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Atrial fibrillation: villain or bystander in vascular brain injury

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Atrial fibrillation (AF) and stroke are inextricably connected, with classical Virchow pathophysiology explaining thromboembolism through blood stasis in the fibrillating left atrium. This conceptualization has been reinforced by the remarkable efficacy of oral anticoagulant (OAC) for stroke prevention in AF. A number of observations showing that the presence of AF is neither necessary nor sufficient for stroke, cast doubt on the causal role of AF as a villain in vascular brain injury (VBI). The requirement for additional risk factors before AF increases stroke risk; temporal disconnect of AF from a stroke in patients with no AF for months before stroke during continuous ECG monitoring but manifesting AF only after stroke; and increasing recognition of the role of atrial cardiomyopathy and atrial substrate in AF-related stroke, and also stroke without AF, have led to rethinking the pathogenetic model of cardioembolic stroke. This is quite separate from recognition that in AF, shared cardiovascular risk factors can lead both to non-embolic stroke, or emboli from the aorta and carotid arteries. Meanwhile, VBI is now expanded to include dementia and cognitive decline: research is required to see if reduced by OAC. A changed conceptual model with less focus on the arrhythmia, and more on atrial substrate/cardiomyopathy causing VBI both in the presence or absence of AF, is required to allow us to better prevent AF-related VBI. It could direct focus towards prevention of the atrial cardiomyopathy though much work is required to better define this entity before the balance between AF as villain or bystander can be determined.

Context of atrial fibrillation and vascular brain injury

Importance of atrial fibrillation-related stroke in the setting of decreasing burden of other stroke risk factors in developed countries

At the population level, atrial fibrillation (AF) and stroke are inextricably intertwined. A significant world-wide

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increase in AF prevalence has been projected over the next decades.[1,2] With the population aging, lifetime AF risk has increased to 1:3 of European descent, and 1:5 African Americans.[3] Whereas stroke incidence after AF onset decreased in earlier studies,[4] this has not continued in the last decade,[5] until the last 3 years when oral anticoagulant (OAC) use increased, with a concomitant reduction in AF-related stroke.[6,7] The prevalence of AF in ischaemic stroke has risen,[8] and one in three strokes remains associated with AF.[9]

The future importance of AF-related strokes becomes evident when compared to overall trends of decreasing ischaemic stroke incidence and mortality in adults ≥60 years, and less pronounced, in mid-life.[10,11] Approximately 20% reduction in stroke incidence was observed in community cohorts[10,12] and inpatient datasets over the last decades.[13,14] More than 1:4 mid-life strokes were AF-related.[10] Trends were explained by lower smoking prevalence, better blood pressure, and cholesterol control, whereas obesity prevalence increased.[10,15] In contrast, ischaemic stroke hospitalizations in younger adults did not follow these trends and increased since the mid-90s in parallel with the rising prevalence of their stroke and AF risk factors, especially hypertension, and more than doubling of obesity, smoking, dyslipidaemia, and diabetes. A small but significant rise in AF between 45 and 64 years was reported in both women and men,[16] whereas in younger adults, diagnosed AF played a lesser role, with prevalence <10% in stroke.[16]

In the context of the above changes in demographics and risk factor burden, the attributable proportion of AF-explained stroke will also increase in all age groups. In the Oxford Vascular Study almost half disabling or fatal ischaemic strokes in patients aged ≥80 years were attributed to AF.[17] The authors observed three-fold higher AF-related strokes over 25 years despite broad OAC availability and projected a similar increase by 2050. No right-shift towards older individuals on average is expected. Healthcare costs, in particular acute stroke care with AF are higher compared to other stroke entities.[18] Notwithstanding the large impact of OAC prophylaxis,[7] a better understanding of the pathophysiological relationship between AF and stroke including true AF-related stroke burden, is necessary to address risk factors specific to AF[15] and effective prevention of AF-related strokes.

Increasing recognition of atrial fibrillation-related dementia and cognitive decline

Stroke has been the main focus of brain injury in AF, and recommendations for OAC to reduce stroke are well entrenched[19] with solid, consistent results indicating large treatment effects in relatively small randomized trials.[20] Recently, however, the association between AF and dementia or cognitive impairment has received increasing attention. Alzheimer's disease and vascular dementia are increasing globally as the population ages and dies less from competing causes. There is no specific effective therapy, providing an imperative to seek preventive measures. Because AF is similarly increasing, it is not surprising that associations have been made between AF presence and subsequent dementia,[21] independent of clinical stroke.[22] These associations are consistently found in cohort studies, registries, and administrative databases, with hazard ratios between 1.34 and 1.52.[21–24] The potential that AF is causal is intuitive but unproven: AF is related to, or results in cardioembolic silent ischaemic brain infarcts. In the seminal Swiss-AF study,[25] MRI imaging showed multiple clinically known or silent infarcts, with large non-cortical or cortical infarcts related to lower cognitive function. This also fuels the interesting proposition that OAC therapy might reduce cognitive decline and dementia.[26]

Observational studies suggest that OAC therapy for AF may prevent the onset of dementia, or slow cognitive decline. Three Swedish registry studies showed those with AF given OAC therapy were less likely to develop dementia over a few years.[22,27,28] The 2019 Swedish study is notable for examining younger patients with lower $CHADS_2$-VA scores ≤1, who also showed the same changes.[28] Nevertheless, despite adjusting for multiple covariates or propensity score matching, there is always a concern in observational studies that the decision not to anticoagulate includes subliminal cues of reduced cognition, so residual confounding contributes to the OAC therapy association with less subsequent dementia. This may be less likely in the study examining younger (age ≤74), lower-risk patients,[28] though benefit using a composite brain outcome of dementia or ischaemic stroke, was restricted to patients aged 64–74: in those aged <60, there appeared to be harm with OAC therapy.

Another approach compared to lower and higher time in therapeutic range (TTR) only in those on OAC:[29] reduced dementia was confined to those with TTR in the highest two quartiles. Ultimately, randomized controlled trials will be required to settle the question. This will be examined in the BRAIN-AF study,[30] with results eagerly awaited.

While 'silent' cardioembolism to the brain is the obvious mechanism for both AF-related dementia/cognitive impairment and its prevention by OAC, there are alternate hypotheses.[31,32] These include lower brain perfusion in persistent AF,[33,34] shared risk factors for vascular dementia not adequately controlled for in multivariable adjustment,[32,35] and the intriguing possibilities of thrombin activation directly causing neuronal damage when the blood-brain barrier is compromised, or indirectly via cerebrovascular damage or thrombosis.[36–40] In a mouse Alzheimer's disease model,[36] Dabigatran (direct anti-thrombin) slowed deterioration in cognitive function, and many pathological changes associated with disease progression, suggesting that OAC may work in any dementia, potentially in the absence of AF. Against this, in the Swiss study,[25] many clinically unrecognized brain lesions were seen despite ~90% taking OAC, though it is uncertain whether brain lesions predated OAC prescription. The precise relationship between AF and VBI leading to dementia/cognitive decline, and the role of OAC in its prevention, is certainly worthy of a more intensive research focus.

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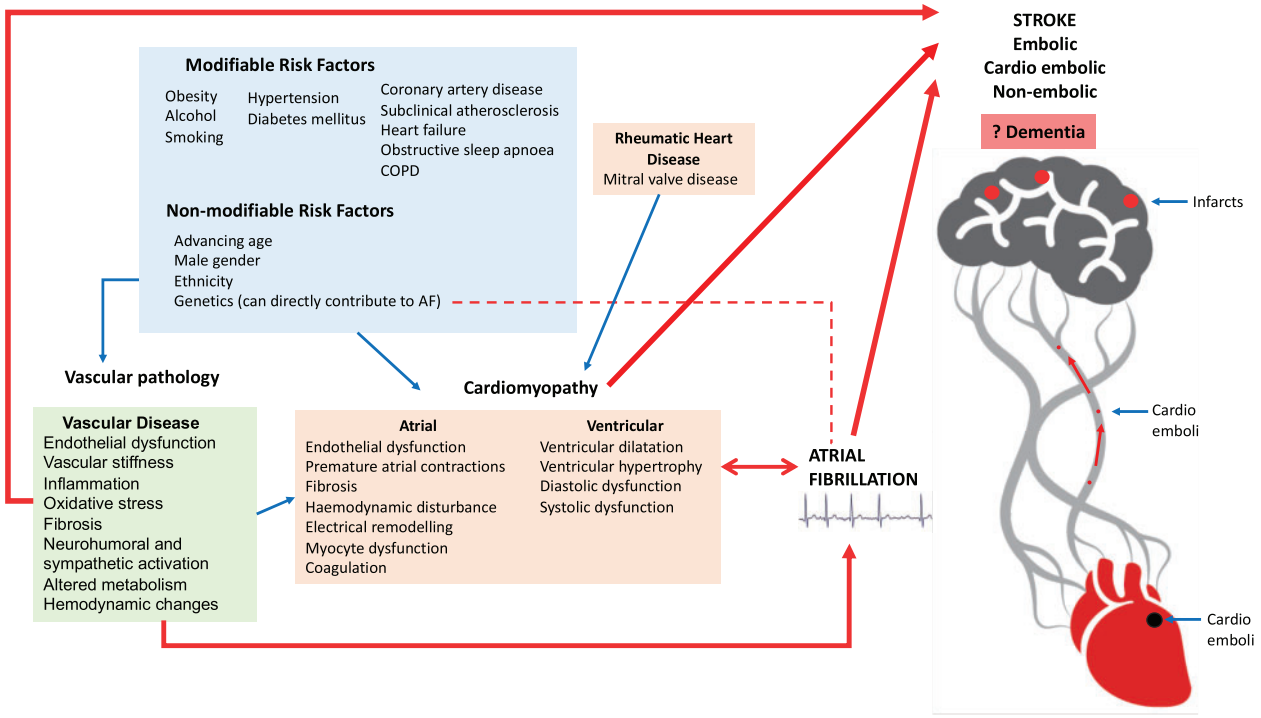

Figure 1. Links between risk factors, vascular dysfunction, cardiomyopathy, AF, and VBI.

Unresolved questions about mechanisms of vascular brain injury in atrial fibrillation

Temporal disconnection

The pathogenesis of thrombus formation follows Virchow's triad for thrombogenesis: alterations in blood flow, vascular endothelium, and hypercoagulability. The strong association between AF and VBI has long been thought directly caused by blood stasis in the fibrillating left atrium leading to thrombus formation and brain embolism.[41,42] Recent data indicate this cannot entirely explain the relationship. In studies demonstrating association between subclinical device-detected AF and stroke, approximately one-third with AF and stroke had no evidence of AF before stroke and only manifested AF for the first time after stroke.[43–46] Only a minority of patients with stroke had AF during the 30 days preceding stroke.[46] There are two potential explanations for temporal dissociation between AF and stroke. First, the association between AF and stroke may reflect residual confounding from shared vascular risk factors (*Figure 1*), which are more prevalent in AF. Therefore, some strokes before AF onset may result from large-artery atherosclerosis and artery-to-artery embolism, or hypertension-induced cerebral small-vessel occlusion. Second, new AF after stroke may be a lagging marker of thrombogenic left atrial (LA) substrate.[47] Markers of atrial myopathy, e.g., LA enlargement, impaired mechanical function, myocyte injury, and fibrosis, have been associated with stroke risk independent of AF.[48–52] These two explanations are not mutually exclusive. Further investigation is required to determine their relative role, but the strong link between AF and VBI cannot be explained by arrhythmia alone.

Effect modification by systemic substrate

For AF to be the direct cause of atrial thromboembolism and VBI, AF should be *necessary* and *sufficient* for thromboembolism. The evidence outlined above is inconsistent with AF being *necessary* for thromboembolism. If AF were *sufficient* for thromboembolism, then AF should be associated with thromboembolism regardless of systemic risk factors. However, patients with clinical AF but no vascular risk factors do not have a higher ischaemic stroke risk than patients without AF.[53] Conversely, clinical AF with other vascular risk factors increases stroke risk,[54] though against this, even very-low-risk patients with paroxysmal AF show hypercoagulability.[55] There is evidence of significant interaction between systemic substrate and AF in stroke risk. The CHA_2DS_2-VASc score, summarizing systemic vascular risk factor burden,[56] modifies the association between AF and stroke.[57] The presence of such effect modification suggests AF is not *sufficient* for LA thromboembolism and that thromboembolism requires an interplay between AF, systemic substrate, and hypercoagulability.

Atrial fibrillation cardioversion and increased stroke risk: association or causal?

One of the critical reasons for invoking a direct causal relationship between AF and VBI is the long-recognized association between AF cardioversion and cardioembolic stroke.[58] This occurs in both electrical and chemical cardioversion, and potentially also in spontaneous cardioversion. Observational studies showing OAC reduce thromboembolism from 2.0% to 0.3% have guided the management of patients undergoing direct current cardioversion for many years.[59] Cardioversion is recommended without prior OAC only when the duration of AF is known and brief.[19,60,61]

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When AF duration is longer, or unknown, or if AF is persistent, then OACs are required before and after cardioversion to prevent stroke. Even if the LA appendage is free of clot before cardioversion, atrial cardiomyopathy, and stunning can lead to clot formation and cardioembolism after cardioversion,[62] so OAC is always required for 4 weeks after the procedure, regardless of CHA_2DS_2-VASc score.[63]

Further retrospective observational work from the Finnish group suggested that risk was increased even when AF duration was $>12<48$ h.[64] A recent study confirmed early risk <48 h without anticoagulation,[65] but the exact duration before stroke risk rises is unknown. Whatever the time window, conventional wisdom is that change from AF to sinus rhythm, with the return of atrial function, is the reason for cardioembolism and stroke. This notion has been questioned in a recent analysis of the ACTIVE trials in which 962/10 889 patients randomized to single or dual antiplatelet therapy underwent cardioversion during the study.[66] Stroke risk was increased post-cardioversion as anticipated, but was also increased in the pre-cardioversion period, though only for those hospitalized for a cardiovascular reason, particularly heart failure, prior to cardioversion. This suggests risk factors and comorbidities may be more important than change in rhythm for cardioembolism. While intriguing, further corroboration is required because cardioembolic event numbers were small: only four pre-cardioversion and nine post-cardioversion.

Role of cardiac and atrial substrate in relation to vascular brain injury

Patients with known atrial fibrillation

Several cardiac variables are associated with thromboembolism risk and VBI in patients with known AF (*Figure 2*). (i) LA size and morphology are related to stroke risk in AF. Left atrial enlargement has long been established as a risk factor for stroke in AF patients.[67] Left atrial appendage shape also appears to modify risk: e.g. 'chickenwing-shaped' appendages are associated with lower stroke risk than other morphologies.[68] (ii) Left atrial and appendage function are risk factors for AF-related thromboembolism. Lower LA appendage flow velocity, and related spontaneous echo contrast, are associated with thromboembolism in AF.[69,70] The association between flow abnormalities and appendage thrombus suggests causality.[69] Left atrial strain, an early marker of LA dysfunction, has also been associated with AF stroke risk.[71,72] (iii) Atrial remodelling is associated with AF stroke risk. Larger LA fibrosis extent detected by late gadolinium enhancement on cardiac MRI, is associated with AF stroke risk,[51,73] and also LA appendage thrombus,[74] lending further support for a causal relationship between atrial fibrosis, thrombo-embolic stroke, and VBI. ECG markers of LA remodelling are also associated with AF-related stroke risk.[75,76]

Several MRI and ECG variables have been shown to improve stroke risk prediction beyond traditional clinical risk factors.[70,73,75,76] Two serum biomarkers of myocardial stress and injury, N-terminal B-type natriuretic peptide (NT-proBNP) and cardiac troponin, presumably manifestations of thrombogenic cardiac, and atrial substrate, have also been shown to improve stroke risk prediction compared to CHA_2DS_2-VASc alone.[77]

Patients without known atrial fibrillation

While atrial cardiomyopathy contribution to AF-related thromboembolism is well appreciated,[67,78] it now appears that atrial cardiomyopathy can be involved in atrial thromboembolism in the absence of AF. (i) LA size and morphology may be associated with stroke independently of AF. There are conflicting reports on the relationship between LA size and VBI without AF or after adjustment for known AF, and more data are required to test this relationship. After adjustment for AF, two early population-based studies found that echocardiographic LA size was associated with stroke risk, but only in men.[48,79] More recent studies found a relationship regardless of sex,[80–83] and identified a subgroup with embolic strokes of undetermined source (ESUS) benefitting from anticoagulation,[84] while others found no association between LA size and stroke risk.[52,85] Patients with cardioembolic stroke or ESUS without AF may also have a higher prevalence of *non*-chickenwing or other high-risk appendage morphology than patients with non-cardioembolic stroke.[86,87] (ii) LA and appendage function on echocardiography[83,88] and cardiac MRI[52] are risk factors for thromboembolism/VBI independent of AF. (iii) Remodelling and LA tissue substrate are associated with stroke risk independent of AF. A small case–control study suggests LA fibrosis on MRI is more common in ESUS than controls.[89] Similarly, multiple population studies have found consistent associations between ECG markers of LA remodelling and stroke risk,[50,85,90–92] particularly embolic-appearing stroke.[91,92]

Role of atrial fibrillation-burden

The concept of AF burden was coined to describe the range of duration of paroxysmal AF, compared to long-term persistent AF, where AF burden approaches 100%. For many years, guidelines emphasized that paroxysmal AF prognosis/stroke risk was no different from persistent/permanent AF.[93,94] Recent studies have shown that stroke risk of paroxysmal AF is lower than non-paroxysmal AF,[95] albeit not sufficiently low that OAC is not recommended.[60,96,97] Interest in burden has been spurred by studies examining prognostic implications of largely asymptomatic subclinical AF detected by implanted electronic devices, which appears associated with lower stroke risk than clinical AF.[98,99] Meta-analyses show that stroke risk of patients with only shorter episodes e.g. <24 h, or lower daily AF burden (<5.5 h), is less than for patients with a greater burden or longer episode length.[100,101]

Recently, an AHA scientific statement recommended the concept of AF burden [including longest episode duration, number of episodes, or proportion of time (%) in AF during a given monitoring period] be incorporated into considerations of AF, rather than as a binary concept i.e. AF presence or absence.[102] However, it was unclear whether stroke risk increases continuously with AF burden or whether a threshold exists, and if so, its definition. Atrial fibrillation-burden must also be defined in relation to duration and temporal distribution of AF monitoring—ranging from intermittent

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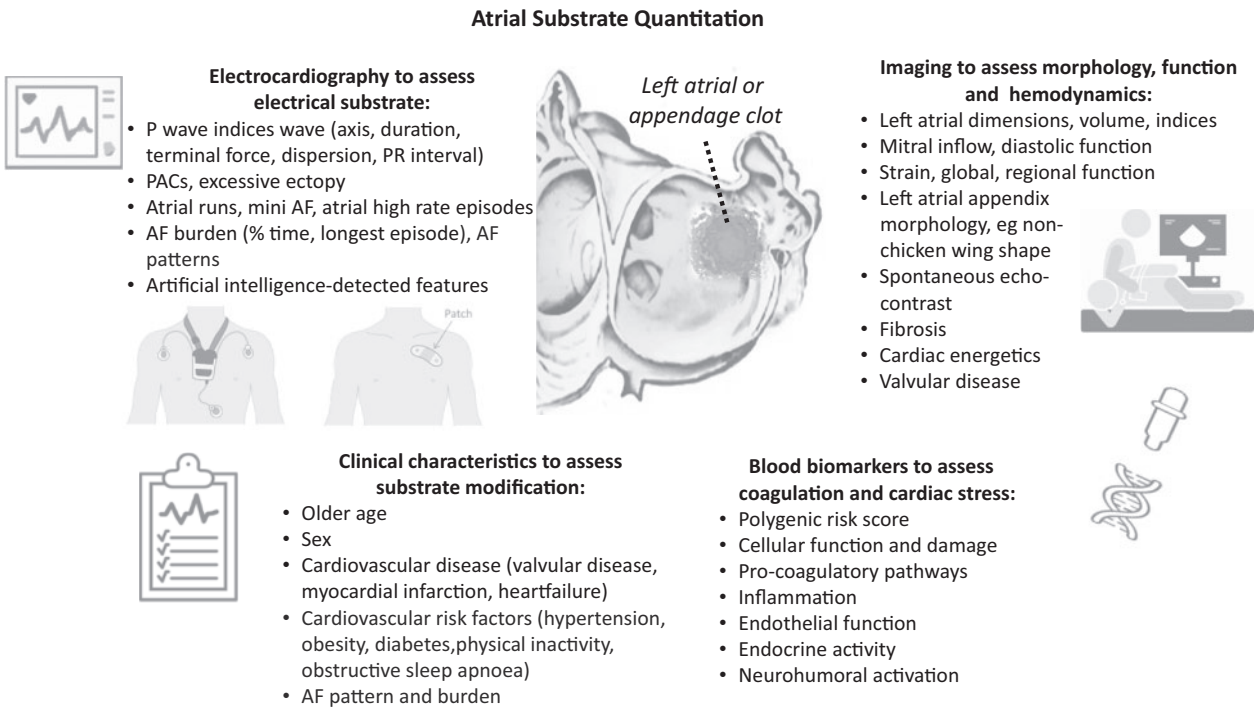

Figure 2. Quantitation of atrial substrate/atrial cardiomyopathy.

30 s snapshots over 2 weeks or 1 year, or continuous monitoring of various durations and repetitions by external ECG devices, or by continuous monitoring over years by implanted monitors.[103] In the KP-RHYTHM study of 2-week patch recordings performed for a clinical indication, only AF burden in the highest tertile (>11% of the total period) was associated with increased stroke risk.[104] Yet in patients given an identical patch to screen for unknown AF, those discovered with AF had a much lower median burden (0.9%, IQR (interquartile range) <1.0%–4.0%) than in the KP-RHYTHM study (4.4%, IQR 1.1%–17.23%).[104–106] Therefore, it is uncertain whether prognostically significant burden will have an absolute threshold, or vary depending on the indication for recording. Recently, patients with paroxysmal self-terminating AF followed with continuous implanted rhythm monitoring for 6 months demonstrated a very heterogeneous temporal AF pattern:[107] one-third showed no recurrence, while in those with recurrences, longer AF episodes and higher AF burden was associated with more severe underlying comorbidities.

Whatever the relationship, one has to carefully consider whether AF burden, however defined, acting solely as an arrhythmia, is directly related to the likelihood of VBI, or whether high AF burden is in fact a surrogate measure of the presence or severity of an underlying atrial or general cardiomyopathy which determines the thrombo-embolic potential. Lower burden short episodes with a benign prognosis,[108] may be more driven by arrhythmic triggers. Much more work is required to answer these questions, though the ongoing ARTESIA[109] and NOAH-AFNET6[110] studies will provide some answers.

Is atrial cardiomyopathy a manifestation of a general cardiomyopathy?

Traditional risk factors for developing AF including advancing age, hypertension, heart failure, coronary artery disease, diabetes mellitus, and valve disease are well known (*Table 1*).[72] It has become increasingly clear that almost all AF patients have either traditional, or borderline or less-established risk factors.[111,112] Weijs *et al*. showed that almost half originally diagnosed with 'lone AF' developed cardiovascular disease within 5 years.[113] Patients with 'lone AF' have abnormal left ventricular function and energetics even after successful ablation, suggesting more generalized cardiomyopathy.[114] Moreover, almost all patients presenting with AF to emergency departments without traditional AF risk factors appeared to have less-established/borderline risk factors.[115] Thus, 'lone AF', i.e., AF without risk factors or comorbidity, seems extremely rare.[116]

Atrial cardiomyopathy results from progressive atrial remodelling due to aging and stretch. Atrial stretch is a consequence of pressure and/or volume overload due to risk factors and comorbidities, eventually triggering atrial dilatation, dysfunction, and fibrosis, i.e., atrial cardiomyopathy (*Figure 3*).[117–119] Once AF develops, the atrial cardiomyopathy further deteriorates. Due to underlying risk factors and comorbidities an overall cardiomyopathy develops, including ventricular involvement.[114] Thus, an in-depth search for risk factors and comorbidities is key, not only to prevent hospitalizations but also the occurrence of major adverse cerebro- and cardiovascular events (MACCE), including stroke and other VBI resulting from the cardiomyopathy (*Figure 3*).

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Table 1. Overview of modifiable and non-modifiable risk factors for non-valvular AF

Non-modifiable	Modifiable
Conventional risk factors	**Conventional risk factors**
Age	Hypertension
Male sex	Heart failure
Genetic factors	with reduced ejection fraction
Increased height	with preserved ejection fraction
Less established risk factors	Diabetes mellitus
Ethnic background	Coronary artery disease
	Valvular disease
	Hyperthyroidism
	Obesity
	Less established risk factors
	Chronic obstructive pulmonary disease
	Obstructive sleep apnoea
	LA dilatation
	Atrial conduction delay/long PR interval
	Left ventricular diastolic function
	Left ventricular hypertrophy
	Subclinical atherosclerosis
	Borderline hypertension
	Chronic kidney disease
	Subclinical hyperthyroidism
	Hypothyroidism
	Inflammation
	Chronic inflammatory diseases
	Pulse pressure
	Vigorous exercise
	Physical inactivity
	Excessive alcohol intake
	Increased birth weight
	Depression
	Psychosocial stress
	Smoking

Atrial fibrillation: risk marker or risk factor or both

The available evidence suggests that AF is *both* an independent, causal risk factor for LA thromboembolism and a marker of an underlying, thrombogenic atrial substrate that can lead to LA thromboembolism independently of AF.

Atrial fibrillation as an independent, causal risk factor for left atrial thromboembolism

(i) *AF and LA stasis*. Patients in AF have lower LA appendage flow velocities than patients in sinus rhythm. Sinus rhythm restoration after AF ablation is associated with significant improvement in LA appendage flow velocity.[120] The robust association between reduced LA appendage flow velocity in AF and LA thrombus,[69] and clinical evidence of temporary stroke risk increase during periods of active AF,[42] supports the longstanding hypothesis that AF leads to relative stasis of blood flow in the left atrium and LA appendage, in turn leading to thrombus formation and embolization. (ii) *AF and LA substrate remodelling*. In addition to immediate LA hemodynamic effects, sustained AF leads to atrial contractile dysfunction and dilatation which in turn leads to atrial remodelling and fibrosis.[121,122] Therefore, it appears likely AF directly increases thromboembolic risk via haemodynamic effects, and indirectly via remodelling which drives thrombogenic atrial substrate (atrial cardiomyopathy).

Atrial fibrillation as marker of underlying thrombogenic atrial substrate

As outlined above, abnormal atrial substrate markers are associated with thrombo-embolic risk with or without clinically apparent AF. Moreover, it is difficult to develop a model of AF-related thromboembolism that fully fits available data without accounting for thrombogenic atrial substrate. Incorporating atrial substrate as an independent cause of thromboembolism results in a more satisfactory model in which age- and disease-related atrial remodelling result in atrial substrate prone to both AF and thromboembolism. Usually, AF occurs first and thromboembolism later, but sometimes the order is reversed, and in either case, there is not necessarily a close temporal relationship between episodes of AF and thromboembolism. This would explain the notable temporal disconnection between subclinical AF and stroke.[43-45] As AF progresses and becomes more sustained, it exerts an independent remodelling effect on the atrium, worsening the thrombogenic atrial substrate. This would explain the relationship between AF burden and stroke. Recent experimental data show that the hypercoagulable state during AF causes pro-fibrotic and pro-inflammatory responses in adult atrial fibroblasts and the development of a substrate for AF in both transgenic mice and goats with persistent AF,[122] illustrating the further complexity of the relationship.

Implications of updated model of atrial fibrillation and vascular brain injury

Population screening for atrial fibrillation before stroke

Whether AF is a villain or bystander, OAC thromboprophylaxis of AF-related cardioembolic risk unquestionably reduces ischaemic stroke by a large margin. Stroke is often the first manifestation of AF before symptoms of AF are recognized, with up to 10% of ischaemic strokes associated with previously unknown AF, detected first at the time of stroke,[123] and even more, with monitoring after stroke.[124] This has fuelled the push to detect asymptomatic AF by opportunistic or systematic screening as a stroke-prevention strategy in those at increased risk of AF and/or stroke.[125] Single-timepoint screening will detect unknown AF in 1.4% of people aged $\geq$65, and most AF found this way has high enough stroke risk to justify OAC thromboprophylaxis.[126] This type of screening identifies largely non-paroxysmal AF. While the prognosis untreated is unknown, it is likely the same as incidentally-detected asymptomatic AF

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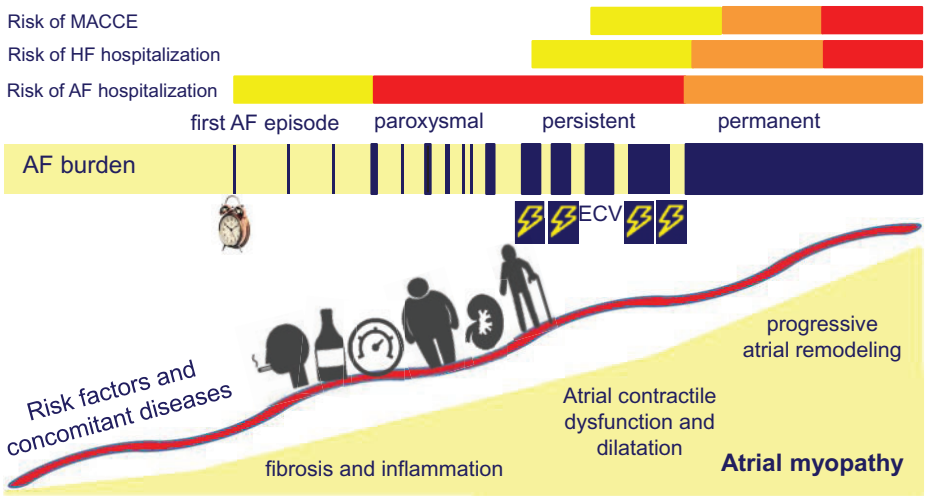

Figure 3: Risk factors, co-morbidities, and AF all involved in the development of an atrial cardiomyopathy (modified from Kloosterman *et al.*[117] with permission).

discovered in primary care, which has a similar stroke rate as clinical AF.[127] Accordingly, opportunistic single-timepoint AF screening is recommended by guidelines, consensus documents, and white papers.[63,125,128,129]

The place of systematic screening using greater screening intensity, including continuous ECG recordings, is less certain, because stroke risk may be lower if the detected AF burden is lower.[130] This has led to an 'I' recommendation (insufficient evidence) by USPSTF regarding ECG screening to prevent stroke.[131] To change this recommendation requires randomized studies showing systematic screening strategies will do more good than harm. There are a number of large ongoing trials set up to answer this question,[103,132,133] and more have commenced (SAFER ISRCTN16939438, GUARD-AF NCT04126486), so we will soon know whether such screening will reduce AF-related stroke burden. It is also important to consider other VBI endpoints including dementia that might be impacted by OAC, but cognitive assessment is not part of most ongoing screening studies.

Upstream therapy/lifestyle interventions

An important unmet need in patients with AF is improved long-term maintenance of sinus rhythm and prevention of cardiovascular events.[134,135] This has led to the concept that 'upstream therapy' or 'prevention of atrial remodelling' could improve the outcome of rhythm control therapy and prognosis in patients with AF.[136] Retrospective and observational studies with ACE (angiotensin converting enzyme) inhibitors, ARBs (angiotensin receptor blockers), and statins have shown encouraging results in reducing AF recurrences. Larger prospective randomized trials, however, failed to show a significant reduction in AF recurrences or adverse cardiovascular outcomes, possibly because these studies addressed only one risk factor.[137,138] More recently, intervening in a combination of risk factors including lifestyle seemed beneficial.[139-143] An important randomized structured weight loss and exercise intervention in overweight patients with symptomatic AF led to a greater reduction of weight, AF burden, and symptoms than routine care,[139] with further similar non-randomized studies confirming beneficial effects of sustained weight loss of 10% body mass index.[139-143] While this approach may be difficult to replicate in routine practice, it would be important to establish whether it restores atrial function and reverses remodelling and substrate change. In contrast to this approach, the RACE 3 trial showed feasibility and efficacy of comprehensive cardiovascular risk reduction in patients with persistent AF and moderate heart failure.[143] Upstream therapy (including ACE-inhibitor/ARB, mineralocorticoid receptor antagonist, statin, guided regular sports program and dietary advice, and counselling to improve physical activity and drug adherence), reduced blood pressure and NT-proBNP levels more than conventional treatment. Moreover, sinus rhythm was maintained more often at 1 year of follow-up.[143] Our focus must therefore broaden from a concern just about rhythm to one addressing risk factors and comorbidities: 'joint upstream and downstream therapy can provide a double lock to slow AF progression'.[135] One suspects this strategy, if successful, will also reduce VBI, but the proof is urgently needed.

Management of embolic stroke of undetermined source

A thrombogenic atrial myopathy leading to VBI independently of AF has important implications for the management of ESUS.[144] (i) Atrial myopathy may explain a substantial proportion of strokes that are currently classified as ESUS. The term *ESUS* applies to ischaemic strokes that appear embolic but lack an identifiable embolic source.[145] Since AF is currently a required criterion for establishing an atrial thrombo-embolic source, strokes resulting from LA thromboembolism without AF are currently classified as ESUS. In this context, accumulating evidence linking atrial myopathy and thromboembolism suggests many ESUS cases may actually be cardioembolic strokes. (ii) Many cases of ESUS result from non-stenosing atherosclerotic plaque. Some cases of ESUS represent artery-to-artery embolism from atherosclerotic plaques that currently go unrecognized because there is $<50\%$

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arterial lumen stenosis,[146-148] i.e., below the criterion for large-artery atherosclerotic source.[149] (iii) Aetiological heterogeneity of ESUS explains the lack of OAC benefit in ESUS trials. Two large randomized clinical trials found OAC therapy did not reduce stroke recurrence post-ESUS.[150,151] It is increasingly accepted these trials had neutral results because OAC provided no benefit in the large subset with non-stenosing atherosclerotic plaques.[144,152] (iv) OACs may benefit the ESUS subset with atrial myopathy. Given the close connection between atrial myopathy and AF, and the proven benefit of anticoagulation for stroke prevention in AF, it is plausible that anticoagulation may also reduce stroke risk in atrial myopathy without AF. *Post hoc* subgroup-analyses of two randomized clinical trials finding no overall benefit suggest that OACs reduce recurrent stroke in patients with markers of atrial myopathy.[153,84] This hypothesis is being prospectively tested in the ongoing ARCADIA trial, enrolling only the ESUS subset with evidence of atrial myopathy.[154]

Post-stroke search for atrial fibrillation and quantification of atrial substrate

Since the role of AF and atrial substrate in stroke and its high risk of recurrence is assumed, a post-stroke search for these conditions should be implemented in clinical practice (*Figure 2*).[124] To render the post-stroke search for AF efficient, the intensity of AF monitoring could be determined by the underlying atrial substrate.[119] Abnormal substrate may result in disturbances of action potential/ion-channel properties, Ca^{++}-handling, intercellular coupling properties, and autonomic regulation through neighbouring ganglia. Left atrial reservoir and booster-pump function may be impaired, microvascular function disturbed, and the complex three-dimensional structure altered, even in 'lone AF'.[155-157] However, non-invasive quantitation of these remains a challenge. Most alterations correlate with age and prevalent cardiovascular disease.[119] They may all modify atrial substrate prothrombotic characteristics and have been used to define subsets with a higher probability of post-stroke AF.[84,158,159]

Electrophysiological changes, many detected on the surface ECG, may be more specific for advanced atrial impairment. These include increased P wave terminal force, P or PR prolongation, or excessive supraventricular ectopic activity,[75,160-162] or short atrial runs.[163] They are related to AF post-stroke, but with small effect size.

Echocardiographic measures of left atrial (LA) size and function are broadly available. Rheumatic mitral stenosis indicates a highly prothrombotic milieu. Consistent data are available for standardized LA size/volume measurements and their predictive value for AF post-stroke,[84,164,165] as well as tissue Doppler measures of diastolic function.[166] Echocardiographic LA strain imaging showed a good discriminatory ability for AF diagnosis post-stroke.[167,168] Other imaging techniques may be more specific for architectural and functional changes but are not yet widely available.[169]

Blood biomarkers and genetics applied as polygenic risk scores[170] may be indicative of AF-related stroke. Markers of hypercoagulability have been related to post-stroke AF,[171,172] or, more generally, thyroid-stimulating hormone.[162] Cardiac biomarkers including troponins and natriuretic peptides as markers of cardiac stress are associated with thrombo-embolic propensity.[173] NT-proBNP is strongly associated with post-stroke AF and could to be used to guide the intensity of post-stroke AF-search.[171,174,175] However, if the concept of atrial myopathy is robust, a search for arrhythmia may not remain the major pillar for OAC therapeutic decisions.

Future directions

Working definition and quantitation of atrial cardiomyopathy

Atrial cardiomyopathy is central in patients with AF and determines rhythm and VBI (*Figure 2*).[119,176] Unfortunately, there is no uniform working definition nor risk score for clinical practice. Recently, atrial cardiomyopathy has been characterized as any complex of structural, architectural, contractile, or electrophysiological changes affecting the atria with the potential to produce clinically relevant manifestations.[119] Four classes were defined based on histological changes. Echocardiography is currently the imaging technique of choice. Two-dimensional speckle-tracking echocardiography and atrial strain have been used as more sensitive markers to detect early functional remodelling before anatomical changes occur. Cardiac CT (computed tomography) or MRI (magnetic resonance imaging) can be used for a more accurate assessment of atrial volumes, while late gadolinium enhancement on MRI may quantify atrial fibrosis.[177] Further refining from blood biomarkers may provide information on the underlying pathophysiology. An easy to use practical definition and/or risk score should include combinations of clinical, imaging, and blood biomarker data, taking into account pathophysiological contributors and their consequences, and is urgently needed.

Defining mechanisms of vascular brain injury from cardiac disease and atrial fibrillation

Cardiac disease is clearly associated with VBI.[83,90,178,179] Apart from cardioembolism from the left atrium (which has been visualized by transoesophageal echocardiography),[180] the role of other mechanisms including cardiac microemboli, hypoperfusion, shared risk factors, and unknown factors require elucidation. (i) Compared to controls, patients with sources of cardiac embolism have a higher rate of microemboli in the intracranial circulation.[181,182] (ii) Among patients with known cardiovascular disease, the lower cardiac output appears to be associated with more severe cerebral white matter disease[183] and reduced brain volume[184] on MRI. (iii) Unmeasured confounding from shared risk factors will always be a distractor, but their severity requires a better definition: e.g. hypertension, leading to heart failure and cerebral white matter disease. (iv) A higher prevalence of atherosclerosis in cardiac disease[185,186] may be difficult to detect in the aorta. (v) Unknown mechanisms linking cardiac disease and VBI are likely, with novel determinants including aortic stiffness

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and its effect on brain pulsatility,[187] and thrombin activation.[36–40]

Conclusion

The relationship between AF, cardiac disease, and VBI remains enigmatic and will require much future research to determine whether AF is more bystander than a villain.

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REFERENCES

1. Di Carlo A, Bellino L, Consoli D, Mori F, Zaninelli A, Baldereschi M, Cattarinussi A, D'Alfonso MG, Gradia C, Sgherzi B, Pracucci G, Piccardi B, Polizzi B, Inzitari D, Aliprandi ML, Bonsangue E, Locatelli P, Saurgnani P, Senziani LG, Tarantini D, Rota RP, Boninsegni R, Feltrin T, Lancia E, Latella F, Monici G, Portera F, Ceccherini S, Borello G, Contartese A, D'Amico A, D'Urzo G, Grillo GC, Mellea F, Ramondino C; National Research Program: Progetto FAI. La Fibrillazione Atriale in Italia. Prevalence of atrial fibrillation in the Italian elderly population and projections from 2020 to 2060 for Italy and the European Union: the FAI Project. *Europace* 2019;**21**:1468–1475.
2. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH Jr, Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M, Murray CJ. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014;**129**:837–847.
3. Mou L, Norby FL, Chen LY, O'Neal WT, Lewis TT, Loehr LR, Soliman EZ, Alonso A. Lifetime risk of atrial fibrillation by race and socioeconomic status: ARIC study (Atherosclerosis Risk in Communities). *Circ Arrhythm Electrophysiol* 2018;**11**:e006350.
4. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, Newton-Cheh C, Lubitz SA, Magnani JW, Ellinor PT, Seshadri S, Wolf PA, Vasan RS, Benjamin EJ, Levy D. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet* 2015;**386**:154–162.
5. Chamberlain AM, Brown RD, Alonso A, Gersh BJ, Killian JM, Sa W, Vl R. No decline in the risk of stroke following incident atrial fibrillation since 2000 in the community: a concerning trend. *J Am Heart Assoc* 2016;**5**:e003408.
6. Cowan JC, Wu J, Hall M, Orlowski A, West RM, Gale CP. A 10 year study of hospitalized atrial fibrillation-related stroke in England and its association with uptake of oral anticoagulation. *Eur Heart J* 2018;**39**:2975–2983.
7. Freedman B. Major progress in anticoagulant uptake for atrial fibrillation at last: does it translate into stroke prevention? *Eur Heart J* 2018;**39**:2984–2986.
8. Alkhouli M, Alqahtani F, Aljohani S, Alvi M, Holmes DR. Burden of atrial fibrillation-associated ischemic stroke in the United States. *JACC Clin Electrophysiol* 2018;**4**:618–625.
9. Yiin GS, Li L, Bejot Y, Rothwell PMJS. Time trends in atrial fibrillation-associated stroke and premorbid anticoagulation: population-based study and systematic review. *Stroke* 2019;**50**:21–27.
10. Aparicio HJ, Himali JJ, Satizabal CL, Pase MP, Romero JR, Kase CS, Beiser AS, Seshadri SJS. Temporal trends in ischemic stroke incidence in younger adults in the Framingham Study. *Stroke* 2019;**50**:1558–1560.
11. GBD 2016 Stroke Collaborators Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019;**18**:439–458.
12. Koton S, Schneider AL, Rosamond WD, Shahar E, Sang Y, Gottesman RF, Coresh JJJ. Stroke incidence and mortality trends in US communities, 1987 to 2011. *JAMA* 2014;**312**:259–268.
13. Rand K, Dahl FA, Viana J, Rønning OM, Faiz KW, Barra M. Fewer ischemic strokes, despite an ageing population: stroke models from observed incidence in Norway 2010–2015. *BMC Health Serv Res* 2019;**19**:705.
14. George MG, Tong X, Bowman B. Prevalence of cardiovascular risk factors and strokes in younger adults. *JAMA Neurol* 2017;**74**:695–703.
15. Lackland DT, Roccella EJ, Deutsch AF, Fornage M, George MG, Howard G, Kissela BM, Kittner SJ, Lichtman JH, Lisabeth LDJS. Factors influencing the decline in stroke mortality: a statement from the American Heart Association/American Stroke Association. *Stroke* 2014;**45**:315–353.
16. George MG, Tong X, Kuklina EV, Labarthe D. Trends in stroke hospitalizations and associated risk factors among children and young adults, 1995–2008. *Ann Neurol* 2011;**70**:713–721.
17. Yiin GS, Howard DP, Paul NL, Li L, Luengo-Fernandez R, Bull LM, Welch SJ, Gutnikov SA, Mehta Z, Rothwell PMJC. Age-specific incidence, outcome, cost, and projected future burden of atrial fibrillation-related embolic vascular events: a population-based study. *Circulation* 2014;**130**:1236–1244.
18. Brüggenjürgen B, Rossnagel K, Roll S, Andersson FL, Selim D, Müller-Nordhorn J, Nolte CH, Jungehülsing GJ, Villringer A, Willich S. The impact of atrial fibrillation on the cost of stroke: the Berlin acute stroke study. *Value in Health* 2007;**10**:137–143.
19. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P. 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 ESC, Endorsed by the European Stroke Organisation (ESO). *Eur Heart J* 2016;**37**:2893–2962.
20. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;**146**:857–867.
21. Santangeli P, Di Biase L, Bai R, Mohanty S, Pump A, Cereceda Brantes M, Horton R, Burkhardt JD, Lakkireddy D, Reddy YM, Casella M, Dello Russo A, Tondo C, Natale A. Atrial fibrillation and

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the risk of incident dementia: a meta-analysis. *Heart Rhythm* 2012;**9**:1761–1768.
22. Kim D, Yang PS, Yu HT, Kim TH, Jang E, Sung JH, Pak HN, Lee MY, Lee MH, Lip GYH, Joung B. Risk of dementia in stroke-free patients diagnosed with atrial fibrillation: data from a population-based cohort. *Eur Heart J* 2019;**40**:2313–2323.
23. Madhavan M, Graff-Radford J, Piccini JP, Gersh BJ. Cognitive dysfunction in atrial fibrillation. *Nat Rev Cardiol* 2018;**15**:744–756.
24. Liu DS, Chen J, Jian WM, Zhang GR, Liu ZR. The association of atrial fibrillation and dementia incidence: a meta-analysis of prospective cohort studies. *J Geriatric Cardiol* 2019;**16**:298–306.
25. Conen D, Rodondi N, Müller A, Beer JH, Ammann P, Moschovitis G, Auricchio A, Hayoz D, Kobza R, Shah D, Novak J, Schläpfer J, Di Valentino M, Aeschbacher S, Blum S, Meyre P, Sticherling C, Bonati LH, Ehret G, Moutzouri E, Fischer U, Monsch AU, Stippich C, Wuerfel J, Sinnecker T, Coslovsky M, Schwenkglenks M, Kühne M, Osswald S, Berger S, Bernasconi R, Fröhlich L, Göldi T, Gugganig R, Kofler T, Krisai P, Mongiat M, Pudenz C, Repilado JR, Schweizer A, Springer A, Stempfel S, Szucs T, van der Stouwe J, Voellmin G, Zwimpfer L, Aujesky D, Fuhrer J, Roten L, Jung S, Mattle H, Adam L, Aubert CE, Feller M, Schneider C, Loewe A, Flückiger T, Groen C, Schwab N, Beynon C, Dillier R, Eberli F, Fontana S, Franzini C, Juchli I, Liedtke C, Nadler J, Obst T, Schneider X, Studerus K, Weishaupt D, Kuest S, Scheuch K, Hischier D, Bonetti N, Bello C, Isberg H, Grau A, Villinger J, Papaux M-M, Baumgartner P, Filipovic M, Frick M, Anesini A, Camporini C, Conte G, Caputo ML, Regoli F, Moccetti T, Brenner R, Altmann D, Forrer M, Gemperle M, Firmann M, Foucras S, Berte B, Kaeppeli A, Mehmann B, Pfeiffer M, Russi I, Schmidt K, Weberndoerfer V, Young M, Zbinden M, Vicari L, Frangi J, Terrot T, Gallet H, Guillermet E, Lazeyras F, Lovblad K-O, Perret P, Teres C, Lauriers N, Méan M, Salzmann S, Arenja N, Grêt A, Vitelli S, Frangi J, Gallino A, Schoenenberger-Berzins R, Witassek F, Radue E-W, Benkert P, Fabbro T, Simon P, Schmid R. Relationships of overt and silent brain lesions with cognitive function in patients with atrial fibrillation. *J Am Coll Cardiol* 2019;**73**:989–999.
26. Dagres N, Chao T-F, Fenelon G, Aguinaga L, Benhayon D, Benjamin EJ, Bunch TJ, Chen LY, Chen S-A, Darrieux F, de Paola A, Fauchier L, Goette A, Kalman J, Kalra L, Kim Y-H, Lane DA, Lip GYH, Lubitz SA, Márquez MF, Potpara T, Pozzer DL, Ruskin JN, Savelieva I, Teo WS, Tse H-F, Verma A, Zhang S, Chung MK, Bautista-Vargas W-F, Chiang C-E, Cuesta A, Dan G-A, Frankel DS, Guo Y, Hatala R, Lee YS, Murakawa Y, Pellegrini CN, Pinho C, Milan DJ, Morin DP, Nadalin E, Ntaios G, Prabhu MA, Proietti M, Rivard L, Valentino M, Shantsila A, ESC Scientific Document Group. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) expert consensus on arrhythmias and cognitive function: what is the best practice? *Europace* 2018;**20**:1399–1421.
27. Friberg L, Rosenqvist M. Less dementia with oral anticoagulation in atrial fibrillation. *Eur Heart J* 2018;**39**:453–460.
28. Friberg L, Andersson T, Rosenqvist M. Less dementia and stroke in low-risk patients with atrial fibrillation taking oral anticoagulation. *Eur Heart J* 2019;**40**:2327–2335.
29. Madhavan M, Hu TY, Gersh BJ, Roger VL, Killian J, Weston SA, Graff-Radford J, Asirvatham SJ, Chamberlain AM. Efficacy of warfarin anticoagulation and incident dementia in a community-based cohort of atrial fibrillation. *Mayo Clin Proc* 2018;**93**:145–154.
30. Rivard L, Khairy P, Talajic M, Tardif JC, Nattel S, Bherer L, Black S, Healey J, Lanthier S, Andrade J, Massoud F, Nault I, Guertin MC, Dorian P, Kouz S, Essebag V, Ellenbogen KA, Wyse G, Racine N, Macle L, Mondesert B, Dyrda K, Tadros R, Guerra P, Thibault B, Cadrin-Tourigny J, Dubuc M, Roux JF, Mayrand H, Greiss I, Roy D. Blinded Randomized Trial of Anticoagulation to Prevent Ischemic Stroke and Neurocognitive Impairment in Atrial Fibrillation (BRAIN-AF): methods and design. *Can J Cardiol* 2019;**35**:1069–1077.
31. Kalantarian S, Ruskin JN. Atrial fibrillation and cognitive decline: phenomenon or epiphenomenon? *Cardiol Clin* 2016;**34**:279–285.
32. Kuhne M, Krisai P, Conen D, Osswald S. The heart-brain connection: further establishing the relationship between atrial fibrillation and dementia? *Eur Heart J* 2019;**40**:2324–2326.
33. Efimova I, Efimova N, Chernov V, Popov S, Lishmanov Y. Ablation and pacing: improving brain perfusion and cognitive function in patients with atrial fibrillation and uncontrolled ventricular rates. *Pacing Clin Electrophysiol* 2012;**35**:320–326.
34. Friedman HS, O'Connor J, Kottmeier S, Shaughnessy E, McGuinn R. The effects of atrial fibrillation on regional blood flow in the awake dog. *Can J Cardiol* 1987;**3**:240–245.
35. Demeestere J, Lemmens R. Anticoagulation in low-risk patients with atrial fibrillation: beyond prevention of ischaemic stroke. *Eur Heart J* 2019;**40**:2336–2338.
36. Cortes-Canteli M, Kruyer A, Fernandez-Nueda I, Marcos-Diaz A, Ceron C, Richards AT, Jno-Charles OC, Rodriguez I, Callejas S, Norris EH, Sanchez-Gonzalez J, Ruiz-Cabello J, Ibanez B, Strickland S, Fuster V. Long-term dabigatran treatment delays Alzheimer's disease pathogenesis in the TgCRND8 mouse model. *J Am Coll Cardiol*2019;**74**:1910–1923.
37. Festoff BW, Sajja RK, van Dreden P, Cucullo L. HMGB1 and thrombin mediate the blood-brain barrier dysfunction acting as biomarkers of neuroinflammation and progression to neurodegenera tion in Alzheimer's disease. *J Neuroinflamm* 2016;**13**:194.
38. Machida T, Dohgu S, Takata F, Matsumoto J, Kimura I, Koga M, Nakamoto K, Yamauchi A, Kataoka Y. Role of thrombin-PAR1-PKCtheta/delta axis in brain pericytes in thrombin-induced MMP-9 production and blood-brain barrier dysfunction in vitro. *Neuroscience* 2017;**350**:146–157.
39. Shin Y, Choi SH, Kim E, Bylykbashi E, Kim JA, Chung S, Kim DY, Kamm RD, Tanzi RE, Blood-brain barrier dysfunction in a 3d in vitro model of Alzheimer's disease. *Adv Sci* 2019;**6**:1900962.
40. Zamolodchikov D, Renne T, Strickland S. The Alzheimer's disease peptide beta-amyloid promotes thrombin generation through activation of coagulation factor XII. *J Thromb Haemost* 2016;**14**:995–1007.
41. Lackay H, Housel EL. The arrest of recurrent embolism due to auricular fibrillation with mitral stenosis by quinidine-anticoagulant therapy. *Ann Intern Med* 1951;**35**:1143–1149.
42. Turakhia MP, Ziegler PD, Schmitt SK, Chang Y, Fan J, Than CT, Keung EK, Singer DE. Atrial fibrillation burden and short-term risk of stroke: case-crossover analysis of continuously recorded heart rhythm from cardiac electronic implanted devices. *Circ Arrhythm Electrophysiol* 2015;**8**:1040–1047.
43. Glotzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD, Hilker C, Miller C, Qi D, Ziegler PD. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. *Circ Arrhythm Electrophysiol* 2009;**2**:474–480.
44. Brambatti M, Connolly SJ, Gold MR, Morillo CA, Capucci A, Muto C, Lau CP, Van Gelder IC, Hohnloser SH, Carlson M, Fain E, Nakamya J, Mairesse GH, Halytska M, Deng WQ, Israel CW, Healey JS; ASSERT Investigators. Temporal relationship between subclinical atrial fibrillation and embolic events. *Circulation* 2014;**129**:2094–2099.
45. Martin DT, Bersohn MM, Waldo AL, Wathen MS, Choucair WK, Lip GY, Ip J, Holcomb R, Akar JG, Halperin JL; IMPACT Investigators. Randomized trial of atrial arrhythmia monitoring to guide anticoagulation in patients with implanted defibrillator and cardiac resynchronization devices. *Eur Heart J* 2015;**36**:1660–1668.
46. Mahajan R, Perera T, Elliott AD, Twomey DJ, Kumar S, Munwar DA, Khokhar KB, Thiyagarajah A, Middeldorp ME, Nalliah CJ, Hendriks JML, Kalman JM, Lau DH, Sanders P. Subclinical device-detected atrial fibrillation and stroke risk: a systematic review and meta-analysis. *Eur Heart J* 2018;**39**:1407–1415.
47. Kamel H, Okin PM, Elkind MS, Iadecola C. Atrial fibrillation and mechanisms of stroke: time for a new model. *Stroke* 2016;**47**:895–900.
48. Benjamin EJ, D'Agostino RB, Belanger AJ, Wolf PA, Levy D. Left atrial size and the risk of stroke and death. The Framingham Heart Study. *Circulation* 1995;**92**:835–841.
49. Folsom AR, Nambi V, Bell EJ, Oluleye OW, Gottesman RF, Lutsey PL, Huxley RR, Ballantyne CM. Troponin T, N-terminal pro-B-type natriuretic peptide, and incidence of stroke: the Atherosclerosis Risk In Communities study. *Stroke* 2013;**44**:961–967.
50. Kamel H, Soliman EZ, Heckbert SR, Kronmal RA, Longstreth WT Jr, Nazarian S, Okin PM. P-wave morphology and the risk of incident

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ischemic stroke in the Multi-Ethnic Study of Atherosclerosis. *Stroke* 2014;**45**:2786–2788.
51. King JB, Azadani PN, Suksaranjit P, Bress AP, Witt DM, Han FT, Chelu MG, Silver MA, Biskupiak J, Wilson BD, Morris AK, Kholmovski EG, Marrouche N. Left atrial fibrosis and risk of cerebrovascular and cardiovascular events in patients with atrial fibrillation. *J Am Coll Cardiol* 2017;**70**:1311–1321.
52. Habibi M, Zareian M, Ambale Venkatesh B, Samiei S, Imai M, Wu C, Launer LJ, Shea S, Gottesman RF, Heckbert SR, Bluemke DA, Lima JAC. Left atrial mechanical function and incident ischemic cerebrovascular events independent of AF: insights from the MESA study. *JACC Cardiovasc Imaging* 2019;**12**:2417–2427.
53. Chao TF, Liu CJ, Chen SJ, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Wu TJ, Chen TJ, Tsao HM, Chen SA. Atrial fibrillation and the risk of ischemic stroke: does it still matter in patients with a CHA2DS2-VASc score of 0 or 1? *Stroke* 2012;**43**:2551–2555.
54. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH, Investigators A. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012;**366**:120–129.
55. Hobbelt AH, Spronk HM, Crijns H, Ten Cate H, Rienstra M, Van Gelder IC. Prethrombotic state in young very low-risk patients with atrial fibrillation. *J Am Coll Cardiol* 2017;**69**:1990–1992.
56. 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**:263–272.
57. Gialdini G, Nearing K, Bhave PD, Bonuccelli U, Iadecola C, Healey JS, Kamel H. Perioperative atrial fibrillation and the long-term risk of ischemic stroke. *JAMA* 2014;**312**:616–622.
58. Bjerkelund CJ, Orning OM. The efficacy of anticoagulant therapy in preventing embolism related to D.C. electrical conversion of atrial fibrillation. *Am J Cardiol* 1969;**23**:208–216.
59. Moreyra E, Finkelhor RS, Cebul RD. Limitations of transesophageal echocardiography in the risk assessment of patients before nonanticoagulated cardioversion from atrial fibrillation and flutter: an analysis of pooled trials. *Am Heart J* 1995;**129**:71–75.
60. Lip GYH, Banerjee A, Boriani G, Chiang CE, Fargo R, Freedman B, Lane DA, Ruff CT, Turakhia M, Werring D, Patel S, Moores L. Antithrombotic therapy for atrial fibrillation: CHEST Guideline and Expert Panel Report. *Chest* 2018;**154**:1121–1201.
61. Brieger D, Amerena J, Attia JR, Bajorek B, Chan KH, Connell C, Freedman B, Ferguson C, Hall T, Haqqani HM, Hendriks J, Hespe CM, Hung J, Kalman JM, Sanders P, Worthington J, Yan T, Zwar NA. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the diagnosis and management of atrial fibrillation 2018. *Med J Aust* 2018;**209**:356–362.
62. Thomas L, McKay T, Byth K, Marwick TH. Abnormalities of left atrial function after cardioversion: an atrial strain rate study. *Heart* 2007;**93**:89–95.
63. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener H-C, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GYH, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;**37**:2893–2962.
64. Nuotio I, Hartikainen JE, Gronberg T, Biancari F, Airaksinen KE. Time to cardioversion for acute atrial fibrillation and thromboembolic complications. *JAMA* 2014;**312**:647–649.
65. Garg A, Khunger M, Seicean S, Chung MK, Tchou PJ. Incidence of thromboembolic complications within 30 days of electrical cardioversion performed within 48 hours of atrial fibrillation onset. *JACC Clin Electrophysiol* 2016;**2**:487–494.
66. McIntyre WF, Connolly SJ, Wang J, Masiero S, Benz AP, Conen D, Wong JA, Beresh H, Healey JS. Thromboembolic events around the time of cardioversion for atrial fibrillation in patients receiving antiplatelet treatment in the ACTIVE trials. *Eur Heart J* 2019;**40**:3026–3032.
67. SPAF: Stroke Prevention in Atrial Fibrillation Investigators. Predictors of thromboembolism in atrial fibrillation: II. Echocardiographic features of patients at risk. *Ann Internal Med* 1992;**116**:6–12.
68. Lupercio F, Carlos Ruiz J, Briceno DF, Romero J, Villablanca PA, Berardi C, Faillace R, Krumerman A, Fisher JD, Ferrick K, Garcia M, Natale A, Di Biase L. Left atrial appendage morphology assessment for risk stratification of embolic stroke in patients with atrial fibrillation: a meta-analysis. *Heart Rhythm* 2016;**13**:1402–1409.
69. Goldman ME, Pearce LA, Hart RG, Zabalgoitia M, Asinger RW, Safford R, Halperin JL. Pathophysiologic correlates of thromboembolism in nonvalvular atrial fibrillation: I. Reduced flow velocity in the left atrial appendage (The Stroke Prevention in Atrial Fibrillation [SPAF-III] study). *J Am Soc Echocardiogr* 1999;**12**:1080–1087.
70. Inoue YY, Alissa A, Khurram IM, Fukumoto K, Habibi M, Venkatesh BA, Zimmerman SL, Nazarian S, Berger RD, Calkins H, Lima JA, Ashikaga H. Quantitative tissue-tracking cardiac magnetic resonance (CMR) of left atrial deformation and the risk of stroke in patients with atrial fibrillation. *J Am Heart Assoc* 2015;**4**: DOI: 10.1161/JAHA.115.001844.
71. Obokata M, Negishi K, Kurosawa K, Tateno R, Tange S, Arai M, Amano M, Kurabayashi M. Left atrial strain provides incremental value for embolism risk stratification over CHA(2)DS(2)-VASc score and indicates prognostic impact in patients with atrial fibrillation. *J Am Soc Echocardiogr* 2014;**27**:709–716 e4.
72. Shih JY, Tsai WC, Huang YY, Liu YW, Lin CC, Huang YS, Tsai LM, Lin LJ. Association of decreased left atrial strain and strain rate with stroke in chronic atrial fibrillation. *J Am Soc Echocardiogr* 2011;**24**:513–519.
73. Daccarett M, Badger TJ, Akoum N, Burgon NS, Mahnkopf C, Vergara G, Kholmovski E, McGann CJ, Parker D, Brachmann J, Macleod RS, Marrouche NF. Association of left atrial fibrosis detected by delayed-enhancement magnetic resonance imaging and the risk of stroke in patients with atrial fibrillation. *J Am Coll Cardiol* 2011;**57**:831–838.
74. Akoum N, Fernandez G, Wilson B, McGann C, Kholmovski E, Marrouche N. Association of atrial fibrosis quantified using LGE-MRI with atrial appendage thrombus and spontaneous contrast on transesophageal echocardiography in patients with atrial fibrillation. *J Cardiovasc Electrophysiol* 2013;**24**.
75. Maheshwari A, Norby FL, Roetker NS, Soliman EZ, Koene RJ, Rooney MR, O'Neal WT, Shah AM, Claggett BL, Solomon SD, Alonso A, Gottesman RF, Heckbert SR, Chen LY. Refining prediction of atrial fibrillation-related stroke using the P2-CHA2DS2-VASc score. *Circulation* 2019;**139**:180–191.
76. Inoue YY, Ipek EG, Khurram IM, Ciuffo L, Chrispin J, Zimmerman SL, Marine JE, Rickard J, Spragg DD, Nazarian S, Kusano K, Lima JA, Berger RD, Calkins H, Ashikaga H. Relation of electrocardiographic left atrial abnormalities to risk of stroke in patients with atrial fibrillation. *Am J Cardiol* 2018;**122**:242–247.
77. Hijazi Z, Lindback J, Alexander JH, Hanna M, Held C, Hylek EM, Lopes RD, Oldgren J, Siegbahn A, Stewart RA, White HD, Granger CB, Wallentin L, Aristotle Investigators S. The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. *Eur Heart J* 2016;**37**:1582–1590.
78. Goldberger JJ, Arora R, Green D, Greenland P, Lee DC, Lloyd-Jones DM, Markl M, Ng J, Shah SJ. Evaluating the atrial myopathy underlying atrial fibrillation: identifying the arrhythmogenic and thrombogenic substrate. *Circulation* 2015;**132**:278–291.
79. Di Tullio MR, Sacco RL, Sciacca RR, Homma S. Left atrial size and the risk of ischemic stroke in an ethnically mixed population. *Stroke* 1999;**30**:2019–2024.
80. Barnes ME, Miyasaka Y, Seward JB, Gersh BJ, Rosales AG, Bailey KR, Petty GW, Wiebers DO, Tsang TSM. Left atrial volume in the prediction of first ischemic stroke in an elderly cohort without atrial fibrillation. *Mayo Clin Proc* 2004;**79**:1008–1014.
81. Karas MG, Devereux RB, Wiebers DO, Whisnant JP, Best LG, Lee ET, Howard BV, Roman MJ, Umans JG, Kizer JR. Incremental value

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of biochemical and echocardiographic measures in prediction of ischemic stroke: the Strong Heart Study. *Stroke* 2012;**43**:720–726.
82. Yaghi S, Moon YP, Mora-McLaughlin C, Willey JZ, Cheung K, Di Tullio MR, Homma S, Kamel H, Sacco RL, Elkind MS. Left atrial enlargement and stroke recurrence: the Northern Manhattan Stroke Study. *Stroke* 2015;**46**:1488–1493.
83. Russo C, Jin Z, Liu R, Iwata S, Tugcu A, Yoshita M, Homma S, Elkind MS, Rundek T, Decarli C, Wright CB, Sacco RL, Di Tullio MR. LA volumes and reservoir function are associated with subclinical cerebrovascular disease: the CABL (Cardiovascular Abnormalities and Brain Lesions) study. *JACC Cardiovasc Imaging* 2013;**6**: 313–323.
84. Healey JS, Gladstone DJ, Swaminathan B, Eckstein J, Mundl H, Epstein AE, Haeusler KG, Mikulik R, Kasner SE, Toni D, Arauz A, Ntaios G, Hankey GJ, Perera K, Pagola J, Shuaib A, Lutsep H, Yang X, Uchiyama S, Endres M, Coutts SB, Karlinski M, Czlonkowska A, Molina CA, Santo G, Berkowitz SD, Hart RG, Connolly SJ. Recurrent stroke with rivaroxaban compared with aspirin according to predictors of atrial fibrillation: secondary analysis of the NAVIGATE ESUS randomized clinical trial. JAMA Neurol 2019;**76**:764–773.
85. Kamel H, Bartz TM, Elkind MSV, Okin PM, Thacker EL, Patton KK, Stein PK, deFilippi CR, Gottesman RF, Heckbert SR, Kronmal RA, Soliman EZ, Longstreth WT Jr. Atrial cardiopathy and the risk of ischemic stroke in the CHS (Cardiovascular Health Study). *Stroke* 2018;**49**:980–986.
86. Yaghi S, Chang AD, Hung P, Mac Grory B, Collins S, Gupta A, Reynolds J, Finn CB, Hemendinger M, Cutting SM, McTaggart RA, Jayaraman M, Leasure A, Sansing L, Panda N, Song C, Chu A, Merkler A, Gialdini G, Sheth KN, Kamel H, Elkind MSV, Greer D, Furie K, Atalay M. Left atrial appendage morphology and embolic stroke of undetermined source: a cross-sectional multicenter pilot study. *J Stroke Cerebrovasc Dis* 2018;**27**:1497–1501.
87. Yaghi S, Chang AD, Akiki R, Collins S, Novack T, Hemendinger M, Schomer A, Grory BM, Cutting S, Burton T, Song C, Poppas A, McTaggart R, Jayaraman M, Merkler A, Kamel H, Elkind MSV, Furie K, Atalay MK. The left atrial appendage morphology is associated with embolic stroke subtypes using a simple classification system: a proof of concept study. *J Cardiovasc Comput Tomogr* 2019.
88. Leong DP, Joyce E, Debonnaire P, Katsanos S, Holman ER, Schalij MJ, Bax JJ, Delgado V, Marsan NA. Left atrial dysfunction in the pathogenesis of cryptogenic stroke: novel insights from speckle-tracking echocardiography. *J Am Soc Echocardiogr* 2017;**30**:71–79 e1.
89. Tandon K, Tirschwell D, Longstreth WT Jr., Smith B, Akoum N. Embolic stroke of undetermined source correlates to atrial fibrosis without atrial fibrillation. *Neurology* 2019;**93**:e381–e387.
90. Kamel H, Bartz TM, Longstreth WT Jr., Okin PM, Thacker EL, Patton KK, Stein PK, Gottesman RF, Heckbert SR, Kronmal RA, Elkind MS, Soliman EZ. Association between left atrial abnormality on ECG and vascular brain injury on MRI in the Cardiovascular Health Study. *Stroke* 2015;**46**:711–716.
91. Kamel H, O'Neal WT, Okin PM, Loehr LR, Alonso A, Soliman EZ. Electrocardiographic left atrial abnormality and stroke subtype in the atherosclerosis risk in communities study. *Ann Neurol* 2015; **78**:670–678.
92. Kamel H, Hunter M, Moon YP, Yaghi S, Cheung K, Di Tullio MR, Okin PM, Sacco RL, Soliman EZ, Elkind MS. Electrocardiographic left atrial abnormality and risk of stroke: Northern Manhattan study. *Stroke* 2015;**46**:3208–3212.
93. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Halperin JL, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL. ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 2006;**114**:e257–e354.
94. Camm AJ, Lip GYH, Caterina RD, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P; ESC Committee for Practice Guidelines (CPG). 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. An update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012;**33**:2719–2747.
95. Ganesan AN, Chew DP, Hartshorne T, Selvanayagam JB, Aylward PE, Sanders P, McGavigan AD. The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. *Eur Heart J* 2016;**37**: 1591–1602.
96. Brieger D, Connell C, Freedman B. Stroke risk stratification: CHA2DS2-VA or CHA2DS2-VASc? *Heart Lung Circ* 2019;**28**:e103.
97. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, Heidenreich PA, Murray KT, Shea JB, Tracy CM, Yancy CW. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation* 2019;**140**:e125–e151.
98. Freedman B, Boriani G, Glotzer TV, Healey JS, Kirchhof P, Potpara TS. Management of atrial high-rate episodes detected by cardiac implanted electronic devices. *Nat Rev Cardiol* 2017;**14**:701–714.
99. Van Gelder IC, Healey JS, Crijns H, Wang J, Hohnloser SH, Gold MR, Capucci A, Lau CP, Morillo CA, Hobbelt AH, Rienstra M, Connolly SJ. Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. *Eur Heart J* 2017;**38**: 1339–1344.
100. Mahajan R, Perera T, Elliott AD, Twomey DJ, Kumar S, Munwar DA, Khokhar KB, Thiyagarajah A, Middeldorp ME, Nalliah CJ, Hendriks JML, Kalman JM, Lau DH, Sanders P. Subclinical device-detected atrial fibrillation and stroke risk: a systematic review and meta-analysis. *Eur Heart J* 2018;**39**:1407–1415.
101. Rahimi K. Subclinical atrial fibrillation in need of more assertive evidence. *Eur Heart J* 2017;**38**:1345–1347.
102. Chen LY, Chung MK, Allen LA, Ezekowitz M, Furie KL, McCabe P, Noseworthy PA, Perez MV, Turakhia MP. Atrial fibrillation burden: moving beyond atrial fibrillation as a binary entity: a scientific statement from the American Heart Association. *Circulation* 2018; **137**:e623–e644.
103. Diederichsen SZ, Haugan KJ, Brandes A, Graff C, Krieger D, Kronborg C, Holst AG, Nielsen JB, Kober L, Hojberg S, Svendsen JH. Incidence and predictors of atrial fibrillation episodes as detected by implantable loop recorder in patients at risk: from the LOOP study. *Am Heart J* 2020;**219**:117–127.
104. Go AS, Reynolds K, Yang J, Gupta N, Lenane J, Sung SH, Harrison TN, Liu TI, Solomon MD. Association of burden of atrial fibrillation with risk of ischemic stroke in adults with paroxysmal atrial fibrillation: the KP-RHYTHM study. *JAMA Cardiol* 2018;**3**:601.
105. Steinhubl SR, Waalen J, Edwards AM, Ariniello LM, Mehta RR, Ebner GS, Carter C, Baca-Motes K, Felicione E, Sarich T, Topol EJ. Effect of a home-based wearable continuous ECG monitoring patch on detection of undiagnosed atrial fibrillation: the mSToPS randomized clinical trial. *JAMA* 2018;**320**:146–155.
106. Quer G, Freedman B, Steinhubl SR. Screening for atrial fibrillation: predicted sensitivity of short, intermittent electrocardiogram recordings in an asymptomatic at-risk population. *Europace* 2020; **DOI: 10.1093/europace/euaa186**.
107. de With RR, Erküner O, Rienstra M, Schotten U, Ten Cate H, Spronk HM, Blaauw Y, Tieleman R, Hemels MEW, de Groot JR, Al-Jazairi MIH, Kroon AA, Leurmans JGLM, Van Gelder IC, Crijns H. Paroxysmal atrial fibrillation is not one entity: data from RACE V. *Europace* 2019;**23**:ii291.
108. Swiryn S, Orlov MV, Benditt DG, DiMarco JP, Lloyd-Jones DM, Karst E, Qu F, Slawsky MT, Turkel M, Waldo AL;Rate Registry Investigators. Clinical implications of brief device-detected atrial tachyarrhythmias in a cardiac rhythm management device population: results from the registry of atrial tachycardia and atrial fibrillation episodes. *Circulation* 2016;**134**:1130–1140.

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109. Lopes RD, Alings M, Connolly SJ, Beresh H, Granger CB, Mazuecos JB, Boriani G, Nielsen JC, Conen D, Hohnloser SH, Mairesse GH, Mabo P, Camm AJ, Healey JS. Rationale and design of the Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESiA) trial. *Am Heart J* 2017;**189**:137–145.
110. Kirchhof P, Blank BF, Calvert M, Camm AJ, Chlouverakis G, Diener HC, Goette A, Huening A, Lip GYH, Simantirakis E, Vardas P. Probing oral anticoagulation in patients with atrial high rate episodes: rationale and design of the Non-vitamin K antagonist Oral anticoagulants in patients with Atrial High rate episodes (NOAH-AFNET 6) trial. *Am Heart J* 2017;**190**:12–18.
111. Emdin CA, Anderson SG, Salimi-Khorshidi G, Woodward M, MacMahon S, Dwyer T, Rahimi K. Usual blood pressure, atrial fibrillation and vascular risk: evidence from 4.3 million adults. *Int J Epidemiol* 2017;**46**:162–172.
112. Kirchhof P, Lip GY, Van Gelder IC, Bax J, Hylek E, Kaab S, Schotten U, Wegscheider K, Boriani G, Brandes A, Ezekowitz M, Diener H, Haegeli L, Heidbuchel H, Lane D, Mont L, Willems S, Dorian P, Aunes-Jansson M, Blomstrom-Lundqvist C, Borentain M, Breitenstein S, Brueckmann M, Cater N, Clemens A, Dobrev D, Dubner S, Edvardsson NG, Friberg L, Goette A, Gulizia M, Hatala R, Horwood J, Szumowski L, Kappenberger L, Kautzner J, Leute A, Lobban T, Meyer R, Millerhagen J, Morgan J, Muenzel F, Nabauer M, Baertels C, Oeff M, Paar D, Polifka J, Ravens U, Rosin L, Stegink W, Steinbeck G, Vardas P, Vincent A, Walter M, Breithardt G, Camm AJ. Comprehensive risk reduction in patients with atrial fibrillation: emerging diagnostic and therapeutic options – a report from the 3rd Atrial Fibrillation Competence NETwork/European Heart Rhythm Association consensus conference. *Europace* 2012;**14**:8–27.
113. Weijs B, de Vos CB, Tieleman RG, Peeters FE, Limantoro I, Kroon AA, Cheriex EC, Pisters R, Crijns HJ. The occurrence of cardiovascular disease during 5-year follow-up in patients with idiopathic atrial fibrillation. *Europace* 2013;**15**:18–23.
114. Wijesurendra RS, Liu A, Eichhorn C, Ariga R, Levelt E, Clarke WT, Rodgers CT, Karamitsos TD, Bashir Y, Ginks M, Rajappan K, Betts T, Ferreira VM, Neubauer S, Casadei B. Lone atrial fibrillation is associated with impaired left ventricular energetics that persists despite successful catheter ablation. *Circulation* 2016;**134**:1068–1081.
115. Kloosterman M, Rienstra M, Crijns HJ, Healey JS, Van Gelder IC. The left atrium: an overlooked prognostic tool. *Eur J Prev Cardiol* 2017;**24**:389–391.
116. Wyse DG, Van Gelder IC, Ellinor PT, Go AS, Kalman JM, Narayan SM, Nattel S, Schotten U, Rienstra M. Lone atrial fibrillation: does it exist? *J Am Coll Cardiol* 2014;**63**:1715–1723.
117. Kloosterman M, Oldgren J, Conen D, Wong JA, Connolly SJ, Avezum A, Yusuf S, Ezekowitz M, Wallentin L, Ntep-Gweth M, Joseph P, Barrett TW, Tanosmsup S, McIntyre WF, Lee SF, Parkash R, Amit G, Grinvalds A, Van Gelder IC, Healey J. Characteristics and outcomes of atrial fibrillation in patients without traditional risk factors: a RE-LY AF registry analysis. *Europace* 2020;**22**:870–877.
118. Cosio FG, Aliot E, Botto GL, Heidbuchel H, Geller CJ, Kirchhof P, De Haro JC, Frank R, Villacastin JP, Vijgen J, Crijns H. Delayed rhythm control of atrial fibrillation may be a cause of failure to prevent recurrences: reasons for change to active antiarrhythmic treatment at the time of the first detected episode. *Europace* 2007;**10**:21–27.
119. Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, Chugh SS, Corradi D, D'Avila A, Dobrev D, Fenelon G, Gonzalez M, Hatem SN, Helm R, Hindricks G, Ho SY, Hoit B, Jalife J, Kim Y-H, Lip GYH, Ma C-S, Marcus GM, Murray K, Nogami A, Sanders P, Uribe W, Van Wagoner DR, Nattel S. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Europace* 2016;**18**:1455–1490.
120. Kusa S, Komatsu Y, Taniguchi H, Uchiyama T, Takagi T, Nakamura H, Miyazaki S, Hachiya H, Iesaka Y. Left atrial appendage flow velocity after successful ablation of persistent atrial fibrillation: clinical perspective from transesophageal echocardiographic assessment during sinus rhythm. *Am Heart J* 2015;**169**:211–221.
121. Heijman J, Voigt N, Nattel S, Dobrev D. Cellular and molecular electrophysiology of atrial fibrillation initiation, maintenance, and progression. *Circ Res* 2014;**114**:1483–1499.
122. Spronk HM, De Jong AM, Verheule S, De Boer HC, Maass AH, Lau DH, Rienstra M, van Hunnik A, Kuiper M, Lumeij S, Zeemering S, Linz D, Kamphuisen PW, Ten Cate H, Crijns HJ, Van Gelder IC, van Zonneveld AJ, Schotten U. Hypercoagulability causes atrial fibrosis and promotes atrial fibrillation. *Eur Heart J* 2017;**38**:38–50.
123. Freedman B, Potpara TS, Lip GY. Stroke prevention in atrial fibrillation. *Lancet* 2016;**388**:806–817.
124. Schnabel RB, Haeusler KG, Healey JS, Freedman B, Boriani G, Brachmann J, Brandes A, Bustamante A, Casadei B, Crijns H, Doehner W, Engstrom G, Fauchier L, Friberg L, Gladstone DJ, Glotzer TV, Goto S, Hankey GJ, Harbison JA, Hobbs FDR, Johnson LSB, Kamel H, Kirchhof P, Korompoki E, Krieger DW, Lip GYH, Lochen ML, Mairesse GH, Montaner J, Neubeck L, Ntaios G, Piccini JP, Potpara TS, Quinn TJ, Reiffel JA, Ribeiro ALP, Rienstra M, Rosenqvist M, Themistoclakis S, Sinner MF, Svendsen JH, Van Gelder IC, Wachter R, Wijeratne T, Yan B. Searching for atrial fibrillation poststroke: a white paper of the AF-SCREEN International Collaboration. *Circulation* 2019;**140**:1834–1850.
125. Freedman B, Camm J, Calkins H, Healey JS, Rosenqvist M, Wang J, Albert CM, Anderson CS, Antoniou S, Benjamin EJ, Boriani G, Brachmann J, Brandes A, Chao T-F, Conen D, Engdahl J, Fauchier L, Fitzmaurice DA, Friberg L, Gersh BJ, Gladstone DJ, Glotzer TV, Gwynne K, Hankey GJ, Harbison J, Hillis GS, Hills MT, Kamel H, Kirchhof P, Kowey PR, Krieger D, Lee VWY, Levin L-Å, Lip GYH, Lobban T, Lowres N, Mairesse GH, Martinez C, Neubeck L, Orchard J, Piccini JP, Poppe K, Potpara TS, Puererfellner H, Rienstra M, Sandhu RK, Schnabel RB, Siu C-W, Steinhubl S, Svendsen JH, Svennberg E, Themistoclakis S, Tieleman RG, Turakhia MP, Tveit A, Uittenbogaart SB, Van Gelder IC, Verma A, Wachter R, Yan BP, Al Awwad A, Al-Kalili F, Berge T, Breithardt G, Bury G, Caorsi WR, Chan NY, Chen SA, Christophersen I, Connolly S, Crijns H, Davis S, Dixen U, Doughty R, Du X, Ezekowitz M, Fay M, Frykman V, Geanta M, Gray H, Grubb N, Guerra A, Halcox J, Hatala R, Heidbuchel H, Jackson R, Johnson L, Kaab S, Keane K, Kim YH, Kollios G, Løchen ML, Ma C, Mant J, Martinek M, Marzona I, Matsumoto K, McManus D, Moran P, Naik N, Ngarmukos T, Prabhakaran D, Reidpath D, Ribeiro A, Rudd A, Savalieva I, Schilling R, Sinner M, Stewart S, Suwanwela N, Takahashi N, Topol E, Ushiyama S, Verbiest van Gurp N, Walker N, Wijeratne T. Screening for atrial fibrillation: a report of the AF-SCREEN International Collaboration. *Circulation* 2017;**135**:1851–1867.
126. Lowres N, Olivier J, Chao TF, Chen SA, Chen Y, Diederichsen A, Fitzmaurice DA, Gomez-Doblas JJ, Harbison J, Healey JS, Hobbs FDR, Kaasenbrood F, Keen W, Lee VW, Lindholt JS, Lip GYH, Mairesse GH, Mant J, Martin JW, Martin-Rioboo E, McManus DD, Muniz J, Munzel T, Nakamya J, Neubeck L, Orchard JJ, Perula de Torres LA, Proietti M, Quinn FR, Roalfe AK, Sandhu RK, Schnabel RB, Smyth B, Soni A, Tieleman R, Wang J, Wild PS, Yan BP, Freedman B. Estimated stroke risk, yield, and number needed to screen for atrial fibrillation detected through single time screening: a multicountry patient-level meta-analysis of 141,220 screened individuals. PLoS Med 2019;**16**:e1002903.
127. Martinez C, Katholing A, Freedman SB. Adverse prognosis of incidentally detected ambulatory atrial fibrillation. A cohort study. *Thromb Haemost asis* 2014;**112**:276–286.
128. Brieger D, Amerena J, Attia JR, Bajorek B, Chan KH, Connell C, Freedman B, Ferguson C, Hall T, Haqqani HM, Hendriks J, Hespe CM, Hung J, Kalman JM, Sanders P, Worthington J, Yan T, Zwar NA. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the diagnosis and management of atrial fibrillation 2018. *Med J Aust* 2018;**209**:356–362.
129. Mairesse GH, Moran P, Van Gelder IC, Elsner C, Rosenqvist M, Mant J, Banerjee A, Gorenek B, Brachmann J, Varma N, Glotz de Lima G, Kalman J, Claes N, Lobban T, Lane D, Lip GYH, Boriani G, Fauchier L, Jung W, Savelieva I, Freedman B, Chen SA, Isa R, Turakhia M, Sapp JL, Lip G, Gorenek B, Sticherling C, Fauchier L, Goette A, Jung W, Vos MA, Brignole M, Elsner C, Dan G-A, Marin F, Boriani G, Lane D, Blomstrom Lundqvist C, Savelieva I, ESC Scientific Document Group. Screening for atrial fibrillation: a European Heart Rhythm Association (EHRA) consensus document endorsed by the Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLAECE. *Europace* 2017;**19**:1589–1623.

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130. Freedman B, Schnabel R, Calkins H. Opportunistic electrocardiogram screening for atrial fibrillation to prevent stroke. *JAMA Cardiol* 2019;**4**:91–92.
131. Force U, Curry SJ, Krist AH, Owens DK, Barry MJ, Caughey AB, Davidson KW, Doubeni CA, Epling JW Jr, Kemper AR, Kubik M, Landefeld CS, Mangione CM, Silverstein M, Simon MA, Tseng CW, Wong JB; US Preventive Services Task Force. Screening for atrial fibrillation with electrocardiography: US preventive services task force recommendation statement. *JAMA* 2018;**320**:478–484.
132. 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**:2176–2184.
133. Kemp Gudmundsdottir K, Fredriksson T, Svennberg E, Al-Khalili F, Friberg L, Frykman V, Hijazi Z, Rosenqvist M, Engdahl J. Stepwise mass screening for atrial fibrillation using N-terminal B-type natriuretic peptide: the STROKESTOP II study. *Europace* 2020;**22**:24–32.
134. Lau DH, Schotten U, Mahajan R, Antic NA, Hatem SN, Pathak RK, Hendriks JM, Kalman JM, Sanders P. Novel mechanisms in the pathogenesis of atrial fibrillation: practical applications. *Eur Heart J* 2016;**37**:1573–1581.
135. Pavlovic D, Kirchhof P, Fabritz L. The RACE-3 is on: double-locking sinus rhythm by upstream and downstream therapy. *Eur Heart J* 2018;**39**:2997–2999.
136. Nattel S, Guasch E, Savelieva I, Cosio FG, Valverde I, Halperin JL, Conroy JM, Al-Khatib SM, Hess PL, Kirchhof P, De Bono J, Lip GY, Banerjee A, Ruskin J, Blendea D, Camm AJ. Early management of atrial fibrillation to prevent cardiovascular complications. *Eur Heart J* 2014;**35**:1448–1456.
137. Savelieva I, Kakouros N, Kourliouros A, Camm AJ. Upstream therapies for management of atrial fibrillation: review of clinical evidence and implications for European Society of Cardiology guidelines. Part II: secondary prevention. *Europace* 2011;**13**:610–625.
138. Zheng Z, Jayaram R, Jiang L, Emberson J, Zhao Y, Li Q, Du J, Guarguagli S, Hill M, Chen Z, Collins R, Casadei B. Perioperative rosuvastatin in cardiac surgery. *N Engl J Med* 2016;**374**:1744–1753.
139. Abed HS, Wittert GA, Leong DP, Shirazi MG, Bahrami B, Middeldorp ME, Lorimer MF, Lau DH, Antic NA, Brooks AG, Abhayaratna WP, Kalman JM, Sanders P. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. *JAMA* 2013;**310**:2050–2060.
140. Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, Twomey D, Elliott AD, Kalman JM, Abhayaratna WP, Lau DH, Sanders P. Long-term effect of goal-directed weight management in an atrial fibrillation cohort: a long-term follow-up study (LEGACY). *J Am Coll Cardiol* 2015;**65**:2159–2169.
141. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, Alasady M, Hanley L, Antic NA, McEvoy RD, Kalman JM, Abhayaratna WP, Sanders P. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol* 2014;**64**:2222–2231.
142. Pathak RK, Elliott A, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Hendriks JM, Twomey D, Kalman JM, Abhayaratna WP, Lau DH, Sanders P. Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence In Obese Individuals With Atrial Fibrillation: the CARDIO-FIT study. *J Am Coll Cardiol* 2015;**66**:985–996.
143. Rienstra M, Hobbelt AH, Alings M, Tijssen JGP, Smit MD, Brugemann J, Geelhoed B, Tieleman RG, Hillege HL, Tukkie R, Van Veldhuisen DJ, Crijns H, Van Gelder IC; for the RACE 3 Investigators. Targeted therapy of underlying conditions improves sinus rhythm maintenance in patients with persistent atrial fibrillation: results of the RACE 3 trial. *Eur Heart J* 2018;**39**:2987–2996.
144. Ntaios G. Embolic stroke of undetermined source: JACC review topic of the week. *J Am Coll Cardiol* 2020;**75**:333–340.
145. Hart RG, Diener H-C, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, Sacco RL, Connolly SJ; Cryptogenic Stroke/ESUS International Working Group. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014;**13**:429–438.
146. Freilinger TM, Schindler A, Schmidt C, Grimm J, Cyran C, Schwarz F, Bamberg F, Linn J, Reiser M, Yuan C, Nikolaou K, Dichgans M, Saam T. Prevalence of nonstenosing, complicated atherosclerotic plaques in cryptogenic stroke. *JACC Cardiovasc Imaging* 2012;**5**:397–405.
147. Ntaios G, Swaminathan B, Berkowitz SD, Gagliardi RJ, Lang W, Siegler JE, Lavados P, Mundl H, Bornstein N, Meseguer E, Amarenco P, Cucchiara B, Camps-Renom P, Makaritsis K, Korompoki E, Papavasileiou V, Marti-Fabregas J, Milionis H, Vemmos K, Connolly SJ, Hart RG; on behalf of the NAVIGATE ESUS Investigators. Efficacy and safety of rivaroxaban versus aspirin in embolic stroke of undetermined source and carotid atherosclerosis. *Stroke* 2019;**50**:2477–2485.
148. Kamel H, Navi BB, Merkler AE, Baradaran H, Diaz I, Parikh NS, Kasner SE, Gladstone DJ, Iadecola C, Gupta A. Reclassification of ischemic stroke etiological subtypes on the basis of high-risk nonstenosing carotid plaque. *Stroke* 2020;**51**:504–510.
149. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE 3rd. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993;**24**:35–41.
150. Hart RG, Sharma M, Mundl H, Kasner SE, Bangdiwala SI, Berkowitz SD, Swaminathan B, Lavados P, Wang Y, Wang Y, Davalos A, Shamalov N, Mikulik R, Cunha L, Lindgren A, Arauz A, Lang W, Czlonkowska A, Eckstein J, Gagliardi RJ, Amarenco P, Ameriso SF, Tatlisumak T, Veltkamp R, Hankey GJ, Toni D, Bereczki D, Uchiyama S, Ntaios G, Yoon BW, Brouns R, Endres M, Muir KW, Bornstein N, Ozturk S, O'Donnell MJ, De Vries Basson MM, Pare G, Pater C, Kirsch B, Sheridan P, Peters G, Weitz JI, Peacock WF, Shoamanesh A, Benavente OR, Joyner C, Themeles E, Connolly SJ; NAVIGATE ESUS Investigators. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med* 2018;**378**:2191–2201.
151. Diener HC, Sacco RL, Easton JD, Granger CB, Bernstein RA, Uchiyama S, Kreuzer J, Cronin L, Cotton D, Grauer C, Brueckmann M, Chernyatina M, Donnan G, Ferro JM, Grond M, Kallmunzer B, Krupinski J, Lee BC, Lemmens R, Masjuan J, Odinak M, Saver JL, Schellinger PD, Toni D, Toyoda K; Committee R-SES and Investigators. Dabigatran for prevention of stroke after embolic stroke of undetermined source. *N Engl J Med* 2019;**380**:1906–1917.
152. Paciaroni M, Kamel H. Do the results of RE-SPECT ESUS call for a revision of the embolic stroke of undetermined source definition? *Stroke* 2019;**50**:1032–1033.
153. Longstreth WT Jr, Kronmal RA, Thompson JL, Christenson RH, Levine SR, Gross R, Brey RL, Buchsbaum R, Elkind MS, Tirschwell DL, Seliger SL, Mohr JP, deFilippi CR. Amino terminal pro-B-type natriuretic peptide, secondary stroke prevention, and choice of antithrombotic therapy. *Stroke* 2013;**44**:714–719.
154. Kamel H, Longstreth WT Jr, Tirschwell DL, Kronmal RA, Broderick JP, Palesch YY, Meinzer C, Dillon C, Ewing I, Spilker JA, Di Tullio MR, Hod EA, Soliman EZ, Chaturvedi S, Moy CS, Janis S, Elkind MS. The AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke randomized trial: rationale and methods. *Int J Stroke* 2019;**14**:207–214.
155. Stiles MK, John B, Wong CX, Kuklik P, Brooks AG, Lau DH, Dimitri H, Roberts-Thomson KC, Wilson L, De Sciscio P, Young GD, Sanders P. Paroxysmal lone atrial fibrillation is associated with an abnormal atrial substrate: characterizing the "second factor". *J Am Coll Cardiol* 2009;**53**:1182–1191.
156. Skalidis EI, Hamilos MI, Karalis IK, Chlouverakis G, Kochiadakis GE, Vardas PE. Isolated atrial microvascular dysfunction in patients with lone recurrent atrial fibrillation. *J Am Coll Cardiol* 2008;**51**:2053–2057.
157. Corradi D, Callegari S, Manotti L, Ferrara D, Goldoni M, Alinovi R, Pinelli S, Mozzoni P, Andreoli R, Asimaki A, Pozzoli A, Becchi G, Mutti A, Benussi S, Saffitz JE, Alfieri O. Persistent lone atrial fibrillation: clinicopathologic study of 19 cases. *Heart Rhythm* 2014;**11**:1250–1258.
158. Bisson A, Bodin A, Clementy N, Babuty D, Lip GYH, Fauchier L. Prediction of incident atrial fibrillation according to gender in patients with ischemic stroke from a nationwide cohort. *Am J Cardiol* 2018;**121**:437–444.
159. Israel C, Kitsiou A, Kalyani M, Deelawar S, Ejangue LE, Rogalewski A, Hagemeister C, Minnerup J, Schabitz WR. Detection of atrial fibrillation in patients with embolic stroke of undetermined source by prolonged monitoring with implantable loop recorders. *Thromb Haemost* 2017;**117**:1962–1969.
160. Gladstone DJ, Dorian P, Spring M, Panzov V, Mamdani M, Healey JS, Thorpe KE, Aviv R, Boyle K, Blakely J, Cote R, Hall J, Kapral MK,

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Kozlowski N, Laupacis A, O'Donnell M, Sabihuddin K, Sharma M, Shuaib A, Vaid H, Pinter A, Abootalebi S, Chan R, Crann S, Fleming L, Frank C, Hachinski V, Hesser K, Kumar BS, Soros P, Wright M, Basile V, Boyle K, Hopyan J, Rajmohan Y, Swartz R, Vaid H, Valencia G, Ween J, Aram H, Barber PA, Coutts S, Demchuk AM, Fischer K, Hill MD, Klein G, Kenney C, Menon B, McClelland M, Russell A, Ryckborst K, Stys P, Smith EE, Watson TW, Chacko S, Sahlas D, Sancan J, Côté R, Durcan L, Ehrensperger E, Minuk J, Wein T, Wadup L, Asdaghi N, Beckman J, Esplana N, Masigan P, Murphy C, Tang E, Teal P, Villaluna K, Woolfenden A, Yip S, Bussière M, Dowlatshahi D, Sharma M, Stotts G, Robert S, Ford K, Hackam D, Miners L, Mabb T, Spence JD, Buck B, Griffin-Stead T, Jassal R, Siddiqui M, Hache A, Lessard C, Lebel F, Mackey A, Verreault S, Astorga C, Casaubon LK, del Campo M, Jaigobin C, Kalman L, Silver FL, Atkins L, Coles K, Penn A, Sargent R, Walter C, Gable Y, Kadribasic N, Schwindt B, Shuaib A, Kostyrko P, Selchen D, Saposnik G, Christie P, Jin A, Hicklin D, Howse D, Edwards E, Jaspers S, Sher F, Stoger S, Crisp D, Dhanani A, John V, Levitan M, Mehdiratta M, Wong D; EMBRACE Steering Committee or Operations Committee. Atrial premature beats predict atrial fibrillation in cryptogenic stroke: results from the EMBRACE trial. *Stroke* 2015;**46**:936–941.

161. Weber-Krüger M, Gröschel K, Mende M, Seegers J, Lahno R, Haase B, Niehaus C-F, Edelmann F, Hasenfuß G, Wachter R, Stahrenberg R. Excessive supraventricular ectopic activity is indicative of paroxysmal atrial fibrillation in patients with cerebral ischemia. *PLoS One* 2013;**8**:e67602.
162. Renati S, Stone DK, Almeida L, Wilson CA. Predictors of atrial fibrillation in patients with cryptogenic stroke. *Neurohospitalist* 2019;**9**:127–132.
163. Poli S, Diedler J, Hartig F, Gotz N, Bauer A, Sachse T, Muller K, Muller I, Stimpfle F, Duckheim M, Steeg M, Eick C, Schreieck J, Gawaz M, Ziemann U, Zuern CS. Insertable cardiac monitors after cryptogenic stroke – a risk factor based approach to enhance the detection rate for paroxysmal atrial fibrillation. *Eur J Neurol* 2016;**23**:375–381.
164. Broughton ST, O'Neal WT, Salahuddin T, Soliman EZ. The influence of left atrial enlargement on the relationship between atrial fibrillation and stroke. *J Stroke Cerebrovasc* 2016;**25**:1396–1402.
165. Sebasigari D, Merkler A, Guo Y, Gialdini G, Kummer B, Hemendinger M, Song C, Chu A, Cutting S, Silver B, Elkind MSV, Kamel H, Furie KL, Yaghi S. Biomarkers of atrial cardiopathy and atrial fibrillation detection on mobile outpatient continuous telemetry after embolic stroke of undetermined source. *J Stroke Cerebrovasc Dis* 2017;**26**:1249–1253.
166. Waldenhjort D, Doliwa PS, Alam M, Frykman-Kull V, Engdahl J, Rosenqvist M, Persson H. Echocardiographic measures of atrial function may predict atrial fibrillation in stroke patients. *Scand Cardiovasc J* 2016;**50**:236–242.
167. Pathan F, Sivaraj E, Negishi K, Rafiudeen R, Pathan S, D'Elia N, Galligan J, Neilson S, Fonseca R, Marwick TH. Use of atrial strain to predict atrial fibrillation after cerebral ischemia. *JACC Cardiovasc Imaging* 2018;**11**:1557–1565.
168. Kawakami H, Ramkumar S, Pathan F, Wright L, Marwick TH. Use of echocardiography to stratify the risk of atrial fibrillation: comparison of left atrial and ventricular strain. *Eur Heart J Cardiovasc Imaging* 2019;**21**:399–407.
169. Delgado V, Di Biase L, Leung M, Romero J, Tops LF, Casadei B, Marrouche N, Bax JJ. Structure and function of the left atrium and left atrial appendage: AF and stroke implications. *J Am Coll Cardiol* 2017;**70**:3157–3172.
170. Lubitz SA, Parsons OE, Anderson CD, Benjamin EJ, Malik R, Weng LC, Dichgans M, Sudlow CL, Rothwell PM, Rosand J, Ellinor PT, Markus HS, Traylor M. Atrial fibrillation genetic risk and ischemic stroke mechanisms. *Stroke* 2017;**48**:1451–1456.
171. Kneihsl M, Gattringer T, Bisping E, Scherr D, Raggam R, Mangge H, Enzinger C, Fandler-Hofler S, Eppinger S, Hermetter C, Bucnik B, Poltrum B, Niederkorn K, Fazekas F. Blood biomarkers of heart failure and hypercoagulation to identify atrial fibrillation-related stroke. *Stroke* 2019;**50**:2223–2226.
172. Montaner J, Perea-Gainza M, Delgado P, Ribó M, Chacón P, Rosell A, Quintana M, Palacios ME, Molina CA, Alvarez-Sabín J, Etiologic diagnosis of ischemic stroke subtypes with plasma biomarkers. *Stroke* 2008;**39**:2280–2287.
173. Berg DD, Ruff CT, Jarolim P, Giugliano RP, Nordio F, Lanz HJ, Mercuri MF, Antman EM, Braunwald E, Morrow DA. Performance of the ABC scores for assessing the risk of stroke or systemic embolism and bleeding in patients with atrial fibrillation in ENGAGE AF-TIMI 48. *Circulation* 2019;**139**:760–771.
174. Rodriguez-Yanez M, Arias-Rivas S, Santamaria-Cadavid M, Sobrino T, Castillo J, Blanco M. High pro-BNP levels predict the occurrence of atrial fibrillation after cryptogenic stroke. *Neurology* 2013;**81**:444–447.
175. Llombart V, Antolin-Fontes A, Bustamante A, Giralt D, Rost NS, Furie K, Shibazaki K, Biteker M, Castillo J, Rodríguez-Yáñez M, Fonseca AC, Watanabe T, Purroy F, Zhixin W, Etgen T, Hosomi N, Jafarian Kerman SR, Sharma JC, Knauer C, Santamarina E, Giannakoulas G, García-Berrocoso T, Montaner J. B-type natriuretic peptides help in cardioembolic stroke diagnosis: pooled data meta-analysis. *Stroke* 2015;**46**:1187–1195.
176. Guichard JB, Nattel S. Atrial cardiomyopathy: a useful notion in cardiac disease management or a passing fad? *J Am Coll Cardiol* 2017;**70**:756–765.
177. Burstein B, Nattel S. Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation. *J Am Coll Cardiol* 2008;**51**:802–809.
178. Indja B, Woldendorp K, Vallely MP, Grieve SM. Silent brain infarcts following cardiac procedures: a systematic review and meta-analysis. *J Am Heart Assoc* 2019;**8**:e010920.
179. Sundbøll J, Horváth-Puhó E, Adelborg K, Schmidt M, Pedersen L, Bøtker HE, Henderson VW, Toft Sørensen H. Higher risk of vascular dementia in myocardial infarction survivors. *Circulation* 2018;**137**:567–577.
180. Parekh A, Jaladi R, Sharma S, Van Decker WA, Ezekowitz MD. Images in cardiovascular medicine. The case of a disappearing left atrial appendage thrombus: direct visualization of left atrial thrombus migration, captured by echocardiography, in a patient with atrial fibrillation, resulting in a stroke. *Circulation* 2006;**114**:e513.
181. Tinkler K, Cullinane M, Kaposzta Z, Markus HS. Asymptomatic embolisation in non-valvular atrial fibrillation and its relationship to anticoagulation therapy. *Eur J Ultrasound* 2002;**15**:21–27.
182. Tong DC, Bolger A, Albers GW. Incidence of transcranial Doppler-detected cerebral microemboli in patients referred for echocardiography. *Stroke* 1994;**25**:2138–2141.
183. Jefferson AL, Tate DF, Poppas A, Brickman AM, Paul RH, Gunstad J, Cohen RA. Lower cardiac output is associated with greater white matter hyperintensities in older adults with cardiovascular disease. *J Am Geriatr Soc* 2007;**55**:1044–1048.
184. Alosco ML, Brickman AM, Spitznagel MB, Griffith EY, Narkhede A, Raz N, Cohen R, Sweet LH, Hughes J, Rosneck J, Gunstad J. Independent and interactive effects of blood pressure and cardiac function on brain volume and white matter hyperintensities in heart failure. *J Am Soc Hypertens* 2013;**7**:336–343.
185. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Rooij FJ, Lip GY, Witteman JC. Subclinical atherosclerosis and risk of atrial fibrillation: the Rotterdam study. *Arch Intern Med* 2007;**167**:382–387.
186. Willeit K, Kiechl S. Atherosclerosis and atrial fibrillation - two closely intertwined diseases. *Atherosclerosis* 2014;**233**:679–681.
187. de Roos A, van der Grond J, Mitchell G, Westenberg J. Magnetic resonance imaging of cardiovascular function and the brain: is dementia a cardiovascular-driven disease? *Circulation* 2017;**135**:2178–2195.

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