

Atrial fibrillation in heart failure: The sword of Damocles revisited

Muhammad A Khan, Fozia Ahmed, Ludwig Neyses, Mamas A Mamas

Muhammad A Khan, Fozia Ahmed, Ludwig Neyses, Mamas A Mamas, Manchester Heart Centre, Manchester Royal Infirmary, Manchester, M13 9WL, United Kingdom
Ludwig Neyses, Mamas A Mamas, Cardiovascular Institute, University of Manchester, Manchester, M13 9PT, United Kingdom

Author contributions: Khan MA wrote the article, Ahmed F and Neyses L reviewed the draft; Mamas MA critically revised the manuscript.

Correspondence to: Muhammad A Khan, MBBS, MRCP, Manchester Heart Centre, Manchester Royal Infirmary, Oxford Road, Manchester, M13 9PT,

United Kingdom. muhammad.khan3@cmft.nhs.uk

Telephone: +44-161-2764271 Fax: +44-161-2767956

Received: May 11, 2013 Revised: June 6, 2013

Accepted: June 19, 2013

Published online: July 26, 2013

Abstract

Heart failure (HF) and atrial fibrillation (AF) frequently coexist and have emerged as major cardiovascular epidemics. There is growing evidence that AF is an independent prognostic marker in HF and affects patients with both reduced as well as preserved LV systolic function. There has been a general move in clinical practice from a rhythm control to a rate control strategy in HF patients with AF, although recent data suggests that rhythm control strategies may provide better outcomes in selected subgroups of HF patients. Furthermore, various therapeutic modalities including pace and ablate strategies with cardiac resynchronisation or radio-frequency ablation have become increasingly adopted, although their role in the management of AF in patients with HF remains uncertain. This article presents an overview of the multidimensional impact of AF in patients with HF. Relevant literature is highlighted and the effect of various therapeutic modalities on prognosis is discussed. Finally, while novel anticoagulants usher in a new era in thromboprophylaxis, research continues in a

variety of new pathways including selective atrial antiarrhythmic agents and genomic polymorphisms in AF with HF.

© 2013 Baishideng. All rights reserved.

Key words: Heart failure; Atrial fibrillation; Epidemiology; Prognosis; Thromboprophylaxis

Core tip: Atrial fibrillation commonly coexists with heart failure and there is growing evidence that it confers an adverse prognostic impact on the natural course of the disease. This review analyses the demographics and relevant literature highlighting this impact as well as the effect of various therapeutic modalities in improving outcomes. Finally some of the future trends in this exciting cardiovascular discipline are discussed.

Khan MA, Ahmed F, Neyses L, Mamas MA. Atrial fibrillation in heart failure: The sword of Damocles revisited. *World J Cardiol* 2013; 5(7): 215-227 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v5/i7/215.htm> DOI: <http://dx.doi.org/10.4330/wjc.v5.i7.215>

INTRODUCTION

Heart failure (HF) and atrial fibrillation (AF) have emerged as major global epidemics^[1]. Both frequently coexist and are associated with several common predisposing risk factors such as hypertension, coronary artery disease, structural heart disease (non-ischaemic, valvular), diabetes mellitus, obesity and obstructive sleep apnoea. This co-prevalence increases with advancing age and each predicts/compounds the course of the other^[2,3].

Data from Acute Decompensated Heart Failure National Registry demonstrated a 30% prevalence of AF among patients admitted with acute decompensated HF^[4].

The EuroHeart survey looked at HF hospitalisation data from 24 countries over a 6-wk duration. It revealed that out of a total of 10701 patients, 34% were known to have AF previously while 9% developed new onset AF^[5]. There is good data suggesting that AF is more prevalent in HF with preserved ejection fraction as compared to HF with reduced ejection fraction^[6-8]. The prevalence of AF also correlates directly with the severity of HF symptoms. It can vary from under 10% in those with functional New York Heart Association (NYHA) class 1 to as high as 50% in those in NYHA class 4^[9]. Similar prevalence figures have been reported from the T-wave Alternans in Patients with Heart Failure^[10] as well.

PATHOPHYSIOLOGICAL INTER-RELATIONSHIP

The interplay between HF and AF is complex. HF predicts the development of AF and conversely AF predisposes to HF^[2]. There are a number of mechanisms through which HF predisposes to an arrhythmogenic atrial substrate. These include elevated left sided-filling pressures, mitral regurgitation, atrial enlargement, interstitial fibrosis and electromechanical remodelling^[3]. Activation of autonomic and renin-angiotensin axis contributes while changes in the intracellular calcium are thought to play a role as well^[11].

Conversely, AF can lead to HF through multiple adverse effects including loss of atrial systole, functional mitral/tricuspid regurgitation, tachycardiomyopathy and reduced ventricular diastolic filling time^[2]. Irregularity in the RR interval can also have a potentially deteriorating influence on cardiac output irrespective of the heart rate^[12]. Moreover, deterioration of sinus rhythm into AF in patients with HF can lead to acute decompensation. A prospective study of 344 HF patients (who were in sinus rhythm at baseline) revealed significant haemodynamic deterioration with the onset of AF. Development of AF in this cohort led to reduced cardiac output, bi-atrial dilatation and functional atrioventricular valve regurgitation. This was reflected as a decline in the functional NYHA symptom class as well as peak exercise oxygen consumption^[13]. Details of the pathophysiological pathways involved are beyond the remit of this review and have been reviewed well previously^[14].

EPIDEMIOLOGY

According to the National Health And Nutrition Examination Survey, the prevalence of HF in Americans older than 20 years of age, is around 5.7 million (2.4%). It ranges from around 1.5% in those over 40 years to as high as 11% in the above 80 years age group. The lifetime likelihood of developing HF at the age of forty years has been estimated as 1 in 5^[15]. Similarly, estimate from existing data suggests that as many as 30 million people in Europe are living with HF^[16]. HF incidence also increases progressively with age ranging from a rate of 1.4 per 1000 person-years in 55-59 year-old

group to 47.4 per 1000 person-years in above 90-year-old bracket^[17].

AF is the commonest arrhythmia encountered in medical practice^[18]. The prevalence of AF in the United States is estimated between 2.7 and 6.1 million. This is projected to increase to between 5.6 and 12.0 million^[15] rising progressively to two and a half-fold by 2050^[19]. According to the Rotterdam as well as the Framingham studies, the lifetime risk of developing AF has been estimated to be around 1 in 4^[20,21]. Incidence of AF also increases progressively with age approaching a risk of 11%-18% by 90 years^[22].

IMPACT OF AF ON HF PROGNOSIS

There has been increasing evidence regarding the adverse role of AF in patients with HF, both in terms of morbidity as well as prognosis (Table 1).

Mountantonakis *et al*^[23] analysed the data from patients enrolled in the Get With The Guidelines-Heart Failure Registry between 2005 and 2010. They looked at 99810 patients hospitalised with HF across 255 ultrasonography sites. One-third of the cohort had AF and when compared to those in sinus rhythm, it was independently associated with a longer length of hospital stay (mean 5 vs 4 d; $P < 0.001$) as well as higher in-hospital mortality (4.0% vs 2.6%, $P < 0.001$). A post hoc analysis of the data from the Efficacy of Vasopressin antagonism in hEart failure: outcome Study with Tolvaptan looked at the clinical characteristics of 4133 patients out of which 29% had atrial fibrillation/atrial flutter at baseline. In contrast to patients in sinus rhythm, AF was found to confer an increased risk of death (HR = 1.23, 95%CI: 1.04-1.46) and cardiovascular mortality/HF admission (HR = 1.26, 95%CI: 1.07-1.47)^[24]. Retrospective subset analysis of studies of left ventricular dysfunction (SOLVD) looked at 6517 patients with LVEF less than 35%^[25]. It showed that patients in AF had an increased risk of all-cause mortality of 34% as compared to 23% for those in sinus rhythm. The higher mortality was largely attributable to increased risk of pump failure deaths. These findings were applicable to symptomatic as well as asymptomatic patients. Data from the candesartan in heart failure assessment of reduction in mortality and morbidity trials demonstrated an independent detrimental effect of AF on long term cardiovascular outcomes in HF patients (either reduced or preserved LV systolic function)^[26]. Similarly, an adjusted meta-analysis by Mamas *et al*^[27] has demonstrated a worse prognostic impact of AF in HF. This was based on 16 studies including 7 randomised trials and 9 observational studies and included data from 53969 patients. The impact of AF on mortality was reflected by an OR of 1.40 (95%CI: 1.32-1.48, $P < 0.0001$) in randomised trials and an OR of 1.14 (95%CI: 1.03-1.26, $P < 0.05$) in observational trials. This was irrespective of the LV systolic function. Middlekauff *et al* conducted a prospective study of 390 patients with NYHA class 3-4 symptoms and a mean LV Ejection Fraction (LVEF) of around 20%. Nineteen

Table 1 Prognostic impact of atrial fibrillation in heart failure

Ref.	Setting	n	LVEF	Mean follow up (yr)	AF	Deaths n (%)		P-value
						SR	AF	
Randomised trials								
Dries <i>et al</i> ^[25]	SOLVD	6517	< 35%	2.8	6%	1395 (23)	149 (34)	< 0.0001
Olsson <i>et al</i> ^[26]	CHARM	7601	All LVEF included	3.1	15%	1466 (23)	365 (32)	< 0.001
Swedberg <i>et al</i> ^[38]	COMET	3029	< 35%	4.8	20%	874 (36)	258 (43)	< 0.0005
Carson <i>et al</i> ^[109]	V-HEFT I&II	1427	< 45%	2.5	19%	480 (39)	75 (36)	NS
Mathew <i>et al</i> ^[110]	DIG	7788	All LVEF included	3.1	11%	2231 (32)	375 (43)	< 0.0001
Crijns <i>et al</i> ^[111]	PRIME II	409	< 35%	3.4	21%	153 (47)	50 (60)	< 0.05
Pederson <i>et al</i> ^[112]	DIAMOND	3587	< 35%	N/A	24%	1951 (73)	634 (77)	< 0.001
Observational studies								
Rivero-Ayerza <i>et al</i> ^[5]	EuroHeart Failure Survey	10701	All LVEF included	N/A	43%	419 (7)	372 (8)	< 0.05
Ahmed <i>et al</i> ^[28]	Medicare AL	944	All LVEF included	4.0 yr	27%	439 (62)	166 (71)	< 0.01
Mahoney <i>et al</i> ^[37]	Heart Transplantation	234	< 45%	1.1 yr	27%	26 (15)	14 (22)	NS
Middlekauff <i>et al</i> ^[113]	Heart Transplantation	390	< 35%	265 d	19%	123 (29)	36 (48)	< 0.005
Stevenson <i>et al</i> ^[114]	Heart Transplantation	750	< 40%	2.0 yr	22%	336 (45)	104 (61)	< 0.01
Wojtkowska <i>et al</i> ^[115]	Bilastok, Poland	120	< 30%	3.0 yr	50%	26 (43)	33 (55)	NS
Corell <i>et al</i> ^[116]	Danish HF clinic Network	1019	< 45%	1.9 yr	26%	180 (24)	89 (33)	< 0.05
Pai <i>et al</i> ^[117]	Loma Linda VA	8931	All LVEF included	2.5 yr	18%	2164 (28)	529 (44)	< 0.0001
Rusinaru <i>et al</i> ^[118]	Somme, France	368	> 50%	N/A	36%	125 (53)	84 (64)	< 0.05
Hamaguchi <i>et al</i> ^[119]	Japanese Registry data	2659	All LVEF included	2.4 yr	35%	N/A	N/A	NS
Shotan <i>et al</i> ^[120]	National HF Survey, Israel	4102	All LVEF included	4	33%	1480 (54.3)	882 (64.9)	0.000

SR: Sinus rhythm; AF: Atrial fibrillation; LVEF: Left ventricular ejection fraction; NS: Not significant; N/A: Not applicable; SOLVD: Studies of left ventricular dysfunction; CHARM: Candesartan in heart failure assessment of reduction in mortality and morbidity; COMET: Carvedilol or metoprolol European trial; DIG: Digitalis investigation group; DIAMOND: Danish investigations of arrhythmia and mortality on dofetilide.

percent of this cohort had AF and this was shown to be an independent predictor of all-cause mortality (actuarial survival at 1 year with AF 52% *vs* 71% with sinus rhythm). A retrospective study of 944 Medicare beneficiaries looked at 30-d re-hospitalisation and 4-year mortality figures in HF patients older than 65 years (mean age of 79 years). No distinction was made between reduced and preserved LV systolic function. Risk of readmission was not significantly higher^[28] but patients in AF had a 52% increased likelihood of mortality over 4 years as compared to the ones in sinus rhythm. Finally, Caldwell *et al*^[29] studied a cohort of 162 patients who had received biventricular device implants for advanced HF (NYHA 3 and 4). Almost a third of the patients (who were thought to be in sinus rhythm) were found to have silent episodes of paroxysmal AF. There was a trend of increased mortality but not towards thromboembolic episodes or hospitalisation.

Studies have also focused specifically on the prognostic effect of AF in ischaemic cardiomyopathy. The VALsartan In Acute myocardial iNfarction Trial involved over 14000 patients who had suffered from acute myocardial infarction complicated with LV systolic dysfunction. Patients in AF (both chronic AF at baseline as well as new-onset) had higher mortality at 3 years follow up as compared to those in sinus rhythm (37% *vs* 20%)^[30]. Analysis of the danish investigations of arrhythmia and mortality on dofetilide in congestive heart failure (DIAMOND-CHF) data compared ischaemic *vs* non ischaemic subsets^[31]. Three thousand five hundred and eighty-seven HF patients were followed for up to 8 years. AF had a

significant prognostic effect in those with ischaemic heart disease (HR = 1.25, 95%CI: 1.09-1.42, $P < 0.001$) as compared to those without ischaemic heart disease (HR = 1.01, 95%CI: 0.88-1.16, $P = 0.88$). A likely explanation may be that AF aggravates ischaemia in such cases (due to its association with increased coronary vascular resistance and reduced myocardial perfusion) thus affecting prognosis adversely^[32]. Four-year follow up of 2881 participants of the Echocardiographic Heart Of England Screening study showed similar results^[33].

A limited number of small studies have been conducted to evaluate the temporal significance of AF and it is not entirely clear whether AF prior to HF portends a worse prognostic influence or vice versa. The EuroHeart Failure survey indicated that new onset acute AF is associated with increased mortality as compared to chronic AF (12% *vs* 7%). The likely explanation may be related to tachycardia-related adverse haemodynamics as well as higher utilization of anti-arrhythmic agents in the acute setting^[5]. Data from the community-based study by Chamberlain *et al*^[34] divided 1664 HF patients into 3 groups namely HF without AF ($n = 727$), HF with AF preceding HF ($n = 553$) and HF with onset of AF after developing HF ($n = 384$). In comparison to the group in sinus rhythm, the prior-AF group had 29% higher all-cause mortality. This contrasted to the AF-after-HF group who had more than twice the mortality. Similarly, in the cohort assessed by Smit *et al*^[35], prognosis of patients who developed AF first was comparatively better as compared to those who developed AF after HF. A hundred and eighty two consecutive AF patients admitted for HF were

followed up for 16 ± 11 mo looking at the primary composite end point of cardiovascular hospitalisation and all-cause mortality. Seventy five percent of the cohort were known to have AF prior to onset of HF while 25% developed AF preceding HF. When compared to the HF-first group, AF-first cohort was less likely to reach the primary end-point (49.6% *vs* 77.7%, $P = 0.001$). The recently published Worcester HF Study has also demonstrated higher inpatient death rates as well as post-discharge mortality in HF patients with concurrent AF^[36].

Other studies, however, have not corroborated this independent impact of AF in HF. For instance, Mahoney *et al*^[37] showed that in patients referred for cardiac transplantation, AF was not associated with an increased mortality. However, given the end-stage disease (where prognosis is poor irrespective of AF) and small numbers involved (as well as the cross-sectional design of the study), it is difficult to generalize these results to a wider non-selected HF population. Similarly, an analysis of the carvedilol or metoprolol European trial data looked at the potential prognostic effect of AF in HF. When corrected for other prognostic markers, AF lost its independent effect on mortality^[38]. However, the criterion for diagnosing AF was limited to a single baseline ECG. This may have failed to pick up paroxysmal AF or future AF events. Thus, the reported prevalence of 19.8% of the study cohort who had AF may represent an underestimate.

Conversely, HF also impacts prognosis in AF. This is in keeping with the bidirectional interaction between the two disorders. For instance, the Framingham studies as well as EuroHeart Survey have demonstrated the vicious effect one condition has on the prognosis of the other^[39,40].

EFFECT OF AF THERAPY ON PROGNOSIS

Although several of the studies outlined above demonstrate an adverse prognostic influence of AF in HF, yet the optimal approach of managing such patients still remains unclear.

Pharmacological therapy

Rate control: Ventricular rate control remains a major therapeutic target for AF in HF patients. Beta-blockers and digoxin (as adjunctive therapy) are the main agents available for systolic HF. In addition, non-dihydropyridine calcium channel antagonists (verapamil, diltiazem) can be used instead of beta-blockers in HF with preserved EF. Finally, amiodarone can be considered for rate control if combination of beta-blocker and digoxin is inadequate^[41]. A number of studies have demonstrated prognostic benefit of beta-blockers in AF with HF. A retrospective analysis of the US Carvedilol HF trial data focused categorically on patients who had AF at the time of enrolment. In comparison to the placebo arm, the beta-blocker group had improved LV ejection fractions and better physician-determined global assessment. Moreover, there was a tendency towards reduced combined cardiovascular mortality and hospitalisation^[42]. The

digitalis investigation group trial showed that although digoxin did not affect mortality in HF, it reduced the number of hospital admissions. AF was among the exclusion criteria and as such these results may not be applicable to AF in HF^[43]. Moreover, digoxin loses its effect during periods of catecholamine excess and is not recommended as monotherapy. Of note, a recent post-hoc analysis of the the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial has cast doubt on the safety of digoxin in HF patients^[44]. It was shown that digoxin is associated with increased all-cause mortality including a 41% increased risk of death in patients with CHF or LVEF of less than 40%. This should, however, be interpreted with caution as AFFIRM was designed to compare rate and rhythm control and patients were not randomised to digoxin therapy. Moreover, only 25% of the AFFIRM cohort had HF. Moreover, a propensity matched analysis of the same cohort failed to demonstrate any increase in mortality with digoxin. It is likely that the patients on digoxin in the study had higher risk of mortality^[45]. Finally, data on the use of verapamil and diltiazem in HF is limited^[46]. Verapamil has been shown to be useful in HF patients with normal LV systolic function^[47] and current ESC guidelines recommend their use in HF with preserved ejection fraction as an alternative to beta-blockers^[41]. However, these should be avoided in HF with reduced ejection fraction due to negative inotropic effect on LV contractility^[41,48].

Another point that needs further clarification relates to the optimal target ventricular rate for permanent AF patients in HF. Rate control efficacy in permanent Atrial fibrillation: a Comparison between lenient *vs* strict rate control II (RACE II) trial looked at lenient (110 bpm) *vs* strict (< 80 bpm) ventricular rate control in patients with AF. The primary end-point was a composite of cardiovascular death, HF admission, bleeding and embolic events including stroke. No significant difference was observed in the two arms^[49]. Again less than 35% of the cohort had HF (15% in NYHA class 4) and results may not be generalizable to the HF patients. Routine versus Aggressive upstream rhythm Control for prevention of Early atrial fibrillation in HF (RACE III) is currently recruiting and will provide definitive answers for the HF population^[50].

Rhythm control: Amiodarone and dofetilide are the main anti-arrhythmic agents assessed in HF patients with AF. Survival trial of antiarrhythmic therapy in congestive heart failure (CHF-STAT) and atrial fibrillation and congestive heart failure (AF-CHF) trials have demonstrated the efficacy of amiodarone in cardioversion and maintenance of sinus rhythm in patients with moderate to severe LV systolic dysfunction^[51,52]. Its overall effect on mortality was shown to be neutral but long-term clinical use remains limited due to a risk of significant side effects. DIAMOND-CHF trial looked at the effect of dofetilide on a cohort of mainly ischaemic HF patients. A pooled sub-study analysis incorporated 506 patients

who were in AF. Dofetilide was shown to be safe with an overall neutral effect on mortality. It was superior to placebo in cardioversion and patients on the drug were more likely to be in sinus rhythm at one year as compared to placebo (79% *vs* 42%). Moreover, it was also associated with reduced HF admissions^[53]. Importantly, patients who converted to sinus rhythm had lower all-cause mortality (in the dofetilide as well as placebo arms) signifying the beneficial prognostic impact of sinus rhythm. However, torsade de pointes (1.6%) remains a cause for concern with dofetilide and requires initiation in hospital under close monitoring. Furthermore, it is not available in Europe. Subsequently, dronedarone (an iodine-free amiodarone derivative) was introduced with a promising adverse effect profile. A post hoc analysis of the ATHERNA (A Trial with dronedarone to prevent Hospitalization or death in patiENTS with Atrial fibrillation) looked at stable patients with LVEF less than 40% and NYHA 2-3 symptoms. It showed a reduced risk of all-cause mortality and/or hospitalisation due to cardiovascular events^[54]. However, ANtiarrhythmic trial with dronedarone in Moderate-to-severe congestive heart failure Evaluating morbidity Decrease (ANDROMEDA) trial (which looked at patients with severe HF in sinus rhythm and not AF) had to be terminated prematurely because dronedarone increased mortality in such patients^[55]. As a result, it is no longer licensed for use in patients with unstable/severe HF.

Rate *vs* rhythm control: There is no convincing scientific evidence so far to support a rhythm control strategy in preference to rate control. Given the negative impact of AF in HF, the concept of maintaining sinus rhythm appears attractive, yet a number of randomised trials have failed to demonstrate improved long-term outcomes with a rhythm control approach^[56-59]. The results are, however, limited by the fact that these trials were not exclusive to HF (for instance only 25% of the AFFIRM cohort had depressed LV function) and it may be difficult to apply these findings to the HF population. On the other hand, there have been trials looking exclusively at HF patients as well. AF-CHF enrolled 1376 patients with systolic HF. They were randomized to either rhythm or rate control and followed up for 3 years looking at prospective data for mortality, HF admissions and stroke^[52]. The difference in cardiovascular mortality observed in the two arms was not significant (27% in rhythm control *vs* 25% in rate control respectively). It is noteworthy, however, that only 80% of patients in the rhythm control arm remained entirely AF-free (65% when looking at overall 3 year follow up visits as well as the 21% who crossed over to rate control arm)^[11]. Interestingly, a post hoc analysis of the AFFIRM trial looked at the rhythm control arm of the trial. Sinus rhythm was associated with less severe NYHA symptomatic class and better functional capacity (assessed by 6-min walk test)^[60]. Similarly, in a subgroup analysis of CHF-STAT trial, Kaplan-Meier analysis of the survival curves for those who converted to SR with amiodarone

showed significantly better survival as compared to those who remained in AF^[51]. Same conclusion can be derived from the DIAMOND sub-study as well^[53]. However, these results are based on post-hoc subgroup analyses and should be applied with caution. A recent meta-analysis of the 4 main randomised control trials of AF rate *vs*. rhythm control in HF (incorporating 2486 patients) has demonstrated no significant difference in terms of mortality and thromboembolic events^[61].

Thromboprophylaxis: Although beyond the scope of this review, it would be amiss not to mention the enormous clinical, social and economic impact of stroke in HF patients with AF. Due to various co-morbidities, patients with HF have a significantly higher risk of thromboembolic events particularly stroke. Hence, oral anticoagulation is imperative unless there are equally binding contraindications. ACCF/AHA/HRS guidelines have kept the option of either aspirin or anticoagulation for patients with a CHADS₂ score of 1 while European Society of Cardiology (ESC) and Canadian Cardiovascular Society (CCS) guidelines indicate anticoagulation for such patients in preference to aspirin. Nevertheless, there is unanimous agreement in recommending long-term anticoagulation for all patients with a CHADS₂ score of 2 and above^[62]. Warfarin is well recognized in this regard and has been the mainstay of thromboprophylaxis in AF^[63] for the last 60 years. It has been shown to reduce the risk of stroke by as much as 65% and is thrice as efficacious as aspirin^[64]. Its clinical utility, however, is fraught with a variety of limitations (both real and perceived, by patients and physicians alike). These include a narrow therapeutic window, need for meticulous monitoring of INR levels, unreliable blood levels due to interaction with various drugs/food and risk of bleeding in an increasingly frail/ ageing population.

The last few years have witnessed the exciting development of a novel group of oral anticoagulants (NOACs) with the advantage of rapid onset of action, fewer drug/food interactions and predictable blood levels thus exonerating patients from laborious INR monitoring. They have been shown to carry a lesser risk of intracranial bleeding in comparison to warfarin while maintaining the same level of protection against stroke. However, widespread use is restricted by higher costs, unavailability of a reversal agent in the event of a major bleed and no validated lab markers of anticoagulant effect^[65]. The two main classes consist of direct thrombin inhibitors (dabigatran) and activated factor X inhibitors (apixaban, rivaroxaban, edoxaban) while several others are under development. Dabigatran was the first to be approved by Food and Drug Administration in 2010 for non-valvular AF following the Randomized Evaluation of Long-term anticoagulation therapy (RE-LY) trial^[66] which enrolled 18113 patients with AF. One-third of the study population had symptomatic HF or LVEF < 40%. Patients were randomized to receive either 150 or 110 mg twice daily (blinded dose groups) of dabigatran or INR-guided war-

farin therapy. In comparison to warfarin, 110 mg twice daily dose was non-inferior in efficacy and superior in safety while the 150 mg twice daily dose was superior in efficacy and had similar rates of major bleeding. Consequently, dabigatran has been recommended as an alternative to warfarin in recent ESC, AHA/ACCF as well as CCS guidelines^[67-69]. Similarly, Rivaroxaban was studied in the Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) looking at over 14000 patients. Data demonstrate non-inferiority to warfarin in terms of efficacy. It was associated with less intracranial haemorrhage as well albeit a higher risk of gastrointestinal bleed^[70]. Finally, Apixaban is the only one so far which has been shown to be superior to warfarin in reducing the primary end-point of thromboembolic events including stroke (annual event rate 1.27% *vs* 1.60%; $P < 0.001$ for non-inferiority; $P = 0.01$ for superiority). This is derived from the Apixaban in Preventing Stroke and Systemic Embolism in Subjects With Nonvalvular Atrial Fibrillation trial which enrolled over 18000 patients. The 21% reduction in primary safety end-point was mainly derived from a lower likelihood of haemorrhagic strokes. There was no significant difference in the rates of ischaemic strokes between the two^[71]. All three NOACs available so far have been licensed for use in non-valvular AF.

Non-pharmacological therapy

Drug therapy is the mainstay of AF management. However, many patients are unable to achieve rhythm or rate control targets due to therapeutic inefficacy or side effects respectively. Consequently, device therapy and electrophysiological catheter interventions have gained importance.

“Pace and ablate” strategy: Atrio-ventricular node (AVN) ablation accompanied by a permanent pacemaker is often used as an extreme option for definitive rate control. However, AF is not eliminated per se and rate control with a regular RR length may not suffice in compensating for the haemodynamic detriment caused by A-V dys-synchrony and loss of atrial systole. Thus, arguably, the procedure may only be of symptomatic benefit^[72]. Moreover, there is a potential for progressive inter-ventricular dys-synchrony due to chronic RV pacing. Hence, cardiac resynchronisation therapy (CRT) has emerged as the pacing option of choice in all patients with systolic HF^[73,74] who require pacing for AVN ablation. On the other hand, it is well recognized that clinical response to CRT is hampered if adequate AF rate control cannot be achieved. This is likely to be due to a lower percentage of biventricular pacing and here AVN ablation can be very helpful. This has been demonstrated in a recent meta-analysis of 23 observational studies involving 7495 CRT patients (25% of the total had AF). When compared to patients in sinus rhythm, presence of AF conferred a higher likelihood of CRT non-response and increased

all-cause mortality (10.8% *vs* 7.1% per year, pooled RR = 1.50, 95%CI: 1.08-2.09, $P = 0.015$). In addition, there was a lesser improvement in quality of life, exercise capacity and LV end-systolic dimensions. On the other hand, in patients with AF, AVN ablation not only improved response to CRT (RR = 0.40, 95%CI: 0.28-0.58, $P < 0.001$) but was associated with a reduced risk of mortality as well^[75]. A number of other small, mostly single-centre, non-randomized studies of CRT (in HF patients with AF) have also shown improvement in soft end-points such as reduced mitral regurgitation, improved LV ejection fraction and better exercise capacity but clearly more data is required^[76-78]. For instance, a registry-based analysis of patients with severe HF compared 139 patients who had AF with 445 in sinus rhythm. One year follow up revealed comparable CRT-related improvement in NYHA symptom class and LV ejection fractions in the two cohorts. Of note, mortality was higher in the AF group (12% *vs* 7%; OR = 1.80, 95%CI: 0.95-3.4)^[78]. Although the results are encouraging, yet large scale placebo controlled randomised trials are still required to confirm long term prognostic benefit.

AF ablation: As noted above, “pace and ablate” strategy is effective in controlling the ventricular rate but it does not eliminate AF as such. Also, like all invasive procedures CRT is not free of potential complications. Consequently, radio-frequency catheter ablation (RFA) using pulmonary vein isolation (PVI) has gained momentum in the management of AF. A number of observational studies (albeit small) provide supportive data for such a strategy. The non-randomized observational study by Hsu *et al*^[79] compared 58 patients in HF with an equivalent number of age/sex matched controls without HF. All underwent RFA for AF. At the completion of one year, 78% of the HF cohort and 84% of controls remained in sinus rhythm (although 50% had required a second procedure due to recurrence of AF). RFA led to significantly improved LV function (mean increase 21%) in the HF cohort. In addition, significant improvement was seen in NYHA symptom class, quality of life (assessed by SF-36 QoL scores) and exercise capacity (assessed by bicycle-ergometer stress test) as well. The trial was, however, not powered to look at mortality trends. Similar results have been obtained in a number of other small non-randomized studies demonstrating improvement in LVEF and patient symptoms^[80-82]. Pulmonary vein Antrum isolation *vs* atrioventricular node ablation with Biventricular pacing for treatment of atrial fibrillation in patients with congestive heart failure (PABA-CHF) was a multi-centre study which prospectively randomized 81 drug-refractory AF patients (with a LVEF of 40% or less and NYHA functional class 2-3) to undergo PVI or AVN ablation with biventricular ICD implant. They were followed up at 6 mo. The composite primary end point consisted of LVEF, 6-min walk distance and Minnesota Living with Heart Failure score. PVI patients fared better in all three components of the end point than the cohort who

underwent AVN ablation and biventricular pacing^[83]. Recently, MacDonald *et al.*^[84] conducted a randomised controlled trial in HF patients comparing rhythm control by RFA ($n = 22$) to rate control by medical therapy ($n = 19$). RFA failed to show any significant improvement in radionuclide LV ejection fractions as compared to the rate control arm. Only 50% were able to retain sinus rhythm at the end of one year and a significant (15%) complication rate was observed. A meta-analysis of AF ablation trials in patients with moderate LV systolic dysfunction looked at 9 studies involving a total of 354 patients. RFA led to an overall improvement in LV systolic function. However, the results are limited by heterogeneous study cohorts and lack of long-term outcome data^[85]. Hence, large scale, multicentre, randomized controlled trials with longer follow up will be required for further definitive clarification. Finally, in patients undergoing cardiac surgery, surgical ablation techniques (variations of Cox Maze procedure) are available as a safe and effective alternative^[86] including for those with depressed LV function^[87].

FUTURE TRENDS

Selective AV nodal stimulation

Selective AV nodal vagal stimulation (AVN-VS) has emerged as a potentially viable therapeutic intervention for ventricular rate control in AF. Loss of vagal tone followed by sympathetic overstimulation is thought to contribute to the pathophysiology of HF. Epicardial AV nodal fat pad stimulation (using catheter electrodes) targets parasympathetic efferents in the vagal ganglia and confers negative chronotropic and dromotropic effects. This can then be potentially used to modulate AF rate control in patients with HF. Small-scale, randomised preclinical case-control studies have shown effective heart rate control along with improvement in LV function in acute^[88] as well as chronic settings^[89]. Investigators induced HF and AF in canine models using rapid ventricular pacing for 4 wk followed by continued rapid atrial pacing respectively. Similar reversible negative chronotropic effects have been demonstrated in a cohort of 25 patients who underwent efferent vagal nerve stimulation with a multipolar catheter in superior vena cava or coronary sinus^[90]. Although it is only hypothesis generating at this stage, yet it showed consistent slowing of the heart rate and this was associated with improved LV function. Larger trials are needed to ascertain the true potential of this technique.

Atrial-specific anti-arrhythmic agents

Currently available anti-arrhythmic agents used for AF act on multiple ion-channels located in the atria as well as ventricles. Consequently, there is a risk of ventricular pro-arrhythmia and this is a particular concern in patients with structural heart disease/HF. Development of atrial specific anti-arrhythmics with a reduced risk of ventricular pro-arrhythmia is indeed an attractive strategy^[91]. Vernakalant is a potassium-channel blocker which has undergone successful phase II and III trials.

It is different to the conventional class III agents in that it selectively delays atrial repolarization by blocking atrial specific potassium-channels. As a result it suppresses AF by prolonging the atrial refractory period and is not associated with ventricular pro-arrhythmic effects such as QT prolongation and torsades^[92]. A phase III superiority study of Vernakalant *vs* Amiodarone in Subjects With Recent Onset Atrial Fibrillation (AVRO) demonstrated superior efficacy of vernakalant as compared to amiodarone^[93]. However, only 20% of the patients in the cohort had HF. Also, there is no experience yet in advanced HF as patients with unstable congestive HF, NYHA class 4 symptoms, or HF requiring inotropes were excluded from the study.

Left atrial appendage occlusion devices

A significant minority of patients in AF are unable to benefit from oral anticoagulation—either due to contraindications (bleeding, allergy) or therapeutic failure (ischaemic stroke despite effective anticoagulation). Studies have shown that in non-rheumatic AF, left atrial appendage serves as the source of thromboemboli in around 90% of cases^[94]. Consequently, percutaneous devices for the occlusion/exclusion of the left atrial appendage have emerged as a potentially promising answer to this challenging conundrum^[95]. Results from the recent randomised WATCHMAN left atrial appendage system for embolic PROTECTION in patients with Atrial Fibrillation (PROTECT AF) trial have established the feasibility of this technique^[96] while demonstrating non-inferiority with warfarin therapy. The initially high rate of procedural complications has subsequently improved with greater operator experience^[97] and combination with PVI has been successfully carried out^[98] as well. Long term outcome data is not available yet. Trials are also underway assessing further devices such as the Amplatzer cardiac plug and LARIAT suture delivery system^[99].

Genomics

Despite the frequent coexistence of AF and HF, it is intriguing that more than half of even severe HF patients do not develop AF. It is postulated that there may be a genetic predilection for AF in certain HF patients. If such is the case, then modulating these factors may provide a potential therapeutic target. Indeed, familial clustering of AF is well recognized. Moreover, genome wide association studies have demonstrated several common AF-related mutations and polymorphisms^[100]. Recently, a large population study showed a strong genetic association between AF and a polymorphism in the *ZFX3* gene (which encodes a cardiac transcription factor). This was associated with increased AF risk in HF patients when compared to the general population^[101]. The mechanism by which this translates into pathology is not known. Polymorphisms have also been identified in the beta1-adrenergic receptor gene in patients with systolic HF and AF^[102]. Again the exact significance is not clear yet but it may help risk stratify HF patients in terms of favourable response to beta blocker therapy^[103].

Upstream therapy

Apart from ion-channel blockers, other pharmacologic agents have been investigated for potential anti-AF effects with the hope that modification of the arrhythmogenic atrial substrate and neuroendocrine axis may be of benefit. Limited data is available for polyunsaturated fatty acids^[104], statin therapy^[105] and renin-angiotensin-aldosterone system blockade^[106,107]. At best, the findings have been inconclusive so far and larger randomized controlled trials are required^[108].

CONCLUSION

HF and AF have emerged as global cardiovascular epidemics. They commonly coexist accounting for an enormous clinical and economic burden on healthcare. Emerging evidence suggests that AF confers an adverse prognostic impact on HF. Despite the negative impact of AF in HF, to date there is no definite evidence that rhythm control is prognostically superior to a rate control strategy. Trials of AF ablation have been encouraging yet larger studies (looking at hard end-points) are required before it can be incorporated into mainstream clinical practice. Development of novel anticoagulants constitutes an important step towards minimizing the thromboembolic toll of AF. Genomics, pharmacological “upstream” modification of the atrial substrate and development of selective atrial anti-arrhythmic agents provide further insights into this exciting field. It is not clear yet whether these will translate into clinically tangible benefits for the HF patient.

REFERENCES

- 1 **Braunwald E.** Shattuck lecture—cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. *N Engl J Med* 1997; **337**: 1360-1369 [PMID: 9358131 DOI: 10.1056/NEJM199711063371906]
- 2 **Caldwell JC, Mamas MA.** Heart failure, diastolic dysfunction and atrial fibrillation; mechanistic insight of a complex inter-relationship. *Heart Fail Rev* 2012; **17**: 27-33 [PMID: 21103928 DOI: 10.1007/s10741-010-9204-4]
- 3 **Deedwania PC, Lardizabal JA.** Atrial fibrillation in heart failure: a comprehensive review. *Am J Med* 2010; **123**: 198-204 [PMID: 20193823 DOI: 10.1016/j.amjmed.2009.06.033]
- 4 **Adams KF, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, Berkowitz RL, Galvao M, Horton DP.** Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J* 2005; **149**: 209-216 [PMID: 15846257 DOI: 10.1016/j.ahj.2004.08.005]
- 5 **Rivero-Ayerza M, Scholte Op Reimer W, Lenzen M, Theuns DA, Jordaens L, Komajda M, Follath F, Swedberg K, Cleland JG.** 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**: 1618-1624 [PMID: 18515809 DOI: 10.1093/eurheartj/ehn217]
- 6 **Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Gong Y, Liu PP.** Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med* 2006; **355**: 260-269 [PMID: 16855266 DOI: 10.1056/NEJ-

Moa051530]

- 7 **Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM.** Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006; **355**: 251-259 [PMID: 16855265 DOI: 10.1056/NEJMoa052256]
- 8 **Hogg K, Swedberg K, McMurray J.** Heart failure with preserved left ventricular systolic function; epidemiology, clinical characteristics, and prognosis. *J Am Coll Cardiol* 2004; **43**: 317-327 [PMID: 15013109]
- 9 **Maisel WH, Stevenson LW.** Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. *Am J Cardiol* 2003; **91**: 2D-8D [PMID: 12670636 DOI: 10.1016/S0002-9149(02)03373-8]
- 10 **De Ferrari GM, Klersy C, Ferrero P, Fantoni C, Salerno-Uriarte D, Manca L, Devecchi P, Molon G, Revera M, Curnis A, Sarzi Braga S, Accardi F, Salerno-Uriarte JA.** Atrial fibrillation in heart failure patients: prevalence in daily practice and effect on the severity of symptoms. Data from the ALPHA study registry. *Eur J Heart Fail* 2007; **9**: 502-509 [PMID: 17174599 DOI: 10.1016/j.ejheart.2006.10.021]
- 11 **Anter E, Jessup M, Callans DJ.** Atrial fibrillation and heart failure: treatment considerations for a dual epidemic. *Circulation* 2009; **119**: 2516-2525 [PMID: 19433768 DOI: 10.1161/CIRCULATIONAHA.108.821306]
- 12 **Clark DM, Plumb VJ, Epstein AE, Kay GN.** Hemodynamic effects of an irregular sequence of ventricular cycle lengths during atrial fibrillation. *J Am Coll Cardiol* 1997; **30**: 1039-1045 [PMID: 9316536 DOI: 10.1016/S0735-1097(97)00254-4]
- 13 **Pozzoli M, Cioffi G, Traversi E, Pinna GD, Cobelli F, Tavazzi L.** Predictors of primary atrial fibrillation and concomitant clinical and hemodynamic changes in patients with chronic heart failure: a prospective study in 344 patients with baseline sinus rhythm. *J Am Coll Cardiol* 1998; **32**: 197-204 [PMID: 9669270 DOI: 10.1016/S0735-1097(98)00221-6]
- 14 **Lubitz SA, Benjamin EJ, Ellinor PT.** Atrial fibrillation in congestive heart failure. *Heart Fail Clin* 2010; **6**: 187-200 [PMID: 20347787 DOI: 10.1016/j.hfc.2009.11.001]
- 15 **Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Mather DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB.** Executive summary: heart disease and stroke statistics—2012 update: a report from the American Heart Association. *Circulation* 2012; **125**: 188-197 [PMID: 22215894 DOI: 10.1161/CIR.0b013e3182456d46]
- 16 **McMurray JJ, Petrie MC, Murdoch DR, Davie AP.** Clinical epidemiology of heart failure: public and private health burden. *Eur Heart J* 1998; **19** Suppl P: P9-P16 [PMID: 9886707]
- 17 **Bleumink GS, Knetsch AM, Sturkenboom MC, Straus SM, Hofman A, Deckers JW, Witteman JC, Stricker BH.** Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. *Eur Heart J* 2004; **25**: 1614-1619 [PMID: 15351160 DOI: 10.1016/j.ehj.2004.06.038]
- 18 **Kannel WB, Benjamin EJ.** Status of the epidemiology of atrial fibrillation. *Med Clin North Am* 2008; **92**: 17-40, ix [PMID: 18060995 DOI: 10.1016/j.mcna.2007.09.002]
- 19 **Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE.** 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* 2001; **285**: 2370-2375 [PMID: 11343485 DOI: 10.1001/jama.285.18.2370]
- 20 **Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, Stijnen T, Lip GY, Witteman JC.** Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J* 2006; **27**: 949-953 [PMID:

- 16527828 DOI: 10.1093/eurheartj/ehi825]
- 21 **Lloyd-Jones DM**, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ, Levy D. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. *Circulation* 2002; **106**: 3068-3072 [PMID: 12473553 DOI: 10.1161/01.CIR.0000039105.49749.6F]
 - 22 **Magnani JW**, Rienstra M, Lin H, Sinner MF, Lubitz SA, McManus DD, Dupuis J, Ellinor PT, Benjamin EJ. Atrial fibrillation: current knowledge and future directions in epidemiology and genomics. *Circulation* 2011; **124**: 1982-1993 [PMID: 22042927 DOI: 10.1161/CIRCULATIONAHA.111.039677]
 - 23 **Mountantonakis SE**, Grau-Sepulveda MV, Bhatt DL, Hernandez AF, Peterson ED, Fonarow GC. Presence of atrial fibrillation is independently associated with adverse outcomes in patients hospitalized with heart failure: an analysis of get with the guidelines-heart failure. *Circ Heart Fail* 2012; **5**: 191-201 [PMID: 22361078 DOI: 10.1161/CIRCHEARTFAILURE.111.965681]
 - 24 **Mentz RJ**, Chung MJ, Gheorghiu M, Pang PS, Kwasny MJ, Ambrosy AP, Vaduganathan M, O'Connor CM, Swedberg K, Zannad F, Konstam MA, Maggioni AP. Atrial fibrillation or flutter on initial electrocardiogram is associated with worse outcomes in patients admitted for worsening heart failure with reduced ejection fraction: findings from the EVEREST Trial. *Am Heart J* 2012; **164**: 884-92.e2 [PMID: 23194489 DOI: 10.1016/j.ahj.2012.09.011]
 - 25 **Dries DL**, Exner DV, Gersh BJ, Domanski MJ, Waclawiw MA, Stevenson LW. 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**: 695-703 [PMID: 9741514 DOI: 10.1016/S0735-1097(98)00297-6]
 - 26 **Olsson LG**, Swedberg K, Ducharme A, Granger CB, Michelson EL, McMurray JJ, Puu M, Yusuf S, Pfeffer MA. 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**: 1997-2004 [PMID: 16697316 DOI: 10.1016/j.jacc.2006.01.060]
 - 27 **Mamas MA**, Caldwell JC, Chacko S, Garratt CJ, Fath-Ordoubadi F, Neyses L. A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure. *Eur J Heart Fail* 2009; **11**: 676-683 [PMID: 19553398 DOI: 10.1093/eurjhf/hfp085]
 - 28 **Ahmed A**, Thornton P, Perry GJ, Allman RM, DeLong JF. Impact of atrial fibrillation on mortality and readmission in older adults hospitalized with heart failure. *Eur J Heart Fail* 2004; **6**: 421-426 [PMID: 15182766 DOI: 10.1016/j.ejheart.2003.11.011]
 - 29 **Caldwell JC**, Contractor H, Petkar S, Ali R, Clarke B, Garratt CJ, Neyses L, Mamas MA. Atrial fibrillation is under-recognized in chronic heart failure: insights from a heart failure cohort treated with cardiac resynchronization therapy. *Europace* 2009; **11**: 1295-1300 [PMID: 19648586 DOI: 10.1093/europace/eup201]
 - 30 **Køber L**, Swedberg K, McMurray JJ, Pfeffer MA, Velazquez EJ, Diaz R, Maggioni AP, Mareev V, Opolski G, Van de Werf F, Zannad F, Ertl G, Solomon SD, Zelenkofske S, Rouleau JL, Leimberger JD, Califf RM. Previously known and newly diagnosed atrial fibrillation: a major risk indicator after a myocardial infarction complicated by heart failure or left ventricular dysfunction. *Eur J Heart Fail* 2006; **8**: 591-598 [PMID: 16507350 DOI: 10.1016/j.ejheart.2005.11.007]
 - 31 **Pedersen OD**, Søndergaard P, Nielsen T, Nielsen SJ, Nielsen ES, Falstie-Jensen N, Nielsen I, Køber L, Burchardt H, Seibæk M, Torp-Pedersen C. Atrial fibrillation, ischaemic heart disease, and the risk of death in patients with heart failure. *Eur Heart J* 2006; **27**: 2866-2870 [PMID: 17101637 DOI: 10.1093/eurheartj/ehl359]
 - 32 **Range FT**, Schäfers M, Acil T, Schäfers KP, Kies P, Paul M, Hermann S, Brisse B, Breithardt G, Schober O, Wichter T. Impaired myocardial perfusion and perfusion reserve associated with increased coronary resistance in persistent idiopathic atrial fibrillation. *Eur Heart J* 2007; **28**: 2223-2230 [PMID: 17604290 DOI: 10.1093/eurheartj/ehm246]
 - 33 **Raunso J**, Pedersen OD, Dominguez H, Hansen ML, Møller JE, Kjaergaard J, Hassager C, Torp-Pedersen C, Køber L. 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**: 692-697 [PMID: 20403817 DOI: 10.1093/eurjhf/hfq052]
 - 34 **Chamberlain AM**, Redfield MM, Alonso A, Weston SA, Roger VL. Atrial fibrillation and mortality in heart failure: a community study. *Circ Heart Fail* 2011; **4**: 740-746 [PMID: 21920917 DOI: 10.1161/CIRCHEARTFAILURE.111.962688]
 - 35 **Smit MD**, Moes ML, Maass AH, Achekar ID, Van Geel PP, Hillege HL, van Veldhuisen DJ, Van Gelder IC. The importance of whether atrial fibrillation or heart failure develops first. *Eur J Heart Fail* 2012; **14**: 1030-1040 [PMID: 22733981 DOI: 10.1093/eurjhf/hfs097]
 - 36 **McManus DD**, Saczynski JS, Lessard D, Kinno M, Pidikiti R, Esa N, Harrington J, Goldberg RJ. Recent trends in the incidence, treatment, and prognosis of patients with heart failure and atrial fibrillation (the Worcester Heart Failure Study). *Am J Cardiol* 2013; **111**: 1460-1465 [PMID: 23465093 DOI: 10.1016/j.amjcard.2013.01.298]
 - 37 **Mahoney P**, Kimmel S, DeNofrio D, Wahl P, Loh E. 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**: 1544-1547 [PMID: 10363868 DOI: 10.1016/S0002-9149(99)00144-7]
 - 38 **Swedberg K**, Olsson LG, Charlesworth A, Cleland J, Hanrath P, Komajda M, Metra M, Torp-Pedersen C, Poole-Wilson P. Prognostic relevance of atrial fibrillation in patients with chronic heart failure on long-term treatment with beta-blockers: results from COMET. *Eur Heart J* 2005; **26**: 1303-1308 [PMID: 15767288 DOI: 10.1093/eurheartj/ehi166]
 - 39 **Wang TJ**, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation* 2003; **107**: 2920-2925 [PMID: 12771006 DOI: 10.1161/01.CIR.0000072767.89944.6E]
 - 40 **Nieuwlaet R**, Eurlings LW, Cleland JG, Cobbe SM, Vardas PE, Capucci A, López-Sendón JL, Meeder JG, Pinto YM, Crijns HJ. Atrial fibrillation and heart failure in cardiology practice: reciprocal impact and combined management from the perspective of atrial fibrillation: results of the Euro Heart Survey on atrial fibrillation. *J Am Coll Cardiol* 2009; **53**: 1690-1698 [PMID: 19406345 DOI: 10.1016/j.jacc.2009.01.055]
 - 41 **McMurray JJ**, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012; **33**: 1787-1847 [PMID: 22611136 DOI: 10.1093/eurheartj/ehs104]
 - 42 **Joglar JA**, Acosta AP, Shusterman NH, Ramaswamy K, Kowal RC, Barbera SJ, Hamdan MH, Page RL. Effect of carvedilol on survival and hemodynamics in patients with atrial fibrillation and left ventricular dysfunction: retrospec-

- tive analysis of the US Carvedilol Heart Failure Trials Program. *Am Heart J* 2001; **142**: 498-501 [PMID: 11526364 DOI: 10.1067/mhj.2001.117318]
- 43 The effect of digoxin on mortality and morbidity in patients with heart failure. The Digitalis Investigation Group. *N Engl J Med* 1997; **336**: 525-533 [PMID: 9036306 DOI: 10.1056/NEJM199702203360801]
- 44 **Whitbeck MG**, Charnigo RJ, Khairy P, Ziada K, Bailey AL, Zegarra MM, Shah J, Morales G, Macaulay T, Sorrell VL, Campbell CL, Gurley J, Anaya P, Nasr H, Bai R, Di Biase L, Booth DC, Jondeau G, Natale A, Roy D, Smyth S, Moliterno DJ, Elayi CS. Increased mortality among patients taking digoxin--analysis from the AFFIRM study. *Eur Heart J* 2013; **34**: 1481-1488 [PMID: 23186806 DOI: 10.1093/eurheartj/ehs348]
- 45 **Gheorghiade M**, Fonarow GC, van Veldhuisen DJ, Cleland JG, Butler J, Epstein AE, Patel K, Aban IB, Aronow WS, Anker SD, Ahmed A. Lack of evidence of increased mortality among patients with atrial fibrillation taking digoxin: findings from post hoc propensity-matched analysis of the AFFIRM trial. *Eur Heart J* 2013; **34**: 1489-1497 [PMID: 23592708 DOI: 10.1093/eurheartj/ehs120]
- 46 **Heywood JT**. Calcium channel blockers for heart rate control in atrial fibrillation complicated by congestive heart failure. *Can J Cardiol* 1995; **11**: 823-826 [PMID: 7585281]
- 47 **Setaro JF**, Zaret BL, Schulman DS, Black HR, Soufer R. Usefulness of verapamil for congestive heart failure associated with abnormal left ventricular diastolic filling and normal left ventricular systolic performance. *Am J Cardiol* 1990; **66**: 981-986 [PMID: 2220622 DOI: 10.1016/0002-9149(90)90937-V]
- 48 **Goldstein RE**, Boccuzzi SJ, Cruess D, Nattel S. Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. The Adverse Experience Committee; and the Multicenter Diltiazem Postinfarction Research Group. *Circulation* 1991; **83**: 52-60 [PMID: 1984898 DOI: 10.1161/01.CIR.83.1.52]
- 49 **Van Gelder IC**, Groeneweld HF, Crijns HJ, Tuininga YS, Tijssen JG, Alings AM, Hillege HL, Bergsma-Kadijk JA, Cornel JH, Kamp O, Tukkij R, Bosker HA, Van Veldhuisen DJ, Van den Berg MP. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med* 2010; **362**: 1363-1373 [PMID: 20231232 DOI: 10.1056/NEJMoa1001337]
- 50 **Van Gelder IC**, Smit MD, Alings M, Crijns HJ. Upstream therapy in patients with early atrial fibrillation: The relevance of the Routine versus Aggressive upstream rhythm Control for prevention of Early atrial fibrillation in heart failure (RACE 3) study. *Neth Heart J* 2010; **18**: 522-523 [PMID: 21113375 DOI: 10.1007/s12471-010-0827-9]
- 51 **Deedwania PC**, Singh BN, Ellenbogen K, Fisher S, Fletcher R, Singh SN. Spontaneous conversion and maintenance of sinus rhythm by amiodarone in patients with heart failure and atrial fibrillation: observations from the veterans affairs congestive heart failure survival trial of antiarrhythmic therapy (CHF-STAT). The Department of Veterans Affairs CHF-STAT Investigators. *Circulation* 1998; **98**: 2574-2579 [PMID: 9843465 DOI: 10.1161/01.CIR.98.23.2574]
- 52 **Roy D**, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, Bourassa MG, Arnold JM, Buxton AE, Camm AJ, Connolly SJ, Dubuc M, Ducharme A, Guerra PG, Hohnloser SH, Lambert J, Le Heuzey JY, O'Hara G, Pedersen OD, Rouleau JL, Singh BN, Stevenson LW, Stevenson WG, Thibault B, Waldo AL. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med* 2008; **358**: 2667-2677 [PMID: 18565859 DOI: 10.1056/NEJMoa0708789]
- 53 **Pedersen OD**, Bagger H, Keller N, Marchant B, Køber L, Torp-Pedersen C. Efficacy of dofetilide in the treatment of atrial fibrillation-flutter in patients with reduced left ventricular function: a Danish investigations of arrhythmia and mortality on dofetilide (diamond) substudy. *Circulation* 2001; **104**: 292-296 [PMID: 11457747 DOI: 10.1161/01.CIR.104.3.292]
- 54 **Hohnloser SH**, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C, Connolly SJ. Dronedarone in patients with congestive heart failure: insights from ATHENA. *Eur Heart J* 2010; **31**: 1717-1721 [PMID: 20436046 DOI: 10.1093/eurheartj/ehq113]
- 55 **Køber L**, Torp-Pedersen C, McMurray JJ, Gøtzsche O, Lévy S, Crijns H, Amlie J, Carlsen J. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 2008; **358**: 2678-2687 [PMID: 18565860 DOI: 10.1056/NEJMoa0800456]
- 56 **Wyse DG**, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002; **347**: 1825-1833 [PMID: 12466506 DOI: 10.1056/NEJMoa021328]
- 57 **Van Gelder IC**, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, Said SA, Darmanata JI, Timmermans AJ, Tijssen JG, Crijns HJ. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* 2002; **347**: 1834-1840 [PMID: 12466507 DOI: 10.1056/NEJMoa021375]
- 58 **Hohnloser SH**, Kuck KH, Lillenthal J. Rhythm or rate control in atrial fibrillation--Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial. *Lancet* 2000; **356**: 1789-1794 [PMID: 11117910 DOI: 10.1016/S0140-6736(00)03230-X]
- 59 **Carlsson J**, Miketic S, Windeler J, Cuneo A, Haun S, Micus S, Walter S, Tebbe U. 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**: 1690-1696 [PMID: 12767648 DOI: 10.1016/S0735-1097(03)00332-2]
- 60 **Guglin M**, Chen R, Curtis AB. Sinus rhythm is associated with fewer heart failure symptoms: insights from the AFFIRM trial. *Heart Rhythm* 2010; **7**: 596-601 [PMID: 20159046]
- 61 **Caldeira D**, David C, Sampaio C. Rate vs rhythm control in patients with atrial fibrillation and heart failure: a systematic review and meta-analysis of randomised controlled trials. *Eur J Intern Med* 2011; **22**: 448-455 [PMID: 21925051 DOI: 10.1016/j.ejim.2011.05.001]
- 62 **Wasmer K**, Eckardt L. Management of atrial fibrillation around the world: a comparison of current ACCF/AHA/HRS, CCS, and ESC guidelines. *Europace* 2011; **13**: 1368-1374 [PMID: 21712281]
- 63 **McNamara RL**, Tamariz LJ, Segal JB, Bass EB. Management of atrial fibrillation: review of the evidence for the role of pharmacologic therapy, electrical cardioversion, and echocardiography. *Ann Intern Med* 2003; **139**: 1018-1033 [PMID: 14678922 DOI: 10.7326/0003-4819-139-12-200312160-00012]
- 64 **Hart RG**, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007; **146**: 857-867 [PMID: 17577005 DOI: 10.7326/0003-4819-146-12-200706190-00007]
- 65 **Tzeis S**, Andrikopoulos G. Novel anticoagulants for atrial fibrillation: a critical appraisal. *Angiology* 2012; **63**: 164-170 [PMID: 22007032 DOI: 10.1177/0003319711422808]
- 66 **Connolly SJ**, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; **361**: 1139-1151 [PMID: 19717844 DOI: 10.1056/NEJMoa0905561]
- 67 **Camm AJ**, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohnloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten

- FH. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace* 2010; **12**: 1360-1420 [PMID: 20876603]
- 68 **Anderson JL**, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Wann LS, Curtis AB, Ellenbogen KA, Estes NA, Ezekowitz MD, Jackman WM, January CT, Lowe JE, Page RL, Slotwiner DJ, Stevenson WG, Tracy CM, Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Le Heuzey JY, Kay GN, Olsson SB, Prystowsky EN, Tamargo JL, Wann S. Management of patients with atrial fibrillation (compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS recommendations): a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; **61**: 1935-1944 [PMID: 23558044 DOI: 10.1161/CIR.0b013e318290826d]
- 69 **Cairns JA**, Connolly S, McMurray S, Stephenson M, Talajic M. Canadian Cardiovascular Society atrial fibrillation guidelines 2010: prevention of stroke and systemic thromboembolism in atrial fibrillation and flutter. *Can J Cardiol* 2011; **27**: 74-90 [PMID: 21329865 DOI: 10.1016/j.cjca.2010.11.007]
- 70 **Patel MR**, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; **365**: 883-891 [PMID: 21830957 DOI: 10.1056/NEJMoa1009638]
- 71 **Lopes RD**, Alexander JH, Al-Khatib SM, Ansell J, Diaz R, Easton JD, Gersh BJ, Granger CB, Hanna M, Horowitz J, Hylek EM, McMurray JJ, Verheugt FW, Wallentin L. Apixaban for reduction in stroke and other Thromboembolic events in atrial fibrillation (ARISTOTLE) trial: design and rationale. *Am Heart J* 2010; **159**: 331-339 [PMID: 20211292 DOI: 10.1016/j.ahj.2009.07.035]
- 72 **Kurita T**, Motoki K, Yasuoka R, Hirota T, Akaiwa Y, Kotake Y, Miyazaki S. Rhythm control should be better for the management of patients with atrial fibrillation and heart failure—rhythm control vs. rate control: which is better in the management of atrial fibrillation? (Rhythm-side). *Circ J* 2011; **75**: 979-985 [PMID: 21415549]
- 73 **Leon AR**, Greenberg JM, Kanuru N, Baker CM, Mera FV, Smith AL, Langberg JJ, DeLurgio DB. Cardiac resynchronization in patients with congestive heart failure and chronic atrial fibrillation: effect of upgrading to biventricular pacing after chronic right ventricular pacing. *J Am Coll Cardiol* 2002; **39**: 1258-1263 [PMID: 11955841 DOI: 10.1016/S0735-1097(02)01779-5]
- 74 **Valls-Bertault V**, Fatemi M, Gilard M, Pennec PY, Etienne Y, Blanc JJ. Assessment of upgrading to biventricular pacing in patients with right ventricular pacing and congestive heart failure after atrioventricular junctional ablation for chronic atrial fibrillation. *Europace* 2004; **6**: 438-443 [PMID: 15294269]
- 75 **Wilton SB**, Leung AA, Ghali WA, Faris P, Exner DV. Outcomes of cardiac resynchronization therapy in patients with versus those without atrial fibrillation: a systematic review and meta-analysis. *Heart Rhythm* 2011; **8**: 1088-1094 [PMID: 21338711 DOI: 10.1016/j.hrthm.2011.02.014]
- 76 **Linde C**, Braunschweig F, Gadler F, Bailleur C, Daubert JC. Long-term improvements in quality of life by biventricular pacing in patients with chronic heart failure: results from the Multisite Stimulation in Cardiomyopathy study (MUSTIC). *Am J Cardiol* 2003; **91**: 1090-1095 [PMID: 12714152 DOI: 10.1016/S0002-9149(03)00154-1]
- 77 **Brignole M**, Gammage M, Puggioni E, Alboni P, Raviele A, Sutton R, Vardas P, Bongioni MG, Bergfeldt L, Menozzi C, Musso G. Comparative assessment of right, left, and biventricular pacing in patients with permanent atrial fibrillation. *Eur Heart J* 2005; **26**: 712-722 [PMID: 15618036 DOI: 10.1093/eurheartj/ehi069]
- 78 **Luedorff G**, Grove R, Kowalski M, Wolff E, Thale J, Kranig W. Impact of chronic atrial fibrillation in patients with severe heart failure and indication for CRT: data of two registries with 711 patients (1999-2006 and 2007-6/2008). *Herzschrittmacherther Elektrophysiol* 2011; **22**: 226-232 [PMID: 22160274 DOI: 10.1007/s00399-011-0155-9]
- 79 **Hsu LF**, Jaïs P, Sanders P, Garrigue S, Hocini M, Sacher F, Takahashi Y, Rotter M, Pasquié JL, Scavée C, Bordachar P, Clémenty J, Haïssaguerre M. Catheter ablation for atrial fibrillation in congestive heart failure. *N Engl J Med* 2004; **351**: 2373-2383 [PMID: 15575053 DOI: 10.1056/NEJMoa041018]
- 80 **Tondo C**, Mantica M, Russo G, Avella A, De Luca L, Pappalardo A, Fagundes RL, Picchio E, Laurenzi F, Piazza V, Bisceglia I. Pulmonary vein vestibule ablation for the control of atrial fibrillation in patients with impaired left ventricular function. *Pacing Clin Electrophysiol* 2006; **29**: 962-970 [PMID: 16981920 DOI: 10.1111/j.1540-8159.2006.00471.x]
- 81 **Chen MS**, Marrouche NF, Khaykin Y, Gillinov AM, Wazni O, Martin DO, Rossillo A, Verma A, Cummings J, Erciyes D, Saad E, Bhargava M, Bash D, Schweikert R, Burkhardt D, Williams-Andrews M, Perez-Lugones A, Abdul-Karim A, Saliba W, Natale A. Pulmonary vein isolation for the treatment of atrial fibrillation in patients with impaired systolic function. *J Am Coll Cardiol* 2004; **43**: 1004-1009 [PMID: 15028358 DOI: 10.1016/j.jacc.2003.09.056]
- 82 **Gentlesk PJ**, Sauer WH, Gerstenfeld EP, Lin D, Dixit S, Zado E, Callans D, Marchlinski FE. Reversal of left ventricular dysfunction following ablation of atrial fibrillation. *J Cardiovasc Electrophysiol* 2007; **18**: 9-14 [PMID: 17081210 DOI: 10.1111/j.1540-8167.2006.00653.x]
- 83 **Khan MN**, Jaïs P, Cummings J, Di Biase L, Sanders P, Martin DO, Kautzner J, Hao S, Themistoclakis S, Fanelli R, Potenza D, Massaro R, Wazni O, Schweikert R, Saliba W, Wang P, Al-Ahmad A, Beheiry S, Santarelli P, Starling RC, Dello Russo A, Pelargonio G, Brachmann J, Schibgilla V, Bonso A, Casella M, Raviele A, Haïssaguerre M, Natale A. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. *N Engl J Med* 2008; **359**: 1778-1785 [PMID: 18946063 DOI: 10.1056/NEJMoa0708234]
- 84 **MacDonald MR**, Connelly DT, Hawkins NM, Steedman T, Payne J, Shaw M, Denvir M, Bhagra S, Small S, Martin W, McMurray JJ, Petrie MC. Radiofrequency ablation for persistent atrial fibrillation in patients with advanced heart failure and severe left ventricular systolic dysfunction: a randomised controlled trial. *Heart* 2011; **97**: 740-747 [PMID: 21051458 DOI: 10.1136/hrt.2010.207340]
- 85 **Dagres N**, Varounis C, Gaspar T, Piorkowski C, Eitel C, Ilidromitis EK, Lekakis JP, Flevari P, Simeonidou E, Rallidis LS, Tsougos E, Hindricks G, Sommer P, Anastasiou-Nana M. Catheter ablation for atrial fibrillation in patients with left ventricular systolic dysfunction. A systematic review and meta-analysis. *J Card Fail* 2011; **17**: 964-970 [PMID: 22041335 DOI: 10.1016/j.cardfail.2011.07.009]
- 86 **Khargi K**, Hutten BA, Lemke B, Deneke T. Surgical treatment of atrial fibrillation; a systematic review. *Eur J Cardiothorac Surg* 2005; **27**: 258-265 [PMID: 15691679]
- 87 **Ad N**, Henry L, Hunt S. The impact of surgical ablation in patients with low ejection fraction, heart failure, and atrial fibrillation. *Eur J Cardiothorac Surg* 2011; **40**: 70-76 [PMID: 21169029 DOI: 10.1016/j.ejcts.2010.11.016]
- 88 **Wallick DW**, Zhang Y, Tabata T, Zhuang S, Mowrey KA, Watanabe J, Greenberg NL, Grimm RA, Mazgalev TN. Selective AV nodal vagal stimulation improves hemodynamics during acute atrial fibrillation in dogs. *Am J Physiol Heart Circ Physiol* 2001; **281**: H1490-H1497 [PMID: 11557537]
- 89 **Zhang Y**, Yamada H, Bibevski S, Zhuang S, Mowrey KA, Wallick DW, Oh S, Mazgalev TN. Chronic atrioventricular nodal vagal stimulation: first evidence for long-term ventricular rate control in canine atrial fibrillation model. *Circu-*

- lation 2005; **112**: 2904-2911 [PMID: 16260638]
- 90 **Schauerte P**, Mischke K, Plisiene J, Waldmann M, Zarse M, Stellbrink C, Schimpf T, Knackstedt C, Sinha A, Hanrath P. Catheter stimulation of cardiac parasympathetic nerves in humans: a novel approach to the cardiac autonomic nervous system. *Circulation* 2001; **104**: 2430-2435 [PMID: 11705820 DOI: 10.1161/hc4501.099307]
 - 91 **Dobrev D**, Nattel S. New antiarrhythmic drugs for treatment of atrial fibrillation. *Lancet* 2010; **375**: 1212-1223 [PMID: 20334907 DOI: 10.1016/S0140-6736(10)60096-7]
 - 92 **Tian D**, Frishman WH. Vernakalant: a new drug to treat patients with acute onset atrial fibrillation. *Cardiol Rev* 2011; **19**: 41-44 [PMID: 21135602]
 - 93 **Camm AJ**, Capucci A, Hohnloser SH, Torp-Pedersen C, Van Gelder IC, Mangal B, Beatch G. A randomized active-controlled study comparing the efficacy and safety of vernakalant to amiodarone in recent-onset atrial fibrillation. *J Am Coll Cardiol* 2011; **57**: 313-321 [PMID: 21232669 DOI: 10.1016/j.jacc.2010.07.046]
 - 94 **Blackshear JL**, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg* 1996; **61**: 755-759 [PMID: 8572814 DOI: 10.1016/0003-4975(95)00887-X]
 - 95 **Lewalter T**, Ibrahim R, Albers B, Camm AJ. An update and current expert opinions on percutaneous left atrial appendage occlusion for stroke prevention in atrial fibrillation. *Europace* 2013; **15**: 652-656 [PMID: 23625943 DOI: 10.1093/europace/eut043]
 - 96 **Holmes DR**, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sick P. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. *Lancet* 2009; **374**: 534-542 [PMID: 19683639 DOI: 10.1016/S0140-6736(09)61343-X]
 - 97 **Reddy VY**, Holmes D, Doshi SK, Neuzil P, Kar S. Safety of percutaneous left atrial appendage closure: results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT AF) clinical trial and the Continued Access Registry. *Circulation* 2011; **123**: 417-424 [PMID: 21242484 DOI: 10.1161/CIRCULATIONAHA.110.976449]
 - 98 **Swaans MJ**, Post MC, Rensing BJ, Boersma LV. Ablation for atrial fibrillation in combination with left atrial appendage closure: first results of a feasibility study. *J Am Heart Assoc* 2012; **1**: e002212 [PMID: 23316289 DOI: 10.1161/JAHA.112.002212]
 - 99 **Patel TK**, Yancy CW, Knight BP. Left atrial appendage exclusion for stroke prevention in atrial fibrillation. *Cardiol Res Pract* 2012; **2012**: 610827 [PMID: 23119222]
 - 100 **Ellinor PT**, Lunetta KL, Albert CM, Glazer NL, Ritchie MD, Smith AV, Arking DE, Müller-Nurasyid M, Krijthe BP, Lubitz SA, Bis JC, Chung MK, Dörr M, Ozaki K, Roberts JD, Smith JG, Pfeufer A, Sinner MF, Lohman K, Ding J, Smith NL, Smith JD, Rienstra M, Rice KM, Van Wagener DR, Magnani JW, Wakili R, Clauss S, Rottler JI, Steinbeck G, Launer LJ, Davies RW, Borkovich M, Harris TB, Lin H, Völker U, Völzke H, Milan DJ, Hofman A, Boerwinkle E, Chen LY, Soliman EZ, Voight BF, Li G, Chakravarti A, Kubo M, Tedrow UB, Rose LM, Ridker PM, Conen D, Tsunoda T, Furukawa T, Sotoodehnia N, Xu S, Kamatani N, Levy D, Nakamura Y, Parvez B, Mahida S, Furie KL, Rosand J, Muhammad R, Psaty BM, Meitinger T, Perz S, Wichmann HE, Wittmann JC, Kao WH, Kathiresan S, Roden DM, Uitterlinden AG, Rivadeneira F, McKnight B, Sjögren M, Newman AB, Liu Y, Gollob MH, Melander O, Tanaka T, Stricker BH, Felix SB, Alonso A, Darbar D, Barnard J, Chasman DI, Heckbert SR, Benjamin EJ, Gudnason V, Kääb S. Meta-analysis identifies six new susceptibility loci for atrial fibrillation. *Nat Genet* 2012; **44**: 670-675 [PMID: 22544366]
 - 101 **Smith JG**, Melander O, Sjögren M, Hedblad B, Engström G, Newton-Cheh C, Platonov PG. Genetic polymorphisms confer risk of atrial fibrillation in patients with heart failure: a population-based study. *Eur J Heart Fail* 2013; **15**: 250-257 [PMID: 23132824 DOI: 10.1093/eurjhf/hfs176]
 - 102 **Nascimento BC**, Pereira SB, Ribeiro GS, Mesquita ET. Beta1-adrenergic receptor polymorphisms associated with atrial fibrillation in systolic heart failure. *Arq Bras Cardiol* 2012; **98**: 384-389 [PMID: 22499333 DOI: 10.1590/S0066-782X2012005000037]
 - 103 **Liu WN**, Fu KL, Gao HY, Shang YY, Wang ZH, Jiang GH, Zhang Y, Zhang W, Zhong M. β 1 adrenergic receptor polymorphisms and heart failure: a meta-analysis on susceptibility, response to β -blocker therapy and prognosis. *PLoS One* 2012; **7**: e37659 [PMID: 22815685 DOI: 10.1371/journal.pone.0037659]
 - 104 **Savelieva I**, Camm AJ. Polyunsaturated fatty acids for prevention of atrial fibrillation: a 'fishy' story. *Europace* 2011; **13**: 149-152 [PMID: 21252194]
 - 105 **Savelieva I**, Camm AJ. Statins and atrial fibrillation: do we need a further study? *Expert Rev Cardiovasc Ther* 2011; **9**: 801-804 [PMID: 21809959 DOI: 10.1586/erc.11.96]
 - 106 **Savelieva I**, Kakouros N, Kourliouros A, Camm AJ. Upstream therapies for management of atrial fibrillation: review of clinical evidence and implications for European Society of Cardiology guidelines. Part I: primary prevention. *Europace* 2011; **13**: 308-328 [PMID: 21345926]
 - 107 **Savelieva I**, Kakouros N, Kourliouros A, Camm AJ. Upstream therapies for management of atrial fibrillation: review of clinical evidence and implications for European Society of Cardiology guidelines. Part II: secondary prevention. *Europace* 2011; **13**: 610-625 [PMID: 21515595]
 - 108 **Bhuriya R**, Singh M, Sethi A, Molnar J, Bahekar A, Singh PP, Khosla S, Arora R. Prevention of recurrent atrial fibrillation with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers: a systematic review and meta-analysis of randomized trials. *J Cardiovasc Pharmacol Ther* 2011; **16**: 178-184 [PMID: 21285399 DOI: 10.1177/1074248410389045]
 - 109 **Carson PE**, Johnson GR, Dunkman WB, Fletcher RD, Farrell L, Cohn JN. The influence of atrial fibrillation on prognosis in mild to moderate heart failure. The V-HeFT Studies. The V-HeFT VA Cooperative Studies Group. *Circulation* 1993; **87**: VI102-VI110 [PMID: 8500233]
 - 110 **Mathew J**, Hunsberger S, Fleg J, Mc Sherry F, Williford W, Yusuf S. Incidence, predictive factors, and prognostic significance of supraventricular tachyarrhythmias in congestive heart failure. *Chest* 2000; **118**: 914-922 [PMID: 11035656 DOI: 10.1378/chest.118.4.914]
 - 111 **Crijns HJ**, Tjeerdsma G, de Kam PJ, Boomsma F, van Gelder IC, van den Berg MP, van Veldhuisen DJ. Prognostic value of the presence and development of atrial fibrillation in patients with advanced chronic heart failure. *Eur Heart J* 2000; **21**: 1238-1245 [PMID: 10924313 DOI: 10.1053/eurh.1999.2107]
 - 112 **Pedersen OD**, Brendorp B, Køber L, Torp-Pedersen C. Prevalence, prognostic significance, and treatment of atrial fibrillation in congestive heart failure with particular reference to the DIAMOND-CHF study. *Congest Heart Fail* 2003; **9**: 333-340 [PMID: 14688506 DOI: 10.1111/j.1527-5299.2003.01238.x]
 - 113 **Middlekauff HR**, Stevenson WG, Stevenson LW. Prognostic significance of atrial fibrillation in advanced heart failure. A study of 390 patients. *Circulation* 1991; **84**: 40-48 [PMID: 2060110 DOI: 10.1161/01.CIR.84.1.40]
 - 114 **Stevenson WG**, Stevenson LW, Middlekauff HR, Fonarow GC, Hamilton MA, Woo MA, Saxon LA, Natterson PD, Steimle A, Walden JA, Tillisch JH. Improving survival for patients with atrial fibrillation and advanced heart failure. *J Am Coll Cardiol* 1996; **28**: 1458-1463 [PMID: 8917258 DOI: 10.1016/S0735-1097(96)00358-0]
 - 115 **Wojtkowska I**, Sobkowicz B, Musiał WJ, Kozuch M. Persistent atrial fibrillation as a prognostic factor of outcome

- in patients with advanced heart failure. *Kardiol Pol* 2006; **64**: 777-783; discussion 784-785 [PMID: 16981052]
- 116 **Corell P**, Gustafsson F, Schou M, Markenvard J, Nielsen T, Hildebrandt P. Prevalence and prognostic significance of atrial fibrillation in outpatients with heart failure due to left ventricular systolic dysfunction. *Eur J Heart Fail* 2007; **9**: 258-265 [PMID: 17027330 DOI: 10.1016/j.ejheart.2006.08.004]
- 117 **Pai RG**, Varadarajan P. Prognostic significance of atrial fibrillation is a function of left ventricular ejection fraction. *Clin Cardiol* 2007; **30**: 349-354 [PMID: 17674374 DOI: 10.1002/clc.20107]
- 118 **Rusinaru D**, Leborgne L, Peltier M, Tribouilloy C. Effect of atrial fibrillation on long-term survival in patients hospitalized for heart failure with preserved ejection fraction. *Eur J Heart Fail* 2008; **10**: 566-572 [PMID: 18456551 DOI: 10.1016/j.ejheart.2008.04.002]
- 119 **Hamaguchi S**, Yokoshiki H, Kinugawa S, Tsuchihashi-Makaya M, Yokota T, Takeshita A, Tsutsui H. Effects of atrial fibrillation on long-term outcomes in patients hospitalized for heart failure in Japan: a report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). *Circ J* 2009; **73**: 2084-2090 [PMID: 19755750]
- 120 **Shotan A**, Garty M, Blondhein DS, Meisel SR, Lewis BS, Shochat M, Grossman E, Porath A, Boyko V, Zimlichman R, Caspi A, Gottlieb S. Atrial fibrillation and long-term prognosis in patients hospitalized for heart failure: results from heart failure survey in Israel (HFSIS). *Eur Heart J* 2010; **31**: 309-317 [PMID: 19837682 DOI: 10.1093/eurheartj/ehp422]

P- Reviewers Aronow WS, Chawla M, Di Bella G, Ng T
S- Editor Zhai HH **L- Editor** A **E- Editor** Lu YJ

