Antithrombotic therapy in diabetes: which, when, and for how long?

Ramzi A. Ajjan1,*, Noppadol Kietsiriroje1,2, Lina Badimon3,4,5, Gemma Vilahur3,4, Diana A. Gorog6,7, Dominick J. Angiolillo8, David A. Russell1,9, Bianca Rocca10, and Robert F. Storey11

1The LIGHT Laboratories, Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds LS2 7JT, UK; 2Endocrinology and Metabolism Unit, Internal Medicine Department, Faculty of Medicine, Prince of Songkla University, Songkhla 90110, Thailand; 3Cardiovascular Program ICCC, Research Institute Hospital de la Santa Creu i Sant Pau, IIB-Sant Pau, Sant Antoni M. Claret 167, 08025 Barcelona, Spain; 4Centro de Investigación Biomédica en Red Cardiovascular (CIBERCV), Instituto de Salud Carlos III, Sant Antoni M. Claret 167, 08025 Barcelona, Spain; 5Cardiovascular Research Chair, Universidad Autónoma Barcelona (UAB), Sant Antoni M. Claret 167, 08025 Barcelona, Spain; 6University of Hertfordshire, College Lane Campus Hatfield, Hertfordshire AL10 9AB, UK; 7National Heart and Lung Institute, Guy Scadding Building, Dovehouse St, London SW3 6LY, UK; 8Division of Cardiology, University of Florida College of Medicine – Jacksonville, 655 West 8th Street, Jacksonville, FL 32209, USA; 9Leeds Vascular Institute, Leeds General Infirmary, Great George Street, Leeds LS1 3EX, UK; 10Institute of Pharmacology, Catholic University School of Medicine, Rome, Italy; and 11Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Beech Hill Road, Sheffield S10 2RX, UK

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Cardiovascular disease remains the main cause of mortality in individuals with diabetes mellitus (DM) and also results in significant morbidity. Premature and more aggressive atherosclerotic disease, coupled with an enhanced thrombotic environment, contributes to the high vascular risk in individuals with DM. This prothrombotic milieu is due to increased platelet activity together with impaired fibrinolysis secondary to quantitative and qualitative changes in coagulation factors. However, management strategies to reduce thrombosis risk remain largely similar in individuals with and without DM. The current review covers the latest in the field of antithrombotic management in DM. The role of primary vascular prevention is discussed together with options for secondary prevention following an ischaemic event in different clinical scenarios including coronary, cerebrovascular, and peripheral artery diseases. Antiplatelet therapy combinations as well as combination of antplatelet and anticoagulant agents are examined in both the acute phase and long term, including management of individuals with sinus rhythm and those with atrial fibrillation.

The difficulties in tailoring therapy according to the variable atherothrombotic risk in different individuals are emphasized, in addition to the varying risk within an individual secondary to DM duration, presence of complications and predisposition to bleeding events. This review provides the reader with an up-to-date guide for antithrombotic management of individuals with DM and highlights gaps in knowledge that represent areas for future research, aiming to improve clinical outcome in this high-risk population.
Introduction

Despite advances in therapy, a diagnosis of diabetes mellitus (DM) is associated with increased morbidity and reduced lifespan, mainly due to vascular complications. Premature and more severe vascular disease, as well as a prothrombotic environment, represent key mechanisms for adverse vascular outcomes in this population. The prothrombotic milieu develops secondary to increased platelet reactivity coupled with hypofibrinolysis.

Current treatment strategies to improve vascular outcomes in individuals with DM are focused on revascularization of acute atherothrombotic occlusions, where possible, together with early introduction of antithrombotic therapies, usually by inhibiting platelet function. This continues long-term coupled with multifactorial therapy targeting hypertension, dyslipidaemia and dysglycaemia in order to limit the progression of vascular pathology.

In this review, we discuss the latest in antithrombotic therapies for the management of coronary artery disease (CAD), cerebrovascular disease, and peripheral artery disease (PAD) in DM, covering therapies for primary prevention, acute vascular occlusion and long-term secondary prevention. Special emphasis is placed on the benefits and risks of antithrombotic therapy combinations, with the overall aim of providing the reader with an up-to-date guide for antithrombotic management in DM. Search strategy is detailed in the Supplementary material online.

The thrombotic environment in diabetes

Individuals with DM are prone to both arterial and venous thrombosis. DM is characterized by multiple pathological processes, including hyperglycaemia, chronic inflammation, oxidative stress, and associated metabolic conditions, that damage the endothelium and increase platelet reactivity, resulting in a prothrombotic environment. Endothelial dysfunction is a consistent finding in DM patients and contributes to the prothrombotic shift (Figure 1).

An array of mechanisms operate in platelets to enhance their reactivity. Hyperglycaemia is associated with higher expression of platelet receptors, including glycoprotein (GP) Ibα, GPIIb/IIIa and P2Y12, reduced platelet membrane fluidity secondary to increased glycation, higher thromboxane (TX) A2 synthesis together with...
Increased platelet activation markers. Diabetes-associated oxidative stress also increases production of F2-isoprostanes, TXA2 and F2-isoprostanes, in turn, activate the thromboxane receptors and amplify platelet activation (Figure 1). Platelet hyper-reactivity also results from diminished sensitivity to the inhibitory agents prostacyclin, nitric oxide, and insulin, and from changes in platelet content of miRNAs known to regulate platelet function (miR-223, miR-26b, and miR-140).18,19 Moreover, the imbalance in intraplatelet magnesium and calcium homeostasis renders platelets more sensitive to epinephrine, adenosine diphosphate (ADP), and thrombin. DM is also characterized by altered platelet turnover, as evidenced by release of more reactive, reticulated platelets that display a reduced response to antiplatelet agents. Finally, platelets from DM patients more easily externalize phosphatidylserine in the outer platelet membrane, thereby providing a better surface for the assembly of clotting factors and tissue factor activation.21,22

Other associated metabolic conditions like obesity, dyslipidaemia, and systemic inflammation also contribute to thrombosis risk. Circulating inflammatory molecules [tumour necrosis factor-α, interleukin (IL)-1 and IL-6, selectin, soluble CD40 ligand], besides enhancing platelet reactivity, favour a hypercoagulable environment. Furthermore, bone marrow transplants that created chimeras of normal rats with bone marrow cells from diabetic rats resulted in a prothrombotic phenotype similar to the donor animals, indicating the imprinting effects of DM on haematopoietic cells.22

Several prothrombotic alterations in the coagulation-fibrinolytic system also occur in DM, including increased levels of tissue factor, prothrombin, factor VII and fibrinogen coupled with impaired anticoagulant and fibrinolytic activity (Figure 1). Diabetic thrombi display compact fibrin networks with densely-packed thin fibres that are resistant to fibrinolysis. Furthermore, hyperglycaemia induces qualitative changes in plasminogen, hindering its fibrinolytic activity. Concomitantly, elevated levels of anti-fibrinolytic proteins (plasminogen activator inhibitor-1 and thrombin-activatable fibrinolysis inhibitor), along with increased incorporation of anti-fibrinolytic proteins (complement C3 and plasmin inhibitor) into the clot further compromise fibrinolysis. Despite this prothrombotic environment, DM patients have a paradoxical increased risk of bleeding, particularly...
following an acute coronary syndrome (ACS). However, data on stable patients are less clear: the dual antiplatelet therapy (DAPT) study (detailed below under ‘Secondary Prevention’) reported no increase in long-term moderate or severe bleeding events in those with DM, possibly related to excluding those with bleeding events in the first 12 months, while increased risk was documented in the REACH and CORONOR registries. The exact mechanisms for the increase in both thrombosis and bleeding risk in some diabetes patients are not fully understood, although renal complications may have a role. Also, chronic activation of platelet and coagulation proteins may ‘exhaust’ the system in some DM patients, thus increasing bleeding risk.

Antithrombotic targets

For decades, the two main antithrombotic targets have been platelet TXA2 production and platelet P2Y12 receptor activation.

Aspirin

Low-dose aspirin irreversibly inhibits platelet cyclooxygenase-1 enzyme, preventing the conversion of arachidonic acid into bioactive prostanoid TXA2. Given the short half-life of aspirin and increased platelet turnover in DM, a proportion of platelets may escape 24-h inhibition by once-daily aspirin, which can be re-established by twice-daily dosing.

P2Y12 receptor antagonists

ADP-stimulated effects on platelets are mediated primarily by G-coupled P2Y12 receptor activation, leading to persistent platelet aggregation, whereas P2Y1 is responsible for an initial weak, transient phase of platelet aggregation. There are two main classes of orally administered P2Y12 inhibitors: thienopyridines (ticlopidine, clopidogrel, and prasugrel) and non-thienopyridine agents (ticagrelor). Thienopyridines require conversion to an active metabolite that acts irreversibly. Ticlopidine is no longer marketed in many countries due to safety concerns. Ticagrelor is a direct-acting cyclopentyltriazolo-pyrimidine that requires no metabolism and binds reversibly to the P2Y12 receptor.

Other antithrombotic approaches

Warfarin and other vitamin K antagonists (VKAs) require regular monitoring and this, together with high bleeding risk when combined with antiplatelet therapy, prevented widespread use. More modern approaches include modulation of thrombin activity either by blocking protease-activated receptor-1 on platelet membrane (vorapaxar) or by directly inhibiting protein function (dabigatran). Other non-VKA oral anticoagulants (NOAC) include inhibitors of activated factor Xa (apixaban, rivaroxaban, and edoxaban).

Antithrombotic therapy for primary prevention of ischaemic events

Primary prevention is defined as offering therapy to individuals without a history of a vascular ischaemic event. In the largest individual data meta-analysis of primary prevention trials (n = 95 000 individuals), aspirin use in DM was associated with a non-significant 12% relative risk reduction (RRR) of major adverse cardiac events (MACE), from 1.87% to 1.63% per year [hazard ratio (HR) 0.88 (0.67–1.15); Table 1]. Although non-significant, this benefit was comparable to non-DM individuals, in whom aspirin reduced yearly MACE from 0.57% to 0.51% [HR 0.88 (0.82–0.94); P = 0.0001]. Aspirin was associated with an increase in extracranial, mainly gastrointestinal, bleeding in both non-DM and DM populations (P = 0.20 for heterogeneity; Table 1). Following this meta-analysis, the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) (n = 25 399) and prevention of progression of arterial disease and diabetes (POPADAD) (n = 12 726) trials investigated aspirin in primary prevention but, being small and underpowered, failed to provide conclusive data. The recent ASCEND trial is the largest, longest and only adequately powered trial investigating primary prevention in DM, randomizing 15 480 DM patients without symptomatic cardiovascular disease to aspirin (100 mg daily) or placebo. Serious vascular events occurred in 8.5% of individuals on aspirin vs. 9.6% on placebo [RRR 12%, HR 0.88 (0.79–0.97); P = 0.01]. Major bleeding, according to the Bleeding Academic Research Consortium (BARC) 2, 3, and 5 categories, occurred in 4.1% and 3.2% in the aspirin and placebo arms, respectively, without significant differences in fatal or intracranial bleeding, although the absolute number of events was lower (Table 1). Notably, >50% of major bleeding excess with aspirin was gastrointestinal. The number needed to treat (NNT)/number needed to harm (NNH) ratio was 0.8, favouring treatment. Importantly, BARC 2–5 bleeding criteria are less restrictive as compared to the Thrombolysis in Myocardial Infarction (TIMI) major criteria. Of note, there was no significant heterogeneity in the effect of aspirin according to the estimated vascular risk at baseline. A meta-analysis of 12 randomized controlled trials (RCTs) (34 227 individuals), including the ASCEND population, showed that aspirin reduces MACE by 11% compared with placebo [HR 0.89 (0.83–0.95)] (Table 1).

The THEMIS study tested intensification of antiplatelet regimen in 19 220 DM patients without previous myocardial infarction (MI) or stroke but with evidence of clinical CAD and already on low-dose aspirin therapy (Table 1). Individuals randomized to aspirin and ticagrelor had a modest reduction in vascular events compared with aspirin alone [7.7% and 8.5%, respectively, HR 0.90 (0.81–0.99); P = 0.04], associated with a 2.3-fold increase in TIMI major bleeding and a 1.7-fold increase in intracranial bleeding (Table 1), giving an unfavourable NNT/NNH ratio of 1.48 and arguing against routine DAPT with aspirin and ticagrelor in this population.

The recent European Society of Cardiology (ESC) guidelines indicate that those with DM and >1 organ damage or >3 major risk factors, or any risk factor and >10 years disease duration without organ damage, should be considered for primary prevention, in the absence of contraindications (Supplementary material online, Table S2) but routine use of aspirin for all DM individuals is not recommended.
## Table 1  Primary prevention in diabetes

| Study             | Patients | Primary efficacy endpoint                                                                 | Median follow-up | Predicted vs. observed incidence and expected benefit | Absolute and relative benefit | Absolute and relative harm | Comments                                                                 |
|-------------------|----------|-------------------------------------------------------------------------------------------|-------------------|-------------------------------------------------------|-----------------------------|--------------------------|-------------------------------------------------------------------------|
| ATT meta-analysis (2009) | 95 000 patients from six primary prevention trials which included 4% of DM patients (n = 3818) | Stroke, MI, and CV death | NA | NA | Overall population: Aspirin: 0.51% Control: 0.57% HR 0.88 (0.82–0.94) | | | No difference in fatal bleeding |
| JPAD (2008)      | 2539 T2DM patients without a history of atherosclerotic disease | Sudden death; death from coronary, cerebrovascular, and aortic causes; non-fatal acute MI; UA; exertional angina; non-fatal ischaemic and haemorrhagic stroke; TIA; or non-fatal aortic and PVD | 4.4 years | Predicted: 5.2%/year vs. Observed: 1.7%/year Expected benefit: 30% RRR | Aspirin: 5.4% Placebo: 6.7% HR 0.80 (0.58–1.10) | | Expected benefit likely unrealistic based on previous data (trial largely underpowered). |
| POPADAD (2008)   | 1276 adults aged ≥40 years with T1DM or T2DM and ABI ≤0.99 (asymptomatic) | Death from CAD or stroke, non-fatal MI or stroke, or amputation for critical limb ischaemia; and death from CAD or stroke | 6.7 years | Predicted: 28%/year vs. observed: 2.9%/year Expected benefit: 25% RRR | Aspirin: 18.2% Placebo: 18.3% HR 0.98 (0.76–1.26) | | Observed events were approx. 1/10 of predicted. The expected benefit was likely unrealistic based on previous data (trial was largely underpowered). |
| ASCEND (2018)    | 15 480 Patients aged ≥40 years with DM and no evident CV disease | Non-fatal MI, non-fatal stroke (excluding confirmed ICH), TIA, or death from any vascular | 7.4 years | Predicted: 1.2–1.3%/year vs. Observed: 1.3%/year Expected benefit: | Aspirin: 8.5% Placebo: 9.6% HR 0.88 (0.79–0.97) | | Consistency between predicted and observed incidence event rate |
| Study                  | Patients                                                                 | Primary efficacy endpoint | Median follow-up | Predicted vs. observed incidence and expected benefit | Absolute and relative benefit | Absolute and relative harm | Comments                                      |
|-----------------------|--------------------------------------------------------------------------|----------------------------|------------------|------------------------------------------------------|------------------------------|---------------------------|-----------------------------------------------|
| THEMIS (2019)         | 19 220 patients with DM, ≥50 years, stable CAD with no previous MI or stroke Randomized to ticagrelor or placebo on a background of aspirin therapy | Stroke, MI, and CV death   | 3.3 years        | Predicted benefit: 16% RRR                           |                              |                           | ICH: Aspirin: 0.7% Placebo: 0.6% HR 1.22 (0.82–1.81) Fatal bleeding: Aspirin: 0.2% Placebo: 0.2% HR 1.18 (0.61–2.30) |
|                       |                                                                          |                            |                  | Ticagrelor: 7.7% Placebo: 8.5% HR 0.90 (0.81–0.99)     |                              |                           | High rate of ticagrelor discontinuation: Placebo 25% vs. Ticagrelor: 35% HR 1.50 (1.42–1.58) Predicted benefit higher than observed. NNT/NNH: 1.48 (TIMI major defined bleeding) |
| Meta-analysis          | 34 227 participants with DM, individual patient data from 2306 participants | Stroke, MI, and CV death   | 5 years          | NA                                                   | Aspirin: 8.6% Control: 9.6% HR 0.89 (0.83–0.95)       |                           | Major bleeding: Aspirin: 4% Control: 3.5% HR 1.30 (0.92–1.82) |

Summary of primary prevention studies. Significant differences are reported in bold.

ABI, ankle-brachial index; BARC, Bleeding Academic Research Consortium; CAD, coronary artery disease; CV, cardiovascular; DM, diabetes mellitus; GI, gastrointestinal; HR, hazard ratio; ICH, intracranial haemorrhage; MI, myocardial infarction; NA, not applicable; NNH, number needed to harm; NNT, number needed to treat; PVD, peripheral vascular disease; RRR, relative risk reduction; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TIA, transient ischaemic attack; TIMI, Thrombolysis in Myocardial Infarction; UA, unstable angina.
Overall, guidelines recommend aspirin monotherapy for DM patients with additional risk factor(s) and/or with an estimated annual risk of vascular events ≥1% (Supplementary material online, Table S2).52–54

**Secondary prevention in the absence of atrial tachyarrhythmias**

**Following acute coronary events**

ACS guidelines recommend DAPT comprising aspirin and prasugrel or ticagrelor, which applies to DM individuals.33,51,55,56 Patients with DM, however, exhibit enhanced platelet reactivity and reduced sensitivity to thienopyridines (but not ticagrelor),57,58 although the clinical significance of these biochemical observations remains unclear.

**Aspirin**

Guidelines recommend routine early administration of aspirin in ACS, which seems to offer similar benefits in individuals with and without DM. Based on pharmacodynamic studies in DM,33,59,60 the clinical benefit of twice-daily aspirin administration is being evaluated in the ANDAMAN trial (NCT02520921). Higher aspirin doses (300–325 mg vs. 75–100 mg) failed to reduce MACE 30 days post-ACS in the CURRENT-OASIS 7 study (23% had DM).61 The ongoing ADAPTABLE study is assessing alternative aspirin dosing, although this is not limited to the DM population.52 Moreover, ongoing studies are aiming to identify new low-dose aspirin formulations with potentially improved safety and efficacy profiles.63,64

**P2Y12 inhibitors**

In individuals with DM, prasugrel or ticagrelor combination with aspirin is preferred to clopidogrel, which shows reduced efficacy.30,56,65–67 Post hoc analysis of the DM population in the TRITON-TIMI 38 trial showed marked benefit of prasugrel over clopidogrel,66 while, in PLATO, the absolute benefit of ticagrelor over clopidogrel was greatest in patients with both DM and chronic kidney disease (CKD).68 In patients with ACS and insulin-requiring DM, ticagrelor may achieve more potent platelet inhibition than prasugrel,69 although the clinical significance is unclear. The recent ISAR-REACT 5 study, an open-label trial, demonstrated superiority of a prasugrel-based strategy over a ticagrelor-based strategy in reducing MACE in ACS patients.69 However, this was not the case in the DM subgroup: the composite primary endpoint (death, stroke, or MI) occurred in 11.2% and 13.0% in ticagrelor and prasugrel arms, respectively [HR 0.84 (0.58–1.24); P = 0.383] with treatment interaction shown for DM status (P = 0.0035).70 Bleeding complications were similar in ticagrelor- and prasugrel-treated DM individuals.

A difficulty with more potent oral P2Y12 inhibitors is the limited evidence in the older population who are at higher bleeding risk. Two smaller studies in ACS patients aged ≥70 years, of whom a third had DM, indicated that de-escalation from prasugrel or ticagrelor to clopidogrel may be safe.71 Moreover, platelet-function-guided de-escalation from prasugrel to clopidogrel at hospital discharge may be non-inferior to continued prasugrel but this strategy appears safer in those without DM.72 The TWILIGHT study (n = 7119) assessed safety of de-escalating DAPT, from ticagrelor plus aspirin to ticagrelor monotherapy, after 3 months of DAPT following high-risk percutaneous coronary intervention (PCI) for ACS or chronic coronary syndromes (CCS).73 Monotherapy reduced the primary endpoint of BARC type 2, 3, or 5 bleeding compared with DAPT at 12 months [4.0% vs. 7.1%, HR 0.56 (0.45–0.68); P < 0.001], similarly in those with and without DM, without increasing the secondary combined endpoint of death, MI, or stroke. More specifically, ticagrelor monotherapy in the DM subgroup did not increase ischaemic events compared with DAPT [4.6% vs. 5.9%; HR 0.77 (0.55–1.09); P = 0.14] but significantly decreased bleeding complications [4.5% vs. 6.7%; HR 0.65 (0.47–0.91); P = 0.012].74 The GLOBAL LEADERS trial randomized individuals undergoing PCI with drug-eluting stents for CCS or ACS to standard care (DAPT for 12 months followed by aspirin alone) or ticagrelor with aspirin for 1 month followed by ticagrelor monotherapy for 23 months. The study failed to show superiority for the intervention, although a trend towards a reduction in the primary composite endpoint of death or new Q-wave infarction was apparent [HR 0.87 (0.75–1.01); P = 0.073]. Risk of bleeding was almost identical in the two groups, regardless of DM status.75,76 The more recent analysis of the subgroup of DM individuals and CKD (higher risk of thrombosis and bleeding) showed no significant reduction in the primary endpoint with the intervention, although lower rates of the patient-oriented composite endpoint (POCE; death, stroke, site-reported MI/vascularization) were observed in the ticagrelor group compared with controls [20.6% vs. 25.9%, HR 0.74 (0.55–0.99)] with similar reduction in net adverse clinical events (POCE plus BARC 3 and 5 bleeding events) [22.7% vs. 28.3%, HR 0.75 (0.56–0.99)].76 Moreover, a recent meta-analysis has shown that, following PCI, monotherapy with a P2Y12 inhibitor is preferable to DAPT in older individuals and those with diabetes, CKD or multivessel disease due to reduction in bleeding risk.78 Therefore, de-escalation of DAPT may be an option in some patients, particularly when using potent P2Y12 inhibitors as monotherapy.79 However, de-escalation is perhaps best avoided in the DM population, given the high vascular risk, unless there are major concerns over bleeding risk and this remains an area for future research.

**Glycoprotein IIb/IIIa inhibitors**

GP inhibitor (GPI) use in ACS significantly reduced 30-day mortality, particularly in DM patients undergoing PCI, but this benefit was observed before routine P2Y12 inhibitor use.80 Abciximab reduced MACE in ACS patients undergoing PCI, even with clopidogrel pre-treatment, but the benefit in DM patients was less pronounced (abciximab has now been withdrawn in Europe).81 In contemporary practice using potent P2Y12 inhibitors, GPI therapy is mainly reserved for ‘bail-out’ in case of no-reflow or a thrombotic complication during PCI,82 although some benefit has been suggested also in opiate-treated patients undergoing emergency PCI.83

**Very-low-dose non-VKA oral anticoagulant**

In the ATLAS ACS 2-TIMI 51 trial, the addition of very-low-dose rivaroxaban (2.5 mg twice daily) to DAPT (in the form of aspirin and clopidogrel) in ACS patients, of whom 32% had DM, significantly reduced MACE compared to placebo but the DM group appeared to derive less benefit.84 An increase in bleeding events, including intracranial, was documented and therefore this triple therapy (TT) can only be advocated for individuals at very high vascular risk with
relatively low bleeding risk, accepting the challenge that ischaemic and bleeding risk factors overlap substantially. A summary of the agents used following ACS is given in Figure 2.

**Long-term therapy for secondary prevention**

Default practice is DAPT for 1 year post-ACS followed by antiplatelet monotherapy, usually with aspirin. However, DM patients have increased long-term risk of recurrent atherothrombotic events and should be carefully considered for more intensive long-term antithrombotic therapy.85

The CAPRIE trial (n = 19 185) showed that clopidogrel for secondary prevention (75 mg daily) reduced the composite endpoint of ischaemic stroke, MI, or vascular death compared with daily 325 mg aspirin [5.32% vs. 5.83% (0.3–16.5); P = 0.043], mostly driven by PAD events, which showed a significant heterogeneity vs. MI and stroke.86 DM patients (n = 3866) showed a similar pattern (P = 0.36 for interaction) but with an amplified absolute risk reduction (15.6% vs. 17.7%; P = 0.042), without an increase in bleeding events.87 Given the high aspirin dose used, it is difficult to recommend a routine switch to clopidogrel for secondary prevention, except in special clinical scenarios, such as individuals with PAD (discussed below). The benefit of 12 vs. 30 months of DAPT, mostly consisting of aspirin and clopidogrel, was tested in the DAPT trial,88 including 9961 individuals who had not experienced ischaemic or bleeding events at 1 year post-PCI. Prolonged DAPT significantly reduced the composite of all-cause mortality, MI, or stroke [4.3% vs. 5.9%, HR 0.71 (0.59–0.85); P < 0.001] but at the expense of increased moderate/severe bleeding events [2.5% vs. 1.6%, HR 1.61 (1.21–2.16); P = 0.001]. However, in DM patients (n = 3391), this strategy did not affect the composite outcome [6.6% vs. 7.0%, HR 0.92 (0.71–1.20); P = 0.55] although the limitation of subgroup analysis should be acknowledged.89,90

The PEGASUS-TIMI 54 trial evaluated prolonged ticagrelor use in 21 162 patients with a history of MI 1–3 years prior to enrolment. Patients also needed to have at least one additional risk factor, which included DM requiring medication.91 Patients were randomized to either one of two doses of ticagrelor (90 mg twice daily or 60 mg twice daily) or placebo in addition to aspirin. At 3 years, the primary efficacy endpoint (cardiovascular death, MI, and stroke) was reduced with ticagrelor 60 mg twice daily compared with placebo [7.8% vs. 9.0% in placebo, HR 0.84 (0.74–0.95); P = 0.004]. TIMI major bleeding events increased [2.30% vs. 1.06% in placebo, HR 2.32 (1.68–3.21); P < 0.001], but no difference was detected in fatal or intracranial bleeding. Similar data were documented in the DM subgroup (n = 6806, 32% of study population) with a higher absolute risk reduction in the 60 mg twice daily ticagrelor arm compared with placebo [11.6% vs. 10.0% in DM subgroup and 7.8% vs. 6.7% in non-DM subgroup]. TIMI major bleeding in those with DM was higher in ticagrelor-treated individuals compared with placebo [2.5% and 1.0%, HR 2.5 (1.4–4.4); P = 0.0004], an increase that was similar to the non-DM group (2.3%; P = 0.89).91

![Figure 2](image-url)
The COMPASS study in patients with either prior MI or multivessel CAD (n = 27,395; 38% with DM) showed that rivaroxaban 2.5 mg twice daily added to low-dose aspirin reduced the risk of MACE compared with aspirin alone [4.1% vs. 5.4%; HR 0.76 (0.66–0.86); P < 0.001].94,95 making this an option, particularly in DM patients who showed greater absolute net benefit.94 While the combination therapy increased bleeding risk, there was still a net clinical benefit. Vorapaxar was investigated in the TRA 2P-TIMI 50 study, detailed in Supplementary material online given the limited clinical use of this agent.95–97

In summary, following ACS, DAPT for 1 year is the current standard of care. De-escalation of DAPT intensity or duration may be considered after 3 months if bleeding concerns prevail.98 One year post-ACS, options include switching to aspirin monotherapy or, in high ischaemic and low bleeding risk DM patients, continuation of dual antithrombotic therapy in the form of aspirin and low-dose ticagrelor (PEGASUS-TIMI 54 study) or aspirin and very-low-dose rivaroxaban (COMPASS trial).35,85 Studies addressing antithrombotic agents for secondary prevention are summarized in Table 2 and Supplementary material online, Figure S1.

Antithrombotic therapy in the presence of atrial fibrillation

Individuals with DM have a 40% greater risk of developing atrial fibrillation (AF) compared to those without DM.99,100 Whilst epidemiological data suggest a causal association, the effect of confounders cannot be excluded (further discussed in Supplementary material online, S1).101–109

Antithrombotic therapy

Oral anticoagulation (OAC) is recommended for male and female AF patients with CHA2DS2-VASc score ≥2 and ≥3, respectively, but can also be considered in those with lower scores on an individual basis.51 In those without absolute indication for VKAs (e.g. mechanical valve or moderate/severe mitral stenosis), NOACs are preferred due to lower rates of severe bleeding and reduced monitoring requirements.51,99 In studies comparing NOACs with VKA in non-valvular AF, about a third of individuals had DM and showed similar RRR to those without DM.111 However, given the increased risk in DM, therapy with NOACs translated into a greater absolute benefit, while rates of major bleeding are similar regardless of DM status. If OAC is contraindicated, percutaneous left atrial appendage closure is an option in those with or without DM.112

Antithrombotic therapy in patients with atrial fibrillation and acute coronary syndrome

Patients with AF on OAC who develop ACS and/or undergo PCI generally require combination treatment with OAC and antiplatelet therapy, with NOACs preferred over VKA.82,85,113 For TT with OAC and DAPT, clopidogrel is recommended over more potent P2Y12 inhibitors.82,85

After elective PCI in patients with AF who require OAC, a switch from TT (DAPT and OAC) to dual therapy (OAC and single antiplatelet therapy) should be considered in those at low risk of stent thrombosis or when bleeding risk is high. North American guidance encourages dual therapy with early aspirin cessation (i.e. by the time of hospital discharge).114,115 ESC guidance endorses TT for at least 1 month if stent thrombosis risk outweighs bleeding risk, followed by an antiplatelet agent (usually clopidogrel) and OAC until 12 months post-PCI, and thereafter OAC monotherapy, unless long-term dual therapy is considered due to very high ischaemic risk with low bleeding risk.82,85,102,113 Similar differences in international guidance exist for AF patients with ACS treated with stent implantation.55,56,116,117 The above applies to all individuals regardless of DM status as no specific studies have been conducted in this group. A summary of the agents used in patients with AF and ACS is provided in Figure 2.

Peripheral artery disease

PAD is thought to affect 202 million people worldwide118 and these individuals are at a higher MACE risk,119 with an even higher event rate with two or more arterial beds affected.119,120

Asymptomatic peripheral artery disease

Two relatively small trials have compared aspirin vs. placebo in asymptomatic PAD, the POPADAD trial88 specific to DM and the AAA trial,121 which included 3% (n = 88) of DM patients. Neither showed a difference in MACE in a combined overall cohort of 4626 patients (1256 with DM). While it can be argued these studies were underpowered, guidelines generally do not support routine antiplatelet therapy for asymptomatic lower extremity arterial disease and these individuals are best managed as per primary prevention recommendations described above.

Symptomatic peripheral artery disease

A meta-analysis of 17,000 individuals with symptomatic PAD has shown that aspirin reduced serious vascular events by 18.2% per year (P < 0.0001), marginally offset by a non-significant increase in haemorrhagic stroke.42

Subgroup analysis of 6,452 patients with PAD (21% with DM) in the CAPRIE study showed potentially greater benefit with clopidogrel vs. aspirin [3.71% vs. 4.86%; RRR 24% (8.9–36.2); P = 0.0028] compared with the overall study population [5.32% vs. 5.83%; RRR 8.7% (0.3–16.5); P = 0.043].86 The EUCLID trial compared ticagrelor and clopidogrel in 13,885 patients with symptomatic PAD (38% with DM), finding no difference in MACE [10.8% vs. 10.6%; HR 1.02 (0.92–1.13); P = 0.65] or major bleeding over a median follow-up of 30 months, regardless of DM status.122

A subgroup analysis of PAD patients in the CHARISMA trial (n = 30,962, 36.2% with DM) showed no significant difference in MACE comparing aspirin and clopidogrel therapy with aspirin and placebo [7.6% vs. 8.9%, HR 0.85 (0.66–1.08); P = 0.18], similar to the overall trial cohort [6.8% vs. 7.3%, HR 0.93 (0.83–1.05); P = 0.22].123 There was an increase in minor bleeding with DAPT [34.4% vs. 20.8%, odds ratio 1.99 (1.69–2.34); P < 0.001] but no difference in severe/moderate bleeding. The role of vorapaxar is described in the Supplementary material online.124

A systematic review and network meta-analysis reported that aspirin, ticlopidine, and ticagrelor or clopidogrel used as monotherapy
| Table 2 | Secondary prevention in diabetes |
|---------|----------------------------------|
| **Sample size** | **Population** | **Intervention** | **Control** | **Diabetes (%)** | **Primary endpoint** | **Duration of follow-up** | **Relative and absolute benefit** | **Relative and absolute harm** | **Comments** |
| **CAPRIE (1996)**<sup>86</sup> | 19 185 | Prior ischaemic stroke (within 1 week–6 months), recent MI (within 35 days), or symptomatic atherosclerotic PAD | Clopidogrel (75 mg) | Aspirin (325 mg) | 20 | Aggregate of MI, ischaemic stroke, and vascular death | 1–3 years | 5.32% vs. 5.83% RRR 8.7% (0.30–16.5%); P = 0.043 | GI bleed 1.99% vs. 2.66%; P < 0.002 | Treatment effect by subgroup suggests heterogeneity in response with a benefit in PAD, but not post-MI or stroke patients |
| **DAPT (2014)**<sup>88</sup> | 9961 | Prior coronary stent with DES after 12 months of DAPT (thienopyridine and aspirin) | Thienopyridine (clopidogrel 65% or prasugrel 35%) | Placebo | 30 | (i) Stent thrombosis and (ii) MACCE (death, MI, or stroke) | 18 months | (i) Stent thrombosis 0.4% vs. 1.4%; HR 0.29 (0.17–0.48); P < 0.001 (ii) MACCE 4.3% vs. 5.9% HR 0.71 (0.59–0.85); P < 0.001 | Moderate–severe bleeding 2.5% vs. 1.6%; P = 0.001 |
| **PEGASUS-TIMI 54 (2015)**<sup>91</sup> | 21 162 | MI 1–3 years earlier | Ticagrelor 90 mg b.i.d. vs. placebo | Placebo | 32 | Composite of CV death, MI, or stroke | 33 months | 7.85% vs. 9.04% HR 0.85 (0.75–0.96); P = 0.008 7.77% vs. 9.04% HR 0.84 (0.74–0.95); P = 0.004 | TIMI major bleeding 2.60% vs. 1.06%, P < 0.001 TIMI major bleeding 2.30% vs. 1.06%, P < 0.001 | No difference was detected in fatal or intracranial bleeding |
| **TRA 2P-TIMI 50 (2012)**<sup>95</sup> | 26 449 | History of MI, ischaemic stroke, or PAD | Vosapaxar (2.5 mg daily) | Placebo | 25 | Composite of death from CV causes, MI, or stroke | 30 months | 9.3% vs. 10.5% HR 0.87 (0.80–0.94); P < 0.001 | Moderate or severe bleeding 4.2% vs. 2.5%; HR 1.66 (1.43–1.93); P < 0.001 | Premature trial termination at 2 years, due to safety concerns over |

*Continued*
| Sample size | Population | Intervention | Control | Diabetes (%) | Primary endpoint | Duration of follow-up | Relative and absolute benefit | Relative and absolute harm | Comments |
|-------------|------------|--------------|---------|--------------|------------------|----------------------|-----------------------------|--------------------------|----------|
| COMPASS (2017)\(^{92}\) | 27 395 | Stable CAD, PAD, or both | Rivaroxaban (2.5 mg b.i.d.) plus aspirin (100 mg/day) | Aspirin (100 mg/day) | 38 | Composite of CV death, stroke, or MI | 23 months | 4.1% vs. 5.4% | ICH 1.0% vs. 0.5%; \(P < 0.001\) |
| RCT 1:1:1 | Rivaroxaban (5 mg b.i.d.) | 4.9% vs. 5.4% | HR 0.90 (0.79–1.03); \(P = 0.12\) | Any bleeding 2.8% vs. 1.9% | HR 1.51 (1.25–1.84); \(P < 0.001\) | Major bleeding was not significantly different |

Long-term therapy for secondary prevention trials in patients with established cardiovascular disease. This is a general guide and healthcare professionals should follow local guidelines as appropriate. Significant differences are highlighted in bold.

b.i.d., twice daily; CAD, coronary artery disease; CV, cardiovascular; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; GI, gastrointestinal; HR, hazard ratio; ICH, intracranial haemorrhage; MACE, major adverse cardiovascular or cerebrovascular events; MI, myocardial infarction; PAD, peripheral arterial disease; RCT, randomized controlled trial; RRR, relative risk reduction.
combination therapy [HR 1.43 (0.97–2.10); major bleeding, but not BARC bleeding, was documented with the treatment of individuals with DM and PAD is summarized in the DM subgroup analysis are awaited. Antithrombotic management of major amputation, MI, ischaemic stroke, or cardiovascular death [HR 0.30 (0.11–0.80); (0.35–0.84); P = 0.005], including lower incidence of major amputation [HR 0.30 (0.11–0.80); P = 0.011].

Post-revascularization
Limited evidence suggests that DAPT with aspirin and clopidogrel is beneficial for lower limb revascularization, particularly following prosthetic bypass.125,127 Similarly, warfarin, with or without aspirin, may improve graft patency after vein bypass.128,129 The VOYAGER PAD trial, assessing aspirin plus rivaroxaban vs. aspirin post-lower limb revascularization, included 6564 individuals (40% had DM) and combination therapy reduced the composite of acute limb ischaemia, any antiplatelet therapy can be immediately started provided that diabetes subgroup behaved differently and therefore DAPT in DM should be initiated within 24 h following acute minor stroke not requiring thrombolysis or thrombectomy and continued for 21–30 days. Future work is required to clarify the optimal duration of DAPT after acute minor stroke, or the benefit of DAPT following reperfusion therapy.132,137

Long-term non-cardioembolic stroke prevention
The effect of aspirin on secondary prevention in stroke/TIA patients is well-established, as are the effects of clopidogrel and aspirin/dipyridamole combination.138 The benefits of aspirin (75–150 mg daily) appear to be most pronounced in the first 6–12 weeks following the event, while combination with dipyridamole may offer better longer-term protection.139 Clopidogrel is as good as aspirin/dipyridamole combination and is preferred for secondary prevention, particularly with the frequent headaches with aspirin/dipyridamole combination leading to discontinuation.140,141

DAPT for long-term use is discouraged as studies showed excessive bleeding without a vascular benefit.142–145

Taken together, for the management of DM individuals, aspirin is justified 24 h after an acute event requiring reperfusion therapy followed by a switch to clopidogrel 3 months later (or continue aspirin while adding dipyridamole). In those not receiving reperfusion therapy, DAPT can be immediately started (provided haemorrhagic stroke is ruled out) and continued for 21 days followed by long-term monotherapy with clopidogrel (or a combination of aspirin/dipyridamole), which applies to individuals with and without diabetes (Figure 2).139–141

Stroke prevention in association with non-valvular atrial fibrillation
As discussed above, anticoagulation is recommended for those with AF and elevated CHA2DS2-VASc score, of which DM is a component.133,146,147

Potential superior efficacy of NOACs, together with reduced bleeding events and reduced need for monitoring, offers distinct advantages over VKAs. An analysis of four large RCTs [RE-LY, ARISTOTLE, ROCKET-AF, and ENGAGE AF-TIMI 48 (23%, 25%, 40%, and 36% with DM, respectively)]]148–151 enrolling over 70 000 patients with non-valvular AF with at least one additional risk factor for stroke, demonstrated that dabigatran or factor Xa inhibitors (apixaban, rivaroxaban, edoxaban) are at least as efficacious as warfarin, and in some cases superior, in preventing stroke, whilst reducing bleeding risk. Sub-analysis of DM patients in these trials showed similar anti-thrombotic benefits of NOACs but bleeding risk reduction appeared to be attenuated.152–154

Treatment of individuals with cerebrovascular disease
Due to lack of DM-specific studies, antithrombotic therapy in individuals sustaining a stroke is similar regardless of DM status and therefore studies are discussed accordingly.

Following acute events
In acute severe ischaemic stroke, reperfusion is attempted either through thrombolysis or endovascular thrombectomy, followed by antiplatelet monotherapy, usually with aspirin, administered 24 h later.131,132 Ticagrelor monotherapy showed no superiority over aspirin133 and, therefore, is only recommended if aspirin is contraindicated.132

In those with minor events [National Institute of Health Stroke Scale (NIHSS) score <3], high-risk transient ischaemic attack (TIA) (ABCD2 score ≥4) or TIA not requiring thrombolysis or invasive measures, antiplatelet therapy can be immediately started provided haemorrhagic stroke is excluded. DAPT (aspirin and clopidogrel) is recommended given findings from the CHANCE and POINT trials (21% and 28% of the study population had diabetes, respectively).134,135 Starting within 24 h of the event for 21 days followed by clopidogrel only.132 While severe haemorrhagic events showed no increase in CHANCE, a doubling was noticed in POINT (Table 4 and Supplementary material online, Figure S1), although the benefit of DAPT still outweighed bleeding risk.135 The more recent THALES trial randomized 11 016 individuals (29% with diabetes), with ischaemic stroke or TIA (NIHSS score ≤5; 29% with DM) within 24 h of presentation to DAPT with ticagrelor and aspirin or aspirin alone for 30 days. The primary composite outcome of stroke or death at 30 days occurred in 5.5% in the combination group vs. 6.6% in those on aspirin alone [HR 0.83 (0.71–0.96); P = 0.02] but incidence of disability showed no difference, while DAPT was associated with increased rate of severe bleeding (0.5% vs. 0.1%; P = 0.001).136 There was no suggestion in any of the studies that the diabetes subgroup benefited differently and therefore DAPT in DM should be initiated within 24 h following acute minor stroke not requiring thrombolysis or thrombectomy and continued for 21–30 days. Future work is required to clarify the optimal duration of DAPT after acute minor stroke, or the benefit of DAPT following reperfusion therapy.132,137

Supplementary material online, Figure S1
| Trial | Sample size | Population | Investigation | Control | % with diabetes | Follow-up | Outcomes | Absolute and relative benefits | Absolute and relative harms | Other comments |
|-------|-------------|------------|---------------|---------|-----------------|-----------|----------|---------------------------------|--------------------------|-----------------|
| **Asymptomatic** | | | | | | | | | | |
| POPADAD (2008) | 1276 | Type 1 or 2 diabetes mellitus and ABI ≤ 0.99 with no PAD symptoms | Aspirin 100 mg ± antioxidant | Placebo ± antioxidant | 100% | Median 6.7 years | MACCE or above ankle amputation for critical limb ischaemia | 18.2% vs. 18.3% | GI bleed 4.4% vs. 4.9% | HR 0.98 (0.76–1.26); P = 0.86 |
| AAA (2010) | 335 | ABI ≤ 0.95; free from clinical CV disease | Aspirin 100 mg | Placebo | 3% | Mean 8.2 years | MACCE or revascularization | 13.7% vs. 13.3 events/1000 person-years | Major bleed 2.0% vs. 1.2% | HR 1.03 (0.84–1.27) |
| **Symptomatic** | | | | | | | | | | |
| ATT Collaboration (2009) | 17,000 | Meta-analysis of secondary prevention trials (not PAD specific) | Aspirin 75–500 mg | No aspirin | Not stated | NA | MACCE | 6.7% vs. 8.2% per year; HR 0.81 (0.75–0.87); P < 0.0001 | Major extracranial bleed (incompletely reported) 23 vs. 6 events | HR 2.69 (1.25–5.76) |
| CAPRIE (1996) | 645 | Symptomatic PAD and ABI ≤ 0.85; or symptomatic PAD with previous amputation or revascularization | Clopidogrel 75 mg | Aspirin 325 mg | 21% | Mean 1.9 years | MACCE | 3.7% vs. 4.86% per year; RR 23.8% (8.9–56.2); P = 0.0028 | GI bleed 1.99% vs. 2.66% per year; P < 0.002 (for the whole group) |
| EUCLID (2017) | 13,85 | PAD with ABI ≤ 0.8 or previous lower limb revascularization >30 days before randomization | Ticagrelor 90 mg b.i.d. | Clopidogrel 75 mg | 38% | Median 30 months | MACCE | 108.8% vs. 106.0% | TIMI major bleeding 1.6% vs. 1.6% | HR 1.02 (0.92–1.13); P = 0.65 |
| CHARISMA subgroup PAD (2009) | 3096 | (2838 symptomatic, 258 asymptomatic) | Aspirin | Aspirin | 36% | Median 28 months | MACCE | 7.6% vs. 8.9% | Severe bleeding 1.7% vs. 1.7% | HR 0.85 (0.66–1.08); P = 0.183 |

Continued
Table 3  Continued

| Trial                  | Sample size | Population                                                                                       | Investigation | Control | % with diabetes | Follow-up | Outcomes | Absolute and relative benefits | Absolute and relative harms | Other comments |
|------------------------|-------------|-------------------------------------------------------------------------------------------------|---------------|---------|-----------------|-----------|----------|--------------------------------|-----------------------------|----------------|
| TRA2 *P-TIMI 50 (2013)* | 3787        | Symptomatic PAD and ABPI <0.85 or previous lower limb revascularization                         | Vorapaxar 2.5 mg | Placebo | 36%             | Median    | MACCE    | 11.3% vs. 11.9%                   | GUSTO moderate/severe bleeding: 7.4% vs. 4.5% |                |
|                        |             |                                                                                                |               |         |                 | 36 months |          | HR 0.94 (0.78–1.14); P = 0.53    |                              |                |
|                        |             |                                                                                                |               |         |                 | Median    | Acute limb ischaemia | 2.3% vs. 3.9%                   | HR 0.58 (0.39–0.86); P = 0.006 |                |
|                        |             |                                                                                                |               |         |                 | 21 months | Revascularization | 18.4% vs. 22.2%                   | Major bleeding 3.1% vs. 1.9% |                |
|                        |             |                                                                                                |               |         |                 | Median    | MACCE    | 5% vs. 7%                         | HR 0.72 (0.57–0.90); P = 0.005 |                |
| COMPASS (2018)        | 7470        | Previous lower limb revascularization or amputation; symptomatic PAD and ABPI <0.9 or stenosis ≥50% on arterial imaging; carotid revascularization or asymptomatic carotid artery stenosis ≥50% | Rivaroxaban 2.5 mg b.i.d + aspirin 100 mg | Placebo | 44%             | Median    | MACCE    | HR 0.72 (0.57–0.90); P = 0.005   | Major adverse limb event (acute/chronic ischaemia; amputation) |                |
|                        |             |                                                                                                |               |         |                 | 21 months |          | HR 0.72 (0.57–0.90); P = 0.005   | Major adverse limb event (acute/chronic ischaemia; amputation) |                |
|                        |             |                                                                                                |               |         |                 | Median    | Graft occlusion/revascularization/death | 35.4% vs. 35.0%                   | Total bleeding 16.7% vs. 7.1%; P < 0.001 |                |
|                        |             |                                                                                                |               |         |                 | 12 months | All grafts | 35.4% vs. 35.0%                   | Graft occlusion 16.7% vs. 7.1%; P < 0.001 |                |
|                        |             |                                                                                                |               |         |                 |          | Venous    | HR 0.98 (0.78–1.23)               | HR 0.63 (0.42–0.93) and severe bleeding 2.1% vs. 1.2%; P = NS |                |
|                        |             |                                                                                                |               |         |                 |          | Acute limb ischaemia | 23.8% vs. 20.0%                   | Venous HR 0.48 (0.24–0.96) significantly reduced in prosthetic but not in bypass |                |
|                        |             |                                                                                                |               |         |                 |          | HR 1.25 (0.94–1.67)               |                               |                |
|                        |             |                                                                                                |               |         |                 |          | Prosthetic | 37.5% vs. 52.8%                   |                               |                |

Continued
### Table 3

| Trial | Sample size | Population | Investigation | Control | % with diabetes | Follow-up | Outcomes | Absolute and relative benefits | Absolute and relative harms | Other comments |
|-------|-------------|------------|---------------|---------|-----------------|-----------|----------|--------------------------------|-----------------------------|-----------------|
| BOA (2000) | 128 269 | Infrainguinal bypass graft for obstructive arterial disease | Oral anticoagulants (target INR 3.0–4.5) | Pulverized calcium 100 mg (equivalent to aspirin 80 mg) | 26% | Mean 21 months | Occlusion | HR 0.65 (0.45–0.95); \( P = 0.025 \) | Total bleeding 119 vs. 59 events | Fatal intracranial bleeding events were higher (8 vs. 3 events) in oral anticoagulants, whereas bleeding events in other sites were similar between groups |
| Sarac et al. (1998) | 129 56 | Infrainguinal bypass with autogenous vein and deemed high risk for graft occlusion (suboptimal venous conduit, poor arterial runoff or redo bypass) | Warfarin (target INR 2–3) + aspirin 325 mg | Aspirin 325 mg | 64% | Not stated (outcomes derived from Kaplan-Meier survival curves) | 30-day graft patency | HR 1.26 (1.03–1.55) | MACE plus acute limb ischaemia or amputation 36% vs. 30% \( P = 0.04 \) | Haematoma 32% vs. 4%; \( P = 0.004 \) |
| VOYAGER-PAD (2020) | 130 6564 | Post-lower limb revascularization | Rivaroxaban 2.5 mg b.i.d. + aspirin 100 mg | Aspirin 100 mg + placebo | 40% | Median 28 months | MACE plus acute limb ischaemia or amputation | HR 0.85 (0.76–0.96) | Major bleeding 1.9% vs. 1.35% | HR 1.43 (0.97–2.10); \( P = 0.07 \) |

Summary of antiplatelet and anticoagulant studies in individuals with peripheral vascular disease. Significant differences are highlighted in bold.

ABR, ankle brachial pressure index; b.i.d., twice daily; CV, cardiovascular; DAPT, dual antiplatelet therapy; GI, gastrointestinal; HR, hazard ratio; INR, international normalized ratio; MACE, major adverse cardiovascular or cerebrovascular events; NA, not available; PAD, peripheral arterial disease.
### Table 4 Antithrombotic therapy in cerebrovascular disease

#### Antiplatelet randomized trial for secondary prevention in patients with acute minor ischaemic stroke/high-risk TIA

| Study               | Patients | Intervention | Control | Follow-up | Composite vascular events (stroke, MI or CVD death) | Recurrent ischaemic stroke | Intracranial haemorrhage | Major haemorrhage |
|---------------------|----------|--------------|---------|-----------|-----------------------------------------------------|-----------------------------|---------------------------|---------------------|
| CHANCE (2013)       | Minor stroke (NIHSS <3)/high-risk TIA, onset <24 h | Clopidogrel 300 mg loading then 75 mg/day on days 2–90 | Clopidogrel 75 mg/day on days 1–90 | 90 days | 8.4% vs. 11.9% HR 0.69 (0.58–0.82) | 7.9% vs. 11.4% HR 0.67 (0.56–0.81) | 0.3% vs. 0.3% HR 1.01 (0.38–3.20) (haemorrhagic stroke) | 0.2% vs. 0.2% HR 0.94 (0.24–3.79) (severe bleeding) |
| POINT (2018)        | Minor stroke (NIHSS <3)/high-risk TIA, onset <12 h | Clopidogrel 600 mg loading then 75 mg/day on days 2–90 | Aspirin 50–325 mg on days 2–21 | 90 days | 5.0% vs. 6.5% HR 0.75 (0.59–0.95) | 4.6% vs. 6.3% HR 0.72 (0.56–0.92) | 0.2% vs. 0.1% HR 1.68 (0.40–7.03) (haemorrhagic stroke) | 0.9% vs. 0.4% HR 2.32 (1.10–4.87) |
| SOCRATES (2016)     | Non-severe stroke (NIHSS <5)/high-risk TIA, onset <24 h | Ticagrelor 180 mg loading then 90 mg b.i.d. on days 2–90 | Aspirin 300 mg loading then 100 mg/day on days 2–90 | 90 days | 6.5% vs. 7.2% HR 0.89 (0.78–1.01) | 5.9% vs. 6.6% HR 0.87 (0.76–1.00) | 0.2% vs. 0.3% HR 0.68 (0.33–1.41) | 0.5% vs. 0.6% HR 0.83 (0.52–1.34) |
| THALES (2020)       | Mild–moderate stroke (NIHSS ≤5)/high-risk TIA (ABCD2 > 6), onset <24 h | Ticagrelor 180 mg loading then 90 mg b.i.d. on days 2–30 | Aspirin 300–325 mg loading then 75–100 mg o.d. on days 2–30 | 30 days | 5.5% vs. 6.6% HR 0.83 (0.71–0.96) | 5.0% vs. 6.3% HR 0.79 (0.68–0.93) | 0.4% vs. 0.1% HR 3.33 (1.34–8.28) | 0.5% vs. 0.1% HR 3.99 (1.74–9.14) |

#### Anti-platelet randomized trials for long-term secondary prevention in patients with previous non-cardioembolic ischaemic stroke/TIA

| Study               | Patient | Intervention | Control | Follow-up | Non-fatal MI, non-fatal stroke, death from vascular causes | Recurrent ischaemic stroke | Intracranial haemorrhage | Major haemorrhage |
|---------------------|---------|--------------|---------|-----------|-----------------------------------------------------------|-----------------------------|---------------------------|---------------------|
| CAPRIE (1996)       | Recent MI, PAD, or stroke | Clopidogrel 75 mg/day | Aspirin 325 mg/day | 1.9 years | 5.32% vs. 5.83% HR 0.91 (0.84–1.00) | Not reported | 0.35% vs. 0.49% HR 1.38 vs. 1.55% | (severe bleeding) |
| ESPRIT (2008)       | Recent minor stroke/TIA (mRS <3)/within 6 months | Dipyridamole 200 mg b.i.d. plus | Aspirin 30–325 mg/day (median 75 mg/day) | 3.5 years | 3.3% vs. 4.3% HR 0.78 (0.63–0.97) | 2.1% vs. 2.6% HR 0.84 (0.64–1.10) | 0.8% vs. 1.5% | 2.5% vs. 3.9% |
| PRoFESS (2008)      | Recent stroke within 90 days | Extended release dipyridamole 200 mg b.i.d. plus | Clopidogrel 75 mg/day | 2.5 years | 13.1% vs. 13.1% HR 0.99 (0.92–1.07) | 7.7% vs. 7.9% HR 0.97 (0.88–1.07) | 1.4% vs. 1.0% HR 1.42 (1.11–1.83) | 4.1% vs. 3.6% HR 1.15 (1.00–1.32) |
### Anti-platelet randomized trials for long-term secondary prevention in patients with previous non-cardioembolic ischaemic stroke/TIA

| Study                  | Patient Intervention | Control | Follow-up | Non-fatal MI, non-fatal stroke, death from vascular causes | Recurrent ischaemic stroke | Intracranial haemorrhage | Major haemorrhage |
|------------------------|----------------------|---------|-----------|----------------------------------------------------------|-----------------------------|----------------------------|----------------------|
| MATCH (2004)           | Aspirin 25 mg b.i.d.  | Clopidogrel 75 mg/day plus | 1.5 years | 16% vs. 17% HR 0.94 (0.84–1.05) vs. 8% vs. 9% HR 0.93 (0.80–1.09) | 1.1% vs. 0.7% | 1.9% vs. 0.6% (P < 0.001) |
| CHARISMA (2006)        | Aspirin 75 mg/day    | Clopidogrel 75 mg/day plus | 2.3 years | 6.0% vs. 7.3% HR 0.93 (0.83–1.05) vs. 1.7% vs. 2.1% HR 0.81 (0.64–1.02) | 0.3% vs. 0.3% HR 0.96 (0.56–1.65) | 2.1% vs. 1.3% HR 1.62 (1.27–2.08) |
| SP3 (2012)             | Aspirin 325 mg/day   | Clopidogrel 75 mg/day plus | 3.4 years | 3.1% vs. 3.4% HR 0.89 (0.72–1.11) vs. 20% vs. 2.4% HR 0.82 (0.63–1.09) | 0.4% vs. 0.3% HR 1.65 (0.83–3.31) | 2.1% vs. 1.1% HR 1.97 (1.41–2.71) |
| Greving et al. (2019)  | Clopidogrel         | Aspirin            | 2.0 years | 0.88 (0.78–0.98) vs. 0.91 (0.81–1.02) HR 0.79 (0.66–0.95) vs. 0.88 (0.60–1.13) | 0.96 (0.63–1.09) HR 1.65 (0.83–3.31) | 0.76 (0.43–0.91) HR 0.88 (0.60–1.13) |

### Anti-coagulant randomized trials for primary and secondary preventions in patients with atrial fibrillation

| Study                  | Patients Intervention | Control | Follow-up | Stroke or systemic embolic event | Ischaemic stroke | Intracranial haemorrhage | Major haemorrhage |
|------------------------|-----------------------|---------|-----------|----------------------------------|------------------|--------------------------|------------------|
| ARISTOTLE (2011)       | Patients with AF      | Apixaban 5 mg b.i.d. or Apixaban 2.5 mg b.i.d. in age >80 years, body weight <60 kg, creatinine >1.5 mg/mL | Warfarin (keep INR 2.0–2.5) | 1.27% vs. 1.60% HR 0.79 (0.66–0.95) vs. 0.97% vs. 1.05% HR 0.92 (0.74–1.13) | 0.33% vs. 0.80% HR 0.42 (0.30–0.58) vs. 0.69 (0.60–0.80) | 2.13% vs. 3.09% |
| ARISTOTLE (2015)       | DM patients were younger, more CAD, higher CHADS 2 and HAS-BLED | | | 1.39% vs. 1.86% HR 0.75 (0.53–1.05) vs. Not reported | 0.34% vs. 0.70% HR 0.49 (0.25–0.95) vs. 0.96 (0.74–1.25) | |
| RELY (2009)            | Patients with AF      | Dabigatran 110 mg b.i.d. or Dabigatran 150 mg b.i.d. in CHA2DS2-VASc >2 for men or >3 for women | Warfarin (keep INR 2.0–2.5) | 1.53% vs. 1.69% HR 0.91 (0.74–1.11) vs. 1.34% vs. 1.20% HR 1.11 (0.89–1.40) | 0.23% vs. 0.74% HR 0.31 (0.20–0.47) vs. 0.80 (0.69–0.93) | 2.71% vs. 3.36% |
| RELY (2015)            | DM patients were younger, more CAD and PAD, higher CHA2DS2-VASc scores | Dabigatran 150 mg b.i.d. | Warfarin (keep INR 2.0–2.5) | 1.76% vs. 2.35% HR 0.74 (0.51–1.07) vs. 1.62% vs. 1.65% HR 0.97 (0.64–1.40) | 0.22% vs. 0.81% HR 0.26 (0.11–0.65) vs. 0.80 (0.70–1.19) | 3.81% vs. 4.19% |

Continued
Table 4  Continued

| Study               | Patients                          | Intervention                   | Control                        | Follow-up | Stroke or systemic embolic event | Ischaemic stroke | Intracranial haemorrhage | Major haemorrhage |
|---------------------|-----------------------------------|--------------------------------|--------------------------------|-----------|----------------------------------|------------------|-------------------------|------------------|
| ROCKET AF (2011)150 | Patients with AF CHADS2 >2        | Rivaroxaban 20 mg/day          | Warfarin (keep INR 2.0–3.0)    | 1.9 years | 1.7% vs. 2.2%                    | 2.11% vs. 2.27%  | 0.8% vs. 1.2%           | 5.6% vs. 5.4%    |
| DM subgroup         | DM patients were younger, more obese, higher BP, similar CHADS2 scores (N=5695) | Rivaroxaban 15 mg/day if creatinine clearance 30–49 mL/min | Warfarin (keep INR 2.0–3.0)    | 1.7% vs. 2.1% | 1.35% vs. 1.45%                | 0.5% vs. 0.8%    | 3.8% vs. 3.9%           |                  |
| ROCKET AF (2015)154 | DM subgroup                        | Rivaroxaban 20 mg/day          | Warfarin (keep INR 2.0–3.0)    | 2.11% vs. 2.27% | 0.94 (0.75–1.17)        |                  |                        |                  |
| ENGAGE AF-TIMI 48   | Patients with AF CHADS2 >2        | Edoxaban 30 mg/day             | Warfarin (keep INR 2.0–2.8 years) | 1.61% vs. 1.50% | 1.77% vs. 1.25%            | 0.26% vs. 0.85%  | 1.61% vs. 3.43%         |                  |
| DM subgroup         | DM subgroup                        | Edoxaban 30 mg/day             | Warfarin (keep INR 2.0–2.8 years) | 1.61% vs. 1.50% | 1.77% vs. 1.25%            | 0.26% vs. 0.85%  | 1.61% vs. 3.43%         |                  |
| AVERROES (2011)155  | Patients with AF CHADS2 >1, or documented PAD | Apixaban 5 mg b.i.d. & Aspirin 81–324 mg/day | Aspirin 81–324 mg/day | 1.1 years | 1.18% vs. 1.50%                  | 1.25% vs. 1.25%  | 0.39% vs. 0.85%         | 2.75% vs. 3.43%  |
| DM                  | FS+PAD                            | Apixaban 5 mg b.i.d. in age >80 years, body weight <60 kg, creatinine >1.5 mg/dL | Aspirin 81–324 mg/day | 1.1 years | 2.0% vs. 1.5%                   | 1.25% vs. 1.25%  | 0.39% vs. 0.85%         | 2.75% vs. 3.43%  |

| Study               | Patients                          | Intervention                   | Control                        | Follow-up | Stroke, systemic emboli, MI, CVD death | Ischaemic stroke | Intracranial haemorrhage | Major haemorrhage |
|---------------------|-----------------------------------|--------------------------------|--------------------------------|-----------|----------------------------------------|------------------|-------------------------|------------------|
| AVERROES (2011)155  | Patients with AF CHADS2 >1, or documented PAD | Apixaban 5 mg b.i.d. & Aspirin | Aspirin 81–324 mg/day | 1.1 years | 4.2% vs. 6.4%                        | 1.1% vs. 3.0%    | 0.4% vs. 0.4%           | 1.4% vs. 1.2%    |
| DM                  | FS+PAD                            | Apixaban 2.5 mg b.i.d. in age >80 years, body weight <60 kg, creatinine >1.5 mg/dL | Aspirin 81–324 mg/day | 1.1 years | 3.8% vs. 3.0%                        | 1.1% vs. 3.0%    | 0.4% vs. 0.4%           | 1.4% vs. 1.2%    |

Antiplatelet and anticoagulant studies for secondary prevention in individuals with cerebrovascular disease. Significant differences are highlighted in bold.

b.i.d., twice daily; CAD, coronary artery disease; CHA2DS2-VASc score, Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female); CHADS2 score, Cardiac failure, Hypertension, Age, Diabetes, Stroke (doubled); CVD, cardiovascular disease; DM, diabetes mellitus; HAS-BLED score, hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (65 years), drug/alcohol concomitantly (1 point each); HR, hazard ratio; MI, myocardial infarction; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; PAD, peripheral artery disease; TIA, transient ischaemic stroke; VKA, vitamin K antagonist.
In AF patients who are ineligible for VKA, apixaban (ACCORD trial; 20% with diabetes) is the only NOAC that has demonstrated superior efficacy to aspirin in preventing MACE (stroke, systemic embolism, MI, and vascular death) with similar bleeding risk in the whole study population with no subgroup analysis conducted for those with DM. 155

In summary, current evidence supports OAC in DM individuals with AF with or without a history of stroke who fulfill treatment criteria and do not have excessive bleeding risk. NOACs are preferable to VKAs in eligible patients.

Timing of initiation (or therapy resumption) of OAC in AF patients suffering an acute stroke is a challenging area. Based largely on two studies, RAF and RAF-NOACs,156,157 the American Heart Association/American Stroke Association 2018/2019 guidelines recommend starting OAC within 4–14 days of an acute ischaemic stroke.152 The European Heart Rhythm Association-ESC guidelines give a more structured recommendation with the ‘1–3–6–12 days rule’.158 In brief, OAC should be initiated or reinstated after 1 day for TIA, 3 days for mild stroke (NIHSS score <8), 6 days for moderate stroke (NIHSS score 8–15), and 12 days for severe stroke (NIHSS score ≥16). These recommendations are based solely on expert consensus without robust RCTs supporting this approach. Of note, bridging with full-dose low-molecular-weight heparin before or together with VKA is not recommended.159 Table 4 summarizes key studies on antithrombotic agents in cerebrovascular disease.

Conclusions and future directions

While a large number of studies investigated the best antithrombotic strategy in vascular disease patients, there is still a distinct lack of DM-specific RCTs, particularly for secondary prevention. The heterogeneous vascular risk in DM patients, which can vary in the same individual according to DM duration and development of complications, adds to the complexity and prevents guidelines from making concrete recommendations. For example, advanced renal disease may alter both thrombosis and bleeding risk and may even limit the use of some antithrombotic therapies.43 The increased weight in DM individuals may also affect the response to antithrombotic agents, reviewed elsewhere.160 A key difficulty remains the lack of biomarker(s) that accurately predicts thrombotic/bleeding risk and response to therapy.

Given current knowledge, primary prevention with antiplatelet agents, mainly aspirin, may only be considered in higher-risk individuals. Following ACS, DAPT is necessary using aspirin and ticagrelor or prasugrel, usually for 12 months but also longer term with aspirin and ticagrelor in high thrombotic risk patients. In stable atherosclerotic disease, the combination of aspirin and very-low-dose rivaroxaban is useful, particularly in the presence of PAD (Figure 2).161 In individuals with stroke, the choice of antithrombotic therapy is dictated by whether the individual required reperfusion and the presence of AF (Figure 2 and Graphical Abstract).

Areas for future research include the development of reliable biomarkers and/or in silico model, able to assess thrombotic risk and response to therapy. Moreover, DM-specific studies are warranted rather than subgroup, and often post hoc, analyses of cardiovascular trials designed for the wider population (DM-specific studies are summarized in Supplementary material online, Table S3 and gaps in knowledge/future work in Supplementary material online, Table S4). This will require greater collaboration between metabolic and vascular medical disciplines to design appropriate studies aiming to reduce vascular events and improve clinical outcomes in the high-risk DM population.

Supplementary material

Supplementary material is available at European Heart Journal online.

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References

1. Emerging Risk Factors Collaboration; Di Angelantonio E, Kaptoge S, Waterman C, Benn J, Cleroux D, Gaziano J, Hohmann J, Davey Smith G, Mancia G, De Backer G. Blood pressure, blood pressure variability, and risk of cardiovascular disease: a collaborative meta-analysis of 61 prospective studies and 2 million people. Lancet 2015; 386:52–60.

2. Emerging Risk Factors Collaboration; Sarwar N, Gao P, Seshasai SR, Gobin R, La COMMAND. J Cardiovasc Dis Dis 2010; 113:1046–1054.

3. Cosentino F, Ceriello A, Baeres FMM, Fioretto P, Garber A, Stough WG, Standl E, Tuomilehto J, Zannad F. Addressing cardiovascular risk in type 2 diabetes mellitus: from bench to bedside. Cardiovasc Diagn Ther 2015; 5:532–545.

4. Carrizosa A, Izzo C, Oliveti M, Allano A, Virtuso N, Capunzo M, Di Pietro P, Calabrese M, De Simone E, Scarretta F, Frati G, Migliarino S, Damato A, Ambrosio M, De Carlo F, Vecchione C. The main determinants of diabetes mellitus vascular complications: endothelial dysfunction and platelet hyperaggregability. Int J Mol Sci 2018; 19:3968.

5. Rivia Rios JR, Franchi F, Rollini F, Angiolillo DJ. Diabetes and platelet dysfunction: from bench to bedside. Cardiovasc Diagn Ther 2018; 8:594–609.

6. Kearney K, Tomlinson D, Smith K, Ajan R. Hypofibrinolysis in diabetes: a therapeutic target for the reduction of cardiovascular risk. Cardiovasc Diabetol 2017; 16:34.

7. Mi Y, Yan S, Lu Y, Liang Y, Li C. Venous thromboembolism has the same risk factors as atherothrombosis: a PRISMA-compliant systematic review and meta-analysis. Medicine (Baltimore) 2016; 95:e4995.

8. Pretorius E. Platelets as potent signaling entities in type 2 diabetes mellitus. Trends Cardiovasc Med 2019; 30:532–545.

9. Soma P, Swanevoel AC, Du Plooy JN, Mpcpo T, Pretorius E. Flow cytometric analysis of platelets type 2 diabetes mellitus reveals ‘angry’ platelets. Cardiovasc Diabetol 2016; 15:32.

10. Ghoshal K, Bhatcharyya M. Overview of platelet physiology: its hemostatic and nonhemostatic role in disease pathogenesis. ScientificWorldJournal.com 2014; 2014:78157.

11. Patrano C, Rocca B. Measurement of thromboxane biosynthesis in health and disease. Front Pharmacol 2019; 10:1244.

12. Watala C, Boncer M, Golitski J, Kozlozkiewicz W, Trojanowski Z, Walkowiak A. Platelet membrane lipid fluidity and intraplatelet calciun mobilization in type 2 diabetes mellitus. Eur J Haematol 2009; 83:379–376.

13. Santilli F, Simeone P, Liani R, Davi G. Platelets and diabetes mellitus. Prostaglandins Other Lipid Mediat 2015; 120:28–39.

14. Audoly LP, Rocca B, Fabre JE, Koller BH, Thomas D, Loeb AL, Coffman TM, FitzGerald GA. Cardiovascular responses to the isotopanes iPFI(2alpa)-III and iPFE(2)-III are mediated via the thromboxane A(2) receptor in vivo. Circulation 2000; 101:2833–2840.

15. Hunter RW, Hors L. Insulin/GF-1 hybrid receptor expression on human platelets: consequences for the effect of insulin on platelet function. J Thromb Haemost 2009;7:2123–2130.

16. Westen E, Hoefer T, Calkin AC. Thrombosis in diabetes: a shear flow effect? Clin Sci (Lond) 2017;131:1245–1260.

17. Vink AI, Erbas T, Park TS, Nolan P, Pitterger GL. Platelet dysfunction in type 2 diabetes. Diabetes Care 2004; 27:1476–1485.

18. Fejes Z, Poliska S, Czimmerer Z, Klapa M, Penyie A, Gal Szabo G, Beke Debreceni I, Knapuli SP, Kappelmayr J. Njagy BJ. Hyperglycaemia suppresses microRNA expression in platelets to increase P2RY12 and SELP levels in type 2 diabetes mellitus. Thromb Haemost 2017;117:529–542.

19. Pordzik J, Jakubik D, Jarosz-Popek J, Wick Z, Eyteken C, De Rosa S, Indolfi C, Siller-Matula JM, Czajka P, Postula M. Significance of circulating microRNAs in diabetes mellitus type 2 and platelet reactivity: bioinformatic analysis and review. Cardiovasc Diabetol 2018; 17:43.

20. Gawaz M, Ott I, Reiningr AJ, Neumann FJ. Effects of magnesium on platelet aggregation and adhesion. Magnesium modulates surface expression of glycoprotein on platelets in vitro and ex vivo. Thromb Haemost 1994; 72:912–918.

21. Hernandez Vera R, Vilahur G, Ferrer-Lorente P, Peña I, Badimon L. Platelets derived from the bone marrow of diabetic animals show dysregulated endothelial protein C receptors that contribute to increased thrombosis. Arterioscler Thromb Vasc Biol 2012; 32:2141–2148.

22. Yang W, Beck W, Depisch P, Marshall SM, Hoenich NA, Thompson MG. Advanced glycation end products elicit externalization of phosphatidylserine in a subpopulation of platelets via S+HTZ/2A/2C receptors. Am J Physiol Cell Physiol 2007; 293:C238–C336.

23. Rocca B, Santilli F, Pitacco D, Mucci L, Petrucci G, Viscasolana E, Lattanzio S, Mattascio D, Zaccardi F, Liani R, Vazzana N, Del Ponte A, Ferrante E, Martin F, Cardillo C, Morosetti R, Mirabella M, Ghirlanda G, Davi G, Patrono C. The recovery of platelet cyclooxygenase activity explains interindividual variability in responsiveness to low-dose aspirin in patients with and without diabetes. J Thromb Haemost 2010; 8:1220–1230.

24. Vilahur G, Ben-Acha S, Badimon L. New insights into the role of adipose tissue in thrombosis. Nat Rev Cardiol 2010; 7:1046–1054.

25. Ferreiro JL, Gomez-Hospital JA, Angiolillo DJ. Platelet abnormalities in diabetes mellitus. Diab Vasc Dis Res 2010; 7:251–259.

26. Alzahrani SH, Ajan RA. Coagulation and fibrinolyis in diabetes. Diab Vasc Dis Res 2010; 7:260–273.

27. Kim HK, Kim JE, Park SH, Kim YL, Nam-Goong IS, Kim ES. High coagulation factor levels and low protein C levels contribute to enhanced thrombin generation in patients with diabetes who do not have macrovascular complications. J Diabetes Complications 2014; 28:365–369.

28. Ajan RA, Gamlen T, Standeven KF, Mughal S, Hess K, Smith KA, Dunn EJ, Amarow MM, Rabbani N, Thornalley PJ, Philippou H, Grant PJ. Diabetes is associated with posttranslational modifications in plasminogen resulting in reduced plasmin generation and enzyme-specific activity. Blood 2013;122:134–142.

29. Du XL, Edelstein D, Rossetti L, Fantus IG, Goldberg H, Ziyadeh F, Wu J, Brownlee M. Hyperglycemia-induced mitochondrial superoxide overproduction activates the hexosamine pathway and increases plasinogen activator inhibitor-1 expression by increasing Sp1 glycolysis. Proc Natl Acad Sci USA 2000; 97:12222–12226.

30. James S, Angiolillo DJ, Cornell JH, Erlinge D, Husted S, Kortny F, Myldia J, Nicolau JC, Spinari J, Storey RF, Stevens SR, Wallentin L; PLATO Study Group. Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATelet inhibition and patient Outcomes (PLATO) trial. Eur Heart J 2010; 31:3006–3016.

31. Ducroq G, Wallace JS, Baron G, Ravaud P, Alberts MJ, Wilson PWF, Ohman EM, Brennan DM, D’Agostino RB, Bhatt DL, Steg PG, on behalf of the REACH investigators. Risk score to predict serious bleeding in stable outpatients with or at risk of atherothrombosis. Eur Heart J 2010; 31:1257–1265.

32. Lemesle G, Meurice T, Tricot O, Lamblin N, Bauters C. Association of diabetic status and glycemic control with ischemic and bleeding outcomes in patients with stable coronary artery disease: the 5-Year CORONOR Registry. J Am Heart Assoc 2018; 7:e008354.

33. Goel N, Jain D, Haddad DB, Shanbhogue D. Anticoagulation in patients with end-stage renal disease and atrial fibrillation: confusion, concerns and consequences. J Stroke 2020; 5:306–316.

34. Nogami K, Muraki I, Imao H, Iso H. Risk of disseminated intravascular coagulation in patients with type 2 diabetes mellitus: retrospective cohort study. BMJ Open 2017; 7:e013894.

35. Patrano C, Garcia Rodrigo LA, Landolfi R, Baigent C. Low-dose aspirin for the prevention of atherothrombosis. N Engl J Med 2005;353:2373–2383.

36. Angiolillo DJ, Ueno M, Goto S. Basic principles of platelet biology and clinical implications. Curr Opin 2017;7:597–607.

37. Franchi F, Angiolillo DJ. Novel antiplatelet agents in acute coronary syndrome. Eur Heart J 2017;38:1579–1594.

38. Angiolillo DJ, Ueno M, Goto S. Platelet thrombin receptor antagonism and atherothrombosis. Eur Heart J 2010;31:17–28.
41. Angiolillo DJ, Ferreiro JL. Antiplatelet and anticoagulant therapy for atherothrombotic disease: the role of current and emerging agents. Am J Cardiol 2013;112:233–250.

42. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, Buring J, Wolski K. Antiplatelet and anticoagulant therapy for atherosclerotic events in patients with type 2 diabetes: a randomised controlled trial. JAMA 2008;300:2314–2141.

43. Ongwa H, Nakayama M, Morimoto T, Umemura S, Kanauchi M, Doi N, Jinnouchi H, Sugiyama S, Saito Y. Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (IPAD) Trial Investigators. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomised controlled trial. JAMA 2009;301:1849–1860.

44. Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R, Lee R, Nicolau JC, Ruzyllo W, Harrington RA, Tricoci P. Validation of BARC bleeding events with ticagrelor in diabetic patients with prior myocardial infarction in the Ticagrelor in patients with stable coronary disease and diabetes (TASP3) trial. Diabetes Care 2016;39:1136–1144.

51. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Sousa-Uva M, Valensi P, Wheeler DC; ESC Scientific Document Group. 2019 ESC Guidelines for the Management of Aneurysms and Dissections of the Aorta. Eur Heart J 2019;40:786–835.

52. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Sousa-Uva M, Valensi P, Wheeler DC; ESC Scientific Document Group. 2019 ESC Guidelines for the Management of Aneurysms and Dissections of the Aorta. Eur Heart J 2019;40:786–835.

53. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Sousa-Uva M, Valensi P, Wheeler DC; ESC Scientific Document Group. 2019 ESC Guidelines for the Management of Aneurysms and Dissections of the Aorta. Eur Heart J 2019;40:786–835.

54. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Sousa-Uva M, Valensi P, Wheeler DC; ESC Scientific Document Group. 2019 ESC Guidelines for the Management of Aneurysms and Dissections of the Aorta. Eur Heart J 2019;40:786–835.

55. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Sousa-Uva M, Valensi P, Wheeler DC; ESC Scientific Document Group. 2019 ESC Guidelines for the Management of Aneurysms and Dissections of the Aorta. Eur Heart J 2019;40:786–835.

56. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Sousa-Uva M, Valensi P, Wheeler DC; ESC Scientific Document Group. 2019 ESC Guidelines for the Management of Aneurysms and Dissections of the Aorta. Eur Heart J 2019;40:786–835.

57. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Sousa-Uva M, Valensi P, Wheeler DC; ESC Scientific Document Group. 2019 ESC Guidelines for the Management of Aneurysms and Dissections of the Aorta. Eur Heart J 2019;40:786–835.

58. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Sousa-Uva M, Valensi P, Wheeler DC; ESC Scientific Document Group. 2019 ESC Guidelines for the Management of Aneurysms and Dissections of the Aorta. Eur Heart J 2019;40:786–835.

59. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Sousa-Uva M, Valensi P, Wheeler DC; ESC Scientific Document Group. 2019 ESC Guidelines for the Management of Aneurysms and Dissections of the Aorta. Eur Heart J 2019;40:786–835.

60. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Sousa-Uva M, Valensi P, Wheeler DC; ESC Scientific Document Group. 2019 ESC Guidelines for the Management of Aneurysms and Dissections of the Aorta. Eur Heart J 2019;40:786–835.

61. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Sousa-Uva M, Valensi P, Wheeler DC; ESC Scientific Document Group. 2019 ESC Guidelines for the Management of Aneurysms and Dissections of the Aorta. Eur Heart J 2019;40:786–835.

62. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Sousa-Uva M, Valensi P, Wheeler DC; ESC Scientific Document Group. 2019 ESC Guidelines for the Management of Aneurysms and Dissections of the Aorta. Eur Heart J 2019;40:786–835.

63. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Sousa-Uva M, Valensi P, Wheeler DC; ESC Scientific Document Group. 2019 ESC Guidelines for the Management of Aneurysms and Dissections of the Aorta. Eur Heart J 2019;40:786–835.

64. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Sousa-Uva M, Valensi P, Wheeler DC; ESC Scientific Document Group. 2019 ESC Guidelines for the Management of Aneurysms and Dissections of the Aorta. Eur Heart J 2019;40:786–835.

65. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Sousa-Uva M, Valensi P, Wheeler DC; ESC Scientific Document Group. 2019 ESC Guidelines for the Management of Aneurysms and Dissections of the Aorta. Eur Heart J 2019;40:786–835.

66. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Sousa-Uva M, Valensi P, Wheeler DC; ESC Scientific Document Group. 2019 ESC Guidelines for the Management of Aneurysms and Dissections of the Aorta. Eur Heart J 2019;40:786–835.

67. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Sousa-Uva M, Valensi P, Wheeler DC; ESC Scientific Document Group. 2019 ESC Guidelines for the Management of Aneurysms and Dissections of the Aorta. Eur Heart J 2019;40:786–835.
70. Niderrepe G, Kastrati A, Menichelli M, Neummann FJ, Wohlrabe J, Bernlochner I, Richardt G, Witzenbichler B, Sibbing D, Gewalt S, Angiolillo DJ, Hamm CW, Hafempfeiler A, Tenck D, Laugwitz KL, Schunkert H, Schupke S, Mayer K. Ticagrelor or prasugrel in patients with acute coronary syndromes and diabetes mellitus. JACC Cardiovasc Interv. 2020;13:2228–2247.

71. Cayla G, Cuisset T, Silvain J, Leclercq F, Maillot-Sibulman S, Saint-Etienne C, Deschamps N, Bellenger Y, Daniel A, Gheissari D, McInnes I, Mechaief R, Carde D, Bella S, Louteynyard G, Aubry P, Sabourret P, Du Frety XY, Béguy F, Bonnet JT, Lattuca B, Pouillot C, Varenne O, Bouveri Z, Van Belle E, Henry P, Motreff P, Elhadad S, Salem JE, Abtan J, Rсужov H, Collet JP, Vïcut A, Montalescot G; ANTARCITIC Investigators. Platelet function monitoring to adjust antithrombotic therapy in a subgroup of patients stented for an acute coronary syndrome (ANTARCITIC): an open-label, blinded-endpoint, randomised controlled superiority trial. Lancet 2016;388:2015–2022.

72. Hein R, Gross L, Aradi D, Rieber J, Hamedtzya M, Merkely B, Huczek Z, Ince H, Hummel A, Baylischer M, Massberg S, Tenck D, Sibbing D. Diabetes and outcomes following guided de-escalation of antithrombotic treatment in acute coronary syndrome patients undergoing percutaneous coronary intervention: a pre-specified analysis from the randomised TROPICAL-ACS trial. Eur Intervention 2019;15:e53–e52.

73. Mehran R, Baber U, Sharma SK, Cohen DJ, Angiolillo DJ, Briegul C, Cha JY, Collier T, Dangas G, Dudek D, Dzakic V, Escaned J, Gil R, Gurbel P, Hann MW, Henry T, Huber K, Kastrati A, Kaul U, Kornowski R, Krakoff M, Kundan V, Marx SO, Melzer MA, Moliterno D, Oldroyd KG, Saccardi S, Simonazzi R, Sölzbacher FL, SPCS, Weste G, Witzenbichler B, Han YL, Pocock S, Gibson CM. Ticagrelor with or without aspirin in high-risk patients after PCI. N Engl J Med 2019;381:2032–2042.

74. Angiolillo DJ, Baber U, Sartori C, Briegul C, Dans G, Cohen DJ, Melzer MA, Gibson CM, Chandramani R, Huber K, Kornowski R, Weerts G, Kundan V, Oldroyd KG, Yang L, Kaul U, Witzenbichler B, Dudek D, Saccardi S, Escaned J, Sharma S, Sulimatz RS, Roller T, Pocock S, Mehran R. Ticagrelor with or without aspirin in high-risk patients with diabetes mellitus undergoing percutaneous coronary intervention. J Am Coll Cardiol 2020;75:2403–2413.

75. Vranckx P, Valgimigli M, Juni P, Hamm CM, Steg PG, Mehta SR, Moliterno D, Oldroyd KG, Wiviott SD, Steinhubl SR, Yusuf S, Mehta SS, Ezekowitz MD, Agewall S, Hirsch AT, Faxon DP, Stone GW, Stortecky S, Pfeffer MA, Braunwald E,bona MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Yusuf S, Mehta SS, Ezekowitz MD, Agewall S, Hirsch AT, Faxon DP, Stone GW, Stortecky S, Pfeffer MA, Braunwald E, Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Yusuf S, Mehta SS, Ezekowitz MD, Agewall S, Hirsch AT, Faxon DP, Stone GW, Stortecky S, Pfeffer MA, Braunwald E.
Antithrombotic therapy in diabetes

112. Reddy VY, Doshi SK, Kar S, Gibson DN, Price MJ, Huber K, Horton RP, Management of antithrombotic therapy in atrial fibrillation patients undergoing PCI. JACC state-of-the-art review. J Am Coll Cardiol 2019;74:83–99.

113. Boriani G, Fauchier L, Aguinaga L, Beattie JM, Blomstrom Lundqvist C, Cohen A, Dan G-A, Genovesi I, Scalco C, Jong B, Kalarus Z, Lampert R, Malafarina V, Mansourati J, Mark L, Patapaa T, Thornton A, Lip GYH, Gorenek B, Marin F, Obel I, Rubboli A, Storey RF, Valgimigi M, Huber K, Potpara T, Blomstrom Lundqvist C, Crijns H, Steffel J, Heidbuchel H, Stankovic G, Anakaseni J, Ten Berg JM, Capodanno D, James S, Bueno H, Morais J, Sibbing D, Roocs B, Hoes M-H, Akoum N, Lockwood DJ, Gomez Flores JR, Jardine R; ESC Scientific Document Group. 2018 Joint European consensus document on the management of arrhythmias and cardiac electronic devices in the critically ill and post-surgery patient, endorsed by Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), Cardiac Arrhythmia Society of Southern Africa (CASSA), and Latin American Heart Rhythm Society (LAHRS). Europace 2019;21:7–8.

114. Lip GYH, Collet JP, Haude M, Byrne R, Chung EH, Fauchier L, Halversen V, Lau D, Lopez-Cabanillas N, Lettino M, Marin F, Obel I, Rubboli A, Storey RF, Valgimigi M, Huber K, Potpara T, Blomstrom Lundqvist C, Crijns H, Steffel J, Heidbuchel H, Stankovic G, Arakaseni J, Ten Berg JM, Capodanno D, James S, Bueno H, Morais J, Sibbing D, Roocs B, Hoes M-H, Akoum N, Lockwood DJ, Gomez Flores JR, Jardine R; ESC Scientific Document Group. 2018 Joint European consensus document on the management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventions: a joint consensus document of the European Heart Rhythm Association (EHRA), European Society of Cardiology (ESC), Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA). Europace 2019;21:192–193.

115. Fowkes FG, Ruidan D, Ruidan I, Abayons V, Denenberg JO, McDermott MM, Normand PE, Sampson UK, Williams LJ, Mensah GA, Criqui MH. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet 2013;382:129–134.

116. Alberts MJ, Bhatt DL, Mas JL, Ohman EM, Hirsh AT, Rother J, Salette G, Goto S, Smith SC, Liao C-S, Wilson PW, Steg PG, for the REDUCTION of Atherothrombosis for Continued Health (REACH) Investigators. Three-year follow-up and event rates in the international REDUCTION of Atherothrombosis for Continued Health Registry. Eur Heart J 2009;30:2318–2326.

117. Verma S, Bhatt DL, Bain SC, Buse JB, Mann JF, Marso SP, Nauck MA, Poulter NR, Pratley RE, Zinman B, Michelson MM, Monk Fries T, Rasmussen S, Leiter LA, Leiter PC, On B. Of The LTI. LEADER Publication Committee on behalf of the LEADER Trial Investigators. Effect of iragilizumab on cardiovascular events in patients with type 2 diabetes mellitus and polycystic ovary syndrome: results of the LEADER trial. Circulation 2018;137:2179–2183.

118. Fowkes FG, Price JF, Stewart MC, Butcher I, Leng GC, Pell AC, Sandercock PA, Fox KA, Lowe GD, Murray GD; Aspirin for Asymptomatic Atherosclerosis Trialists. Aspirin for prevention of cardiovascular events in a general population: pooled analysis of a low antiplatelet index: a randomized controlled trial. JAMA 2010;303:841–848.

119. Hiatt WR, Fowkes FG, Heeger I, Berger JS, Baumgartner I, Held P, Katona BG,可以通过您的请求来提供其他支持。

120. Fowkes FG, Price JF, Stewart MC, Butcher I, Leng GC, Pell AC, Sandercock PA, Fox KA, Lowe GD, Murray GD; Aspirin for Asymptomatic Atherosclerosis Trialists. Aspirin for prevention of cardiovascular events in a general population: pooled analysis of a low antiplatelet index: a randomized controlled trial. JAMA 2010;303:841–848.

121. Hiatt WR, Fowkes FG, Heeger I, Berger JS, Baumgartner I, Held P, Katona BG,可以通过您的请求来提供其他支持。
Pallesen LP, Kepplinger J, Bodechtel U, Gerber J, Deleu D, Melikyan G, Ibrahim F, Akhtar N, Mosconi MG, Bubba V, Silvestri I, Lees KR. Early recurrence and cerebral bleeding in patients with acute ischemic stroke and atrial fibrillation: effect of anticoagulation and its timing: the RAF study. Stroke 2015;46:2175–2182.

157. Paciaroni M, Agnelli G, Falocci N, Tsivgoulis G, Vadikolias K, Liantinioti C, Chondrogiani M, Bovi P, Carletti M, Cappellari M, Zedde M, Ntaios G, Karagiози K, Athanasakis G, Mairatizii K, Silvestrelli G, Lani A, Ciccone A, Putalni J, Tompso L, Latismum T, Abdul-Rahim AH, Lees KR, Alberti A, Venti M, Acciarresi M, D’Amore C, Becattini C, Mosconi MG, Cimini LA, Soloperto R, Masotti L, Vannucchi V, Lorenzini G, Tassi R, Guidieri F, Acampa M, Martini G, Sohn S, Marcheselli S, Mumo M, de Lodovici ML, Bono G, Furie KL, Tadi P, Yaghi S, Toni D, Letteri F, Tassinari T, Karagiози K, Maccarrone M, Giannini N, Bandini F, Pezzini A, Poli L, Padovan A, Zedde M, Abdul-Rahim AH, Lees KR, Alberti A, Venti M, Acciarresi M, D’Amore C, Giulia Mosconi M, Anna Cimini L, Fusaro J, Bovi P, Carletti M, Rigatelli A, Cappellari M, Putalni J, Tompso L, Latismum T, Marcheselli S, Pezzini A, Poli L, Padovan A, Massoti L, Vannucchi V, Sohn S-I, Lorenzini G, Tassi R, Guidieri F, Acampa M, Martini G, Ntaios G, Athanasakis G, Mairatizii K, Karagiози E, Vadikolias K, Liantinioti C, Chondrogiani M, Mumoli N, Consoli D, Galati F, Sacco S, Carolei A, Tiseo C, Corea F, Agemo B, Bellesini M, Silvestrelli G, Ciccone A, Lani A, Zedde M, Denti L, Maccarrone M, Ulivi L, Orlandi G, Giannini N, Giardini G, Tassinari T, De Lodovici ML, Bono G, Ruckert C, Baldi A, D’Anna S, Toni D, Letteri F, Giuntini M, Maria Lotti E, Flomin Y, Pieroni A, Kargiotis O, Karapanayiotides T, Monaco S, Maimone Baranello M, Cai E, Szabo L, Chiti A, Pieroni A, Sibbling D, Zabzuni D, Doronkin B, Volodina V, Michel P, Vanacke P, Barlin M, Palles-L, Barlin M, Deleu D, Melikyan G, Ibrahim F, Akhtar N, Gourbali V, Paciaroni M. Anticoagulation after stroke in patients with atrial fibrillation. Stroke 2019;50:2093–2100.

158. Steffel J, Verhamme P, Potpara T, Balsevchel H, ESC Scientific Document Group. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K oral anticoagulants (RAF-NOACs) study. J Am Heart Assoc 2017;6:e007034.

159. Altavilla R, Caso V, Bandini F, Agnelli G, Tsivgoulis G, Yaghi S, Furie KL, Tadi P, Becattini C, Zedde M, Abdul-Rahim AH, Lees KR, Alberti A, Venti M, Acciarresi M, D’Amore C, Giulia Mosconi M, Anna Cimini L, Fusaro J, Bovi P, Carletti M, Rigatelli A, Cappellari M, Putalni J, Tompso L, Latismum T, Marcheselli S, Pezzini A, Poli L, Padovan A, Massoti L, Vannucchi V, Sohn S-I, Lorenzini G, Tassi R, Guidieri F, Acampa M, Martini G, Ntaios G, Athanasakis G, Mairatizii K, Karagiози E, Vadikolias K, Liantinioti C, Chondrogiani M, Mumoli N, Consoli D, Galati F, Sacco S, Carolei A, Tiseo C, Corea F, Agemo B, Bellesini M, Silvestrelli G, Ciccone A, Lani A, Zedde M, Denti L, Maccarrone M, Ulivi L, Orlandi G, Giannini N, Giardini G, Tassinari T, De Lodovici ML, Bono G, Ruckert C, Baldi A, D’Anna S, Toni D, Letteri F, Giuntini M, Maria Lotti E, Flomin Y, Pieroni A, Kargiotis O, Karapanayiotides T, Monaco S, Maimone Baranello M, Cai E, Szabo L, Chiti A, Pieroni A, Sibbling D, Zabzuni D, Doronkin B, Volodina V, Michel P, Vanacke P, Barlin M, Palles-L, Barlin M, Deleu D, Melikyan G, Ibrahim F, Akhtar N, Gourbali V, Paciaroni M. Anticoagulation after stroke in patients with atrial fibrillation. Stroke 2019;50:2093–2100.

160. Rocca B, Fox KAA, Ajan RA, Andreotti F, Baigent C, Collet JP, Grove EL, Halvorsen S, Huber K, Morais J, Patrono C, Rubboli A, Seljeflot I, Sibbing D, Siegah A, Ten Berg J, Vilahur G, Verheugt FWA, Wallentin L, Weiss TV, Wijers J, Stoor YR. Antithrombotic therapy and body mass: an expert position paper of the ESC Working Group on Thrombosis. Eur Heart J 2018;39:1672–1686f.

161. Bhatt DL, Elkboom JW, Connolly SJ, Steg PG, Anand SS, Verma S, Branch KR, Probstfield J, Bosch J, Shestakouskia O, Szarek M, Maggioni AP, Widsmyk P, Avezum A, Diaz R, Lewis BS, Berkowitz SD, Fox KAA, Ryden L, Yusuf S; COMPASS Steering Committee and Investigators. Role of combination antiplatelet and anticoagulation therapy in diabetes mellitus and cardiovascular disease: insights from the COMPASS trial. Circulation 2020;141:1841–1854.