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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 AF¹⁵ 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 entrenched¹⁹ 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 CHADS₂-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 $\sim 90\%$ 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.

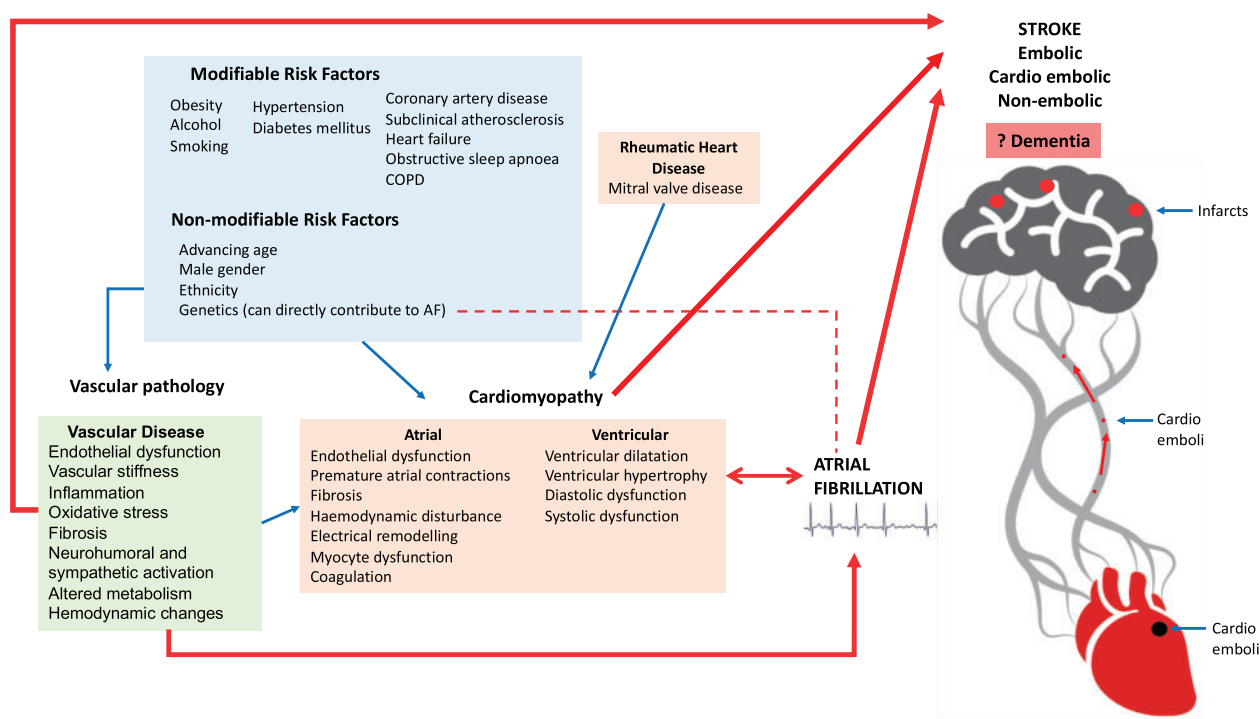


Figure 1. Links between risk factors, vascular dysfunction, cardiomyopathy, AF, and VBI.

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 CHA₂DS₂-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}

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 CHA₂DS₂-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 CHA₂DS₂-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 MRI⁵² 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

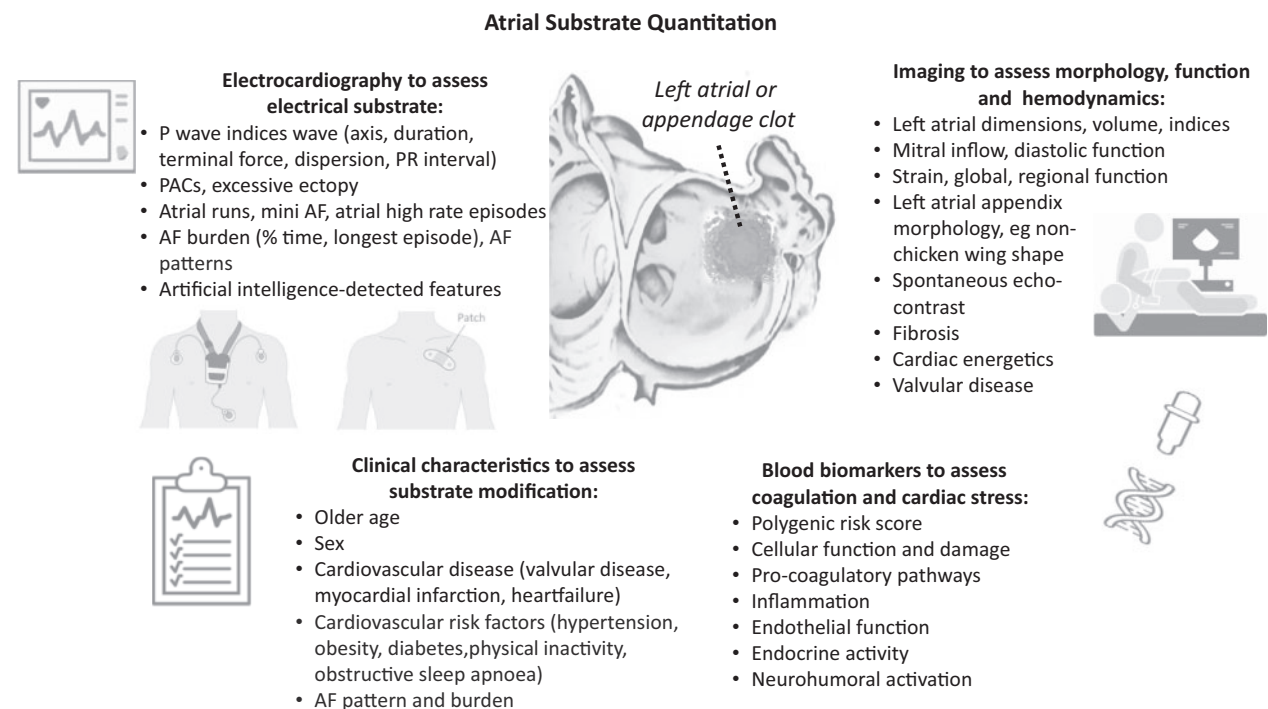


Figure 2. Quantitation of atrial substrate/atrial cardiomyopathy.

30s 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 ARTESIA¹⁰⁹ and NOAH-AFNET6¹¹⁰ 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} Weijis *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).

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 ≥ 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

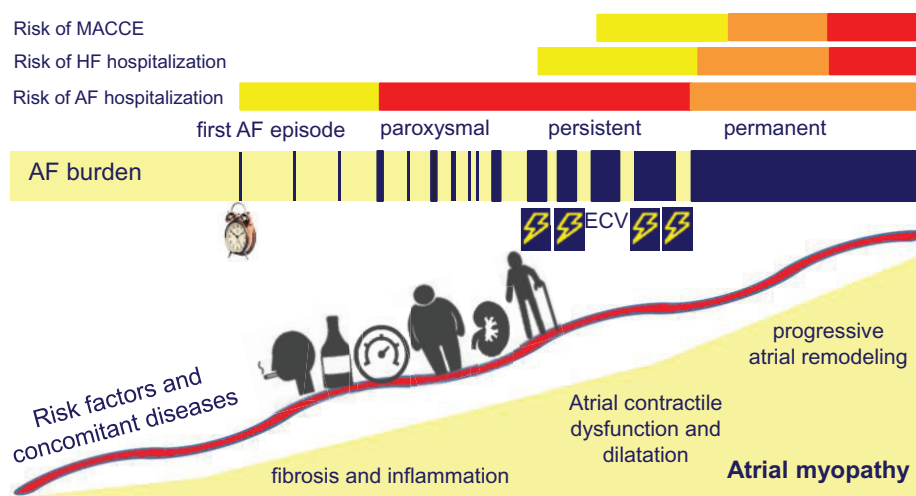


Figure 3: Risk factors, co-morbidities, and AF all involved in the development of an atrial cardiomyopathy (modified from Kloosterman *et al.*¹¹⁷ with permission).

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 remodeling' 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%

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 scores¹⁷⁰ 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 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 disease¹⁸³ and reduced brain volume¹⁸⁴ 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

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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