



## LJMU Research Online

**Qin, S, Boidin, M, Buckley, BJ, Lip, GYH and Thijssen, DHJ**

**Endothelial dysfunction and vascular maladaptation in atrial fibrillation.**

<http://researchonline.ljmu.ac.uk/id/eprint/14285/>

### Article

**Citation** (please note it is advisable to refer to the publisher's version if you intend to cite from this work)

**Qin, S, Boidin, M, Buckley, BJ, Lip, GYH and Thijssen, DHJ (2021)  
Endothelial dysfunction and vascular maladaptation in atrial fibrillation.  
European Journal of Clinical Investigation, 51 (5). ISSN 0014-2972**

LJMU has developed **LJMU Research Online** for users to access the research output of the University more effectively. Copyright © and Moral Rights for the papers on this site are retained by the individual authors and/or other copyright owners. Users may download and/or print one copy of any article(s) in LJMU Research Online to facilitate their private study or for non-commercial research. You may not engage in further distribution of the material or use it for any profit-making activities or any commercial gain.

The version presented here may differ from the published version or from the version of the record. Please see the repository URL above for details on accessing the published version and note that access may require a subscription.

For more information please contact [researchonline@ljmu.ac.uk](mailto:researchonline@ljmu.ac.uk)

<http://researchonline.ljmu.ac.uk/>



DR. MAXIME BOIDIN (Orcid ID : 0000-0002-1522-1223)

Article type : Review

**Title:** Endothelial dysfunction and vascular maladaptation in atrial fibrillation

**Authors:** Shuguang Qin<sup>1-3</sup>, Maxime Boidin<sup>1,2,4,5</sup>, Benjamin JR Buckley<sup>1</sup>, Gregory YH Lip<sup>1</sup>, Dick HJ Thijssen<sup>1,2,6</sup>

**Affiliations**

<sup>1</sup>Liverpool Centre for Cardiovascular Science, Liverpool John Moores University and University of Liverpool, Liverpool, United Kingdom

<sup>2</sup>Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, United Kingdom

<sup>3</sup>Institute of Sports and Exercise Biology, School of Physical Education, Shaanxi Normal University, Xi'an, Shaanxi, China.

<sup>4</sup>Cardiovascular Prevention and Rehabilitation (EPIC) Center, Montreal Heart Institute, Montreal, Canada

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/EJC.13477](https://doi.org/10.1111/EJC.13477)

This article is protected by copyright. All rights reserved

---

<sup>5</sup>School of Kinesiology and Exercise Science, Faculty of Medicine, Université de Montréal,  
Montreal, Canada

<sup>6</sup>Department of Physiology, Radboudumc, Nijmegen, The Netherlands

**Corresponding to:** Professor Dick HJ Thijssen, PhD, D.Thijssen@ljmu.ac.uk

**Short title:** Vascular function in atrial fibrillation

**Abstract:**

Atrial fibrillation (AF) is the most common arrhythmia and is associated with worsened morbidity and mortality. The prevalence of AF is estimated to increase with an ageing population resulting in an ever-increasing burden on the healthcare system. Despite improvements in AF treatment, several questions remain unanswered in relation to the development and progression of AF. In this review, we discuss the evidence supporting the presence of vascular dysfunction in the development of AF, but also as a final common pathway explaining why AF constitutes a markedly increased risk of cardiovascular morbidity and mortality. Specifically, we summarise the work performed in humans related to the impact of AF on vascular structure and function, and whether measures of vascular function predict AF progression and the development of cardiovascular events. Subsequently, we discuss the potential mechanisms linking AF to the development of vascular dysfunction. Finally, we propose future perspectives of vascular health and AF, advocating a strong focus on regular exercise training as a safe and effective strategy to improve vascular function and, hence, reduce the risk for development and progression of AF and its associated risk for cardiovascular events.

**Key words:** atrial fibrillation; vascular health; endothelial function; pathophysiology; risk factors

---

## 1. Introduction

Atrial fibrillation (AF) is the most common clinically significant arrhythmia <sup>1</sup>. The clinical consequences of AF relate to an increased risk of mortality and morbidity from stroke, heart failure and death <sup>2</sup>. Even short episodes of AF are associated with atrial myocardial damage, expression of prothrombotic factors, activation of platelets and inflammatory cells, collectively contributing to a generalized prothrombotic state and, subsequently, increased risk for clinical events <sup>3</sup>. Several studies have examined the complex and, most likely, multi-faceted aetiology of AF, with a likely central role for inflammation <sup>4</sup>. The presence of a systemic inflammatory, prothrombotic state may also contribute to the higher risk for co-morbidities <sup>5</sup>. Interestingly, the presence of cardiovascular risk factors, but also inflammation, have previously been related to the presence of vascular dysfunction <sup>6</sup>. Hence, this review poses that endothelial dysfunction may contribute to both the development and progression of AF, but also represents a final common pathway explaining how AF constitutes a markedly increased risk of cardiovascular morbidity and mortality (*Fig. 1*).

In this review article, we discuss the evidence supporting a potential central role for the presence of vascular dysfunction to contribute to the development of AF and cardiovascular comorbidities. Specifically, we summarise the work related to the impact of AF on peripheral and central vascular structure and function, and whether measures of vascular function predict AF progression and development of cardiovascular events in patients with AF. Subsequently, we discuss the potential mechanisms linking AF to the development of vascular dysfunction. Importantly, vascular and endothelial function are often used interchangeably in current literature, but likely represent distinct characteristics. Measures of vascular function captures the interplay between the regulation of endothelial function and (structural) characteristics of the vasculature. For this reason, we will separately discuss measures of endothelial function (e.g. flow-mediated dilatation, intra-arterial infusion of vasoactive substances, reactive hyperaemia) and vascular structure (intima-media thickness, arterial stiffness, coronary artery calcification).

---

## **2. Endothelial dysfunction and vascular maladaptation in primary prevention of AF**

### **2.1 Is AF related to the presence of endothelial dysfunction?**

A frequently used measure of peripheral artery endothelial function relates to the flow-mediated dilation (FMD). Several studies support the notion that AF patients demonstrate an impaired FMD<sup>7,8</sup>. Indeed, Komatsu *et al.* found that FMD also related to AF severity, with an FMD of 6.5±3.5% in non-AF individuals, 5.4±2.6% in paroxysmal AF patients, and 4.3±2.1% in chronic AF patients<sup>9</sup>. A 1% drop in FMD relates to a 13% increase in cardiovascular risk<sup>10</sup>. The impaired FMD in AF patients may be restored following cardioversion<sup>8</sup>, with preserved FMD after catheter ablation if sinus rhythm is maintained<sup>11</sup>. This suggests that the impaired endothelial dysfunction is linked to AF itself and is not simply the consequence of cardiovascular risk factors, as these have unlikely changed upon cardioversion.

Comparable to FMD findings (reflecting conduit artery endothelial function), reactive hyperaemia pulse amplitude tonometry index (RHI), a marker of microvascular endothelial function<sup>12</sup>, is lower in paroxysmal and permanent AF compared to healthy controls without AF. Further, permanent AF was an independent predictor of lower RHI<sup>13</sup>. Other studies have found that pulse wave velocity (PWV)<sup>14</sup> and the augmentation index (AIx)<sup>15</sup> are correlated with AF, even in those without underlying cardiovascular disease<sup>14</sup>. These studies add further evidence that the presence of systemic vascular dysfunction, present in central and peripheral arteries, relates to AF *per se* rather than associated disease processes and/or cardiovascular risk factors<sup>16</sup>.

### **2.2 Can measures of endothelial function predict occurrence of AF?**

In a population-based study that included non-AF individuals, a higher baseline brachial artery diameter (Hazard ratio [HR]: 1.20 ; 95% confidence interval [CI]: 1.01-1.43, P=0.04), and lower FMD (HR: 0.79 ; 95% CI: 0.63-0.99, P=0.04) were both associated with increased risk of incident AF after a 7.1-year follow-up<sup>17</sup>. Furthermore, a previous study which enrolled 2,936 individuals free of AF (mean age 61±9.9 years; 50% women), followed individuals for a median 8.5 years<sup>18</sup>. Endothelial dysfunction preceded the development of AF, whereas each 2.8% increase in FMD was associated with a 16% decrease in AF incidence (HR: 0.84 ; 95% CI: 0.70-0.99, P<0.05)<sup>18</sup>.

---

Studies related to measures of vascular stiffness have presented mixed findings, which may at least partially be explained by the measure of stiffness used. Studies that use pulse pressure, a surrogate index of central arterial stiffness and calculated through the difference between systolic and diastolic blood pressure, have presented consistent results. Age and hypertension are two important risk factors of incidence of AF and are both associated with increased arterial stiffness<sup>19</sup>. Progressive stiffness of the left ventricle leads to a decline in diastolic and systolic function, accompanied by an increase in end-diastolic pressure, which in turn, increases the left atrium diameter, as observed in hypertensive individuals<sup>20</sup>. This possible mechanism may represent the close relation between arterial stiffness, cardiac remodelling, and AF<sup>20</sup>. Interestingly, pulse pressure seems a strong predictor of future AF onset, an effect that is independent of traditional (e.g. age, blood pressure) and novel cardiovascular risk factors (e.g. 24h pulse pressure, left atrial diameter)<sup>19</sup>. AIx, another marker of central arterial stiffness, was also identified as an independent predictor of incident AF<sup>17</sup>. In contrast, measures of peripheral vascular stiffness, e.g. finger plethysmograph, was only unidirectionally (using a two-sample Mendelian randomization approach to estimate the causal effect) associated with risk of incident AF<sup>21</sup>.

These observations suggest that measures of central arterial stiffness (e.g. AIx, central pulse pressure) present a stronger relation with AF development than peripheral arterial stiffness measures. This may fit with the aetiology of AF, that is strongly linked to atrial structural abnormalities that are more likely to be linked to central than peripheral measures of arterial stiffness (*Fig. 1*).

### **2.3 Is AF related to the presence of structural vascular abnormalities?**

A popular ultrasound-based technique to examine vascular structure relates to the intima-media thickness (IMT) of conduit arteries, which is an early marker of atherosclerosis, and has been associated with risk of major adverse cardiovascular events. A recent meta-analysis aggregated three population-based cohort studies (25,767 individuals) and evaluated the association of carotid

---

artery IMT and incidence of AF<sup>22</sup>. Larger IMT and presence of carotid plaques, were strongly correlated with AF incidence<sup>22</sup>. Another study confirmed the close association between an elevated carotid IMT (>0.90 mm) and the presence of AF, suggesting that AF and systemic atherosclerosis are strongly associated<sup>23</sup>. Moreover, a larger carotid IMT was found in persistent/permanent AF patients compared to paroxysmal AF patients<sup>16,23</sup>, suggesting a potential graded association between AF severity and subclinical atherosclerosis.

Coronary artery calcium (CAC) burden is another useful marker of subclinical atherosclerosis, and examines vascular structure in more proximity to the cardiac origin of AF<sup>24,25</sup>. Higher CAC-scores have been reported in AF patients<sup>26</sup>, especially in persistent AF highlighting that the ‘severity’ of AF may relate to coronary structural abnormalities<sup>27</sup>. In addition, there is a stronger association between CAC progression and AF in young and middle-aged adults (<61 years old, HR: 3.53, 95% CI: 1.29-9.69) compared with older humans (≥61 years old, HR: 1.42, 95% CI: 0.99-2.04, Interaction-effect: P=0.04), which may be explained by a more rapid development of abnormal electrophysiology in those with CAC progression<sup>28,29</sup>.

#### **2.4 Do structural vascular abnormalities predict occurrence of AF?**

A number of studies have linked the presence of structural vascular abnormalities to the risk of developing AF. In 7,062 hypertensive patients without AF or cardiovascular disease, 117 (1.7%) developed AF after a median 36-month follow-up<sup>30</sup>, higher carotid IMT was identified as an independent predictor of incident AF (HR: 1.51, 95% CI: 1.27-1.79, P<0.001), while some traditional cardiovascular risk factors (e.g. gender, duration of hypertension) did not predict AF. It is consistent with previous work reporting that higher IMT was an independent predictor of new-onset AF in formerly asymptomatic individuals<sup>23</sup>.

In line with these findings pertaining to the carotid artery IMT, CAC scores have also been identified as an independent risk factor for future AF<sup>28,31</sup>. In a multi-ethnic study including 5,612 individuals, any CAC progression (defined as a CAC score >0/year)<sup>32</sup> was associated with an increased risk for AF (HR=1.55, 95% CI=1.10, 2.19). In summary, there is link between structural

---

vascular abnormalities including arteries in close proximity to the heart (i.e. CAC scores) and systemic atherosclerotic burden (i.e. carotid IMT), and the risk for incident AF.

## **2.5 What are the potential mechanisms explaining the presence of vascular dysfunction in AF?**

Although many factors contribute to vascular dysfunction in AF including irregular stroke volume and disturbed pulsatile blood flow<sup>33</sup>, we highlight two highly likely candidates: inflammation and oxidative stress. Inflammation and oxidative stress are major determinants of vascular (dys)function<sup>34</sup>. Therefore, atrial dysfunction in AF may create a pro-inflammatory state and enhance oxidative stress, which aggravates the imbalance of vascular homeostasis. Furthermore, inflammation and oxidative stress are major determinants of vascular function.

*Inflammation.* Inflammatory biomarkers C-reactive protein (CRP) and interleukin-6 (IL-6) are increased in patients with AF, but also strongly correlated with FMD<sup>35</sup>, suggesting a possible link between inflammation, endothelial dysfunction and progression of AF. In support of this notion, CRP is significantly higher in persistent AF compared to paroxysmal AF<sup>34</sup>. Furthermore, Von Willebrand factor (vWF; a marker of endothelial dysfunction) initiates platelet adhesion upon vascular damage, leads to activation of the thrombo-inflammatory pathways stimulating thromboembolism, and has an increased expression in AF patients<sup>36</sup>. Circulating extracellular vesicles may also play a key role in AF pathophysiological process including inflammation, coagulation and angiogenesis<sup>37</sup>. Together, inflammation is strongly linked to the presence of AF. Recent evidence suggests a significant association between infection (inflammatory response) severity and AF progression and adverse events<sup>38, 39</sup>. Inflammation seems to be involved in atrial remodelling leading to the development of AF. Moreover, inflammation could also contribute to the maintenance of AF, making inflammation a central component in a positive feedback loop contributing to both the development and progressive worsening of AF<sup>4</sup>.

---

*Oxidative stress.* Reactive oxygen species (ROS) accelerates the release and activation of pro-MMPs (matrix metalloproteinases) and the stimulation of pro-fibrotic cascades, which can lead to atrial structural remodelling and induce AF. Enhanced oxidative injury and deletion of mitochondrial deoxyribonucleic acid (mtDNA) in cardiac muscle can be found in patients with AF, which may further impair the bioenergetic function of mitochondria and lead to the oxidative cycle involved in the pathogenesis of atrial myopathy in AF<sup>40</sup>. In addition, some oxidative stress related pathophysiological changes in AF have been consistently demonstrated, such as increased NADPH and xanthine oxidase activity, upregulation of the renin-angiotensin system. Moreover, oxidative stress is involved in the development of a range of cardiovascular diseases which are associated with AF<sup>41</sup>. These combined effects of structure maladaptation, increased inflammation<sup>4</sup> and oxidative stress<sup>42</sup> contribute to endothelial dysfunction and subsequently an increased risk for both development and progression of AF.

In summary, related to the primary prevention of AF, studies examining the relation between AF and vascular function have provided strong evidence for the presence of endothelial dysfunction and structural maladaptation in patients with AF, especially when examining arteries that are in close proximity and/or relation with the heart. More importantly, presence of endothelial dysfunction and vascular abnormalities predict occurrence of AF, most likely through shared pathophysiological processes of inflammation process and oxidative stress. However, these two pathways are closely intertwined. Oxidative stress can promote inflammasome activation, which in turn, leads to increased production of cytokines (e.g. interleukin-1 and -6, IL-1 and IL-6) that develop arterial ectopy and fibrotic remodelling that can promote AF<sup>43</sup>. These observations of a link between endothelial dysfunction and occurrence of AF seem largely independent of the presence of cardiovascular risk factors. The clinical implication of this observation is that measuring vascular function and/or structure improves prediction of new-onset AF and possible reflects a target for pharmacological and non-pharmacological strategies to lower the risk of AF (*Fig. 2*).

---

### **3. Endothelial dysfunction and vascular maladaptation in secondary prevention of AF**

In line with the observation for a potential role for vascular dysfunction to contribute to the development of AF <sup>11</sup>, vascular dysfunction may also predict cardiovascular co-morbidities in subjects with AF. Of note, AF seems associated with development of a high number of cardiovascular risk factors, which may exacerbate endothelial dysfunction <sup>44</sup>. In addition, AF leads to hemodynamic changes that may also aggravate endothelial dysfunction, further contributing to the development of cardiovascular events <sup>45, 46</sup>.

#### **3.1 Does endothelial dysfunction predict AF recurrence?**

Several studies have examined whether endothelial dysfunction relates to poor outcomes in AF. For example, measures of impaired endothelial function in macrovessel (i.e. lower FMD) <sup>11</sup> or in microvessels (i.e. lower RHI) <sup>47, 48</sup> at baseline appears to be an independent predictor for arrhythmia recurrence following catheter ablation. Similar findings have been observed when examining arterial stiffness, for example, AF patients within the highest quartile of arterial stiffness having a 1.6-fold higher AF recurrence rate compared to those in the lowest quartile <sup>49</sup>. To support this concept, higher AIx has been linked to the recurrence of AF <sup>50</sup> and the development of paroxysmal AF <sup>51</sup>, perhaps related to left ventricular hypertrophy <sup>17</sup>.

These observations are consistent with endothelial dysfunction independently predicting incident AF, suggesting that endothelial dysfunction represents an integrated pathway in the development and progression of AF. Despite the strong evidence for a relationship between vascular dysfunction and AF recurrence, no studies have explored whether structural vascular characteristics are related to AF recurrence.

#### **3.2 Does endothelial dysfunction predict AF-related cardiovascular events?**

Despite the overwhelming evidence that measures of endothelial function independently predict cardiovascular disease <sup>52, 53</sup> and adverse events <sup>54</sup> in individuals with established and pre-clinical cardiovascular disease, few studies have explored whether measures of endothelial function relate to cardiovascular events in AF patients. For example, impaired endothelial function measured using the FMD is an independent and significant predictor of cardiovascular events in AF patients <sup>55, 56</sup>. In AF patients, arterial stiffness, assessed using the peripheral PWV, is considered as an

---

independent predictor of cardiovascular events and improve the prediction of adverse cardiovascular events when it is added to the standard clinical, biochemical, and echocardiographic parameters <sup>57</sup>.

In a meta-analysis including 5,648 individuals free of AF with a follow-up of 45 months, AIx was determined as an independent predictor of future incident of cardiovascular and all-cause mortality, independent from peripheral pressure and heart rate measures <sup>58</sup>. Higher AIx has also been significantly correlated with AF-specific cardiac remodelling such as left atrial enlargement <sup>51</sup>, which could lead ultimately to cardiovascular events such as stroke and atrial thrombosis.

### **3.3 Do structural vascular adaptations predict cardiovascular events?**

Carotid IMT has been shown to be associated with both coronary and cerebral vascular events in several AF studies <sup>59-61</sup>. For example, abnormal IMT and presence of carotid plaque in the ARIC study significantly increased the risk of stroke, and marginally increased the clinical risk prediction of stroke in combination with the CHA<sub>2</sub>DS<sub>2</sub>-VASc score <sup>61</sup>. AF patients with carotid plaque have significantly increased risk of cardio- and cerebrovascular adverse outcomes <sup>62</sup>, and complex aortic plaque is an independent predictor of ischaemic stroke in patients with AF <sup>63</sup>. Indeed, patients with both AF and aortic atherosclerotic plaque  $\geq 4.0$ mm demonstrated worse atherosclerosis burden and predicted long-term cardiovascular events, including stroke <sup>64</sup>. It is also consistent with the work related to carotid and aorta atherosclerotic burden, where CAC scores independently predict coronary artery disease <sup>65</sup>, stroke <sup>66</sup>, and future cardiovascular events in AF patients <sup>24, 25</sup>. Patients with persistent AF have a significantly higher prevalence of subclinical coronary artery disease (due to a higher coronary artery disease-burden [CAC score]) when compared to paroxysmal AF patients <sup>27</sup>.

In summary, studies provide compelling support that presence of vascular dysfunction and/or structural vascular maladaptation (inward remodelling) is frequently present in AF. Furthermore, vascular dysfunction seems to predict AF recurrence following ablation therapy, whilst vascular dysfunction and structural maladaptation are both independently related to the occurrence of adverse cardiovascular events in these patients. Therefore, these studies therefore support an important role for vascular dysfunction in mediating AF-related morbidity and mortality, and

---

provide a rationale for measuring vascular function and structural maladaptation in AF patients to improve risk stratification and targeted therapy.

### **3.4 Mechanisms explaining the association between vascular dysfunction and AF-related cardiovascular events.**

The presence of traditional cardiovascular risk factors in patients with AF represent one factor contributing to the development and progression of endothelial dysfunction and vascular maladaptation, both contributing to an increased risk for AF-related cardiovascular disease and events. In addition, other pathways may contribute to these vascular adaptations (**Fig. 3**).

From a mechanistic point of view, the loss of organised atrial contraction associated with AF may lead to a beat-to-beat haemodynamic variations<sup>13</sup>. These irregular patterns in flow and pressure reduces maximal blood flow and atrial perfusion dysregulation, leading to a detrimental effect on atrial blood supply<sup>67, 68</sup>. The latter also includes a reduction of capillary density, imbalanced myocardial oxygen supply-demand ratio, and coronary perfusion impairment<sup>69</sup>, all resulting in impaired microvascular function in the coronary arteries<sup>70</sup>. The irregular haemodynamic changes also lead to an irregular pulse wave, blood flow and shear stress pattern through central (and to a lesser extent, peripheral) arteries<sup>33</sup>. These shear stress patterns, characterised by increased retrograde flow and bidirectional flow, results from the irregular blood flow velocity<sup>71-73</sup>. Consequently, AF is associated with a marked decrease in eNOS expression and NO bioavailability<sup>74</sup>, and higher levels of the vasoconstrictor endothelin-1<sup>75, 76</sup>, all of which exacerbate endothelial dysfunction<sup>77</sup> and plaque formation<sup>78</sup>. These abnormal patterns seem to especially affect central arteries, possibly contributing to the observation that central measures of vascular function and structure may have stronger prognostic value for AF-related events compared to more peripheral measures. However, this hypothesis requires further exploration (**Fig. 3**).

## **4. Exercise and AF**

Emerging evidence demonstrates a variety of benefits of increased physical activity levels for patients with AF. Specifically, one fourth of new cases of AF in older adults may be attributable to absence of moderate leisure-time activity and regular walking<sup>79</sup>. A recent systematic review of 4 interventional studies (498 participants) found a positive effect of lifestyle and risk factor

---

management interventions significantly decreased AF episode severity, AF frequency, and AF duration<sup>80</sup>.

One randomised controlled trial demonstrated that weight reduction with intensive risk factor management (e.g. goals for regular exercise, lipid management, glycaemic control, and blood pressure reduction) was associated with beneficial cardiac remodelling and reduced AF burden and severity in overweight or obese patients<sup>81, 82</sup>. Indeed, regular exercise in patients with AF has been associated with lower risk of all-cause mortality and thromboembolic events irrespective of gender, age, or risk of stroke<sup>83</sup> and improved sinus rhythm maintenance<sup>84</sup>. In addition, for every 1 MET increase in cardiorespiratory fitness via exercise training, AF recurrence is reduced by 9%<sup>82, 85</sup>.

These studies highlight the potency of regular physical activity as an additive therapy in the management of AF, both related to the primary and secondary prevention of AF<sup>86, 87</sup>. Nonetheless, important questions remain unanswered. First, a key question relates to the optimal dose, type and frequency of exercise training to optimally benefit from exercise training. Related to this topic, little work has focused on the optimal timing of exercise prior to and/or after cardioversion in AF. Finally, little work has focused on the potential underlying mechanisms explaining the cardioprotective effects of regular physical activity for AF, which may relate to the direct effect on cardiac remodelling and health, but also on circulating factors and/or improvement in vascular function and structure. Better understanding of these mechanisms will contribute to optimal prescription of exercise as medicine for AF.

## **5. Future perspectives for vascular function and AF**

Although the pathogenesis of AF is complex and most likely multifaceted, the work summarised in this review strongly supports a central role for endothelial dysfunction and structural vascular abnormalities to contribute, as a potential final common pathway, to the development and progression of AF. Another observation from this review is that AF is related to vascular dysfunction and structural vascular abnormalities that is closely linked to AF recurrence and development of cardiovascular events.

The evidence is suggestive of a potential causative role for endothelial dysfunction and vascular remodelling for AF occurrence, recurrence and AF-related complications, but firmly establishing

---

causation would require large prospective studies, supported by randomised trials. Nonetheless, such vascular abnormalities could also reflect common risk factors, including ageing, hypertension, diabetes etc – and the dynamic nature of risk factors changing with ageing and incident comorbidities <sup>88-90</sup>. The full evaluation is part of the overall characterisation of AF, the 4S-AF scheme: Stroke risk, Symptom severity, Severity of arrhythmia burden and Substrate <sup>91</sup>. The latter clearly includes evaluation of comorbidities and structural heart disease, as recommended by guidelines <sup>92</sup>.

A potential clinical consequence is that measures of vascular function and structure may improve on existing assessments and risk stratification of new onset and recurrence of AF. This could lead to improved and personalised risk prediction in patients with AF. Another potential clinical consequence of these observations is that presence of systemically present endothelial dysfunction and structural maladaptation may be an important target in the primary and secondary prevention of AF, but also in minimising risks for AF-related cardiovascular disease and/or events. Whilst pharmaceutical strategies could specifically target endothelial function in AF patients, one other highly relevant strategy may relate to adopting regular exercise training <sup>93</sup>. It seems especially relevant given the well-established effect of regular exercise on improving vascular function and structure <sup>93-95</sup>, but also on improving the risk factors management in addition to the regular care such as appropriate anticoagulation and rate and rhythm control <sup>96, 97</sup>. Indeed, regular exercise in patients with AF has been associated with lower risk of all-cause mortality and thromboembolic events <sup>83</sup>, but also improved sinus rhythm maintenance <sup>84</sup>. At the very least, a stronger focus on endothelial function in AF patients likely enhances clinical management of AF as it improves prediction of AF, AF recurrence, and AF-related cardiovascular events, but also represents a sensible target in the treatment of AF.

---

## 6. Conclusion and clinical perspective

Cardiovascular diseases are a major cause of global mortality<sup>98</sup>, accounting for approximately 31% of all deaths<sup>99</sup>. Endothelial dysfunction is one of the major determinants of atherosclerosis<sup>100, 101</sup>, significantly associated with higher thrombotic events<sup>102</sup> and cardiovascular mortality<sup>103</sup>. So far, a number of techniques have been developed to assess endothelial function, which provide reliable references for the diagnosis and prognosis of vascular disease<sup>104</sup>. Evidence confirm that some risk factors such as obesity<sup>105</sup>, age<sup>106</sup>, hypertension<sup>107</sup>, and physical inactivity<sup>108-110</sup> can exacerbate endothelial dysfunction. These lines of evidence strongly support future studies to pay more attention to the evaluation and maintenance of vascular endothelial function in patients with AF. These recommendations are on top of improvements of vascular disease risk, but also lifestyle modification<sup>111</sup>.

## 7. References

1. Schnabel RB, Yin X, Gona P, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet*. Jul 11 2015;386(9989):154-62. doi:10.1016/s0140-6736(14)61774-8
2. Panchal G, Mahmood M, Lip GY. Revisiting the risks of incident atrial fibrillation: a narrative review. Part 2. *Kardiologia polska*. 2019;77(5):515-524.
3. Lim HS, Willoughby SR, Schultz C, et al. Effect of atrial fibrillation on atrial thrombogenesis in humans: impact of rate and rhythm. *Journal of the American College of Cardiology*. 2013;61(8):852-860.
4. Patel P, Dokainish H, Tsai P, Lakkis N. Update on the association of inflammation and atrial fibrillation. *Journal of cardiovascular electrophysiology*. 2010;21(9):1064-1070.
5. Watson T, Shantsila E, Lip GY. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *The Lancet*. 2009;373(9658):155-166.
6. Poer JS, Sessa WC. Evolving functions of endothelial cells in inflammation. *Nat Rev Immunol*. Oct 2007;7(10):803-15. doi:10.1038/nri2171

- 
7. Borschel CS, Rubsam N, Ojeda FM, et al. Noninvasive peripheral vascular function and atrial fibrillation in the general population. *Journal of Hypertension*. May 2019;37(5):928-934. doi:10.1097/hjh.0000000000002000
  8. Skolidis EI, Zacharis EA, Tsetis DK, et al. Endothelial cell function during atrial fibrillation and after restoration of sinus rhythm. *The American journal of cardiology*. 2007;99(9):1258-1262.
  9. Komatsu T, Kunugita F, Ozawa M, et al. Relationship between impairment of the vascular endothelial function and the CHA2DS2-VASc score in patients with sinus rhythm and non-valvular atrial fibrillation. *Internal Medicine*. 2018:9831-17.
  10. Inaba Y, Chen JA, Bergmann SR. Prediction of future cardiovascular outcomes by flow-mediated vasodilatation of brachial artery: a meta-analysis. *Int J Cardiovasc Imaging*. Aug 2010;26(6):631-40. doi:10.1007/s10554-010-9616-1
  11. Shin SY, Na JO, Lim HE, et al. Improved endothelial function in patients with atrial fibrillation through maintenance of sinus rhythm by successful catheter ablation. *Journal of cardiovascular electrophysiology*. 2011;22(4):376-382.
  12. Odotayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. *Bmj-British Medical Journal*. Sep 2016;354:i4482. doi:10.1136/bmj.i4482
  13. Okawa K, Miyoshi T, Tsukuda S, et al. Differences in endothelial dysfunction induced by paroxysmal and persistent atrial fibrillation: Insights from restoration of sinus rhythm by catheter ablation. Article. *International Journal of Cardiology*. 2017;doi:10.1016/j.ijcard.2017.06.038
  14. Lee S-H, Choi S, Jung J-H, Lee N. Effects of atrial fibrillation on arterial stiffness in patients with hypertension. *Angiology*. 2008;59(4):459-463.
  15. Cui R, Yamagishi K, Muraki I, et al. Association between markers of arterial stiffness and atrial fibrillation in the Circulatory Risk in Communities Study (CIRCS). *Atherosclerosis*. 2017/08/01/ 2017;263:244-248. doi:https://doi.org/10.1016/j.atherosclerosis.2017.06.918

- 
16. Chen LY, Foo DC, Wong RC, et al. Increased carotid intima-media thickness and arterial stiffness are associated with lone atrial fibrillation. *Int J Cardiol.* Oct 3 2013;168(3):3132-4. doi:10.1016/j.ijcard.2013.04.034
17. Shaikh AY, Wang N, Yin XY, et al. Relations of Arterial Stiffness and Brachial Flow-Mediated Dilation With New-Onset Atrial Fibrillation The Framingham Heart Study. *Hypertension.* Sep 2016;68(3):590-596. doi:10.1161/hypertensionaha.116.07650
18. O'Neal WT, Efird JT, Yeboah J, et al. Brachial flow-mediated dilation and incident atrial fibrillation: the multi-ethnic study of atherosclerosis. *Arteriosclerosis, thrombosis, and vascular biology.* 2014;34(12):2717-2720.
19. Cremer A, Lainé M, Papaioannou G, Yeim S, Gosse P. Increased arterial stiffness is an independent predictor of atrial fibrillation in hypertensive patients. *Journal of Hypertension.* 2015;33(10):2150-2155. doi:10.1097/hjh.0000000000000652
20. Lantelme P, Laurent S, Besnard C, et al. Arterial stiffness is associated with left atrial size in hypertensive patients. *Arch Cardiovasc Dis.* Jan 2008;101(1):35-40. doi:10.1016/s1875-2136(08)70253-5
21. Zekavat SM, Roselli C, Hindy G, et al. Genetic Link Between Arterial Stiffness and Atrial Fibrillation. Letter. *Circulation Genomic and precision medicine.* 2019;doi:10.1161/CIRCGEN.118.002453
22. Chen LY, Leening MJG, Norby FL, et al. Carotid Intima-Media Thickness and Arterial Stiffness and the Risk of Atrial Fibrillation: The Atherosclerosis Risk in Communities (ARIC) Study, Multi-Ethnic Study of Atherosclerosis (MESA), and the Rotterdam Study. *J Am Heart Assoc.* 2016;5(5):e002907. doi:10.1161/JAHA.115.002907
23. Proietti M, Calvieri C, Malatino L, et al. Relationship between carotid intima-media thickness and non valvular atrial fibrillation type. *Atherosclerosis.* 2015/02/01/ 2015;238(2):350-355. doi:https://doi.org/10.1016/j.atherosclerosis.2014.12.022

- 
24. Paixao ARM, Ayers CR, El Sabbagh A, et al. Coronary Artery Calcium Improves Risk Classification in Younger Populations. Article. *JACC: Cardiovascular Imaging*. 11/01/November 2015 2015;8(11):1285-1293. doi:10.1016/j.jcmg.2015.06.015
25. Elias-Smale SE, Proenca RV, Koller MT, et al. Coronary Calcium Score Improves Classification of Coronary Heart Disease Risk in the Elderly The Rotterdam Study. *Journal of the American College of Cardiology*. Oct 2010;56(17):1407-1414. doi:10.1016/j.jacc.2010.06.029
26. Pan N-H, Tsao H-M, Chang N-C, Lee C-M, Chen Y-J, Chen S-A. Dilated left atrium and pulmonary veins in patients with calcified coronary artery: a potential contributor to the genesis of atrial fibrillation. *Journal of cardiovascular electrophysiology*. 2009;20(2):153-158.
27. Chaikriangkrai K, Valderrabano M, Bala SK, et al. Prevalence and Implications of Subclinical Coronary Artery Disease in Patients With Atrial Fibrillation. *The American Journal of Cardiology*. 2015/10/15/ 2015;116(8):1219-1223. doi:https://doi.org/10.1016/j.amjcard.2015.07.041
28. O'Neal WT, Efird JT, Qureshi WT, et al. Coronary Artery Calcium Progression and Atrial Fibrillation The Multi-Ethnic Study of Atherosclerosis. *Circulation-Cardiovascular Imaging*. Dec 2015;8(12)e003786. doi:10.1161/circimaging.115.003786
29. Okwuosa TM, Greenland P, Ning H, Liu K, Lloyd-Jones DM. Yield of screening for coronary artery calcium in early middle-age adults based on the 10-year Framingham Risk Score: the CARDIA study. *JACC Cardiovasc Imaging*. Sep 2012;5(9):923-30. doi:10.1016/j.jcmg.2012.01.022
30. Losi M-A, Izzo R, De Marco M, et al. Cardiovascular ultrasound exploration contributes to predict incident atrial fibrillation in arterial hypertension: The Campania Salute Network. *International Journal of Cardiology*. 2015/11/15/ 2015;199:290-295. doi:https://doi.org/10.1016/j.ijcard.2015.07.019

- 
31. O'Neal WT, Efird JT, Dawood FZ, et al. Coronary Artery Calcium and Risk of Atrial Fibrillation (from the Multi-Ethnic Study of Atherosclerosis). *American Journal of Cardiology*. Dec 2014;114(11):1707-1712. doi:10.1016/j.amjcard.2014.09.005
32. Budoff MJ, Young R, Lopez VA, et al. Progression of coronary calcium and incident coronary heart disease events: MESA (Multi-Ethnic Study of Atherosclerosis). *Journal of the American College of Cardiology*. 2013;61(12):1231-1239.
33. Yoshino S, Yoshikawa A, Hamasaki S, et al. Atrial fibrillation-induced endothelial dysfunction improves after restoration of sinus rhythm. *International Journal of Cardiology*. Sep 2013;168(2):1280-1285. doi:10.1016/j.ijcard.2012.12.006
34. Münzel T, Sinning C, Post F, Warnholtz A, Schulz E. Pathophysiology, diagnosis and prognostic implications of endothelial dysfunction. *Ann Med*. 2008;40(3):180-96. doi:10.1080/07853890701854702
35. Weiner SD, Ahmed HN, Jin Z, et al. Systemic inflammation and brachial artery endothelial function in the Multi-Ethnic Study of Atherosclerosis (MESA). *Heart*. 2014;100(11):862-866.
36. Kaireviciute D, Lip G, Balakrishnan B, et al. Intracardiac expression of markers of endothelial damage/dysfunction, inflammation, thrombosis, and tissue remodeling, and the development of postoperative atrial fibrillation. *Journal of Thrombosis and Haemostasis*. 2011;9(12):2345-2352.
37. d'Alessandro E, Becker C, Bergmeier W, et al. Thrombo-Inflammation in Cardiovascular Disease: An Expert Consensus Document from the Third Maastricht Consensus Conference on Thrombosis. *Thrombosis and Haemostasis*. 2020;120(04):538-564.
38. Klein Klouwenberg PM, Frencken JF, Kuipers S, et al. Incidence, Predictors, and Outcomes of New-Onset Atrial Fibrillation in Critically Ill Patients with Sepsis. A Cohort Study. *Am J Respir Crit Care Med*. Jan 15 2017;195(2):205-211. doi:10.1164/rccm.201603-0618OC

- 
39. Korantzopoulos P, Letsas KP, Tse G, Fragakis N, Goudis CA, Liu T. Inflammation and atrial fibrillation: A comprehensive review. *J Arrhythm.* Aug 2018;34(4):394-401. doi:10.1002/joa3.12077
40. Lin P-H, Lee S-H, Su C-P, Wei Y-H. Oxidative damage to mitochondrial DNA in atrial muscle of patients with atrial fibrillation. *Free Radical Biology and Medicine.* 2003;35(10):1310-1318.
41. Korantzopoulos P, Kolettis TM, Galaris D, Goudevenos JA. The role of oxidative stress in the pathogenesis and perpetuation of atrial fibrillation. *Int J Cardiol.* Feb 7 2007;115(2):135-43. doi:10.1016/j.ijcard.2006.04.026
42. Korantzopoulos P, Kolettis TM, Galaris D, Goudevenos JA. The role of oxidative stress in the pathogenesis and perpetuation of atrial fibrillation. *International journal of cardiology.* 2007;115(2):135-143.
43. Yao C, Veleva T, Scott L, Jr., et al. Enhanced Cardiomyocyte NLRP3 Inflammasome Signaling Promotes Atrial Fibrillation. *Circulation.* Nov 13 2018;138(20):2227-2242. doi:10.1161/circulationaha.118.035202
44. Khan AA, Thomas GN, Lip GY, Shantsila A. Endothelial function in patients with atrial fibrillation. *Annals of Medicine.* 2020:1-11.
45. Kirchhof P. The future of atrial fibrillation management: integrated care and stratified therapy. *The Lancet.* 2017/10/21/ 2017;390(10105):1873-1887. doi:https://doi.org/10.1016/S0140-6736(17)31072-3
46. Smiljic S. The clinical significance of endocardial endothelial dysfunction. Review. *Medicina (Lithuania).* 2017;doi:10.1016/j.medic.2017.08.003
47. Bonetti PO, Pumper GM, Higano ST, Holmes DR, Kuvin JT, Lerman A. Noninvasive identification of patients with early coronary atherosclerosis by assessment of digital reactive hyperemia. *Journal of the American College of Cardiology.* 2004;44(11):2137-2141.

- 
48. Kobayashi H, Okada A, Tabata H, et al. Association between reactive hyperemia peripheral arterial tonometry index and atrial fibrillation recurrence after catheter ablation. *IJC Heart & Vasculature*. 2019/09/01/ 2019;24:100385. doi:<https://doi.org/10.1016/j.ijcha.2019.100385>
49. Lau DH, Middeldorp ME, Brooks AG, et al. Aortic Stiffness in Lone Atrial Fibrillation: A Novel Risk Factor for Arrhythmia Recurrence. *Plos One*. Oct 2013;8(10):e76776. doi:10.1371/journal.pone.0076776
50. Lau DH, Middeldorp ME, Brooks AG, et al. Aortic stiffness in lone atrial fibrillation: a novel risk factor for arrhythmia recurrence. *PloS one*. 2013;8(10)
51. Doi M, Miyoshi T, Hirohata S, et al. Increased augmentation index of the radial pressure waveform in patients with paroxysmal atrial fibrillation. *Cardiology*. 2009;113(2):138-145.
52. Matsuzawa Y, Sugiyama S, Sumida H, et al. Peripheral endothelial function and cardiovascular events in high-risk patients. *Journal of the American Heart Association*. 2013;2(6):e000426.
53. Yufu K, Shinohara T, Ebata Y, et al. Endothelial function predicts new hospitalization due to heart failure following cardiac resynchronization therapy. *Pacing and Clinical Electrophysiology*. 2015;38(11):1260-1266.
54. Rubinshtein R, Kuvin JT, Soffler M, et al. Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events. *Eur Heart J*. 2010;31(9):1142-1148.
55. Yeboah J, Crouse JR, Hsu FC, Burke GL, Herrington DM. Brachial flow-mediated dilation predicts incident cardiovascular events in older adults: the Cardiovascular Health Study. *Circulation*. May 8 2007;115(18):2390-7.
56. Yeboah J, Folsom AR, Burke GL, et al. Predictive value of brachial flow-mediated dilation for incident cardiovascular events in a population-based study: the multi-ethnic study of atherosclerosis. *Circulation*. Aug 11 2009;120(6):502-9.

- 
57. Chen S-C, Lee W-H, Hsu P-C, et al. Association of brachial–ankle pulse wave velocity with cardiovascular events in atrial fibrillation. *American journal of hypertension*. 2015;29(3):348-356.
58. Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. *European heart journal*. 2010;31(15):1865-1871.
59. Eryd SA, Östling G, Rosvall M, et al. Carotid intima-media thickness is associated with incidence of hospitalized atrial fibrillation. *Atherosclerosis*. 2014;233(2):673-678.
60. Grosse GM, Biber S, Sieweke JT, et al. Plasma dimethylarginine levels and carotid intima–media thickness are related to atrial fibrillation in patients with embolic stroke. Article. *International Journal of Molecular Sciences*. 2019;20(3)730. doi:10.3390/ijms20030730
61. Bekwelem W, Jensen PN, Norby FL, et al. Carotid Atherosclerosis and Stroke in Atrial Fibrillation: The Atherosclerosis Risk in Communities Study. *Stroke*. Jun 2016;47(6):1643-6. doi:10.1161/strokeaha.116.013133
62. Bunch TJ, Bair TL, Crandall BG, et al. Stroke and dementia risk in patients with and without atrial fibrillation and carotid arterial disease. *Heart rhythm*. 2020;17(1):20-26.
63. Transesophageal echocardiographic correlates of thromboembolism in high-risk patients with nonvalvular atrial fibrillation. The Stroke Prevention in Atrial Fibrillation Investigators Committee on Echocardiography. *Annals Of Internal Medicine*. 1998;128(8):639-647.
64. Okura H, Kataoka T, Yoshiyama M, Yoshikawa J, Yoshida K. Aortic atherosclerotic plaque and long-term prognosis in patients with atrial fibrillation. *Circulation Journal*. 2012:CJ-12-0583.
65. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *New England Journal of Medicine*. Mar 2008;358(13):1336-1345. doi:10.1056/NEJMoa072100

- 
66. Hermann DM, Gronewold J, Lehmann N, et al. Coronary artery calcification is an independent stroke predictor in the general population. *Stroke*. 2013;44(4):1008-1013.
67. Skalidis EI, Kochiadakis GE, Igoumenidis NE, Vardakis KE, Vardas PE. Phasic coronary blood flow velocity pattern and flow reserve in the atrium: regulation of left atrial myocardial perfusion. *Journal of the American College of Cardiology*. 2003;41(4):674-680.
68. White CW, Kerber RE, Weiss HR, Marcus ML. The effects of atrial fibrillation on atrial pressure-volume and flow relationships. *Circulation research*. 1982;51(2):205-215.
69. Scarsoglio S, Gallo C, Saglietto A, Ridolfi L, Anselmino M. Impaired coronary blood flow at higher heart rates during atrial fibrillation: Investigation via multiscale modelling. *Comput Methods Programs Biomed*. Jul 2019;175:95-102. doi:10.1016/j.cmpb.2019.04.009
70. Skalidis EI, Hamilos MI, Karalis IK, Chlouverakis G, Kochiadakis GE, Vardas PE. Isolated Atrial Microvascular Dysfunction in Patients With Lone Recurrent Atrial Fibrillation. *Journal of the American College of Cardiology*. 2008/05/27/ 2008;51(21):2053-2057. doi:https://doi.org/10.1016/j.jacc.2008.01.055
71. Uematsu M, Ohara Y, Navas JP, et al. Regulation of endothelial cell nitric oxide synthase mRNA expression by shear stress. *American Journal of Physiology-Cell Physiology*. 1995;269(6):C1371-C1378.
72. Nishida K, Harrison D, Navas J, et al. Molecular cloning and characterization of the constitutive bovine aortic endothelial cell nitric oxide synthase. *The Journal of clinical investigation*. 1992;90(5):2092-2096.
73. Davis ME, Cai H, Drummond GR, Harrison DG. Shear stress regulates endothelial nitric oxide synthase expression through c-Src by divergent signaling pathways. *Circulation research*. 2001;89(11):1073-1080.
74. Cai H, Li Z, Goette A, et al. Downregulation of endocardial nitric oxide synthase expression and nitric oxide production in atrial fibrillation: potential mechanisms for atrial thrombosis and stroke. *Circulation*. 2002;106(22):2854-2858.

- 
75. Brundel BJ, VAN GELDER IC, Tuinenburg AE, et al. Endothelin system in human persistent and paroxysmal atrial fibrillation. *Journal of cardiovascular electrophysiology*. 2001;12(7):737-742.
76. Mayyas F, Niebauer M, Zurick A, et al. Association of left atrial endothelin-1 with atrial rhythm, size, and fibrosis in patients with structural heart disease. *Circulation: Arrhythmia and Electrophysiology*. 2010;3(4):369-379.
77. Yiin GS, Howard DP, Paul NL, Li L, Mehta Z, Rothwell PM. Recent time trends in incidence, outcome and premorbid treatment of atrial fibrillation-related stroke and other embolic vascular events: a population-based study. *J Neurol Neurosurg Psychiatry*. Jan 2017;88(1):12-18. doi:10.1136/jnnp-2015-311947
78. Gambillara V, Chambaz C, Montorzi G, Roy S, Stergiopoulos N, Silacci P. Plaque-prone hemodynamics impair endothelial function in pig carotid arteries. *American Journal of Physiology-Heart and Circulatory Physiology*. 2006;290(6):H2320-H2328.
79. Mozaffarian D, Furberg CD, Psaty BM, Siscovick D. Physical activity and incidence of atrial fibrillation in older adults: the cardiovascular health study. *Circulation*. Aug 19 2008;118(8):800-7. doi:10.1161/circulationaha.108.785626
80. Larsen RT, Gottlieb CR, Wood KA, Risom SS. Lifestyle interventions after ablation for atrial fibrillation: a systematic review. *Eur J Cardiovasc Nurs*. May 6 2020:1474515120919388. doi:10.1177/1474515120919388
81. Abed HS, Wittert GA, Leong DP, et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. *Jama*. Nov 20 2013;310(19):2050-60. doi:10.1001/jama.2013.280521
82. Pathak RK, Middeldorp ME, Lau DH, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol*. Dec 2 2014;64(21):2222-31. doi:10.1016/j.jacc.2014.09.028

- 
83. Proietti M, Boriani G, Laroche C, et al. Self-reported physical activity and major adverse events in patients with atrial fibrillation: a report from the EURObservational Research Programme Pilot Survey on Atrial Fibrillation (EORP-AF) General Registry. *Europace*. Apr 1 2017;19(4):535-543. doi:10.1093/europace/euw150
84. Rienstra M, Hobbelt AH, Alings M, et al. Targeted therapy of underlying conditions improves sinus rhythm maintenance in patients with persistent atrial fibrillation: results of the RACE 3 trial. *Eur Heart J*. Aug 21 2018;39(32):2987-2996. doi:10.1093/eurheartj/ehx739
85. Pathak RK, Elliott A, Middeldorp ME, et al. Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation: The CARDIO-FIT Study. *J Am Coll Cardiol*. Sep 1 2015;66(9):985-96. doi:10.1016/j.jacc.2015.06.488
86. Semaan S, Dewland TA, Tison GH, et al. Physical activity and atrial fibrillation: Data from wearable fitness trackers. *Heart Rhythm*. 2020;17(5):842-846.
87. Kato M, Ogano M, Mori Y, et al. Exercise-based cardiac rehabilitation for patients with catheter ablation for persistent atrial fibrillation: A randomized controlled clinical trial. *Eur J Prev Cardiol*. 2019;26(18):1931-1940.
88. Chao TF, Lip GYH, Lin YJ, et al. Incident Risk Factors and Major Bleeding in Patients with Atrial Fibrillation Treated with Oral Anticoagulants: A Comparison of Baseline, Follow-up and Delta HAS-BLED Scores with an Approach Focused on Modifiable Bleeding Risk Factors. *Thromb Haemost*. Apr 2018;118(4):768-777. doi:10.1055/s-0038-1636534
89. Chao TF, Liao JN, Tuan TC, et al. Incident Co-Morbidities in Patients with Atrial Fibrillation Initially with a CHA2DS2-VASc Score of 0 (Males) or 1 (Females): Implications for Reassessment of Stroke Risk in Initially 'Low-Risk' Patients. *Thromb Haemost*. Jul 2019;119(7):1162-1170. doi:10.1055/s-0039-1683933
90. Chang TY, Lip GYH, Chen SA, Chao TF. Importance of Risk Reassessment in Patients With Atrial Fibrillation in Guidelines: Assessing Risk as a Dynamic Process. *Can J Cardiol*. May 2019;35(5):611-618. doi:10.1016/j.cjca.2019.01.018

- 
91. Potpara TS, Lip GYH, Blomstrom-Lundqvist C, et al. The 4S-AF Scheme (Stroke Risk; Symptoms; Severity of Burden; Substrate): A Novel Approach to In-Depth Characterization (Rather than Classification) of Atrial Fibrillation. *Thromb Haemost.* Aug 24 2020;doi:10.1055/s-0040-1716408
92. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* Aug 29 2020;doi:10.1093/eurheartj/ehaa612
93. Green DJ, Hopman MT, Padilla J, Laughlin MH, Thijssen DH. Vascular adaptation to exercise in humans: role of hemodynamic stimuli. *Physiological reviews.* 2017;97(2):495-528.
94. Hellsten Y, Nyberg M. Cardiovascular adaptations to exercise training. *Comprehensive Physiology.* 2011;6(1):1-32.
95. Green DJ, Smith KJ. Effects of exercise on vascular function, structure, and health in humans. *Cold Spring Harbor Perspectives in Medicine.* 2018;8(4):a029819.
96. Lau DH, Nattel S, Kalman JM, Sanders P. Modifiable Risk Factors and Atrial Fibrillation. *Circulation.* Aug 8 2017;136(6):583-596. doi:10.1161/circulationaha.116.023163
97. Nalliah CJ, Sanders P, Kalman JM. The Impact of Diet and Lifestyle on Atrial Fibrillation. *Curr Cardiol Rep.* Oct 12 2018;20(12):137. doi:10.1007/s11886-018-1082-8
98. Mortal G. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet.* 2015;385(9963):117-171.
99. Organization WH. Cardiovascular Diseases (CVDs) World Health Organization. *Geneva, Switzerland.* 2017;
100. Juonala M, Viikari JS, Laitinen T, et al. Interrelations between brachial endothelial function and carotid intima-media thickness in young adults: the cardiovascular risk in young Finns study. *Circulation.* 2004;110(18):2918-2923.

- 
101. Widlansky ME, Gokce N, Keaney JF, Vita JA. The clinical implications of endothelial dysfunction. *Journal of the American College of Cardiology*. 2003;42(7):1149-1160.
102. Bochenek ML, Schäfer K. Role of endothelial cells in acute and chronic thrombosis. *Hämostaseologie*. 2019;
103. Lima BB, Hammadah M, Kim JH, et al. Association of Transient Endothelial Dysfunction Induced by Mental Stress With Major Adverse Cardiovascular Events in Men and Women With Coronary Artery Disease. *JAMA cardiology*. 2019;4(10):988-996.
104. Thijssen DH, Bruno RM, van Mil AC, et al. Expert consensus and evidence-based recommendations for the assessment of flow-mediated dilation in humans. *European heart journal*. 2019;
105. Kwaifa IK, Bahari H, Yong YK, Noor SM. Endothelial Dysfunction in Obesity-Induced Inflammation: Molecular Mechanisms and Clinical Implications. *Biomolecules*. 2020;10(2):291.
106. Banki E, Sosnowska D, Tucsek Z, et al. Age-related decline of autocrine pituitary adenylate cyclase-activating polypeptide impairs angiogenic capacity of rat cerebrovascular endothelial cells. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences*. 2015;70(6):665-674.
107. Chaudhary P, Pandey A, Azad CS, Tia N, Singh M, Gambhir IS. Association of oxidative stress and endothelial dysfunction in hypertension. *Analytical Biochemistry*. 2020;590:113535.
108. Rossman MJ, Kaplon RE, Hill SD, et al. Endothelial cell senescence with aging in healthy humans: prevention by habitual exercise and relation to vascular endothelial function. *American journal of physiology-Heart and circulatory physiology*. 2017;313(5):H890-H895.
109. Patino-Alonso MC, Recio-Rodríguez JI, Magdalena-Belio JF, et al. Clustering of lifestyle characteristics and their association with cardio-metabolic health: the Lifestyles and Endothelial Dysfunction (EVIDENT) study. *British Journal of Nutrition*. 2015;114(6):943-951.
110. Suvorava T, Lauer N, Kojda G. Physical inactivity causes endothelial dysfunction in healthy young mice. *Journal of the American College of Cardiology*. 2004;44(6):1320-1327.

---

111. Widmer RJ, Lerman A. Endothelial dysfunction and cardiovascular disease. *Global Cardiology Science and Practice*. 2014;2014(3):43.

#### **Funding**

Not applicable

#### **Conflict of interest**

The authors declare that there is no conflict of interest

#### **Authors' contributions**

S.Q. and D.T. contributed to the conception or design of the work. S.Q. contributed to writing the original draft, reviewing and editing. M.B. and B.B. contributed to writing the original draft and reviewing. G.L. and D.T. critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

#### **Figure Legends**

##### **Fig.1 The association among endothelial dysfunction, AF and cardiovascular events**

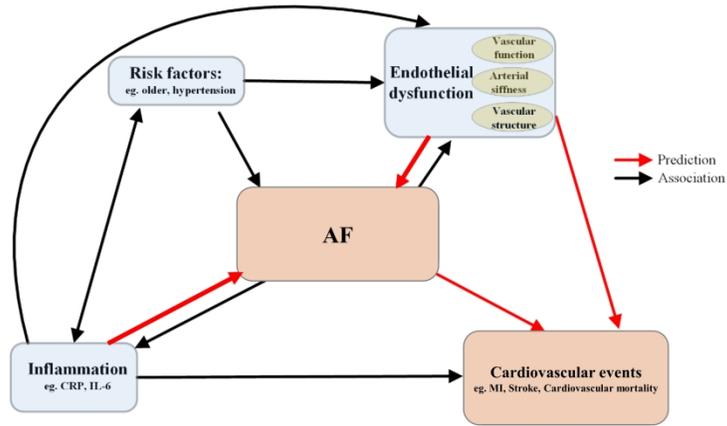
AF: atrial fibrillation, CRP: c-reactive protein, IL-6: interleukin 6, vWF: von willebrand factor, MI: myocardial infarction

##### **Fig.2 The key role of endothelial function in the primary prevention of AF**

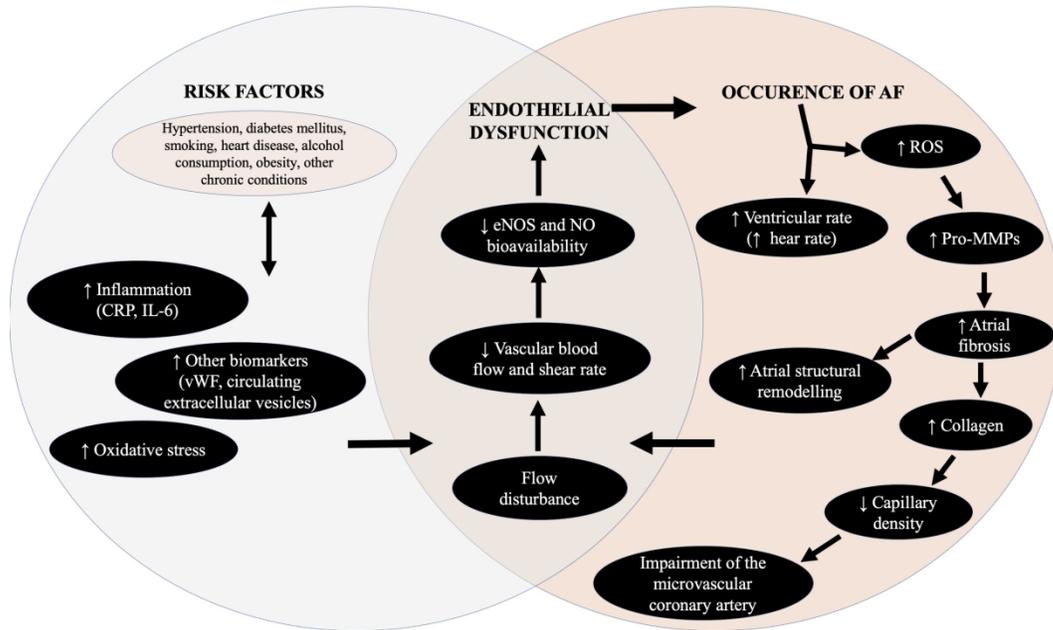
AF: atrial fibrillation, CRP: c-Reactive Protein, IL-6: interleukin-6, eNOS: endothelial nitric oxide synthase, NO: nitric oxide, ROS: reactive oxygen species, Pro-MMPs: matrix metalloproteinases, vWF: von Willebrand factor

##### **Fig.3 The key role of endothelial function in secondary prevention of AF**

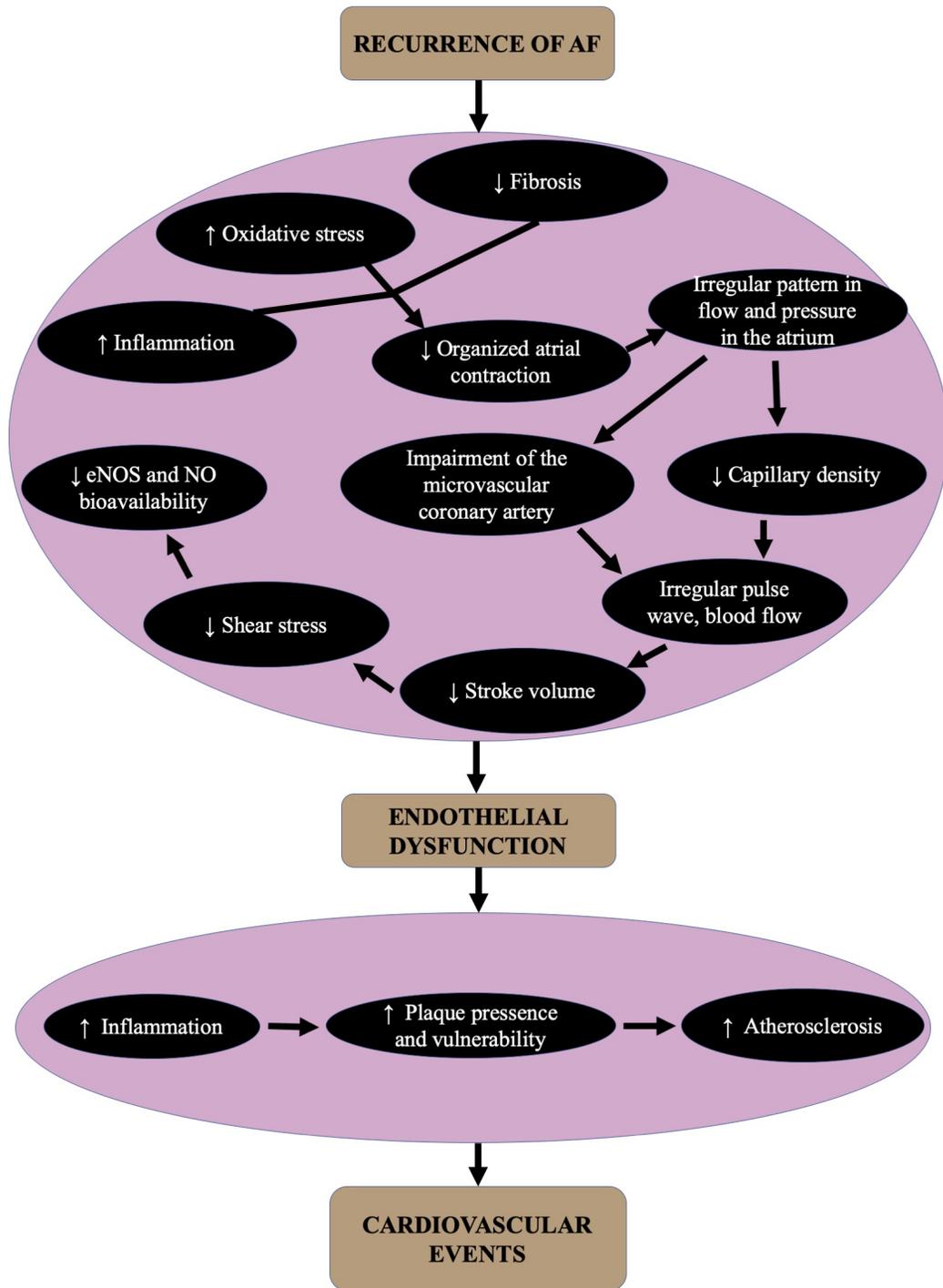
AF: Atrial fibrillation; eNOS: Endothelial nitric oxide synthase; NO: Nitric oxide



eci\_13477\_f1.jpg



eci\_13477\_f2.jpg



eci\_13477\_f3.jpg