

How does Chronic Atrial Fibrillation Influence Mortality in the Modern Treatment Era?

Rajiv Sankaranarayanan*¹, Graeme Kirkwood¹, Rajaverma Visweswariah² and David J. Fox³

¹Cardiology Specialist Registrar in Electrophysiology and British Heart Foundation Clinical Research Fellow, University Hospital South Manchester and University of Manchester, Manchester, UK; ²Cardiology Specialist Registrar in Devices, Manchester Heart Centre, Manchester Royal Infirmary; ³Consultant Cardiologist and Electrophysiologist, Department of Cardiology, University Hospital South Manchester, Manchester, UK

Abstract: Atrial fibrillation (AF) continues to impose a significant burden upon healthcare resources. A sustained increase in the ageing population and better survival from conditions such as ischaemic heart disease have ensured that both the incidence and prevalence of AF continue to increase significantly. AF can lead to complications such as embolism and heart failure and these acting in concert with its associated co-morbidities portend increased mortality risk. Whilst some studies suggest that the mortality risk from AF is due to the “bad company it keeps” i.e. the associated co-morbidities rather than AF itself; undoubtedly some of the mortality is also due to the side-effects of various therapeutic strategies (anti-arrhythmic drugs, bleeding side-effects due to anti-coagulants or invasive procedures). Despite several treatment advances including newer anti-arrhythmic drugs and developments in catheter ablation, anti-coagulation remains the only effective means to reduce the mortality due to AF. Warfarin has been used as the oral anticoagulant in the treatment of AF for many years but suffers from disadvantages such as unpredictable INR levels, bleeding risks and need for haematological monitoring. This has therefore spurred a renewed interest in research and clinical studies directed towards developing safer and more efficacious anti-coagulants. We shall review in this article the epidemiological features of AF-related mortality from several studies as well as the cardiovascular and non-cardiac mortality mechanisms. We shall also elucidate why a rhythm control strategy has appeared to be counter-productive and attempt to predict the likely future impact of novel anti-coagulants upon mortality reduction in AF.

Keywords: Atrial fibrillation, arrhythmia, mortality, anti-arrhythmic drugs.

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice. 2.2 million people in America and 4.5 million people in Europe are affected by either paroxysmal or persistent AF [1]. It is usually associated with cardiovascular co-morbidities such as hypertension, coronary artery disease, valvular heart disease and heart failure [2]. The presence of AF has been shown to independently increase the risk of death [3-7] and the mortality risk is highest during the first year after AF manifests [5-8]. The incidence of death due to AF has been shown to vary from 1.6-4.2% per annum in various controlled trials [9, 10]. Whilst some studies suggest that the mortality risk from AF is due to the “bad company it keeps” i.e. the associated co-morbidities rather than AF itself; undoubtedly some of the mortality is also due to the side-effects of the various therapeutic strategies for AF (anti-arrhythmic drugs, bleeding side-effects due to anti-coagulants or invasive procedures).

EPIDEMIOLOGY

Large population studies both in North America and Europe have demonstrated incontrovertibly the impact of AF

upon mortality. The landmark Framingham Heart Study analysed a cohort of 621 individuals who developed AF (out of a study population of over 5000) during 40 years of follow-up; the excess in all-cause mortality rates attributable to AF was 50% for men, and 90% for women, even when controlled for the presence of a wide range of cardiovascular co-morbidities [5]. This effect on mortality became apparent early, with 15% of deaths occurring within 30 days of diagnosis. Amongst the group of patients aged between 55-74 years, the 10 year mortality was 61.5% in men with AF compared to 30% in men without AF. Amongst women in a similar age group, the 10 year mortality was 57.6% in the AF group versus 20.9% in women without AF. Similar findings have been found from many other cohorts. The Renfrew-Paisley study followed-up 100 patients with AF for 20 years out of a cohort of over 15,000 men and women aged between 45-64 years in two Scottish towns and showed that AF increased all-cause mortality by 50% amongst men and 120% amongst women [3]. Ruigomez *et al.* followed a cohort of 1035 chronic AF patients in the UK for a mean duration of 2 years and reported a trebling of all cause mortality after matching for confounding factors [7]. The Olmsted County study was a community based study of 4618 patients with AF, followed-up for 5.3±5 years and demonstrated that relative to the general age and sex-matched population, AF significantly increased the mortality risk especially during the first four months following diagnosis (HR 9.62; 95% CI 8.93 to 10.32) and

*Address correspondence to this author at the Cardiology Specialist Registrar in Electrophysiology and British Heart Foundation Clinical Research Fellow, University Hospital South Manchester and University of Manchester, Manchester, UK; Tel: 00447525826672; Fax: 00441612751234; E-mail: rajiv.sankaranarayanan@manchester.ac.uk

also thereafter (HR 1.66; 95% CI 1.59 to 1.73) [8]. The Manitoba study followed-up nearly 4000 young Canadian male air crew for 44 years and demonstrated that AF increased total mortality by 31% [11].

As might be expected, the annual mortality rates associated with AF vary substantially depending on the population demographics. Based on medical insurance claim data, values range from 2.6% in asymptomatic untreated individuals, to 24.2% amongst an elderly population with high rates of co-morbidities [12, 13]. There do not appear to have been significant reductions in AF-associated mortality between the years 1993 – 2007; this population-based data is supported by recent trials of novel anticoagulants and anti-arrhythmic therapies, which report annual mortality rates between 1.9 and 6.6% even with optimal contemporary treatment [14-16].

It is unambiguous from the epidemiological data that, although the presence of AF has a significant and dramatic effect to increase the mortality rate within a population, the effect on an individual is less clear-cut and is highly dependent on demographic risk factors and the presence of co-morbidities as discussed below.

AGE

Age is a major risk factor for developing AF, and older patients are more likely to have co-morbidities that might impact on survival. Nevertheless, patient age is the most powerful and consistent independent factor in determining the AF-associated mortality risk. Although the Framingham study found that all age groups demonstrated an excess mortality attributable to AF, the absolute risk increase seen in those aged over 75 years was approximately 3 times that seen in those under 65 years [5]. This was confirmed in the Paisley/Renfrew study, where the excess mortality was increased 3.5 times in the age group 60–64 years compared to 45–49 years [3]. Essentially, amongst all age groups, individuals with AF are more likely to die early than those without, and older patients with AF are substantially more at risk than younger patients. The annual mortality in 2007 amongst a large cohort of AF patients who were also Medicare beneficiaries aged >65 years was as high as 25% [13].

SEX

In developed societies, healthy females possess a survival advantage over males [17]. The mortality associated with AF is slightly but significantly higher in females than in males, such that this survival advantage is lost and the life expectancy of a woman with AF is similar to that of an age-matched man [5]. The Renfrew-Paisley study showed AF portends a higher all-cause and cardiovascular mortality amongst women [3]. There is also evidence that stroke-related mortality in AF is higher in women [18].

RACE /ETHNIC DIFFERENCES

During AF-related hospitalisations, in-hospital mortality has been shown to be highest amongst African-Americans in comparison to other ethnic groups [19].

LONE AF VS. CO-MORBIDITIES

‘Lone AF’ is defined as AF in the absence of structural heart disease or additional cardiovascular co-morbidities such as diabetes or hypertension. In reality, lone AF is an uncommon entity; 70% of patients with AF have additional risk factors at the time of diagnosis and of the remaining 30% many will have unrecognised co-morbidities such as sleep apnoea or obesity [20]. With a 15 year mortality of only 8%, survival amongst patients with lone AF has been shown to be not significantly different to that of age and sex-matched population control data [21-23]; this is in keeping with subgroup analysis from the Paisley/ Renfrew study which also did not identify a significant mortality excess attributable to lone AF [3].

In contrast, multivariate analysis from the aforementioned population studies indicates that cardiovascular and non-cardiovascular co-morbidities impact dramatically upon survival. Factors such as smoking, lung disease, hypertension, diabetes and obesity act to increase mortality by around 20 – 60% each, and the effects are additive with additional risk factors. These findings have led to the development of clinical scoring systems to aid therapeutic decisions.

TEMPORAL PROFILE OF AF

There is convincing evidence that AF burden may impact upon stroke rates [24], however the stroke risk due to paroxysmal AF is comparable to that of chronic AF [25]. In contrast, permanent AF is associated with higher mortality risk whereas paroxysmal AF has been shown to portend similar mortality risk as that of age and gender-matched general population [26, 27]. However, analysis of the mortality effect due to persistent AF in comparison to paroxysmal AF, has shown contrasting results [26, 28].

ISCHAEMIC HEART DISEASE (IHD) AND HEART FAILURE

AF and coronary artery disease share risk factors, but there is no clear evidence linking AF with increased risk of acute coronary syndromes [29]. Co-existing IHD has been shown to increase all-cause mortality due to AF three fold with up to 21% of deaths shown to be related to IHD [7]. Nevertheless, there is a clear association between AF and poor prognosis in myocardial infarction; multiple studies have shown that the development of AF following myocardial infarction is associated with a substantial increase in in-hospital as well as post-discharge mortality (reviewed in [30]). Many studies (including large-scale RCTs such as the OPTIMAAL trial, GUSTO-3 trial and TRACE study) have shown that chronic AF independently increases post-MI mortality (reviewed in [30]). A study by one of the authors of this paper (Sankaranarayanan *et al.* [31]) showed that chronic AF could increase post-MI mortality risk by increasing the risk of ventricular fibrillation in this setting [31]. The OPTIMAAL trial noted a significant increase in 30 day mortality only where new AF complicated acute MI, but that both acute and pre-existing AF were associated with reduced survival over the subsequent 3 years [32].

AF in congestive heart failure (CHF) has recently attracted substantial interest; AF can either exacerbate or com-

plicate CHF [33], and in the modern era of device therapy it is becoming apparent that AF in CHF is under-recognised [34]. 24% out of 3288 individuals with AF in the Olmsted County study developed CHF over a mean follow-up of 6.1 ± 5.2 years, leading to a significant increase in mortality (HR 3.4) [35]. The Framingham study illustrated the close relationship between these two pathologies showing that amongst 1470 participants who developed either or both these conditions, 382 individuals had both (36% of these developed AF first, 41% CHF first and 21% were diagnosed with both on the same day) [36]. The incidence of CHF amongst AF patients was 33 per 1000 person years, with 4 out of 10 AF subjects developing heart failure at some point during their lifetime and also significantly increasing mortality (men HR 1.6, women HR 2.7). Further analysis also demonstrated a significant mortality impact where AF complicated CHF, (incidence 54 per 1000 person years) with relative increases of 60% and 170% in men and women respectively compared to individuals with CHF in sinus rhythm. The Manitoba follow-up study showed that AF increases the risk of development of CHF by three-fold and increased cardiac mortality by 37% [11].

However, therapeutic CHF studies demonstrated conflicting results as to whether the presence of AF conferred an independent impact on mortality, or simply reflected disease state at baseline [37-40]. A recent meta-analysis of 16 studies including 53,969 patients appears to confirm that AF increases total mortality in CHF patients by around 40%, with an independent effect remaining after controlling for demographics and disease severity irrespective of impaired or preserved LV function [41]. Nevertheless, it remains controversial whether it is the arrhythmia or the co-morbidities that impacts upon mortality, with a recent analysis [42] suggesting that this effect is only seen where heart failure results from ischaemic heart disease. A post hoc analysis of the AF-FIRM trial sub-set of patients with CHF and preserved ejection fraction showed a lower all-cause and cardiovascular mortality in comparison to patients with impaired systolic function [43].

In view of the strong association of AF with co-morbidities, several studies have attempted to analyse if the effects of AF upon mortality are truly independent or simply a risk marker for the cumulative pre-terminal effects of co-morbidities. The Olmsted County study for instance illustrated the very high 4 month and 1 year mortality following AF diagnosis, however there were no changes in early (<4 months) versus late mortality (after 4 months) in the whole cohort or within the sub-group of patients without pre-morbid cardiovascular disease [8]. These results and others showing that lone AF does not increase mortality, suggest that AF could simply represent a risk marker for mortality in a very sick population with multiple co-morbidities [3, 6, 8].

MECHANISMS OF AF-RELATED MORTALITY

1. Cardiac

Several large population-based studies have shown that AF independently increases cardiac mortality [3, 5, 11]. Increased cardiovascular mortality risk due to AF varies between 2 to 12 times [44]. The cardiac causes in-

clude heart failure, arrhythmia and possibly coronary heart disease.

AF has an intricate relationship with CHF whereby one can precipitate the other [45]. AF leads to a loss of atrial systole (which usually contributes up to 30% of pre-load in sinus rhythm). In addition to this, the loss of atrio-ventricular synchrony and irregular, uncontrolled ventricular rates contribute to development of CHF ("tachycardia-induced cardiomyopathy") [46-48]. Uncontrolled ventricular rates during AF can also worsen mitral regurgitation and cause rate-related left bundle branch block, thereby reducing cardiac output [49].

AF can lead to arrhythmic sudden death by potentiating VT or VF in patients with ICDs [50], pre-excitation syndromes [49] and in the acute MI setting [31].

AF can also impair coronary perfusion and increase myocardial oxygen demand especially due to uncontrolled ventricular rates and this could worsen coronary ischaemia and thus increase mortality especially in the subset of patients with pre-existing ischaemic heart disease [48-50].

2. Vascular

AF contributes to 15-25% of all strokes and these contribute to a significant proportion of AF-related mortality [51, 52]. AF-related strokes tend to be associated with higher mortality, and more severe disability [52, 53]. The Olmsted County study followed up 4117 individuals with AF and reported a 11% incidence of stroke over a mean follow-up period of 5.5 ± 5 years, with AF-related stroke significantly increasing the mortality hazard ratio to 3.03 for men and 3.8 for women in comparison to the general population [18]. The Manitoba follow-up study showed that AF increased cardiovascular mortality including fatal stroke by 41% [11]. Even amongst anti-coagulated patients with therapeutic INR, stroke risk due to AF can be up to 3% in high-risk individuals such as those with prior stroke [54, 55]. Un-coordinated atrial contraction leads to stasis of blood in the left atrium [56]. In addition to this, thrombogenesis is also perpetuated by haematological abnormalities such as platelet activation, inflammation and structural factors such as atrial dilatation, loss of endothelium and progressive fibrosis [56]. The left atrial appendage is the site responsible for the majority of thrombi in non-valvular AF [56]. However, it has been demonstrated that not all thrombo-embolic events necessarily predict mortality risk. For instance, the ACTIVE-W trial showed that only disabling strokes (both ischaemic and haemorrhagic with Rankin score ≥ 3) increase mortality risk whereas transient ischaemic attacks do not [57]. Major bleeding secondary to anti-coagulation can also contribute to mortality [57].

3. Non-cardiovascular Deaths

Most therapeutic strategies for AF such as anti-arrhythmic drugs, anti-thrombotics and catheter ablation can increase mortality risk in AF as a side-effect or seri-

ous adverse event. Anti-arrhythmic drugs can lead to potentially lethal pro-arrhythmic effects (such as torsade de pointes) but also cause multi-systemic side-effects and thus contribute to non-cardiovascular deaths [10, 58, 59]. A rhythm control strategy has also been shown to unmask non-cardiovascular co-morbidities such as malignancies or lung pathology, thus contributing to mortality burden (covered in greater detail in section on AADs) [10, 48]. Bleeding risk is inextricably linked to use of anti-thrombotics and can be fatal. Severe bleeding events (such as fatal events, drop in haemoglobin of at least 5 g/decilitre), need for inotropic agents, loss of vision due to intra-ocular bleeding, surgical intervention due to bleeding, symptomatic intra-cranial haemorrhage, need for transfusion of at least 4 units of blood) treble the mortality risk (HR. 3.35; 95% CI, 2.12-5.27) whilst non-severe major bleeding or minor bleeding events do not increase mortality.

RISK PREDICTION FOR AF-RELATED MORTALITY

In view of the significant mortality risk due to AF and the associated co-morbidities, several useful risk-predictors have been identified. The CHADS₂ Score (1 point each for Congestive Heart Failure, Hypertension, Age \geq 75 years, Diabetes Mellitus and 2 points for Stroke/TIA) was introduced over a decade back as a scoring system to assess thrombo-embolic risk due to AF [60] but can also predict mortality risk. Khumri *et al.* showed in a study that patients with CHADS₂ score of \geq 5 have a 50 fold higher mortality risk in comparison to patients with a score of 0 [61]. Similarly, while the HAS-BLED score has been mainly used in clinical practice to predict risk of major haemorrhagic episodes due to anticoagulation [62], this risk score has also been shown to predict adverse cardiovascular events as well as all-cause mortality, thus illustrating that thrombogenesis and haemorrhage are inextricably linked by sharing many common risk predictors [63]. Whilst the CHA₂DS₂Vasc score has been recommended in the latest guidelines to supersede CHADS₂ as a better risk predictor for thrombo-embolic risk, its role as a risk predictor for mortality remains to be established.

Abnormal ankle brachial index (ratio of ankle and brachial systolic blood pressure) has been shown to independently predict all-cause mortality after adjusting for CHADS₂ score and also predict major haemorrhagic episodes irrespective of the HAS-BLED score [64]. Cardiovascular related hospitalisation in AF patients also significantly predicts risk of death (HR 2.69; 95% CI 1.96-3.68) and it has been suggested that this end-point could be used as a surrogate for mortality in trials [65].

Clinical investigations also help to identify patients at increased risk of AF-related adverse events. Serum biomarkers such as interleukin-6, high sensitivity troponin T and von Willebrand factor have been shown to predict all-cause mortality independent of CHADS₂ score in anticoagulated AF patients, possibly reflecting coronary microvascular dysfunction, global endothelial dysfunction or athero-thrombosis [66-68]. High sensitivity CRP has also been shown to predict all-cause and cardiovascular mortality amongst AF patients [69]. Patients with renal failure (eGFR

<45 ml/min and proteinuria) have been shown to have increased risk of AF-related thrombo-embolism, bleeding and mortality [70]. Echocardiographic markers such as mitral annular calcification, presence of spontaneous left atrial contrast, severe LV impairment and greater than moderate mitral regurgitation also help to predict increased mortality risk amongst chronic AF patients [61, 71].

TREATMENTS

Anti-arrhythmic Drugs (AADs)

Several AADs have been shown to cause pro-arrhythmic side-effects and thus increased mortality in patients [58]. The class I agent flecainide gained particular attention following the CAST trial [72] where increased mortality was observed in patients with history of myocardial infarction. These results have been extrapolated to extend its contraindication to patients with coronary artery disease, heart failure or left ventricular hypertrophy. Coplen, in a meta-analysis published in 1990, showed that treatment with quinidine was more effective than no anti-arrhythmic therapy in suppressing recurrences of atrial fibrillation but appeared to be associated with increased total mortality [73]. Class III medications such as amiodarone and sotalol, have also received similar attention, and are also well known for their risk of QT prolongation and Torsades de Pointes.

Indeed all AADs have the potential to have serious, pro-arrhythmic side effects [58]. This has implications when determining the optimal treatment strategy for atrial fibrillation (AF): the restoration and maintenance of sinus rhythm (rhythm control strategy) or control of heart rate alone (rate control strategy). Several studies have sought to answer this question, including the Strategies of Treatment of Atrial Fibrillation (STAF) [74], Pharmacological Intervention in Atrial Fibrillation (PIAF) [75], Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) [10], Rate Control vs. Electrical Cardioversion (RACE) [76], the HOT CAFÉ [77] and J-RHYTHM Study [78]. None of these studies has shown any significant difference in all-cause or cardiovascular mortality and stroke outcome between rate and rhythm control and in fact a meta-analysis of five major trials showed a trend towards reduced risk of death (rate vs. rhythm control; OR 0.87, 0.74-1.02- P=0.09) [79]. This has generally led to the adoption of rate control strategy as the pragmatic approach especially in the elderly or in presence of significant co-morbidities.

AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) in particular showed a non-significant trend toward increased all-cause mortality in the rhythm control group (hazard ratio 1.14; 95% CI, 1-1.32) [10]. A retrospective analysis of the cause-specific mortality in the AFFIRM trial showed that the incidence of cardiac (including arrhythmic, heart failure and MI deaths) and vascular (including ischaemic and haemorrhagic strokes) deaths was not significantly different between the rhythm control and rate-control groups [48]. Thus the increased all-cause mortality in the rhythm-control group could be entirely accounted for by the significant difference between the incidences of non-cardiovascular deaths (47.5% in rhythm control group versus 36.5% in rate-control group; p=0.0008). These non-cardiovascular deaths were mainly due to malignancies and

pneumonia. This was attributed to earlier discontinuation of warfarin and higher incidence of stroke rather than risk of the anti-arrhythmic itself which highlights the importance of anticoagulation in atrial fibrillation. Even in patients with heart failure (LVF<35%) complicated by AF, the AF-CHF trial did not demonstrate that rhythm control could lead to mortality benefit [33]. However, there has been some evidence demonstrating the benefits of rhythm control particularly in the longer term. For instance, a retrospective, “on-treatment analysis” of the AFFIRM study that analysed presence of sinus rhythm and use of anti-arrhythmic drugs as separate variables, showed a significant reduction in death due to presence of sinus rhythm [80]. Thus the mortality increase of 49% due to anti-arrhythmic drugs could have overshadowed the 53% mortality reduction due to maintenance of sinus rhythm [48]. The survival benefits of sinus rhythm were similar to that seen in the DIAMOND AF (dofetilide versus placebo in AF patients with LV dysfunction) study which did not show an all-cause mortality benefit; however, restoration and maintenance of sinus rhythm significantly reduced mortality (risk ratio 0.44; 95% CI 0.30-0.64) and risk of hospitalisation [81]. In a population-based study of rate versus rhythm control strategies among 26, 130 AF patients, showed that the rhythm control group demonstrated a small increase in mortality within six months of treatment initiation which then became similar to mortality in the rate-control group until year 4. In the longer term however (after year 5), the mortality was lower in the rhythm control group in comparison to that in the rate-control group (HR 0.89; 95% CI 0.81-0.96 after 5 years and HR 0.77; 95% CI 0.62-0.95 after 8 years) [82]. From the above studies, it is likely that the pro-arrhythmic effects and multi-systemic side-effects of existing AADs dilute and even offset the survival advantage provided by maintenance of sinus rhythm.

The most commonly used AAD for rhythm control in all these trials was amiodarone, which was shown in the studies to have a low pro-arrhythmic potential, with its adverse side effects being mainly extra-cardiac [59]. Amiodarone has been demonstrated to be the most efficacious drug in maintaining sinus rhythm [59, 79]. Some studies have found it to be associated with an increased risk of non-cardiac mortality (particularly cancer-related and pulmonary) [83-85] whilst this was not observed in other studies [86, 87]. Recently Freemantle *et al.* included thirty nine randomised controlled trials in a mixed treatment comparison of dronedarone, amiodarone, sotalol, flecainide and propafenone used for the management of AF and reported (from eighteen trials including about 10,000 patients) that sotalol in particular was associated with increased mortality whereas amiodarone (but not dronedarone) showed a trend towards increased all-cause mortality [59]. A meta-analysis by Piccini *et al.* also demonstrated an insignificant trend towards increased mortality due to amiodarone [88].

More recently, there has been the arrival of dronedarone, an AAD developed to have fewer side effects and improved safety profile compared to amiodarone [88]. The EURIDIS and ADONIS trials showed dronedarone was significantly more effective than placebo in maintaining sinus rhythm, and in reducing ventricular rate during recurrence of arrhythmia, with post hoc analysis also suggesting a 44% reduction in cardiovascular hospitalisation or death at 12

months [89]. Although dronedarone is less efficacious than amiodarone [88], a subsequent trial (ATHENA) showed that dronedarone reduces the composite endpoint of cardiovascular hospitalisation or death by 24% [14]. However, subsequent studies have shown that dronedarone can lead to increased early mortality in certain sub-sets of patients. For instance, in the ANDROMEDA trial (Anti-arrhythmic trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease), dronedarone (in comparison with placebo) led to a doubling of mortality (95%CI, 1.07-4.25) due to worsening heart failure after a median follow-up of only 2 months [90]. Dronedarone also led to increased cardiovascular deaths (hazard ratio 2.11; 95% CI, 1-4.49), arrhythmic deaths (hazard ratio 3.26; 95% CI, 1.06-10) in addition to increased incidence of stroke and heart failure hospitalisations when used in patients with high-risk permanent AF (PALLAS) [91].

ANTI-COAGULATION

Effective anticoagulation is the most effective method of reducing mortality in AF patients [92]. In the absence of anti-coagulation, AF patients who develop a stroke have a 1 month mortality of nearly 25% [92]. In a meta-analysis of 29 trials of anti-thrombotic therapy for AF, compared to control, adjusted-dose warfarin reduced significantly stroke risk by 64% and all-cause mortality by 26%. Aspirin in contrast showed a non-significant 19% reduction in stroke risk and did not reduce mortality significantly [93]. In addition to anti-coagulation with warfarin, it is also important to closely monitor the therapeutic range of INR closely to both prevent thrombo-embolic complications as well as avoid major bleeding complications. Patients who spend at least 70% of the time with INR within therapeutic range demonstrate significantly lower mortality compared to patients whose INR is therapeutic <70% of the time [94]. Analysis of 30-day mortality due to ischaemic stroke whilst on warfarin, has shown that warfarin significantly reduces 30 day mortality if INR is between 2-3 (OR 0.38; 95% CI, 0.2-0.7) but patients with INR>3 demonstrate increased odds of mortality due to intracranial haemorrhage 2.66 fold (95% CI, 1.21-5.86) [95].

Despite the obvious benefits of warfarin, the ATRIA study showed that it was being under-prescribed, particularly in those AF patients below 55 years and above 85 years, presumably due to physicians' concerns regarding bleeding risk [96]. Interestingly, in contrast to this predominant view held by most physicians, patients are willing to accept the higher risk of bleeding associated with anti-coagulants in order to avoid disabling strokes which some even view as worse than death [97]. The search for more efficacious and potentially safer anti-thrombotics has heralded the era of novel anti-coagulants, as detailed below.

In the RELY study [98], dabigatran, a novel oral direct thrombin inhibitor, given at a dose of 110 mg to AF patients, was associated with rates of stroke and systemic embolism similar to warfarin, but with lower rates of major haemorrhage, whilst at doses of 150 mg, it was associated with lower rates of stroke and systemic embolism compared to warfarin, and similar rates of major haemorrhage. There was a trend towards reduction in all-cause mortality with the 150 mg dose (p=0.051) and a significant reduction in vascular

mortality ($p=0.04$). The rates of death from any cause were 4.13% per year with warfarin, compared with 3.75% per year with 110 mg dabigatran ($P=0.13$), and 3.64% with 150 mg dabigatran ($P=0.051$). A meta-analysis of seven dabigatran studies (including 30514 patients) also showed a 11% reduction in all-cause mortality in comparison to warfarin [99].

Following this there has been the addition of the oral factor Xa inhibitors: rivaroxaban, assessed by the ROCKET-AF trial [100]; and apixaban, analysed by the AVERROES [16] and ARISTOTLE [101] trials. In the ROCKET-AF trial, in comparison with warfarin for non-valvular AF, rivaroxaban was shown to be non-inferior for prevention of stroke or systemic embolism. There was no significant difference in risk of major bleeding, though intracranial and fatal bleeding occurred less frequently in the rivaroxaban group. There was no significant difference in mortality between the two groups. In the ARISTOTLE trial, apixaban was shown to be superior to warfarin by reducing the risk of stroke or systemic embolism by 21%, major bleeding by 31% and all-cause mortality by 11% [101].

The future for these novel anticoagulants is very promising, with significant progress being made in morbidity and mortality reduction compared to warfarin, mainly by way of further reduction in ischaemic strokes and less bleeding risks. However there are also several concerns regarding the use of the newer anticoagulants as detailed below. These include the lack of robust safety data in patients with creatinine clearance <30 ml/min, elderly patients and those with extremes of body weight. Whilst the lack of need to closely monitor anticoagulation whilst on newer anticoagulants can be viewed as an advantage by reducing patient inconvenience as well as the burden on healthcare resources, this feature can also be a disadvantage if patients miss one or more doses (due to the short offset time of these drugs leading to a rebound stroke risk). Additionally the lack of a specific antidote to these drugs is also of concern during major bleeding episodes. Thus there is a need for further studies in order to clarify the above concerns about these drugs before they can be incorporated into widespread clinical practice.

INTERVENTIONAL TREATMENTS

Catheter ablation is recommended in the management of symptomatic paroxysmal AF after failed AAD therapy and has not yet been demonstrated to confer mortality benefits possibly due to lack of long-term follow-up data. Being an invasive procedure, the procedure itself carries a mortality risk of up to 0.7% [2]. However, newer technological developments are consistently improving the safety and efficacy of catheter-based techniques. Left atrial appendage closure using occlusion devices has been suggested as an alternative for patients deemed unsuitable for oral anti-coagulation and again data on mortality benefits from this procedure is lacking currently.

CONCLUSIONS

AF and its associated co-morbidities continue to impose a significant mortality risk despite several new therapeutic advances. Indeed a proportion of the AF-related mortality is caused by side-effects due to attempts at restoring and main-

taining sinus rhythm or major bleeding due to anti-coagulation. However effective anti-coagulation is the only therapeutic strategy that has been shown to reduce AF-related mortality and newer anticoagulants with improved efficacy and lesser bleeding side-effects, are only likely to improve the risk-benefit profile. Currently available AADs have limited efficacy and possess significant side-effects which seem to offset benefits of rhythm control; hence there is a pressing need to develop improved AADs in order to unmask the survival benefit that could accrue from maintenance of sinus rhythm. The impact of catheter ablation in the management of AF has currently been increasing and with improvements in safety and efficacy, is likely to reduce the use of AADs in the future.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

- [1] Feinberg WM, Cornell ES, Nightingale SD, *et al.* Relationship between prothrombin activation fragment F1.2 and international normalized ratio in patients with atrial fibrillation. *Stroke Prevention in Atrial Fibrillation Investigators.* *Stroke* 1997; 28(6): 1101-6.
- [2] Camm AJ, Kirchhof P, Lip GY, *et al.* 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* 2010; 31(19): 2369-429.
- [3] Stewart S, Hart CL, Hole DJ, *et al.* A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med* 2002; 113(5): 359-64.
- [4] Kirchhof P, Auricchio A, Bax J, *et al.* Outcome parameters for trials in atrial fibrillation: executive summary. *Eur Heart J* 2007; 28(22): 2803-17.
- [5] Benjamin EJ, Wolf PA, D'Agostino RB, *et al.* Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation* 1998; 98(10): 946-52.
- [6] Vidaillet H, Granada JF, Chyou PH, *et al.* A population-based study of mortality among patients with atrial fibrillation or flutter. *Am J Med* 2002; 113(5): 365-70.
- [7] Ruigomez A, Johansson S, Wallander MA, *et al.* Risk of mortality in a cohort of patients newly diagnosed with chronic atrial fibrillation. *BMC Cardiovasc Disord* 2002; 2: 5.
- [8] Miyasaka Y, Barnes ME, Bailey KR, *et al.* Mortality trends in patients diagnosed with first atrial fibrillation: a 21-year community-based study. *J Am Coll Cardiol* 2007; 49(9): 986-92.
- [9] Olsson SB. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. *Lancet* 2003; 362(9397): 1691-8.
- [10] Wyse DG, Waldo AL, DiMarco JP, *et al.* A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002; 347(23): 1825-33.
- [11] Krahn AD, Manfreda J, Tate RB, *et al.* The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. *Am J Med* 1995; 98(5): 476-84.
- [12] Gajewski J, Singer RB. Mortality in an insured population with atrial fibrillation. *JAMA* 1981; 245(15): 1540-4.
- [13] Piccini JP, Hammill BG, Sinner MF, *et al.* Incidence and prevalence of atrial fibrillation and associated mortality among Medicare beneficiaries, 1993-2007. *Circ Cardiovasc Qual Outcomes* 2012; 5(1): 85-93.

- [14] Hohnloser SH, Crijns HJ, van EM, *et al.* Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med* 2009; 360(7): 668-78.
- [15] Go AS. The ACTIVE pursuit of stroke prevention in patients with atrial fibrillation. *N Engl J Med* 2009; 360(20): 2127-9.
- [16] Connolly SJ, Eikelboom J, Joyner C, *et al.* Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011; 364(9): 806-17.
- [17] Arias E. United States Life Tables, 2006. National vital statistics reports. Hyattsville, MD: National Centre for Health Statistics; 2010. Report No.: Volume 58, Number 21.
- [18] Miyasaka Y, Barnes ME, Gersh BJ, *et al.* Time trends of ischemic stroke incidence and mortality in patients diagnosed with first atrial fibrillation in 1980 to 2000: report of a community-based study. *Stroke* 2005; 36(11): 2362-6.
- [19] Turagam MK, Velagapudi P, Visotcky A, *et al.* African Americans have the highest risk of in-hospital mortality with atrial fibrillation related hospitalizations among all racial/ethnic groups: a nationwide analysis. *Int J Cardiol* 2012; 158(1): 165-6.
- [20] Rosiak M, Dziuba M, Chudzik M, *et al.* Risk factors for atrial fibrillation: Not always severe heart disease, not always 'lonely'. *Cardiol J* 2010; 17(5): 437-42.
- [21] Kopecky SL, Gersh BJ, McGoon MD, *et al.* The natural history of lone atrial fibrillation. A population-based study over three decades. *N Engl J Med* 1987; 317(11): 669-74.
- [22] Rostagno C, Bacci F, Martelli M, *et al.* Clinical course of lone atrial fibrillation since first symptomatic arrhythmic episode. *Am J Cardiol* 1995; 76(11): 837-9.
- [23] Potpara T, Grujic M, Marinkovic J, *et al.* Mortality of patients with lone and idiopathic atrial fibrillation is similar to mortality in general population of Serbia. *Vojnosanit Pregl* 2010; 67(2): 132-5.
- [24] Botto GL, Padeletti L, Santini M, *et al.* Presence and duration of atrial fibrillation detected by continuous monitoring: crucial implications for the risk of thromboembolic events. *J Cardiovasc Electrophysiol* 2009; 20(3): 241-8.
- [25] Lip GY, Hee FL. Paroxysmal atrial fibrillation. *QJM* 2001; 94(12): 665-78.
- [26] Keating RJ, Gersh BJ, Hodge DO, *et al.* Effect of atrial fibrillation pattern on survival in a community-based cohort. *Am J Cardiol* 2005; 96(10): 1420-4.
- [27] Ruigomez A, Johansson S, Wallander MA, *et al.* Predictors and prognosis of paroxysmal atrial fibrillation in general practice in the UK. *BMC Cardiovasc Disord* 2005; 5: 20.
- [28] Tuinenburg AE, Van G, I, van den Berg MP, *et al.* Lack of prevention of heart failure by serial electrical cardioversion in patients with persistent atrial fibrillation. *Heart* 1999; 82(4): 486-93.
- [29] Brown AM, Sease KL, Robey JL, *et al.* The risk for acute coronary syndrome associated with atrial fibrillation among ED patients with chest pain syndromes. *Am J Emerg Med* 2007; 25(5): 523-8.
- [30] Sankaranarayanan R. Mortality Risk Associated with AF in Myocardial Infarction Patients. *J Atr Fibrillation* 2012; 5(3): 138-52.
- [31] Sankaranarayanan R, James MA, Nuta B, *et al.* Does atrial fibrillation beget ventricular fibrillation in patients with acute myocardial infarction? *Pacing Clin Electrophysiol* 2008; 31(12): 1612-9.
- [32] Lehto M, Snapinn S, Dickstein K, *et al.* Prognostic risk of atrial fibrillation in acute myocardial infarction complicated by left ventricular dysfunction: the OPTIMAAL experience. *Eur Heart J* 2005; 26(4): 350-6.
- [33] Roy D, Talajic M, Nattel S, *et al.* Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med* 2008; 358(25): 2667-77.
- [34] Caldwell JC, Contractor H, Petkar S, *et al.* Atrial fibrillation is under-recognized in chronic heart failure: insights from a heart failure cohort treated with cardiac resynchronization therapy. *Eurpace* 2009; 11(10): 1295-300.
- [35] Miyasaka Y, Barnes ME, Gersh BJ, *et al.* Incidence and mortality risk of congestive heart failure in atrial fibrillation patients: a community-based study over two decades. *Eur Heart J* 2006; 27(8): 936-41.
- [36] Wang TJ, Larson MG, Levy D, *et al.* Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation* 2003; 107(23): 2920-5.
- [37] Olsson LG, Swedberg K, Ducharme A, *et al.* Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. *J Am Coll Cardiol* 2006; 47(10): 1997-2004.
- [38] Rivero-Ayerza M, Scholte Op RW, Lenzen M, *et al.* New-onset atrial fibrillation is an independent predictor of in-hospital mortality in hospitalized heart failure patients: results of the EuroHeart Failure Survey. *Eur Heart J* 2008; 29(13): 1618-24.
- [39] Dries DL, Exner DV, Gersh BJ, *et al.* Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. *Studies of Left Ventricular Dysfunction. J Am Coll Cardiol* 1998; 32(3): 695-703.
- [40] Mahoney P, Kimmel S, DeNofrio D, *et al.* Prognostic significance of atrial fibrillation in patients at a tertiary medical center referred for heart transplantation because of severe heart failure. *Am J Cardiol* 1999; 83(11): 1544-7.
- [41] Mamas MA, Caldwell JC, Chacko S, *et al.* A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure. *Eur J Heart Fail* 2009; 11(7): 676-83.
- [42] Raunso J, Pedersen OD, Dominguez H, *et al.* Atrial fibrillation in heart failure is associated with an increased risk of death only in patients with ischaemic heart disease. *Eur J Heart Fail* 2010; 12(7): 692-7.
- [43] Badheka AO, Rathod A, Kizilbash MA, *et al.* Comparison of mortality and morbidity in patients with atrial fibrillation and heart failure with preserved versus decreased left ventricular ejection fraction. *Am J Cardiol* 2011; 108(9): 1283-8.
- [44] Domanski MJ. The epidemiology of atrial fibrillation. *Coron Artery Dis* 1995; 6(2): 95-100.
- [45] Cha YM, Redfield MM, Shen WK, *et al.* Atrial fibrillation and ventricular dysfunction: a vicious electromechanical cycle. *Circulation* 2004; 109(23): 2839-43.
- [46] Daoud EG, Weiss R, Bahu M, *et al.* Effect of an irregular ventricular rhythm on cardiac output. *Am J Cardiol* 1996; 78(12): 1433-6.
- [47] Shinbane JS, Wood MA, Jensen DN, *et al.* Tachycardia-induced cardiomyopathy: a review of animal models and clinical studies. *J Am Coll Cardiol* 1997; 29(4): 709-15.
- [48] Steinberg JS, Sadaniantz A, Kron J, *et al.* Analysis of cause-specific mortality in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *Circulation* 2004; 109(16): 1973-80.
- [49] Fuster V, Ryden LE, Cannom DS, *et al.* 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 developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *J Am Coll Cardiol* 2011; 57(11): e101-98.
- [50] Stein KM, Euler DE, Mehra R, *et al.* Do atrial tachyarrhythmias beget ventricular tachyarrhythmias in defibrillator recipients? *J Am Coll Cardiol* 2002; 40(2): 335-40.
- [51] Grau AJ, Weimar C, Buggle F, *et al.* Risk factors, outcome, and treatment in subtypes of ischemic stroke: the German stroke data bank. *Stroke* 2001; 32(11): 2559-66.
- [52] Kimura K, Minematsu K, Yamaguchi T. Atrial fibrillation as a predictive factor for severe stroke and early death in 15,831 patients with acute ischaemic stroke. *J Neurol Neurosurg Psychiatry* 2005; 76(5): 679-83.
- [53] Jorgensen HS, Nakayama H, Reith J, *et al.* Acute stroke with atrial fibrillation. The Copenhagen Stroke Study. *Stroke* 1996; 27(10): 1765-9.
- [54] EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet* 1993; 342(8882): 1255-62.

- [55] Akins PT, Feldman HA, Zoble RG, *et al.* Secondary stroke prevention with ximelagatran versus warfarin in patients with atrial fibrillation: pooled analysis of SPORTIF III and V clinical trials. *Stroke* 2007; 38(3): 874-80.
- [56] Watson T, Shantsila E, Lip GY. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *Lancet* 2009; 373(9658): 155-66.
- [57] De CR, Connolly SJ, Pogue J, *et al.* Mortality predictors and effects of antithrombotic therapies in atrial fibrillation: insights from ACTIVE-W. *Eur Heart J* 2010; 31(17): 2133-40.
- [58] Nattel S. Experimental evidence for proarrhythmic mechanisms of antiarrhythmic drugs. *Cardiovasc Res* 1998; 37(3): 567-77.
- [59] Freemantle N, Lafuente-Lafuente C, Mitchell S, *et al.* Mixed treatment comparison of dronedarone, amiodarone, sotalol, flecainide, and propafenone, for the management of atrial fibrillation. *Europace* 2011; 13(3): 329-45.
- [60] Gage BF, Waterman AD, Shannon W, *et al.* Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001; 285(22): 2864-70.
- [61] Khumri TM, Idupulapati M, Rader VJ, *et al.* Clinical and echocardiographic markers of mortality risk in patients with atrial fibrillation. *Am J Cardiol* 2007; 99(12): 1733-6.
- [62] Pisters R, Lane DA, Nieuwlaat R, *et al.* 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* 2010; 138(5): 1093-100.
- [63] Gallego P, Roldan V, Torregrosa JM, *et al.* Relation of the HAS-BLED bleeding risk score to major bleeding, cardiovascular events, and mortality in anticoagulated patients with atrial fibrillation. *Circ Arrhythm Electrophysiol* 2012; 5(2): 312-8.
- [64] Gallego P, Roldan V, Marin F, *et al.* Ankle brachial index as an independent predictor of mortality in anticoagulated atrial fibrillation. *Eur J Clin Invest* 2012; 42(12): 1302-8.
- [65] Friberg L, Rosenqvist M. Cardiovascular hospitalization as a surrogate endpoint for mortality in studies of atrial fibrillation: report from the Stockholm Cohort Study of Atrial Fibrillation. *Europace* 2011; 13(5): 626-33.
- [66] Roldan V, Marin F, Diaz J, *et al.* High sensitivity cardiac troponin T and interleukin-6 predict adverse cardiovascular events and mortality in anticoagulated patients with atrial fibrillation. *J Thromb Haemost* 2012; 10(8): 1500-7.
- [67] Providencia R. High sensitivity cardiac troponin T and interleukin-6 predict adverse cardiovascular events and mortality in anticoagulated patients with atrial fibrillation: a rebuttal. *J Thromb Haemost* 2012; 10(11): 2413; author reply 2014-5.
- [68] Roldan V, Marin F, Muina B, *et al.* Plasma von Willebrand factor levels are an independent risk factor for adverse events including mortality and major bleeding in anticoagulated atrial fibrillation patients. *J Am Coll Cardiol* 2011; 57(25): 2496-504.
- [69] Hermida J, Lopez FL, Montes R, *et al.* Usefulness of high-sensitivity C-reactive protein to predict mortality in patients with atrial fibrillation (from the Atherosclerosis Risk In Communities [ARIC] Study). *Am J Cardiol* 2012; 109(1): 95-9.
- [70] Go AS, Fang MC, Udaltsova N, *et al.* Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Circulation* 2009; 119(10): 1363-9.
- [71] Potpara TS, Vasiljevic ZM, Vujisic-Tesic BD, *et al.* Mitral annular calcification predicts cardiovascular morbidity and mortality in middle-aged patients with atrial fibrillation: the Belgrade Atrial Fibrillation Study. *Chest* 2011; 140(4): 902-10.
- [72] Echt DS, Liebson PR, Mitchell LB, *et al.* Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 1991; 324(12): 781-8.
- [73] Coplen SE, Antman EM, Berlin JA, *et al.* Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis of randomized control trials. *Circulation* 1990; 82(4): 1106-16.
- [74] Carlsson J, Miketic S, Windeler J, *et al.* 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* 2003; 41(10): 1690-6.
- [75] Hohnloser SH, Kuck KH, Lilienthal J. Rhythm or rate control in atrial fibrillation--Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial. *Lancet* 2000; 356(9244): 1789-94.
- [76] Van G, I, Hagens VE, Bosker HA, *et al.* A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* 2002; 347(23): 1834-40.
- [77] Opolski G, Torbicki A, Kosior DA, *et al.* Rate control vs rhythm control in patients with nonvalvular persistent atrial fibrillation: the results of the Polish How to Treat Chronic Atrial Fibrillation (HOT CAFE) Study. *Chest* 2004; 126(2): 476-86.
- [78] Ogawa S, Yamashita T, Yamazaki T, *et al.* Optimal treatment strategy for patients with paroxysmal atrial fibrillation: J-RHYTHM Study. *Circ J* 2009; 73(2): 242-8.
- [79] Testa L, Biondi-Zoccai GG, Dello RA, *et al.* Rate-control vs. rhythm-control in patients with atrial fibrillation: a meta-analysis. *Eur Heart J* 2005; 26(19): 2000-6.
- [80] Corley SD, Epstein AE, DiMarco JP, *et al.* Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study. *Circulation* 2004; 109(12): 1509-13.
- [81] Pedersen OD, Brendorp B, Elming H, *et al.* Does conversion and prevention of atrial fibrillation enhance survival in patients with left ventricular dysfunction? Evidence from the Danish Investigations of Arrhythmia and Mortality ON Dofetilide/(DIAMOND) study. *Card Electrophysiol Rev* 2003; 7(3): 220-4.
- [82] Ionescu-Ittu R, Abrahamowicz M, Jackevicius CA, *et al.* Comparative effectiveness of rhythm control vs rate control drug treatment effect on mortality in patients with atrial fibrillation. *Arch Intern Med* 2012; 172(13): 997-1004.
- [83] Bardy GH, Lee KL, Mark DB, *et al.* Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005; 352(3): 225-37.
- [84] Julian DG, Camm AJ, Frangin G, *et al.* Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. European Myocardial Infarct Amiodarone Trial Investigators. *Lancet* 1997; 349(9053): 667-74.
- [85] Causes of death in the Antiarrhythmics Versus Implantable Defibrillators (AVID) Trial. *J Am Coll Cardiol* 1999; 34(5): 1552-9.
- [86] Singh SN, Fletcher RD, Fisher SG, *et al.* Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmia. Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. *N Engl J Med* 1995; 333(2): 77-82.
- [87] Cairns JA, Connolly SJ, Roberts R, *et al.* Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: CAMIAT. Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Investigators. *Lancet* 1997; 349(9053): 675-82.
- [88] Piccini JP, Hasselblad V, Peterson ED, *et al.* Comparative efficacy of dronedarone and amiodarone for the maintenance of sinus rhythm in patients with atrial fibrillation. *J Am Coll Cardiol* 2009; 54(12): 1089-95.
- [89] Duray GZ, Torp-Pedersen C, Connolly SJ, *et al.* Effects of dronedarone on clinical outcomes in patients with lone atrial fibrillation: pooled post hoc analysis from the ATHENA/EURIDIS/ADONIS studies. *J Cardiovasc Electrophysiol* 2011; 22(7): 770-6.
- [90] Kober L, Torp-Pedersen C, McMurray JJ, *et al.* Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 2008; 358(25): 2678-87.
- [91] Connolly SJ, Camm AJ, Halperin JL, *et al.* Dronedarone in high-risk permanent atrial fibrillation. *N Engl J Med* 2011; 365(24): 2268-76.
- [92] Hylek EM, Go AS, Chang Y, *et al.* Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med* 2003; 349(11): 1019-26.
- [93] Hart RG, Pearce LA, Aguilar MI. Adjusted-dose warfarin versus aspirin for preventing stroke in patients with atrial fibrillation. *Ann Intern Med* 2007; 147(8): 590-2.

- [94] Gallagher AM, Setakis E, Plumb JM, *et al.* Risks of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients. *Thromb Haemost* 2011; 106(5): 968-77.
- [95] Fang MC, Go AS, Chang Y, *et al.* Thirty-day mortality after ischemic stroke and intracranial hemorrhage in patients with atrial fibrillation on and off anticoagulants. *Stroke* 2012; 43(7): 1795-9.
- [96] Go AS, Hylek EM, Borowsky LH, *et al.* Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Ann Intern Med* 1999; 131(12): 927-34.
- [97] Devereaux PJ, Anderson DR, Gardner MJ, *et al.* Differences between perspectives of physicians and patients on anticoagulation in patients with atrial fibrillation: observational study. *BMJ* 2001; 323(7323): 1218-22.
- [98] Connolly SJ, Ezekowitz MD, Yusuf S, *et al.* Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; 361(12): 1139-51.
- [99] Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials. *Arch Intern Med* 2012; 172(5): 397-402.
- [100] Patel MR, Mahaffey KW, Garg J, *et al.* Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; 365(10): 883-91.
- [101] Granger CB, Alexander JH, McMurray JJ, *et al.* Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; 365(11): 981-92.