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The bidirectional association between atrial fibrillation and myocardial infarction

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Abstract

Atrial fibrillation (AF) is associated with an increased risk of myocardial infarction (MI) and vice versa. This bidirectional association relies on shared risk factors as well as several direct and indirect mechanisms, through which one condition can predispose to the other — including inflammation, atrial ischaemia, left ventricular remodelling, myocardial oxygen supply–demand mismatch and coronary artery embolism. Patients with both AF and MI are at greater risk of stroke, heart failure (HF) and death than patients with only one of the conditions. In this Review, we describe the bidirectional association between AF and MI. We discuss the pathogenic basis of this bidirectional relationship, describe the risk of adverse outcomes when the two conditions co-exist, and review current data and guidelines on the prevention and management of both

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Author contributions

T.C.F., E.J.B. and J.K. researched data for the article. T.C.F., S.R.P., H.L., E.J.B. and J.K. discussed the content of the article. T.C.F. and S.R.P. wrote the manuscript. C.C.D., H.L., L.T., E.J.B. and J.K. reviewed and edited the manuscript before submission.

Competing interests

The authors declare no competing interests.

Review criteria

Several PubMed searches were conducted, using different combinations of MESH terms and non-MESH terms. These searches yielded 14,645 studies that were screened by title, after which, 723 studies were eligible for inclusion and assessed by abstract; 516 studies were excluded 207 studies were assessed by full text. Finally, 172 studies were included in the Review.

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conditions. We also identify important gaps in the literature and propose directions for future research on the bidirectional association between AF and MI. The Review also features a summary of methodological approaches for studying bidirectional associations in population-based studies.

Introduction

Atrial fibrillation (AF) and myocardial infarction (MI) are major contributors to cardiovascular disease burden worldwide[1]. The numbers of prevalent cases of both AF and MI have almost doubled over the past 30 years, and both conditions are associated with a substantial risk of adverse outcomes[1]. Regardless of temporality, co-occurrence of AF and MI is common[2].

The risk of MI in patients with AF is especially high in the first 30 days after AF diagnosis[3], pointing to mechanisms beyond accumulation of underlying shared risk factors such as inflammation, coronary artery embolism and increased myocardial oxygen demand. In addition, the risk of new-onset AF is especially high in the first couple of days after acute MI (AMI)[4], suggesting that AF is the result of atrial ischaemia, inflammation, remodelling and heart failure (HF). Patients with new-onset AF at the time of AMI have a higher risk of HF, stroke and death than those with AMI who do not develop AF, even several years after the cardiac event[5–7]. Studies published in the past 2 years have shown that the co-existence of AF and MI is associated with higher mortality than with one of these conditions alone[8,9], highlighting the importance of future studies on prevention.

In this Review, we begin by summarizing historical data on the association between AF and MI and then describe studies, published in the past ~15 years, on the risk of MI in patients with AF and vice versa. We discuss the pathogenic basis of their bidirectional relationship, including shared risk factors and direct pathophysiological mechanisms. Furthermore, we describe the risk of adverse outcomes in patients with a coexistence of MI and AF and discuss potential preventive and management strategies. The Review also includes a summary of methodological approaches to the analysis of bidirectional associations in population-based studies (Box 1). Finally, we identify important gaps in the literature and propose directions for future research on the bidirectional association between AF and MI.

Historical data

Studies published in the 1930s describe AF complicating the clinical course of AMI[10,11]. Before the mid-1980s, when thrombolysis for the treatment of AMI was introduced[12], the incidence of AF in the setting of AMI ranged from 3% to 12%[13,14], and mortality was reported to be up to 38% in patients with concomitant AF and AMI[15]. Eldar and colleagues reported that the incidence of AF was similar in the periods immediately before (1981–1983) and after (1992) the introduction of thrombolysis (8.9% and 9.9%, respectively), but then decreased over time to 7.6% in 1996[16]. Crude mortality did not change after the introduction of thrombolysis; however, after adjustment for comorbidities and conventional risk factors, mortality was >30% lower after thrombolysis was introduced[16]. In the ARIC study[17], the prevalence of AF accompanying AMI increased slightly from 11% in 1987 to 15% in 2009, whereas survival did not change over time[17]. In patients with AMI,

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the prevalence of comorbidities increased over time, and substantial changes occurred in revascularization procedures and medication use over the study period. Temporal trends in AF prevalence differed by type of AMI; among patients with non-ST-segment elevation MI (NSTEMI), the prevalence of AF increased, whereas the prevalence of AF decreased in patients with ST-segment elevation MI (STEMI)[17]. This finding could possibly be explained by the introduction during the study period of primary percutaneous coronary intervention (PCI) as a treatment for STEMI, which decreases infarct size and reduces morbidity and mortality in these patients[18,19].

Risk of MI in patients with AF

Although the risk of AF in the setting of AMI has been known and examined for a century, this association has been systematically studied and described only in the past decade (Fig. 1), and AF was not established as an independent risk factor for AMI in large observational studies until 2014[20–22]. The first report from a cohort study that AF predisposes to MI was the population-based REGARDS study[20]. The risks of AMI and coronary heart disease were approximately twofold higher in patients with AF than in those without AF[20]. This observation was validated in several subsequent studies[3,22,23]. Among individuals with newly diagnosed AF or atrial flutter who were identified through Danish national health registries, the cumulative risk of MI at 10 years was 3.5%[3]. In meta-analyses published in 2016–2017, the rate of MI was approximately 50% higher for patients with AF than for patients without AF[24,25]. Observational studies on the risk of MI in patients with AF are summarized in Table 1.

Age and sex

In one study, the 5-year incidence of MI in patients with AF increased with advancing age, with a cumulative incidence of 3.3% in patients aged 67–69 years and 4.4% in patients aged 85–89 years[26]. However, in several other studies, no significant difference in the rate of AF-associated MI was found between age groups[20,21,23].

In a large study conducted in Taiwan, men with AF had a higher absolute risk of AMI than women with AF (annual incidence of AF: 0.37% and 0.18%, respectively; HR for AMI: 2.24, 95% CI 1.61–3.11, $P < 0.001$)[22]. By contrast, the association between AF and subsequent AMI was stronger for women (HR for AF versus no AF: 2.47, 95% CI 1.87–3.25) than for men (HR for AF versus no AF: 1.08 95% CI 0.78–1.50) in the ARIC study[23]. The discrepancy in these findings could be due to diagnostic, preventive and treatment inequities, as well as hormonal variability and the differing effects of other risk factors[27].

Race and ethnicity

In the ARIC study[28], the rates of adverse outcomes after AF, including ischaemic stroke, HF, coronary artery disease and death, were greater in African American patients than in white patients. A greater risk of MI after AF in African American individuals than in white people has been reported in several other studies[20,21,23,29]. This finding is probably the result of racial inequities in the diagnosis, prevention and treatment of AF[30]. Comparative studies of AF incidence in other races and ethnicities are sparse; however, one study reported that the

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risk of MI did not significantly differ between white, Asian and Hispanic individuals with AF who were resident in the USA[29].

Risk of AF in patients with AMI

The risk of AF in the setting of AMI has been extensively examined (Table 1). Patients with MI who developed AF are, on average, older and more likely to be women than those with MI who do not develop AF[6,31]. In addition, patients with new-onset AF after MI demonstrate signs of HF more frequently and have higher burdens of cardiovascular and non-cardiovascular comorbidities than patients with AMI and no AF[6,31]. Moreover, patients with newly diagnosed AF after MI are more likely to have reduced ejection fraction and a higher prevalence of STEMI and cardiogenic shock than those without AF[9].

The prevalence of AF in patients with MI varies substantially across studies, depending on the population studied, the definition of AF and the duration of follow-up. AF was found in up to 11% of hospitalized patients with AMI assessed using 12-lead electrocardiograms or continuous electronic monitoring[4,31]. AF onset was often reported within days of AMI, suggesting a substantial risk of AF in the very short-term setting[4,31].

Intense and long-term monitoring of patients with an implantable cardiac monitor revealed a greater incidence of AF after AMI than detected with in-hospital continuous electronic monitoring or consecutive 12-lead electrocardiograms[32,33]. In the CARISMA study[33], the incidence of AF (no previous MI) was about 28%, whereas the incidence of AF was 58% in patients with STEMI in the ARREST study[32], in which the majority of confirmed AF (93%) was asymptomatic[32]. In a report from the prospective, community-based Rotterdam study[34], clinically recognized and unrecognized MI were both associated with a higher risk of AF compared with no MI. Observational studies on the risk of AF in patients with MI are summarized in Table 1.

Temporality of AF and MI

In the ULSAM study[2] from Sweden, in which men enrolled at 50 years of age have been followed up for 40 years, participants with concomitant AF and MI more frequently had MI first and then developed AF than the other way around. In an observational study of 3,220 individuals hospitalized with MI, most cases of incident AF occurred after, rather than before, the MI[35]. In 30% of the individuals who developed AF after MI, AF occurred on the same day or within 2 days of MI. In 16%, AF onset was from 3–30 days after MI and, in 54%, AF occurred >30 days after MI. The risk of AF gradually decreased after the first year following AMI[35]. In both the ARREST[32] and CARISMA[33] studies, in which patients had implantable cardiac monitors, the majority of AF onset occurred in the first year after AMI.

Among patients who had AF before MI, the rate of MI has been reported to be particularly high during the first months after AF diagnosis[3,36]. In a study from Danish health registries[3], during the first 30 days after AF diagnosis, the incidence of MI was similar to the risk of ischaemic stroke (adjusted incidence rate ratio 8.0, 95% CI 6.8–9.5 and 9.9, 95% CI 8.5–11.5, respectively) compared with individuals who did not have AF. The rate of

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MI decreased gradually after AF diagnosis, and after 6–10 years was similar to that of individuals without AF (adjusted incidence rate ratio 0.91, 95% CI 0.77–1.08)[3].

Shared risk factors for AF and MI

Many risk factors are common to both AF and MI. These include non-modifiable demographic factors, modifiable risk factors, social determinants and comorbidities (Box 2). Some of these factors are discussed in more detail below.

Demographic factors

AF and MI share several non-modifiable risk factors. Advancing age is a prominent risk factor for both AF and MI. In a report from the Framingham Heart Study[37], the prevalence and incidence of AF increased for each decade beyond 60 years of age. Similarly, hospitalization rates for AMI increased with advancing age and peaked in individuals aged >85 years[38].

Biological sex is also strongly associated with both AF and MI. In the Framingham Heart Study[39], lifetime risk of AF was higher in men than in women. The incidence of AF worldwide was also higher in men in the 2017 Global Burden of Disease Study[40]. However, using the clinical risk factors, researchers reported that the risk of AF conferred by male sex was no longer observed after accounting for height, weight and other risk factors[41]. In the ARIC study[42], the lifetime risk of AF was similar for African American men and women (21% and 22%, respectively). For NSTEMI, a study from Finland showed a 2.4-fold higher risk in men than in women[43], while the same researchers found a threefold higher risk of STEMI in men than in women in another study[44].

Race and ethnicity are also associated with variation in incidence and outcome in both AF and MI. The incidence per 1,000 person-years of diagnosed AF has been estimated to be higher among white (11.2, 95% CI 9.8–12.8) than Hispanic (6.1, 95% CI 4.7–7.8), African American (5.8, 95% CI 4.8–7.0) or Chinese (3.9, 95% CI 2.5–6.1) individuals[45]. Part of the variation in clinically diagnosed AF reflects ascertainment biases[46]. In the ARIC study[47], white participants had a higher rate of clinically recognized MI than African American participants (5.04 versus 3.24 per 1,000 person years, $P = 0.002$). This finding could be partly explained by social determinants, including residential environment (urban versus rural), availability of health care, access to treatment and socioeconomic position[48].

Modifiable risk factors and comorbidities

AF and MI also share several modifiable risk factors. In the ARIC study[49], the prevalence of cardiovascular risk factors in patients with AF was higher than in matched AF-free controls, even >15 years before AF diagnosis. Trajectories of multiple risk factors over time were associated with future risk of AF. In addition, the prevalence of stroke, MI and HF increased gradually in the period close to AF diagnosis, suggesting that shared modifiable risk factors have an important role in the co-occurrence of the two conditions[49].

Smoking.—Tobacco smoking is a risk factor for both AF and MI[50]. In an Australian study, current smoking was associated with a 2.5-fold higher risk of acute MI and a 1.3-fold higher

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risk of AF than non-smoking[51]. In a large, multinational study, the risk of recurrent MI was reduced in patients who stopped smoking after AMI compared with those who persisted with smoking (OR 0.57, 95% CI 0.36–0.89)[52]. Smoking cessation has also been reported to be associated with a reduced risk of incident AF[53].

Alcohol intake.—Observational studies have demonstrated a protective association between light-to-moderate alcohol intake and MI[54,55]. However, in a Mendelian randomization study, a causal relationship was found between alcohol intake and risk of MI at all levels of intake[56]. A linear dose–response relationship between alcohol and AF was reported in an observational study[57]. This finding is supported by the results of a Mendelian randomization study, in which each additional drink of alcohol per day was associated with an increased risk of AF (OR 1.26, 95% CI 1.07–1.48)[58]. In observational studies, the association between alcohol intake and the risk of disease is subject to residual confounding, which is likely to be the reason for conflicting results between observational studies and Mendelian randomization studies. In a study on patients with AF who had a regular alcohol intake (≥10 standard drinks per week) and were randomly assigned to abstinence from alcohol or no intervention, the reduction in AF recurrence and AF burden was greatest among individuals in the abstinence group (HR 0.55, 95% CI 0.36–0.84)[59].

Body weight and physical activity.—Obesity is a causal risk factor for both AF and MI[50]. In addition, weight gain and fluctuating weight are associated with a higher risk of incident AF than steady weight[60,61], and weight loss is associated with a reduced AF burden[62]. In addition, weight changes have been associated with an increased risk of first AMI compared with stable weight[63]. In pooled analyses and meta-analyses, inverse dose–response associations have been found between guideline-recommended levels of physical activity and both AF[64] and fatal MI[65].

Hypertension.—Elevated blood pressure (BP) is a major risk factor for both AF and MI[50,66]. In the SPRINT trial[67,68], participants were randomly assigned to intensive (systolic BP <120 mmHg) or standard (<140 mmHg) BP reduction. Intensive BP lowering led to a significant reduction in the risk of new-onset AF (HR 0.74, 95% CI 0.56–0.98) and a composite outcome including MI, acute coronary syndrome, stroke, HF or death from cardiovascular disease (HR 0.75, 95% CI 0.64–0.89)[67,68]. A meta-analysis of 14 trials demonstrated an overall relative risk of MI of 0.86 (95% CI 0.78–0.96) in individuals treated with intensive BP-lowering therapy compared with less-intensive therapy[69].

Diabetes mellitus.—Type 2 diabetes mellitus (T2DM) is a causal risk factor for MI[50]. In a meta-analysis of randomized controlled trials, glycaemic control in patients with T2DM reduced the risk of MI (relative risk 0.90, 95% CI 0.82–0.98)[70]. Mendelian randomization studies do not support a causal relationship between T2DM and AF[50,71]. However, an earlier observational study showed that, in patients with T2DM, longer disease duration and poor glycaemic control were associated with an increased risk of AF[72]. The association between T2DM and AF might be confounded by shared risk factors, such as obesity and hypertension, or mediated by coronary artery disease.

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Social determinants

Both AF and MI have been found to be more frequent among individuals with lower socioeconomic status[48,73]. Low levels of education and wealth have been shown to be independent predictors of MI[73], and the risk of incident and prevalent AF has been reported to be greater in individuals with lower levels of education, income and employment[48,74]. The incidence of adverse events related to AF, such as death and stroke, is also increased among patients with low income[48]. Results from a Finnish study published in 2001 also showed substantial differences in survival after MI according to income[75]. Approximately 49% of men with low income died within 12 months of MI, compared with 27% in the high-income group. The difference in mortality after MI among women with low or high income was less marked (30% and 20%, respectively)[75].

Rurality could also have an influence on AF and MI incidence. Individuals living in rural areas are at higher risk of AF than those in urban areas, possibly due to an increased burden of risk factors such as older mean age, smoking and obesity, and social factors, such as lower levels of income and education[48]. In addition, access to health care can be limited in rural areas[48]. In a large study of 70,424 patients with STEMI from the USA, patients living in rural areas were less likely to receive primary PCI and had longer times to reperfusion compared with patients living in urban areas[76]. However, the investigators found no significant difference in adjusted in-hospital mortality between patients from rural or urban areas[76].

Environmental risk factors

Air pollution is associated with both AF and MI. In a meta-analysis of five studies, long-term exposure to air pollution was associated with increased risk of AF incidence[77]. In addition, a large Swedish study showed that higher 24-h mean levels of air pollutants recorded in Stockholm were associated with an increased incidence of AF in study participants aged >75 years compared with lower levels of pollutants[78]. A strong association was reported between short-term exposure to air pollution as well as weather changes and increased risk of STEMI in populations from two large urban areas of Italy[79]. Moreover, a meta-analysis of 24 studies, including >70 million individuals, showed a significant association between long-term exposure to air pollution and the risk of MI[80].

Pathophysiology

We have discussed how shared risk factors can lead to the co-occurrence of AF and MI; however, several direct mechanisms explain how one condition might predispose to the other. AF and MI are both associated with inflammation[81–83], which contributes to the bidirectional association. The onset of AF in the setting of MI is partially a result of structural changes caused by ischaemia and inflammation[84–86], whereas MI in patients with a history of AF can be the result of coronary artery embolism[87] or a mismatch between oxygen supply and demand[88]. The various pathophysiological mechanisms involved in the bidirectional interaction between AF and MI are shown in Figs 2,3 and discussed in more detail below.

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Inflammation

Inflammation has a major role in coronary artery disease[89]. Immune cells are involved in the development of atherosclerotic plaques and the transformation from stable to vulnerable plaque morphology[89]. In MI, inflammatory cells and mediators are involved in erosion and rupture of the atherosclerotic plaque[89]. In addition, inflammation in the setting of systemic disease, including obesity and hypertension, and ischaemia can cause electrical and structural remodelling of the atria, leading to AF[90] (Fig. 2). In turn, AF might also promote inflammation, but the underlying mechanisms are poorly understood[90].

Increased systemic levels of inflammatory markers, such as IL-6 and C-reactive protein, are associated with incident AF[81] and MI[82,83]. In a Mendelian randomization study, a causal link was found between levels of circulating interleukins and both AF and coronary artery disease[91]. In patients with AF, biomarkers of inflammation and platelet activation are independent predictors of cardiovascular events, including MI[92,93]. Furthermore, markers of oxidative stress and inflammation are associated with AF in the setting of AMI[94,95].

In the CANTOS trial[96], anti-inflammatory therapy in patients with previous MI was associated with a reduced risk of recurrent MI. Whether treatment with anti-inflammatory drugs reduces incident or recurrent AF is unclear. The use of colchicine, prednisolone and canakinumab in the treatment and prevention of AF has been reviewed previously[97]. In small studies, these drugs tended to have beneficial effects, but larger trials are warranted to validate these findings[97].

Mechanisms involved in AF after MI

Atrial ischaemia.—Several factors contribute to the development of AF after AMI, including atrial ischaemia (Fig. 3a). Ischaemia causes damage to cardiomyocytes and leads to their replacement by fibrotic tissue, which can disrupt electrical conduction in the atria, causing the initiation of AF[98]. In animal models and small clinical studies, occlusion of atrial coronary branches leading to atrial ischaemia independently predicted incident AF after AMI[84–86]. In a dog model, chronic ventricular MI without atrial involvement caused alterations in atrial electrical restitution and sympathetic hyperinnervation[99]. This finding suggests mechanisms beyond atrial ischaemia in the risk of AF after AMI.

Left ventricular dysfunction.—Ventricular ischaemia caused by MI can lead to left ventricular dysfunction and HF[100,101], which can induce AF, possibly due to secondary processes such as atrial dilatation (due to pressure or volume overload), neurohumoral modulation and atrial ion channel remodelling[102] (Fig. 3a). Left ventricular dysfunction has been associated with new-onset AF in patients with AMI in several studies[9,103]. Therefore, left ventricular dysfunction is a possible pathophysiological explanation for AF occurring in the setting of MI. However, in a study of 786 patients with STEMI, no correlation was found between infarct size, assessed by cardiac MRI, and the development of AF[103].

Mechanisms involved in MI after AF

Type II MI.—AF with a rapid ventricular response (tachycardia) can cause oxygen supply–demand mismatch due to an increased demand for oxygen and less time for subendocardial

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perfusion and thus lead to type II MI[104] (Fig. 3b). In an assessment of coronary blood flow and myocardial perfusion in patients with AF, both were found to be impaired, despite the absence of coronary obstructive disease[105], and coronary blood flow worsened with AF burden[105]. The reduction in coronary blood flow in AF is partly reversible after cardioversion[88].

Coronary artery embolism.—During episodes of AF, blood can pool, coagulate and form thrombi in the left atrial appendage[106]. Thrombi can then embolize directly to the coronary arteries and lead to AMI[106] (Fig. 3b). In a study of 1,232 patients with STEMI, the prevalence of coronary artery embolism was low (4.3%)[87]. However, among those patients with coronary artery embolism, AF was the most common underlying cause (28%)[87].

Clinical outcomes

Mortality

In a meta-analysis of 43 studies, mortality was 46% higher among patients with concomitant AF and MI than in patients with MI who were free from AF[107]. Across these studies, mortality was assessed over varying follow-up periods, from the time of hospital admission until discharge, to up to 8 years after the index MI[107]. In-hospital, short-term and long-term mortality were all higher in patients with MI and either previous or new-onset AF than in patients without AF[107,108]. Whether the temporality of AF and MI has an influence on mortality is unclear. In several studies, increased mortality has been reported among patients with new-onset AF compared with patients with a history of AF at the time of AMI[8,109–111]. A community-based study conducted in Olmsted County, MN, USA, demonstrated that mortality was highest for patients with new-onset AF developing >30 days after MI[35]. However, other studies have shown no significant difference in mortality between patients with previous or new-onset AF after MI[9,107].

Heart failure

HF is a common complication after AMI[38], and the risk of subsequent HF hospitalization is increased in patients with AMI accompanied by AF[5,9]. In patients with AF after AMI, the rate of HF hospitalization was 5.8-fold higher in persistent and 2.6-fold in transient new-onset AF ($P = 0.008$ for interaction) compared with patients with AMI and no AF[5]. However, whether the risk of HF is dependent on the temporality of AF and MI is unclear[8,9,109].

Stroke

AF and MI are both associated with an increased risk of ischaemic stroke[2]. In patients with AMI, concomitant AF is associated with a greater risk of ischaemic stroke compared with patients with AMI and no AF[8,9,108,109]. Studies published in the past 2 years have demonstrated that the risk of stroke is higher in patients with new-onset AF than in patients with previous AF, and the risk was especially high during the first 30 days after AMI[8,9]. In an observational study, the incidence of stroke among patients with new-onset AF after AMI was higher in those with permanent AF than in those with paroxysmal AF (22.0% versus

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8.3%; HR 5.16, 95% CI 2.24–11.87 for permanent AF and HR 1.97, 95% CI 1.16–3.35 for paroxysmal AF)[6].

Prevention

Prevention of MI in patients with AF

In the European and US guidelines on AF, recommendations largely focus on anticoagulation therapy for the prevention of stroke, but they do not specifically address the prevention of MI in patients with AF[112,113]. In a study of data from US registries, less than half of patients with AF received all the indicated, evidence-based preventive therapies for comorbid cardiovascular risk factors and conditions[114]. Anticoagulation is pivotal to reducing the risk of stroke in patients with AF and might also reduce the risk of MI[115]. Importantly, however, randomized trials of oral anticoagulation (OAC) therapy are designed with stroke, rather than MI, as the primary outcome. In the RE-LY trial[116], patients with AF were randomly assigned to receive dabigatran or a vitamin K antagonist (VKA) for stroke prevention. The rate of MI was higher among patients receiving dabigatran than among those receiving a VKA (0.74% versus 0.53% per year)[116]. However, trials of apixaban or rivaroxaban versus VKA have shown lower absolute rates of MI in patients assigned to direct OACs than in those in the VKA groups[117,118]. In an observational study, patients receiving a VKA had a higher risk of MI than those receiving OACs, whereas no significant differences in the rate of MI were found between the various direct OACs (apixaban, dabigatran, edoxaban and rivaroxaban)[119]. However, the study design is subject to confounding by indication.

The management of comorbidities and risk factors in patients with AF is essential for the prevention of subsequent MI. In the ORBIT-AF registry[120], every 5% increase in systolic BP from baseline was associated with a 5% increase in the risk of MI (adjusted HR 1.05, 95% CI 1.00–1.11) in patients with AF. In a study of 2,372 South Korean men, smoking cessation after AF onset was associated with a reduction in the rate of adverse outcomes, including incident CVD[121]. However, smoking cessation was not significantly associated with a reduction in the risk of MI alone, probably due to the low number of events and low statistical power[121].

Prevention of AF in patients with MI

Currently, no specific guidelines exist for the prevention of AF in patients with MI. Angiotensin-converting enzyme (ACE) inhibition after MI attenuates left ventricular remodelling and thus prevent HF[122]. As left ventricular dysfunction is associated with a risk of AF[102], studies have been conducted to assess whether treatment with ACE inhibitors is associated with a reduced risk of AF after MI. In the randomized TRACE study[123], patients with HF secondary to AMI who received an ACE inhibitor had a significantly reduced incidence of AF than those in the placebo group (HR 0.45, 95% CI 0.26–0.76)[123]. However, in two large, population-based studies, no association was found between renin–angiotensin–aldosterone inhibition and AF incidence in patients with AMI or coronary artery disease[124,125]. The divergent findings could be related to differences in study population characteristics, such as age, sex and comorbidities. In the CAPRICORN

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study[126], patients with AMI and HF were randomly assigned to receive a β-blocker or placebo. The investigators found a significant reduction in the incidence of AF in the treatment group (HR 0.41, 95% CI 0.25–0.68). Data from observational and clinical preventive studies in patients with AF, MI or both are presented in Table 2.

Management

ST-segment elevation MI

In the European and US guidelines, the recommendation is for all patients with AMI (either STEMI or NSTEMI), including those with AF, to be treated with a loading dose of 150–300 mg of aspirin (class IA)[127–130]. Patients with STEMI and AF who are treated with OACs should also be given parenteral anticoagulation (unfractionated heparin and low-molecular-weight heparin) before primary PCI[127]. Fibrinolysis is often contraindicated in patients treated with OACs, so primary PCI should be the first choice when possible[127,130]. If PCI is not possible, fibrinolysis can be used despite OAC therapy.

Non-ST-segment elevation MI

In addition to the loading dose of aspirin, the European and US guidelines recommend parenteral anticoagulation at the time of diagnosis of NSTEMI and during revascularization procedures[128,129]. However, in patients with AF who are already receiving OACs, the European guidelines recommend that oral treatment be continued[128]. This recommendation is based on a subgroup analysis of the randomized WOEST trial[131], in which there was no significant difference in the risk of bleeding and major adverse events between patients receiving uninterrupted OAC therapy and those with bridging therapy during PCI. Therefore, the safety of bridging direct OAC with parenteral anticoagulation in patients undergoing PCI is unclear[128]. Whether direct OAC can be discontinued without parenteral anticoagulation is also unclear. Therefore, the European guidelines recommend that low-dose parenteral anticoagulation is added to direct OAC[128]. For patients with AF who are receiving VKA and have an international normalized ratio >2.5, no additional parenteral anticoagulation is recommended[128]. In an observational study, no association was found between cardiovascular events and adding parenteral anticoagulation to VKA treatment, whereas dual treatment was associated with procedural complications[132].

AF and chronic ischaemic heart disease

For patients with AF and chronic ischaemic heart disease, OAC therapy is recommended in both the European and the US guidelines[133,134]. For patients who undergo PCI, VKA should be continued, whereas direct OACs should be discontinued 12–48 h before an elective procedure[133].

Post-procedural management

In patients with AF and acute or chronic ischaemic heart disease, triple antithrombotic therapy with direct OAC and dual antiplatelet therapy is associated with a high risk of major bleeding compared with dual antithrombotic therapy with OACs and a $P2Y_{12}$ inhibitor[135–138]. Uncertainty exists as to whether dual antithrombotic therapy increases the risk of stent thrombosis and recurrent MI compared with triple therapy, as four large trials comparing

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the two strategies were underpowered to assess ischaemic outcomes[139–142]. However, meta-analyses have demonstrated a significantly higher risk of stent thrombosis and MI with dual antithrombotic therapy than with triple therapy, but no significant difference in all-cause mortality[135,137,138]. Clopidogrel is preferred over prasugrel or ticagrelor in patients receiving concomitant OAC therapy, due to the lower risk of major bleeding with clopidogrel[143].

The European guidelines recommend early cessation of triple antithrombotic therapy (≤1 week after PCI) and continuation of dual therapy for up to 12 months if the risk of stent thrombosis is low[112]. Monotherapy with an OAC is recommended after 12 months, or after 6 months in patients with a high risk of bleeding or medically treated MI[112,128,133]. However, if the risk of stent thrombosis outweighs the bleeding risk, triple therapy for >1 week, but ≤1 month, should be considered[112]. The US guidelines recommend dual therapy with a $P2Y_{12}$ inhibitor and an OAC for patients with AF and a CHA_2DS_2-VASc risk score of ≥2 undergoing PCI[113]. If triple therapy is prescribed, a transition to dual therapy should be considered at 4–6 weeks after intervention[113].

Rate and rhythm control

In patients with AMI and haemodynamically compromising AF, rate control in the acute setting can be pursued with an intravenous β-blocker if there are no signs of acute HF and the treatment does not compromise BP[112,113,127]. In patients with AMI and acute HF, digoxin can be considered for acute rate control[113]. If rate control is not adequate, acute rhythm control with intravenous amiodarone or electrical cardioversion is recommended[113,127].

When pursuing long-term rhythm control in patients with AF and ischaemic heart disease, amiodarone, β-blockers, digoxin and calcium-channel blockers (verapamil or diltiazem) can be used, although calcium-channel blockers are contraindicated in patients with HF with reduced ejection fraction due to negative inotropic effects[112]. In addition, vernakalant can be used, but is contraindicated in the first month after AMI[112]. This recommendation is made because patients with recent AMI (<30 days) were excluded from placebo-controlled randomized trials of vernakalant[144,145]. Flecainide is not recommended in patients with ischaemic heart disease[112,134] due to the findings of the CAST study[146], in which 1,498 patients were randomly assigned to either class Ib antiarrhythmics (flecainide or encainide) or placebo after AMI to reduce ventricular ectopy[146]. The investigators observed excess deaths due to arrhythmia and recurrent MI in the treatment group[146]. In another study, treatment with propafenone in patients with structural heart disease resulted in a greater incidence of serious adverse events than placebo[147]. Therefore, propafenone is not recommended in patients with known coronary artery disease[112,134]. Finally, AF ablation can be considered for long-term rhythm control[112,113].

Knowledge gaps and future directions

There are several gaps in our knowledge about the bidirectional association between AF and MI. First, there is a lack of studies in individuals of African ancestry on the inequities in the prevention, diagnosis and treatment of both conditions that should be addressed to

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mitigate the increased risk of MI in individuals with AF and vice versa. It is also unclear whether biological sex is a modifier of the risk of AF in patients with MI and on adverse outcomes, such as HF, stroke and death. Therefore, we encourage the future study of the risk and temporality of AF in patients with MI, and MI in patients with AF, according to race, ethnicity and sex. Moreover, whether the bidirectional risk of AF and MI differs according to socioeconomic status, residential environments, availability of health care and health literacy has not been adequately explored.

In the prevention of MI in patients with AF, there is a lack of knowledge on the protective role of OAC therapy and modifiable risk factors on MI risk. Ideally, types of OAC drug should be compared in randomized controlled trials powered for MI as a primary outcome. In addition, we suggest future studies comparing rate and rhythm control, as well as risk factor modification, in patients with AF for the prevention of MI. Another potential study direction is the comparison of catheter ablation and pharmacological rhythm control and risk of MI in patients with AF. For the prevention of AF in patients with MI, the potential effects of new drugs, such as sodium–glucose cotransporter 2 inhibitors should be investigated. In addition, antithrombotic regimens for NSTEMI, STEMI and chronic ischaemic heart disease in patients with AF treated with OACs are still challenging and should be investigated further.

Conclusions

The association between AF and MI is bidirectional, and the pathogenesis of their co-occurrence is multifactorial. AF and MI not only share common risk factors leading to their co-existence, but each condition also increases the risk of subsequently experiencing the other through direct and indirect mechanisms. The coexistence of AF and MI is associated with worse prognosis than each condition alone, with increased mortality and risk of HF and ischaemic stroke, emphasizing the importance of prevention and management of both conditions. Understanding of the increased risk of adverse events in patients with both conditions should lead future studies to focus on preventive measures for MI in patients with AF and vice versa. Finally, balancing the risk between bleeding and thrombotic events is challenging in the management of patients with concomitant AF and MI and needs to be further explored.

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Box 1 |

Assessing bidirectional relationships

Various statistical methodologies exist to assess bidirectional relationships between two conditions in population-based studies. The collection of longitudinal data allows the determination of temporality between exposure and outcome. In a classical analysis of survival data, by comparing Kaplan–Meier curves and using the Cox proportional hazards model, one would assess bidirectionality by testing two separate hypotheses to determine whether event ‘A’ is associated with event ‘B’ and vice versa[154].

Multistate models are particularly well suited for analysing the temporality between multiple events[155]. These models use a life-course framework, in which individuals are allowed to transition between different disease ‘states’. Multistate models can be used to assess multiple disease pathways simultaneously, as was done in a study of the temporal association between myocardial infarction, chronic heart failure, atrial fibrillation (AF) and stroke[2]. These models are very flexible and allow for repeated events and multiple event types, and account for temporality. Special cases of multistate models include the competing risks model and the illness–death model. As an example, an illness–death model was used as a study of AF and fracture risk, which allowed the analysis to account for the time-varying nature of the exposure (AF status) and for the competing risk of death[155]. It should be noted that overly complex multistate models should be avoided as they can be difficult to interpret and can be limited by an insufficient sample size or number of events that prevents estimation of all transitions.

Mendelian randomization is one method that allows the assessment of causality in the setting of observational data[156,157]. Briefly, Mendelian randomization uses a genetic variant as an instrumental variable, or proxy, for the exposure variable. As the genetic variant is present at birth and is free from confounding by post-birth factors, the analysis resembles a randomized controlled trial, in which causal relationships can be identified. Bidirectional Mendelian randomization extends this technique by using two genetic instrumental variables, one for each exposure, A and B[158–160]. If a bidirectional relationship exists, the genetic instrumental variables for A will be associated with B, and the genetic instrumental variables for B will be associated with A. The challenges with assessing bidirectional relations include finding genetic instrumental variables that have a similar magnitude of association with each trait of interest, and ensuring that the two genetic variants are independent[160]. Three bidirectional Mendelian randomization studies showed that genetic predisposition to coronary artery disease was a causal risk factor for AF, but no causal association was found between genetic predisposition to AF and the risk of coronary artery disease[66,161,162].

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Box 2 |

Shared risk factors for AF and MI

Shared risk factors for atrial fibrillation (AF) and myocardial infarction (MI) overlap and interact.

Demographic

- Age
- Sex
- Race/ethnicity

Lifestyle

- Alcohol intake
- Smoking
- Physical inactivity

Comorbidities

- Heart failure
- Hypertension
- Obesity
- Type 2 diabetes mellitus
- Chronic kidney disease

Social determinants

- Education
- Employment
- Income and wealth
- Social network
- Rurality and neighbourhood
- Structural racism

Environmental

- Air pollution

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Key points

- Atrial fibrillation (AF) is a risk factor for myocardial infarction (MI); the rate of MI is approximately 50% higher in patients with AF than in those without AF.
- MI is associated with subsequent AF, and the rate of AF is particularly high in the first days after MI.
- The bidirectional association between AF and MI might be partly explained by indirect mechanisms related to shared risk factors such as age, sex, modifiable risk factors, comorbidities and social determinants of health.
- There are several mechanisms through which one condition can lead directly to the other, such as coronary embolism, oxygen supply–demand mismatch, atrial ischaemia, cardiac remodelling and inflammation.
- Patients with coexisting AF and MI have an increased risk of stroke, heart failure and death compared with those with either condition alone, emphasizing the importance of prevention and management.
- Medical treatment in patients with both AF and MI is challenging, owing to the need to balance the risks of thromboembolic complications, bleeding and stent thrombosis.

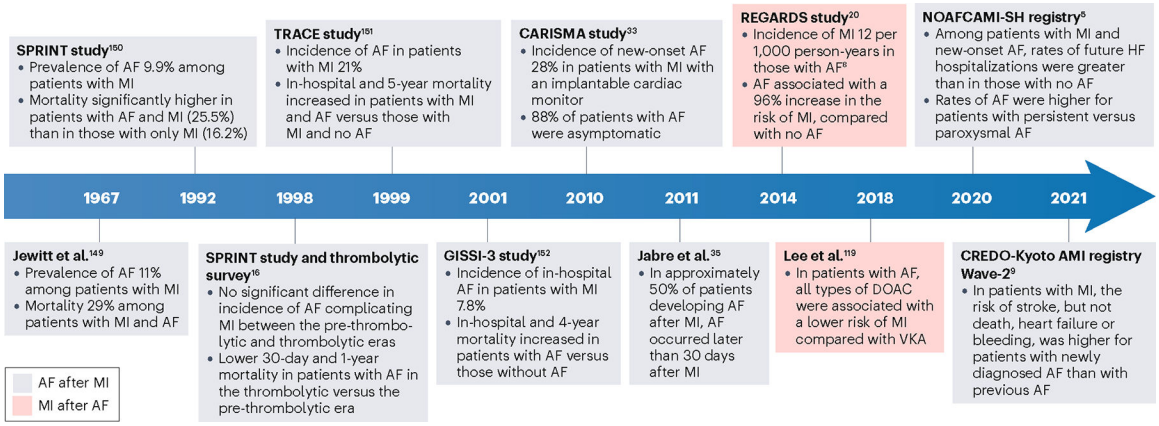

Fig. 1 |. Timeline of selected literature on the bidirectional relationship between AF and MI. Grey boxes refer to studies examining patients with atrial fibrillation (AF) after myocardial infarction (MI), and red boxes refer to studies on patients with MI after AF. REFS.[149–152]. DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

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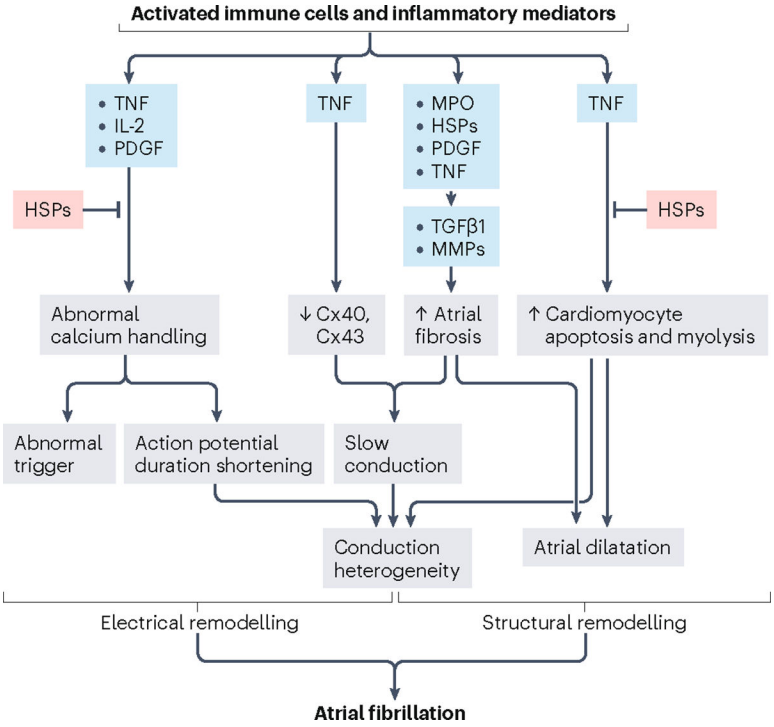

Fig. 2 |. Inflammatory cells and mediators of inflammation modulate cardiac electrophysiology and structural properties leading to atrial fibrillation.

Calcium homeostasis in cardiomyocytes is regulated by tumour necrosis factor (TNF), IL-2 and platelet-derived growth factor (PDGF), which are associated with increased triggering and shortening of the action potential duration. The atrial expression of connexin 40 (Cx40) and Cx43 is downregulated by inflammation via TNF. Myeloperoxidase (MPO), heat shock proteins (HSPs), PDGF and TNF activate fibroblasts, which express transforming growth factor-β1 (TGFβ1) and matrix metallopeptidases (MMPs), leading to increased collagen synthesis and atrial fibrosis. TNF also increases cardiomyocyte apoptosis and myolysis. These changes contribute to heterogeneous atrial conduction and increased vulnerability to atrial fibrillation. HSPs protect cardiomyocytes against abnormal calcium handling, apoptosis, and myolysis. Adapted with permission from REF.[153], Springer Nature.

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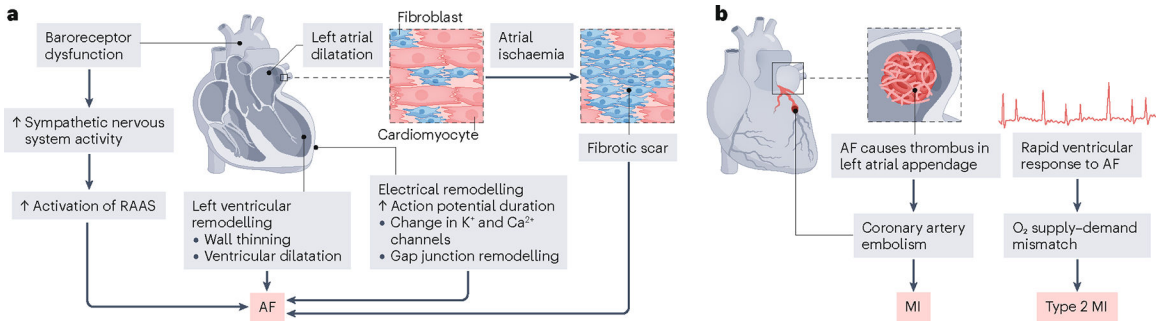

Fig. 3 |. Pathophysiology of MI leading to AF and AF leading to MI.

a, Acute myocardial infarction (MI) can initiate several mechanisms that ultimately result in atrial fibrillation (AF). Left ventricular remodelling with wall thinning and left ventricular dysfunction potentiate left atrial dilatation (due to pressure and/or volume overload), electrical remodelling (increases in action potential duration, alterations to K^+ and Ca^{2+} ion channels and gap junction remodelling) and neurohumoral modulation (stimulation of the renin–angiotensin–aldosterone system (RAAS), vasopressin and atrial natriuretic peptide). In addition, atrial ischaemia caused by MI can lead to cardiomyocyte death and fibrotic replacement, producing an arrhythmogenic substrate that alters electrical conduction and can result in AF. **b,** In the setting of AF, blood can pool in the left atrial appendage, leading to thrombus formation, which can be dispersed as a coronary artery embolism. During episodes of AF with a rapid ventricular response rate (tachycardia), myocardial oxygen demand increases and can cause a mismatch with oxygen supply, which can lead to type 2 MI.

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Table 1 |

Observational studies on the association between AF and MI

Study (year)	Number of patients	Patient and study characteristics	Exposures	Outcomes	Main findings	Refs
Soliman et al. (2014)	23,298 (57% women; 43% African American)	Mean age: 66.5 ± 9.7 years Median follow-up: 4.5 years	AF	MI	Age-adjusted incidence of MI in those with AF: 12.0 per 1,000 person-years (95% CI 9.6–14.9), and in those without AF: 6.0 per 1,000 person-years (95% CI 5.6–6.6). AF associated with a higher risk of MI (HR 1.70, 95% CI 1.26–2.30) than no AF. Age-stratified analyses: no significant difference in risk between age groups (<75 years versus >75 years).	20
O'Neal et al. (2014)	4,608 (60% women; 85% white)	Age 65–70 years: 44% Age 71–75 years: 24% Age 75–80 years: 22% Age >80 years: 10% Median follow-up: 12.2 years	AF	MI	Incidence of MI in those with AF: 25.5 per 1,000 person-years (95% CI 20.5–31.6), and in those without AF: 13.9 per 1,000 person-years (95% CI 12.9–14.9). Risk of MI higher in those with AF than in those without AF (HR 1.7, 95% CI 1.4–2.2).	21
Chao et al. (2014)	24,228 (40% women)	Mean age: 47 ± 11.5 years Mean follow-up: 5.7 years	AF	MI	Annual incidence of MI in those with AF: 0.29%, and in those without AF: 0.10%. Risk of MI higher in those with AF than in those without AF (HR 2.93, 95% CI 2.21–3.87). Risk of MI higher in men with AF than in women with AF (HR 2.24, 95% CI 1.61–3.11).	22
Soliman et al. (2015)	14,462 (56% women; 26% African American)	Mean age: 54 ± 5.7 years Median follow-up: 21.6 years	AF	MI	Incidence of MI in those with AF: 11.6 per 1,000 person-years (95% CI 10.49–12.8), and in those without AF: 3.96 per 1,000 person-years (95% CI 3.71–4.22). Risk of MI higher in those with AF than in those without AF (HR 1.63, 95% CI 1.32–2.02). Association between AF and MI stronger for women than for men. No significant differences in risk by age or race. Stratified by MI type: AF significantly associated with NSTEMI but not with STEMI.	23
Magnani et al. (2016)	15,080 (55% women; 75% white)	Mean age: 54.2 ± 5.8 years Mean follow-up: 20.6 years	AF	CHD (defined by definite or probable MI)	Incidence of AF in white individuals: 8.1 per 1,000 person-years (95% CI 7.7–8.5), and in African American individuals: 5.8 per 1,000 person-years (95% CI 5.2–6.3). Risk of CHD higher in those with AF than in those without AF (rate ratio 6.8, 95% CI 6.2–7.5).	28
Sundbøll et al. (2017)	623,924 (47% women)	Median age: 72.6 years (Q1–Q3 63.0–81.7 years) Median follow-up: 2.8 years	AF	MI	10-year cumulative risk of MI in AF: 3.5%. Adjusted incidence rate ratio for MI in first 30 days after AF: 8.0 (95% CI 6.8–9.5). No significant difference in adjusted incidence rate ratio for MI in those with AF versus those without AF after 5 years.	3
Rathore et al. (2000)	106,780 (50.1% women; 92% white)	Median age: 79.2 years (Q1–Q3 73–85 years) Follow up: 1 year after hospitalization for MI	MI	AF, mortality	Prevalence of AF in MI at hospital admission: 10.8%, and during hospitalization: 11.3%. AF versus no AF associated with higher in-hospital mortality (OR 1.21, 95% CI 1.17–1.26), 30-day mortality (OR 1.20, 95% CI 1.16–1.24) and 1-year mortality (OR 1.34, 95% CI 1.30–1.39). Mortality higher for AF onset during	7

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Study (year)	Number of patients	Patient and study characteristics	Exposures	Outcomes	Main findings	Refs
					hospitalization than AF at hospital admission.	
Jabre et al. (2011)	3,220 (42% women)	Mean age: 68 ± 15 years Mean follow-up: 6.6 years	First MI and AF	Mortality	AF before MI: 10%. AF onset after MI: 23%. Cumulative 5-year incidence of AF: 19%. AF events within 2 days after MI: 30%; 3–30 days after MI: 16%; >30 days after MI: 54%. AF associated with increased mortality (HR 3.77, 95% CI 3.37–4.21). Highest risk of death with AF onset >30 days after MI.	35
Krijthe et al. (2013)	6,175 (54% women)	Mean age: 68.8 ± 9 years Mean follow-up: 11.7 years	Clinically recognized and unrecognized MI	AF	Risk of AF higher for men with unrecognized MI than with no MI (HR 2.21, 95% CI 1.51–3.23). Risk of AF higher for men with recognized MI than with no MI (HR 1.66, 95% CI 1.21–2.29). No significant association between recognized or unrecognized MI and AF in women.	34
Almendro-Delia et al. (2014)	39,237 (26% women	Mean age: 71.2 ± 9.8 years Maximum follow-up: 15 days	AMI	In-hospital mortality	In-hospital mortality higher for AMI and previous AF than no AF (HR 1.89, 95% CI 1.6–2.4). In-hospital mortality higher for AMI and new-onset AF than no AF (HR 2.19, 95% CI 1.9–2.53). In-hospital mortality higher for AMI and new-onset AF than previous AF (HR 1.70, 95% CI 1.12–3.40).	111
Lee et al. (2020)	2,523 (24% women)	Mean age: 61.6 ± 13.2 years Median follow-up: 7.2 years	MI and AF	Mortality, stroke	Incidence of AF in MI: 10.7%. Higher risk of death for persistent (but not paroxysmal) AF than no AF (HR 1.75, 95% CI 1.03–2.96). Risk of stroke higher for persistent AF (HR 5.16, 95% CI 2.24–11.87) and paroxysmal AF (HR 1.97, 95% CI 1.16–3.35) than no AF.	6
Luo et al. (2021)	2,399 (23% women)	Mean age: 64.7 ± 12.2 years Median follow-up: 2.7 years	MI and AF (low or high burden defined by % time in AF)	HF hospitalization, all-cause death, ischaemic stroke	In-hospital AF: 11.6% (low-burden: 55.8%; high-burden: 44.2%). Risk of HF hospitalization higher in low-burden AF (HR 2.05, 95% CI 1.37–3.07) and high-burden AF (HR 4.50, 95% CI 3.05–6.66) than no AF. Risk of all-cause death and ischaemic stroke higher in high-burden AF (but not low-burden AF) than no AF.	31
Obayashi et al. (2021)	6,228 (25% women)	Mean age: 68.1 ± 12.3 years Median follow-up: 5.5 years	MI and AF	All-cause death, HF hospitalization, major bleeding, MI, stroke	In patients with MI, 9.5% had previous AF and 7.9% had new-onset AF. Higher risk of all-cause death with previous AF (HR 1.31, 95% CI 1.12–1.54) and new-onset AF (HR 1.32, 95% CI 1.14–1.52) than no AF. Risk of HF hospitalization higher with AF than without AF (no significant difference between previous and new-onset AF). Risk of major bleeding higher with AF than without AF. Risk of recurrent MI did not significantly differ with or without AF. Risk of stroke higher with AF than without AF.	9
Fauchier et al. (2021)	797,212, (34% women)	Mean age: 67.5 ± 14.8 years Mean follow-up: 1.8 years	MI and AF	All-cause death, cardiovascular death, HF hospitalization, ischaemic stroke	In patients with MI, 9.5% had previous AF and 4.4% had new-onset AF. Risk of all-cause death higher with previous AF (HR 1.17, 95% CI 1.16–1.19) and new-onset AF (HR 2.11, 95% CI 2.07–2.15) than no AF. Risks of cardiovascular death, HF hospitalization and ischaemic stroke higher with AF than without AF; higher	8

Study (year)	Number of patients	Patient and study characteristics	Exposures	Outcomes	Main findings	Refs
					risks with new-onset AF than with previous AF.	

AF, atrial fibrillation; CHD, coronary heart disease; HF, heart failure; Q1–Q3, 25th to 75th percentiles; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

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Table 2 |

Studies on the prevention of AF in patients with MI and vice versa

Study (year)	Number of patients	Patient and study characteristics	Exposures or interventions	Outcomes	Main findings	Refs
Prevention of MI in patients with AF						
Connolly et al. (2006)	6,706 (34% women)	Mean age: 70.2 ± 9.4 years RCT Follow up: 1.28 years	OAC or clopidogrel plus aspirin	Composite (MI, stroke, embolus, vascular death), MI	Higher risk of composite end point with clopidogrel plus aspirin than with OAC (HR 1.44, 95% CI 1.18–1.76); no significant difference in the risk of MI alone between groups (HR 1.58, 95% CI 0.94–2.67)	148
Lee et al. (2017)	71,959 (47% women)	Median age: 75 years Retrospective cohort study Follow up: 4.1 years	Aspirin monotherapy, VKA monotherapy or dual therapy	First-time MI	Higher risk of MI with aspirin monotherapy than with VKA monotherapy (IRR 1.54, 95% CI 1.40–1.68); higher risk of MI with dual therapy than with VKA monotherapy (IRR 1.22, 95% CI 1.06–1.40)	115
Lee et al. (2018)	31,739 (47% women)	Median age: 74 years Retrospective cohort study Follow up: 3 years	Apixaban, dabigatran, rivaroxaban or VKA	MI	Standardized absolute 1-year risk of MI with apixaban 1.16% (95% CI 0.94–1.39%), dabigatran 1.20% (95% CI 0.95–1.47%), rivaroxaban 1.07% (95% CI 0.83–1.32%) and VKA 1.56% (95% CI 1.33–1.80%); no significant difference in the risk of MI between DOACs; higher risk of MI with VKA than with any of the three DOACs	119
Vemulapalli et al. (2019)	10,098 (42% women)	Mean age 73.5±11 years Prospective cohort study Follow up: 2 years	Changes in systolic blood pressure	MI	Risk of MI increased by 5% (HR 1.05, 95% CI 1.00–1.11) for every 5-mmHg increase in systolic blood pressure from baseline	120
Prevention of AF in patients with MI						
Pedersen et al. (1999)	1,577 (28% women)	Mean age: 68 years Reduced LVEF RCT Follow up: 4 years	ACEi versus placebo	New-onset AF	AF in ACEi group: 2.8%; AF in placebo group: 5.3%; lower risk of AF with ACEi than with placebo (HR 0.45, 95% CI 0.26–0.76)	123
Batra et al. (2017)	112,648 (35.5% women)	Median age: 72 years (Q1–Q3 62–81) Retrospective cohort study Follow up: 3 years	ACEi or ARB	New-onset AF	No reduction in the risk of new-onset AF with ACEi or ARB (HR 1.07, 95% CI 1.00–1.15)	124
Singh et al. (2012)	28,620 (72.9% women)	Mean age: 78.3 ± 7.1 years Retrospective cohort study Mean follow up: 3.8 years	ACEi or ARB	New-onset AF	No reduction in risk of new-onset AF with ACEi or ARB (HR 0.99, 95% CI 0.94–1.04)	125
McMurray et al. (2005)	1,959 (26% women)	Mean age: 63 years (range: 25–90 years) RCT Follow up: 1.3 years	β-Blocker versus placebo	AF	AF in β-blocker group: 2.3%; AF in placebo group: 5.4%; lower risk of AF with β-blocker than with placebo (HR 0.41, 95% CI 0.25–0.68)	126

AF, atrial fibrillation; ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin-receptor blocker; DOAC, direct oral anticoagulant; Q1–Q3, 25th to 75th percentiles; IRR, incidence rate ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; OAC, oral anticoagulant; RCT, randomized controlled trial; VKA, vitamin K antagonist.