature of safety outcomes, benefits clearly outweighed the risks [57].

The BAFTA study specifically studied an elderly (≥75 years old) primary care population, and compared warfarin with ASA in a randomised controlled trial. In this patient population, which is commonly seen in primary care practices, warfarin was clearly more effective than ASA in reducing stroke (see *table 6*). Risk of stroke per year was 1.6% with warfarin, and 3.4% with ASA, giving a relative risk of 0.46 (95%CI: 0.26-0.79, P=0.003) for warfarin vs. ASA. A non-significant relative risk for systemic embolism of 0.32 (95%CI: 0.01-3.99, P=0.36) was observed when comparing warfarin and ASA (0.1% vs. 0.2% risk per year). Both treatments had low intracranial bleeding rates (0.2% vs. 0.1% per year, relative risk: 1.92 95%CI: 0.10-113.3, P=0.65) (see *table 6*)[61].
Strokes occurring in the elderly are more likely to originate from the heart, i.e. they are embolic strokes [61]. The data from BAFTA suggest that ASA may be less effective at preventing AF stroke in the elderly, who represent the majority of the AF population. These data were strengthened by the individual patient data (IPD) meta-analysis of the totality of available warfarin and aspirin data in preventing AF stroke by age, which showed that aspirin became less effective and more likely to cause bleeding with increasing age, with no benefits observed beyond 75 [62].

Do patients receive treatment recommended in current guidelines?

A systematic review on the use of anticoagulation in AF revealed that many high-risk patients who were eligible for oral anticoagulation therapy were not treated with oral anticoagulation. In some studies, the proportion of untreated eligible patients amounted to 80% [63].

The Global Anticoagulant Registry in the FIELD (GARFIELD) is an international observational study that is evaluating therapeutic management of patients newly diagnosed with non-valvular AF [64]. The GARFIELD data reveal that 38.0% of patients at high risk of stroke ($CHADS_2$ score ≥ 2) did not receive anticoagulant therapy, while 42.5% of those at low risk ($CHADS_2$ score 0) were on anticoagulants. Similarly, 40.7% of patients with a CHA_2DS_2-VASc score ≥2 did not receive anticoagulant therapy, while 38.7% of low-risk patients with CHA_2DS_2-VASc score 0 did receive this therapy. Thus, anticoagulant therapy is often not prescribed according to current stroke risk scores and guidelines, as both over-treatment in patients at low risk, and under-treatment in patients at high risk of stroke were common. The GARFIELD study also examined reasons for not providing anticoagulants when applicable ($CHADS_2$ score ≥ 2), and found that nearly half of the reasons were related to physician's choice, rather than patient characteristics [64].

Comorbidity in atrial fibrillation

Patients with AF often have other chronic conditions, which may be a cause or consequence of the arrhythmia or simply co-exist. Multimorbidity increases with age, and is common in people over 65 years old. Patients between 65 and 84 were found to have on average 2.6 (SD: 2.09) morbidities, and 64.9% (95%CI: 64.7-65.1) of people in this age group have multimorbidity. In patients of 85 years and older the mean number of morbidities is 3.62 (SD: 2.30), and 81.5% (95%CI: 81.1-81.9) of individuals have multimorbidity. Socioeconomic deprivation is associated with earlier onset of multimorbidity [28].

The presence of several diseases can limit the optimisation of therapy for any one disease. Patients may need to take many medications, which may interact or have effects on other conditions. Medical specialists traditionally deal with single organ diseases, whereas primary care physicians are well placed to manage complex cases of multimorbidity and polypharmacy in a holistic way to optimise the care of the individual patient.

Stroke risk management in atrial fibrillation patients with rate or rhythm control strategies

In very symptomatic AF patients, it is important to optimise and control heart rate and it may also be appropriate to try to re-establish and maintain sinus-rhythm. Now that all guidelines advocate consideration of the use of antithrombotic therapy in all patients based on risk calculation, it is important to consider that control of rate and rhythm should only be attempted alongside controlling for the stroke risk.

Importantly, antithrombotic therapy should be continued, even if rhythm control is obtained; both the AFFIRM and RACE and other trials showed respectively worse mortality and event-free survival in the rhythm control arm than in the rate control arm, which was mostly driven by higher rates of ischaemic stroke and heart failure [20, 22-24]. Although sinus rhythm was re-established, patients continued to be at risk of stroke. If a decision is taken to stop anticoagulation in primary care, this should only be based on an explicit specialist recommendation and after patient consent.

Practical recommendations

Based on current evidence and experiences, we recommend the following stroke risk reduction management in primary care patients who have been diagnosed with AF:

Management strategies that should or should not be used

- **Patients assessed as low risk on the CHA_2DS_2-VASc score (0) should not be offered antiplatelet or anticoagulation therapy, but**
- **may be offered standard advice regarding improving vascular risk factors (smoking cessation, BP and cholesterol control).**
- **Patients with a CHA_2DS_2-VASc score of 2 or above *should* be offered anticoagulation.**

Management strategies that may be used

- In patients with a CHA_2DS_2-VASc score of 1, *consider* anticoagulation and base any decision to treat or not to treat on patient preference after balancing the benefits with risks of treatment. In this situation, the decision to treat with anticoagulation or not should be based upon patient preferences of their primary desire to reduce their stroke risk or to avoid bleeding risk. Since their stroke risk is moderate rather than high, it is also very important to attempt to modify any bleeding risk factors.
- Only in those intolerant of, or refusing, anticoagulation *may* a combination of anti-platelets be considered (though the bleeding risk of this strategy will approach that of anticoagulation).

5. What are the Therapeutic Options to Treat Stroke Risk in Atrial Fibrillation?

While Vitamin K antagonists (VKAs) and to a lesser extent other antithrombotic agents importantly reduced the risk of stroke in patients with AF, they have several drawbacks and a lot of effort has been dedicated to developing new anticoagulant agents. VKAs require intensive monitoring of International Normalised Ratio (INR) to ensure the drug is effective yet safe by maintaining figures within a therapeutic range (INR target 2.5, range 2-3 for NVAF). Moreover, it is important to achieve INR control above 65% time in therapeutic range (TTR). A study of the UK General Practitioner Research Database showed that good anticoagulation control with TTR > 70% was associated with 79% reduction of stroke and a similar reduction of mortality, as compared with poor TTR [65] *(See figure 1)*. A systematic review into treatment practices for SPAF concluded that most studies documented underuse of VKAs, defined as <70% treatment of high-risk patients, further underscoring the need for improved treatment options. Four new oral anticoagulants (NOACs) are now available, namely dabigatran etexilate, a direct thrombin inhibitor [66, 67], and the direct factor Xa inhibitors apixaban [68][56] rivaroxaban [69] and edoxaban [69, 70]. These new agents represent a valuable addition to current treatment options for SPAF, as outlined below.

Efficacy of NOACS vs. warfarin in non-valvular AF

In recent years, the new classes of anticoagulants have been developed and tested. Data of large trials on their efficacy and safety have been evaluated extensively, including 'real life' follow-up data. In several, large randomised controlled trials (RCTs) of AF patients without severe valve disease or mechanical valves, NOACs have been shown to be effective in reducing stroke risk [66-70]. (The study design of SPAF trials with NOACs is summarised in *table 7*, and patient demographics in *table 8*). These RCTs were designed as non-inferiority studies; thus powered to show that NOACs are at least as good as warfarin in the prevention of stroke in AF.

In the RE-LY trial, over 18000 patients with non-valvular AF and at least one additional risk factor for stroke were randomised to one of two doses of dabigatran (110 mg or 150 mg twice daily) or warfarin dose

TABLE 7: Study design of the SPAF trials evaluating NOACs vs warfarin.

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Study	RE-LY	ROCKET-AF	ARISTOTLE	ENGAGE
Design	PROBE	Double blind	Double blind	Double blind
Median Follow-up	2 years	1.9 years	1.8 years	2.8 years
Population size	>18000	>14000	>18000	>21000
Inclusion	nonvalvular AF + 1 risk factor	nonvalvular AF +2 risk factors (moderate to high risk)	nonvalvular AF + 1 risk factor	nonvalvular AF with $CHADS_2$ > 2
Inclusion ($CHADS_2$)	2.1	3.5	2.1	2.8
Primary endpoint	stroke and SE	stroke and SE	stroke and SE	stroke and SE
Warfarin comparator INR control (mean TTR)	64%	55%	62%	68,40%
Reference	Connolly *et al.*, NEJM 2009 [67]	Patel *et al.*, NEJM 2011 [69]	Granger *et al.*, NEJM 2011 [68]	Giugliano *et al.*, NEJM 2013 [70]

PROBE: prospective randomised open blinded endpoint,SE: systemic embolism.

TABLE 8: Patient demographics of the large SPAF trials evaluating NOACs vs. warfarin.

	RE-LY	ROCKET-AF	ARISTOTLE	ENGAGE
n=	18113	14264	9120	21105
Median age	71	73	70	72
Prior stroke, SE or TIA	20%	55%	19%	28%
Hypertension	79%	91%	87%	94%
CHF	32%	63%	35%	57%
Diabetes mellitus	23%	40%	21%	36%
$CHADS_2$-score	2.1	3.5	2.1	2.8
% renally impaired (CrCl 30-50 ml/min)	~19%	21%	15%	19%
% non-paroxysmal AF patients	~67%	82%	85%	~75%
Reference	Connolly *et al.*, NEJM 2009 [67]	Patel *et al.*, NEJM 2011 [69]	Granger *et al.*, NEJM 2011 [68]	Giugliano *et al.*, NEJM 2013 [70]

SE: systemic embolism, TIA: transient ischaemic attack, CHF: congestive heart failure, CrCl: creatinin clearance

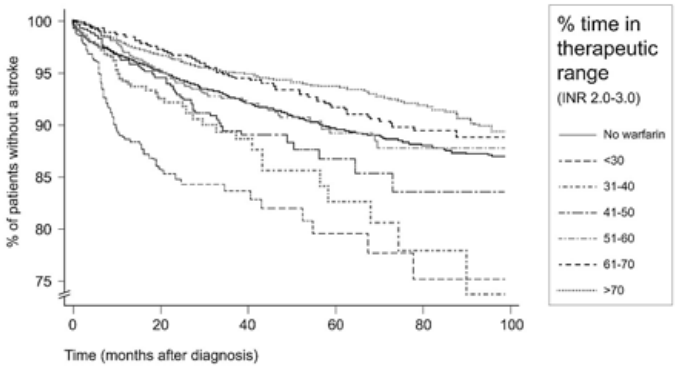


Figure 1. Percent of patients free from stroke over time, stratified by time spent in therapeutic range (INR 2.0 – 3.0). *Adapted from Gallagher* et al., *Thromb and Haem. 2011 [65]*

adjusted to INR 2.0-3.0. The rate of stroke and systemic embolism (SE) was 1.69% per year on warfarin, 1.53% per year on dabigatran 110 mg, and 1.11% per year on dabigatran 150 mg [67]. The advantage of dabigatran over warfarin was greater at centres with poor INR control than in those with good INR control [66]. In the ROCKET-AF trial, over 14000 patients with nonvalvular AF who were at increased risk for stroke were randomised to daily dose of 20 mg rivaroxaban or dose-adjusted warfarin (target INR: 2.0-3.0). The primary outcome of stroke or SE occurred in 2.1% of patients per year in the intention-to-treat rivaroxaban group, and in 2.4% of patients per year on warfarin [69]. In ARISTOTLE, over 18000 patients with non-valvular AF and at least one additional risk factor for stroke were randomised to apixaban 5 mg twice daily, or warfarin (target INR: 2.0-3.0). The primary outcome of ischaemic or haemorrhagic stroke or SE was seen at a rate of 1.27% per year in patients on apixaban, as compared to 1.60% per year in the warfarin group [68]. Two once-daily doses of edoxaban were compared with warfarin in over 21105 patients with moderate-to-high risk AF in the ENGAGE AF-TIMI 48 trial. The annual rate of stroke or SE in the intention-to-treat population was 1.80% with warfarin, 1.57% with high-dose edoxaban and 2.04% with low-dose edoxaban [70].

Thus, with regard to stroke and SE, high-dose dabigatran yields 34% relative risk reduction as compared to warfarin (RR: 0.66, 95%CI: 0.53-0.82, P<0.001 for superiority) [66, 67], apixaban 21% (HR: 0.79, 95%CI: 0.66-0.95, P<0.001 for noninferiority and P=0.01 for superiority) [68], rivaroxaban 12% (HR: 0.88, 95%CI: 0.74-1.03, P<0.001 for noninferiority, P=0.12 for superiority) [60, 69], and high-dose edoxaban showed a trend of 13% risk reduction (HR:0.87, 97.5%CI: 0.73-1.04, P=0.08) [70].
A comparison of stroke rates in patients randomised to apixaban or aspirin, who were deemed unsuitable for VKA, demonstrated that apixaban was significantly more effective at reducing stroke and SE than aspirin alone (HR: 0.45, 95%CI: 0.32-0.62) [71]. Thus, standard of care for SPAF is true anticoagulation, not aspirin or other types of antiplatelet therapy.

When combining all data of the first three large trials studying NOACs (RE-LY, ROCKET-AF and ARISTOTLE), NOACs were found to be at least as effective as VKA; risk of haemorrhagic stroke was consistently lower in patients receiving NOACs (HRs ranging from 0.3 to 0.6 in individual studies). Absolute risks of haemorrhagic stroke were 0.10% per year with dabigatran 150 mg vs. 0.38% per year with warfarin, 0.26% per year with rivaroxaban vs. 0.44% per year with warfarin, and 0.24% vs. 0.47 per year with apixaban vs. warfarin [60]. The absolute risk difference was estimated to be 8 fewer deaths and 4 fewer haemorrhagic strokes for

TABLE 9: Safety outcomes in the RE-LY, ROCKET-AF, ARISTOTLE and ENGAGE trials, in AF patients randomised to a NOAC or warfarin.

	Major bleeding		Intracranial bleeds		GI bleeds		Myocardial infarction		References
	Event rate (%/year)	Relative risk vs. warfarin (RR (95%CI))	Event rate (%/year)	Relative risk vs. warfarin (RR (95%CI))	Event rate (%/year)	Relative risk vs. warfarin (RR (95%CI))	Event rate (%/year)	Relative risk vs. warfarin (RR (95%CI))	
warfarin	3.36		0.74		1.02		0.53		RE-LY: Connolly *et al.*, NEJM 2009 [67]
dabigatran 110 mg	2.71	0.80 (0.69-0.93, P=0.003)	0.23	0.31 (0.20-0.47, P<0.001)	1.12	1.10 (0.86-1.41, P=0.43)	0.72	1.35 (0.98-1.87, P=0.07)	
dabigatran 150 mg	3.11	0.93 (0.81-1.07, P=0.31)	0.3	0.40 (0.27-0.60, P<0.001)	1.151	1.50 (1.19-1.89, P<0.001)	0.74	1.38 (1.00-1.91, P=0.048)	
	major/clinically relevant bleeding								ARISTOTLE: Patel *et al.*, NEJM 2011 [69]
warfarin	3.09		0.8		0.86		0.61		
apixaban	2.13	0.69 (0.60-0.80, P<0.001)	0.33	0.42 (0.30-0.58, P<0.001)	0.76	0.89 (0.70-1.15, P=0.37	0.53	0.88 (0.66-1.17, P=0.37)	
warfarin	3.4		0.7		2.2		1.1		ROCKET-AF: Granger *et al.*, NEJM 2011 [68]
rivaroxaban	3.6	1.04 (0.90-1.20, P=0.58)	0.5	0.67 (0.47-0.93, p=0.02)	3.2	data not given	0.9	0.81 (0.63-1.06, P=0.12)	
warfarin	3.43		0.85		1.23		0.75		ENGAGE: Guigliano *et al.*, NEJM 2013) [70]
low-dose edoxaban	1.61	0.47 (0.41-0.55, P<0.001)	0.26	0.30 (0.21-0.43, P<0.001)	0.82	0.67 (0.53-0.83, P<0.001)	0.89	1.19 (0.95-1.49, P=0.13)	
high-dose edoxaban	2.75	0.80 (0.71-0.91, P<0.001)	0.39	0.47 (0.34-0.63, P<0.001)	1.51	1.23 (1.02-1.50, P=003)	0.7	0.94 (0.74-1.19, P=0.60)	

GI: gastrointestinal

every 1000 patients treated with a NOAC as compared with adjusted-dose warfarin over approximately 2 years of treatment [72]. The first meta-analysis that also included data of the ENGAGE AF-TIMI 48 trial comparing edoxaban with warfarin corroborated the large reduction in haemorrhagic stroke (130 events in 29292 (0.44%) people receiving NOACs vs. 263 event in 29221 (0.90%) persons on warfarin, RR on combined data: 0.49, 95%CI: 0.38-0.64)[73]. Reduction in haemorrhagic stroke appeared the main driver behind the reduction in the composite of stroke (ischaemic plus haemorrhagic) and systemic embolism events in the combined data (911 events in 29312 (3.1%) individuals receiving NOACs vs 1107 events in 29229 (3.8%) people on warfarin, RR: 0.81, 95%CI: 0.73-0.91, P<0.0001)[73]. Dabigatran 150 mg appears similarly effective at reducing stroke and systemic embolism in AF as the lower dose of 110 mg (annual rates were 1.46% and 1.60% respectively, HR: 0.91, 95%CI: 0.69-1.20), in patients enrolled in RELY-ABLE, which included up to four years of follow-up [74]. The efficacy of dabigatran has also been evaluated in each clinical indication within routine practice in a large post-approval clinical cohort. Dabigatran was as effective as warfarin in reducing stroke in these real world patients with AF [75].

The systematic review [72] that evaluated the results of RE-LY, ROCKET-AF and ARISTOTLE, thus NOACs with warfarin, concluded that overall mortality was decreased in patients with AF taking NOACs (risk difference estimated to be 8 (95%CI: 3-11) fewer deaths per 1000 patients, RR: 0.88, 95%CI: 0.82-0.96). In the meta-analysis that also included ENGAGE AF-TIMI 48 all-cause mortality was also significantly reduced with NOACs (2022 events in 29292 patients (6.9%)) vs. warfarin (2245 events in 29221 patients (7.7%), RR: 0.90, 95%CI: 0.85-0.95, P=0.0003) [73].

Safety of NOACs vs. warfarin

Anticoagulation comes with an inherent bleeding risk, thus bleeding events were closely monitored and documented in the NOAC trials. Safety outcomes for the respective NOAC trials are shown in table 9. When considering the separate trial data, NOACs were at least as safe, or safer, than warfarin with respect to major bleeding. A lower risk of intracranial bleeds was consistently seen with NOACs as compared with warfarin. A borderline significantly higher risk of gastrointestinal (GI) bleeds was seen with high-dose dabigatran, rivaroxaban, and high-dose edoxaban, while low-dose edoxaban was associated with a lower risk of GI bleeds. No significant differences in the risk of GI bleeds were seen with low-dose dabigatran and apixaban. A tendency towards a higher risk of myocardial infarction (MI) was seen with low-dose dabigatran, while the higher dose of this NOAC was associated with a statistically significantly higher risk of MI (see Table 9). The other NOACs did not show statistically significantly altered risks of MI as compared with warfarin (see Table 9).

When combining all data of the first three large trials, namely RELY, ROCKET-AF and ARISTOTLE, on direct thrombin inhibitors and Factor Xa inhibitors fatal bleeds were found to be significantly reduced in comparison to anticoagulation with warfarin (RR: 0.60, 95%CI: 0.46-0.77, estimated risk difference is 1 fewer death per 1000 patients). Reduction in major bleeds did not reach statistical significance (RR: 0.80, 95%CI: 0.63-1.01)[60, 72]. The meta-analysis of the RELY, ROCKET-AF, ARISTOTLE and ENGAGE trials showed a non-significant reduction of major bleedings with high-dose NOACs vs warfarin (1541 events in 29287 (5.3%) patients on NOACs vs. 1802 events in 29211 (6.2%) patients on warfarin, RR: 0.86, 95%CI: 0.73-1.00, P=0.06), while a substantial reduction in intracranial haemorrhage was observed (204 events in 29287 (0.70%) patients on NOAC vs. 425 events in 29211 (1.45%) patients on warfarin, RR: 0.48, 95%CI: 0.39-0.59, P<0.0001)[70, 73]. The data of individual trials have been summarised in *table 9*.

While dabigatran 150 mg was more effective at stroke prevention than 110 mg, this was at the cost of major bleeding (HR: 1.20, 95%CI: 1.07-1.35). There was no difference between the two doses for the rate of haemorrhagic stroke (HR: 0.91, 95%CI: 0.50-1.64), in patients in the RE-LY and RELY-ABLE cohorts [74].

GI bleeds may be more common in patients who are treated with NOACs (RR: 1.30, 95%CI: 0.97-1.73) [72]. An increased risk of severe GI bleeds with NOACs as compared with warfarin was also documented in a systematic review and meta-analysis of studies with various clinical indications of anticoagulant therapy, namely prevention of stroke and SE in AF, prevention of venous thromboembolism after orthopaedic surgery or in medically ill patients, and treatment of acute deep vein thrombosis or pulmonary embolism and treatment of acute coronary syndrome (ACS) (pooled OR: 1.45, 95%CI: 1.07-1.97) [76]. It should be noted that substantial heterogeneity exists between patient subgroups and studies, and the pooling of various patient populations has been criticised. The risk of GI bleeds was highest for patients treated for thrombosis (acute coronary syndrome and deep vein thrombosis/pulmonary embolism, 5.3% in patients on NOACs and 1.0% in controls) and an increase in GI bleeding risk was seen for patients receiving NOACs for AF (2.1% with NOACs vs. 1.6% in control groups). A higher risk of clinically relevant bleeds, which included GI bleeds, was associated with use of NOACs, as compared with standard care (OR: 1.16, 95%CI: 1.00-1.34). In a sensitivity analysis that excluded studies comparing NOACs with placebo, thus comparing treatment with NOACs with standard care, the rate of overall clinically relevant bleeds was not increased (OR: 0.98, 95%CI: 0.88-1.10) [76]. The meta-analysis of all NOAC RCTs also showed that NOACs were associated with a higher rate of GI bleeds (751 events in 29287 (2.6%) patients on NOACs vs. 591 events in 29211 (2.0%) warfarin-treated patients, RR: 1.25, 95%CI: 1.01-1.55, P=0.0430) [70].

The risk of MI appears to be increased with dabigatran compared to warfarin (RR: 1.35, 95%CI: 0.99-1.85), but not with the Factor Xa inhibitors (RR: 0.84, 95%CI: 0.70-1.01) [72]. The increased rate of MI appears to be a class effect of direct thrombin inhibitors, rather than an effect specific to dabigatran [77]. A protective effect of warfarin against MI had been proposed [78], but a meta-analysis found no evidence for such a benefit of warfarin [77]. Both meta-analyses of the NOAC trials did not find a difference in the rate of MI with NOACs vs. warfarin on combined data of all trials evaluated (RR: 0.95, 95%CI: 0.81-1.11 [72] and RR: 0.97, 95%CI: 0.78-1.20) [70].

Post-marketing experiences

Matched cohort analyses of the Danish National Patient and Prescription Register show no evidence for a higher rate of stroke, systemic embolism, major bleeding and GI bleeding in patients receiving dabigatran as compared to warfarin. Hazard ratios for MI, pulmonary embolism, and intracranial bleeding are in favour of dabigatran [75]. Hence, these real world data do not confirm the previously observed increased MI rate associated with dabigatran [72, 77]. It should be noted, however, that these analyses do not account for possible confounding by indication of prescription.

A Food and Drug Administration (FDA) analysis used insurance databases to look at how the number of dabigatran-related bleeds related to reporting and to the actual number of warfarin-related bleeds. They considered the number of events in relation to exposure time to either drug [79]. Gastrointestinal haemorrhage was seen in 1.6 per 100,000 days at risk in dabigatran vs. 3.5 in warfarin. Similarly, incidences of intracranial haemorrhage were 0.8 and 2.4 per 100,000 days at risk in dabigatran vs. warfarin respectively. The FDA authors

believed that 'the large number of reported cases of bleeding associated with dabigatran provides a salient example of stimulated reporting' [79]. This is something to keep in mind when confronted with concerns about the safety of the new anticoagulants: bleeding events on VKAs are no longer actively reported.

Overall, in terms of balancing risks and benefits, the balance appears favourable for the NOACs as compared to VKA from trial and post-marketing surveillance data to date. Nevertheless, many clinicians remain reluctant to prescribe NOACs. A prevailing concern is that currently no antidotes exist for NOACs, with which the anticoagulant effects could be reversed in the event of bleeding. This and other potential barriers to use are considered in the next section.

NOACs and mechanical valves (without AF)

The recent RE-ALIGN study reported that dabigatran should not be used in patients with mechanical heart valves, since more thromboembolic and bleeding events were observed in patients on dabigatran, than in the warfarin-treated patients (to a higher target INR than in NVAF) in this study [21]. RE-ALIGN was a dose-validation study in patients who had undergone aortic or mitral valve replacement. The study was stopped prematurely after the enrolment of 252 patients. 9 patients experienced ischaemic stroke in the dabigatran arm (5%), while this did not occur in the warfarin arm. Major bleeding occurred in 7 (4%) and 2 (2%) patients in the respective groups. In NVAF, thrombin generation is believed to be triggered by stasis and endothelial dysfunction, and thrombi typically form in the left atrial appendage under low-flow, low shear conditions. In patients with a mechanical heart valve however, coagulation activation and thrombin generation is believed to be induced by the release of tissue factor from damaged tissue as a consequence of surgery, or by the exposure of blood to the artificial surface of the valve leaflets and sewing ring, which may activate the contact pathway of coagulation. Warfarin may be more effective than dabigatran at suppressing coagulation activity, since it inhibits activation of both these pathways. Also, in the common coagulation pathway, warfarin inhibits synthesis of factor X and thrombin, while dabigatran only inhibits thrombin [21]. Since differences in the working mechanisms of warfarin and dabigatran likely explain the difference in effect and safety, Factor Xa inhibitors may not be suitable alternatives for warfarin either and should not be used for patients with mechanical heart valves.

Potential barriers to NOAC use

Reversibility of the anticoagulant effect

While VKAs can be reversed with vitamin K, for the moment no reversal strategies exist for NOACs. It should be noted however, that administration of vitamin K, even when given intravenously, takes several hours to have an effect on the INR [80]. Studies on the efficacy of vitamin K and clinical bleeding are not available. In an emergency bleeding situation, some prefer the immediate effect of prothrombin complex concentrate (PCC), in combination with vitamin K, although there are wide variations between countries. If an increased INR is seen in a patient on VKA, INR can be decreased both by giving a fixed dose or an INR-guided dose [81]. Over 90% of successful clinical outcomes were achieved for Dutch patients treated with PCC after they presented with acute bleeds [81]. However, other observational data on haematoma growth or clinical outcome of warfarin-associated intracranial haemorrhage treated with PCC are conflicting, and clinical trial data are lacking. Generally, they show that prognosis is poor when there is an intracranial bleed on VKA and INR is reversed [82, 83]. It is suggested that INR correction alone may not be sufficient to alter prognosis after anticoagulation-associated intracranial haemorrhage [82].

Although there are no specific antidotes yet for NOACs, nonspecific reversal strategies may be applied. The same PCC or recombinant factor VII can be given. Since randomised placebo-controlled clinical trials are considered unethical, evidence relies on clinical experience and case series. One study showed the potential of PCC to normalise coagulation tests (prothrombin time: PT) in non-bleeding volunteers who received rivaroxaban 20 mg BID for two and a half days, while on placebo PT did not normalise except for the expected effect of clearance of the drug [84]. No reversal of activated partial thromboplastin time (aPTT) was seen in non-bleeding volunteers on dabigatran [84]. PCC was shown to have the potential to stop bleeding in different animal models, also when treated with dabigatran [85-87].

A large advantage of NOACs in comparison to VKAs is that NOACs have a much shorter half-life. Thus, the duration of the effect is much shorter, thereby decreasing the need for an antidote. Clinical impact of major bleeds, as seen by for instance mortality, or the need for hospitalisation or intensive care unit stay, indeed appears to be less with the new oral anticoagulants than with VKAs, despite the fact that an antidote exists for the latter [88]. Specific antidotes are currently under development, such as an antibody against dabigatran [89] and recombinant factor Xa [90]. Until these reversal agents have been developed and found effective, the European Heart Rhythm Association (EHRA) gives practical guidelines on how to reverse the risks and manage minor or severe bleeding in patients taking NOACs [91]. Thus, the lack of reversibility remains an issue, but it should not necessarily prevent the use of NOACs. The risk benefit needs to be weighed up and discussed with patients on an individual basis.

Costs

A study performed in the United Kingdom found apixaban to be a cost-effective alternative to warfarin and aspirin in VKA suitable and VKA unsuitable patients respectively. With apixaban projected to increase life expectancy and quality-adjusted life years (QALYs) as compared to warfarin and aspirin, the estimated incremental cost-effectiveness ratio (ICER) was GBP 11909 and GBP 7196 per QALY gained with these respective agents [92]. A Belgian study investigating the cost-effectiveness of rivaroxaban vs. warfarin found an ICER of EURO 8809 per QALY or EURO 7493 per life-year gained. Thus, in a Belgian healthcare setting rivaroxaban seems to be a cost-effective alternative to warfarin for SPAF [93]. A Spanish study investigating the cost-effectiveness of dabigatran vs. warfarin found an ICER of EURO 17581 per QALY and EUROS 14118 per QALY when compared to the real-world prescribing pattern [94]. Another study examined cost utility of NOACs in the German market and in comparison to other countries, based on outcome data of the RE-LY, ROCKET-AF and ARISTOTLE trials. From a German public healthcare insurance perspective, current market costs are high in relation to the quality of life gained. The authors note, however, that these results based on clinical studies remain to be confirmed under real life conditions [95].

While they may still be more expensive than VKA, INR monitoring is also expensive. Logistics and available resources may vary between countries or by region and will determine specific cost-effect balances. Cost-effectiveness of AF-related stroke prevention strategies is being explored, and efforts are dedicated to determine the impact of NOACs on health economics. Available evidence suggests that NOACs are a cost-effective alternative to warfarin with regard to efficacy and safety, although the final balance will depend on individual healthcare settings [96]. Comparisons between NOACs are now starting to emerge.

Emerging real-life data

There is much concern about patients in real world practice being older

and having more co-morbidities than patients included in the trials. Although it is inevitable that selected groups are employed in trials, this does not necessarily mean that the data are not generalisable to broader patient populations.

Subgroup analyses of RE-LY patients over 80 years old show similar results to the entire cohort [97]. The subgroup of very elderly was still of substantial size, thus providing fairly trustworthy results. Use of warfarin, on the other hand, at the time of introduction over 50 years ago, was based on smaller trials and a more select population. Therefore, the current trials, which include data on the very elderly and high-risk patients, may suffice for current recommendations in varying patient populations.

Real-life data on the use of VKAs have shown that warfarin is the most commonly implicated medication leading to an emergency department visit, with aspirin and clopidogrel following closely behind [98].

A substudy from RE-LY showed that dabigatran 150 mg lost its superiority over warfarin in reduction of stroke in countries where centre time in therapeutic range (or TTR) control with VKAs was fairly good [66]. In countries where TTR achieved with VKA is low, dabigatran performed better than VKAs. It is less clear whether a similar trend occurs with rivaroxaban and apixaban, due to limited statistical power of these substudies [99].

Hence, if good INR can be achieved, VKA is a very effective drug [66, 99]. TTR is an important aspect to consider. Preferences for NOACs will likely be based on a reduction of harm. Major bleeding rates of 2% per treatment year have been seen in the context of a well-established thrombosis service such as the one that has existed for decades in The Netherlands [100].

Treatment adherence

A possible perceived drawback of NOACs is that patients no longer need to be monitored. Certainly, this can be positive for patients, but physicians may think that compliance will diminish if patients are not seen regularly. Indeed, 'white coat adherence' has been demonstrated to exist, referring to better treatment adherence in the days before an appointment with a medical specialist. INR monitoring might give an indication of treatment adherence, although it has not been evaluated whether measuring INR indeed improves adherence.

Due to the shorter half-life of NOACs as compared to VKAs, compliance is very important. Preliminary studies have shown that treatment adherence to dabigatran is reasonably high with 80% of patients showing good adherence (adherence defined by the proportion of daily doses dispensed in a given time interval after prescription, adherence of at least 80% was considered good), based on pharmacy visits, dispensation data and interviews [101]. Physicians may spend extra time when prescribing a new type of drug, which could facilitate adherence. As a consequence of the shorter half-life, patients are no longer in the effective dose range if NOAC treatment is missed for one day [102]. It is therefore extremely important for physicians to emphasise the need for daily treatment adherence, perhaps more so than is the case with for instance antihypertensives and statins.

An advantage of NOACs may lie in their fixed dose, as compared to VKA doses that need to be adjusted based on INR measurements. It should not be underestimated that although the new agents are more convenient, they are still powerful anticoagulants. In the absence of INR monitoring they should still be treated with the same respect as a VKA. A dosage box with all a patient's medications to dispense may facilitate compliance (although not for dabigatran which requires original packaging). Rivaroxaban needs to be taken with food since taking on an empty stomach may reduce therapeutic drug levels by up to 40%.
In summary, NOACs are at least as safe as or safer than VKA. Barriers for implementation still exist but these may improve with the growing body of trial data on safety and subgroup analyses. Moreover, generalisability may expand as a result of having more registries. In addition, growing confidence in reversal strategies should facilitate implementation.

Practical recommendations

Based on current evidence and experiences, we recommend the following anticoagulation treatment strategy in a primary care setting:

Management strategies that should be used

- **All AF patients at high risk of stroke should be offered anticoagulation.**
- **In patients with mechanical valves or severe valve disease (defined by a specialist), this anticoagulation should be high intensity VKA.**
- **For patients with AF but without mechanical valves or clinically significant valve disease, both warfarin, to adjusted INR target of 2.5, and NOACs are anticoagulant options.**
- **NOACs represent more convenient, at least as safe, and at least equally effective option in the prevention of stroke in AF compared to VKAs, including in elderly patients. However, on the basis of cost and access issues, NOACs and VKAs both represent good treatment options for SPAF.**
- **Patients should be fully counselled, including written information, on the risks and benefits of anticoagulation or on changing to or initiating a NOAC.**
- **Patient preferences should guide decision-making over whether to initiate anticoagulation, and on what to prescribe, including estimation of a patient's compliance.**
- **The patient groups in whom use of a NOAC is preferable to warfarin are patients who are unable or unwilling to take warfarin, and patients who are difficult to maintain at a stable INR (less than 65% time in therapeutic range).**
- **If prescribing NOACs, the importance of treatment adherence must be emphasised. Compliance may be facilitated with the use of a dosage box, except for dabigatran, which should only be dispensed in its original packaging (although dabigatran is available in blister packages so, if desired, individual doses can be cut out with their original blister preserved and put in dosage box).**

Management strategies that may be used

- ASA alone has no role in SPAF.
- In patients at all ages who are unable or unwilling to take VKAs or NOACs, ASA may be used in combination with clopidogrel as antiplatelet therapy to prevent stroke.

Additional work recommended in this area / gaps in the evidence:

- Information on the proportion of ineligible individuals in trials is often missing in publications. Knowing not only who was included in trials, but also who was not, and why not, gives important information on the generalisability of trial results. Future studies will therefore need to include data on individuals who were not enrolled in a trial, including the reasons why.
- An outstanding question is how NOACs will behave with regard to multi-morbidity, and whether they interact with other types of medication. A registry-based real-world observational study that compares NOACs with VKA, including patients with different co-morbidities associated with older age (renal impairment, cognitive decline) is warranted. This will help judge the actual value of those agents in AF patients who are commonly seen in daily general

practice. However, the large evidence base to date shows NOACs have much lower rates of drug, and no food, interactions compared to warfarin.
- Future studies should also monitor renal function closely. This may be more significant with dabigatran, which is substantially renally excreted. Indeed there is current controversy over whether monitoring dabigatran blood levels might be safer for patients than adjusting to one of the two fixed doses merely by renal clearance and age [103-106].
- Furthermore, better insight into the consequences of poor treatment adherence and how compliance might be improved is welcomed.

6. Practical Considerations for Atrial Fibrillation Stroke Prevention in Primary Care

A large evidence base on the effectiveness of warfarin regimes, the limitations of anti-platelets, and the licensing of several new anticoagulants, has meant that traditional management strategies of SPAF have been challenged in recent years. In response, the ESC published the 2012 focused update of the 2010 ESC Guidelines for the management of atrial fibrillation [1] and several European countries have developed national guidelines on how to manage SPAF [3]. Some of these guidelines recommend NOACs above warfarin (ESC 2012, [1]), while others are more conservative or have not considered this directly. However, most of these guidelines have not specifically addressed the management of SPAF, including the role of NOACs, from a primary care perspective.

This EPCCS consensus statement aims to offer guidance on anticoagulation treatment strategy in a primary care setting. We based our recommendations on the existing European guidelines, available evidence and our clinical experience. The ESC 2012 focused update of the 2010 ESC Guidelines for the management of atrial fibrillation [1] served as a starting point, which we adapted for primary care. We also considered the recently updated NICE guideline [3], which recommends that NOACs are an alternative option to warfarin to reduce the number of AF patients dying or becoming impaired due to stroke, since these agents require less monitoring and fewer dose adjustments. According to NICE, NOACs are indicated in AF patients with CHA_2DS_2-VASc of 2 or higher, while taking into account their bleeding risk. Further local adaptations of our recommendations may apply, based on healthcare organisation or available resources and local circumstances will determine what is best for a given patient.
There is still evidence that over- and under-treatment is common in stroke prevention for patients with AF. It is important that patients are diagnosed, stroke risk assessed and then appropriate therapy is offered to ensure as many strokes as possible are avoided, whilst also minimising harm from any intervention. The practicalities of screening, diagnosis, stroke risk assessment, treatment initiation, monitoring and, where appropriate, cessation of therapy will need to be determined at a local level according to the structure of the healthcare system and expertise of the team.

The following patient pathway may be helpful for any healthcare team managing stroke prevention in patients with AF:

Finding the patient with atrial fibrillation
The consequences of AF and subsequent stroke risk are substantial. Clinicians should be alert to the patient with possible AF. Anyone with symptoms suggestive of AF should have a pulse check. The feasibility and benefit of opportunistic screening for AF within the healthcare context should also be considered.

Making the diagnosis of atrial fibrillation
Any patient with an irregular pulse will need an ECG to confirm or rule out AF. If symptoms are intermittent, a longer heart rhythm record may be required. The ECG should be read by someone trained and competent to do so. This may exist within primary care or may require secondary care input. Debate remains about whether or not to refer a patient with suspected or diagnosed AF to secondary, specialist care. When AF is symptomatic or with complications, referral to a cardiologist should be considered, according to the ESC. A structured follow-up plan, developed by the specialist, should be provided prior to discharge back to the GP [2]. All of these recommendations are consensus-driven, due to lack of evidence. If patients are asymptomatic, the clinical skills of the primary care team will determine whether or not the patient can be safely managed within primary care.

Dutch primary care guidelines suggest referral to a cardiologist for AF patients younger than 65, while older patients can often be managed in general practice. Moreover, when cardiac co-morbidity is suspected or in the case of poor response to treatment, consultation with a cardiologist is advised. However, even within The Netherlands regional differences exist, since primary and secondary care get together and decide on the best way to go about AF care in that specific region. Certain regions have developed AF outpatient clinics at hospitals. A clear management plan will be required, whatever the setting, and patients should be followed up regularly.

Risk assessment
The CHA_2DS_2-VASc score is simple and should be used to assess stroke risk in patients with AF and the HAS-BLED score can be used to identify modifiable risk factors to minimise harm from bleeding. The location and clinician carrying out this assessment will also vary by healthcare system. The GP has the benefit of having all of the details from the patient's medical record at hand and often a longitudinal relationship with the patient. The risks and benefits of anticoagulation must be discussed in detail with the patient, in a format that they can understand and with written information where possible, to ensure a patient-centred informed decision is made.

Preferable anticoagulant
Different regional guidelines indicate different preferences for the type of anticoagulants that should be given to patients with AF. While some guidelines still consider VKAs as first line treatment, others prefer NOACs, unless patients are stable on VKAs. Variability is large among European countries. Section 4 and 5 above summarise the existing evidence for both VKA and NOACs. The risks and benefits of each drug should be discussed in detail with the patient to ensure the most effective and safe drug is chosen for the individual. The availability of some drugs may be limited by the funding available within the healthcare system.

NOAC use and impaired renal function
One of the consistently reported caveats of NOAC use in stroke prevention in AF is the concurrent risk of impaired renal function. Chronic kidney disease (CKD) and AF impose a mutually linked and deteriorating correlation: AF is common in patients with CKD, and the prevalence increases (up to ~20%) with further impairment of the renal function; yet also the risk of end-stage renal failure is increased if AF is concurrently present [107]. Thus, antithrombotic management in AF patients with concurrent CKD is not uncommon and poses physicians a difficult dilemma given that bleeding complications are also more

common with anticoagulant use and CKD.

Although these observations certainly are also true for traditional vitamin K antagonist, we have considerable experience in monitoring anticoagulant use in patients with CKD (with often more frequent INR monitoring applied) [108]. Moreover, the liver predominantly eliminates these agents.
In terms of NOAC use, a differentiation needs to be made between the direct thrombin inhibitor dabigatran, and the Factor Xa inhibitors (rivaroxaban, apixaban, edoxaban (not licensed yet in Europe)). The former agent is notably eliminated by the kidney (for ~80%), whereas the other agents are also cleared by the liver (renal elimination ~20 to 40%).

This means that dabigatran is contra-indicated in those with moderate to severe renal impairment (creatinine clearance or estimated glomerular filtration rate (eGFR) < 30 ml/min; this was an exclusion criterion in the RE-LY trial). Although the factor Xa inhibitors are not formally contra-indicated in patients with renal impairment, caution is also warranted for these agents. Renal impairment is known to cause significant fluctuations in plasma levels, and thus may interfere with both efficacy and safety outcomes. This finding is backed-up by FDA reports on adverse effects with NOAC use: reported adverse events with NOAC use predominantly occurred in the elderly (median age, 80 years), and in those with renal impairment [72]

Consequently, both the FDA and the European Medicine Agency have recommended prescribers evaluate kidney function annually, at least for dabigatran, in those aged > 75 years and/or in those with a creatinine clearance < 50 ml/min. This leads us to provide the following recommendations:

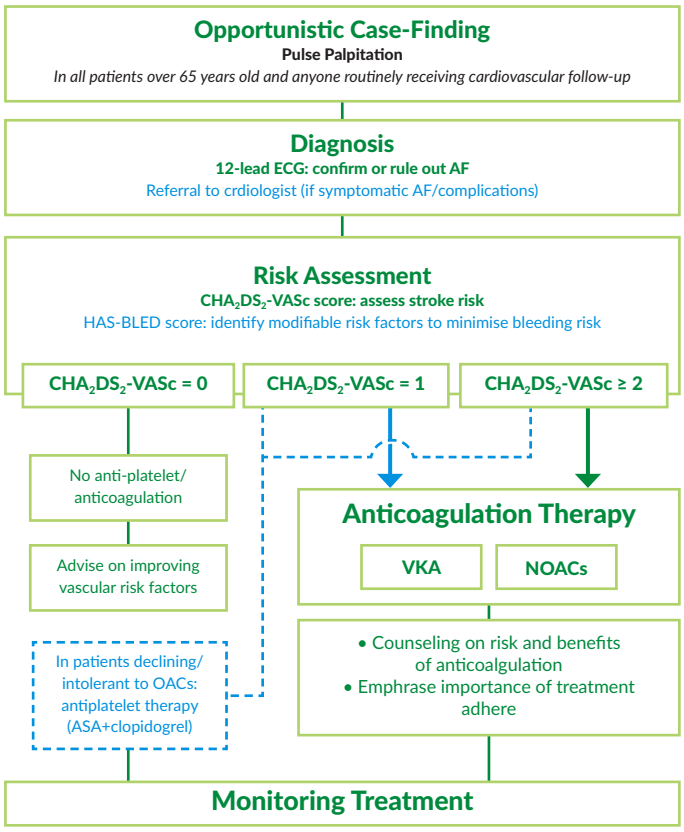
Recommendations:

- **NOACs are best not initiated in those with a creatinine clearance or eGFR < 30 ml/min; dabigatran is specifically contra-indicated <30 ml/min, but caution is also needed for the factor Xa inhibitors (which are contraindicated <15 mls/min) given the expected fluctuations in plasma levels and the subsequent expected impact on both the safety and efficacy profile of these drugs combined with a lack of monitoring of anticoagulant dosing.**
- **In those patients with renal impairment where a Factor Xa inhibitor is prescribed, rivaroxaban dose should be reduced to 15mg daily where eGFR is 15-49 mls/min and apixiban dose should be reduced to 2.5mg bd where eGFR is 15-29 mls/min. These dosage recommendations do slightly vary by country and therefore should be checked locally.**
- **In those patients with renal impairment where NOACs are prescribed, creatinine clearance should be monitored at least annually in those > 75 years of age, and/or in those with a known creatinine clearance < 50 ml/min.**

Initiating and monitoring treatment

The process of initiation and monitoring of anticoagulation will vary according to healthcare system and local expertise and is beyond the scope of this document. The European Heart Rhythm Association (EHRA) has produced guidance on the use of new oral anticoagulants in patients with non-valvular AF, which are summarised in section 7 of this document [91]. The product characteristics of each drug are also crucial in considering dosage, side effects and advice on how treatments should be initiated or changed. The patients other medical problems and concomitant medications must also be considered when deciding which anticoagulant to choose and how often monitoring is required. EHRA furthermore proposes a patient information card, to be carried by those patients treated with NOACs. This uniform card is helpful and crucial for both patient and health care professionals. It includes instructions on correct intake and contact information of the anticoagulant prescriber or clinic in case of questions for the patient, and information on renal function, follow-up schedule, concomitant medication, etcetera for health care workers, as different care-takers are likely involved. The card proposed by EHRA can be downloaded from www.NOACforAF.eu [91].All recommendations given in the current consensus document are summarised in the flow chart in *figure 2* for easy reference.

Figure 2: Flow chart of recommendations.



*Management of stroke prevention in atrial fibrillation as recommended in this document. Strength of recommendations is indicated by colour, with in **green** recommendations that should be used, and in **blue**-text interventions that may be considered. See text for explanation of HAS-BLED and CHA_2DS_2-VASc scores. AF: atrial fibrillation, OACs: oral anticoagulants, NOACs: novel oral anticoagulants, ASA: acetyl salicylic acid, VKA: vitamin K antagonists*

7. Practical Guidance on the Use of NOACs

The EHRA has assembled an excellent practical guide on the use of NOACs, to help physicians use NOACs in specific clinical situations [91]. The different clinical scenarios, as outlined in the EHRA practical guide, are summarised below for both physician and patients to learn how to use these new agents safely and effectively.
The clinical scenario titles are listed below, but for detailed information on these clinical situations, please refer to the original document. Also refer to www.NOACforAF.eu for the latest updated information, as new information may have become available after publication of the EHRA guide.

Clinical scenarios to consider for safe and effective use of NOACs:

1. Establishing a structured start-up and follow-up scheme for patients on NOACs, to ensure safe and effective drug intake. The

EHRA patient information card is intended to document each visit, and observations and treatment decisions made. Follow-up may be performed by the initiator of anticoagulant treatment, an anticoagulant clinic, or the GP. At follow-up, compliance should be checked (patient should bring remaining pills), as well as the occurrence of thrombo-embolic events, bleeding events or other side effects. The use of co-medication and over-the-counter drugs should be interrogated, and the need for blood sampling should be considered. In case of problems, the initiator of anticoagulant treatment should be contacted.

2. While NOACs do not need routine monitoring of coagulation, in emergency situations quantitative assessment of the anticoagulant effect may be needed. Knowing the time delay between NOAC intake and blood sampling is paramount when measuring the anticoagulant effect of NOACs. A table with an overview of the effect of direct thrombin inhibitors and FXa inhibitors on common coagulation assays is available [91].
3. NOACs are expected to have fewer food interactions than VKA, but dose-adjustment may still be needed in case of drug-drug interactions or comorbidites. In patients with a high bleeding risk, or when a higher plasma level of the drug can be anticipated, a lower NOAC dose may be indicated. The EHRA document includes recommendations on the situations in which contraindication or adaptation of NOAC dose may apply, known thus far.
4. When switching between anticoagulant regimens; pharmacokinetics and pharmacodynamics of different regimes need to be appreciated to safeguard the risk/benefit-ratio.
5. Compliance of NOAC intake needs to be ensured, given their short half-life. All means to optimise compliance should be considered, including repeated patient education and their family members.
6. Care providers should be provided with instructions on how to deal with dosing errors.
7. Dose adjustments or contraindications apply for patients with chronic kidney disease, depending on the severity of the renal impairment.
8. In case of a (suspected) overdose, it is important to distinguish between an overdose with and without bleeding complications. Coagulation tests can help determine the degree of the overdose and the possible bleeding risk. In the absence of bleeding, a 'wait-and-see' management may be advocated (given the short half-life of NOACs) in most cases, while in some situations more aggressive normalisation of plasma levels may be indicated (see step 9).
9. In the absence of specific NOAC antidotes, recommended management strategies of bleeding complications are limited and currently mostly based on expert's opinion or laboratory endpoints. Given NOACs relatively short elimination half-lives; time is the most important antidote. It is therefore crucial to inquire about the dosing regime and exact time of last intake, and other factors influencing plasma concentration and haemostasis.
10. Temporary cessation of NOACs may be needed in patients undergoing a planned surgical intervention or ablation. The EHRA document provides recommendations on when to stop and when to restart NOAC therapy.
11. If patients need urgent surgical intervention, NOAC use should be discontinued.
12. Specific attention is needed in case of concomitant use of anticoagulation and antiplatelet therapy in patients with AF and coronary artery disease. Formal risk assessment is recommended. Treatment recommendations are given for different clinical scenarios. .
13. Oral anticoagulation should have been given for at least 3 weeks prior to cardioversion. If patients are treated with NOACs, it is of particular importance to reliably assess treatment adherence over the past weeks. It was recently shown that a NOAC (rivaroxaban) was a safe alternative to VKA in patients with AF who underwent elective cardioversion [109].
14. In patients on NOACs presenting with acute or life-threatening bleeding, restoration of coagulation status should be attempted as soon as possible. Evidence-based strategies for reversal of the anticoagulant effect of NOACs are currently lacking, but some recommendations may be given, including for the management of the post-acute phase.
15. In AF patients with a malignancy, specific attention is needed for their increased thrombo-embolic event risk. Cardiologists and oncologists need to discuss together which anticoagulant treatment may be best, considering the specific oncologic therapy used, the anticipated effects of tumour and therapy on the thrombo-therapeutic considerations (NOACs vs. VKAs) in AF patients with a malignancy.

Conclusions

Atrial fibrillation is a common disorder, especially in those aged over 75, and major cause of preventable embolic stroke. Anticoagulation therapy, available for 50 years as vitamin K antagonist derivatives like warfarin, can reduce this risk by up to two thirds, but its use has been complicated by major food and drug interactions, significant bleeding risks, a narrow therapeutic range, and the need to monitor. As a consequence, in most countries, only around half of those eligible for anticoagulation are on treatment and many of those treated are poorly controlled. The evidence base for atrial fibrillation stroke risk is considerable and growing, resulting in recent major changes to clinical guidance internationally. This guidance has particular implications for primary care with many new recommendations on better AF diagnosis, more reliable methods of determining stroke risk to guide treatment choice for patients and bleeding risks to manage the risk factors better, and revised treatment options, with the exclusion of low dose aspirin as an option for most patients, the importance of good therapeutic control if warfarin is used, and the availability of a range of new rapid onset, short-acting, anticoagulants with few interactions and no monitoring requirements.

Contributions

The European Primary Care Cardiovascular Society (EPCCS) SPAF working group delivered this guidance via
Editors: Hobbs, FD Richard. Nuffield Department of Primary Care Health Sciences, University of Oxford, OX2 6GG, United Kingdom; and Taylor, Clare J. Primary Care Clinical Sciences, School of Health & Population Sciences, University of Birmingham, B15 2TT, United Kingdom.
Contributors (in alphabetical order) and affiliations: Brotons, Carlos. Sardenya Primary Health Care Center. Biomedical Research Institute Sant Pau, ACEBA Teaching Unit of Family Medicine, Barcelona, Spain; Brouwer Judith R. Medcon International, PO Box 916, 2003 RX HAARLEM, The Netherlands; Charra, Clément. General practitioner, Cidex 9Ter rue François - 21550 Ladoix-Serrigny, FRANCE; Del Zotti, Francesco. General practitioner, Verona, Italy; de la Figuera, Mariano. Internist and Family Physician, EAP Sardenya. Unitat Docent ACEBA, Barcelona, Spain; Fitzmaurice, David. University of Birmingham, Primary Care Clinical Sciences, Birmingham, United Kingdom; Geersing, Geert Jan. Julius Center for Health Sciences and Primary Care, Universiteitsweg 100, 3584 CG, Utrecht, The Netherlands; Hoes, Arno W. Julius Center for Health Sciences and Primary Care UMC Utrecht, PO Box 85500, 3508 GA Utrecht, The Netherlands; Hollander, Monika. 1. Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands. 2. Julius Health Centers, Leidsche Rijn, Utrecht,

The Netherlands, Utrechtse Heuvelrug 130, 3452 JA, Vleuten, The Netherlands; Karotsis, Antonis K. DIAGNOSIS Medical Center of Athens/ Primary Health Care dpt. GR17561, Athens, Greece; Lionis, Christos. University of Crete, Clinical of Social and Family Medicine, 71003 Heraklion, Greece; Lucassen Wim, Academic Medical Center, Department of General Medicine J2-218, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands; Lühmann, Dagmar. Institute of Primary Medical Care, University Medical Center Hamburg-Eppendorf, Martinistraße 52, D-20246 Hamburg; Middeldorp, Saskia. Academic Medical Center, University of Amsterdam, Department of Vascular Medicine, F4-276, Meibergdreef 9, 1105, AZ AMSTERDAM, The Netherlands; Rutten, Frans H. Julius Center for Health Sciences and Primary Care, UMC Utrecht, Universiteitsweg 100, 3584 CG, Utrecht, The Netherlands; Schianchi, Paolo. GPs HealthV Practice, Via Perlasca 11, Felino, Parma ITALY; Verheugt, Freek WA. P.C. Hooftstraat 188, 1071 CH Amsterdam, Netherlands; Wagner, Hans-Otto. University Medical Center Hamburg-Eppendorf, Martinistrasse 52, D-20246, Hamburg, Germany
Writing Committee: Hobbs FDR, Taylor CJ, Geersing G-J, Rutten FH, Brouwer JR.

Competing interest statements

The costs of producing this document were met by the EPCCS which itself received an unrestricted educational grant from Bayer, BI and Pfizer/BMS to support these costs. The idea, rationale, and methods in generating the guidance originated with the EPCCS. All preparation, presentations, document drafting and printing was done by the EPCCS and its Secretariat. The EPCCS approached the sponsors. The sponsors had no input or role in producing or commenting on the guidance. In relation to these document costs, for preparing and attending the data presentation and draft recommendations meeting, CB, CC, FDZ, MdlF, DF, GFG, RH, MH, AKK, CL, WL, SM CJT, FWAV and HOW received a fee to support any locum expenses, and travel expenses and accommodation were reimbursed. AWH, DL, FR and DS were only reimbursed an over-night stay.
In addition, CB sits on the Executive Committee for the ARRIVE trial and the Executive Committee for the AEGEAN trial (Bayer and BMS/Pfizer); DF has received honoraria from several companies including BI, Bayer, Sanofi; GJG has received a research grant of BI to study AF; FDRH has consulted with or spoken at scientific meetings for companies with interests in SPAF including BI, Bayer, BMS/Pfizer, Daiichi-Sankyo; AH's institute within the University Medical Center Utrecht has received unrestricted research grants from a number of companies (but no personal funding); MH's host department received an unrestricted research grant from BI for a study on the diagnosis of atrial fibrillation in primary care; CL has received payment for consultancies from GlaxoSmithKline, BI and Pfizer, and his University Clinic received payment for his participation in advisory board meetings from Medtronic, Amgen, MSD, and Alpha Public Relations, but no payments with any

association with stroke prevention; SM has received consulting fees from Bayer, BI, BMS/Pfizer, Daiichi-Sankyo and research support from GSK, BMS/Pfizer and Sanquin; FR's department has received an unrestricted grant from BI; FWAV is an advisor of BI, Daiichi-Sankyo, BMS/Pfizer and Bayer; HOW served as a paid consultant to Pfizer; and CC, CJT, FDZ, MdlF, AKK, WL, DL, PS all declare no other conflicts of interest.

References

1. Camm, A.J., Lip, G.Y., De Caterina, R., Savelieva, I., Atar, D., Hohnloser, S.H., Hindricks, G. and Kirchhof, P. (2012) 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J, 33, 2719-2747.
2. Camm, A.J., Kirchhof, P., Lip, G.Y., Schotten, U., Savelieva, I., Ernst, S., Van Gelder, I.C., Al-Attar, N., Hindricks, G., Prendergast, B. et al. (2010) Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J, 31, 2369-2429.
3. NICE. (2014), NICE Guidance and guidelines. National Institute for Health and Care Excellence.
4. Hobbs, F.D., Fitzmaurice, D.A., Mant, J., Murray, E., Jowett, S., Bryan, S., Raftery, J., Davies, M. and Lip, G. (2005) A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study. Health Technol Assess, 9, iii-iv, ix-x, 1-74.
5. Heeringa, J., van der Kuip, D.A., Hofman, A., Kors, J.A., van Herpen, G., Stricker, B.H., Stijnen, T., Lip, G.Y. and Witteman, J.C. (2006) Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J, 27, 949-953.
6. Fuster, V., Ryden, L.E., Cannom, D.S., Crijns, H.J., Curtis, A.B., Ellenbogen, K.A., Halperin, J.L., Kay, G.N., Le Huezey, J.Y., Lowe, J.E. et al. (2011) 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/ American Heart Association Task Force on practice guidelines. Circulation, 123, e269-367.
7. Friberg, J., Buch, P., Scharling, H., Gadsbphioll, N. and Jensen, G.B. (2003) Rising rates of hospital admissions for atrial fibrillation. Epidemiology, 14, 666-672.
8. DeWilde, S., Carey, I.M., Emmas, C., Richards, N. and Cook, D.G. (2006) Trends in the prevalence of diagnosed atrial fibrillation, its treatment with anticoagulation and predictors of such treatment in UK primary care. Heart, 92, 1064-1070.
9. Miyasaka, Y., Barnes, M.E., Gersh, B.J., Cha, S.S., Bailey, K.R., Abhayaratna, W.P., Seward, J.B. and Tsang, T.S. (2006) Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation, 114, 119-125.
10. Kannel, W.B. and Benjamin, E.J. (2008) Status of the epidemiology of atrial fibrillation. Med Clin North Am, 92, 17-40, ix.
11. Go, A.S., Hylek, E.M., Phillips, K.A., Chang, Y., Henault, L.E., Selby, J.V. and Singer, D.E. (2001) Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA, 285, 2370-2375.
12. Zhang, L., Gallagher, R. and Neubeck, L. (2014) Health-related quality of life in atrial fibrillation patients over 65 years: a review. Eur J Prev Cardiol.
13. Wolf, P.A., Abbott, R.D. and Kannel, W.B. (1991) Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke, 22, 983-988.
14. Albers, G.W., Amarenco, P., Easton, J.D., Sacco, R.L. and Teal, P. (2004) Antithrombotic and thrombolytic therapy for ischemic stroke: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest, 126, 483S-512S.
15. Jorgensen, H.S., Nakayama, H., Reith, J., Raaschou, H.O. and Olsen, T.S. (1996) Acute stroke with atrial fibrillation. The Copenhagen Stroke Study. Stroke, 27, 1765-1769.
16. Lin, H.J., Wolf, P.A., Kelly-Hayes, M., Beiser, A.S., Kase, C.S., Benjamin, E.J. and D'Agostino, R.B. (1996) Stroke severity in atrial fibrillation. The Framingham Study. Stroke, 27, 1760-1764.
17. Lamassa, M., Di Carlo, A., Pracucci, G., Basile, A.M., Trefoloni, G., Vanni, P., Spolveri, S., Baruffi, M.C., Landini, G., Ghetti, A. et al. (2001) Characteristics, outcome, and care of stroke associated with atrial fibrillation in Europe: data from a multicenter multinational hospital-based registry (The European Community Stroke Project). Stroke, 32, 392-398.
18. Friberg, L., Hammar, N. and Rosenqvist, M. (2010) Stroke in paroxysmal atrial fibrillation: report from the Stockholm Cohort of Atrial Fibrillation. Eur Heart J, 31, 967-975.
19. Bang, C.N., Gerdts, E., Aurigemma, G.P., Boman, K., Dahlof, B., Roman, M.J., Kober, L., Wachtell, K. and Devereux, R.B. (2013) Systolic left ventricular function according to left ventricular concentricity and dilatation in hypertensive patients: the Losartan Intervention For Endpoint reduction in hypertension study. J Hypertens, 31, 2060-2068.
20. Wyse, D.G., Waldo, A.L., DiMarco, J.P., Domanski, M.J., Rosenberg, Y., Schron, E.B., Kellen, J.C., Greene, H.L., Mickel, M.C., Dalquist, J.E. et al. (2002) A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med, 347, 1825-1833.
21. Eikelboom, J.W., Connolly, S.J., Brueckmann, M., Granger, C.B., Kappetein, A.P., Mack, M.J., Blatchford, J., Devenny, K., Friedman, J., Guiver, K. et al. (2013) Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med, 369, 1206-1214.
22. Carlsson, J., Miketic, S., Windeler, J., Cuneo, A., Haun, S., Micus, S., Walter, S. and Tebbe, U. (2003) Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. J Am Coll Cardiol, 41, 1690-1696.
23. Gronefeld, G.C., Lilienthal, J., Kuck, K.H. and Hohnloser, S.H. (2003) Impact of rate versus rhythm control on quality of life in patients with persistent atrial fibrillation. Results from a prospective randomized study. Eur Heart J, 24, 1430-1436.
24. Van Gelder, I.C., Hagens, V.E., Bosker, H.A., Kingma, J.H., Kamp, O., Kingma, T., Said, S.A., Darmanata, J.I., Timmermans, A.J., Tijssen, J.G. et al. (2002) A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med, 347, 1834-1840.
25. Wattigney, W.A., Mensah, G.A. and Croft, J.B. (2002) Increased atrial fibrillation mortality: United States, 1980-1998. Am J Epidemiol, 155, 819-826.
26. Wattigney, W.A., Mensah, G.A. and Croft, J.B. (2003) Increasing trends in hospitalization for atrial fibrillation in the United States, 1985 through 1999: implications for primary prevention. Circulation, 108, 711-716.
27. Rosamond, W., Flegal, K., Furie, K., Go, A., Greenlund, K., Haase, N., Hailpern, S.M., Ho, M., Howard, V., Kissela, B. et al. (2008) Heart disease and stroke statistics--2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation, 117, e25-146.
28. Barnett, K., Mercer, S.W., Norbury, M., Watt, G., Wyke, S. and Guthrie, B. (2012) Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet, 380, 37-43.
29. Healey, J.S., Connolly, S.J., Gold, M.R., Israel, C.W., Van Gelder, I.C., Capucci, A., Lau, C.P.,

Fain, E., Yang, S., Bailleul, C. et al. (2012) Subclinical atrial fibrillation and the risk of stroke. N Engl J Med, 366, 120-129.
30. Binici, Z., Intzilakis, T., Nielsen, O.W., Kober, L. and Sajadieh, A. (2010) Excessive supraventricular ectopic activity and increased risk of atrial fibrillation and stroke. Circulation, 121, 1904-1911.
31. Fitzmaurice, D.A., Hobbs, F.D., Jowett, S., Mant, J., Murray, E.T., Holder, R., Raftery, J.P., Bryan, S., Davies, M., Lip, G.Y. et al. (2007) Screening versus routine practice in detection of atrial fibrillation in patients aged 65 or over: cluster randomised controlled trial. BMJ, 335, 383.
32. Fitzmaurice, D.A., McCahon, D., Baker, J., Murray, E.T., Jowett, S., Sandhar, H., Holder, R.L. and Hobbs, F.D. (2014) Is screening for AF worthwhile? Stroke risk in a screened population from the SAFE study. Fam Pract, 31, 298-302.
33. Tieleman, R.G., Plantinga, Y., Rinkes, D., Bartels, G.L., Posma, J.L., Cator, R., Hofman, C. and Houben, R.P. (2014) Validation and clinical use of a novel diagnostic device for screening of atrial fibrillation. Europace.
34. Rhys, G.C., Azhar, M.F. and Foster, A. (2013) Screening for atrial fibrillation in patients aged 65 years or over attending annual flu vaccination clinics at a single general practice. Qual Prim Care, 21, 131-140.
35. van Walraven, C., Hart, R.G., Wells, G.A., Petersen, P., Koudstaal, P.J., Gullov, A.L., Hellemons, B.S., Koefed, B.G. and Laupacis, A. (2003) A clinical prediction rule to identify patients with atrial fibrillation and a low risk for stroke while taking aspirin. Arch Intern Med, 163, 936-943.
36. Gage, B.F., Waterman, A.D., Shannon, W., Boechler, M., Rich, M.W. and Radford, M.J. (2001) Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA, 285, 2864-2870.
37. Fuster, V., Ryden, L.E., Cannom, D.S., Crijns, H.J., Curtis, A.B., Ellenbogen, K.A., Halperin, J.L., Le Heuzey, J.Y., Kay, G.N., Lowe, J.E. et al. (2006) ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation, 114, e257-354.
38. Healey, J.S., Hart, R.G., Pogue, J., Pfeffer, M.A., Hohnloser, S.H., De Caterina, R., Flaker, G., Yusuf, S. and Connolly, S.J. (2008) Risks and benefits of oral anticoagulation compared with clopidogrel plus aspirin in patients with atrial fibrillation according to stroke risk: the atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events (ACTIVE-W). Stroke, 39, 1482-1486.
39. Olesen, J.B., Torp-Pedersen, C., Hansen, M.L. and Lip, G.Y. (2012) The value of the CHA_2DS_2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a $CHADS_2$ score 0-1: a nationwide cohort study. Thromb Haemost, 107, 1172-1179.
40. Olesen, J.B., Lip, G.Y., Hansen, M.L., Hansen, P.R., Tolstrup, J.S., Lindhardsen, J., Selmer, C., Ahlehoff, O., Olsen, A.M., Gislason, G.H. et al. (2011) Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ, 342, d124.
41. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137(2):263-72.
42. Potpara, T.S., Polovina, M.M., Licina, M.M., Marinkovic, J.M., Prostran, M.S. and Lip, G.Y. (2012) Reliable identification of "truly low" thromboembolic risk in patients initially diagnosed with "lone" atrial fibrillation: the Belgrade atrial fibrillation study. Circ Arrhythm Electrophysiol, 5, 319-326.
43. Van Staa, T.P., Setakis, E., Di Tanna, G.L., Lane, D.A. and Lip, G.Y. (2011) A comparison of risk stratification schemes for stroke in 79,884 atrial fibrillation patients in general practice. J Thromb Haemost, 9, 39-48.
44. Abu-Assi, E., Otero-Ravina, F., Allut Vidal, G., Coutado Mendez, A., Vaamonde Mosquera, L., Sanchez Loureiro, M., Caneda Villar, M.C., Fernandez Villaverde, J.M., Maestro Saavedra, F.J. and Gonzalez-Juanatey, J.R. (2013) Comparison of the reliability and validity of four contemporary risk stratification schemes to predict thromboembolism in non-anticoagulated patients with atrial fibrillation. Int J Cardiol, 166, 205-209.
45. Pisters, R., Lane, D.A., Nieuwlaat, R., de Vos, C.B., Crijns, H.J. and Lip, G.Y. (2010) A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest, 138, 1093-1100.
46. Olesen, J.B., Lip, G.Y., Hansen, P.R., Lindhardsen, J., Ahlehoff, O., Andersson, C., Weeke, P., Hansen, M.L., Gislason, G.H. and Torp-Pedersen, C. (2011) Bleeding risk in 'real world' patients with atrial fibrillation: comparison of two established bleeding prediction schemes in a nationwide cohort. J Thromb Haemost, 9, 1460-1467.
47. Gallego, P., Roldan, V., Torregrosa, J.M., Galvez, J., Valdes, M., Vicente, V., Marin, F. and Lip, G.Y. (2012) Relation of the HAS-BLED bleeding risk score to major bleeding, cardiovascular events, and mortality in anticoagulated patients with atrial fibrillation. Circ Arrhythm Electrophysiol, 5, 312-318.
48. Lip, G.Y., Frison, L., Halperin, J.L. and Lane, D.A. (2011) Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. J Am Coll Cardiol, 57, 173-180.
49. Friberg, L., Rosenqvist, M. and Lip, G.Y. (2012) Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J, 33, 1500-1510.
50. Apostolakis, S., Lane, D.A., Buller, H. and Lip, G.Y. (2013) Comparison of the $CHADS_2$, CHA_2DS_2-VASc and HAS-BLED scores for the prediction of clinically relevant bleeding in anticoagulated patients with atrial fibrillation: the AMADEUS trial. Thromb Haemost, 110, 1074-1079.
51. Apostolakis, S., Lane, D.A., Guo, Y., Buller, H. and Lip, G.Y. (2013) Performance of the HEMORR 2 HAGES, ATRIA, and HAS-BLED bleeding risk-prediction scores in nonwarfarin anticoagulated atrial fibrillation patients. J Am Coll Cardiol, 61, 386-387.
52. Roldan, V., Marin, F., Fernandez, H., Manzano-Fernandez, S., Gallego, P., Valdes, M., Vicente, V. and Lip, G.Y. (2013) Predictive value of the HAS-BLED and ATRIA bleeding scores for the risk of serious bleeding in a "real-world" population with atrial fibrillation receiving anticoagulant therapy. Chest, 143, 179-184.
53. Lip, G.Y., Banerjee, A., Lagrenade, I., Lane, D.A., Taillandier, S. and Fauchier, L. (2012) Assessing the risk of bleeding in patients with atrial fibrillation: the Loire Valley Atrial Fibrillation project. Circ Arrhythm Electrophysiol, 5, 941-948.
54. Lip, G.Y., Lin, H.J., Hsu, H.C., Su, T.C., Chen, M.F., Lee, Y.T. and Chien, K.L. (2013) Comparative assessment of the HAS-BLED score with other published bleeding risk scoring schemes, for intracranial haemorrhage risk in a non-atrial fibrillation population: the Chin-Shan Community Cohort Study. Int J Cardiol, 168, 1832-1836.
55. Donze, J., Clair, C., Hug, B., Rodondi, N., Waeber, G., Cornuz, J. and Aujesky, D. (2012) Risk of falls and major bleeds in patients on oral anticoagulation therapy. Am J Med, 125, 773-778.
56. Devereaux, P.J., Anderson, D.R., Gardner, M.J., Putnam, W., Flowerdew, G.J., Brownell, B.F., Nagpal, S. and Cox, J.L. (2001) Differences between perspectives of physicians and patients on anticoagulation in patients with atrial fibrillation: observational study. BMJ, 323, 1218-1222.
57. Hart, R.G., Pearce, L.A. and Aguilar, M.I. (2007) Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med, 146, 857-867.
58. Connolly, S.J., Pogue, J., Hart, R.G., Hohnloser, S.H., Pfeffer, M., Chrolavicius, S., Yusuf, S. and Investigators., A. (2009) Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med, 360, 2066-2078.
59. Investigators, A.W.G.o.t.A., Connolly, S., Pogue, J., Hart, R., Pfeffer, M., Hohnloser, S., Chrolavicius, S., Pfeffer, M., Hohnloser, S. and Yusuf, S. (2006) Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet, 367, 1903-1912.
60. Granger, C.B. and Armaganijan, L.V. (2012) Newer oral anticoagulants should be used as first-line agents to prevent thromboembolism in patients with atrial fibrillation and risk factors for stroke or thromboembolism. Circulation, 125, 159-164; discussion 164.
61. Mant, J., Hobbs, F.D., Fletcher, K., Roalfe, A., Fitzmaurice, D., Lip, G.Y. and Murray, E. (2007) Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet, 370, 493-503.
62. van Walraven, C., Hart, R.G., Connolly, S., Austin, P.C., Mant, J., Hobbs, F.D., Koudstaal, P.J., Petersen, P., Perez-Gomez, F., Knottnerus, J.A. et al. (2009) Effect of age on stroke prevention therapy in patients with atrial fibrillation: the atrial fibrillation investigators. Stroke, 40, 1410-1416.
63. Ogilvie, I.M., Newton, N., Welner, S.A., Cowell, W. and Lip, G.Y. (2010) Underuse of oral anticoagulants in atrial fibrillation: a systematic review. Am J Med, 123, 638-645 e634.
64. Kakkar, A.K., Mueller, I., Bassand, J.P., Fitzmaurice, D.A., Goldhaber, S.Z., Goto, S., Haas, S., Hacke, W., Lip, G.Y., Mantovani, L.G. et al. (2013) Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the international, observational, prospective GARFIELD registry. PLoS One, 8, e63479.
65. Gallagher, A.M., Setakis, E., Plumb, J.M., Clemens, A. and van Staa, T.P. (2011) Risks of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients. Thromb Haemost, 106, 968-977.
66. Wallentin, L., Yusuf, S., Ezekowitz, M.D., Alings, M., Flather, M., Franzosi, M.G., Pais, P., Dans, A., Eikelboom, J., Oldgren, J. et al. (2010) Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet, 376, 975-983.
67. Connolly, S.J., Ezekowitz, M.D., Yusuf, S., Eikelboom, J., Oldgren, J., Parekh, A., Pogue, J., Reilly, P.A., Themeles, E., Varrone, J. et al. (2009) Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med, 361, 1139-1151.
68. Granger, C.B., Alexander, J.H., McMurray, J.J., Lopes, R.D., Hylek, E.M., Hanna, M., Al-Khalidi, H.R., Ansell, J., Atar, D., Avezum, A. et al. (2011) Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med, 365, 981-992.
69. Patel, M.R., Mahaffey, K.W., Garg, J., Pan, G., Singer, D.E., Hacke, W., Breithardt, G., Halperin, J.L., Hankey, G.J., Piccini, J.P. et al. (2011) Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med, 365, 883-891.
70. Giugliano, R.P., Ruff, C.T., Braunwald, E., Murphy, S.A., Wiviott, S.D., Halperin, J.L., Waldo, A.L., Ezekowitz, M.D., Weitz, J.I., Spinar, J. et al. (2013) Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med, 369, 2093-2104.
71. Connolly, S.J., Eikelboom, J., Joyner, C., Diener, H.C., Hart, R., Golitsyn, S., Flaker, G., Avezum, A., Hohnloser, S.H., Diaz, R. et al. (2011) Apixaban in patients with atrial

fibrillation. N Engl J Med, 364, 806-817.
72. Adam, S.S., McDuffie, J.R., Ortel, T.L. and Williams, J.W., Jr. (2012) Comparative effectiveness of warfarin and new oral anticoagulants for the management of atrial fibrillation and venous thromboembolism: a systematic review. Ann Intern Med, 157, 796-807.
73. Ruff, C.T., Giugliano, R.P., Braunwald, E., Hoffman, E.B., Deenadayalu, N., Ezekowitz, M.D., Camm, A.J., Weitz, J.I., Lewis, B.S., Parkhomenko, A. et al. (2014) Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet, 383, 955-962.
74. Connolly, S.J., Wallentin, L., Ezekowitz, M.D., Eikelboom, J., Oldgren, J., Reilly, P.A., Brueckmann, M., Pogue, J., Alings, M., Amerena, J.V. et al. (2013) The Long-Term Multicenter Observational Study of Dabigatran Treatment in Patients With Atrial Fibrillation (RELY-ABLE) Study. Circulation, 128, 237-243.
75. Larsen, T.B., Rasmussen, L.H., Skjoth, F., Due, K.M., Callreus, T., Rosenzweig, M. and Lip, G.Y. (2013) Efficacy and safety of dabigatran etexilate and warfarin in "real-world" patients with atrial fibrillation: a prospective nationwide cohort study. J Am Coll Cardiol, 61, 2264-2273.
76. Holster, I.L., Valkhoff, V.E., Kuipers, E.J. and Tjwa, E.T. (2013) New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis. Gastroenterology, 145, 105-112 e115.
77. Artang, R., Rome, E., Nielsen, J.D. and Vidaillet, H.J. (2013) Meta-Analysis of Randomized Controlled Trials on Risk of Myocardial Infarction from the Use of Oral Direct Thrombin Inhibitors. Am J Cardiol.
78. Lip, G.Y. and Lane, D.A. (2010) Does warfarin for stroke thromboprophylaxis protect against MI in atrial fibrillation patients? Am J Med, 123, 785-789.
79. Southworth, M.R., Reichman, M.E. and Unger, E.F. (2013) Dabigatran and postmarketing reports of bleeding. N Engl J Med, 368, 1272-1274.
80. Watson, H.G., Baglin, T., Laidlaw, S.L., Makris, M. and Preston, F.E. (2001) A comparison of the efficacy and rate of response to oral and intravenous Vitamin K in reversal of over-anticoagulation with warfarin. Br J Haematol, 115, 145-149.
81. Khorsand, N., Veeger, N.J., Muller, M., Overdiek, J.W., Huisman, W., van Hest, R.M. and Meijer, K. (2011) Fixed versus variable dose of prothrombin complex concentrate for counteracting vitamin K antagonist therapy. Transfus Med, 21, 116-123.
82. Dowlatshahi, D., Butcher, K.S., Asdaghi, N., Nahirniak, S., Bernbaum, M.L., Giulivi, A., Wasserman, J.K., Poon, M.C. and Coutts, S.B. (2012) Poor prognosis in warfarin-associated intracranial hemorrhage despite anticoagulation reversal. Stroke, 43, 1812-1817.
83. Huttner, H.B., Schellinger, P.D., Hartmann, M., Kohrmann, M., Juettler, E., Wikner, J., Mueller, S., Meyding-Lamade, U., Strobl, R., Mansmann, U. et al. (2006) Hematoma growth and outcome in treated neurocritical care patients with intracerebral hemorrhage related to oral anticoagulant therapy: comparison of acute treatment strategies using vitamin K, fresh frozen plasma, and prothrombin complex concentrates. Stroke, 37, 1465-1470.
84. Eerenberg, E.S., Kamphuisen, P.W., Sijpkens, M.K., Meijers, J.C., Buller, H.R. and Levi, M. (2011) Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. Circulation, 124, 1573-1579.
85. Zhou, W., Schwarting, S., Illanes, S., Liesz, A., Middelhoff, M., Zorn, M., Bendszus, M., Heiland, S., van Ryn, J. and Veltkamp, R. (2011) Hemostatic therapy in experimental intracerebral hemorrhage associated with the direct thrombin inhibitor dabigatran. Stroke, 42, 3594-3599.
86. Pragst, I., Zeitler, S.H., Doerr, B., Kaspereit, F.J., Herzog, E., Dickneite, G. and van Ryn, J. (2012) Reversal of dabigatran anticoagulation by prothrombin complex concentrate (Beriplex P/N) in a rabbit model. J Thromb Haemost, 10, 1841-1848.
87. Lambourne, M.D., Eltringham-Smith, L.J., Gataiance, S., Arnold, D.M., Crowther, M.A. and Sheffield, W.P. (2012) Prothrombin complex concentrates reduce blood loss in murine coagulopathy induced by warfarin, but not in that induced by dabigatran etexilate. J Thromb Haemost, 10, 1830-1840.
88. Majeed, A., Hwang, H.G., Connolly, S.J., Eikelboom, J.W., Ezekowitz, M.D., Wallentin, L., Brueckmann, M., Fraessdorf, M., Yusuf, S. and Schulman, S. (2013) Management and outcomes of major bleeding during treatment with dabigatran or warfarin. Circulation, 128, 2325-2332.
89. Schiele, F., van Ryn, J., Canada, K., Newsome, C., Sepulveda, E., Park, J., Nar, H. and Litzenburger, T. (2013) A specific antidote for dabigatran: functional and structural characterization. Blood, 121, 3554-3562.
90. Lu, G., DeGuzman, F.R., Hollenbach, S.J., Karbarz, M.J., Abe, K., Lee, G., Luan, P., Hutchaleelaha, A., Inagaki, M., Conley, P.B. et al. (2013) A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. Nat Med, 19, 446-451.
91. Heidbuchel, H., Verhamme, P., Alings, M., Antz, M., Hacke, W., Oldgren, J., Sinnaeve, P., Camm, A.J. and Kirchhof, P. (2013) European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace, 15, 625-651.
92. Dorian, P., Kongnakorn, T., Phatak, H., Rublee, D.A., Kuznik, A., Lanitis, T., Liu, L.Z., Iloeje, U., Hernandez, L. and Lip, G.Y. (2014) Cost-effectiveness of apixaban vs. current standard of care for stroke prevention in patients with atrial fibrillation. Eur Heart J.
93. Kleintjens, J., Li, X., Simoens, S., Thijs, V., Goethals, M., Rietzschel, E.R., Asukai, Y., Saka, O., Evers, T., Faes, P. et al. (2013) Cost-effectiveness of rivaroxaban versus warfarin for stroke prevention in atrial fibrillation in the Belgian healthcare setting. Pharmacoeconomics, 31, 909-918.
94. Gonzalez-Juanatey, J.R., Alvarez-Sabin, J., Lobos, J.M., Martinez-Rubio, A., Reverter, J.C., Oyaguez, I., Gonzalez-Rojas, N. and Becerra, V. (2012) Cost-effectiveness of dabigatran for stroke prevention in non-valvular atrial fibrillation in Spain. Rev Esp Cardiol (Engl Ed), 65, 901-910.
95. Krejczy, M., Harenberg, J., Marx, S., Obermann, K., Frolich, L. and Wehling, M. (2013) Comparison of cost-effectiveness of anticoagulation with dabigatran, rivaroxaban and apixaban in patients with non-valvular atrial fibrillation across countries. J Thromb Thrombolysis.
96. Kasmeridis, C., Apostolakis, S., Ehlers, L., Rasmussen, L.H., Boriani, G. and Lip, G.Y. (2013) Cost effectiveness of treatments for stroke prevention in atrial fibrillation: focus on the novel oral anticoagulants. Pharmacoeconomics, 31, 971-980.
97. Barco, S., Cheung, Y.W., Eikelboom, J.W. and Coppens, M. (2013) New oral anticoagulants in elderly patients. Best Pract Res Clin Haematol, 26, 215-224.
98. Budnitz, D.S., Shehab, N., Kegler, S.R. and Richards, C.L. (2007) Medication use leading to emergency department visits for adverse drug events in older adults. Ann Intern Med, 147, 755-765.
99. Coppens, M. (2013) New oral anticoagulants versus vitamin K antagonists in countries with good INR control. Neth J Med, 71, 168-169.
100. van der Meer, F.J., Rosendaal, F.R., Vandenbroucke, J.P. and Briet, E. (1993) Bleeding complications in oral anticoagulant therapy. An analysis of risk factors. Arch Intern Med, 153, 1557-1562.
101. Schulman, S., Shortt, B., Robinson, M. and Eikelboom, J.W. (2013) Adherence to anticoagulant treatment with dabigatran in a real-world setting. J Thromb Haemost, 11, 1295-1299.
102. Ansell, J. (2012) New oral anticoagulants should not be used as first-line agents to prevent thromboembolism in patients with atrial fibrillation. Circulation, 125, 165-170; discussion 170.
103. Cohen, D. (2014) Concerns over data in key dabigatran trial. BMJ, 349, g4747.
104. Cohen, D. (2014) Dabigatran: how the drug company withheld important analyses. BMJ, 349, g4670.
105. Charlton, B. and Redberg, R. (2014) The trouble with dabigatran. BMJ, 349, g4681.
106. Moore, T.J., Cohen, M.R. and Mattison, D.R. (2014) Dabigatran, bleeding, and the regulators. BMJ, 349, g4517.
107. Bansal, N., Fan, D., Hsu, C.Y., Ordonez, J.D., Marcus, G.M. and Go, A.S. (2013) Incident atrial fibrillation and risk of end-stage renal disease in adults with chronic kidney disease. Circulation, 127, 569-574.
108. Capodanno, D. and Angiolillo, D.J. (2012) Antithrombotic therapy in patients with chronic kidney disease. Circulation, 125, 2649-2661.
109. Cappato, R., Ezekowitz, M.D., Klein, A.L., Camm, A.J., Ma, C.S., Le Heuzey, J.Y., Talajic, M., Scanavacca, M., Vardas, P.E., Kirchhof, P. et al. (2014) Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. Eur Heart J.

MEDCON INTERNATIONAL

This document has been produced by MEDCON International, Heemstede, The Netherlands.

An abbreviated version is published at ejpc.sagepub.com (DOI: 10.1177/2047487315571890).