Managing thrombotic risk in patients with diabetes

A. John Camm¹*, Hani Sabbour²,³, Oliver Schnell⁴, Francesco Summaria⁵ and Atul Verma⁶,⁷

Abstract

It is well known that diabetes is a prominent risk factor for cardiovascular (CV) events. The level of CV risk depends on the type and duration of diabetes, age and additional co-morbidities. Diabetes is an independent risk factor for atrial fibrillation (AF) and is frequently observed in patients with AF, which further increases their risk of stroke associated with this cardiac arrhythmia. Nearly one third of patients with diabetes globally have CV disease (CVD). Additionally, co-morbid AF and coronary artery disease are more frequently observed in patients with diabetes than the general population, further increasing the already high CV risk of these patients. To protect against thromboembolic events in patients with diabetes and AF or established CVD, guidelines recommend optimal CV risk factor control, including oral anticoagulation treatment. However, patients with diabetes exist in a prothrombotic and inflammatory state. Greater clinical benefit may therefore be seen with the use of stronger antithrombotic agents or innovative drug combinations in high-risk patients with diabetes, such as those who have concomitant AF or established CVD. In this review, we discuss CV risk management strategies in patients with diabetes and concomitant vascular disease, stroke prevention regimens in patients with diabetes and AF and how worsening renal function in these patients may complicate these approaches. Accumulating evidence from clinical trials and real-world evidence show a benefit to the administration of non-vitamin K antagonist oral anticoagulants for stroke prevention in patients with diabetes and AF.

Keywords: Atrial fibrillation, Diabetes mellitus, NOAC, Non-vitamin K antagonist oral anticoagulants, Thrombosis

Introduction

Diabetes is a well-established cardiovascular (CV) risk factor, nearly doubling the risk of vascular outcomes, such as coronary heart disease, ischaemic stroke and vascular death [1]. People with diabetes are also at risk of major adverse limb events (MALE), with up to 13% of the global population of diabetes experiencing diabetic foot and limb complications as a result of peripheral vascular disease in the lower limbs or neurological disorders [2]. CV disease (CVD) is a leading cause of mortality and morbidity in patients with type 2 diabetes, accounting for approximately 50% of deaths in the patient population [3]. The CV risk in patients with diabetes can be identified based on various characteristics of the disease, including the duration of the disease, the age of the patient, the type of diabetes and the presence of additional risk factors [4]. These risk factors include a high body mass index, hypertension, dyslipidaemia, smoking, a family history of premature coronary disease and chronic kidney disease (CKD) (Table 1) [4–8].

The primary treatment of patients with diabetes to prevent CV events includes lifestyle changes such as weight loss, smoking cessation and dietary management, along with the monitoring of glycaemic, blood pressure and lipid levels (Fig. 1). The use of an antiplatelet agent for the primary prevention of CV events in patients with diabetes has largely focused on aspirin and has recently been reviewed [9]. A 2009 meta-analysis of six primary...
prevention trials conducted by the Antithrombotic Tri-
lists’ Collaboration found that aspirin significantly
reduced serious CV events [myocardial infarction (MI),
stroke or CV death] by 12% per year compared with
controls in patients with diabetes at low risk of CVD,
but at a cost of significantly increased gastrointestinal
(GI) and extracranial bleeding events [10]. In contrast,
in the Clopidogrel for High Atherothrombotic Risk and
Ischemic Stabilization, Management, and Avoidance
(CHARISMA) trial involving a subgroup of patients
with multiple atherothrombotic risk factors (≈80% of whom had diabetes), an increase in serious CV events (MI, stroke or CV death, including haemorrhage) was observed in patients receiving clopidogrel plus aspirin versus those receiving aspirin alone (6.6% vs 5.5%, \( P=0.20 \)). However, increased rates of Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)-defined severe and moderate bleeding were observed in patients in the subgroup receiving clopidogrel plus aspirin compared with those receiving aspirin alone (2.0% vs 1.2%, \( P=0.07 \) and 2.1% vs 1.3%, \( P<0.001 \) for severe and moderate bleeding, respectively) [11].

More recently, the A Study of Cardiovascular Events in Diabetes (ASCEND) trial also demonstrated a significant reduction in the rate of serious CV events (composite of non-fatal MI or stroke, transient ischaemic attack or CV death, excluding intracranial haemorrhage) over a mean follow-up of 7.4 years in patients with diabetes and no evidence of CV with aspirin compared with placebo [8.5% vs 9.6%, rate ratio (95% CI) 0.79–0.97; \( P=0.01 \)]. Similarly, this benefit was offset by an increase in major bleeding, mainly attributed to GI bleeding (4.1% vs 3.2%, rate ratio = 1.29, 95% CI 1.09–1.52; \( P=0.003 \)) [12]. In the Aspirin in Reducing Events in the Elderly (ASPREE) trial of community-dwelling older adults, of whom 11% had diabetes, there was no reduction in the primary composite CVD endpoint (stroke, MI, fatal coronary heart disease or hospitalization for heart failure [HF]) with aspirin compared with placebo; however, a significantly increased risk of major bleeding was observed [13]. In the Aspirin in Primary Prevention of cardiovascular disease in diabetes (APPRAISE) meta-analysis of 12 trials of patients with diabetes and no history of CVD that compared the use of aspirin versus placebo, including ASCEND and ASPREE, a reduction in major adverse CV events (MACE) was found. No significant difference in bleeding events with aspirin use was found in this meta-analysis, although it should be noted that this conclusion may be imprecise owing to the wide CIs associated with the estimates [14]. However, a Japanese trial of 2539 patients with type 2 diabetes who did not have CVD did not find a reduction in CV events with aspirin compared with no aspirin [hazard ratio (HR) = 1.14, 95% CI 0.91–1.42; \( P=0.2 \)]. Nevertheless, an increase in GI bleeding was observed in patients receiving aspirin compared with those not receiving aspirin (2% vs 0.9%, \( P=0.03 \)) [15]. As a result of these studies, guidelines recommend that after an assessment of bleeding risk, antiplatelet therapy with aspirin may be considered for the primary prevention of CVD in patients with diabetes at a high risk of CV events but is not recommended in patients at moderate or low risk of CV events [4, 5].

Approximately 32% of patients with type 2 diabetes worldwide have existing CVD [3]. Patients with diabetes and established CVD, such as coronary artery disease (CAD) or peripheral artery disease (PAD), have a particularly elevated risk of CV events [4, 16]. An analysis of the REduction of Atherothrombosis for Continued Health (REACH) registry revealed that the 4-year risk of CV death, MI or stroke was 20% in patients with stable atherosclerosis and diabetes [16]. However, patients remain at risk despite traditional CV risk reduction approaches of CV risk factor control and antiplatelet therapy, with approximately 50% of deaths in patients with diabetes being attributed to CV events [3].

Diabetes is also prevalent in patients with atrial fibrillation (AF), a common sustained cardiac arrhythmia associated with an increased risk of stroke [20–22]. Diabetes, an independent risk factor for AF itself [23], has been shown to increase the risk of stroke and mortality in patients with AF by several mechanisms (Fig. 2) [20, 22, 24, 25].

The coexistence of AF and CAD, which raises therapeutic and safety concerns, is more frequently observed in diabetic populations compared with the general population [20]. Recent studies have provided conflicting evidence of the effectiveness of sodium-glucose co-transporter-2 (SGLT2) inhibitors, dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists in demonstrating a reduction in incident AF in patients with diabetes [26–29]. In patients with AF and additional risk factors, such as diabetes, oral anticoagulant therapy is the cornerstone of treatment for the prevention of thromboembolic events [4, 30, 31].

Patients with diabetes exist in a prothrombotic and inflammatory state as a result of endothelial dysfunction and platelet hyperactivity, and a reduction in clot dissolution [25]. Therefore, more potent antithrombotic agents or novel drug combinations may provide greater clinical benefit for high-risk patients with diabetes, such as those who also have AF or established CVD. This review will discuss current and future management approaches to improve CV outcomes in these high-risk patient populations. Figure 1 provides an overview of these approaches, and the supporting evidence, for patients with diabetes and co-morbid CAD, PAD, HF, CKD, AF and concomitant renal impairment.

**CV risk management strategies in patients with diabetes and CAD and/or PAD**

Current guidelines for the management of CV risk in patients with diabetes and CAD and/or PAD recommend CV risk factor control to limit the progression of atherosclerosis and antithrombotic therapy to prevent acute CV
events (Table 1) [4, 5, 7, 17–19]. The control of CV risk factors in patients with diabetes involves a multifactorial approach including lifestyle modifications, as well as glucose, lipid, and hypertension control [5].

The standard of care for the secondary prevention of acute CV events in patients with CAD and prior MI or revascularization, and in patients with symptomatic PAD is single antiplatelet therapy with aspirin or clopidogrel [4, 5, 7, 17]. Despite the use of single antiplatelet therapy, these patients remain at high risk of CV and MALE [32]. According to Dick et al. [2007], nearly half of patients with critical limb ischaemia had diabetes [32]. Furthermore, patients with diabetes and PAD are at a five times greater risk of amputation and three times greater risk of mortality than patients without diabetes [33]. In a sub analysis of patients with diabetes in the Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial, the incidence of ischaemic events was reduced with clopidogrel compared with aspirin; however, the rate was still high; event rates were 15.6% and 17.7% per year for patients with diabetes treated with clopidogrel and aspirin, respectively [34].

Various trials have investigated the efficacy and safety of intensified antiplatelet therapies in patients with chronic CAD and/or PAD and diabetes, including single antiplatelet therapy with ticagrelor, a more potent P2Y12 receptor antagonist, and dual antiplatelet therapy (DAPT; Table 2) [35–41]. In the Examining Use of Ticagrelor in Peripheral Artery Disease (EUCLID) trial, there was no significant difference in the incidence of acute limb ischaemia with ticagrelor compared with clopidogrel (1.7% of patients treated with ticagrelor vs 1.7% of patients treated with clopidogrel, HR=1.03, 95% CI 0.79–1.33; P=0.85) [39]. In contrast, the Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients With Atherosclerosis (TRA 2°P-TIMI 50) that compared vorapaxar with placebo reported mixed results [42, 43]. Vorapaxar was effective in reducing the thrombotic risk in patients with prior MI and diabetes [43], but the incidence of MACE was similar between vorapaxar and placebo in patients with PAD and diabetes (11.3% vs 11.9%; HR=0.94, 95% CI 0.78–1.14; P=0.53) [42]. DAPT was found to have beneficial effects in patients with acute coronary syndrome and diabetes [35]; however, heterogeneous results were reported for intensified antiplatelet therapies in patients with chronic CVD and diabetes [37, 39, 40]. Furthermore, The Effect of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study (THEMIS) demonstrated a significant reduction in the incidence of a composite of CV death, MI or stroke with ticagrelor plus aspirin versus placebo plus aspirin in 19,220 patients aged ≥50 years with stable CAD and type 2 diabetes (7.7% vs 8.5%; HR=0.90, 95% CI 0.81–0.99; P=0.04). This was at a cost of significantly increased Thrombolysis in Myocardial Infarction major bleeding and intracranial haemorrhage (2.2% vs 1.0%; HR=2.32, 95% CI 1.82–2.94; P<0.001 and 0.7% vs 0.5%; HR=1.71, 95% CI 1.18–2.48; P=0.005, respectively) [41]. In the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) study, DAPT with clopidogrel and aspirin was shown to reduce asymptomatic microembolic signals.
### Table 2  Outcomes of trials investigating intensified antiplatelet therapies in patients with diabetes and CAD and/or PAD

| Trial                      | Study population                                                                 | Antiplatelet therapy       | Comparator | Primary endpoint                                      | Patients with diabetes (n) | Events in patients with diabetes (vs comparator, % of patients)                                                                 |
|----------------------------|---------------------------------------------------------------------------------|----------------------------|------------|-------------------------------------------------------|----------------------------|-----------------------------------------------------------------------------------------------------------------------------|
| CHARISMA [136]             | Stable CAD with high atherothrombotic risk                                        | Aspirin plus clopidogrel   | Aspirin    | CV mortality, MI or stroke at 28 months               | 6555                       | 16.5% vs 16.1% with nephropathy (HR = 1.0, 95% CI 0.8–1.3)                                                                    |
| DAPT [38]                  | Stable CAD or ACS treated with DES or BMS implantation                           | Aspirin plus clopidogrel   | Aspirin    | Stent thrombosis, death, MI or stroke at 30 months    | 3391                       | 6.6 vs 7.0 (HR = 0.92, 95% CI 0.71–1.20)                                                                                      |
| EUCLID [39]                | Symptomatic PAD or previous revascularization of the lower limbs                 | Ticagrelor                | Clopidogrel| CV mortality, MI or stroke at 36 months               | 5345                       | 16.2 vs 15.6 (HR = 1.11, 95% CI 0.96–1.28)<sup>a</sup>                                                                       |
| PEGASUS-TIMI 54 [37]       | History of MI (within the prior 3 years) and additional atherothrombotic risk factor<sup>b</sup> | Aspirin plus ticagrelor    | Aspirin    | CV mortality, MI or stroke at 36 months               | 6806                       | 10.0 vs 11.6 (HR = 0.84, 95% CI 0.72–0.99)<sup>c</sup>                                                                       |
| THEMIS [41]                | T2DM and stable CAD receiving anti-hyperglycaemic drugs <6 months                | Aspirin plus ticagrelor    | Aspirin    | CV mortality, MI or stroke at 36 months               | 19,220                     | 6.9 vs 7.6 (HR = 0.9, 95% CI 0.81–0.99)<sup>a</sup>                                                                         |
| THEMIS-PCI [40]            | T2DM and stable CAD receiving anti-hyperglycaemic drugs <6 months and previous PCI | Aspirin plus ticagrelor    | Aspirin    | CV mortality, MI or stroke at 40 months               | 11,154                     | 7.3 vs 8.6 (HR = 0.85, 95% CI 0.74–0.97)                                                                                      |

**ACS**, acute coronary syndrome; **BMS**, bare-metal stent; **CAD**, coronary artery disease; **CI**, confidence interval; **CV**, cardiovascular; **DAPT**, dual antiplatelet therapy; **DES**, drug-eluting stent; **HR**, hazard ratio; **KM**, Kaplan-Meier; **MI**, myocardial infarction; **PAD**, peripheral artery disease; **PCI**, percutaneous coronary intervention; **T2DM**, type 2 diabetes mellitus

<sup>a</sup> KM% at month 36

<sup>b</sup> Age ≥ 65 years, diabetes requiring medication, second prior MI, chronic renal dysfunction, multivessel CAD

<sup>c</sup> Pooled ticagrelor doses
in patients with carotid stenosis by 37.3% after 7 days with no life-threatening or major bleeding. However, the CARESS study population was small (N = 100) [44]. Therefore, there is a need for improved antithrombotic management strategies in patients with chronic CAD and/or PAD and diabetes.

Recently, dual pathway approaches that combine an antiplatelet with an anticoagulant have also been investigated in patients with chronic CVD and diabetes. The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, which investigated the safety and efficacy of the anticoagulant rivaroxaban at a ‘vascular dose’ [5 mg twice daily (bid) or 2.5 mg bid plus aspirin] compared with aspirin alone, demonstrated a reduced incidence of both MACE and MALE in patients with chronic CAD and/or PAD with rivaroxaban 2.5 mg bid plus aspirin treatment [45–47]. This relative risk reduction was consistent in patients with and without diabetes, along with a relative risk reduction in all-cause death and the composite of CV death, MI or stroke in both patient groups and a consistent rate of net clinical benefit outcomes (MI, stroke, CV death, fatal bleeding or symptomatic critical organ bleeding) [46, 48]. Additionally, a risk stratification analysis of the COMPASS trial demonstrated that patients with diabetes represent a subgroup that has an elevated baseline risk of MACE and may, therefore, benefit the most from treatment with rivaroxaban [49]. This is reflected in the increased absolute risk reduction for MACE in patients with diabetes and the notable threefold greater reduction in mortality compared with patients without diabetes [50]. The reduction in MACE events in the COMPASS trial was primarily driven by a 42% reduction in the risk of stroke [45, 51]. Moreover, a recent subanalysis showed that this reduction was consistent in patients with a high risk of stroke at enrolment, such as those who have previously experienced a stroke or patients with diabetes [51]. The increased risk of International Society on Thrombosis and Haemostasis major bleeding with vascular dose rivaroxaban and low-dose aspirin observed in the overall COMPASS trial was also consistent in patients with and without diabetes [45, 50].

Based on the results from the COMPASS trial, the 2019 European Society of Cardiology (ESC) guidelines for the diagnosis and management of chronic coronary syndromes and the 2019 ESC/European Association for the Study of Diabetes (EASD) guidelines for diabetes, prediabetes and CVD recommend that the addition of a second antithrombotic drug to aspirin should be considered in patients with a high risk of ischaemic events and without a high risk of bleeding [4, 7]. This second antithrombotic drug may be clopidogrel 75 mg once daily (od), prasugrel 10 mg od or 5 mg od for patients with a body weight < 60 kg or age > 75 years, ticagrelor 60 mg bid or rivaroxaban ‘vascular dose’ 2.5 mg bid [4, 7]. Patients with a high risk of ischaemic events include those with diffuse multivessel CAD with at least one of the following: diabetes requiring medication, recurrent MI, PAD or CKD with an estimated glomerular filtration rate (eGFR) of 15–59 mL/min/1.73 m² [7].

More recently, the Vascular Outcomes Study of ASA [Acetylsalicylic Acid] Along With Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD (VOYAGER PAD) trial investigated the safety and efficacy of dual pathway inhibition rivaroxaban ‘vascular dose’ 2.5 mg bid plus aspirin compared with aspirin alone in patients with PAD who had undergone revascularization within 10 days [52]. A reduction in the incidence of the primary efficacy outcome (a composite of acute limb ischaemia, major amputation for vascular causes, MI, ischaemic stroke or CV-related mortality) was observed with treatment with rivaroxaban plus aspirin. This benefit was consistent in patients with and without diabetes. A significant increase in the primary safety outcome, Thrombolysis in Myocardial Infarction major bleeding, was not observed in the overall trial; however, the risk of this outcome was significantly increased in patients with diabetes compared with patients without diabetes. Based on these results, specific recommendation updates have been included in the European label for rivaroxaban for vascular dose rivaroxaban plus low-dose aspirin for the prevention of atherothrombotic events in patients with symptomatic PAD at high risk of ischaemic events, to include those with a recent lower-extremity revascularization or diabetes [53]. Guidelines now recommend dual pathway inhibition with rivaroxaban 2.5 mg bid plus aspirin 100 mg od in patients with symptomatic PAD undergoing peripheral revascularization and should be considered following peripheral revascularization in patients with symptomatic PAD without an increased bleeding risk [54, 55].

Management strategies for stroke prevention in patients with diabetes and AF

The Congestive heart failure, Hypertension, Age ≥75 years (2 points), Diabetes mellitus, Stroke or transient ischaemic attack (2 points), Vascular disease, Age 65–74, Sex category (female) (CHA2DS2-VASc) risk score can be used to predict the risk of stroke in patients with AF. An increase in the score correlates with an increased risk of stroke, with a score ≥2 corresponding to a high risk of stroke [56]. Patients with a prior stroke or transient ischaemic attack or those aged ≥75 years are considered to be at high risk of experiencing a stroke by the score. Furthermore, patients are additionally classified as high risk by the
same conclusions [69]. However, there are some efficacy patients from these four phase III trials highlights the more recent meta-analysis published in 2020 of 58,634 ischaemic attack (2 points) (CHADS 2) score. Each of
the four NOACs are recommended for patients with a CHADS2 score of ≥2 in the Japanese Circulation Society guidelines for AF, while apixaban and dabigatran are recommended for patients with a score of 1 and edoxaban and rivaroxaban may be considered as a result of exclusion of patients with a CHADS2 score of 1 in their phase III studies [58]. Canadian guidelines also use an alternative stroke risk assessment algorithm, the Canadian Cardiovascular Society algorithm or CHADS-65, in which every patient aged ≥65 years is recommended a NOAC, as are patients aged <65 years with a CHADS2 score of ≥1 [59]. Therefore, based on the Canadian and Japanese guidelines, every patient with AF and concomitant diabetes should receive a NOAC [58, 59].

The efficacy and safety of NOACs in the prevention of ischaemic stroke/systemic embolism (SE) in patients with AF have been demonstrated in four large phase III trials comparing NOACs with warfarin—Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) for apixaban; Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation—Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) for edoxaban, Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) for dabigatran; and Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) for rivaroxaban [60–63]. A meta-analysis and subgroup analyses of these phase III trials showed that the favourable efficacy and safety profile of NOACs versus warfarin was similar in patients with and without diabetes (Fig. 3) [64–68]. A more recent meta-analysis published in 2020 of 58,634 patients from these four phase III trials highlights the same conclusions [69]. However, there are some efficacy and safety differences in the profiles of the NOACs in patients with diabetes that are worth noting.

In ROCKET AF, patients with AF were randomized to receive rivaroxaban 20 mg od or warfarin [60]. Approximately 40% of these patients had concomitant diabetes, the highest proportion of the four trials [64]. An 18% reduction in stroke/SE was observed in patients with AF and diabetes treated with rivaroxaban compared with those treated with warfarin [65]. Similar incidence rates of efficacy and safety outcomes were seen in patients with and without diabetes, although the absolute stroke risk reduction with rivaroxaban was numerically larger in those with diabetes [65]. Furthermore, rivaroxaban reduced the risk of CV mortality by 20% in patients with diabetes compared with warfarin [65]. It should be noted, however, that diabetes was an inclusion criterion associated with stroke risk in patients with AF. As a result, more patients with diabetes had a CHADS2 score of 5 or 6 than patients without diabetes, yet less than half of patients with diabetes had prior stroke or transient ischaemic attack and were younger on average compared with patients without diabetes [65]. Greater risk reductions, therefore, may be expected in the diabetes subgroup versus the subgroup without diabetes. Nevertheless, the similar rates of the efficacy and safety outcomes suggest that diabetes may confer a substantial risk of stroke; a hypothesis confirmed with 2-year modelling of event rates for patients with diabetes using the co-morbid profiles of patients without diabetes [65].

In ARISTOTLE, one-quarter of patients had AF and concomitant diabetes [62, 64]. Apixaban was superior to warfarin with respect to the primary efficacy endpoint of stroke/SE in patients with diabetes (HR = 0.75, 95% CI 0.53–1.05). In the overall ARISTOTLE population, rates of the primary safety outcome (International Society of Thrombosis and Haemostasis major bleeding) were lower with apixaban compared with warfarin; however, this observation was not seen in patients with diabetes where the rates of major bleeding were similar between apixaban- and warfarin-treated groups [68]. In contrast, the rates of the primary efficacy and safety endpoints were reduced with apixaban versus warfarin in patients without diabetes [68].

RE-LY investigated the efficacy and safety of dabigatran (150 mg bid or 110 mg bid) versus warfarin in patients with AF, and 23% of these patients also had diabetes at baseline [61, 64]. Both dabigatran doses demonstrated a reduction in stroke/SE and intracranial bleeding compared with warfarin in patients with and without diabetes [66]. However, the absolute stroke risk reduction with dabigatran was greater in patients with diabetes than in those without [66].
In ENGAGE AF-TIMI 48, 36% of patients had diabetes at baseline [64]. Edoxaban 60 mg od reduced the risk of CV mortality compared with warfarin in patients with or without diabetes and displayed a similar efficacy in preventing stroke/SE [67]. Patients without diabetes, however, had a significantly lower risk of bleeding [67].

Further evidence from randomized controlled trials in patients with AF undergoing percutaneous coronary intervention have also shown differences between the NOACs in outcomes for patients with or without diabetes. In Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran versus Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (RE-DUAL PCI), the incidence of the primary efficacy endpoint, a composite of time to death, first thromboembolic event (stroke/SE or MI) or unplanned revascularization, was similar between the dabigatran dual therapy (dabigatran 110 mg or 150 mg bid and clopidogrel or ticagrelor) and warfarin triple therapy (warfarin, clopidogrel or ticagrelor, and aspirin) treatment arms for patients with and without diabetes [70]. In contrast, the An Open-Label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban Versus Vitamin K Antagonist and Aspirin Versus Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention (AUGUSTUS) trial showed that apixaban decreased the time to hospitalization or death in patients without diabetes compared with warfarin; however, this outcome was not observed in patients with diabetes [71].

The benefits of NOACs in patients with AF and diabetes have also been demonstrated by real-world evidence (RWE) [72–75]. Among patients with AF and diabetes, the risk of MACE, MALE and major bleeding, including major GI bleeding, was reduced with NOAC use compared with warfarin use in a Taiwanese retrospective cohort study [76]. In a retrospective
MarketScan data analysis, treatment with rivaroxaban was not only associated with a lower risk of MACE in patients with AF and diabetes compared with treatment with warfarin, but also, a reduced risk of MALE [74]. Furthermore, a recent US electronic health record analysis, A Study Using Electronic Health Information to Learn About Rivaroxaban Compared to Warfarin in Participants With Non-valvular Atrial Fibrillation (NVAF) and Diabetes (RIVA-DM), investigated a large population of patients with nonvalvular AF and type 2 diabetes [77]. Not only did RIVA-DM demonstrate significant reductions in typical CV endpoints such as stroke/SE, CV death, critical organ bleeding and intracranial haemorrhage with rivaroxaban versus warfarin, significant reductions in clinically relevant outcomes to patients with diabetes were also observed, including kidney, limb and ophthalmic complications [77, 78]. Reductions in CV and limb events were also seen with dual pathway inhibition with rivaroxaban plus aspirin versus aspirin alone in patients with PAD and concomitant diabetes who had undergone revascularization within 10 days in VOYAGER PAD and in patients with PAD or CAD and concomitant diabetes in COMPASS [50, 52]. This is important considering the significant risk of lower limb amputation in patients with diabetes [74].

Additionally, a Taiwanese nationwide retrospective cohort study of 4930 patients with AF demonstrated that patients treated with NOACs aged < 65 years or with a medication possession ratio of ≥ 80% (inferring adherence) were significantly less likely to develop new-onset diabetes compared with patients receiving warfarin [79]. Therefore, adherence to NOACs may not only provide beneficial effects on CV and limb outcomes in patients with AF and diabetes, but may also reduce the risk of patients with AF developing diabetes.

**Considering renal impairment in thromboembolic prevention strategies for patients with AF and diabetes**

Hyperglycaemia can result in macrovascular complications in patients with diabetes, including stroke, and microvascular complications, including diabetic nephropathy [80]. Patients with AF and/or diabetes have an increased risk of renal impairment, with diabetes being the most common cause of CKD worldwide [81, 82]. The presence of CKD in the natural history of patients with diabetes predisposes them to AF [83]. At the same time, CKD is a risk factor for AF [84]. Worsening of renal function over time is commonly observed in patients with AF treated with anticoagulants [85–88] and has been shown to be amplified in patients with concomitant diabetes [85, 86]. Furthermore, it is estimated that 30–40% of patients with diabetes develop diabetic kidney disease [82]. The progression of CKD increases the risk of CV death in patients with and without diabetes [89–91]. The ESC/EASD 2019 guidelines have identified CKD and microalbuminuria in diabetes as markers of high CV risk, with microalbuminuria also being a marker for the development of renal dysfunction [4].

CKD is associated with an increased risk of thromboembolic events and bleeding in patients with AF [92, 93]. It is, therefore, important to evaluate kidney function when managing patients with AF and diabetes, especially when choosing the type and dose of anticoagulant [4, 94]. Due to the partial elimination of anticoagulants, a reduced risk of renal impairment, in line with label recommendations [94]. Guidelines recommend assessing renal function in anticoagulated patients with AF at least yearly and proportionately more often in patients with impaired renal function to detect changes in kidney function and adjust the anticoagulant dose accordingly [30, 94].

Patients with AF treated with anticoagulants may be at risk of renal function decline due to anticoagulant-related nephropathy (ARN), which is a form of acute kidney injury [95]. ARN can result from excessive anticoagulation and is most commonly associated with warfarin. However, NOACs have also been reported to be associated with ARN—most frequently dabigatran [95–97]. Diabetes and CKD have been identified as risk factors for the development of ARN [97]. A recent meta-analysis has shown that patients with ARN are at significantly greater risk of mortality at 5 years compared with patients without ARN receiving anticoagulation (HR = 1.91, 95% CI 1.22–3.00) [97]. ARN is also associated with increased renal morbidity and accelerated progression of CKD [96, 98], further complicating the management of patients with AF and concomitant diabetes and renal impairment.

Patients with CKD have reduced levels of regulatory molecules or abnormal regulatory molecules that act to inhibit calcium deposition in non-osseous tissue and promote the incorporation of calcium into bone [99]. In addition, VKAs prevent the activation of the matrix Gla protein, thereby promoting vascular calcification in the kidneys (renovascular calcification) [100] and elsewhere in patients with CKD (for example, peripheral arteries, heart valves and coronary arteries) [101, 102]; this causes a further decline of renal function and increased vascular morbidity and mortality [99, 103]. In contrast, RWE studies have demonstrated a beneficial effect of NOACs, in particular rivaroxaban and dabigatran, in reducing the risk of renal function decline due to anticoagulation.
compared with VKAs in patients with AF [75, 88, 104, 105]. This effect has also been frequently observed in patients with co-morbid diabetes [75, 106]. This may be attributed to the activation of prothrombin by factor Xa; factor Xa interacts with the protease-activated receptors 1 and 2, therefore suggesting that factor Xa inhibitors prevent thrombin-mediated effects such as inflammation, tissue fibrosis and vascular remodelling [107].

Due to the renal excretion of NOACs and an increased risk of bleeding in patients with kidney dysfunction, it is important that the appropriate NOAC dose is administered [108]. However, on the basis of more recent evidence, continuing with a NOAC in patients with impaired kidney function rather than switching to a VKA could result in better patient outcomes [75, 88, 104–106]. Apixaban, edoxaban and rivaroxaban are contraindicated in patients with a creatinine clearance (CrCl) < 15 mL/min while dabigatran (at a lowest dose of 110 mg bid) is contraindicated in patients with a CrCl < 30 mL/min [53, 109–111]. Additionally, a reduced dose of dabigatran may be considered for patients at high risk of bleeding, while a reduced dose of edoxaban may be considered in patients with a CrCl 15–50 mL/min, body weight ≤ 60 kg or those receiving treatment with P-glycoprotein inhibitors [110, 111]. A reduced dose of apixaban is also required for patients with AF and at least two of three risk factors: serum creatinine ≥ 1.5 mg/dL, aged ≥ 80 years or with a body weight ≤ 60 kg [109]. Thus, by prescribing the appropriate type of anticoagulant to patients with diabetes, in addition to using a dose appropriate to their clinical characteristics, it might be possible to preserve their renal function and prevent adverse limb events while protecting them from stroke and fatal CV events. The importance of reducing renal function decline and the potential impact of the choice of anticoagulant on renal outcomes in patients with AF have also been highlighted in the 2019 update to the American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines on the management of AF, stating that ‘over time, NOACs (particularly dabigatran and rivaroxaban) may be associated with lower risks of adverse renal outcomes than warfarin in patients with AF’ [31]. This is particularly relevant in patients with AF and diabetes given the impact of worsening GFR on mortality and CV death [31, 112, 113]. Thus, in the context of comprehensive preventive strategies in this very vulnerable population, warfarin is not the preferred anticoagulant at an early stage in patients with diabetes, AF or in the early stages of diabetic renal disease.

The role of anti-hyperglycaemic agents in the management of CV risk in patients with diabetes

GLP-1 is an incretin hormone released from the gut in response to glucose, upregulating insulin secretion and downregulating glucagon release. While the intrinsic GLP-1 peptide has a short half-life, synthetic GLP-1 receptor agonists typically have longer half-lives and bind with similar affinity to the GLP-1 receptor, thereby acting to prevent hyper- and hypo-glycaemia in patients with diabetes [114]. In contrast, SGLT2 inhibitors inhibit SGLT2 activity, a low-affinity sodium-glucose co-transporter in the proximal tubule of the nephron, reducing glucose reabsorption and blood glucose levels in patients with diabetes [115].

By regulating blood glucose levels, anti-glycaemic agents such as GLP-1 receptor agonists and SGLT2 inhibitors aim to prevent hyperglycaemia and resultant vascular complications in patients with diabetes [80]. Several CV outcome trials have indicated that GLP-1 receptor agonists and SGLT2 inhibitors have CV benefit in patients with CVD or at high CV risk [4, 116]. A meta-analysis of eight CV outcome trials in patients with type 2 diabetes showed a significant reduction in non-fatal stroke with GLP-1 receptor agonists versus placebo [117]. In contrast, the EMPA-REG trial did not show a reduction in the risk of non-fatal stroke with the SGLT2 inhibitor empagliflozin versus placebo in patients with type 2 diabetes and established CVD [118]. These studies were not in the setting of AF [117, 118]. Both GLP-1 receptor agonists and SGLT2 inhibitors have been shown to reduce the risk of MACE, but some SGLT2 inhibitors reduced the risk of MACE only in patients with prior MI [117–119].

Clinical trial data also suggest a renoprotective effect of both GLP-1 receptor agonists and SGLT2 inhibitors in patients with diabetes, which may contribute to their CV benefits [120–123]. Other evidence has shown a reduction in limb events with GLP-1 receptor agonists. For example, liraglutide reduced the risk of amputations associated with diabetes-related foot ulcerations compared with placebo in patients with type 2 diabetes and a high risk of CV events [124]. The incidence of major adverse limb events was also lower in patients with type 2 diabetes receiving GLP-1 receptor agonists compared with those receiving DPP4 inhibitors [125].

As a result of these CV benefits, the 2022 American Diabetes Association (ADA) standards of medical care in diabetes clinical practice recommendations advise that an SGLT2 inhibitor or GLP-1 receptor agonist with demonstrated CVD benefit should be given...
as part of a regimen in patients with type 2 diabetes with established atherosclerotic CVD. This recommendation also applies to patients with indicators of high CV risk, established kidney disease or HF, with consideration for patient-specific factors, and is independent of glycated haemoglobin [126]. In patients with type 2 diabetes and established atherosclerotic CVD or multiple CV risk factors, an SGLT2 inhibitor or GLP-1 receptor agonist with demonstrated CV benefit is recommended to reduce the risk of MACE, whereas SGLT2 inhibitors are further recommended in these patients to reduce the risk of hospitalization for HF and in those with diabetic kidney disease [127].

The ADA and EASD 2019 consensus report recommends SGLT2 inhibitors for the reduction of MACE, CV mortality and hospitalization for HF in patients with diabetes and concomitant HF or CKD [128]. SGLT2 inhibitors are recommended to reduce the risk of hospitalization for HF in patients with diabetes in the 2019 ESC/EASD guidelines for diabetes, pre-diabetes and CVD, and GLP-1 receptor agonists may be considered for the treatment of diabetes in patients with HF. Moreover, these guidelines recommend GLP-1 receptor agonists and SGLT2 inhibitors as first-line glucose-lowering treatments in patients with type 2 diabetes and CVD, or at high to very high CV risk, to reduce CV events and mortality [4]. It should also be noted that SGLT2 inhibitors are recommended in patients with an eGFR of 30 to < 90 mL/min/1.73 m², whereas GLP-1 receptor agonists should be considered in patients with an eGFR > 30 mL/min/1.73 m² [43].

Glucose-lowering diabetic medications have been shown to reduce the risk of AF development, consequently reducing the risk of stroke [24]. It is hypothesized that this is achieved through the antioxidant and anti-inflammatory effects of the diabetic medications, thereby acting on the pathophysiology of both diabetes and AF (Fig. 2) [129, 130]. An analysis of the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial with the SGLT2 inhibitor dapagliflozin showed a reduction of new and recurrent AF and atrial flutter events [131]. Large cohort studies have shown that metformin and thiazolidinediones are associated with a reduction in the risk of new-onset AF [129, 130], and a recent meta-analysis demonstrated that treatment with thiazolidinediones reduced the risk of developing AF by 27% [132]. Glycaemic fluctuations, however, have been shown to correlate with increased oxidative stress compared with hyperglycaemia, and, therefore, may have a greater contribution to the initiation of CV complications and AF in diabetes [133, 134]. Moreover, long-term glycaemic variability was significantly associated with new-onset AF in a recent cohort study; multiple Cox regression demonstrated that higher glycated haemoglobin levels were a predictor of new-onset AF following adjustment for age, body mass index, left ventricular mass index or left atrium diameter or if the variability of levels was determined by standard deviation or coefficient of variation [135]. This suggests that the management of diabetes should be focused on limiting glycaemic fluctuations in addition to decreasing blood glucose levels [24].

Conclusion
Progress has been made in the development of pharmacological therapies for the prevention of CV events in patients in sinus rhythm with diabetes and CAD and/or PAD, as well as in patients with diabetes and AF. Randomized controlled trial data suggest a benefit for rivaroxaban, as part of a dual pathway approach with aspirin, in the reduction of MACE and MALE in patients with sinus rhythm with diabetes and CAD and/or PAD. Evidence of the benefits of NOACs for stroke prevention in patients with diabetes and AF is accumulating, with data from clinical trials now being supported with emerging RWE. The impact of renal function decline on CV outcomes in patients with AF has been increasingly recognized, which is particularly important for patients with diabetes who have a high risk of developing kidney disease. Future management approaches for patients with diabetes who are at an increased risk of CV events should consider aspects such as renal and lower limb function, in addition to the prevention of CV events. Such optimized care would not only protect the patient from CV events but would also reduce their risk of lower limb amputation and dialysis; complications that are particularly concerning for patients with diabetes.

Abbreviations
ADA: American Diabetes Association; AF: atrial fibrillation; ARISTOTLE: Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; ARN: anticoagulant-related nephropathy; ASCEND: A Study of Cardiovascular Events in Diabetes; APF: Apixaban in Reducing Events in the Elderly; AUGUSTUS: An Open-Label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban Versus Vitamin K Antagonist and Apixaban Versus Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention; bid: twice daily; CAD: Coronary artery disease; CAPRIE: Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events; CARESS: Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis; CHADS2: Congestive heart failure, Hypertension, Age ≥ 75 years (2 points), Diabetes mellitus; Stroke or transient ischaemic attack (2 points), Vascular disease, age 65–74, 75 years (2 points), Diabetes mellitus, Stroke or transient ischaemic attack (2 points); DAPT: dual antiplatelet therapy; DECLARE-TIMI; 

Page 11 of 16
References

1. Collaboration ERF. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010;375:2215–22.
2. International Diabetes Federation. IDF Diabetes atlas, 9th Edition. Brussels, Belgium: International Diabetes Federation. 2019. http://www.diabetesatlas.org/. Accessed 11 June 2020.
3. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. Cardiovasc Diabetol. 2018;17:83.
4. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020;41:255–323.
5. American Diabetes Association. 10. Cardiovascular disease and risk management: standards of medical care in diabetes—2019. Diabetes Care. 2019;42:S103-23.
6. Rawshani A, Rawshani A, Fransen S, Sattar N, Eliasson B, Svensson AM, et al. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2018;379:633–44.
7. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato F, Funck-Brentano C, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020;41:407–77.
8. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41:111–88.
9. Capodanno D, Angiolillo DJ. Antithrombotic therapy for atherosclerotic cardiovascular disease risk mitigation in patients with coronary artery disease and diabetes mellitus: Circulation. 2020;142:2172–88.
10. Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009;373:1849–60.
11. Bhatt DL, Fox KAA, Hacke W, Berger PB, Black HR, Boden WE, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med. 2006;354:1706–17.
12. Ascend Study Collaborative Group, Bowman L, Maffin M, Wallendzus K, Stevens W, Buck G, et al. Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med. 2018;379:1529–39.
13. McNeil JJ, Wolfe R, Woods RL, Tonkin AM, Donnan GA, Nelson MR, et al. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. N Engl J Med. 2018;379:1509–18.
14. Seidu S, Kunutsor SK, Sesso HD, Gaziano JM, Buring JE, Roncaglione MC, et al. Aspirin has potential benefits for primary prevention of cardiovascular outcomes in diabetes: updated literature-based and individual participant data meta-analyses of randomized controlled trials. Cardiovasc Diabetol. 2019;18:70.
15. Saito Y, Okada S, Ogawa H, Sajoima H, Sakuma M, Nakayama M, et al. Low-dose aspirin for primary prevention of cardiovascular events in patients with type 2 diabetes mellitus: 10-year follow-up of a randomized controlled trial. Circulation. 2017;135:659–70.
16. Cavender MA, Steg PG, Smith SC Jr, Eagle K, Ohman EM, Goto S, et al. Impact of diabetes mellitus on hospitalization for heart failure, cardiovascular events, and death: outcomes at 4 years from the REDuction of Atherothrombosis for Continued Health (REACH) Registry. Circulation. 2015;132:923–31.
17. Aboyans V, Rocco JB, Bartelink MEL, Bjorck M, Brodmann M, Cohnert T, et al. 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Medicine, University of Toronto, Toronto, ON, Canada.
Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. Eur Heart J. 2018;39:763–816.

18. Davies MJ, D’Alessio DA, Fradkin J, Kemeny WN, Mathieu C, Mingrone G, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2018;61(6):2461–98.

19. Das SR, Everett BM, Birringer KK, Brown JM, Cefalu WT, Januzzi JL Jr, et al. 2018 ACC expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes and atherosclerotic cardiovascular disease: a report of the American College of Cardiology task force on expert consensus decision pathways. J Am Coll Cardiol. 2018;72:3200–23.

20. Echouffo-Tcheugui JB, Shrader P, Thomas L, Gersh BJ, Kouwe PR, Mahaffey KW, et al. Care patterns and outcomes in atrial fibrillation patients with and without diabetes. ORBIT-AF registry. J Am Coll Cardiol. 2017;70:1325–35.

21. LaMori JC, Mody SH, Gross HJ, daCosta DM, Patel AA, Schein JR, et al. Burden of comorbidities among patients with atrial fibrillation. Ther Adv Cardiovasc Dis. 2013;7:53–62.

22. The Stroke Risk in Atrial Fibrillation Working Group. Independent pre-term stroke predictors of stroke in patients with atrial fibrillation: a systematic review. Neurology. 2018;90:546–54.

23. Movahed MR, Hashemzadeh M, Jamal MM. Diabetes mellitus is a strong, independent risk for atrial fibrillation and flutter in addition to other cardiovascular diseases. Int J Cardiol. 2005;105:315–8.

24. Wang A, Green JB, Halperin JL, Piccini JP Sr. Atrial fibrillation and diabetes mellitus: JACC review topic of the week. J Am Coll Cardiol. 2019;74:1107–15.

25. Plitt A, McGuire DK, Giugliano RP. Atrial fibrillation, type 2 diabetes, and non-vitamin K antagonist oral anticoagulants: a review. JAMA Cardiol. 2017;2:442–8.

26. Chang CY, Yeh YH, Chan YH, Liu JR, Chang SH, Lee HF, et al. Dipeptidyl peptidase-4 inhibitor decreases the risk of atrial fibrillation in patients with type 2 diabetes: a nationwide cohort study in Taiwan. Cardiovasc Diabetol. 2017;16:159.

27. Liou YS, Yang FY, Chen HY, Jong GP. Glucagon-like peptide-1 receptor agonists and atrial fibrillation: a systematic review and meta-analysis of randomised controlled trials. J Endocrinol Invest. 2017;40:1251–8.

28. Usman MS, Siddiqi TJ, Memon MM, Khan MS, Ravasia WF, Talha Ayub M, et al. Sodium-glucose co-transporter 2 inhibitors and cardiovascular outcomes: a systematic review and meta-analysis. Eur J Prev Cardiol. 2018;25:495–502.

29. Kirchhof P, Benussi S, Cotecha D, Ahlsson A, Atar D, Casadei B, et al. ESC guidelines for the management of atrial fibrillation in collaboration with EACTS. Eur Heart J. 2016;37:2893–962.

30. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in collaboration with the Society of Thoracic Surgeons. Circulation. 2019;140:e125–51.

31. Dick F, Diehm N, Galimain A, Husmann M, Schmidt J, Baumgartner I. Surgical or endovascular revascularization in patients with critical limb ischemia: influence of diabetes mellitus on clinical outcome. J Vasc Surg. 2007;45:751–61.

32. Jude EB, Oyibo SO, Chalmers N, Boulton AJ. Peripheral arterial disease. Eur Heart J. 2007;28:2732–40.

33. Jude EB, Oyibo SO, Chalmers N, Boulton AJ. Peripheral arterial disease. Eur Heart J. 2018;39:1319–30.

34. Bhatt DL, Steg PG, Mehta SR, Leiter LA, Simon T, Fox K, et al. Ticagrelor in patients with diabetes and stable coronary artery disease with a history of previous percutaneous coronary intervention (THERMIS-PCLI): a phase 3, placebo-controlled, randomised trial. Lancet. 2019;394:1169–80.

35. Steg PG, Bhatt DL, Simon T, Fox K, Mehta SR, Harrington RA, et al. Ticagrelor in patients with stable coronary disease and diabetes. N Engl J Med. 2019;381:1311–20.

36. Bonaca MP, Scirica BM, Creager MA, Olin J, Bounameaux H, Dellborg M, et al. Vorapaxar in patients with peripheral artery disease: results from TRA2°P-TIMI 50. Circulation. 2013;127:1522–9.

37. Caovender MA, Scirica BM, Bonaca MP, Angiolillo DJ, Dalby AJ, Dellborg M, et al. Vorapaxor in patients with diabetes mellitus and previous myocardial infarction: findings from the thrombin receptor antagonist in secondary prevention of atherothrombotic ischemic events-TIMI 50 trial. Circulation. 2015;131:1047–53.

38. Markus HS, Droste DW, Kaps M, Larue V, Lees KR, Siebler M, et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Embolic in Symptomatic Carotid Stenosis (CARESS) trial. Circulation. 2005;111:2233–40.

39. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakova O, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med. 2017;377:1319–30.

40. Connolly SJ, Eikelboom JW, Bosch J, Dagenais GS, Dyal L, Laras F, et al. Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet. 2018;391:205–18.

41. Anand SS, Caron F, Eikelboom JW, Bosch J, Dyal L, Aboyans V, et al. Major adverse limb events and mortality in patients with peripheral artery disease: the COMPASS trial. J Am Coll Cardiol. 2018;71:2306–15.

42. Anand SS, Bosch J, Eikelboom JW, Connolly SJ, Diaz R, Widimsky P, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet. 2018;391:219–29.

43. Anand SS, Eikelboom JW, Dyal L, Bosch J, Neumann C, Widimsky P, et al. Rivaroxaban plus aspirin versus aspirin in relation to vascular risk in the COMPASS trial. J Am Coll Cardiol. 2019;73:3271–80.

44. Bhatt DL, Eikelboom JW, Connolly SJ, Steg PG, Anand SS, Verma S, et al. Role of combination antiplatelet and anticoagulation therapy in diabetes and cardiovascular disease: insights from the COMPASS trial. Circulation. 2020;141:1841–54.

45. Sharma M, Hart RG, Connolly SJ, Bosch J, Shestakova O, Ng KH, et al. Stroke outcomes in the Cardiovascular OutcoMes for People using Anti-coagulation StrategieS (COMPASS) Trial. Circulation. 2019;139:1134–45.

46. D’Alessio DA, Bauschert RM, Anand SS, Debus ES, Nehler MR, Patel MR, et al. Rivaroxaban in peripheral artery disease after revascularization. N Engl J Med. 2020;382:1994–2004.

47. Bayer AG. Xarelto (rivaroxaban) Summary of Product Characteristics. 2021. https://www.ema.europa.eu/documents/product-information/xarelto-evar-product-information_enpdf. Accessed 19 May 2022.

48. Belch JJF, Brodmann M, Baumgartner L, Binder CJ, Casula M, Heiss C, et al. Lipid-lowering and anti-thrombotic therapy in patients with peripheral arterial disease: European Atherosclerosis Society/
European Society of Vascular Medicine Joint Statement. Atherosclerosis. 2021;3:383:55–63.

55. Abayomi V, Baurersachs R, Mazzolai L, Brodmann M, Palomares JFR, Debus S, et al. Antithrombotic therapies in aortic and peripheral arterial diseases in 2021: a consensus document from the ESC working group on aorta and peripheral vascular diseases, the ESC working group on thrombosis, and the ESC working group on cardiovascular pharmacotherapy. Eur Heart J. 2021;42:4013–24.

56. Lip GYH, Nieuwlaat R, Pisters R, Lane D, Crijns H. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor based approach. The Euro Heart Survey on Atrial Fibrillation. Chest. 2010;137:623–72.

57. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstöm-Lundqvist C, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2021;42:373–498.

58. Japanese Circulation Society Joint Working Group. Guidelines for pharmacotherapy of atrial fibrillation (JCS 2013). Circ. J. 2014;78:1997–2021.

59. Andrade JG, Aguilar M, Atzema C, Bell A, Cairns JA, Cheung CC, et al. 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society comprehensive guidelines for the management of atrial fibrillation. Can J Cardiol. 2020;36:1319–91.

60. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883–91.

61. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2021;42:373–498.

62. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1339–51.

63. Granger CB, Alexander JH, McMurray JV, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981–92.

64. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Vlietvoet SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369:2093–104.

65. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deedwany U, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383:955–62.

66. Bansal S, Bloomgarden Z, Halperin JL, Hellkamp AS, Lokhnygina Y, Patel MR, et al. Efficacy and safety of rivaroxaban in patients with diabetes and nonvalvular atrial fibrillation: the rivaroxaban once-daily, oral, direct factor xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF trial). Am Heart J. 2015;169:765–82.

67. Brambati M, Darius H, Oldgren J, Clemens A, Parekh A, et al. Comparison of dabigatran versus warfarin in diabetic patients with atrial fibrillation: results from the RE-LY trial. Int J Cardiol. 2015;195:127–31.

68. Plat A, Zelniker TA, Park JG, McGuire DK, Ruff CT, Antman EM, et al. Patients with diabetes mellitus and atrial fibrillation treated with apixaban: results from the ARISTOTLE trial. Eur Heart J Cardiovasc Pharmacother. 2015;1:85–92.

69. Efthymiou I, Hoogendoorn CM, Scholten T, Dekker JM, Boersma E, et al. Effectiveness of antithrombotic therapy in relation to renal function over time: Insights from the ARISTOTLE randomized clinical trial. JAMA Cardiol. 2016;1:451–60.

70. Fordyce CB, Hellkamp AS, Lokhnygina Y, Lindner SM, Piccini JP, Becker RC, et al. On-treatment outcomes in patients with worsening renal function with rivaroxaban compared with warfarin: insights from the ROCKET AF Circulation. 2016;134:37–47.

71. Yao X, Tangri N, Gersh B, Sangaralingham LR, Shah ND, Nath K, et al. Renal outcomes in anticoagulated patients with atrial fibrillation. Am J Cardiol. 2017;120:2621–32.

72. Heerspink HJL, Stefansson BV, Correa-Rotter R, Cheetham GM, Greene T, Hou FF, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383:1436–46.
Go AS, Fang MC, Uddalova N, Chang Y, Pomeracki NK, Borowsky L, et al. Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. Circulation. 2009;119:1363–9.

Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al. The 2018 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018;39:1330–93.

Sharifuddin N, Nourbakhsh M, Box A, Benedikttson H, Muruve DA. Anticoagulant related nephropathy induced by dabigatran. Case Rep Nephrol. 2018;2018:738105.

Brodsky SV, Collins M, Park E, Rovin BH, Satoskar AA, Nadasdy G, et al. Warfarin therapy that results in an International Normalization Ratio above the therapeutic range is associated with accelerated progression of chronic kidney disease. Nephron Clin Pract. 2010;115:e12–6.

de Aquino Moura KB, Behrens PMP, Pirolli R, Sauer A, Melamed D, Veronez FV, et al. Anticoagulant-related nephropathy: systematic review and meta-analysis. Clin Kidney J. 2019;12:400–7.

Wheeler D, Grugliano R, Rangasawami J. Anticoagulation-related nephropathy. J Thoron Haemost. 2016;14:461–7.

Palooan NJ, Garellici CM. A current understanding of vascular calcification in CKD. Am J Physiol Renal Physiol. 2014;307:F891-900.

Sayer JA, Carr G, Simmons NL. Nephrocalcinosis: molecular insights into calcium precipitation within the kidney. Clin Sci. 2004;106:549–61.

Koos R, Mahrenk AH, Muhlenbruch G, Brandenburg V, Pflueger B, Wildberger JE, et al. Relation of oral anticoagulation to cardiac valvular and coronary calcium assessed by multislice spiral computed tomography. Am J Cardiol. 2005;96:747–9.

Peeters MTJ, Houben R, Postma AA, van Oostenbrugge RJ, Schurgers LJ. Vitamin K antagonist use and risk for intracranial carotid artery calcification in patients with intracranial hemorrhage. Front Neurol. 2019;10:1278.

Hughes S, Szaki L, Nash MJ, Thachil J. Anticoagulation in chronic kidney disease patients—the practical aspects. Clin Kidney J. 2014;7:442–9.

Shin JI, Luo S, Alexander GC, Inker LA, Coresh J, Chang AR, et al. Direct oral anticoagulants and risk of acute kidney injury in patients with atrial fibrillation. J Am Coll Cardiol. 2018;71:251–2.

Coleman CI, Kreutz R, Sood N, Bunz TJ, Meinecke AK, Eiriksson D, et al. Rivaroxaban’s impact on renal decline in patients with nonvalvular atrial fibrillation: a US MarketScan claims database analysis. Clin Appl Thromb Hemost. 2019;25:107629619868535.

Hernandez AV, Bradley G, Khan M, Fratoni A, Gasparini A, Roman YM, et al. Rivaroxaban versus warfarin and renal outcomes in non-valvular atrial fibrillation patients with diabetes. Eur Heart J Qual Care Clin Outcomes. 2019;6:301–7.

van Gorp RH, Schurgers LJ. New insights into the pros and cons of the clinical use of vitamin K antagonists (VKAs) versus direct oral anticoagulants (DOACs). Nutrients. 2015;7:9538–57.

Turpie AGG, Purdham D, Ciaccia A. Vitamin K antagonist oral anticoagulant use in patients with renal impairment. Ther Adv Cardiovasc Dis. 2017;11:243–56.

Brillon MY, Quib澎湃新闻, Pfister E. Eliquis (apixaban) Summary of product characteristics. 2022. https://www.ema.europa.eu/documents/product-information/elixi product-information_en.pdf. Accessed 25 April 2022.

Daichi Sankyo Europe GmbH. Lixiana® (edoxaban) Summary of Product Characteristics. 2021. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002629/WC500189045.pdf. Accessed 19 May 2022.

Boehringer Ingelheim International GmbH. Pradaxa (dabigatran etexilate) Summary of product characteristics. 2022. https://www.ema.europa.eu/documents/product-information/pradaxa-epar-product-information_en.pdf. Accessed 25 April 2022.

Nelson SE, Shroff GR, Li S, Herzog CA. Impact of chronic kidney disease on risk of arterial fibrillation and subsequent survival in medicare patients. J Am Heart Assoc. 2012;1:e002097.

Premuzic V, Stevanovic R, Radic P, Salveti M, Lovnic-Bencic M, Jelakovic A, et al. Chronic kidney disease and cardiovascular mortality in patients with atrial fibrillation: European Society of Hypertension project—ESH A Fib. Medicine. 2021;100:e23975.

Meloni AR, De'Young MB, Lowe C, Parke DS. GLP-1 receptor activated insulin secretion from pancreatic beta-cells: mechanism and glucose dependence. Diabetes Obes Metab. 2013;15:15–27.

Hummel CS, Lu C, Loo DD, Hirayama BA, Voss AA, Wright EM. Glucose transport by human renal Na+-glucose cotransporters SGLT1 and SGLT2. Am J Physiol Cell Physiol. 2011;300:C14-21.

American Diabetes Association. 9. Pharmacologic approaches to glycemetic treatment: standards of medical care in diabetes—2021. Diabetes Care. 2021;44:S111–24.

Giugliano D, Scappaticcio L, Longo M, Caruso P, Maiorino MI, Bellastella G, et al. GLP-1 receptor agonists and cardio-renal outcomes in type 2 diabetes: an updated meta-analysis of eight CVOTs. Cardiovasc Diabetol. 2021;20:189.

Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117–28.

Furtado RMS, Bonaca MP, Razl, Zelniker TA, Mosesson Z, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in patients with type 2 diabetes mellitus and previous myocardial infarction. Circulation. 2019;139:2516–27.

Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondo N, et al. Cardiogfilzin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377:644–57.

Marso SP, Bain SC, Consoli A, Elaischwitz FG, Jodar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375:1834–44.

Wanner C, Inzucchi SE, Lachin JM, Fitchett D, von Eynatten M, Mattheus M, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med. 2016;375:323–34.

Mann JF, Orsted DD, Brown-Brandes K, Marso SP, Poultier NR, Rasmussen S, et al. Liraglutide and renal outcomes in type 2 diabetes. N Engl J Med. 2017;377:839–48.

Dhathiyai K, Bain SC, Buse JB, Simpson R, Tamow L, Kaltoft MS, et al. The impact of liraglutide on diabetes-related foot ulceration and associated complications in patients with type 2 diabetes at high risk for cardiovascular events: results from the LEADER trial. Diabetes Care. 2018;41:2299–35.

Lin DS, Lee JK, Chen WJ. Major adverse cardiovascular and limb events in patients with diabetes treated with GLP-1 receptor agonists vs DPP-4 inhibitors. Diabetologia. 2021;64:1949–62.

American Diabetes Association Professional Practice C, Draznin B, Aroda A. 10. Cardiovascular disease patients—the practical aspects. Clin Kidney J. 2014;7:442–9.

Buse JB, Wexler DJ, Taspas A, Rossing P, Mingrone G, Mathieu C, et al. 2019 update to: management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2020;2020(63):221–8.

Chao TF, Leu HB, Huang CC, Chen JW, Chan WL, Lin SJ, et al. Thiazolidinediones can prevent new onset atrial fibrillation in patients with non-insulin dependent diabetes. Int J Cardiol. 2012;156:199–202.

Chang SH, Wu LS, Chiuoi MJ, Liu JR, Yu KH, Kuo CF, et al. Association of metformin with lower atrial fibrillation risk among patients with type 2 diabetes mellitus: a population-based dynamic cohort and in vitro studies. Cardiovasc Diabetol. 2014;13:123.

Zelniker TA, Bonaca MP, Furtado RH, Mosesson Z, Kuder JF, Murphy SA, et al. Effect of dapagliflozin on atrial fibrillation in patients with type 2 diabetes mellitus: insights from the DECLARE-TIMI 58 trial. Circulation. 2020;2020(141):1227–34.

Zhang Z, Zhang X, Korantzopoulos P, Letsas KP, Tse G, Gong M, et al. Thiazolidinedione use and atrial fibrillation in diabetic patients: a meta-analysis. BMC Cardiovasc Disord. 2017;17:96.

Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained with.
chronic hyperglycemia in patients with type 2 diabetes. JAMA. 2006;295:1681–7.

134. Ceriello A, Esposito K, Piconi L, Ihnat MA, Thorpe JE, Testa R, et al. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. Diabetes. 2008;57:1349–54.

135. Gu J, Fan YQ, Zhang JF, Wang CQ. Impact of long-term glycemic variability on development of atrial fibrillation in type 2 diabetic patients. Anatol J Cardiol. 2017;18:410–6.

136. Dasgupta A, Steinhubl SR, Bhatt DL, Berger PB, Shao M, Mak KH, et al. Clinical outcomes of patients with diabetic nephropathy randomized to clopidogrel plus aspirin versus aspirin alone (a post hoc analysis of the clopidogrel for high atherothrombotic risk and ischemic stabilization, management, and avoidance [CHARISMA] trial). Am J Cardiol. 2009;103:1359–63.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.