ESC European Society of Cardiology

Europace (2021) 00, 1–19
doi:10.1093/europace/euab184

REVIEW

Medical therapies for prevention of cardiovascular and renal events in patients with atrial fibrillation and diabetes mellitus

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Received 20 April 2021; editorial decision 3 July 2021; accepted 5 July 2021

Abstract

Atrial fibrillation (AF), type 2 diabetes mellitus (DM), and chronic kidney disease (CKD) are three global epidemics with significant effects on morbidity and mortality. Diabetes is a risk factor for AF, and a risk factor for thromboembolism, comorbidity, and mortality when AF is present. The pathophysiology of diabetes-related AF and interrelationships with cardiovascular events and renal events is not fully understood but is in part related to structural, electrical, electromechanical, and autonomic remodelling. The current practice guidelines offer limited recommendations on the management of patients with AF (or risk of AF) and diabetes with its own heterogeneity for the prevention of cardiovascular and renal events. This document discusses possible clinical approaches for these patients. In the last decade, there have been major improvements for the prevention of stroke in AF patients with direct oral anticoagulants, which are preferable to vitamin K antagonists for stroke prevention in DM. Because of the increased risk rate for several cardiovascular adverse events in diabetic patients, a similar relative risk reduction generally translates into greater absolute risk reduction in the diabetic population. Recent trials with non-insulin diabetes drugs using glucagon-like peptide-1 agonists and sodium-glucose cotransporter-2 inhibitors showed a significant reduction for the risk of major adverse cardiovascular events in patients with type 2 DM. Sodium-glucose cotransporter-2 inhibitors also showed a large reduction in hospitalization for heart failure and renal events, which need to be more completely evaluated in patients with AF. Mechanisms, risks, and optimal management of AF patients with DM who have or are under risk of developing heart failure or CKD are also discussed in this document. The benefits of medical therapies for these patients still need to be put into perspective, and gaps in evidence on some of these issues are likely to be addressed in future years.

Keywords Atrial fibrillation • Diabetes mellitus • Chronic kidney disease • Ischaemic stroke • Oral anticoagulation • Antidiabetic drugs

Introduction

Atrial fibrillation (AF), type 2 diabetes (DM), and chronic kidney disease (CKD) have emerged as global epidemics with significant effects on morbidity and mortality.[1,2] The risk for thromboembolism is increased when AF and DM coexist. However, the current practice guidelines offer limited recommendations on the approach and treatment of patients with concomitant AF and DM. In the last decade, there have been major developments for the prevention of stroke in AF patients with direct oral anticoagulants (DOACs) and for treating DM with noninsulin DM drugs. The purpose of this document is to

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provide an evidence-based update of therapy when treating patients with concomitant AF (or risk of AF) and DM and the associated risks of cardiovascular (CV) and renal events.

Atrial fibrillation: diabetes as a risk factor

Diabetes as a risk factor for atrial fibrillation

A clear relationship of type I DM (T1DM) with AF was not established until recently, with initial suggestions that long-term hyperglycaemia in T1DM does not itself promote AF.[3] Although studies on T1DM concerning AF risk are rare, recent large analyses eventually confirmed that T1DM was also independently associated with a higher incidence of AF.[3–5] When comparing patients with T1DM from the Swedish National Diabetes Register to controls, the risk of AF with T1DM was increased with an adjusted HR of 1.13 (95% CI 1.01–1.25, $P = 0.029$) in men and 1.50 (95% CI 1.30–1.72, $P < 0.0001$) in women ($P = 0.002$ for interaction).[3]

Considering T2DM, AF is not uncommon, and for example, 7.6% of patients had AF at baseline in the ADVANCE study (Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation).[6] The prevalence of AF is at least two-fold higher in patients with DM compared with people without DM,[7] and AF incidence may be even higher in patients with microvascular complications (retinopathy, renal disease).[8] In Huxley's meta-analysis, which included seven prospective studies and four case–control studies on 1.7 million subjects, 109 000 of whom had incident AF, it was found that DM was associated with about 40% higher risk of AF [relative risk (RR) 1.39; 95% confidence interval (CI) 1.10–1.75]. However, after adjusting for possible confounding factors, the effect appeared to be more limited with an increased risk of only 24%.[9] The authors assumed that the proportion of AF that was attributable to DM in the population was only 2.5%. In Ostgren's study, patients with both T2DM and high blood pressure had a three-fold higher risk of associated AF compared to non-diabetic non-hypertensive patients, but this association was no longer significant after adjusting for the presence of insulin resistance, which therefore appeared to be a major determinant for the development of AF.[10] Insulin resistance is also a mechanism by which hypertension and obesity might be associated with an increased risk of AF.[11] Diabetes mellitus and glucose intolerance are also associated with an increased risk of left ventricular hypertrophy (LVH) which could be one of the factors promoting AF.[7] Long-term inflammation is also a suspected link between DM and AF: inflammation may be found in the two conditions, it can partly predict the development of DM and of AF, and anti-inflammatory treatments have shown to be efficient on a few indirect parameters for some patients with DM and/or with AF (*Figure 1*).[12]

In a subsequent analysis carried out in 35 000 healthcare professionals, and followed for 16 years, the 3% of women with T2DM had a doubled risk of developing AF during follow-up but again, the attributable risk was quite markedly reduced after adjusting for possible confounding factors in the patient characteristics: the risk was only 15% after multivariable analysis.[13]

This would overall suggest that patients with T2DM have a higher risk of prevalent AF (around 15%) (*Figure 2*), and then of incident AF (around 0.8%/year), which however seems partly related to other associated risk factors frequently encountered in these patients.[17] It also appears that DM would be an independent risk factor for AF when one specifically considers patients aged <75.[18] In contrast, when searching for AF after a stroke, since DM may be more closely associated with non-cardioembolic ischaemic stroke, the search may not find as much AF.[19,20]

Both T1DM and T2DM have been associated with atrial electrical and structural remodelling that may underly increased vulnerability for AF.[21] Patients with T1DM have more fractionated atrial electrograms and diastolic dysfunction. Animal models of T1DM demonstrate reduced Na^+ current in the atrial cardiomyocyte with a subsequent reduced upstroke of the action potential and lower conduction velocity.[22] Also, increased structural remodelling through interstitial fibrosis formation has been demonstrated in T1DM models.[23] In patients with T2DM Ca^{2+} handling was impaired, which could add to AF induction.[24,25] Furthermore, atrial fibroblasts from T2DM patients had a more profibrotic phenotype compared to fibroblasts of patients without DM, evident from increased expression of collagen type 1, which adds to structural remodelling of the atrium.[26] The rate of new-onset AF is not obviously affected by intensive glycaemic control,[27] but may be affected by DM therapy (see Diabetes subtypes, diabetes severity, and the risk of atrial fibrillation section).

Diabetes as a risk factor for mortality, complications, and more symptoms in atrial fibrillation

Diabetes mellitus and AF frequently coexist (*Figure 2*),[14–16] and when this occurs there is a substantially higher risk of all-cause death, CV death, stroke, CKD disease, and heart failure (HF).[28–30] Risk of death may be 25–60% higher in AF patients with DM (vs. AF and no DM).[29,30] This was confirmed with the observations from the ORBIT-AF (Outcomes Registry for Better Informed Treatment of AF) registry showing the incremental worsening of AF prognosis over all-cause death, CV death, and several other CV endpoints when DM was present.[31] Risk factors commonly associated with DM (and not fully dissociable, e.g. hypertension and obesity) are also likely to worsen prognosis. Diabetes mellitus and declined renal function are also closely interlinked with increased CV risk. Importantly, the combination of DM and renal impairment is associated with a higher risk of CV events and mortality than either co-morbidity alone[32] underlining the importance of CV prevention in these vulnerable patients when AF is also present (*Figure 1*). Atrial fibrillation is associated with substantially increased risks of death and CV events in patients with T2DM, meaning that AF further increases the already elevated risk of CV disease in these patients. Atrial fibrillation identifies individuals with DM who are likely to obtain greater absolute benefits from blood pressure-lowering treatment.[6] Atrial fibrillation in diabetic patients should be regarded as a marker of adverse outcomes suggesting prompt and aggressive management of all risk factors.

The detection of AF in patients with DM has major clinical consequences because the risk of stroke is markedly higher in these patients. In the absence of other co-morbidities, the annual risk of stroke can be estimated at 2.2% per year in isolated DM.[33] It is also

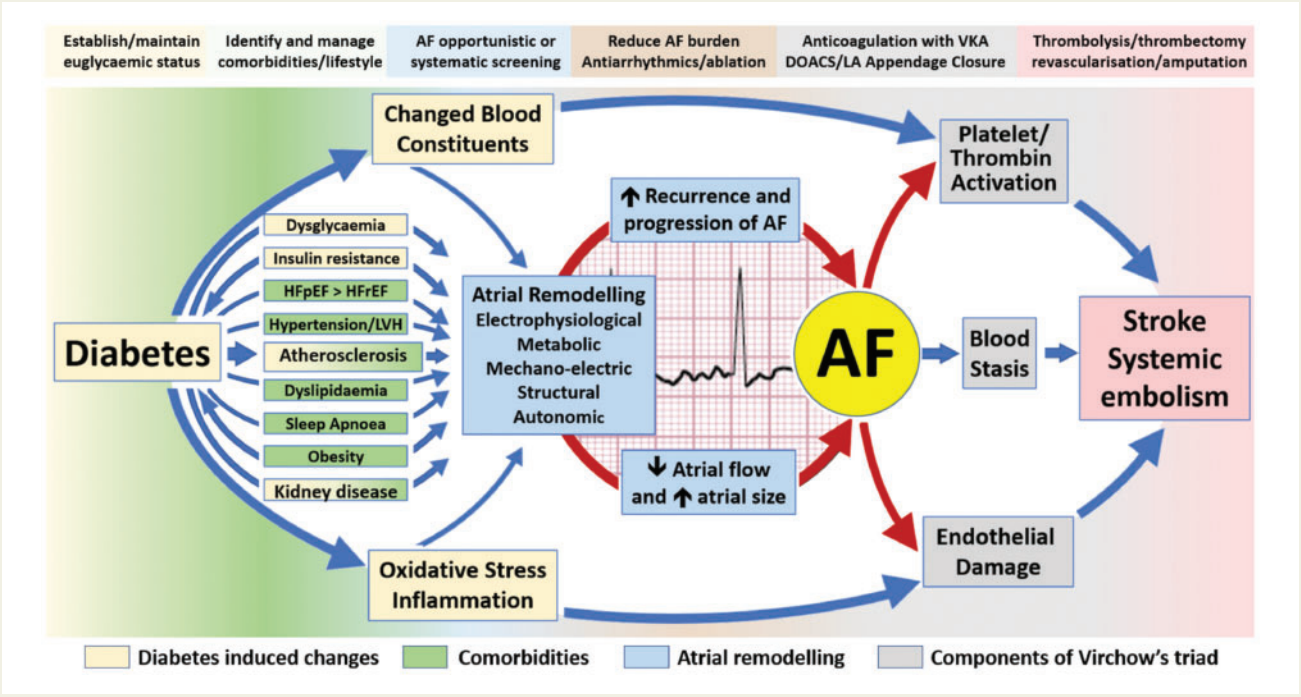


Figure 1 Pathophysiology linking diabetes, AF, and risk of stroke. AF, atrial fibrillation; DOACs, direct oral anticoagulants; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LA, left atrium; LVH, left ventricular hypertrophy; VKA, vitamin K antagonist.

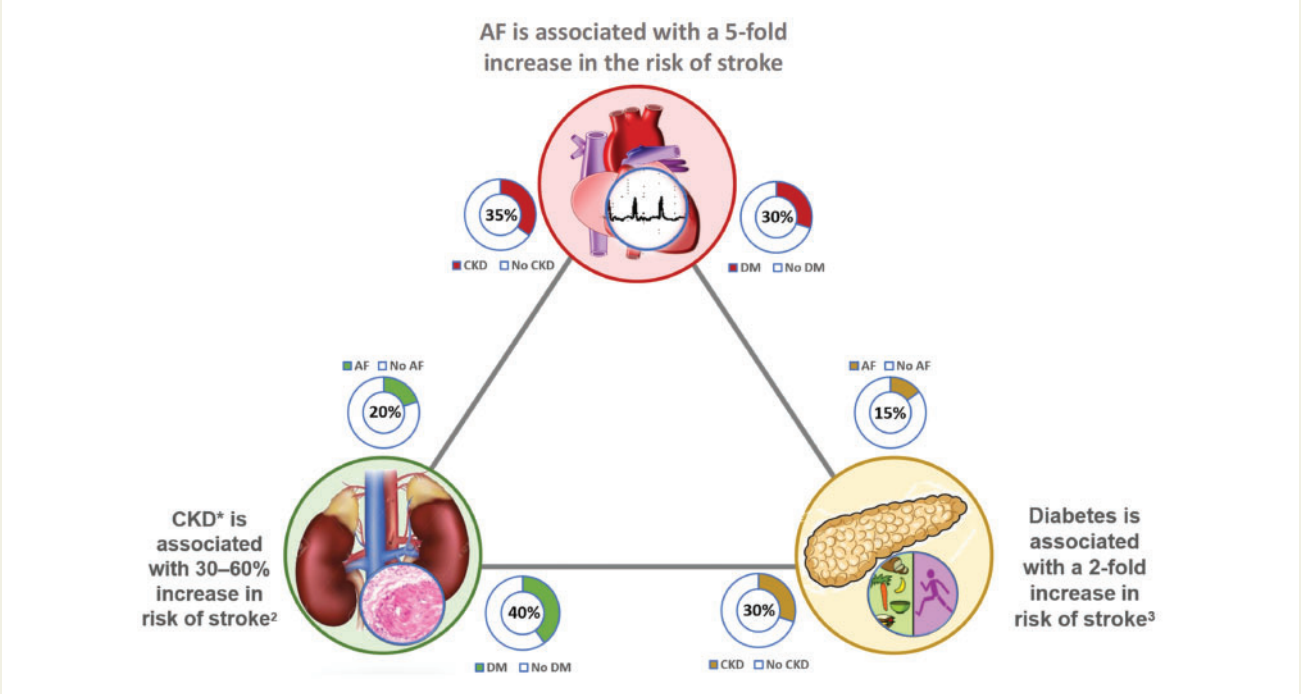


Figure 2 Interplay between atrial fibrillation (AF), diabetes (DM), and chronic kidney disease (CKD) showing the proportion of AF, CKD, and diabetes seen as co-morbidities with each other. For example, about 35% of AF patients have CKD and 30% have diabetes. Percentages vary depending on the definitions of CKD, diabetes, and atrial fibrillation and on specific populations but the figures are reasonable generalizations.[14–16]

higher in diabetic patients due to the common association with other risk factors for stroke, among which the existence of arterial hypertension, an age over 65 or 75, associated vascular disease, or HF. All of them are identified in the items of the Congestive HF, Hypertension, Age [≥75 years; 2 points], Diabetes mellitus, Stroke/transient ischaemic attack [2 points], Vascular disease, Age [65–74 years], Sex category [female] (CHA2DS2-VASc) score. Although there may be some variations in the literature, several studies found that the presence of DM was an independent predictor for stroke in patients with AF.[34] However, DM may not be a significant risk factor for stroke in the elderly.[35] More specifically, the Stroke in AF Working Group attributed a RR: 1.7 (95% CI 1.4–2.0) for stroke in diabetic patients with AF and an absolute stroke risk of 2–3.5%/year in the same population for non-anticoagulated patients.[36] Overall, DM is probably not the most potent independent risk factor for stroke in AF compared to the other items in the CHA2DS2-VASc score, the widely used risk stratifier adopted to guide anticoagulation therapy, but it is included in this risk stratification tool, giving a point as well as for most other items.[37–41]

Beyond the higher risk of mortality and CV events, DM in AF patients is likely to modify symptoms, particularly breathlessness, which is linked to the higher prevalence of obesity and higher risk of HF. However, the adverse effect of DM in AF patients might be related to the possible masking of AF-related palpitations, which can cause a delay in initiation of treatment and therefore poorer outcomes in diabetic patients.[1,42] This characterization of symptoms has been well described in the ORBIT-AF registry with the AF symptom checklist. Compared to AF patients with no DM, those with DM less often reported palpitations (29.2% vs. 33.6%) or syncope (3.3% vs. 4.9%), but they reported significantly more frequent dyspnoea on exertion (29.7% vs. 26.6%) or at rest (11.1% vs. 9.8%), exercise intolerance (11.9% vs. 9.2%), and fatigue (27.9% vs. 25.6%). Although these differences were statistically significant, they may not be obvious from a clinical point of view. Overall, AF patients with DM had worse functional status as reflected by higher European Heart Rhythm Association (EHRA) scores (although % of asymptomatic patients seemed similar) and also had a slightly lower overall quality-of-life scores than those without DM.[31] Diabetes mellitus has also been identified as an independent predictor of AF recurrence after AF ablation.[43] While AF ablation usually reduces palpitations and improves New York Heart Association (NYHA) class in patients without DM, patients with DM may report less improvement of NYHA class despite a reduction of palpitations.[44]

Screening for atrial fibrillation in diabetes

Due to the high prevalence of AF in DM and an estimated development rate of nearly 1%/year, more active screening of diabetic patients for AF may influence therapeutic management. For symptomatic patients with palpitations (or possibly fatigue and dyspnoea) related to persistent or permanent AF, the diagnosis is likely to be made during an outpatient visit or in the hospital if the patient consults emergently. However, AF may also be asymptomatic in 30–50% of cases, as mentioned above. It can be found in different ways: on a conventional 12-lead electrocardiogram at a routine consultation or in hospital, on a 24-h (sometimes 72-h) ambulatory ECG recording, or in a patient with a pacemaker or a defibrillator by analysing the diagnostic functions (used as a simplified long-term ambulatory ECG) during a check in-office or during remote monitoring. Subcutaneously implantable loop recorders with long-term information over 24–36 months have the technical capacity to diagnose symptomatic or asymptomatic AF, but their usefulness is only recognized in most countries for the evaluation of patients with unexplained syncope or for those with ischaemic stroke and no known AF. However, AF detection with an implantable loop recorder in patients with DM may have similar clinical consequences with regard to the need for oral anticoagulation. Nowadays, AF may be detected by consumer devices and wearables that detect an irregular pulse (e.g. photoplethysmography), with the need in these cases to confirm the diagnosis of AF by means of an ECG recording, or by direct recording of an ECG tracing (e.g. using the Apple watch).[41]

Potential advantages and disadvantages of detecting previously undiagnosed AF through screening have been reported in the 2020 European Society of Cardiology (ESC) guidelines for the diagnosis and management of AF.[41] There are currently no specific recommendations on strategies and tools for routinely screening AF in diabetic patients (without known AF) who are asymptomatic, but data are emerging that is consistent on two points:

(1) when DM is associated with other risk factors, in other words when the CHA2DS2-VASc score is high, the risk of developing AF increases during follow-up, is reaching nearly 40% within 2 years in some high-risk subgroups.[45]
(2) simultaneously, in these patients with AF, the annual thrombo-embolic risk increases exponentially, which can reach 8–10% per year.[46,47]

It would seem quite logical on a population scale to systematically seek AF in patients with a CHA2DS2-VASc score of 2 or higher in order to reduce the risk of stroke which is the major complication to be feared in this context. However, this approach has not yet been validated in a randomized study: such a strategy would require extensive screening, and then the treatment of a large group of patients where AF would be detected and then treated with oral anticoagulant for obtaining a possible statistically lower risk of stroke. Such a design would be challenging. However, the ESC guidelines for the management of AF do recommend opportunistic screening for any patient over 65 years and systematic screening for patients at high risk of developing AF.[41] Thus, both opportunistic and systemic screening for AF in diabetic patients is clearly appropriate.

The association between AF and DM appears to be well established at the population level.[5] The causal link between DM and AF needs to be further clarified. Diabetes mellitus associated with AF results in a worse prognosis and several reports or statements from some health authorities indicate that efforts must be made for the prevention of AF, but there is not yet a strong level of evidence that this strategy will result in a significant benefit in terms of morbidity (the most important of which is stroke) or mortality.

Clinical complications in atrial fibrillation with diabetes

The increased risk of cerebrovascular and cardiovascular complications when diabetes and atrial fibrillation coexist

Diabetes mellitus is a disease linked to lifestyle, and therefore usually associated with additional CV risk factors for stroke such as obesity,

hypertension, and dyslipidaemia, thus creating a complex interplay of adverse influences resulting in an increased risk of cerebrovascular events.[48] Both T2DM and T1DM are associated with an increased risk of stroke, even if the risk may be lower in T1DM.[49] In epidemiological studies performed in different populations, the relative risk of stroke in DM ranged between 1.4 and 5.8,[49] being 2.5 for males and 3.6 for females in the 20-year follow-up of the cohort of the historical Framingham study, aged 30–62 years at study entry.[50]

The patterns of strokes associated with DM are different from strokes associated with AF since even if most of the strokes in diabetic patients are ischaemic, and not haemorrhagic, the most common type corresponds to lacunar infarcts (i.e. small 0.2–15 mm, non-cortical infarcts), related to microvascular disease and the coexistence of hypertension.[51] Moreover, the strokes associated with DM have an increased risk of mortality, as well as more stroke recurrences and stroke-related dementia as compared with non-diabetic patients.[49]

In view of the interplay between AF and DM, with around 15% of patients with DM presenting with AF (*Figure 2*), according to data from a meta-analysis on T2DM[9] and around 30% of AF patients affected by DM,[52,53] it is difficult to assess the effects of DM control and antidiabetic drugs on stroke risk in patients with AF. The role of glycaemic control and duration of DM on stroke risk has been object of several investigations. In an analysis based on the Danish National registry, Overvad *et al.*[54] found that duration of DM, when analysed as a continuous variable, was associated with the risk of stroke/thromboembolism in a dose–response-dependent manner but was not associated with a higher risk of bleeding during anticoagulant treatment. In an analysis of a group of patients enrolled in the Anticoagulation and Risk Factors in AF (ATRIA) study, focusing on periods where patients were not anticoagulated,[55] an increased rate of ischaemic stroke was found in a relationship with a longer duration of DM [adjusted hazard ratio (HR) 1.74; 95% CI 1.10–2.76] but no significant relationship with increased HbA1c. The latter finding is in contrast with what was reported by Saliba *et al.*[56] who found a clear dose–response relationship between HbA1c and risk of incident stroke/transient ischaemic attacks, in a relatively short follow-up period (<1 year) (*Figure 3*).

The complexity of the relationship between glycaemic control and stroke risk is highlighted by an additional analysis of the Danish registry[57] where, in patients with incident AF and T2DM, increasing levels of HbA1c were associated with a higher risk of thromboembolism, but this association was not confirmed when DM duration was ≥10 years. Recent data from Taiwan[58] indicate that in diabetic patients with AF the risk of stroke/systemic embolism is significantly increased once HbA1c levels exceed the value of 6.5%, among patients not treated with oral anticoagulants according to guidelines. The risk of major bleeding was comparable across all HbA1c levels categories.

Independently to the extent of glycaemic control, the data from PREFER in AF (European Prevention of Thromboembolic Events–European Registry in AF) showed that the risk of stroke/thromboembolism was the highest in individuals with DM treated with insulin compared with those not treated with insulin (5.2% vs. 1.8%; HR 2.96; 95% CI 1.49–5.87) and compared with non-diabetic patients.[59] Whether this association reflects a causal effect or a clustering of risk factors and long DM duration in patients treated with insulin compared to other glucose-lowering agents is not clear. Apart from insulin, the effects of other drugs for glycaemic control on stroke risk is still object of investigation, with a lower risk of stroke when using metformin[60] and thiazolidinediones.[61]

Beyond stroke, DM is associated with worse outcomes in patients with AF enrolled in contemporary registries.[31] In interpreting these associations, the higher prevalence of persistent and permanent AF, as well as the higher prevalence of HF, CKD, and coronary artery disease (CAD), among patients with DM has to be considered. The worse profile of diabetic patients with AF was also confirmed in EORP-AF (EURObservational Research Programme Atrial Fibrillation) General Registry, where diabetic patients had a higher prevalence of co-morbidities and a higher occurrence of all-cause, CV, and non-CV mortality at 1 year.[62] The reciprocal relationship was also found in DM patients, in whom AF was associated with worse outcomes. In the ADVANCE study, diabetic patients with AF had increased risks of major coronary events, stroke, HF, CV death, and all-cause mortality compared with T2DM patients without AF.[6]

Diabetic retinopathy is a typical microvascular complication of DM and in the Loire Valley AF project[63] crude rates of stroke/thromboembolism increased in a stepwise fashion when patients without DM and with AF were compared with patients with DM with no retinopathy and patients with DM with retinopathy. However, the presence of diabetic retinopathy did not emerge as an independent predictor for stroke/thromboembolism or severe bleeding on multivariate analysis.

Diabetes subtypes, diabetes severity, and the risk of atrial fibrillation

Diabetes mellitus is a heterogeneous chronic metabolic disease that is characterized by hyperglycaemia which may be caused by several different mechanisms, such as low insulin production and/or decreased insulin sensitivity. T1DM (10–15% of cases) often has a young age of onset and is characterized by a lack of insulin production that is associated with autoimmunity, whereas T2DM (80–85% of cases) has an older age of onset and is characterized by abnormally high circulating insulin levels that are associated with obesity-related insulin resistance.[64] Furthermore, additional rare forms of DM exist, which often have a genetic background, such as maturity-onset DM of the young (MODY) and neonatal DM.[65]

The risk for AF has been found increased both for T1DM and TT2DM. The risk in T1DM was studied in a cohort of 36 258 patients with T1DM the Swedish National Diabetes Register, matched with 17 980 controls followed for approximately 10 years.[3] The excess risk of AF in individuals with T1DM increased with worsening glycaemic control and renal complications. Among individuals with normoalbuminuria, no excess risk of AF was noted in men with T1DM who had HbA1c lower than 9.7% (<83 mmol/mol) or in women with T1DM who had HbA1c lower than 8.8% (<73 mmol/mol).

In a similar study of the risk for AF in T2DM, a total of 421 855 patients with T2 DM from the Swedish National Diabetes Register and 2 131 223 controls from the Swedish Population Registry were included and followed for 13 years.[66] In the fully adjusted Cox regression, the risk of T2DM on incident AF was 28% greater vs. controls, HR 1.28; 95% CI 1.26–1.30, $P < 0.0001$. The excess risk of AF in individuals with T2DM increased with worsening glycaemic control and

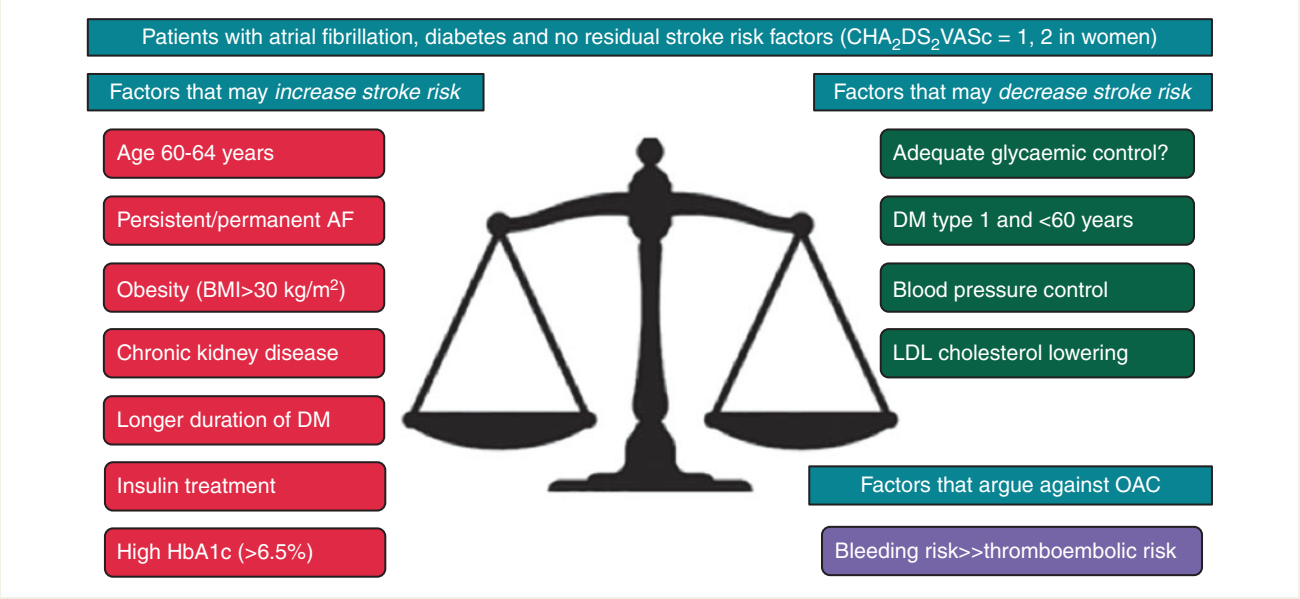


Figure 3 Stroke risk assessment in patient with diabetes and no formal stroke risk factors CHA2DS2-VASc = 1 in men and 2 in women. AF, atrial fibrillation; BMI, body mass index; DM, diabetes mellitus.

renal complications. For individuals with HbA1c ≤ 6.9% (≤ 52 mmol/mol) and normo-albuminuria the excess risk vs. controls was still increased, adjusted HR: 1.16; 95% CI, 1.14–1.19 ($P < 0.0001$).[66]

When applying the CHA2DS2-VASc score to assess risk for stroke in AF the D (diabetes) is simply defined as fasting blood glucose ≥7 mmol/L (or ≥126 mg/dL), or treatment with oral hypoglycaemic drugs and/or insulin.[41] It has been included in the 2020 ESC Guidelines for the diagnosis and management of AF that the excess risk for stroke associated with AF and DM, is very similar in T1DM and T2DM except perhaps for a slightly increased risk in T2DM compared to T1DM in patients <65 years of age.[41] This was based on a study using data from Danish nationwide registries to identify patients with a prior diagnosis of DM and an incident AF diagnosis from 2005 to 2015, who were followed with thromboembolism as the outcome. The study population included 10 058 people with a prior diagnosis of DM and an incident diagnosis of AF. At 3-year follow-up, there was no difference in the risk for thromboembolism in T2DM compared to T1DM, with an adjusted HR 1.15, 95% CI 0.91–1.44. In an age-stratified analysis, patients with T2DM aged below 65 years of age had an adjusted HR 1.97, 95% CI 1.07–3.61 compared to T1DM, whereas there were no differences in the older populations.[67]

In addition to the DM types, DM is heterogeneous with different degrees of target organ damage affecting eye, nerves, and kidney, which affects the associated risk for CV complications.[32,68] The risk for stroke in subjects with DM and AF increases with longer DM duration, as well as with more DM co-morbidities such as nephropathy and retinopathy.[63]

The impact of DM therapy on the risk for AF has been debated (*Figure 4*). It has been suggested that metformin and pioglitazone may reduce the risk for AF.[69] SGLT2 inhibitors compared to placebo were associated with more new-onset AF in EMPA-REG OUTCOME (empagliflozin vs. placebo), but fewer incident AF cases in CANVAS (canagliflozin vs placebo) and DECLARE TIMI-58 (dapagliflozin vs. placebo).[70–73]

In the DECLARE TIMI-58 trial, dapagliflozin reduced the risk of AF/AFL events by 19% (264 vs. 325 events; 7.8 vs. 9.6 events per 1000 patient-years; HR 0.81, 95% CI 0.68–0.95, $P = 0.009$). The reduction in AF/AFL events was consistent regardless of the presence or absence of a history of AF/AFL or atherosclerotic CVD at baseline.[73] These findings were exploratory but are relevant with increasing use of SGLT2 inhibitors in the treatment of T2DM, particularly in the presence of HF or CKD.[74] Glucagon-like peptide-1 receptor antagonists (GLP1-RA) have been investigated in various populations with an increased CV risk, but only a few studies reported new onset of AF with no significant differences when using GLP1-RA.[75,76]

The sub-classification of DM types is more complex than distinguishing just two types. Recently, Ahlqvist *et al.*[77] presented a novel data-driven approach to subclassification. They identified five patient clusters in 8980 adults with newly diagnosed DM. The cluster analysis was based on six preselected parameters: age at diagnosis; body mass index (BMI); presence or absence of glutamate decarboxylase antibodies (GADA) to identify autoimmune DM; glycated haemoglobin A1c (HbA1c) levels to assess glycaemic control; homoeostatic model assessment 2 (HOMA2)-B to assess β-cell function on the basis of C-peptide and glucose concentration; and HOMA2-IR to assess insulin sensitivity. The subtypes has subsequently been confirmed in other studies.[78] In relation to CV complications, the subtypes seem to be important as the severe insulin-resistant diabetes (SIRD) cluster had the highest risk of coronary events (HR 1.76, 95% CI 1.36–2.27) and stroke (HR 1.72, 95% CI 1.20–2.48) compared with the mild age-related diabetes (MARD) cluster,[77] but the importance in relation to AF and stroke risk is not known. Finally, gestational DM defined as glucose intolerance with onset or first recognition during pregnancy, which occurs in approximately 3–4% of all pregnancies, have not as

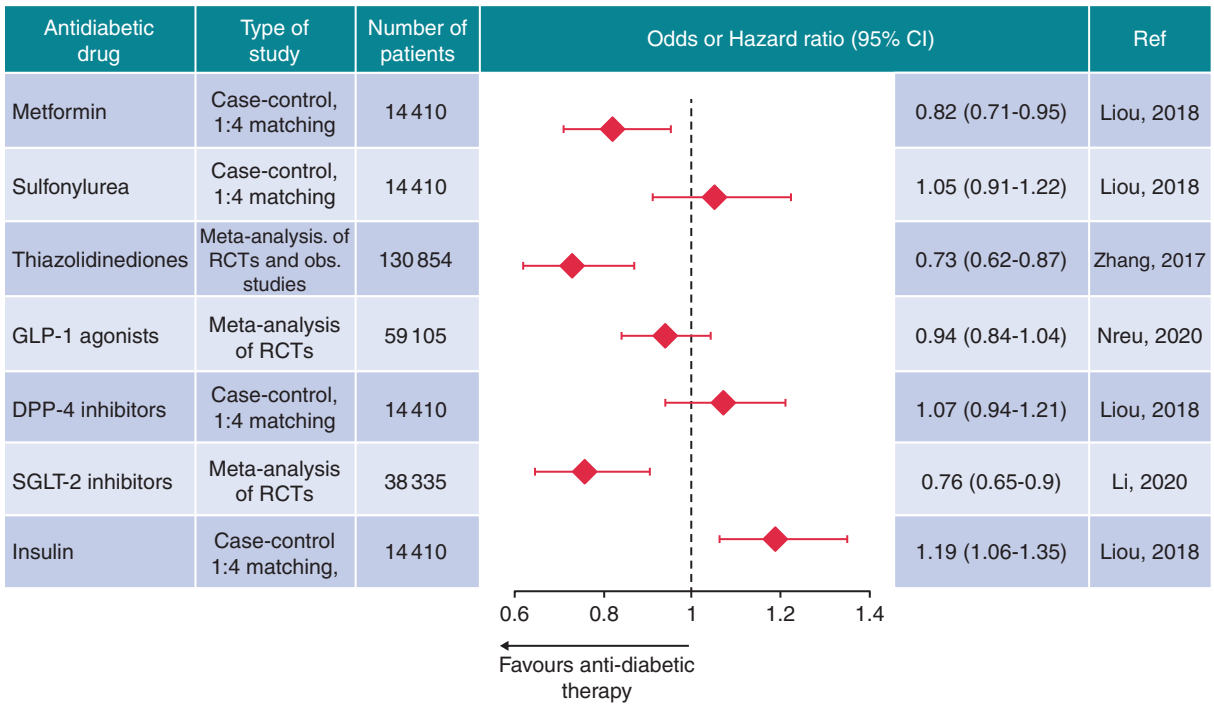


Figure 4 Risk of incident AF with use of glucose-lowering therapies in recent meta-analyses or large observational analyses. AF, atrial fibrillation; CI, confidence interval.

such been linked to AF, but the presence of gestational DM increases the risk for later development of T2DM significantly.[79]

Anticoagulation and its effects on morbidity and mortality (in diabetes with atrial fibrillation)

Treatment with an oral anticoagulant of patients with AF at high risk of stroke leads to a substantial reduction in stroke and systemic embolism (SE).[80] Original data concerned vitamin K antagonists (VKAs), particularly warfarin. It is nowadays universally agreed that the efficacy of anticoagulant therapy is far superior than an antiplatelet agent and aspirin should not be used for the purpose of reducing the risk of AF-associated stroke/SE.[41] Oral anticoagulation is the main part in the 'A' pillar of the 'ABC' AF management ('A': Anticoagulation/Avoid stroke).[41]

Patients with AF can be stratified according to their risk for stroke and systemic embolism. The preferred cardioembolic risk stratification scheme (recommended by the ESC and ACC/AHA guidelines) is now the CHA2DS2-VASc system, particularly to exclude from anticoagulation those at sufficiently low risk of stroke.[41,81] This scoring system includes DM as a risk factor for stroke because the likelihood of developing a thrombo-embolic event is substantially increased in diabetic patients with AF. The use of VKAs in patients with DM is effective in reducing stroke and systemic embolism but anticoagulation control is more difficult to achieve than in non-diabetics [82,83] and adverse bleeding events are more likely in diabetics.

The development of DOACs included evaluation in five pre-approval Phase III randomized controlled trials (RCTs). In four of these, the DOAC was compared with dose-adjusted warfarin: dabigatran in the RE-LY (Randomized Evaluation of Long Term Anticoagulant Therapy) trial, rivaroxaban in the ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial, apixaban in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial and edoxaban in the ENGAGE-AF (Effective aNticoaGulation with factor XA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48) trial. In the AVERROES (Apixaban vs. Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trial, apixaban was compared with aspirin in patients who were unable to use warfarin. In each of the trials comparing a DOAC with warfarin, the results have been reported for the trial as a whole and in a subgroup of diabetic patients (*Figure 5*).

In the RE-LY trial,[84] there were 4221 diabetic patients out of the total of 18 113 patients.[85] Co-morbidities such as coronary disease and peripheral vascular disease were more common in diabetic patients and the rates of stroke, systemic embolism, mortality, and major bleeding were higher. Those treated with dabigatran had a similar relative risk reduction of stroke/SE but absolute risk reductions

were greater in diabetic than non-diabetic patients (dabigatran 110 mg: 0.59% per year vs. 0.05% per year; dabigatran 150 mg: 0.89% per year vs. 0.51% per year).

ROCKET-AF compared rivaroxaban against dose-adjusted warfarin in 14 264 patients in whom the mean CHADS2 score was 3.6.[86] Forty percent of the patients in ROCKET-AF were diabetic patients who were younger and more obese than their non-diabetic counterparts.[87] Stroke, mortality, and major bleeding were more common in diabetic patients but the primary efficacy endpoint (reduction of stroke/SE) and safety endpoints (major haemorrhage) were similar in diabetic and non-diabetic subjects.

A total of 18 201 AF patients with a mean CHADS2 score of 2.1 were recruited to the ARISTOTLE trial. There were 4547 (24.9%) patients with DM and a higher average CHADS2 score (2.9) in ARISTOTLE.[88] Compared with the whole trial population, diabetic patients treated with apixaban had significantly lower rates of death (HR 0.83, 95% CI 0.67–1.02), stroke/SE (HR 0.75, 95% CI 0.53–1.05), and major haemorrhage (HR 0.49, 95% CI 0.25–0.95).

ENGAGE AF TIMI-48 enrolled 21 105 patients at a moderate-to-high risk of stroke (CHADS2 2.8).[89] In the diabetic subgroup analysis of 7624 diabetic and 13 481 non-diabetic subjects, the diabetic patients were younger, more obese and had a higher CHA2DS2-VASc score than the non-diabetic. There was no difference in efficacy between diabetic and non-diabetic patients. However, the risk of major bleeding was greatest in insulin-dependent diabetic patients. Similarly, there was no statistically significant interaction concerning major safety endpoints. However, since the risk of stroke/SE and major bleeding were higher in the diabetic patients, the absolute risk reduction associated with edoxaban treatment was greater in diabetic compared with non-diabetic patients. Cardiovascular deaths and major bleeding were reduced in both diabetic and non -diabetic patients to a similar extent in the higher dose subgroups ($P > 0.0.05$).[90]

The AVERROES trial was terminated early, after the recruitment of 5599 patients because of the obvious efficacy of apixaban when compared with aspirin.[91] The patients in the trial included 1098 (19.5%) with DM but there has been no analysis of this subgroup except that DM remained a significant risk factor for stroke in those who were treated with apixaban (HR 2.15, 95% CI 1.00–4.35; $P = 0.05$).[92]

The results across all four DOAC vs. dose-adjusted warfarin trials have been the subject of several meta-analyses. Ruff and colleagues provided an analysis of these trials consisting of 42 411 participants who received a DOAC and 29 272 who received warfarin. When considering patients who received the higher dose in the four DOACs (RE-LY, dabigatran 150 mg b.i.d; ENGAGE-AF–TIMI 48, edoxaban 60 mg o.d.; ROCKET-AF, rivaroxaban 20 mg o.d. and ARISTOTLE, apixaban 5 mg b.i.d.) stroke/SE was reduced by 19% (HR 0.81, 95% CI 0.73–0.91; $P < 0.0001$) in those who received a DOAC and major bleeding and mortality were also reduced by 14%, $P = 0.06$ and 10% respectively ($P = 0.0003$). In this group, there were 40 454 non-diabetics and 18 086 with DM and the risk reduction for stroke/SE seen with DOAC treatment was similar for both groups (P-int = 0.73) and for major bleeding (P-int = 0.12).[93]

The diabetic subgroups of these trials have also been accumulated in a metanalysis.[94] In the higher dose groups ($n = 58\,634$), there were similar relative risk reductions for both stroke/SE (DM HR 0.80, 95%

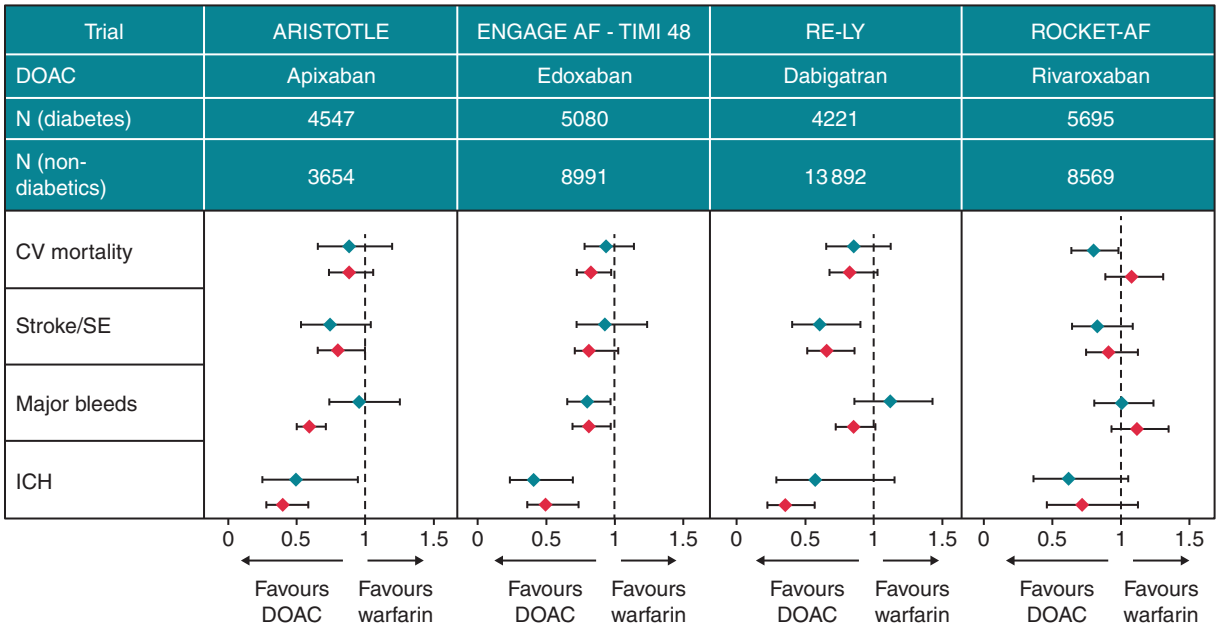


Figure 5 Hazard ratios with DOACs compared to warfarin in patients with atrial fibrillation according to the presence of diabetes (blue symbols) or not (red symbols) in four randomized controlled trials. CV, cardiovascular; DOAC, direct oral anticoagulants; ICH, intracranial haemorrhage; SE, systemic embolism.

CI 0.69–0.93; non-DM HR 0.80, 95% CI 0.69–0.93, *P*-int = 0.81) and major haemorrhage (DM HR 0.95, 95% CI 0.75–1.20; non-DM HR 0.83, 95% CI 0.55–1.24; *P*-int 0.37) associated with DOAC treatment. When individual DOACs were considered, there was no significant difference for stroke/SE reduction, but for major bleeding with apixaban, there was a trend towards a more pronounced reduction of bleeding in non-diabetic patients in ARISTOTLE (*P*-int ≤0.1).[95] In the four pivotal DOAC trials, Patti *et al.*[96] observed that vascular death rates were reduced in diabetic patients with DOAC treatment compared with warfarin (4.97% vs. 5.99% with warfarin; RR 0.83, 95% CI 0.72–0.96; *P* = 0.01), but not in non-DM, probably because the absolute death rate reduction was higher in the diabetic than in non-diabetic patients (1.02% vs. 0.27%).

In a further meta-analysis, Plitt *et al.*[97] also showed that in comparison to warfarin DOACs reduced both CV death and intracranial haemorrhage similarly in both diabetic and non-diabetic subjects. This analysis also emphasized that dabigatran was the only DOAC to significantly reduce stroke/SE in diabetic and non-diabetic subjects alike and edoxaban was the only DOAC to significantly reduce major bleeding in patients both with and without DM. From their analysis, they also pointed out that although diabetic patients treated with insulin had higher rates of bleedings and stroke/SE both rivaroxaban and edoxaban were effective in reducing these outcome events in insulin-dependent and non-dependent patients, but data for dabigatran and apixaban were lacking.

In addition to data from RCTs, several reports have appeared based on large registries. Any comparisons made from registry data require adjustments to balance confounding factors between groups that are compared but residual confounders may also be present that will potentially confuse the data as will many other biases in the data. Nevertheless, information from these so-called 'real-world' settings are valuable to assess risks and outcomes in non-clinical trial situations and to confirm or question differences between treatments or interventions previously studied in more formal trial environments. Registry data have generally confirmed the results from RCTs and the results of some selected studies are summarized below.

Hsu *et al.*[98] used propensity weighting to compare diabetic patients taking DOACS rivaroxaban (*n* = 320) or dabigatran (*n* = 322) with patients taking warfarin (*n* = 1899) using data from the Taiwan National Health Insurance Research Database. The results were very similar to the relevant RCT. Rivaroxaban was similar to warfarin. Compared with warfarin, dabigatran decreased the risk of all-cause mortality (HR 0.348, 95% CI 0.157–0.771) and gastrointestinal bleeding (HR 0.558, 95% CI 0.327–0.955). Interestingly, Korgaonkar *et al.*,[99] who studied elderly patients with AF and DM from the Medicare database—2291 propensity-matched pairs of who were taking warfarin or one of the four approved DOACs also confirmed the interesting observation that DOAC use was not associated with more major GI bleeding when compared to warfarin.

The largest observational study of anticoagulation in diabetic patients (*n* = 154 324) was recently reported by Lip *et al.*[100] who compared warfarin with three DOACs. Lower risk of stroke was seen with apixaban (HR 0.67, 95% CI 0.57–0.77) and rivaroxaban (HR 0.79, 95% CI 0.71–0.89) whereas dabigatran was associated with a similar risk of stroke (HR 0.84, 95% CI 0.67–1.07), both apixaban (HR 0.60, 95% CI 0.56–0.65) and dabigatran (HR 0.78, 95% CI 0.69–0.88) were associated with a lower risk of major bleeding but rivaroxaban (HR 1.02, 95% CI 0.94–1.10) was associated with a similar risk of bleeding when compared with warfarin. Cohorts were compared through propensity score matching, there were potential residual confounders and only statistical associations could be concluded, not causal relationships.

Baker *et al.* used MarketScan data to study 10 700 diabetic patients taking rivaroxaban and compared them to a matched group of 13 946 warfarin users. In addition to endorsing previous findings related to the reduction of MACE associated with DOAC use they also found that major adverse limb events were very reduced by treatment with rivaroxaban rather than with warfarin. The studied population was relatively high risk (CHA2DS2-VASc = 4) and 11% had peripheral artery disease. Rivaroxaban was associated with a 25% reduction in MACE and a 63% reduction of major limb adverse events, including an 80% reduction of major limb amputation (HR 0.20, 95% CI 0.06–0.69)[101] (*Figure 6*). The mechanism whereby rivaroxaban might reduce adverse limb events may be a reduction in AF-related systemic arterial embolization, allowing activation of matrix proteins that inhibit vascular calcification or counteracting atherothrombotic effects of DM.

Chan *et al.* extended this observation using data drawn from the Taiwan National Health Insurance Research Database. In this study of diabetic patients, 5812 taking warfarin were compared, using propensity weighting, with 20 967 patients taking a DOAC. Major adverse limb events (MALE) were 28% less in patients taking a DOAC (aHR 0.72, 95% CI 0.57–0.92; *P* = 0.0083) (*Figure 6*). Interestingly the advantage associated with DOAC treatment persisted in patients also taking antiplatelet drugs.[102] In this study, the favourable effect on limb events was not confined to rivaroxaban but seemed to apply to all four DOACs. Controlled trial data are needed to clarify the effect of DOACs in general and each DOAC in particular on limb amputation, etc. but none is yet available.

There is some limited vascular outcome data in the setting of a RCTs post-acute coronary syndrome/revascularisation. In the RE-DUAL (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran vs. Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) trial setting, 2725 patients with AF of whom 993 had DM, dabigatran plus clopidogrel or ticagrelor, compared with conventional triple therapy, was equally effective at reducing bleeding and had comparable efficacy endpoints in diabetic and non-diabetic patients post angioplasty.[103] However, this trial was not designed to demonstrate effects specifically in diabetic patients and was underpowered for this purpose.

In a large meta-analysis, Abdool *et al.* added four observational studies to the results of randomized DOAC vs. warfarin trials to bring the total number of patients in their pooled analysis to 147 943. They confirmed previous observations that there was no interaction between DM status and adverse outcomes and added that absolute risk reduction was more in diabetic patients because of their higher untreated adverse outcome risk.[104]

Diabetic patients very often have some degree of renal impairment and frank CKD. Both DM and CKD share common aetiologies and DM is the single biggest cause of CKD. Diabetes mellitus increases the likelihood of stroke, major bleeding, and mortality in patients with AF, and CKD amplifies these risks. There is clear evidence from

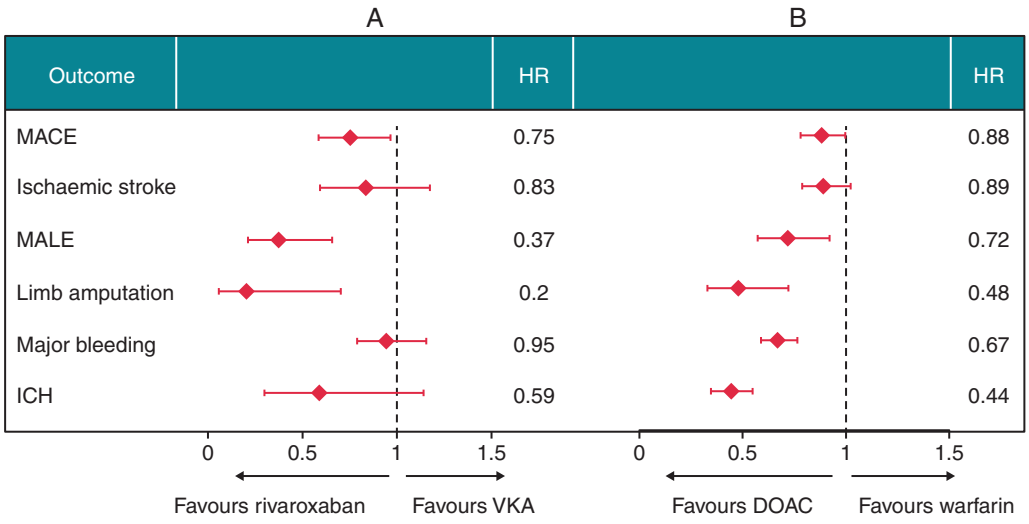


Figure 6 Effectiveness, safety, and major adverse limb events in large databases of AF patients with concomitant diabetes mellitus treated with direct oral anticoagulants or vitamin K antagonists. (*A*) Baker *et al.*; (*B*) Chen *et al.* DOAC, direct oral anticoagulants; ICH, intracranial haemorrhage; MACE, major adverse cardiovascular events; MALE, major adverse limb events; VKA, vitamin K antagonist.

numerous studies that for mild and moderate CKD, DOAC therapy is at least non-inferior to and in many instances superior to dose-adjusted warfarin. Recently, a flurry of observational studies and at least one RCT (RE-LY) have raised the possibility that renal function may be progressively impaired when VKA therapy, as opposed to DOAC treatment, is prescribed.[105–107] Observational evidence also exists that AF patients with DM in addition to CKD can also be protected from progressive renal impairment by avoiding a VKAs and in favour of DOAC therapy (*Figure 7*).[108]

Since DM is part of most risk scoring schemes used to decide which patients with AF should be anticoagulated many diabetic patients do receive anticoagulation. However, because DM is probably the strongest of the individual risk factors allocated one point in the CHA2DS2-VASc score, one may advocate anticoagulating every diabetic patient with AF, especially when DM has been present for some time or is associated with an uncontrolled glycaemic status. Of course, those jurisdictions where the CHADS2 score is still in use, at least in part—for example, in Canada and Japan, most diabetic patients with AF are recommended for anticoagulation.

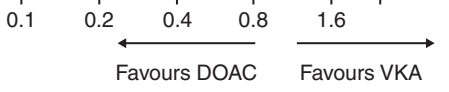
All the data suggest that when comparing dose-adjusted warfarin to DOAC therapy there is a similar relative risk reduction for all major efficacy outcomes including all-cause mortality, (cardio)-vascular mortality, life-threatening bleeding, and intracranial haemorrhage in the diabetic and non-diabetic populations.[97,104] Because of the increased risk rate for these adverse events in diabetic patients a similar relative risk reduction generally translates into greater absolute risk reduction in the diabetic population.[104] As with non-diabetic patients, major bleeding and major gastrointestinal bleeding associated with different DOACs compared with warfarin seem to vary similarly in diabetic patients. For these reasons and because RCTs show better results with DOACs, DOAC drugs are preferable to VKAs for stroke prevention in DM as for the general population of at-risk AF patients.

There have been some observations suggesting differences between DOACs, such as the statistically significant reduction in vascular mortality associated with the use of rivaroxaban in diabetic patients and the far greater reduction of major bleeding seen with apixaban when used in non-diabetic rather than diabetic patients (*Figure 5*).[94,95,97] However, there is no head-to-head comparison between the different DOACs and even when pooling data from controlled trials and observational studies there is insufficient evidence to distinguish between DOACS concerning their suitability for the management of patients with AF and DM.

There is considerable speculation that DOAC treatment might suppress atrial fibrosis and collagen deposition induced by hypercoagulability.[109] Currently observational registries (e.g. RACE 5) and randomized clinical trial (e.g. ARTESiA [NCT01938248] and NOAH-AFNET 6 [NCT02618577]) are exploring whether AF will develop, recur or progress as quickly in patients treated with DOACS rather than VKAs. There is no conclusive data at present. Conversely, a recent registry study involving 10 746 patients with recent-onset AF reported that the development of diabetes was far less probable in the DOAC treated group than in those treated with VKAs (aHR 0.80, 95% CI 0.68–0.94; $P = 0.007$). This difference was seen with rivaroxaban, apixaban, and dabigatran, and was most obvious in patients older than 65 years and in those with good adherence to treatment.[110] This study could not demonstrate a causal relationship between treatment with a VKA and more development of diabetes but such an effect might relate to an increase of vitamin K-dependent osteocalcin which is known to stimulate insulin and adiponectin.

The recent revelation that diabetic AF patients treated with rivaroxaban, and possibly other DOACS, rather than warfarin are far less likely to suffer from major adverse limb events, including major amputation, adds to the conviction that DOAC treatment is far preferable to the use of VKAs in DM. Since CKD is a frequent comorbidity in patients with AF and DM and that treatment with a VKA leads to

Outcome	DOAC	Number of patients		HR (95% CI)	HR (95% CI)
		VKA	DOAC		
Progression to stage 5 CKD *	Rivaroxaban	11 665	10 017		0.82 (0.70-0.96)
Progression to stage 5 CKD **	Rivaroxaban	3160	746		0.50 (0.30-0.83)
Progression to stage 5 CKD ***	Rivaroxaban	8545	6887		0.32 (0.19-0.53)
Progression to stage 5 CKD ***	Apixaban	8545	5438		0.60 (0.40-0.89)
Acute kidney injury *	Rivaroxaban	11 665	10 017		0.83 (0.74-0.92)
Acute kidney injury ***	Rivaroxaban	8545	6887		0.72 (0.53-0.97)
Acute kidney injury ***	Apixaban	8545	5438		1.07 (0.82-1.41)
Acute kidney injury ***	Edoxaban	8545	865		0.56 (0.23-1.37)



*Hernandez AV et al. Eur Heart J Qual Care Clin Outcomes 2019; pii: qcz047.
** Vaitsiakhovich T et al, presented at ESC 2019
*** Bonnemeier H et al. Presented at ESOC 2019, Milan, Italy, AS25-069.

Figure 7 Comparison of the progression of chronic kidney disease (CKD) to Stage 5 CKD/haemodialysis or development of acute kidney injury in atrial fibrillation patients treated with a direct oral anticoagulants (DOAC) or vitamin K antagonist (VKA). CI, confidence interval; HR, hazard ratio.
*Hernandez AV et al. Eur Heart J Qual Care Clin Outcomes 2019; pii: qcz047
**Vaitsiakhovich T et al. Presented at ESC 2019
***Bonnemeier H et al. Presented at ESOC 2019, Milan, italy, AS25-069

further progression of renal impairment, stroke prevention with DOAC therapy seems eminently preferable to the use of VKAs.

Beyond macrovascular complications of atrial fibrillation with diabetes: heart failure and chronic kidney disease

Mechanisms, risks, and optimal management of patients who have or are at risk of developing heart failure

The first letter 'C' representing congestive HF in the CHA2DS2-VASc score, highlights the predictive role of HF for stroke risk in AF which is particularly important in diabetic patients who are at increased risk for both stroke and HF.[28,41] The prevalence of DM in HF patients is about 30–40% and similar in HF with reserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF).[28,111,112] Patients with DM are at higher risk of developing HFrEF or HFpEF[28] and the risk increases with age.[113–115] Conversely, HF itself is a risk factor for the development of DM,[116] most likely related to insulin resistance.[28] The presence of HF results in a higher risk of HF hospitalization, CV death, and all-cause death in patients with DM,[6,28] with the strongest predictive value of DM seen in patients with HFrEF.[28] At the time of new-onset AF, patients with DM are at increased risk for developing acute HF due to the loss of atrial kick and impaired LV filling.[117] AF and acute HF frequently coexist and can exacerbate each other.[118] In acute HF, the risk is magnified by the presence of DM, because the DM will significantly increase short-term risk including in-hospital death and risk for rehospitalization due to HF and all-cause death within 1 year.[117,119,120]

In addition to the direct detrimental effect of insulin resistance and hyperglycaemia on LV dysfunction, major risk factors promoting the development of HF in DM are CAD, CKD, and hypertension.[28] LV diastolic dysfunction is frequent in DM and already observed in patients with pre-diabetes as it shows a strong correlation with insulin resistance and hyperglycaemia.[28,121] Heart failure with reserved ejection fraction represents the most frequent form of HF in DM (about 75%) and its prevalence is higher in older, female, and hypertensive patients with DM.[122] Guideline-directed medical treatment and device therapies for HF are equally effective in patients with and without DM as shown in RCTs in which on average about 30–40% of patients had DM.[28]

Beta-blockers play *per se* an important role for rate and symptom control in patients with AF.[41] They are the main part in the 'B' pillar of the 'ABC' AF management ('B': better symptom control with rate or rhythm control therapies)[41] and fully relevant for rate control in AF patients with DM. Interestingly, while their treatment benefits strongly support their general use also in patients with HFrEF and DM in sinus rhythm,[28,41] their prognostic benefit in patients with AF has been questioned.[123] In patients with acute HF, beta-blockers should be cautiously initiated in the hospital, once the patient is stabilized.[124]

Non-dihydropyridine calcium channel blocker (verapamil or diltiazem) can be used as an alternative to beta-blockers for rate control in AF patients and for treatment of hypertension in patients with or without HFpEF, but their use is contraindicated in patients with HFrEF.[41,124] In addition, due to their inhibitory effect on of P-glycoprotein and the cytochrome P 450 3A4 enzyme, drug interactions between verapamil

and diltiazem with DOACs should be considered. They could lead to higher drug levels of DOACs and thus increased bleeding risk.[41,125,126] Among patients with permanent AF and symptoms of HF, low-dose digoxin may also be used considering that this may result in a similar quality of life at 6-months than with bisoprolol.[127]

For several decades, the available evidence from clinical studies indicated that glycaemic control in DM with glucose-lowering therapies had, if anything, only moderate beneficial effects on macrovascular endpoints and on the risk for HF-related outcomes.[128] However, the clinical development of SGLT2 inhibitors and glucagon-like peptide 1 receptor agonists during recent years, with the completion of several important CV outcome trials resulted in fundamental changes.[28,74]

Particularly, the SGLT2 inhibitors have been shown to significantly lower the risk for hospital admissions for HF in T2DM patients at high CV risk.[70–72,129,130] The risk reductions for HF hospital admission were consistent and in the range of 27–39% in these trials. However, the prevalence of patients with AF in these studies was relatively low or originally not reported.[70–72,129,130] Nevertheless, a dedicated *post hoc* study compared patients with AF at baseline ($n = 389$) and patients without AF ($n = 6631$) in the EMPA-REG OUTCOME trial.[131] This analysis demonstrated that empagliflozin compared to placebo reduced CV death or HF hospitalization consistently in diabetic patients with AF (HR 0.58, 95% CI 0.36–0.92) and without AF (HR: 0.67, 95% CI 0.55 to −0.82, *P*-int = 0.56).[131] Of interest, the absolute number of prevented events was higher in patients with AF, resulting in larger absolute treatment effects of empagliflozin.

A subgroup analysis investigating the impact of AF (about 38% of the study population) is available in DAPA-HF.[132] It showed in patients with AF at baseline a somewhat weaker protective effect (HR 0.82; 95% CI 0.63–1.06) compared to patients without AF (HR 0.72; 95% CI 0.61–0.84) on the primary composite outcome of worsening HF or CV death.[132] This analysis included, however, both HFrEF patients with and without DM as enrolled in DAPA-HF. Thus, more dedicated analyses on the effects of SGTL2 inhibitors in diabetic patients with AF are needed. More recently, however, a study investigating the effect of the combined SGLT2 and SGLT1 inhibitor sotagliflozin in patients with DM and a history of recent worsening of HF, confirmed the protective effect of this treatment approach.[133] In this trial, a subgroup analysis showed in patients with AF/atrial flutter ($n = 576$, HR 0.68, 95% CI 0.48–0.95) a similar risk reduction as compared to patients without AF/atrial flutter ($n = 646$, HR 0.69, 95% CI 0.49–0.97) for the primary composite outcome of the total number of deaths from CV causes and hospitalizations and urgent visits for HF.[133]

Mechanisms, risks, and optimal management of patients who have or are at risk of developing chronic kidney disease

Diabetic kidney disease

In addition to being a risk factor for the development of AF and for complicated stroke in the presence of AF, DM is associated with an increased risk for the development of kidney disease. On average 30–40% of patients with DM develop diabetic kidney disease or CKD in DM, with increasing albuminuria and declining renal function as well as increased risk for CV disease.[32] Diabetes mellitus is the leading cause of kidney failure in most parts of the world accounting for up to 50% of kidney failure, but the majority of patients with DM and CKD die from CV events before reaching kidney failure.

There seems to be a familial disposition for diabetic kidney disease, and many genetic variants have been associated with diabetic kidney disease, although major single-gene effects have not been demonstrated.[134,135] In addition to hyperglycaemia, risk factors for CKD in DM include hypertension and smoking (*Figure 8*). Markers of risk also include oxidative stress, endothelial dysfunction, inflammation, uric acid, and dyslipidaemia.[136]

Comprehensive management of CKD in DM includes lifestyle factors such as exercise, a healthy diet with a focus on protein intake and salt, and smoking cessation is important. For the kidney as well as the CV risk, management of blood pressure with blockade of the renin-angiotensin-system (RAS), including use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), as well as lipid control and glucose management is important.[137]

In T2DM, SGLT2 inhibitors are recommended for their protective effect on kidney function.[138] They also have beneficial effects on CV disease and HF as seen in the dedicated kidney studies CREDENCE (Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy) with canagliflozin[72] and DAPA-CKD with dapagliflozin,[139] including patients with urinary albumin creatinine ratio from 200 mg/g creatinine and eGFR from 25 to 90 mL/min/1.73 m^2.

As mentioned in Mechanisms, risks, and optimal management of patients who have or are at risk of developing heart failure section, in a *post hoc* analysis the SGLT2 inhibitor dapagliflozin reduced the incidence of AF in the DECLARE TIMI 58 study, which was a CV outcome study in T2DM with previous CVD or risk factors for CVD.[73]

Anticoagulation-related nephropathy

In patients with AF and CKD treated with anticoagulants, there is an increased risk of bleeding, but there are also concerns about the risk of anticoagulation-related nephropathy (*Figure 9*).[140] The latter is a newly recognized form of acute kidney injury in which over-anticoagulation causes profuse glomerular haemorrhage, which manifests on renal biopsy as numerous renal tubules filled with red cells and red cell casts. The glomeruli show changes, but they are not sufficient to account for the glomerular haemorrhage.[140]

Although anticoagulation-related nephropathy (*Figure 9*) may develop in response to any anticoagulant including VKAs and DOACs, it has been particularly associated with overdosing of warfarin with International Normalized Ratio (INR) levels >3.[140] Older patients with DM and diabetic kidney disease are particularly prone to develop anticoagulation related nephropathy that may trigger episodes of acute kidney injury more frequently in AF patients than previously thought.[140,141] These acute kidney injury episodes can in turn accelerate the progression of CKD and are associated with an increased mortality rate.[142]

Both DM and CKD increase the risk of stroke and other CV complications in patients with AF and as discussed in the other sections DOACs are preferred to VKA. In patients with significantly impaired renal function (CrCl < 30 mL/min) a reduced dose of rivaroxaban, apixaban, or edoxaban is recommended in patients with a CrCl between 15–30 mL/min, but patients with a CrCl <25–30 mL/min were

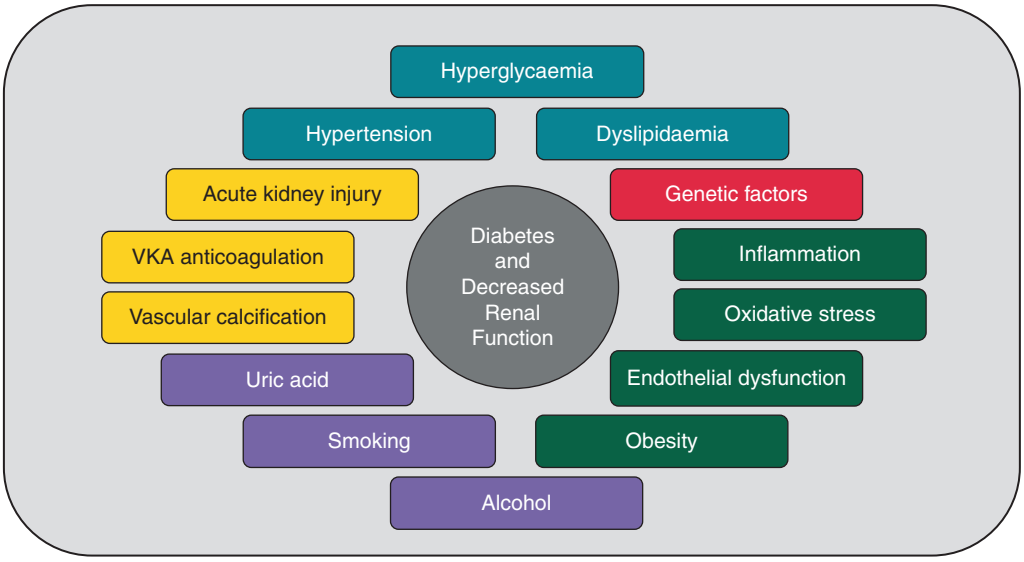


Figure 8 Factors potentially responsible for the high prevalence of chronic kidney disease in diabetic patients.

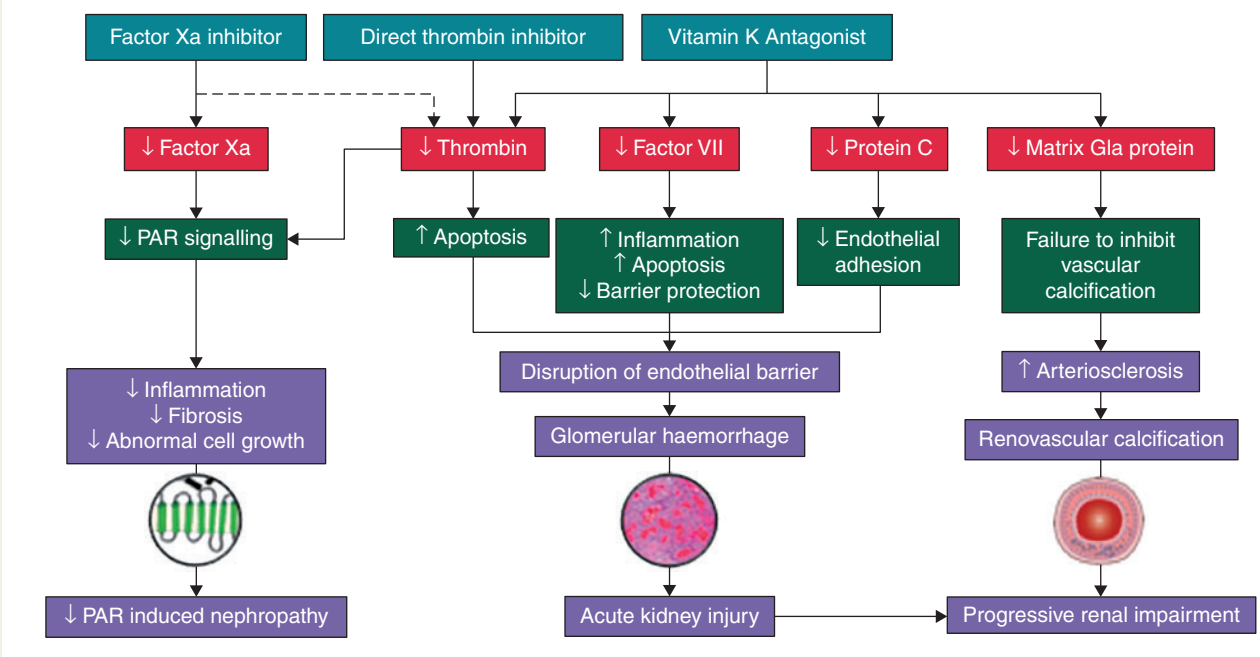


Figure 9 Possible mechanisms for changes in renal function in patients treated with anticoagulants. PAR, protease-activated receptors. [a]Dose dependent/or during low sustained activation.

not included in the randomized trials. The FDA approved a low 75 mg bid dose of dabigatran for patients with a CrCl <30 mL/min, available in the USA, but it has not been tested in a prospective trial, and it is not approved for use within Europe. Vitamin K antagonist has been suggested if time in therapeutic range (TTR) > 70% but harm may exceed benefit with increased risk for bleeding, anticoagulation-nephropathy, and vascular calcification. Until ongoing studies clarify the optimal anticoagulation strategy in severe kidney disease, this has to be based on individual assessment of risk and benefits.

Vascular calcification theory

Diabetes mellitus and CKD share complementary pathophysiology for increased vascular calcification processes[143,144] which may contribute to declining renal function in patients with DM and CKD. In addition to glucose-related pathways in DM, further factors

related to CKD such as disturbance in calcium–phosphate balance, accumulation of uraemic toxins, and severe vitamin K deficiency have been implicated in the pathogenesis of vascular calcification. In anticoagulated AF patients and particularly in patients with comorbid diabetic kidney disease, the use of VKAs may aggravate vascular calcification[145] including calcification in the vascular bed of the kidney and thereby contribute to worsening renal function in these patients (*Figure 9*).[146,147] This is mechanistically based on inhibition of the vitamin K-dependent gamma-glutamyl carboxylation that applies not only to the clotting factors II, VII, IX, and X but also to the other vitamin K dependent gamma-carboxyglutamic acid (Gla) proteins including the matrix Gla protein.[144,148] Matrix Gla protein represents the most potent endogenous protector against vascular calcification and its diminished function has been linked to vascular calcification during VKA treatment.[148] In contrast, DOACs, such as the factor Xa inhibitor rivaroxaban, due to their different mode of action do not only lack this negative effect but may even provide beneficial protective effects against vascular injury and renal functional decline by decreasing vascular inflammation, remodelling, and vascular calcifications through reduced protease-activated receptor (PAR) signalling via PAR-1 and PAR-2 (*Figure 9*).[149,150]

In accordance with this, observational studies of subjects with AF treated with VKAs vs. DOACs found more progression of kidney disease (development of CKD Stage 5, i.e., eGFR < 15 mL/min/1.73 m^2 or need for kidney replacement therapy) with VKAs than DOACs. Thus, a recent study using USA IBM MarketScan data included patients with AF and DM that were newly initiated on rivaroxaban ($N = 10\ 017$) or warfarin ($N = 11\ 665$).[106] Patients were matched using propensity scores. In comparison to warfarin, rivaroxaban was associated with lower risks of acute kidney injury events (HR 0.83, 95% CI 0.74–0.92) and development of Stage 5 CKD or need for haemodialysis (HR 0.82, 95% CI 0.70–0.96). The protective effect in favour of rivaroxaban was particularly pronounced in the subgroup of diabetic patients with pre-existing Stages 3–4 CKD for both acute kidney injury (HR 0.63, 95% CI 0.49–0.79) and the risk of stage 5 CKD or need for haemodialysis (HR 0.66, 95% CI 0.46–0.94).[106] A similar retrospective study on data from a claims database in Germany found the relative risks for acute kidney injury was decreased by 28% (HR 0.72, 95% CI 0.53–0.97) and for kidney failure by 68% (HR 0.32, 95% CI 0.19–0.53) in AF patients with DM prescribed rivaroxaban vs. phenprocoumon.[151] These observational findings should be confirmed in prospective randomized controlled trials.

Kidney function monitoring

Due to the high risk for kidney disease, screening for this complication is mandated in the regular Follow-up of all patients with DM, with annual measurements of urine albumin excretion (urinary albumin to creatinine ratio in morning spot urine) and assessment of renal function (estimated glomerular filtration rate eGFR) and control of blood pressure. The lower the kidney function, the more frequent it should be measured, and for renal function below 60 mL/min/1.73 m^2, it has been proposed that measurements are performed with monthly intervals corresponding to kidney function/10 (e.g. every 4 months when creatinine clearance is 40 mL/min).[125] In diabetes with a fast decline in kidney function even more frequent measurements may be needed. Monitoring of renal function and electrolytes (e.g. hyperkalaemia), is clinically important in patients with AF and DM receiving anticoagulation therapy, because declining kidney function increases the risk for bleeding, and the dose of anticoagulants with renal clearance, i.e., DOACs, should be adjusted according to the level of kidney function.[41, 125] In the trials comparing DOACs with VKAs, kidney function was evaluated as creatine clearance estimated from creatinine, sex, age, and weight using the Cockcroft and Gault equation (mL/min) (not standardized for body surface area).[152] Therefore, it is recommended to use creatinine clearance (CrCl) when adapting dose of anticoagulation therapy with DOACs.

Benefits of medical therapies put into perspective

Sub-analyses with respect to patients with and without DM have been performed of all the four Phase 3 DOAC trials.[153] A meta-analysis of these trials demonstrated that DOACs reduce the risk of stroke/SE in patients with DM to a similar extent as in patients without DM. There was no significant modification of the effect of DM on the relative reduction of major bleeding with DOACs vs. warfarin. CV mortality and intracranial haemorrhage were significantly and to a similar extent reduced by DOACS in both the presence or absence of DM.[97] There are however important differences in patient characteristics between the trials.

The proportion of patients with DM in the four Phase 3 DOAC trials studies were between 23.3%, and 39.9%.[84,86,89,154] Patients with DM were on average 0.8–3 years younger than patients without DM, and had a higher CrCl. The CHA2DS2-VASc scores of the included patients importantly differ between trials. In RELY and ARISTOTLE, these differed more than one point between patients with and without DM. Given the fact that DM is one of the determinants of the CHA2DS2-VASc score, the overall risk of stroke with the exclusion of DM was slightly higher in the patients with vs. without DM in RELY and ARISTOTLE.[85,88] Conversely, in ENGAGE, the difference in CHA2DS2-VASc or CHADS2 score was less than one point in DM patients vs. patients without DM.[87,90] Hence, when excluding DM as a risk factor, the stroke risk of patients without DM in RELY and ARISTOTLE was slightly lower than that of DM patients, possibly caused by the higher age. Conversely, when DM is not taken into consideration, there were fewer residual stroke risk factors in patients with vs. without DM in ROCKET and ENGAGE (more than 0.5 points difference in CHADS2 and CHA2DS2-VASc score).

Patients with DM in these four trials had a higher BMI than subjects without DM. Obesity is an important risk factor for CV complications, but in the four DOAC trials, obesity was shown to protect against stroke/systemic embolism. This effect was not demonstrated in observational studies in that same meta-analysis.[155] Others suggest that obesity may increase the risk of thromboembolism and bleeding.[156]

The patient characteristics in these randomized trials contrast with the data from real-world studies. The proportion of DM patients receiving oral anticoagulants increased between 2001 and 2015, and the prescription of warfarin decreased in favour of DOACs.[157] Diabetes mellitus patients with silent AF episodes had a higher risk of stroke irrespective of glycaemic control.[158] In EORP-AF (20.6% of enrolled subjects had DM), DM patients were significantly older than those without DM, had more CKD and CV co-morbidities, and were

more often prescribed oral anticoagulants. DM patients had a higher rate of all-cause mortality, CV mortality, and non-CV mortality.[62] A recent analysis of the FANTASIIA (Atrial fibrillation: influence of the level and type of anticoagulation on the incidence of ischaemic and haemorrhagic stroke) cohort in Spain demonstrated that time in therapeutic range in acenocoumarol using subjects, was lower in DM patients compared to patients without DM. In this comparison, DM patients had the same age as non-DM patients, but a much higher CHA2DS2-VASc score, but a higher risk of major bleeding, myocardial infarction, CV mortality, total mortality, but no differences in stroke rates.[83]

In contrast, in ORBIT, where 29.5% of patients had DM and were younger, had a higher BMI more likely to have hypertension, CKD, HF, CAD, and stroke.[31] Slower decline of renal function has been attributed to DOACs compared to VKAs, but this effect was partially lost in patients with DM.[159] Diabetes mellitus was associated with earlier CV mortality in GARFIELD (Global Anticoagulant Registry in the FIELD—Atrial Fibrillation), but the contribution of ischaemic stroke to mortality was low.[160] The presence of DM predicted prescription VKAs over DOACs.[161] In propensity score matched cohorts, DM patients using DOACs had fewer ischaemic strokes and MACE than those using warfarin.[102,162] Conversely, in a tapered matched study, DOACs were associated with more bleeding hospitalizations.[163]

Taken together, there is a large heterogeneity within both the randomized and real-world studies on DOACs for stroke prevention in patients with AF and DM. However, the beneficial efficacy and safety of DOACs compared to warfarin seem conserved in AF patients with DM, irrespective of their baseline stroke risk or the presence of other cardiovascular risk factors.

There is controversy on whether better glycaemic control results affect stroke rates in DM patients. Longer duration of DM has been associated with an increased risk of embolic stroke (but not of major bleeding when treated with oral anticoagulants).[54] Further, in registry studies there is an association between the extent glycaemic control and stroke risk, but vascular damage does not seem to affect embolic risk.[57,63] Diabetes mellitus is an independent predictor for the development of AF.[10,66,164] Glucose lowering therapies decrease the incidence of HF and CKD in DM patients, but in many CV outcome studies AF was not a pre-specified outcome.[165,166] Diabetes mellitus patients with higher Hb1AC values had more ischaemic strokes, but this risk was nullified by the use of oral anticoagulation.[58]

Gaps in evidence

- Regarding recent developments for glucose-lowering therapies, the presence of AF at baseline or during follow-up is mostly not systematically reported and information on whether strokes are AF-related is mostly lacking. These drugs, SGLT2 inhibitors in particular, have beneficial effects on the incidence of HF and CKD. Whether a reduction in the incidence of AF accompanies a proportional reduction of the risk of stroke in patients with DM is less well explored.
- The beneficial effects of SGLT2 inhibitors in HFrEF patients have been clearly documented in patients with diabetes. However, their impact on outcome in these patients with both diabetes and AF at baseline is less clear. Thus, more dedicated analyses on the effects of SGTL2 inhibitors in diabetic HFrEF patients with AF and their potential differential impact in patients with HFrEF and HFpEF and concomitant AF and diabetes are needed.
- DM (other than a dichotomous variable) and the characteristics of DM including diabetes sub-classification and the level of glycaemic control were not systematically reported in studies on stroke reduction in AF patients treated with DOACs. Accordingly, the relation between the severity of DM, the level of glycaemic control, and AF-related outcomes is not well documented.
- Diabetes mellitus is associated with an increased risk of deterioration of renal function. Both DM and CKD increase the risk of stroke and other CV complications. Yet, patients with significantly impaired renal function (CrCl < 30 mL/min) were largely excluded from the DOAC trials. The use of a reduced dose of rivaroxaban, apixaban, or edoxaban is recommended in patients with a CrCl between 15 and 30 mL/min, but patients with a CrCl <25–30 mL/min were not included from the randomized trials. The FDA approved a low 75 mg b.i.d. dose of dabigatran for patients with a CrCl <30 mL/min, available in the USA, but it has not been tested in a prospective trial, and it is not approved for use within Europe.
- In patients with AF and acute coronary syndrome, current treatment is based on anticoagulants plus anti-platelets (single or dual) for up to 1 year after the acute event. The general recommendation after 12 months is to omit antiplatelet drugs and prescribe only oral anticoagulants. In view of the complexity of the coronary pattern in ischaemic heart disease and the role of DM in modulating its evolution, more data are needed in order to assess if specific

Key points

- Opportunistic screening for AF by pulse taking or ECG rhythm strip is appropriate in patients ≥65 years of age, and this needs to be carefully applied in diabetic patients in view of their risk.
- Systematic ECG screening should be considered to detect AF in patients aged ≥75 years, or those at high risk of stroke, and this deserves specific consideration in diabetic patients in view of their risk.
- Oral anticoagulation should be prescribed for stroke prevention in AF patients with DM and with at least one additional (CHA2DS2-VASc) risk factor for stroke.
- Oral anticoagulation should be prescribed for stroke prevention in AF patients with DM and no other risk factors for stroke (according to CHA_2DS_2-VASc) in case of inadequate glycaemic control
- Oral anticoagulation may be prescribed for stroke prevention in AF patients with DM and adequate glycaemic control but no other CHA_2DS_2-VASc risk factors for stroke. These include T1DM patients <65 years old.
- For stroke prevention in AF, DOACs should be preferred over vitamin K antagonists, with exception of patients with mechanical valve prostheses or mild to moderate mitral stenosis
- A formal, structured bleeding risk score (HAS-BLED score) helps to identify modifiable and non-modifiable risk factors for bleeding in patients with DM and AF, and to identify patients in need of closer follow-up.

subgroups (including diabetic patients) of patients with AF, CAD and a previous acute event could benefit from the combination of oral anticoagulants and anti-platelets for longer a period.
- The incremental risk of stroke and major bleeding in patients with AF and also DM is not fully understood. Sub-analyses of the randomized trials show that in some diabetic patients had more (i.e. RELY, ARISTOTLE), and in some fewer (ROCKET, ENGAGE) residual stroke risk factors according to the CHADS2 or CHA2DS2-VASc scores. A similar large variation in residual stroke risk can be appreciated in real-world observational studies.
- The potential beneficial effect of DOACs on the development of AF (or AF recurrences/progression) and diabetes have been hypothesized and are supported by data from both basic science and observational clinical studies, but a formal assessment in RCTs is needed.

Acknowledgements

The authors thank the EHRA Scientific Document Committee: Dr Nikolaos Dagres, Prof. Thomas Deneke, Prof. Arthur Wilde, Prof. Frank R. Heinzel, Prof. Christian Meyer, Prof. Lucas Boersma, Prof. Radoslaw Lenarczyk, Prof. Luigi di Biase, Dr Elena Arbelo, Dr Avi Sabbag, Prof. Pierre Jais, Prof. Milos Taborsky, and Asso. Prof. Markus Stühlinger.

Conflict of interest: This document was supported by a grant from Bayer AG; however, the content has not been influenced in any way by its sponsor.

L.F.: consultant or speaker fees of small amounts for Bayer, BMS/Pfizer, Boehringer Ingelheim, Medtronic and Novartis outside of this work.

G.B.: speaker's fees of small amount from Bayer, Boehringer, Boston Scientific and Medtronic.

J.R.d.G.: research grants through his institution from Abbott, Atricure, Boston Scientific, Bayer, Daiichi Sankyo, Johnson&Johnson, Medtronic Servier, and speaker/consultancy fees from Atricure, Bayer, Daiichi Sankyo, Johnson&Johnson and Medtronic outside the submitted work.

R.K.: support of research by Bayer and personal honoraria from Bayer, Berlin-Chemie Menarini, Daiichi Sankyo, Ferrer, Merck, Sanofi, and Servier outside of the submitted work.

P.R.: honoraria to Steno Diabetes Center Copenhagen for consultancy from AstraZeneca, Astellas, Bayer, Boehringer Ingelheim, Gilead, Novo Nordisk, Merck, Mundipharma, Sanofi, Vifor, and research support from Astra Zeneca and Novo Nordisk.

J.C.: Institutional grants and personal fees from Boehringer Ingelheim, Bayer, BMS/Pfizer and Daiichi Sankyo.

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