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CONSENSUS DOCUMENT

Hypertension and cardiac arrhythmias: a consensus document from the European Heart Rhythm Association (EHRA) and ESC Council on Hypertension, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE)

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Hypertension is a common cardiovascular risk factor leading to heart failure (HF), coronary artery disease, stroke, peripheral artery disease and chronic renal insufficiency. Hypertensive heart disease can manifest as many cardiac arrhythmias, most commonly being atrial fibrillation (AF). Both supraventricular and ventricular arrhythmias may occur in hypertensive patients, especially in those with left

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ventricular hypertrophy (LVH) or HF. Also, some of the antihypertensive drugs commonly used to reduce blood pressure, such as thiazide diuretics, may result in electrolyte abnormalities (e.g. hypokalaemia, hypomagnesemia), further contributing to arrhythmias, whereas effective control of blood pressure may prevent the development of the arrhythmias such as AF. In recognizing this close relationship between hypertension and arrhythmias, the European Heart Rhythm Association (EHRA) and the European Society of Cardiology (ESC) Council on Hypertension convened a Task Force, with representation from the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE), with the remit to comprehensively review the available evidence to publish a joint consensus document on hypertension and cardiac arrhythmias, and to provide up-to-date consensus recommendations for use in clinical practice. The ultimate judgment regarding care of a particular patient must be made by the healthcare provider and the patient in light of all of the circumstances presented by that patient.

Keywords Hypertension • Atrial fibrillation • Arrhythmias • Left ventricular hypertrophy • EHRA consensus document

Introduction

Hypertension is a common cardiovascular risk factor and underlies many cardiovascular conditions, including heart failure (HF), coronary artery disease, and stroke, as well as chronic kidney disease. Hypertensive heart disease can manifest as various cardiac arrhythmias, most commonly being atrial fibrillation (AF). Both AF and hypertension individually contribute to an increased risk of stroke, which is further accentuated when both are present in combination. Both supraventricular arrhythmias and ventricular arrhythmias may occur in the hypertensive patients, especially in the presence of associated left ventricular hypertrophy (LVH) or HF. In addition, some of the antihypertensive drugs commonly used to reduce blood pressure, such as thiazide diuretics, may result in electrolyte abnormalities (e.g. hypokalaemia, hypomagnesemia), further contributing to arrhythmias, whereas effective control of blood pressure may prevent the development of the arrhythmias such as AF.

In recognizing this close relationship between hypertension and arrhythmias, the European Heart Rhythm Association (EHRA) and the European Society of Cardiology (ESC) Council on Hypertension convened a Task Force, with representation from the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE), with the remit to comprehensively review the available evidence to publish a Joint Consensus Document on hypertension and cardiac arrhythmias, and to provide up-to-date consensus recommendations for use in clinical practice. The ultimate judgment regarding care of a particular patient must be made by the healthcare provider and the patient in light of all of the circumstances presented by that patient.

Evidence review

Members of the Task Force were asked to perform a detailed literature review, weigh the strength of evidence for or against a particular treatment or procedure, and include estimates of expected health outcomes where data exist. Patient-specific modifiers, comorbidities, and issues of patient preference that might influence the choice of particular tests or therapies are considered, as are frequency of follow-up and cost effectiveness. In controversial areas, or with regard to issues without evidence other than usual clinical practice, a consensus was achieved by agreement of the expert panel after thorough deliberations.

This document was prepared by the Task Force with representation from EHRA, HRS, APHRS, and SOLAECE. The document was peer-reviewed by official external reviewers representing EHRA, HRS, APHRS, and SOLAECE.

Consensus statements are evidence-based, and derived primarily from published data. In contrast to guidelines, we have opted for an easier and user-friendly system of ranking using 'coloured hearts' that should allow physicians to easily assess current status of evidence and consequent guidance (*Table 1*). This EHRA grading of consensus statements does not have separate definitions of Level of Evidence. This categorization used for consensus statements (used in consensus documents) must not be considered as being directly similar to that used for official society guideline recommendations, which apply a classification (Class I–III) and level of evidence (A, B, and C) to recommendations used in official guidelines.[1]

Thus, a green heart indicates a 'should do this' consensus statement or indicated treatment or procedure, that is based on at least one randomized trial, or is supported by strong observational evidence that it is beneficial and effective. A yellow heart indicates that general agreement and/or scientific evidence favouring a 'may do this' statement or the usefulness/efficacy of a treatment or procedure. A 'yellow heart' symbol may be supported by randomized trials based on small number of patients or not widely applicable. Treatment strategies for which there has been scientific evidence that they are potentially harmful and should not be used ('do not do this') are indicated by a red heart.

Finally, this is a consensus document that includes evidence and expert opinions from several countries. The pharmacologic and non-pharmacologic antiarrhythmic approaches discussed may, therefore, include drugs that do not have the approval of governmental regulatory agencies in all countries.

Relationships with industry and other conflicts

It is EHRA/ESC policy to sponsor position papers and guidelines without commercial support, and all members volunteered their time. Thus, all members of the writing group as well as reviewers have disclosed any potential conflict of interest in detail, at the end of this document.

Table 1 Scientific rationale of recommendations*

Definitions where related to a treatment or procedure	Consensus statement instruction	Symbol
Scientific evidence that a treatment or procedure is beneficial and effective. Requires at least one randomized trial, or is supported by strong observational evidence and authors' consensus (as indicated by an asterisk).	'Should do this'	
General agreement and/or scientific evidence favour the usefulness/efficacy of a treatment or procedure. May be supported by randomized trials based on small number of patients or not widely applicable.	'May do this'	
Scientific evidence or general agreement not to use or recommend a treatment or procedure.	'Do not do this'	

*This categorization for our consensus document should not be considered as being directly similar to that used for official society guideline recommendations which apply a classification (I–III) and level of evidence (A, B, and C) to recommendations.

Pathogenesis of arrhythmias in hypertension

The occurrence of arrhythmias may have important implications on the morbidity and even mortality in hypertensive patients, ranging from supraventricular premature beats to AF, or more serious ventricular arrhythmias and sudden cardiac death (SCD).

Haemodynamic changes, neuroendocrine factors, atrial and ventricular structural remodelling (i.e. myocardial fibrosis) and a proarrhythmogenic electrophysiologic phenotype of a hypertrophied left ventricle all contribute to the complex pathophysiology of arrhythmogenesis in hypertension.[2]

Atrial fibrillation is the most frequent arrhythmia in hypertensive patients and hypertension is the most prevalent co-morbidity in patients with AF. Poor BP control seems to worsen outcomes in AF via left ventricular diastolic dysfunction [where associated HF is present, this is referred to as 'heart failure with preserved ejection fraction (HFpEF')], left atrial overload and remodelling. AF is also related to the circadian rhythm of BP whereby a blunted nocturnal fall increases the occurrence of AF, perhaps due to the sustainability of high BP and the resultant hemodynamic burden on the left atrium.[3]

Hypertension may induce an atrial cardiomyopathy, and myocardial changes have been described in detail.[4] Mechanical overload due to high BP may induce an abnormal expression of ion channels and/or junctional complexes, as connexin 40 and connexin 43 which can enhance myocardium vulnerability by triggering focal ectopic and reentry activity.[5] Activation of the renin-angiotensin-aldosterone system (RAAS) occurs in hypertension and is strongly implicated in the development of AF. AF may also induce microvascular dysfunction in the ventricles.[6]

Left ventricular hypertrophy is also the major determinant of the development of ventricular arrhythmias and SCD in hypertensive patients. One of the proarrhythmogenic features in LVH is the presence of early after depolarizations, which may trigger sustained arrhythmias.[10]

Activation of the sympathetic nervous system and RAAS are important components of the pathophysiology and development of LVH (*Figure 1*). Sympathetic activation may trigger ventricular arrhythmias.[11] Prolongation and dispersion of repolarization is another feature of the pro-arrhythmogenic impact of LVH.[12,13] Nocturnal arrhythmias have been reported in up to 50% of sleep apnoea patients, and autonomic changes may be responsible. These arrhythmias including sinus arrest, second-degree atrioventricular (AV) block, ventricular premature beats (VPBs), and non-sustained ventricular tachycardia. Sleep apnoea is also known to predispose to the development of AF. About 50% of sleep apnoea patients are hypertensive,[14] and about 30% of hypertensive patients also have sleep apnoea.[15,16]

Myocardial fibrosis in the left ventricle is part of the structural remodelling process associated with LVH, and may lead to distortion of myocardial structure and increased myocardial stiffness, as part of the hypertensive diastolic dysfunction. At the cellular level, structural remodelling induced by hypertension is associated with impaired cell-to-cell communication at gap junctions, and these changes are the basis of non-homogenous impulse propagation and re-entrant ventricular arrhythmias.[8,17] Finally, LVH is also a source of myocardial ischaemia due to the mismatch of oxygen supply and demand. Microvascular dysfunction with myocardial ischaemia has also been reported in the early stages of hypertension, even in the absence of LVH, particularly in patients treated with thiazide diuretics.[2,18] Such myocardial ischemia may be a trigger of ventricular arrhythmias and SCD in some cases.[2,13,19]

Supraventricular arrhythmias

Supraventricular ectopics

Previous studies demonstrated that supraventricular (SVPBs) and VPBs occur frequently in hypertensive patients with LVH.[20]

Different variables could influence these underlying structural changes. Non-dipping profile (nocturnal BP reduction < 10% vs. diurnal BP) and increased nocturnal BP are markers of more advanced target organ damage; thus, non-dipping is commonly associated with arrhythmias, rather than dipping pattern being causal or directly related to arrhythmia.[21]

Recovery from exercise may be another triggering factor for SVPBs and the subsequent occurrence of AF. For example, in a study of 258 patients with LVH undergoing an exercise test, SVPBs and supraventricular tachycardia (SVT) occurring during the recovery

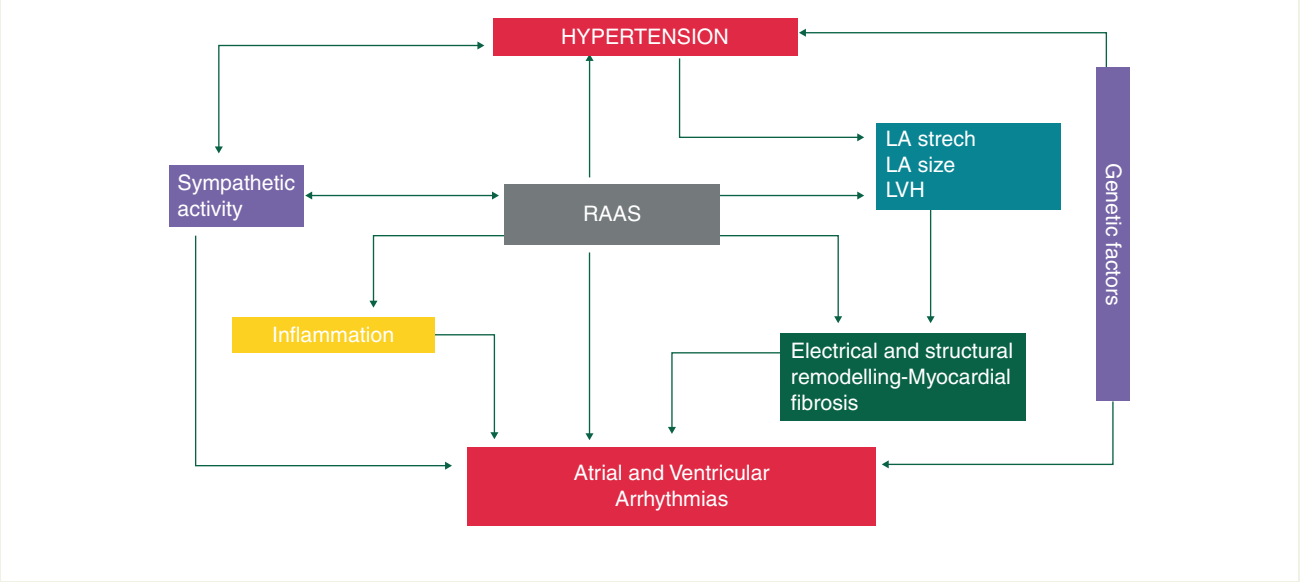


Figure 1 Mechanisms of arrhythmias in hypertension. LA, left atrium; LVH, left ventricular hypertrophy; RAAS, renin-angiotensin-aldosterone system.

phase, but not during exercise, predicted the occurrence of subsequent AF.[22] The number of SVPBs during recovery was correlated to the development of AF, and the incidence of AF increased from 12% if no SVPBs occurred to 15% with 0–1 SVPB/min, and further to 37% if ≥1 SVPB/min or if an SVT was seen.

Thus, patients with excessive SVPBs and LVH have a greater risk of developing AF, which is associated with increased age, systolic blood pressure and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels.[23] Interestingly, stroke was commonly the first clinical presentation, beyond manifest AF, in these study subjects. Even short runs of 20–50 SVPBs are associated with AF or some cryptogenic stroke events. Similarly, SVPBs were previously associated with an increased risk of ischaemic stroke.[24] In the EMBRACE (30-day cardiac event monitor belt for recording AF after a cerebral ischaemic event) trial,[25] among older cryptogenic stroke or transient ischaemic attack (TIA) patients (median $CHADS_2$ score 3), the number of SVPBs on a routine 24-h Holter was a strong independent predictor of subclinical AF.

Consensus statements		References
Patients with frequent SVPBs and LVH have a higher probability of AF and prolonged electrocardiographic (ECG) monitoring for AF detection may be used		23
Lifestyle changes may be used when managing majority of patients with SVPBs, including addressing precipitants relevant to some patients (e.g. alcohol, caffeine) and optimizing BP control especially where LVH is present		20

Atrial fibrillation

Due to its high prevalence in the general population, hypertension is the most significant population-attributable risk for AF and has been estimated to be responsible for 14% of all AF cases.[26] Hypertension was present in >70% of AF patients in epidemiological studies[27,28] and recent AF real-world registries,[29–31] and in 49–90% of patients in randomized AF trials.[32,33]

A pooled risk estimate revealed a 73% greater likelihood of AF in patients with hypertension or taking antihypertensive medication (Odds Ratio [OR] 1.73%; 95% Confidence Interval [CI], 1.31–2.28), especially in the presence of LVH.[34] Increased AF risk was also reported in individuals with upper normal blood pressure.[35,36]

One population-based, case-control study of patients treated for hypertension showed a 'J' shaped relationship between blood pressure and incident AF over a 12-year follow-up, with the lowest rates of incident AF at systolic blood pressure of 120–130 mmHg and diastolic blood pressure of 60–69 mmHg,[37] thus suggesting that optimal blood pressure control might decrease AF burden in hypertensive patients.[38] Atrial fibrillation could represent a manifestation of hypertensive heart disease or hypertensive target organ damage.[39]

In a study of patients with essential hypertension free of other cardiovascular conditions ($n \approx 2500$), the incidence of AF was 0.46% per year, and age or increased left ventricular mass were the only independent predictors of incident AF during a 5-year follow-up.[40] Of note, the annual incidence of stroke in that study was significantly higher in hypertensive patients with intermittent or chronic AF (2.7 and 4.6%, respectively) than in those without AF (0.81%, $P = 0.0005$).

Hypertension has been identified as an independent risk factor for incident AF[41–43] or AF progression,[44–46] AF-related stroke and mortality[47–49] and bleeding complications of oral anticoagulant

therapy in AF patients,[50–52] and a contributor to increased risk of poor quality of treatment with vitamin K antagonists, as predicted by the SAMe-TT_2R_2 score[53] (see Supplementary material online, *Table S1*).

Importantly, AF may be asymptomatic in up to 35% of patients (including those who also have symptomatic AF episodes),[54] particularly in patients with less co-morbidity (e.g. with hypertension only).[55]

Consensus statements	References
AF should be considered as a manifestation of hypertensive heart disease, and optimization of hypertension management should be made.	26,35,36
Given that stroke prevention is central to the management of AF patients, detection of hypertension and good blood pressure control should be done to minimize the risk of stroke and thromboembolism, as well as the bleeding risk whilst on antithrombotic therapy.	47–49

Supraventricular tachycardia

Left ventricular hypertrophy is the most important predictor for developing supraventricular arrhythmias. In a recent meta-analysis of 10 studies with 27 141 patients, the incidence of SVT (especially atrial tachycardias, AF or flutter) in patients with LVH was 11.1% compared with 1.1% among patients without LVH ($P < 0.001$).[56]

Patients with LVH have a 3.4-fold greater odds of developing SVT (OR 3.39; 95% CI, 1.57–7.31) than those without LVH, although significant heterogeneity was present (I^2 = 98%) due to differences in the baseline covariates such as age, male gender, hypertension, and diabetes in the individual studies.[56]

Other arrhythmias

Drug-related bradyarrhythmias

While dihydropyridine calcium channel blockers (CCBs) combine well with β-blockers in the management of hypertension, caution should be exercised when combining non-dihydropyridine CCBs with beta-blockers.[57] There is a risk of bradycardia and AV block with non-dihydropyridine CCBs particularly with the use of verapamil, but also with diltiazem at higher doses. A disproportionality analysis of side-effects caused by drug interactions reported to the US FDA between 1968 and 2001 indicated that the rate of conduction-related interactions between beta-blocker and verapamil leading to bradyarrhythmias was approximately 10%, a two-fold increase in the rate reported for either agent taken alone.[58] In the Diltiazem Reinfarction study,[59] second-degree AV block was noted in 3.4% of patients in the treatment group receiving high-dose (360 mg) diltiazem compared with 0.5% of patients in the placebo group (~60% concomitant use of a beta-blocker in both groups).

In patients with chronic kidney disease, the accumulation of beta-blockers or active metabolites could exacerbate concentration-dependent side effects, such as bradyarrhythmias.[60] Such accumulation occurs with atenolol, nadolol, and bisoprolol, but less so with carvedilol, propranolol, or metoprolol.

Sick sinus syndrome and atrioventricular conduction disturbances

The association of LVH with bradyarrhythmias, including complete atrioventricular block (AVB) and symptomatic sick sinus syndrome (SSS) requiring permanent pacemaker implantation, was examined in a study comprising 260 patients with complete heart block ($n = 130$) or symptomatic SSS ($n = 130$) receiving a permanent pacemaker, who were compared with 45 patients without cardiac conduction disturbances.[61] A significant association with LVH was observed in the AVB group, but not in the SSS group, as the majority of patients with complete AVB were hypertensive with LVH. This association was stronger in patients with infra-Hisian block.

In a *post hoc* analysis of the RACE trial[62] studying differences in outcome between hypertensive and normotensive persistent AF patients, it was demonstrated that morbidity and mortality and in particular SSS and AV conduction disturbances occurred more commonly in persistent AF patients with hypertension as compared to normotensive patients.

According with the results of an autopsy study comprising 35 hearts obtained from patients who died suddenly, and compared with 27 both age- and disease-matched and 30 age-matched control hearts from individuals who had not died suddenly, sclerosis of the sinus node artery was seen in the cases of sudden death with hypertensive heart disease.[63]

Thus, AV conduction disturbances may occur in hypertensive patients with LVH, and sinus node dysfunction may occur. Both clinical conditions may be encountered in the subgroup of hypertensive patients suffering from sleep-disordered breathing.[64]

In these situations, the electrophysiological properties of the sinus node and AV conduction system in obstructive sleep apnoea (OSA) patients with nocturnal bradyarrhythmias are usually normal while awake, and thus primary therapy of bradyarrhythmias in the setting of sleep apnoeas and normal AV conduction would consist of treatment of OSA with continuous positive airway pressure (CPAP) which can reverse these bradyarrhythmias, suggesting that OSA most likely induced the arrhythmias.[64] Finally, beneficial effects, albeit moderate and variable, of CPAP on blood pressure have been reported in patients with OSA; patients with more severe OSA, resistant hypertension, and better CPAP compliance may have a greater blood pressure reduction with CPAP.

Intra- and inter-atrial/inter- and intra-ventricular conduction delays

Interatrial and intra-atrial conduction delays have been reported to be longer in patients with hypertension compared to controls.[65] Among 9131 patients with hypertension and LVH, 564 (0.6%) had left bundle branch block (LBBB).[66] Left bundle branch block was independently associated with 1.6-fold more cardiovascular death

($P < 0.05$), 1.7-fold more hospitalization for HF ($P < 0.01$), 3.5-fold more SCD ($P < 0.001$), and 3.4-fold more cardiovascular death within 24 h ($P < 0.001$). The authors concluded that in hypertension with LVH on ECG, LBBB identifies patients at increased risk of cardiovascular mortality, SCD, and HF.

In an analysis of the losartan intervention for endpoint reduction in hypertension (LIFE) study population, the duration of the QRS complex predicted all-cause and cardiovascular mortality in hypertensive patients with ECG-LVH in the setting of aggressive hypertensive therapy.[67] An ancillary analysis from the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT) also found that lisinopril significantly reduced these conduction disturbances.[68] In a subsequent analysis of the LIFE study, among 9193 hypertensive patients with LVH treated with atenolol or losartan, QRS duration was independently predictive of SCD over an approximate mean 5-year follow-up[69] and remained a significant predictor of SCD even after controlling for the presence or absence of LBBB and for changes in ECG LVH severity over the course of the study.

Elevated resting heart rate in sinus rhythm

A high resting heart rate has been related to an adverse prognosis in patients with coronary artery disease (CAD) and HF.[70–74] In hypertensive patients free from other overt cardiac disease, this is less clear, and an elevated resting heart rate in hypertensive subjects free from overt cardiac disease seems to be more a risk marker than a risk factor.[74,75] Studies assessing ambulatory heart rate tend to demonstrate that night-time heart rate may be a better predictor of cardiovascular events than daytime heart rate. Heart rate during sleep represents persistent sympathetic overactivity and appears to be a better reflection of the mechanical stress on the arterial wall than daytime heart rate. Nevertheless, intervention trials have not demonstrated that lowering the heart rate with use of beta-blockers is beneficial in hypertensive subjects, although some benefit may be evident with ivabradine where concomitant reduced ejection fraction is evident.[76] Paradoxically, the use of ivabradine in HF is associated with more AF. Inappropriate sinus tachycardia can sometimes occur and in symptomatic patients, heart rate control with, e.g. beta blockers may be indicated.[77]

A resting heart rate > 80—85 b.p.m. may be used as a guide to further investigate for occult HF symptoms by clinical examination or determining biomarkers (such as BNP) or performing an echocardiogram, or looking for associated comorbidities, such as arrhythmias (e.g. AF and atrial flutter), anaemia, hyperthyroidism and sepsis.[74] A high resting heart rate may also be associated with obesity.

In addition, a high sleeping heart rate obtained via ambulatory blood pressure measurement may reflect episodes of resistant hypertension with a non-dipping heart rate and blood pressure profile or explore the possibility for sleep apnoea associated with sympathetic overactivity by clinical history and/or by performing a polysomnography study.[74,78]

In AF, note that rate control should initially aim for a HR < 110 b.p.m., with stricter rate control if symptomatic or LV function deteriorates.[79] The beneficial effects of beta-blockers on outcomes may be less apparent in AF and reduced LV systolic function.[80]

Consensus Statements	References
Both sinus node and AV conduction disturbances (particularly in patients with LVH) can occur in hypertensive patients as a consequence of sleep apnoea, and sleep disordered breathing is more common in hypertensive patient. Thus, assessment for these conditions may be performed in hypertensive patients.	61,64
Conduction delays occur both at the atrial and ventricular level in hypertensive patients, particularly in those with LVH, leading to AF or SCD, respectively. The presence of LBBB in hypertension, especially with LVH identifies patients at increased cardiovascular risk. Thus, assessment for these conditions may be performed in hypertensive patients.	65
An increased resting heart rate (>80–85 b.p.m.), portends an adverse prognosis not only in patients with CAD and HF, but in hypertensive patients as well. Routine lowering of the heart rate with use of beta-blockers or other agents may be considered in hypertensive subjects uncomplicated by other comorbidities (e.g. impaired LV function).	70–74

Proposal for a standardized 'workup'

In most patients with hypertension and suspected arrhythmias, all efforts should be made to obtain a diagnosis by documenting the arrhythmia.

First, because regular SVTs including atrioventricular nodal re-entrant tachycardia (AVNTR), atrioventricular re-entrant tachycardia (AVRT), atrial flutter and focal atrial tachycardia may lead to severe symptoms in patients with hypertension (particularly in those with advanced diastolic dysfunction). In these patients, curative treatment with catheter ablation is available (as well as medical therapy) and can be associated with a high success and low complications rates.[82]

Second, AF can rarely be ruled out as the underlying problem on clinical grounds alone, and the diagnosis of AF usually carries important implications at least regarding anticoagulation.[83,84] The increasing evidence that silent AF is associated with a higher risk for stroke[54,85] has led to the recommendation of 'opportunistic screening' for AF using pulse taking or ECG in the most recent guidelines[86]. This recommendation is clearly also valid in hypertensive patients because they are at greater risk of stroke. However, further research is needed to define best practice for younger patients diagnosed, e.g. with hypertension (especially those with asymptomatic organ damage),[87–89] as well as new technologies such as automated BP monitors with algorithms for AF detection, or other new technologies.

Third, a number of studies suggest that lower blood pressure goals reduce the frequency of episodes with paroxysmal SVT.[5,6] Lifestyle changes reducing blood pressure and AF burden may also contribute.[90]

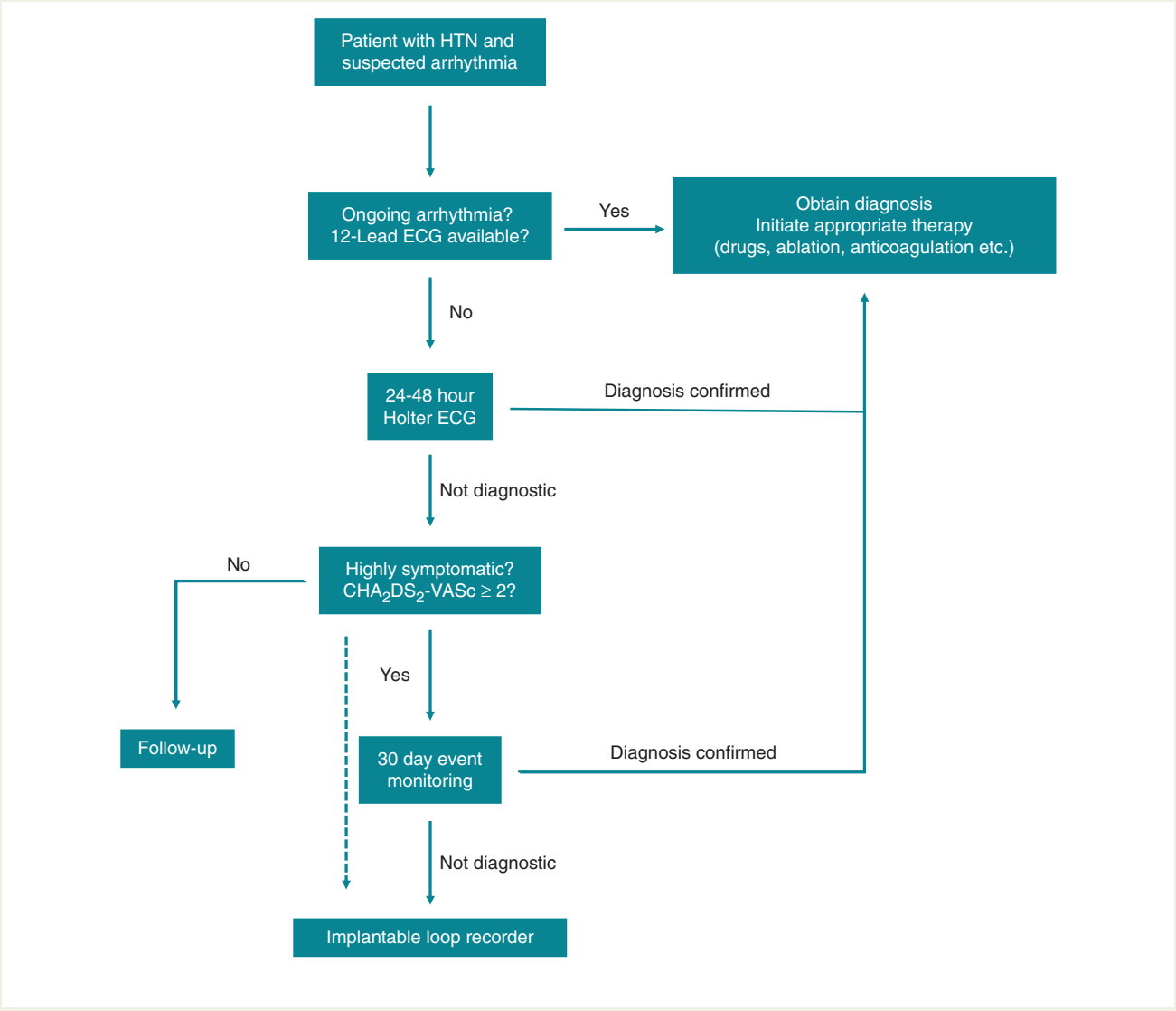


Figure 2 Proposed 'workup' standard for patients with hypertension and suspected cardiac arrhythmias. HTN, Hypertension; ECG, Electrocardiogram.

The order and type of workup of patients with arrhythmias and hypertension depends on various factors including duration and severity of symptoms, frequency of episodes and potential therapeutic implications. A proposal for a standardized initial work up is shown in *Figure 2*. A personal ECG device (e.g., mobile phone applications) may be another option. Implantable loop recorder (ILR) may be indicated earlier in 'high risk' patients with cryptogenic stroke (embolic stroke of uncertain source, ESUS) or presyncope/syncope where bradyarrhythmias are suspected as opposed to patients with palpitations, at least in daily practice. Note that a highly symptomatic patient even with low CHA_2DS_2-VASc score may still warrant a further work up with 30d event monitor or ILR.

With a CHA_2DS_2-VASc score ≥2 (i.e. two or more stroke risk factors) there is sufficient risk to either consider or recommend stroke prevention in patients with AF or suspected AF on basis of (prolonged) atrial high rate episodes (AHRE).

As a final step, 30 day event monitoring or an implantable cardiac monitor (ICM) may be used to detect rare arrhythmias. In the EMBRACE (30-day cardiac event monitor belt for recording AF after a cerebral ischaemic event) trial and CRYSTAL-AF (CRYptogenic STroke and underlying AtriaL Fibrillation) study respectively, these strategies were superior to conventional follow-up (mostly 24 h Holter and symptom-based diagnostics) for the detection of AF in patients post-cryptogenic stroke.[7,8]

The optimal duration cut-off for the definition of device detected AF, however, currently remains elusive; a 6 min cut-off is mostly widely used, based on findings of the ASSERT trial (ASymptomatic AF and Stroke Evaluation in Pacemaker Patients and the AF Reduction Atrial Pacing).[54] Closely connected to this is the question

of the necessary AF burden to initiate anticoagulation, but >5–6 min burden is generally considered as 'significant'. Finally, use of new technology that can be incorporated into a smartphone may be another option to record an infrequent arrhythmic event or detect silent AF.[89] However, there is a disconnect between AHRE and thromboembolic events, raising the possibility that AF is marker of increased risk for stroke rather than a cause of stroke.[91]

Management approaches

Consensus Statements	References
Silent AF is common, and opportunistic screening for underlying AF amongst hypertensive patients should be performed.	87–89
In hypertensive patients with symptoms suggestive of a cardiac rhythm disorder, documentation of the presence and type of arrhythmia should be done, for adequate management of the arrhythmia.	

The management of patients with hypertension and SVT is primarily driven by the type of arrhythmia (see *Figure 3*). In addition, hypertension should be proactively managed, with the type of treatment determined by associated compelling indications and/or comorbidities.[18] In general, RAAS blockade with angiotensin converting enzyme (ACE) inhibitors or ARB should be considered where LVH is present. Rate control in the presence of AF may be facilitated with a beta-blocker or non-dihydropyridine calcium blocker (verapamil, diltiazem). Supraventricular tachycardia may respond to a beta-blocker or non-dihydropyridine calcium blocker.

Supraventricular tachycardia

For acute management of SVT, these patients are treated as other patients with no hypertension according to published guidelines.[92] Vagal manoeuvres or intravenous adenosine are recommended as the initial therapy.[93,94] In haemodynamically unstable patients, synchronized cardioversion is recommended.[94] Intravenous diltiazem, verapamil, or beta-blockers are recommended for haemodynamically stable patients.[93,94] Intravenous esmolol is especially useful for short-term control of SVT and hypertension.[95]

For more chronic management of SVT catheter ablation is the first choice therapy.[94,96] Similarly, focal ectopic atrial tachycardia can usually be treated by ablation. Unlike re-entrant tachycardias, focal atrial tachycardia (AT) is likely reflective of a diseased atrium, particularly in patients with long-standing hypertension and more severe diastolic dysfunction and atrial remodelling. For patients who refuse catheter ablation, possible options in symptomatic patients who do not have ventricular pre-excitation during sinus rhythm include oral beta-blockers, diltiazem, or verapamil. Flecainide, propafenone, or sotalol are reasonable choices in patients without structural heart disease (e.g. severe LVH) who have symptomatic SVT and are not candidates for, or prefer not to undergo, catheter ablation.[94]

Atrial fibrillation

The priority in the treatment of patients with AF is stroke prevention.[83,86] The default is to offer oral anticoagulation (OAC) to all AF patients unless they are at low risk (defined as a CHA_2DS_2-VASc Score 0 in males, 1 in females).[97] Thus, the initial step is to identify 'low risk' patients where no antithrombotic therapy is recommended, following which OAC can be considered for those with ≥1 additional stroke risk factors.[97] Even a single stroke risk factor confers excess risk of stroke and mortality, and the net clinical benefit is positive for treating such patients.[98–100]

Patients with hypertension have a CHA_2DS_2-VASc score of at least 1, and hence at least a Class IIa/Level of Evidence A indication for anticoagulation (which becomes a class I indication with any additional risk factor). Bleeding risk should be assessed using well-validated simple bleeding risk scores that draw attention to the potentially reversible bleeding risk factors,[86] such as the HAS-BLED score, but should not by itself be used to deny anticoagulation to a patient.[83,101] Indeed, patients with a class I indication for anticoagulation and a HAS-BLED score ≥ 3 may profit as much if not more from anticoagulation based on net clinical benefit than those with a lower HAS-BLED score.[102] Uncontrolled hypertension (e.g. SBP > 160 mmHg) and other modifiable risk factors (e.g. concomitant aspirin or non-steroidal anti-inflammatory drug treatment, excessive alcohol use) should be addressed, to minimize the risk of bleeding.[103]

The non-vitamin K antagonist oral anticoagulants (NOACs) are recommended as the preferred treatment modality over vitamin K antagonists for anticoagulation,[83] based on the results of four independent large-scale clinical trials.[104–107] Subgroup analyses in patients with hypertension have mostly been consistent with the main outcome of the trials.[105,107–109] The use of aspirin for stroke prevention in AF is associated with minimal efficacy, but comes with a substantial bleeding risk; thus, aspirin is therefore no longer recommended (Class III).[83]

Persistent as well as permanent AF is common in hypertensive patients, particularly in the elderly, where rhythm control may not be an option. Elderly hypertensives often have associated HFpEF. A beta-blocker or non-dihydropyridine calcium blocker may be considered for rate control in such patients, although RAAS blockade may help LVH regression. In the elderly, digoxin may be a 2nd line option. Note that during rhythm control therapy, persistent AF patients with hypertension have more morbidity and mortality as compared to rate control, albeit in an era before ablation therapy.[62]

Atrial fibrillation ablation has emerged as an effective method for treatment of AF. In paroxysmal AF and normal sized atria, long-term freedom from symptoms can be achieved in up to 80%, but may require multiple procedures.[110,111] In patients with persistent AF and diseased atria, which is frequently found in patients with long-standing hypertension, long term success rates are substantially less below 70%.[110,111]

Consensus statements		References
Oral amiodarone should be used for ongoing management in patients witd symptomatic SVT who are not candidates for, or prefer not to undergo, catheter ablation and in whom beta blockers, diltiazem, flecainide, propafenone, sotalol, or verapamil are ineffective or contraindicated.		94,92,114
The priority in the treatment of patients with AF is stroke prevention, and AF patients with hypertension have a CHA_2DS_2-VASc score of at least 1; thus, effective stroke prevention may be considered with OAC in addition to good BP control.		98–100
With additional stroke risk factors, CHA_2DS_2-VASc score ≥2, OAC should be used, as well controlled VKA (TTR >70%) or a non-vitamin K antagonist oral anticoagulants (NOAC), with a preference for the latter.		
Bleeding risk should be assessed with focus on the modifiable bleeding risk factors, most of which can be identified using the HAS-BLED score.		103,83,101,115
• The HAS-BLED score should be used to identify those 'high risk' patients (score ≥3) for more careful review and follow-up, and to address the reversible bleeding risk factors (e.g. uncontrolled hypertension).		
• A high HAS-BLED score alone is not a reason to withhold OAC.		
Atrial fibrillation ablation should be used in hypertensive patients with symptomatic recurrences of AF on antiarrhythmic drug therapy who prefer further rhythm control therapy, and is first therapy in selected individuals as an alternative to antiarrhythmic drug therapy depending on patient choice, benefit, and risk.		92,110,111
In patients with re-entrant SVT and isthmus dependent flutter, catheter ablation should be used and is associated with a high success and low complication rate.		
In patients with severe structural heart diseases, such as severe LVH, history of myocardial infarction and HF, a haemodynamically significant valvular disease, do not use flecainide or propafenone. Do not use Sotalol in LVH patients, or Diltiazem and verapamil in HFrEF.		112,113

LVH, left ventricular hypertrophy; HFrEF, Heart failure with reduced ejection fraction; SVT, Supraventricular tachycardia; AF, atrial fibrilation; CHA_2DS_2-VASc score, Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female); OAC, oral anticoagulation/oral anticoagulant; VKA, vitamin K anticoagulants; TTR, time in therapeutic range; NOAC, no oral anticoagulation; HAS-BLED score, hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (65 years), drugs/alcohol concomitantly (1 point each); AVNRT, Atrioventricular nodal re-entrant tachycardia; AVRT, Atrioventricular re-entrant tachycardia.

Ventricular arrhythmias

Ventricular ectopics

Ventricular arrhythmias are common among hypertensive patients, and this association may have important clinical implications.[116–118] Data from the Atherosclerosis Risk in Communities (ARIC) study of more than 15 000 African American and white men and women showed that frequent or complex ventricular ectopic beats are associated with high blood pressure.[119] Epidemiological data have shown that hypertension induced LVH is associated with sustained ventricular arrhythmias.[56,120]

High blood pressure is not arrhythmogenic *per se* but the induced ventricular overload. Ventricular arrhythmias are commonly observed in aortic stenosis, even when peripheral blood pressure is low; the frequency of these arrhythmias have been demonstrated to be reduced after transcatheter aortic valve implantation.[121] Changes in electrophysiological properties can occur during volume overload,[122] which may be even more important under pathological conditions, such as ischaemic scars.

Ventricular tachycardia (VT), Ventricular fibrillation (VF), and sudden death

Hypertension is a risk factor for SCD, particularly in the context of increased LV mass.[123] Left ventricular hypertrophy is associated with long-term risk of SCD independent of blood pressure, and the risk of SCD increases progressively with LV mass.[120,124,125]

As discussed in Section II, several mechanisms have been proposed to explain the relationship between the presence of LVH and SCD in hypertension (*Figure 4*). The prolongation of repolarization as measured by the QT interval or transmural dispersion of repolarization, present in hypertensive patients can be related to the degree of LVH and may be associated with an increased risk of ventricular arrhythmias.[13,126] Other mechanisms, such as mismatch between oxygen supply and demand, particularly with stress, reduced coronary flow reserve and subsequent myocardial ischaemia may play a role.[127]

There is evidence that optimal control of blood pressure and regression of LVH by antihypertensive treatment can help prevent cardiac arrhythmias.[128,129] Although an effect on the burden of ventricular ectopy has not been consistently observed even in the context of reversal of LVH,[130–132] a reduced incidence of SCD has been demonstrated with effective BP control and regression of LVH. For example, in one study regression of electrocardiographic LVH during antihypertensive therapy was associated with a 30% lower risk of SCD independently of blood pressure lowering and other known predictors of SCD.[133]

However, it is also important to consider the potential influence of antihypertensive drugs on the risk of SCD. The use of thiazide

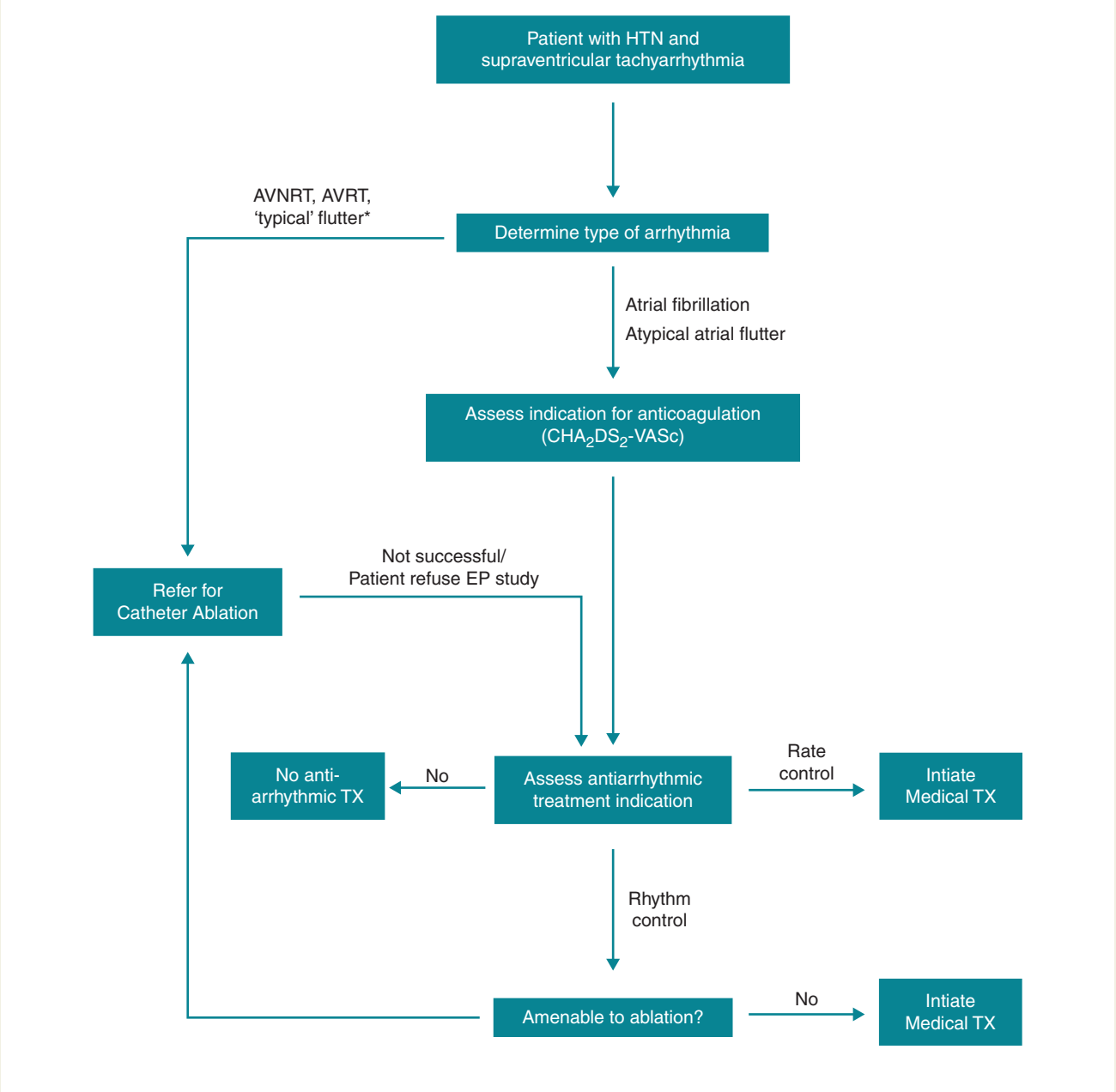


Figure 3 Management of atrial fibrillation in patients with hypertension. *Assess indication for oral anticoagulation in typical isthmus-dependent flutter (the same as in atrial fibrillation); Until further evidence is available, oral anticoagulation needs to be continued post AF and/or AFl ablation depending on the patient's CHA_2DS_2-VASc score, independent of ablation "success" or "failure. HTN, Hypertension; AVNRT, Atrio-ventricular nodal re-entrant tachycardia; AVRT, Atrio-ventricular re-entrant tachycardia; TX, Therapy.

diuretics has been associated with an increased risk of cardiac arrhythmias, with a dose-dependent increase in SCD.[134] Although the exact mechanism is unknown, hypokalaemia may be involved, with increased risk for QT prolongation, QT dispersion, and propensity for arrhythmogenic early and delayed after-depolarizations.[135] There was no difference in SCD among high-risk Japanese patients treated with the ARB candesartan or the calcium antagonist amlodipine, suggesting that blood pressure lowering itself may be important in affecting SCD risk.[136] However, in a high risk group for SCD consisting of hypertensive patients with LVH and diabetes, ARB based treatment with losartan was superior to treatment based on the beta blocker atenolol to prevent SCD.[137] Also, treatment with ACEi in high-risk cardiovascular patients was associated with a 26% reduction in cardiac mortality and a 37% decrease in cardiac arrest compared to placebo.[138] This provides some supportive evidence for blocking the RAAS in hypertensive patients at high risk of SCD.

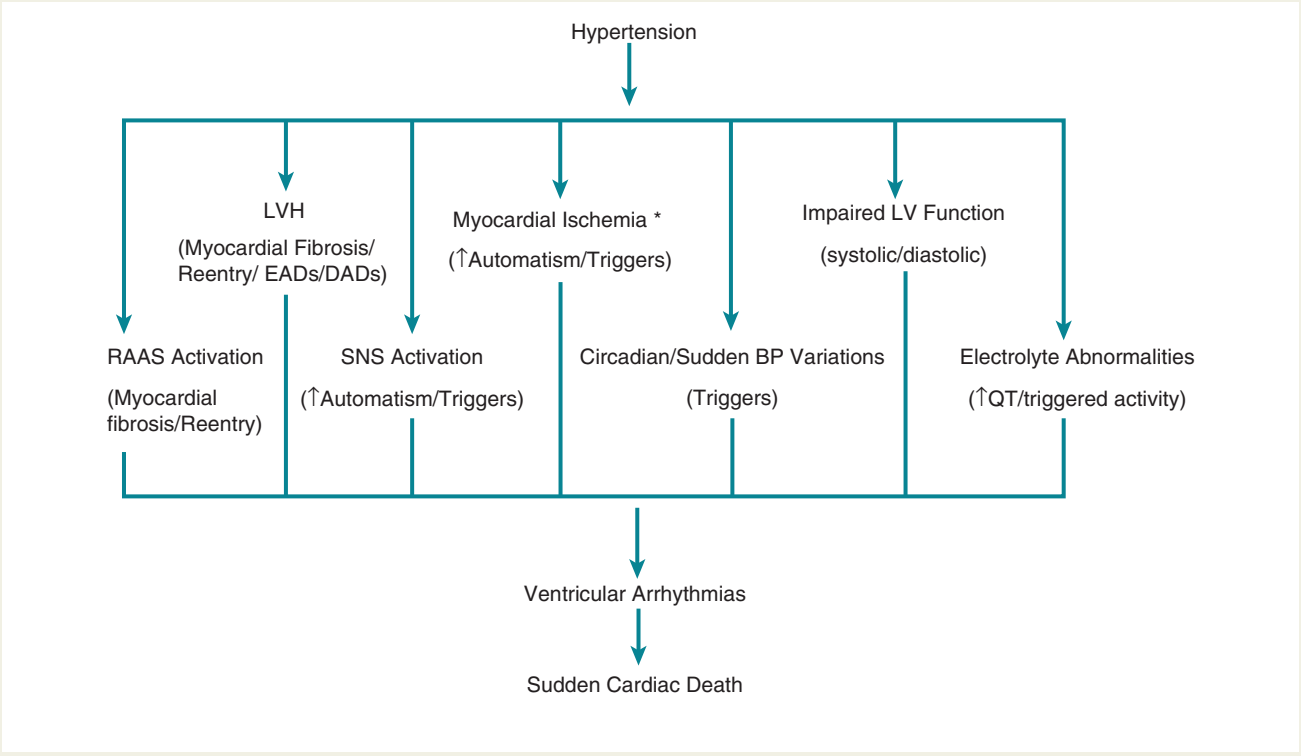


Figure 4 Potential mechanisms of ventricular arrhythmias and sudden cardiac death in hypertensive patients. BP, blood pressure; CAD, coronary artery disease; DADs, delayed afterdepolarizations; EADs, early afterdepolarizations; LV, left ventricular; LVH, left ventricular hypertrophy; RAAS, renin angiotensin aldosterone system; SNS, sympathetic nervous system. * CAD/LVH causing myocardial blood supply and oxygen consumption mismatch/decreased diastolic coronary blood flow causing subendocardial ischemia/microvascular dysfunction.

Proposal for a standardized 'workup'

Frequent non-sustained ventricular tachycardia (NSVT) or single VPBs among patients with hypertension are treated similarly to those found among patients without hypertension. A 12-lead ECG and a 24-h Holter recording may help to potentially localize site(s) of origin and to quantify VPBs. Transthoracic echocardiography may be useful to assess for other signs of hypertensive or structural heart disease, as well as to assess left ventricular systolic function. The latter is particularly important to identify, especially when a high VPB burden, defined as >20% of all beats in a 24-h recording, is documented.[139–141] If underlying coronary disease is suspected, frequent VPBs, associated symptoms, or LV systolic dysfunction, exercise testing may be useful for assessing effect on VPBs and for evaluating the presence of myocardial ischaemia (*Figure 5*).

Since the presence and number of VPBs may be modulated by many factors, a blood biochemistry profile, including electrolytes (potassium, magnesium, calcium), renal function, thyroid function, and glucose should be assessed. Moreover, it is necessary to review prescriptions and over-the-counter agents that may lengthen the QT interval or may induce sympathetic stimulation, particularly if LVH is evident on ECG or echocardiography.[131,142,143] Excessive intake of alcohol or caffeine or other non-pharmacologic stimulants, as well as use of recreational drugs, should be investigated and appropriately corrected. Identification of chronic exposure to high-stress conditions is important in order to counsel avoidance or ways to mitigate the stress, in view of the facilitating effect of adrenergic stimulation on arrhythmogenesis (*Figure 5*).

Additionally, cardiac magnetic resonance imaging (MRI) may be useful for providing a detailed analysis of myocardial substrate and to quantify the extent of myocardial fibrosis and possibly prognosis.[144–146] Coronary angiography may also be indicated to rule out myocardial ischemia and to assess the need for revascularization, particularly if abnormal findings are elicited on exercise stress testing or echocardiography.[144,145] Revascularization can suppress polymorphic ventricular tachycardias and VF secondary to acute myocardial ischaemia; however, revascularization has no effect on sustained ventricular tachycardias related to re-entry utilizing scar tissue related to a previous myocardial infarction and usually has no effect on isolated monomorphic VPBs. With regard to treatments for sustained ventricular arrhythmias and prevention of SCD, hypertension does not modify the indications for ICDs[147] or ablation, as recommended by current guidelines.[145,135]

Management approaches

Management approaches for ventricular arrhythmias in hypertensive patients can vary widely based on primary presenting problem. The most common ventricular arrhythmias associated with hypertension

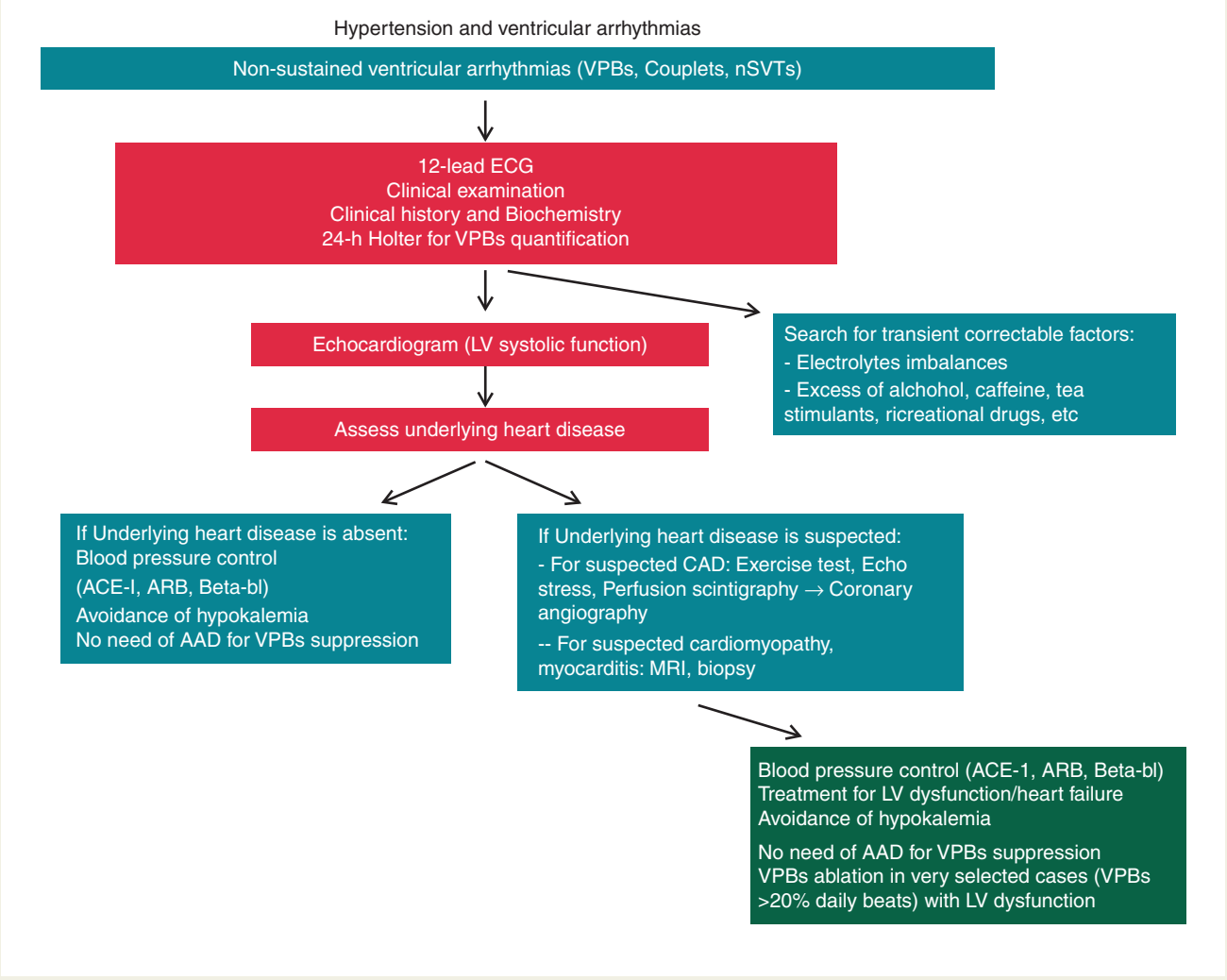


Figure 5 Proposal for a standardized 'workup'. NB. Only in rare cases does myocardial biopsy change management, and the benefit: risk of this is low. Consider ICD implantation if LVEF ≤35% despite goal-directed medical therapy and sustained hypertension control. ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CAD, coronary artery disease; LV, left ventricular; MRI, magnetic resonance imaging; nSVTs, no supraventricular tachycardia; VPBs, ventricular premature beats.

are VPBs, although NSVT also has been observed and can affect prognosis, particularly in the context of LVH (*Figure 5*).[117,130,143,148,149]

Although a direct relation between VPB reduction and antihypertensive treatment has not been clearly shown, reduced fatal ventricular arrhythmia event risk has been demonstrated, and efforts to control blood pressure remain important. Some results suggest that beta blockers are inferior to other major antihypertensive drug classes in reducing LV mass and major cardiovascular event risk.[150,151] However, other studies have indicated overall benefit in SCD reduction with BP lowering regardless of drug classes and demonstrated additional benefit with the use of beta blockers in patients with concomitant coronary heart disease.[152] There is also agent-specific evidence of SCD reduction using ACEI or ARB, which also appears to be independent of blood pressure reduction.[139,152] Thus, ACEI and ARB are also recommended in hypertensive patients at high risk for SCD.

Patients with hypertension-induced LVH may have greater QTc dispersion, particularly in the context of hypokalemia.[131,142,143] A relationship between QT and RR intervals has also been observed in hypertensive patients with LVH, which is similar to other conditions associated with proarrhythmic potential, including subsets of long QT syndrome.[13] Thus, avoiding marked hypokalaemia, or anything that prolongs repolarization time, may be important.

In asymptomatic hypertensive patients with normal LV systolic function and non-sustained ventricular arrhythmias, there is no role for prophylactic use of antiarrhythmic drugs. Sustained monomorphic VT is unusual in the absence of other structural heart disease.[131,142,149] However, the subgroup of hypertensive patients in whom this may present are those who also have CAD with or without preserved LV function, although the hypertensive heart may also have advanced patchy fibrosis even in the absence of coronary heart disease. In the normal heart e.g. outflow tract VT (often sustained) and hypertension can occur together, and may need CMR for work up.

Antiarrhythmic drugs e.g. Class IC agents such as flecainide, is not recommended, especially where structural heart disease such as

Consensus statements		References
Frequent VPBs, couplets, or non-sustained ventricular arrhytdmias should need a careful clinical history and examination, blood chemistry, a 12-lead ECG, and a 24-h Holter recording.		116–118
Transthoracic echocardiography should be used when assessing hypertensive patients with arrhythmias to assess for signs of hypertensive or structural heart disease.		56
Finding of frequent VPBs and/or NSVT should lead to investigation for structural heart disease, including with transthoracic echocardiography or cardiac MRI.		131,142,143
Exercise testing or other functional testing for ischaemia may be used for patients with suspected coronary disease and frequent VPBs or associated symptoms, both for assessing suppression or worsening of VPBs and for evaluating the presence of myocardial ischaemia. Further non-invasive testing or coronary angiography may be used if necessary/needed.		139–141
Serological studies including electrolyte levels, glucose, and thyroid studies may be checked to assess for reversible, secondary causes of increased ventricular ectopy.		131,142,143
Identification of non-prescription or non-pharmacologic sources of increased adrenergic stimulation, including intake of alcohol, caffeine, other stimulants including recreational drugs, may be documented through history taking in order to provide appropriate counselling and/or assistance as needed.		131,142,143

severe LVH or left ventricular systolic dysfunction is evident. In addition to beta blockers and ACE inhibitors or angiotensin receptor blockers (ARB), or catheter ablation should be considered in these patients, as well as implantable cardioverter-defibrillator (ICD).[153] Similarly, among patients with low ejection fraction and persistently high frequency of ventricular ectopic beats (>15–20% of total beats in a day, or >10 000 PVCs/24 h) and/or associated symptoms, antiarrhythmic drugs or catheter ablation should be considered to potentially reverse tachycardia-induced cardiomyopathy.[140,141] In the recent DANISH trial, prophylactic ICD implantation in patients with symptomatic systolic HF not caused by CAD was not associated with a significantly lower long-term rate of death from any cause than was usual clinical care.[154]

Finally, achieving adequate blood pressure control and promoting regression of LVH is a central goal in management, and any combination of antihypertensive drug classes should be considered as needed in order to achieve this goal, with the considerations as discussed above. Importantly, as LV systolic and diastolic dysfunction can result from poorly controlled hypertension alone, efforts to control BP and reduce associated risk of ventricular arrhythmias and SCD by improving LV ejection fraction are important. In the context of persistently severe LV systolic dysfunction (EF < 35%) despite adequate medical management, including BP control, implantation of an ICD should be considered, although in the absence of coronary disease the prognostic benefit is not evident.[154,155]

Complications related to arrhythmias and hypertension

Heart failure

Hypertension is one of the most common causes of HF. Antihypertensive therapy markedly reduces the incidence of HF. About half of all HF patients exhibit reduced ejection fraction.

Coronary artery disease is the cause of approximately two-thirds of cases of systolic HF, although hypertension and diabetes remain contributing factors.[156] Incident HF with preserved ejection fraction (HFpEF) is not always directly a consequence of CAD, and increases with advancing age, hypertension, diabetes, obesity, and chronic renal dysfunction. Important triggers for HFpEF are uncontrolled hypertension and AF, two conditions that require aggressive management.[157] Rhythm control in HFpEF is particularly relevant especially in those patients with substantial atrial contribution to LV filling.

In general, AF is predicted by the same markers of risk predicting HF, including target organ damage.[158] In the context of hypertension, the association with HFpEF is particularly important because the LV filling pattern is always abnormal, requiring a greater atrial contribution.[159] Although uncontrolled hypertension is certainly a trigger for AF, consolidated organ damage is the hallmark of risk.[158] Thus, attention should be paid to the global management of risk (including metabolic factors and obesity) in addition to the aggressive antihypertensive therapy that is always required.

A rate control strategy is mandatory in persistent/permanent AF, to facilitate LV filling, and is obtained more frequently using cardiospecific beta-blockers.[79] Uncontrolled heart rate may lead to a tachycardia-induced cardiomyopathy, with LV dilatation and impairment. In patients with systolic HF, the combination of digoxin and a beta-blocker could be effective. In patients with HFpEF, non-dihydropyridine calcium-channel blockers could be an alternative to a beta-blocker. In patients with chronic HF, a rhythm-control strategy has not been demonstrated to be superior to a rate-control strategy in reducing mortality or morbidity. In acute HF, emergency cardioversion may be required due to hemodynamic instability.

Postural hypotension

Postural (orthostatic) hypotension is usually defined as drop of 20 mmHg in systolic BP or 10 mmHg in diastolic BP within 2–5 min of standing up, and symptoms lasting a few seconds to several minutes of lightheadedness.[161,162]

Consensus statements		References
Achieving and maintaining adequate BP control should be an important priority when managing patients witd hypertension and ventricular arrhytdmias, especially if severe LV systolic dysfunction (EF < 35%) is present		131,132,137,152
Beta blockers should be used for management of hypertension in the setting of CAD and HF		152
Angiotensin converting enzyme inhibitors and ARB a should be used for hypertension management in patients at high risk for SCD		137,152
Avoiding hypokalaemia or QT prolonging drugs should be done in the context of HTN and LVH		13,131,142,143
In patients with sustained ventricular arrhythmias or frequent non-sustained ventricular arrhythmias with LV systolic dysfunction, treatment with beta-blocker, MRA and sacubitril/valsartan reduces the risk of sudden death and should be used for patients with HFrEF and ventricular arrhythmias, and, catheter ablation, and/or ICD implantation should be used in addition to antihypertensive therapy.		155
An ICD should be used to reduce the risk of sudden death and all-cause mortality in patients who have recovered from a ventricular arrhythmia causing haemodynamic instability, and who are expected to survive for >1 year with good functional status. • Persistent, severe LV systolic dysfunction, despite adequate blood pressure and other HF management, with frequent VPBs in patients thought to have a PVC induced cardiomyopathy, ICD implantation may be used, if coronary disease is evident. • An ICD should be used to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA Class II–III), and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than 1 year with good functional status, and they have: (i) IHD (unless they have had an MI in the prior 40 days—(ii) dilated cardiomyopathy.		155
Routine use of antiarrhythmic drugs is not to be used in patients with HF and asymptomatic ventricular arrhythmias because of safety concerns (worsening HF, proarrhythmia, and death).		154

Orthostatic hypotension (OH) is common in the elderly hypertensive population with a reported prevalence ranging from 6–30%. Due to its association with increased risk of falling, the presence of OH in elderly patients with HTN and AF may inappropriately prevent the use of OAC for stroke prevention. Also, the symptoms of lightheadedness or presyncope may raise suspicion of a cardiac arrhythmia in hypertensive patient, thus unnecessarily re-directing the diagnostic work-up.

Hypertension itself and commonly used antihypertensive drugs increase the incidence of OH. Orthostatic hypotension appears to be associated with immediate, and not prolonged, standing balance impairment, which is about three-fold higher in elderly hypertensive patients with OH or uncontrolled hypertension.[160] The risk for OH increases with ageing and diabetes due to slower baroreceptors function, impaired cardiac performance, and stiffer arteries.[163,164] Some antihypertensive and cardiodepressant medications (e.g. diuretics, alpha and beta blockers, calcium channel blockers, RAAS blockers, and nitrates), and drugs for Parkinson's disease and certain antidepressants and antipsychotics may increase the risk of orthostatic hypotension.[165–167]

Thromboembolism and bleeding risk, including safe use of antithrombotic therapy in hypertension

Increased blood pressure (BP, systolic BP of >130 mmHg or a diagnosis/history of hypertension) doubles the risk of stroke in patients with AF.[168,169] Offer oral anticoagulation with VKAs or NOACs reduces stroke risk and mortality in AF[170,171] but their benefit must be balanced against the risk of OAC-related major bleeding (especially ICH, due to its high fatality[172,173]) because uncontrolled hypertension (but not a diagnosis/history of hypertension) increases bleeding risk.[174]

Optimal BP control is crucial for both stroke and bleeding risk reduction in AF patients taking OAC. However, more data are needed to better define the target blood pressure values securing the most favourable risk/benefit ratio of OAC therapy in AF patients. Available evidence from randomized trials clearly shows a substantial increase in stroke risk (including both ischaemic and haemorrhagic stroke) at systolic BP values above 140 mmHg in AF patients taking warfarin.[175] In a *post hoc* analysis of the ARISTOTLE trial Apixaban for Reduction In STroke and Other ThromboembolLic Events in AF), elevated BP (a systolic BP of ≥140 mmHg and/or a diastolic BP of ≥90 mmHg) at any point during the trial was associated with increased risk of stroke or systemic embolism (HR 1.53; 95%CI, 1.26–1.86), haemorrhagic stroke (HR 1.85; 95%CI, 1.26–2.72) and a composite of major and clinically relevant non-major bleeding (HR 1.14; 95%CI, 1.011.28) in both treatment arms (i.e. apixaban or warfarin), whilst history of hypertension was significantly associated with increased stroke, but not major bleeding.

Patients with uncontrolled hypertension defined as a systolic BP of ≥ 170–180 mmHg and/or diastolic BP of ≥ 100 mmHg were excluded in all four NOAC trials, whilst hypertension defined as the use of antihypertensive medications[104, 106, 107] (or persistent systolic

BP > 140 mmHg or diastolic BP > 90 mmHg[107]) was present in 78.8[104]–93.7%[107] of participants. Most AF guidelines now favour the use of NOACs over VKAs (see Supplementary material online, *Table S2*). In patients with AF, all emphasize the importance of well-controlled anticoagulation with VKAs (i.e. the international normalized ratio time in therapeutic range of ≥70%). The SAMe-TT_2R_2 score of >2 (see Supplementary material online, *Table S1*, Section III-2) can be used to identify patients who are unlikely to do well on VKAs and hence should be prescribed NOACs (*Figure 6*).[53]

Given its high prevalence among AF patients, hypertension may often be the single risk factor requiring a decision on OAC use, and data from contemporary real-world AF registries shows that physicians often underestimate the significance of hypertension as a stroke risk factor[176,177] despite clearly positive net clinical benefit (the balance of stroke reduction against serious bleeding) of OAC in patients with ≥1 stroke risk factors in contemporary large AF cohorts.[102,178]

A recent analysis showed that the threshold for OAC use at ≥1.7%/year annual stroke risk considering VKAs should be decreased to ≥0.9%/year annual stroke risk with the safer NOACs.[179] Two recent analyses of large AF cohorts of untreated patients with 1 stroke risk factor reported the annual stroke rates well above the NOACs threshold (1.55%[180] and 2.55–2.75%[181]), and hypertension was associated with significant increase in stroke risk (HR 1.71; 95% CI, 1.48–1.98 [females], and 1.95; 95%CI, 1.73–2.19 [males]).[181] The presence of one stroke risk factor in untreated AF patients was associated with increased rates of stroke, bleeding and death,[180] and warfarin use was associated with a positive net clinical benefit compared to no therapy or aspirin.[99] In clinical practice, shared informed decision-making is useful, as AF patients commonly attribute stronger value to the avoidance of stroke than the risk of bleeding.[182]

Consensus statements	References
Offer oral anticoagulation should be used to reduce tde risk of stroke in most AF patients with hypertension, including tdose with AF in whom hypertension is the single additional stroke risk factor.	97,168,169
Shared, informed decision-making regarding the risks and benefits of OAC therapy should be used, especially where hypertension is the single additional risk factor for stroke.	
Well-controlled anticoagulation intensity (i.e. a TTR of ≥ 65–70%) should be used for achieving the optimal risk/benefit ratio with VKA therapy.	53,97
Compared to VKAs, NOACs offer additional safety benefit provided that there is good adherence to treatment. Optimal blood pressure control should be used for minimizing the risks of AF-related stroke and OAC-related bleeding. Until more data are available, target BP values in AF patients taking OAC should be below 140 mmHg for systolic BP and below 90 mmHg for diastolic BP. Oral anticoagulation should be used with caution in patients with persistent uncontrolled hypertension (systolic BP ≥ 180 mmHg and/or diastolic BP ≥ 100 mmHg) but strenuous efforts to control BP should be made.	97,175

Health economic considerations

Taking into account the risk of cardiovascular events linked to high blood pressure, the costs of untreated or inadequately controlled hypertension are of great relevance for any health care system.[183] According to a meta-regression analyses, every 10 mmHg reduction in systolic blood pressure the risk of major cardiovascular disease events is reduced by 20%, the risk of coronary heart disease by 17%, the risk of stroke by 27%, the risk of HF by 28% and the risk of all-cause mortality by 13%.[150]

The high prevalence of both hypertension and AF and the increasing costs for their treatment constitute an important financial burden, and therefore many economic analyses have been done with the aim to assess the cost-effectiveness of treating these diseases.[184] In these analyses the focus is mainly on the risk of stroke and the savings that can be obtained by preventing stroke occurrence and the consequent health care resources for hospitalization, rehabilitation, and assistance resulting from disability, which are associated with high direct and indirect costs.[185]

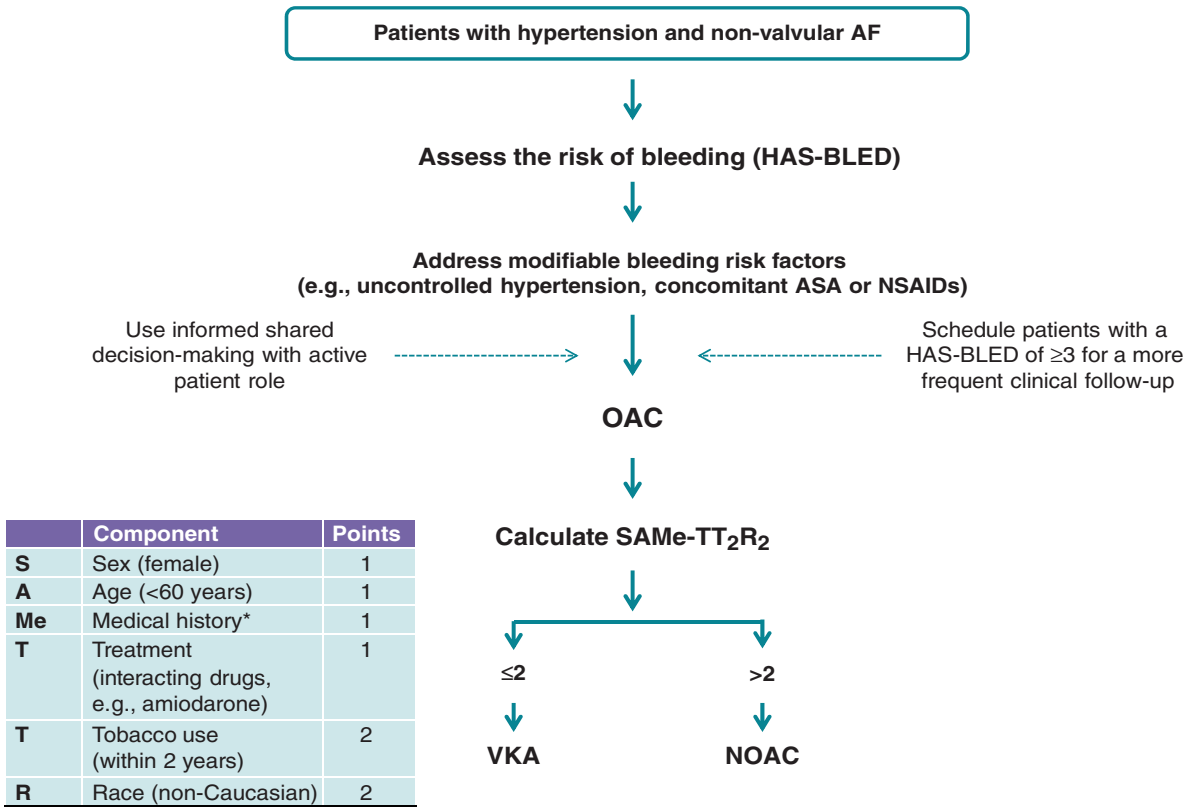
For stroke associated with AF, the direct costs per patient are approximately 33% greater than the costs for stroke unrelated to AF[186] and are in the range of Euro 30 000 over a 2-year period for a severe ischaemic stroke.[197] Within this scenario it is noteworthy that use of NOACs in patients with non-valvular AF has been found to be cost-effective.[188,189] In a series of analysis focused both on cost effectiveness and cost-benefit, the higher initial cost of NOACs compared to warfarin is offset by the reduction in intracranial bleeding and stroke prevention, making these agents cost-effective in the long-term.[188,189]

Finally, from an economic perspective, it is noteworthy to stress that since AF is frequently asymptomatic, opportunistic screening for asymptomatic AF is indicated in order to institute antithromboembolic prophylaxis in patients at risk, and proved to be cost-effective.[89]

Areas for further research

Many areas linking hypertension and cardiac arrhythmias deserve additional clarification and merit future study. Whilst perhaps rather selective, some areas of uncertainty are summarized as follows:

- How different circadian BP profiles, particularly blunted nocturnal blood pressure, influence the presence of different arrhythmias



	Component	Points
S	Sex (female)	1
A	Age (<60 years)	1
Me	Medical history*	1
T	Treatment (interacting drugs, e.g., amiodarone)	1
T	Tobacco use (within 2 years)	2
R	Race (non-Caucasian)	2

*More than two of the following: hypertension, diabetes mellitus, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, and hepatic or renal disease.

Figure 6 Proposed algorithm for antithrombotic management of patients with hypertension and non-valvular atrial fibrillation. ASA, Acetylsalicylic acid; NSAID, Non-steroidal anti-inflammatory drug; OAC, Oral anticoagulant; VKA, Vitamin K antagonist; NOAC, Non-vitamin K oral anticoagulant. SAMe-TT_2R_2, sex female, age, 60 years, medical history (more than two comorbidities), treatment (interacting drugs, e.g. amiodarone for rhythm control), tobacco use (doubled), race (doubled); TTR, time in therapeutic range.

- Detection and management of hypertensive patients with silent AF to prevent stroke risk, and whether OAC instituted in population based screen detected AF results in a meaningful stroke reduction.
- Antihypertensive drugs and regression of myocardial fibrosis in patients with hypertension and LVH
- Primary prevention of arrhythmias in patients with uncomplicated hypertension: is there a preferred antihypertensive drug or combination?
- Optimal antihypertensive treatment in patients with HF and preserved ejection fraction.
- Optimal BP targets in patients with hypertension and OAC therapy
- Atrial fibrillation management in asymptomatic cases detected by remote monitoring of implantable cardiac devices

Supplementary material

Supplementary material is available at *Europace* online.

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References

1. Benhorin J, Bodenheimer M, Brown M, Case R, Dwyer EM Jr, Eberly S *et al*; Multicenter Cardiac Research Group. Improving clinical practice guidelines for practicing cardiologists. *Am J Cardiol* 2015;**115**:1773–6.
2. Yiu KH, Tse HF. Hypertension and cardiac arrhythmias: a review of the epidemiology, pathophysiology and clinical implications. *J Hum Hypertens* 2008;**22**:380–8.
3. Eguchi K, Hoshide S, Schwartz JE, Shimada K, Kario K. Visit-to-visit and ambulatory blood pressure variability as predictors of incident cardiovascular events in patients with hypertension. *Am J Hypertens* 2012;**25**:962–8.

4. Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA *et al*. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Europace* 2016;**18**:1455–90.
5. Fialova M, Dlugosova K, Okruhlicova L, Kristek F, Manoach M, Tribulova N. Adaptation of the heart to hypertension is associated with maladaptive gap junction connexin-43 remodeling. *Physiol Res* 2008;**57**:7–11.
6. Goette A, Bukowska A, Dobrev D, Pfeiffenberger J, Morawietz H, Strugala D *et al*. Acute atrial tachyarrhythmia induces angiotensin II type 1 receptor-mediated oxidative stress and microvascular flow abnormalities in the ventricles. *Eur Heart J* 2009;**30**:1411–20.
7. Canpolat U, Oto A, Hazirolan T, Sunman H, Yorgun H, Sahiner L *et al*. A prospective DE-MRI study evaluating the role of TGF-beta1 in left atrial fibrosis and implications for outcomes of cryoballoon-based catheter ablation: new insights into primary fibrotic atriocardiomyopathy. *J Cardiovasc Electrophysiol* 2015;**26**:251–9.
8. Hirsh BJ, Copeland-Halperin RS, Halperin JL. Fibrotic atrial cardiomyopathy, atrial fibrillation, and thromboembolism: mechanistic links and clinical inferences. *J Am Coll Cardiol* 2015;**65**:2239–51.
9. Spronk HM, De Jong AM, Verheule S, De Boer HC, Maass AH, Lau DH *et al*. Hypercoagulability causes atrial fibrosis and promotes atrial fibrillation. *Eur Heart J* 2016;**38**:38–50.
10. Messerli FH. Hypertension and sudden cardiac death. *Am J Hypertens* 1999;**12**:181S–8S.
11. Fukuda K, Kanazawa H, Aizawa Y, Ardell JL, Shivkumar K. Cardiac innervation and sudden cardiac death. *Circ Res* 2015;**116**:2005–19.
12. Panikkath R, Reinier K, Uy-Evanado A, Teodorescu C, Gunson K, Jui J *et al*. Electrocardiographic predictors of sudden cardiac death in patients with left ventricular hypertrophy. *Ann Noninvasive Electrocardiol* 2013;**18**:225–9.
13. Kahan T, Bergfeldt L. Left ventricular hypertrophy in hypertension: its arrhythmogenic potential. *Heart* 2005;**91**:250–6.
14. Silverberg DS, Oksenberg A. Are sleep-related breathing disorders important contributing factors to the production of essential hypertension? *Curr Hypertens Rep* 2001;**3**:209–15.
15. Lavie P, Silverberg D, Oksenberg A, Hoffstein V. Obstructive sleep apnea and hypertension: from correlative to causative relationship. *J Clin Hypertens (Greenwich)*. 2001;**3**:296–301.
16. Kales A, Bixler EO, Cadieux RJ, Schneck DW, Shaw LC 3rd, Locke TW *et al*. Sleep apnoea in a hypertensive population. *Lancet* 1984;**2**:1005–8.
17. Tribulova N, Okruhlicova L, Novakova S, Pancza D, Bernatova I, Pechanova O *et al*. Hypertension-related intermyocyte junction remodelling is associated with a higher incidence of low-K(+)-induced lethal arrhythmias in isolated rat heart. *Exp Physiol* 2002;**87**:195–205.
18. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M *et al*. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J* 2013;**34**:2159–219.
19. Vaseghi M, Shivkumar K. The role of the autonomic nervous system in sudden cardiac death. *Prog Cardiovasc Dis* 2008;**50**:404–19.
20. Novo S, Barbagallo M, Abrignani MG, Nardi E, Di Maria GU, Longo B *et al*. Increased prevalence of cardiac arrhythmias and transient episodes of myocardial ischemia in hypertensives with left ventricular hypertrophy but without clinical history of coronary heart disease. *Am J Hypertens* 1997;**10**:843–51.
21. Ijiri H, Kohno I, Yin D, Iwasaki H, Takusagawa M, Iida T *et al*. Cardiac arrhythmias and left ventricular hypertrophy in dipper and nondipper patients with essential hypertension. *Jpn Circ J* 2000;**64**:499–504.
22. Folkeringa RJ, Hartgers J, Tieleman RG, Gorgels AP, Dassen WR, Crijns HJ. Atrial extrasystoles after exercise predict atrial fibrillation in patients with left ventricular hypertrophy. *Heart* 2006;**92**:545–6.
23. Larsen BS, Kumarathurai P, Falkenberg J, Nielsen OW, Sajadieh A. Excessive atrial ectopy and short atrial runs increase the risk of stroke beyond incident atrial fibrillation. *J Am Coll Cardiol* 2015;**66**:232–41.
24. Ofoma U, He F, Shaffer ML, Naccarelli GV, Liao D. Premature cardiac contractions and risk of incident ischemic stroke. *J Am Heart Assoc* 2012;**1**:e002519.
25. Gladstone DJ, Dorian P, Spring M, Panzov V, Mamdani M, Healey JS *et al*. Atrial premature beats predict atrial fibrillation in cryptogenic stroke: results from the EMBRACE Trial. *Stroke* 2015;**46**:936–41.
26. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol* 1998;**82**:2n–9n.
27. Kakkar AK, Mueller I, Bassand JP, Fitzmaurice DA, Goldhaber SZ, Goto S *et al*; Investigators GR. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the international, observational, prospective GARFIELD registry. *PLoS One* 2013;**8**:e63479.
28. Chiang CE, Naditch-Brule L, Murin J, Goethals M, Inoue H, O'Neill J *et al*. Distribution and risk profile of paroxysmal, persistent, and permanent atrial fibrillation in routine clinical practice: insight from the real-life global survey evaluating patients with atrial fibrillation international registry. *Circ Arrhythmia Electrophysiol* 2012;**5**:632–9.
29. Lip GY, Laroche C, Dan GA, Santini M, Kalarus Z, Rasmussen LH *et al*. A prospective survey in European Society of Cardiology member countries of atrial fibrillation management: baseline results of EUREObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry. *Europace* 2014;**16**:308–19.
30. Lip GY, Laroche C, Boriani G, Dan GA, Santini M, Kalarus Z *et al*. Regional differences in presentation and treatment of patients with atrial fibrillation in Europe: a report from the EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry. *Europace* 2015;**17**:194–206.
31. Potpara TS, Dan GA, Trendafilova E, Goda A, Kusljugic Z, Manola S *et al*; Investigators B-A. Stroke prevention in atrial fibrillation and 'real world' adherence to guidelines in the Balkan Region: The BALKAN-AF Survey. *Sci Rep* 2016;**6**:20432.
32. 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**:1789–94.
33. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S *et al*; AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011;**364**:806–17.
34. Ball J, Carrington MJ, McMurray JJ, Stewart S. Atrial fibrillation: profile and burden of an evolving epidemic in the 21st century. *Int J Cardiol* 2013;**167**:1807–24.
35. Conen D, Tedrow UB, Koplan BA, Glynn RJ, Buring JE, Albert CM. Influence of systolic and diastolic blood pressure on the risk of incident atrial fibrillation in women. *Circulation* 2009;**119**:2146–52.
36. Grundvold I, Skretteberg PT, Liestol K, Erikssen G, Kjeldsen SE, Arnesen H *et al*. Upper normal blood pressures predict incident atrial fibrillation in healthy middle-aged men: a 35-year follow-up study. *Hypertension* 2012;**59**:198–204.
37. Thomas MC, Dublin S, Kaplan RC, Glazer NL, Lumley T, Longstreth WT Jr *et al*. Blood pressure control and risk of incident atrial fibrillation. *Am J Hypertens* 2008;**21**:1111–6.
38. Marott SC, Nielsen SF, Benn M, Nordestgaard BG. Antihypertensive treatment and risk of atrial fibrillation: a nationwide study. *Eur Heart J* 2014;**35**:1205–14.
39. Lip GY. Atrial fibrillation in patients with hypertension: trajectories of risk factors in yet another manifestation of hypertensive target organ damage. *Hypertension* 2016;**68**:544–5.
40. Verdecchia P, Reboldi G, Gattobigio R, Bentivoglio M, Borgioni C, Angeli F *et al*. Atrial fibrillation in hypertension: predictors and outcome. *Hypertension* 2003;**41**:218–23.
41. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB Sr *et al*. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet* 2009;**373**:739–45.
42. Chamberlain AM, Agarwal SK, Folsom AR, Soliman EZ, Chambless LE, Crow R *et al*. A clinical risk score for atrial fibrillation in a biracial prospective cohort (from the Atherosclerosis Risk in Communities [ARIC] study). *Am J Cardiol* 2011;**107**:85–91.
43. Alonso A, Krijthe BP, Aspelund T, Stepas KA, Pencina MJ, Moser CB *et al*. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. *J Am Heart Assoc* 2013;**2**:e000102.
44. de Vos CB, Pisters R, Nieuwlaat R, Prins MH, Tieleman RG, Coelen RJ *et al*. Progression from paroxysmal to persistent atrial fibrillation clinical correlates and prognosis. *J Am Coll Cardiol* 2010;**55**:725–31.
45. Potpara TS, Stankovic GR, Beleslin BD, Polovina MM, Marinkovic JM, Ostojic MC *et al*. A 12-year follow-up study of patients with newly diagnosed lone atrial fibrillation: implications of arrhythmia progression on prognosis: the Belgrade Atrial Fibrillation study. *Chest* 2012;**141**:339–47.
46. Chen K, Bai R, Deng W, Gao C, Zhang J, Wang X *et al*. HATCH score in the prediction of new-onset atrial fibrillation after catheter ablation of typical atrial flutter. *Heart Rhythm* 2015;**12**:1483–9.
47. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;**285**:2864–70.
48. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010;**137**:263–72.
49. Singer DE, Chang Y, Borowsky LH, Fang MC, Pomernacki NK, Udaltsova N *et al*. A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: the ATRIA study stroke risk score. *J Am Heart Assoc* 2013;**2**:e000250.
50. Gage BF, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW *et al*. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). *Am Heart J* 2006;**151**:713–9.

51. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. 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**:1093–100.
52. Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N *et al*. A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. *J Am Coll Cardiol* 2011;**58**:395–401.
53. Apostolakis S, Sullivan RM, Olshansky B, Lip GY. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: the SAMe-TT(2)R(2) score. *Chest* 2013;**144**:1555–63.
54. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A *et al*; ASSERT Investigators. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012;**366**:120–9.
55. Potpara TS, Polovina MM, Marinkovic JM, Lip GY. A comparison of clinical characteristics and long-term prognosis in asymptomatic and symptomatic patients with first-diagnosed atrial fibrillation: the Belgrade Atrial Fibrillation Study. *Int J Cardiol* 2013;**168**:4744–9.
56. Chatterjee S, Bavishi C, Sardar P, Agarwal V, Krishnamoorthy P, Grodzicki T *et al*. Meta-analysis of left ventricular hypertrophy and sustained arrhythmias. *Am J Cardiol* 2014;**114**:1049–52.
57. Richards TR, Tobe SW. Combining other antihypertensive drugs with beta-blockers in hypertension: a focus on safety and tolerability. *Can J Cardiol* 2014;**30**:S42–6.
58. Almenoff JS, DuMouchel W, Kindman LA, Yang X, Fram D. Disproportionality analysis using empirical Bayes data mining: a tool for the evaluation of drug interactions in the post-marketing setting. *Pharmacoepidemiol Drug Saf* 2003;**12**:517–21.
59. Gibson RS, Boden WE, Theroux P, Strauss HD, Pratt CM, Gheorghiade M *et al*. Diltiazem and reinfarction in patients with non-Q-wave myocardial infarction. Results of a double-blind, randomized, multicenter trial. *N Engl J Med* 1986;**315**:423–9.
60. Group KDIGOKBPW. KDIGO clinical practice guideline for the management of blood pressure in chronic kidney disease. *Kidney Int Suppl* 2012;**2**:337–414.
61. Alexopoulos A, Perpinia A, Michelakakis N, Kossyvakis C, Deftereos S, Pyrgakis V. Evaluation of left ventricular hypertrophy in patients requiring permanent pacing. *Ther Adv Cardiovasc Dis* 2010;**4**:295–9.
62. Rienstra M, Van Veldhuisen DJ, Crijns HJ, Van Gelder IC; RACE Investigators. Enhanced cardiovascular morbidity and mortality during rhythm control treatment in persistent atrial fibrillation in hypertensives: data of the RACE study. *Eur Heart J* 2007;**28**:741–51.
63. Okada R, Kawai S. Histopathology of the conduction system in sudden cardiac death. *Jpn Circ J* 1983;**47**:573–80.
64. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A *et al*. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. *J Am Coll Cardiol* 2008;**52**:686–717.
65. Emiroglu MY, Bulut M, Sahin M, Acar G, Akcakoyun M, Kargin R *et al*. Assessment of atrial conduction time in patients with essential hypertension. *J Electrocardiol* 2011;**44**:251–6.
66. Li Z, Dahlof B, Okin PM, Kjeldsen SE, Wachtell K, Ibsen H *et al*. Left bundle branch block and cardiovascular morbidity and mortality in hypertensive patients with left ventricular hypertrophy: the Losartan intervention for endpoint reduction in hypertension study. *J Hypertens* 2008;**26**:1244–9.
67. Oikarinen L, Nieminen MS, Viitasalo M, Toivonen L, Jern S, Dahlof B *et al*. QRS duration and QT interval predict mortality in hypertensive patients with left ventricular hypertrophy: the Losartan Intervention for Endpoint Reduction in Hypertension Study. *Hypertension* 2004;**43**:1029–34.
68. Dewland TA, Soliman EZ, Davis BR, Magnani JW, Yamal JM, Piller LB *et al*; Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Collaborative Research Group. Effect of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) on conduction system disease. *JAMA Intern Med* 2016;**176**:1085–92.
69. Morin DP, Oikarinen L, Viitasalo M, Toivonen L, Nieminen MS, Kjeldsen SE *et al*. QRS duration predicts sudden cardiac death in hypertensive patients undergoing intensive medical therapy: the LIFE study. *Eur Heart J* 2009;**30**:2908–14.
70. Kannel WB. Vital epidemiologic clues in heart failure. *J Clin Epidemiol* 2000;**53**:229–35.
71. Fox K, Borer JS, Camm AJ, Danchin N, Ferrari R, Lopez Sendon JL *et al*. Resting heart rate in cardiovascular disease. *J Am Coll Cardiol* 2007;**50**:823–30.
72. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. *Lancet* 2008;**372**:817–21.
73. Bohm M, Reil JC, Deedwania P, Kim JB, Borer JS. Resting heart rate: risk indicator and emerging risk factor in cardiovascular disease. *Am J Med* 2015;**128**:219–28.
74. Courand PY, Lantelme P. Significance, prognostic value and management of heart rate in hypertension. *Arch Cardiovasc Dis* 2014;**107**:48–57.
75. Kolloch R, Legler UF, Champion A, Cooper-Dehoff RM, Handberg E, Zhou Q *et al*. Impact of resting heart rate on outcomes in hypertensive patients with coronary artery disease: findings from the INternational VErapamil-SR/trandolapril STudy (INVEST). *Eur Heart J* 2008;**29**:1327–34.
76. Fox K, Komajda M, Ford I, Robertson M, Bohm M, Borer JS *et al*. Effect of ivabradine in patients with left-ventricular systolic dysfunction: a pooled analysis of individual patient data from the BEAUTIFUL and SHIFT trials. *Eur Heart J* 2013;**34**:2263–70.
77. Olshansky B, Sullivan RM. Conventional management of inappropriate sinus tachycardia. *J Interv Card Electrophysiol* 2016;**46**:43–5.
78. Chouchou F, Pichot V, Pepin JL, Tamisier R, Celle S, Maudoux D *et al*. Sympathetic overactivity due to sleep fragmentation is associated with elevated diurnal systolic blood pressure in healthy elderly subjects: the PROOF-SYNAPSE study. *Eur Heart J* 2013;**34**:2122–31, 2131a.
79. Van Gelder IC, Rienstra M, Crijns HJ, Olshansky B. Rate control in atrial fibrillation. *Lancet* 2016;**388**:818–28.
80. Rienstra M, Damman K, Mulder BA, Van Gelder IC, McMurray JJ, Van Veldhuisen DJ. Beta-blockers and outcome in heart failure and atrial fibrillation: a meta-analysis. *JACC Heart Fail* 2013;**1**:21–8.
81. Boriani G, Savelieva I, Dan GA, Deharo JC, Ferro C, Israel CW *et al*; Document reviewers. Chronic kidney disease in patients with cardiac rhythm disturbances or implantable electrical devices: clinical significance and implications for decision making-a position paper of the European Heart Rhythm Association endorsed by the Heart Rhythm Society and the Asia Pacific Heart Rhythm Society. *Europace* 2015;**17**:1169–96.
82. Spector P, Reynolds MR, Calkins H, Sondhi M, Xu Y, Martin A *et al*. Meta-analysis of ablation of atrial flutter and supraventricular tachycardia. *Am J Cardiol* 2009;**104**:671–7.
83. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH *et al*. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the 2010 ESC Guidelines for the management of atrial fibrillation Developed with the special contribution of the European Heart Rhythm Association. *Europace* 2012;**14**:1385–413.
84. Svennberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Mass screening for untreated atrial fibrillation: the STROKESTOP study. *Circulation* 2015;**131**:2176–84.
85. Binici Z, Intzilakis T, Nielsen OW, Kober L, Sajadieh A. Excessive supraventricular ectopic activity and increased risk of atrial fibrillation and stroke. *Circulation* 2010;**121**:1904–11.
86. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B *et al*; 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS: The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESCEndorsed by the European Stroke Organisation (ESO). *Europace* 2016;**50**:e1–88.
87. Potpara TS, Lane DA. Diving to the foot of an iceberg: the SEARCH for undiagnosed atrial fibrillation. *Thromb Haemost* 2014;**112**:1–3.
88. Lowres N, Neubeck L, Redfern J, Freedman SB. Screening to identify unknown atrial fibrillation. A systematic review. *Thromb Haemost* 2013;**110**:213–22.
89. Lowres N, Neubeck L, Salkeld G, Krass I, McLachlan AJ, Redfern J *et al*. Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies. The SEARCH-AF study. *Thromb Haemost* 2014;**111**:1167–76.
90. Pathak RK, Elliott A, Middeldorp ME, Meredith M, Mehta AB, Mahajan R *et al*. Impact of CARDIOrespiratory FITness on arrhythmia recurrence in obese individuals with atrial fibrillation: The CARDIO-FIT Study. *J Am Coll Cardiol* 2015;**66**:985–96.
91. Brambatti M, Connolly SJ, Gold MR, Morillo CA, Capucci A, Muto C *et al*; ASSERT Investigators. Temporal relationship between subclinical atrial fibrillation and embolic events. *Circulation* 2014;**129**:2094–9.
92. Katritsis D, Boriani G, Garcia-Cosio F, Jais P, Josephson M, Hindricks G *et al*. European Heart Rhythm Association (EHRA) consensus document on the management of supraventricular rrhythmias, endorsed by Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulación Cardiaca y Electrofisiologia (SOLAECE). *Europace* 2017;**19**:465–511.
93. Blomström-Lundqvist C, Scheinman MM, Aliot EM, Alpert JS, Calkins H, Camm AJ *et al*. ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias* —executive summary: a report of the American college of cardiology/American heart association task force on practice guidelines and the European society of cardiology committee for practice guidelines

(writing committee to develop guidelines for the management of patients with supraventricular arrhythmias) Developed in Collaboration with NASPE-Heart Rhythm Society. *J Am Coll Cardiol* 2003;**42**:1493–1531.
94. Page RL, Joglar JA, Caldwell MA, Calkins H, Conti JB, Deal BJ *et al*. 2015 ACC/AHA/HRS Guideline for the Management of Adult Patients With Supraventricular TachycardiaA Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2016;**67**:e27–115.
95. Garnock-Jones KP. Esmolol. *Drugs* 2012;**72**:109–32.
96. Katritsis DG, Zografos T, Katritsis GD, Giazitzoglou E, Vachliotis V, Paxinos G *et al*. Catheter ablation vs. antiarrhythmic drug therapy in patients with symptomatic atrioventricular nodal re-entrant tachycardia: a randomized, controlled trial. *Europace* 2017;**19**:602–6.
97. Freedman B, Potpara TS, Lip GY. Stroke prevention in atrial fibrillation. *Lancet* 2016;**388**:806–17.
98. Fauchier L, Clementy N, Ivanes F, Angoulvant D, Babuty D, Lip G. Should atrial fibrillation patients with only 1 nongender-related CHA2DS2-VASc risk factor be anticoagulated? *Stroke* 2016;**47**:1831–6.
99. Lip GY, Skjoth F, Nielsen PB, Larsen TB. Non-valvular atrial fibrillation patients with none or one additional risk factor of the CHA2DS2-VASc score. A comprehensive net clinical benefit analysis for warfarin, aspirin, or no therapy. *Thromb Haemost* 2015;**114**:826–34.
100. Lip GY, Nielsen PB. Should patients with atrial fibrillation and 1 stroke risk factor (CHA2DS2-VASc Score 1 in Men, 2 in Women) be anticoagulated? yes: even 1 stroke risk factor confers a real risk of stroke. *Circulation* 2016;**133**:1498–503.
101. Lip GY, Laroche C, Popescu MI, Rasmussen LH, Vitali-Serdoz L, Dan GA *et al*. Heart failure in patients with atrial fibrillation in Europe: a report from the EURObservational Research Programme Pilot survey on Atrial Fibrillation. *Eur J Heart Fail* 2015;**17**:570–82.
102. Friberg L, Rosenqvist M, Lip GY. Net clinical benefit of warfarin in patients with atrial fibrillation: a report from the Swedish atrial fibrillation cohort study. *Circulation* 2012;**125**:2298–307.
103. Toyoda K, Yasaka M, Uchiyama S, Nagao T, Gotoh J, Nagata K *et al*; Bleeding with Antithrombotic Therapy Study Group. Blood pressure levels and bleeding events during antithrombotic therapy: the Bleeding with Antithrombotic Therapy (BAT) Study. *Stroke* 2010;**41**:1440–4.
104. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A *et al*. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–51.
105. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W *et al*. Rivaroxaban versus Warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;**365**:883–91.
106. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M *et al*. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**:981–92.
107. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL *et al*; EAFTI. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;**386**:2093–104.
108. Nagarakanti R, Wallentin L, Noack H, Brueckmann M, Reilly P, Clemens A *et al*. Comparison of characteristics and outcomes of dabigatran versus warfarin in hypertensive patients with atrial fibrillation (from the RE-LY Trial). *Am J Cardiol* 2015;**116**:1204–9.
109. Rao MP, Halvorsen S, Wojdyla D, Thomas L, Alexander JH, Hylek EM *et al*; Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Steering Committee and Investigators. Blood pressure control and risk of stroke or systemic embolism in patients with atrial fibrillation: results from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial. *J Am Heart Assoc* 2015;**4**. doi:10.1161/JAHA.115.002015.
110. Ganesan AN, Shipp NJ, Brooks AG, Kuklik P, Lau DH, Lim HS *et al*. Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. *J Am Heart Assoc* 2013;**2**:e004549.
111. Nault I, Miyazaki S, Forclaz A, Wright M, Jadidi A, Jais P *et al*. Drugs vs. ablation for the treatment of atrial fibrillation: the evidence supporting catheter ablation. *Eur Heart J* 2010;**31**:1046–54.
112. Slavik RS, Tisdale JE, Borzak S. Pharmacologic conversion of atrial fibrillation: a systematic review of available evidence. *Prog Cardiovasc Dis* 2001;**44**:121–52.
113. Piccini JP, Fauchier L. Rhythm control in atrial fibrillation. *Lancet* 2016;**388**:829–40.
114. Ahmed S, Rienstra M, Crijns HJ, Links TP, Wiesfeld AC, Hillege HL *et al*; CONVERT Investigators. Continuous vs episodic prophylactic treatment with amiodarone for the prevention of atrial fibrillation: a randomized trial. *JAMA* 2008;**300**:1784–92.
115. Lip GY, Lane DA. Bleeding risk assessment in atrial fibrillation: observations on the use and misuse of bleeding risk scores. *J Thromb Haemost* 2016;**14**:1711–4.
116. Zehender M, Meinertz T, Hohnloser S, Geibel A, Gerisch U, Olschewski M *et al*. Prevalence of circadian variations and spontaneous variability of cardiac disorders and ECG changes suggestive of myocardial ischemia in systemic arterial hypertension. *Circulation* 1992;**85**:1808–15.
117. McLenachan JM, Henderson E, Morris KI, Dargie HJ. Ventricular arrhythmias in patients with hypertensive left ventricular hypertrophy. *N Engl J Med* 1987;**317**:787–92.
118. Sideris DA. High blood pressure and ventricular arrhythmias. *Eur Heart J* 1993;**14**:1548–53.
119. Simpson RJ, Cascio WE, Crow RS, Schreiner PJ, Rautaharju PM, Heiss G. Association of ventricular premature complexes with electrocardiographic-estimated left ventricular mass in a population of African-American and white men and women (The Atherosclerosis Risk in Communities. *Am J Cardiol* 2001;**87**:49–53.
120. Levy D, Anderson KM, Savage DD, Balkus SA, Kannel WB, Castelli WP. Risk of ventricular arrhythmias in left ventricular hypertrophy: the Framingham Heart Study. *Am J Cardiol* 1987;**60**:560–5.
121. Tempio D, Pruiti GP, Conti S, Romano SA, Tavano E, Capodanno D *et al*. Ventricular arrhythmias in aortic valve stenosis before and after transcatheter aortic valve implantation. *Europace* 2015;**17**:1136–40.
122. Calkins H, Maughan WL, Weisman HF, Sugiura S, Sagawa K, Levine JH. Effect of acute volume load on refractoriness and arrhythmia development in isolated, chronically infarcted canine hearts. *Circulation* 1989;**79**:687–97.
123. Kannel WB, Schatzkin A. Sudden death: Lessons from subsets in population studies. *J Am Coll Cardiol* 1985;**5**:141B–9B.
124. Levy D, Anderson KM, Savage DD, Kannel WB, Christiansen JC, Castelli WP. Echocardiographically detected left ventricular hypertrophy: prevalence and risk factors. The Framingham Heart Study. *Ann Int Med* 1988;**108**:7–13.
125. Haider AW, Larson MG, Benjamin EJ, Levy D. Increased left ventricular mass and hypertrophy are associated with increased risk for sudden death. *J Am Coll Cardiol* 1998;**32**:1454–9.
126. Malmqvist K, Kahan T, Edner M, Bergfeldt L. Different actions of irbesartan and atenolol on cardiac repolarisation in hypertensive left ventricular hypertrophy. *Am J Cardiol* 2002;**90**:1107–12.
127. Ohtsuka S, Kakihana M, Watanabe H, Enomoto T, Ajisaka R, Sugishita Y. Alterations in left ventricular wall stress and coronary circulation in patients with isolated systolic hypertension. *J Hypertens* 1996;**14**:1349–55.
128. Manolis AJ, Beldekos D, Handansis S, Haralabidis G, Hatzissavas J, Foussas S *et al*. Comparison of spirapril, isradipine, or combination in hypertensive patients with left ventricular hypertrophy: effects on LVH regression and arrhythmogenic propensity. *Am J Hypertens* 1998;**11**:640–8.
129. Novo S. Effects of drug therapy on cardiac arrhythmias and ischemia in hypertensives with LVH. *Am J Hypertens* 2001;**14**:637–43.
130. Mayet J, Chapman N, Shahi M, Poulter NR, Cunningham DA, Dave S *et al*. The effects on cardiac arrhythmias of antihypertensive therapy causing regression of left ventricular hypertrophy. *Am J Hypertens* 1997;**10**:611–8.
131. Siegel D, Hulley SB, Black DM, Cheitlin MD, Sebastian A, Seeley DG *et al*. Diuretics, serum and intracellular electrolyte levels, and ventricular arrhythmias in hypertensive men. *JAMA* 1992;**267**:1083–9.
132. Lumme JA, Jounela AJ. Cardiac arrhythmias in hypertensive outpatients on various diuretics. Correlation between incidence and serum potassium and magnesium levels. *Ann Clin Res* 1986;**18**:186–90.
133. Wachtell K, Okin PM, Olsen MH, Dahlöf B, Devereaux RB, Ibsen H *et al*. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive therapy and reduction in sudden cardiac death. The LIFE Study. *Circulation* 2007;**116**:700–5.
134. Siscovick DS, Raghunathan TE, Psaty BM, Koepsell TD, Wicklund KG, Lin X *et al*. Diuretic therapy for hypertension and the risk of primary cardiac arrest. *N Engl J Med* 1994;**330**:1852–7.
135. Osadchil OE. Mechanisms of hypokalemia-induced ventricular arrhythmogenicity. *Fundam Clin Pharmacol* 2010;**24**:547–59.
136. Ogihara T, Nakao K, Fukui T, Fukiyama K, Ueshima K, Oba K. Effects of candesartan compared with amlodipine in hypertensive patients with high cardiovascular risks: candesartan antihypertensive survival evaluation in Japan trial. *Hypertension* 2008;**51**:393–8.
137. Lindholm LH, Dahlöf B, Edelman JM, Ibsen H, Borch-Johnsen K, Olsen MH *et al*. Effect of losartan on sudden cardiac death in people with diabetes: data from the LIFE study. *Lancet* 2003;**362**:619–20.
138. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;**342**:145–53.
139. Lee GK, Klarich KW, Grogan M, Cha YM. Premature ventricular contraction-induced cardiomyopathy: a treatable condition. *Circ Arrhythm Electrophysiol* 2012;**5**:229–36.

140. Baman TS, Lange DC, Ilg KJ, Gupta SK, Liu TY, Alguire C *et al*. Relationship between burden of premature ventricular complexes and left ventricular function. *Heart Rhythm* 2010;**7**:865–9.
141. El Kadri M, Yokokawa M, Labounty T, Mueller G, Crawford T, Good E *et al*. Effect of ablation of frequent premature ventricular complexes on left ventricular function in patients with nonischemic cardiomyopathy. *Heart Rhythm* 2015;**12**:706–13.
142. Saadeh AM, Evans SJ, James MA, Jones JV. QTc dispersion and complex ventricular arrhythmias in untreated newly presenting hypertensive patients. *J Hum Hypertens* 1999;**13**:665–9.
143. Galinier M, Balanescu S, Fourcade J, Dorobantu M, Boveda S, Massabuau P *et al*. Prognostic value of ventricular arrhythmias in systemic hypertension. *J Hypertens* 1997;**15**:1779–83.
144. Pedersen CT, Kay GN, Kalman J, Borggrefe M, Della-Bella P, Dickfeld T *et al*. EHRA/HRS/APHRS expert consensus on ventricular arrhythmias. *Europace* 2014;**16**:1257–83.
145. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J *et al*; Task Force for the Management of Patients with Ventricular A and the Prevention of Sudden Cardiac Death of the European Society of Cardiology. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Europace* 2015;**17**:1601–87.
146. Blomstrom Lundqvist C, Auricchio A, Brugada J, Boriani G, Bremerich J, Cabrera JA *et al*; European Association of Cardiovascular I, Council of Cardiovascular I and European Society of Cardiac R. The use of imaging for electrophysiological and devices procedures: a report from the first European Heart Rhythm Association Policy Conference, jointly organized with the European Association of Cardiovascular Imaging (EACVI), the Council of Cardiovascular Imaging and the European Society of Cardiac Radiology. *Europace* 2013;**15**:927–36.
147. Boriani G, Diemberger I, Valzania C, Biffi M, Martignani C, Raschi E *et al*. Role of drugs and devices in patients at risk of sudden cardiac death. *Fundam Clin Pharmacol* 2010;**24**:575–94.
148. Sideris DA, Toumanidis ST, Anastasiou-Nana M, Zakopoulos N, Kitsiou A, Tsagarakis K *et al*. The circadian profile of extrasystolic arrhythmia: its relationship to heart rate and blood pressure. *Int J Cardiol* 1992;**34**:21–31.
149. Pringle SD, Dunn FG, Macfarlane PW, McKillop JH, Lorimer AR, Cobbe SM. Significance of ventricular arrhythmias in systemic hypertension with left ventricular hypertrophy. *Am J Cardiol* 1992;**69**:913–7.
150. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J *et al*. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016;**387**:957–67.
151. Fagard RH, Celis H, Thijs L, Wouters S. Regression of left ventricular mass by antihypertensive treatment: a meta-analysis of randomized comparative studies. *Hypertension* 2009;**54**:1084–1091.
152. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009;**338**:b1665.
153. Aliot EM, Stevenson WG, Almendral-Garrote JM, Bogun F, Calkins CH, Delacretaz E *et al*. EHRA/HRS expert consensus on catheter ablation of ventricular arrhythmias. *Europace* 2009;**11**:771–817.
154. Kober L, Thune JJ, Nielsen JC, Haarbo J, Videbaek L, Korup E *et al*; Investigators D. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med* 2016;**375**:1221–30.
155. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NAM III, Freedman RA, Gettes LS *et al*. ACC/AHA/HRS 2008 Guidelines for device-based therapy of cardiac rhythm abnormalities: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing committee to revise the ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices) Developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2008;**51**:e1–62.
156. de Simone G, Devereux RB, Chinali M, Lee ET, Galloway JM, Barac A *et al*. Diabetes and incident heart failure in hypertensive and normotensive participants of the Strong Heart Study. *J Hypertens* 2010;**28**:353–60.
157. Lam CS, Donal E, Kraigher-Krainer E, Vasan RS. Epidemiology and clinical course of heart failure with preserved ejection fraction. *Eur J Heart Fail* 2011;**13**:18–28.
158. Losi MA, Izzo R, De Marco M, Canciello G, Rapacciuolo A, Trimarco V *et al*. Cardiovascular ultrasound exploration contributes to predict incident atrial fibrillation in arterial hypertension: the Campania Salute Network. *Int J Cardiol* 2015;**199**:290–5.
159. Zakeri R, Chamberlain AM, Roger VL, Redfield MM. Temporal relationship and prognostic significance of atrial fibrillation in heart failure patients with preserved ejection fraction: a community-based study. *Circulation* 2013;**128**:1085–93.
160. Shen S, He T, Chu J, He J, Chen X. Uncontrolled hypertension and orthostatic hypotension in relation to standing balance in elderly hypertensive patients. *Clin Interv Aging* 2015;**10**:897–906.
161. Low PA, Tomalia VA. Orthostatic hypotension: mechanisms, causes, management. *J Clin Neurol* 2015;**11**:220–6.
162. Ricci F, De Caterina R, Fedorowski A. Orthostatic Hypotension: Epidemiology, Prognosis, and Treatment. *J Am Coll Cardiol* 2015;**66**:848–60.
163. Milazzo V, Maule S, Di Stefano C, Tosello F, Totaro S, Veglio F *et al*. Cardiac organ damage and arterial stiffness in autonomic failure: comparison with essential hypertension. *Hypertension* 2015;**66**:1168–75.
164. Liu K, Wang S, Wan S, Zhou Y, Pan P, Wen B *et al*. Arterial stiffness, central pulsatile hemodynamic load, and orthostatic hypotension. *J Clin Hypertens (Greenwich)* 2016;**18**:655–62
165. Canney M, O'Connell MD, Murphy CM, O'Leary N, Little MA, O'Seaghdha CM *et al*. Single Agent Antihypertensive Therapy and Orthostatic Blood Pressure Behaviour in Older Adults Using Beat-to-Beat Measurements: The Irish Longitudinal Study on Ageing. *PLoS One* 2016;**11**:e0146156.
166. Nilsson D, Sutton R, Tas W, Burri P, Melander O, Fedorowski A. Orthostatic changes in hemodynamics and cardiovascular biomarkers in dysautonomic patients. *PLoS One* 2015;**10**:e0128962.
167. Jones PK, Shaw BH, Raj SR. Orthostatic hypotension: managing a difficult problem. *Expert Rev Cardiovasc Ther* 2015;**13**:1263–76.
168. Hughes M, Lip GY; Guideline Development Group NCGfMoAFiP, Secondary Care NIfH and Clinical E. Stroke and thromboembolism in atrial fibrillation: a systematic review of stroke risk factors, risk stratification schema and cost effectiveness data. *Thromb Haemost* 2008;**99**:295–304.
169. Stroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. *Neurology* 2007;**69**:546–54.
170. 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**:857–67.
171. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD *et al*. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;**383**:955–62.
172. Lauer A, Pfeilschifter W, Schaffer CB, Lo EH, Foerch C. Intracerebral haemorrhage associated with antithrombotic treatment: translational insights from experimental studies. *Lancet Neurol* 2013;**12**:394–405.
173. Fang MC, Go AS, Chang Y, Hylek EM, Henault LE, Jensvold NG *et al*. Death and disability from warfarin-associated intracranial and extracranial hemorrhages. *Am J Med* 2007;**120**:700–5.
174. Hughes M, Lip GY. Risk factors for anticoagulation-related bleeding complications in patients with atrial fibrillation: a systematic review. *QJM* 2007;**100**:599–607.
175. Lip GY, Frison L, Grind M; Invetigators S. Effect of hypertension on anticoagulated patients with atrial fibrillation. *Eur Heart J* 2007;**28**:752–9.
176. Angaran P, Dorian P, Tan MK, Kerr CR, Green MS, Gladstone DJ *et al*. The Risk stratification and stroke prevention therapy care gap in Canadian atrial fibrillation patients. *Can J Cardiol* 2016;**32**:336–43.
177. Steinberg BA, Kim S, Thomas L, Fonarow GC, Hylek E, Ansell J *et al*; Outcomes Registry for Better Informed Treatment of Atrial Fibrillation I and Patients. Lack of concordance between empirical scores and physician assessments of stroke and bleeding risk in atrial fibrillation: results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry. *Circulation* 2014;**129**:2005–12.
178. Olesen JB, Lip GYH, Lindhardsen J, Lane DA, Ahlehoff O, Hansen ML *et al*. Risks of thromboembolism and bleeding with thromboprophylaxis in patients with atrial fibrillation: a net clinical benefit analysis using a 'real world' nationwide cohort study. *Thromb Haemost* 2011;**106**:739–49.
179. Eckman MH, Singer DE, Rosand J, Greenberg SM. Moving the tipping point: the decision to anticoagulate patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes* 2011;**4**:14–21.
180. Lip GY, Skjoth F, Rasmussen LH, Larsen TB. Oral anticoagulation, aspirin, or no therapy in patients with nonvalvular AF with 0 or 1 stroke risk factor based on the CHA2DS2-VASc score. *J Am Coll Cardiol* 2015;**65**:1385–94.
181. Chao TF, Liu CJ, Wang KL, Lin YJ, Chang SL, Lo LW *et al*. Should atrial fibrillation patients with 1 additional risk factor of the CHA2DS2-VASc score (beyond sex) receive oral anticoagulation? *J Am Coll Cardiol* 2015;**65**:635–42.
182. Lahaye S, Regpala S, Lacombe S, Sharma M, Gibbens S, Ball D *et al*. Evaluation of patients' attitudes towards stroke prevention and bleeding risk in atrial fibrillation. *Thromb Haemost* 2014;**111**:465–73.
183. Elliott WJ. The economic impact of hypertension. *J Clin Hypertens (Greenwich)* 2003;**5**:3–13.

184. Boriani G, Maniadakis N, Auricchio A, Muller-Riemenschneider F, Fattore G, Leyva F *et al.* Health technology assessment in interventional electrophysiology and device therapy: a position paper of the European Heart Rhythm Association. *Eur Heart J* 2013;**34**:1869–74.
185. Hannon N, Callaly E, Moore A, Ni Chroinin D, Sheehan O, Marnane M *et al.* Improved late survival and disability after stroke with therapeutic anticoagulation for atrial fibrillation: a population study. *Stroke* 2011;**42**:2503–8.
186. Bruggenjurgen B, Rossnagel K, Roll S, Andersson FL, Selim D, Muller-Nordhorn J *et al.* The impact of atrial fibrillation on the cost of stroke: the berlin acute stroke study. *Value Health* 2007;**10**:137–43.
187. Cotte FE, Chaize G, Kachaner I, Gaudin AF, Vainchtock A, Durand-Zaleski I. Incidence and cost of stroke and hemorrhage in patients diagnosed with atrial fibrillation in France. *J Stroke Cerebrovasc Dis* 2014;**23**:e73–83.
188. Kasmeridis C, Apostolakis S, Ehlers L, Rasmussen LH, Boriani G, Lip GY. Cost effectiveness of treatments for stroke prevention in atrial fibrillation: focus on the novel oral anticoagulants. *Pharmacoeconomics* 2013;**31**:971–80.
189. Dorian P, Kongnakorn T, Phatak H, Rublee DA, Kuznik A, Lanitis T *et al.* Cost-effectiveness of apixaban vs. current standard of care for stroke prevention in patients with atrial fibrillation. *Eur Heart J* 2014;**35**:1897–906.