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Atrial fibrillation and coronary artery disease: An integrative review focusing on therapeutic implications of this relationship

Atrial fibrillation and coronary artery disease

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Abstract

Background: The incidence of both atrial fibrillation (AF) and coronary artery disease (CAD) increases with advancing age. They share common risk factors and very often coexist. Evidence points to an intricate relationship between atrial tissue excitability and neuronal remodelling with ischemia at microcirculatory level. In this review we sought to delineate this complex relationship, identify a common theme between the two and discuss how the knowledge of this relationship translates into a positive and meaningful impact in patient management.

Main body: Recent research indicates a high prevalence of CAD amongst AF patients undergoing coronary angiography. Further, the incidence of AF is much higher in those suffering from CAD compared to age matched adults without CAD underlying this reciprocal relationship. CAD adversely affects AF by promoting progression *via* re-entry and increasing excitability of atrial tissue as a result of ischemia and electrical inhomogeneity. AF in turn accelerates atherosclerosis *via* endothelial dysfunctional and inflammation and together with enhanced thrombogenicity and hypercoagulability contribute to micro and macrothrombi throughout cardiovascular system. In nutshell, the two form a vicious cycle wherein one disease promotes the other. Most AF

recommendations focuses on rate/rhythm control and prevention of thromboembolism. Very few studies have discussed the importance of unmasking coexistent CAD and how the treatment of underlying ischemia will impact the burden of AF in these patients. Inflammation and endothelial dysfunction remain central to both disease processes and form a handsome therapeutic target in the management of the two diseases.

Conclusion: The relationship between AF and CAD is complex and much more than mere coincidence. The two disease share common risk factor and pathophysiology. Hence, it is impractical to treat them in isolation. Accordingly we share the implications of managing underlying ischemia and inflammation to positively impact and improve quality of life amongst AF patients.

Key Words: Atrial fibrillation; coronary artery disease; Anti thrombotic therapy; Ischemia; Early rhythm control; Endothelial dysfunction.

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Core Tip: Evidence points to an intricate relationship between atrial tissue excitability and neuronal remodeling with ischemia at micro circulatory level. In this review we sought to delineate this complex relationship, identify a common theme between the two and discuss how the knowledge of this relationship translates into a positive and meaningful impact in patient management.

INTRODUCTION

Cardiovascular diseases including coronary artery disease (CAD) and atrial fibrillation (AF) along with other cardiovascular diseases remain the leading cause of morbidity

and mortality worldwide(1). The prevalence of both CAD and AF increases with advancing age and often they coexist (2–5). However, this relationship is not a mere coincidence and recent evidence points to the intricate relationship between the two. Dedicated studies have demonstrated a high prevalence of CAD amongst non-valvular AF patients, with majority of AF (>50%) patients having underlying CAD as identified by invasive or computed tomography coronary angiography (CTCA) (5–7). This is significantly higher than the prevalence of CAD in general population which is estimated to be around 12-14%. Further, there is abundant evidence that AF is an independent risk factor for CAD and incident acute coronary syndromes (4,8,9). The interrelationship of the two is further highlighted by the fact that the people with coexistent AF and CAD have a more severe CAD and higher syntax scores compared to those without AF (8,10). Also, the morbidity and mortality is significantly higher when CAD is associated with paroxysmal or persistent AF with increased odds for developing heart failure, ventricular arrythmias and major adverse cardio-cerebro vascular events (MACCE) (4,8–10). However, despite the obvious association, this relationship is also influenced by a number of confounding risk factors like diabetes, hypertension, age and obesity which are common to both CAD and AF. Hence, this leads to confusion in establishing causality and reverse causality solely based on the results from registries and observational studies.

A recent mendelian randomization study by Yan *et al* throws important light on this relationship and concluded beyond doubt that CAD is an independent risk factor for AF after removing all bias. Further, they made an argument that treatment and prevention of AF is crucial to prevent MACCE amongst CAD patients (4). Hence, the two might be more closely related than thought and logically the therapeutic strategies are expected to be similar too.

PATHOPHYSIOLOGICAL BASIS OF THE RELATIONSHIP

The basic pathology in CAD is the formation and progression of atherosclerotic plaques in coronary arteries leading to narrowing and resultant myocardial ischemia. Indeed

this process is identical in other vascular beds involved by atherosclerotic process and manifests as variable clinical presentation depending on the vasculature involved. In the heart, the same can manifest as an acute coronary syndrome (ACS) or a chronic coronary syndrome (CCS) depending upon the progression and stability of the atherosclerotic plaques. The major pathophysiological pathways involved in initiation and progression of AF include re-entry and focal ectopic activity. The re-entry is in turn promoted by the short refractoriness, slowed conduction and atrial remodelling as a result of atrial dilatation. The enhanced automaticity of the atrial tissue stems from the enhanced early afterdepolarizations (EADs) and delayed afterdepolarizations (DADs) (9,11).

Common risk factors

The two diseases share identical risk factors which trigger varied pathophysiological responses culminating in either or both of the two diseases. Diabetes mellitus (DM), hypertension, advancing age, dyslipidaemia, obesity, smoking and decreased physical activity are the major risk factors for CAD as per abundant evidence in scientific literature. Indeed these very same risk factors remain the most commonly implicated factors responsible for initiation and progression of AF (8,9,11,12). The interplay of the various risk factors and their role in the pathogenesis of AF and CAD has been demonstrated in figure 1.

DM particularly in the setting of poorly controlled blood sugars is a major risk factor for initiation of AF. Research has shown a consistent positive correlation between increasing HBA_1c and AF burden. The most popular hypothesis for this association is the structural alteration and fibroses in atrial myocardium as a result of inflammation, endothelial dysfunction, formation of reactive oxygen intermediates and deposition of advanced glycation end products (13,14). All of these to a large extent result in microvascular dysfunction and atrial tissue hypoxemia. Prolonged action potential duration secondary to ischemia pave way for EADs and DADs. Often there is coexistent

autonomic neuropathy and dysfunction in DM which together with altered Ca^{+2} and I_{na} homeostasis contributes to progression of AF (15).

Hypertension remains the most common risk factor for both AF and CAD. It increases the risk of development of AF by more than 30% for any given age (16). Left ventricular hypertrophy and subsequent diastolic dysfunction in long standing hypertension contributes to atrial dilatation and dysfunction. Further, the alterations in renin angiotensin aldosterone system (RAAS) along with increased expressions of pro-inflammatory cytokines induces atrial fibroses (17,18). The net result of these pathogenic mechanisms is the development of focal aberrant ectopic firing due to altered Ca^{+2} homeostasis and the development of re-entry circuits along clinical or subclinical fibroses in atrial myocardium (19).

Obesity is often associated with other cardiovascular comorbidities which contribute to enhanced overall MACCE risk. In addition, many advocate that obesity is an inflammatory disease process characterized by increased expression of various pro-inflammatory cytokines and resultant endothelial dysfunction. This often correlates with increased left atrial volume and fibroses which have a pathogenic role in the development of AF (20). According to certain estimates the risk of AF increases in a linear fashion with increasing body mass index (BMI) and roughly a $1kg/m^2$ increase in BMI confers a 4% increased risk of developing AF (9,21).

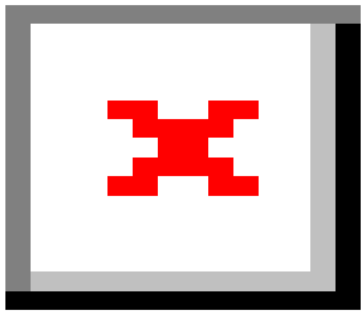

Figure 1: Interplay of various common risk factors in the pathogenesis of coronary artery disease (CAD) and atrial fibrillation (AF). Variable genetic expression manifests as varied clinical phenotype in the form of either or both AF and CAD in an individual. ROS, reactive oxygen species; TGF-*B*, transforming growth factor beta; MPO, myeloperoxidase; IL, interleukin; HSPs, heat shock proteins; NO, nitric oxide; PGs, prostaglandins; EADs, early after depolarization; DADs, delayed after depolarizations; CAD, coronary artery disease; AF, atrial fibrillation.

Positive feedback cycle

Besides sharing common risk factors, CAD and AF by themselves have a direct relationship with each other. A positive feedback mechanism between the two, culminates in a vicious cycle resulting in increased the burden of the two diseases. CAD comprising both macrovascular and microvascular disease leads to ischemia of the atrial tissue which precedes local inflammation and culminates in fibroses and

prolonged conduction times, all of which trigger the three principle mechanisms involved in the pathogenesis of AF:- focal ectopy, re-entry and neural alteration. In addition, there is heterogeneity in the electrical conduction, altered Ca^{+2} and Na^{+} currents and autonomic system dysregulation all of which promote progression and persistence of AF (4,8,9,11,12,22,23). (figure 2)

On the other end, AF by itself can induce the two key pathogenic mechanism involved in CAD namely endothelial dysfunction and inflammation. Decreased release of nitric oxide coupled with increased expression of von Willebrand factor is the key pathogenic process in endothelial dysfunction (9,11,17). AF also triggers systemic and myocardial inflammation by virtue of enhancing expression of protease-activated receptors and inflammatory cytokines which not only initiate atherosclerotic process, but also contribute to plaque instability and resultant ACS. Besides this, the beat-beat variability resulting in inefficient contractility and reduced cardiac output also contributed to reduced coronary blood flow and resultant ischemia independent of atherosclerotic CAD. Coagulation system activation coupled with enhanced platelet activity owing to increased expression of p-selectin and CD63 on endothelial cells leads to micro and macro thrombi which not only increases the risk of cerebrovascular accident, but also ACS (24–26). (Figure 3)

The two more often than not coexist and together they confer worse outcomes than when the two occur occur in isolation. When AF complicates pre-existing CCS or ACS, it leads on to higher MACCE events including stroke, heart failure and cardiogenic shock and also doubles overall cardiovascular mortality (8,9,11,27). Further, it complicates clinical decision making and predisposes an individual to not only increased thrombotic events, but also to major bleeding events secondary to aggressive antithrombotic therapy which is often indicated. As a result, there is a need for a comprehensive assessment and management of the two disease in conjunction and not as separate disease entities. The two diseases more often than not are linked in their aetiopathogenesis and warrant kindred treatment to break the links which propagate the two diseases.

Figure 2: Pathogenic mechanism which predispose an individual suffering from coronary artery disease (CAD) to develop atrial fibrillation (AF). CAD, coronary artery disease; AF, atrial fibrillation.

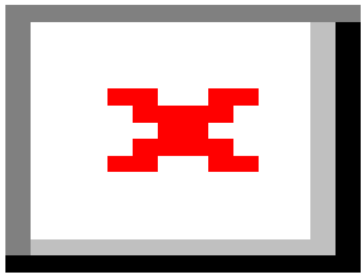

Figure 3: Pathogenic mechanism which predispose an individual suffering from atrial fibrillation (AF) to develop coronary artery disease (CAD). NCX, Na^{+}/Ca^{+2} exchanger; CAD, coronary artery disease; AF, atrial fibrillation.

Differences in pathogenesis of AF in CAD patients compared to those without CAD

The vast majority of patients suffering from AF (>85%) have underlying CAD or cardiovascular risk factors including hypertension, diabetes, obesity and dyslipidemia. In less than 15% of all AF patients, none of these risk factors are present (28,29). Most of them are relatively younger and commonly labelled as lone AF. Familial AF also contributes to a fraction of lone AF patients with well-defined chromosomal abnormalities most notably 10q22-q24 (9,29). The basic difference in the pathophysiology of AF in individuals having underlying cardiovascular risk factors and CAD predominantly is that they have structural alterations in the atrial tissue which predispose them to develop electrical remodeling or directly lead to re-entry and

ectopy culminating in AF. On the other hand, AF occurring in younger individuals without any risk factors is often attributable to the electrical remodeling as a result of abnormal Ca^{+2} homeostasis, dysregulated Ryanodine receptors, altered action potential durations and reduced atrial refractory period. All of these culminate in changes in ion channel function, enhanced automaticity and atrial ectopy which is a precursor to AF (28–30). Whatever may be the initial insult, the pathways soon converge and either of the structural or the electrical remodeling ultimately aggravates the other resulting in a vicious cycle of AF initiation and progression (Figure 4). Other important difference is in the clinical presentation and outcomes. Patients with underlying cardiovascular risk factors and CAD have less of symptoms related to AF, but rather commonly present with complications related to AF including heart failure or stroke. In contrast the risk of thromboembolism is relatively lesser in the lone AF/ familial AF patients who very often present to outpatient clinics with symptoms related to AF like recurrent palpitations or dyspnea (28,30). Given the aggressive disease course with accelerated atherosclerosis and thromboembolism in those with underlying cardiovascular risk factors, there is need for aggressive control of risk factors and institution of effective anti-thrombotic therapies to prevent complications.

Figure 4: Key differences in pathogenesis of AF in patients with underlying CAD or risk factors compared to those without underlying cardiovascular risk factors. CAD; coronary artery disease, AF; atrial fibrillation, LVEDP; left ventricular end-diastolic pressure, LA; left atrium, RyR; ryanodine receptor, APD; action potential duration, ARP; absolute refractory period, DAD; delayed after depolarization, EAD; early after depolarization.

IMPLICATION ON CHA_2DS_2VASC SCORE AND STROKE RISK

Consistent pool of evidence points towards the increased burden of AF in those having coexistent CAD compared to those without CAD (8,11,27). Further, this increased duration and burden of AF translates into increased MACCE events in patients with coexistent CAD compared to those without CAD. Therefore, it makes sense that people with AF and coexistent CAD need better risk factor modification, pharmacological therapy for CAD and more aggressive antithrombotic therapy to prevent adverse outcomes (6,31).

Amongst the components of the CHA_2DS_2VASc score, the symbol 'V' stands for vascular disease. The widely accepted determinants of this vascular disease as per the guidelines are prior myocardial infarction, peripheral artery disease or the presence of an aortic plaque. Most of the current guidelines and online medical calculators thus do not account for CAD as a determinant of 'V' while calculating the CHA_2DS_2VASc score (32,33). Therefore, this gives an impression that underlying CAD status (excluding past myocardial infarction) has no bearing on stroke risk as determined by the CHA_2DS_2VASc score.

However, in a recent, large, prospective study by Steensig *et al*, underlying CAD not only was very frequent amongst AF patients, but more importantly CAD was strongly associated with elevated thromboembolic risk beyond the usual components of the CHA_2DS_2VASc score (6). Hence, the study made a strong case for inclusion of significant angiographically proven CAD in the 'V' component of the CHA_2DS_2VASc score to more comprehensively account for the thromboembolic risk in a given individual with AF. Indeed, this made a turning point in the approach to managing AF patients and the same was reflected in the European Society of Cardiology (ESC) 2020 AF guidelines. For the first time, angiographically proven CAD was included as a determinant of in the 'V' in the CHA_2DS_2VASc score (34). Since then, the inclusion of significant CAD has gained acceptance amongst practicing cardiologist as evidenced by a recent survey by the European Heart Rhythm Association (EHRA) wherein 79% of the respondents were aware of the inclusion of significant CAD and employed the same in their practice (35).

A recent study by Shi *et al*, sheds new insights into the stroke risk in AF patients. They concluded that the amongst AF patients with coexistent CAD, the stroke risk was not dependent on AF but on the atherosclerotic risk factors and the presence of CAD. They made a strong case for aggressive risk factor modification in particularly underlying CAD for stroke reduction in AF patients (36).

CLINICAL IMPACT OF UNDERLYING CAD ON AF

Recent evidence supports the close association of AF and CAD. Not only does underlying CAD increase the odds of developing AF, it also has significant therapeutic and clinical implications. Consistent literature points towards increased MACCE in AF patients who have underlying CAD compared to those without underlying CAD. Further, complexity in administering appropriate antithrombotic regimen is a challenge and it predisposes an individual to increased minor and major bleeding events. Hence, given the significant therapeutic and prognostic implications of CAD on AF, a more holistic and balanced approach is needed while managing the two diseases, as it is impractical to treat either one in isolation. Table 1 highlights the prominent studies over the last 3 decades which have analyzed the clinical impact of underlying CAD in AF patients. Consistently, underlying CAD in AF patients has shown to correlate positively with worse overall outcomes.

Table 1: Prominent studies over the last 3 decades highlighting the clinical impact of underlying CAD in patients suffering from AF.

Study	Year	Type of study	Number of patients	Principal findings and comment
Peterson *et al* (37)	1990	Double blind RCT	516	Active angina was the only independent predictor of stroke on multivariate analysis [OR of 3.3 (95%CI, 1.3-8.9, *P* = 0.02)]

Ezekowitz *et al*(38)

1995

RCT

516

Active angina was an independent predictor of silent brain infarctions (15% *vs* 5% in those without angina; $P = 0.02$)

Van Walraven *et al* (39)

2003

Metanalysis of 6 RCTs

2501

Observed rate of stroke or TIAs was 3-fold higher in group with history of angina (5.6 *vs* 1.4 events/100 patient years; $P = 0.002$)

Goto *et al* (40)

2008

Observational cohort study

63589

MACCE events were consistently higher at 12 mo in AF patients with concomitant CAD compared to those without CAD (19.70 *vs* 14.52; $p< 0.05$)

Olesen *et al* (41)

2011

Registry based cohort study

87202

Stroke risk significantly higher in AF patients who had underlying CAD or past history of MI [HR of 1.14 (1.03-1.27)]

Rasmussen *et al* (42)

2011

Observational cohort study

3315

Risk of stroke or death significantly higher amongst those with underlying CAD [HR of 1.99 (1.46-2.72)]

Anandasundaram *et al* (43)

2013

Systematic review of 19 observational studies

6465

Atherosclerotic vascular disease was a significant independent predictor of stroke, thromboembolism and mortality in AF patients ($p<0.05$)

Steensig *et al* (44)

2018

Prospective cohort study

12690

CAD was independently associated with increased risk of ischemic stroke in AF patients. Concomitant CAD increased stroke risk by 29% compared to AF patients without CAD. (Crude IRR of 1.62; 1.41-1.87)

Steensig *et al* (6)

2018

Observational cohort study

96430

CAD was an independent predictor of composite endpoints (adjusted IRR, 1.25;1.06-1.47) over and above the usual components of vascular disease inCHA_2DS_2VASC score

Shi *et al* (36)

2021

Observational cohort study

2335

Risk of stroke was more dependent on underlying atherosclerotic risk factors than AF per say ($p<0.001$)

Abbreviations:RCT; randomized control trial, TIA; transient ischemic attack, MACCE; major adverse cardio-cerebro vascular events, CAD; coronary artery disease, AF; atrial fibrillation, MI; myocardial infarction, HR; hazard ratio, IRR; incidence rate ratio.

"COMBINED APPROACH" TO REDUCING THE BURDEN OF THE TWO DISEASES

A recent article by Fanaroff *et al* and the accompanying editorial nicely summarizes the impact of coexistent AF and CAD on various clinical end-points (27,45). The main theme of the paper was the heightened thrombogenicity when the two occur together and authors concluded that the downstream risk of recurrent ACS and percutaneous coronary intervention (PCI) was extremely high in these group of patients compared to when they occurred in isolation. While they focused on only one and a very important aspect of this relationship, others have gone beyond the antithrombotic therapy.

Another very relevant aspect is the enhanced atherogenicity throughout the systemic vasculature which has been well documented in literature and elaborated upon in this review. The coexistence of the two sets in motion a vicious cycle that culminates in accelerated atherosclerosis and its various clinical manifestations (9,28,30). Besides the increased thrombogenicity and atherogenicity conferred as a result of the coexistence of the two diseases, there is a direct relationship of one with the other disease. Such that, one disease can directly lead to the other and vise-a-versa (figures 2&3). Hence, targeting and breaking the common links between the two makes sense and should be considered in any individual suffering from either of the two diseases (figure 5).

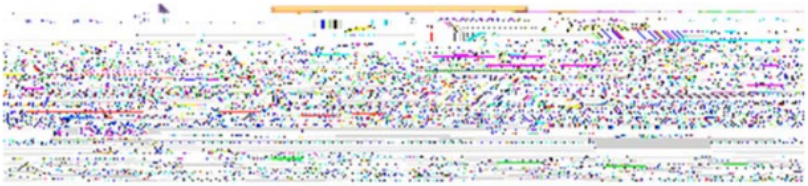

Figure 5: Vicious cycle between coronary artery disease (CAD) and atrial fibrillation (AF) that culminates in a positive feedback as a result of the connections as highlighted in the orange boxes. Strategies to break this cycle are also depicted in the green ovals. CAD, coronary artery disease; AF, atrial fibrillation; HR, heart rate; BP, blood pressure.

THERAPEUTIC STRATEGIES FOR DISRUPTING THE VISCOUS CYCLE

Like all cardiovascular diseases, the prevention starts with risk factor control and modification right at the primary care level. Controlling the most commonly implicated risk factors including physical activity, obesity, dietary modifications with reduced intake of sweetened foods and salt, smoking cessation, blood pressure control and management of dyslipidaemia and blood sugars when altered leads to reduction of both CAD and AF (9,11). Optimal control of these risk factors has shown to markedly reduce ones odds of developing CAD and AF by inhibiting common initiating pathways and weaking the links between them two (figure 5).

When one of the two disease is diagnosed in a given individual, every attempt should be made to unmask the other disease as very often the two are associated. Coexistent CAD has been reported in more than half of AF patients in various studies (5–7,46). Thus, diagnosing the concomitant CAD by invasive or non-invasive seems logical. This translates into optimal management of not only the masked CAD and in reducing the burden of AF, but also predicts an individual's thromboembolic risk and guides optimal antithrombotic regimen (6,27). Similarly, in those with CAD and other risk factors, the occurrence of MACCE events including stroke and heart failure should be followed by active surveillance for paroxysmal or persistent AF by appropriate rhythm monitoring tools. Unmasking paroxysmal AF guides institution of oral anticoagulants which leads to significant reduction of not only thromboembolic risk but also myocardial infarction amongst CAD patients.

Besides primary prevention, in those with established CAD and/or AF, the key to improve outcomes is simultaneous and optimal control of both the disease. Accordingly, given the intricate relationship between the two, its impractical to treat the two in isolation. Most therapies that reduce the burden of either of these diseases, invariably also modifies and reduces the burden of the other disease. For example, statins which are used in CAD, have shown to reduce the incidence and burden of AF (47). Also, therapies aimed at reducing the burden of CAD including percutaneous intervention or bypass graft surgery, have shown to significantly reduce the burden of concomitant AF and improve morbidity and mortality. Likewise therapies like rate

control in AF patients using beta-blockers or calcium channel blockers also significantly reduce coronary ischemia and myocardial oxygen uptake (48).

SPECIFIC THERAPIES

Antithrombotic agents

Antithrombotic agents encompass both antiplatelet and oral anticoagulants. Both CAD and AF are characterized by heightened thrombogenicity in the blood and resultant ischemic events. This is logarithmical increase in this thrombogenicity when the two coexist. To further complicate clinical decision making, there is an increased risk of bleeding as well attributable to these antithrombotic drugs. Balancing ischemic and bleeding risk in a given patient remains the top priority and necessitates adherence to clinical practising guidelines.

The choice of antithrombotic agents in coexistent CAD and AF depends upon the clinical status of the underlying CAD. In patients suffering from CCS and AF, the consensus is towards the use of oral anticoagulants alone, preferably using the newer oral anticoagulants (NOACs). Recent research has shown that NOACs alone fair comparably to the combination of NOACs and aspirin but with the advantage of significantly lower risk of bleeding.

The decision making in AF patients with ACS and those undergoing percutaneous coronary intervention (PCI) and stenting is however complex. In patients with ACS the recommendations are combining a $P2Y_{12}$ antiplatelet agent with an oral anticoagulant (preferably NOAC over vitamin K analogues) for at least 6-12 mo after ACS and then continuing only oral anticoagulant beyond 1 year. In those undergoing PCI, the guidelines recommend triple antithrombotic therapy including aspirin, $P2Y_{12}$ agent and a NOAC for the 1^{st} month following PCI, followed by dual therapy with a $P2Y_{12}$ agent and NOAC for 6-12 mo and continuing only a NOAC in most patients beyond the 1^{st}year. However, despite the evidence and clear guidelines only a minority of AF and CAD patients receive optimal antithrombotic therapy largely attributable to the gaps in

knowledge, fear of bleeding or physician preference rendering these patients at high risk of recurrent ischemic events (27,49,50).

Statins

Statins have emerged as one of the most important and first line therapy for prevention and treatment of CAD. Besides its lipid-lowering effects, it has pleiotropic effects in the form of reduction in inflammation in the atherosclerotic plaques and improving plaque stability. Recent studies have shown that early initiation of statin therapy in ACS patients help in reducing the incidence of atrial and ventricular arrythmias (47,51). These beneficial actions are in part attributable to the improved autonomic control and improved myocardial stability. A large recent metanalysis has shown that prior statin use markedly reduced the incidence of new-onset AF after admission for ACS (47). Hence, early statin use and adequate lipid control is essential for reducing AF burden amongst CAD patients.

Rate controlling and antianginal agents

Tachycardia in AF predisposes patients with underlying CAD to recurrent myocardial ischemia owing to increased myocardial oxygen consumption and reduced diastolic coronary perfusion at higher heart rates. This not only translates into worse symptoms but roughly doubles the risk of ACS in this population. Hence, rate control is the initial and most crucial step in managing people with both CAD and AF. Beta blockers and non-dihydropyridine calcium channel blockers are the preferred agents in this regard and the resting target heart rate is less than 110/min (9,48). Ivabradine is ineffective in controlling heart rates in AF patients and on the contrary may even aggravate AF as was seen in the SIGNIFY trial and a recent meta-analyses (52,53). Hence, it should be avoided in AF. Digoxin although is an effective drug in controlling heart rates in AF patients especially those with left-ventricular dysfunction, it is best avoided in patients

with CAD for the fear of predisposition to arrythmias and worsening myocardial ischemia due to increased myocardial oxygen consumption (48).

Amongst the choice of antianginal agents in patients symptomatic despite adequate rate control, ranolazine is preferred amongst the second line drugs as it prevents the automaticity in atrial tissue by suppressing diastolic depolarization and atrial tissue excitability in addition to suppressing the early and delayed after depolarizations. All of this results in increased initiation and progression of AF. Moreover ranolazine use was tied to better rhythm control in AF patients in a recent meta-analyses (54,55). Trimetazidine is a second line antianginal used especially in those with underlying left ventricular dysfunction. It largely has neutral effect on underlying AF and can be used as an add-on therapy in those with ischemic cardiomyopathy and AF. Limited data has suggested that favourable effects on p-wave duration and dispersion may help reduce the incidence of AF in these subgroup of patients (56). The use of nitrate and nicorandil in AF should be avoided as these have been tied with increased incidence and aggravation of underlying AF in CAD patients (48).

Early rhythm control strategy

Early rhythm control strategy preferably with catheter ablation has been increasingly realized as an effective means of reducing the overall MACCE events in patients suffering from AF (57–59). The benefit is most in those with high comorbidly burden and in those with a recent diagnoses of AF. There has been a clear trend in the superiority of rhythm control compared to rate control in recent years largely attributable to the incremental benefit of early rhythm over rate control alone in terms of improved overall symptoms and quality of life scores and reduced heart failure hospitalizations, stroke, dementia and overall cardiovascular death (57,58). This has reflected in increasing recommendations for catheter ablations in multiple subsets of patients including those with underlying CAD. Since AF is common in patients with underlying CAD and high comorbidity burden, all attempts should be made to

diagnose it early and accordingly if symptoms are not controlled despite initial medical therapy and rate control, catheter ablation should be considered.

Targeting endothelial dysfunction

Robust evidence points towards the central role of endothelial dysfunction in CAD initiation and progression. Further, endothelial dysfunction now is increasingly realized as an important mediator in AF pathogenesis as well (60). Often it coexists with other cardiovascular comorbidity like diabetes, hypertension, dyslipidaemia and obesity. Decreased expression of nitric oxide, inflammation, increased oxidate stress, increased apoptosis and vascular remodelling all contribute to endothelial dysfunction at the cellular level. Endothelial dysfunction as diagnosed by flow mediated vasodilatation often correlates with increased systemic vascular complications and poor outcomes (61). Endothelial dysfunction is a dynamic thing and is reversible to large extent with appropriate intervention. At present, the only therapy to improve endothelial dysfunction include aggressive risk factor modification including smoking cessation, appropriate blood pressure and blood glucose control, weight reduction and exercise. Pharmacological therapies including antithrombotic therapies and statins also have shown incremental benefit in addition to lifestyle intervention. Other pharmacological agents including calcium channel blockers, angiotensin inhibitors, antioxidant agents, betablockers, phosphodiesterase inhibitors, nicorandil, ivabradine and l-arginine have also shown some benefit in small studies but it is yet early stages to comment on the role of these agents in improving endothelial dysfunction in clinical practice (9,60,61).

Therapies targeting inflammation

Inflammation is implicated in pathogenesis of both CAD and AF. The testimony of the same lies in the fact that many anti-inflammatory drugs have shown incremental benefit in reducing the incidence and burden of either of the two disease. While evidence is

more robust for its positive impact in CAD, data is emerging on its role in AF patients (62,63). Two large randomized studies have already shown the positive impact of colchicine and canakinumab in reducing MACCE events in CAD patients attributable to decreased inflammation (64,65). On the other hand emerging evidence shows that therapies targeting inflammation indeed prevent the occurrence or decrease the recurrences of AF in CAD patient. Recent studies have shown that colchicine or corticosteroids administration after catheter ablation can help reduce recurrence of AF (63).

Effect of diabetes and anti-diabetics drugs on AF and CAD

Diabetes remains one of the largest independent risk factors for development of atherosclerosis. Approximately a third of all patients suffering from diabetes have concomitant CAD which remains the leading cause of morbidity and mortality in diabetic population (66). Recent evidence points to the excess prevalence of AF in diabetic population, independent of other cardiovascular risk factors (67,68). Further, patients with concomitant AF and diabetes have worse clinical outcomes including excess stroke, dementia and heart failure compared to AF in the absence of diabetes (67,69). Diabetes confers enhanced systemic vascular atherogenicity and thrombogenicity, which in parts is driven by the endothelial dysfunction and inflammation, a pathogenic process very similar to both AF and CAD. The major contributors to this pathogenesis include the direct glucose and free fatty acid toxicity at the cellular levels which results in excess of reactive oxygen species, advanced glycation end-products, upregulation of the polyol, hexosamine and protein kinase C pathways. This results in dysregulated cellular metabolism and mitochondrial function which is essential for normal endothelial function and its anti-inflammatory and anti-thrombotic properties (67,68). As such this relationship is very relevant while managing patients with AF and/or CAD. Naturally, there is a desire to use anti-diabetic drugs which help improve the burden of these diseases. Table 2 illustrates the prominent effects of various classes of anti-diabetic drugs on AF and CAD. Expectedly, the anti-diabetic

drugs which improve the clinical endpoints of either CAD or AF, are expected to confer a beneficial effect on the other disease as well. Overall, the anti-diabetic drugs which have consistently shown incremental benefit in reducing burden of either AF and CAD include sodium-glucose cotransporter-2 (SGLT-2) inhibitors, Dipeptidyl peptidase- 4 (DPP-4) inhibitors and metformin. Accordingly, we believe that these agents should be preferentially be used during institution of anti-diabetic therapy in these patients ahead of agents which have neutral or harmful effects on either of the two diseases (Sulfonylureas, thiazolidinediones) l(68,70)a.

Table 2: Impact of various anti-diabetic agents on burden of AF and CAD and their surrogate end-points.

ANTI-DIABETIC DRUG CLASS

IMPACT ON AF BURDEN/ SURROGATE END POINTS

IMPACT ON CAD BURDEN/ SURROGATE END POINTS

Insulin (71)

Increased (↑)

Neutral or increased (-/↑)

Metformin (72)

Reduced (↓)

Reduced (↓)

Sulfonylureas (71)

Neutral (-/↑)

Increased (↑↑)

Thiazolidinediones (73)

Reduced or neutral (-/↓)

Increased (↑↑)

DPP-4 inhibitors (74)

Reduced (-/↓)

Reduced (↓)

GLP-1 receptor agonists (75)

Neutral or slightly increased (-/↑)

Reduced (↓↓)

SGLT-2 inhibitors (76)

Reduced (↓↓)

Reduced (↓↓↓)

Abbreviations: DPP-4; Dipeptidyl peptidase- 4, GLP-1; glucose like peptide, SGLT-2; sodium-glucose cotransporter-2 inhibitors.

CONCLUSION

The relationship between AF and CAD is complex and the two are intricately related at the pathophysiological level. The two diseases share common risk factors and pathogenesis and often culminate in a vicious cycle. Hence, it is impractical to treat them in isolation. The worsening of one is invariably accompanied by accelerated progression of the other disease as well. Accordingly we share the implications of this relationship in diagnoses and management of the two diseases. In this review we discuss the key strategies to break the cycle and highlight the recent, evidence-based therapeutic options to break the common links between the two and reduce morbidity and mortality.

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1	Anandasundaram, B., D. A. Lane, S. Apostolakis, and G. Y. H. Lip. "The impact of atherosclerotic vascular disease in predicting a stroke, thromboembolism and mortality in atrial fibrillation patients: a systematic review", Journal of Thrombosis and Haemostasis, 2013. Crossref	22 words — < 1%
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