Endotext

PLATELETS, COAGULATION, AND ANTITHROMBOTIC THERAPY IN DIABETES

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ABSTRACT

Diabetes mellitus is a strong, independent risk factor for the development of atherosclerotic cardiovascular disease (ASCVD) and therefore for atherothrombotic events. Compared to those without diabetes, individuals with diabetes are also at increased risk of cardioembolic stroke in the presence of atrial fibrillation (AF) and of venous thromboembolism. Activation of platelets and the coagulation cascade are the central mechanisms of thrombosis. A range of antiplatelet and anticoagulant drugs are now available. Antithrombotic therapy should be considered in all those with diabetes and established ASCVD or AF. Intensification of antithrombotic therapy is typically indicated during the acute phase of an atherothrombotic event or in those with chronic coronary syndromes who are at high ischemic risk, provided this outweighs bleeding risk. Clinical decisions regarding antithrombotic therapy should be made by assessing an individual's ischemic and bleeding risks, in consultation with the recipient and reviewed upon any change in circumstances.

LIST OF ABBREVIATIONS

5HT	5-hydroxytryptamine
ACS	acute coronary syndrome
ADP	adenosine diphosphate
AF	atrial fibrillation
ALI	acute limb ischemia
APT	antiplatelet therapy
ASCVD	atherosclerotic cardiovascular disease
ATP	adenosine triphosphate
ATT	antithrombotic therapy
CAD	coronary artery disease
CCS	chronic coronary syndromes

CI	confidence interval
COX	cyclo-oxygenase
DAPT	dual antiplatelet therapy
DATT	dual antithrombotic therapy
DM	diabetes mellitus
DVT	deep vein thrombosis
GP	glycoprotein
HR	hazard ratio
LEAD	lower extremity artery disease
MACE	major adverse cardiovascular event
MI	myocardial infarction
miR	microribonucleic acid
NOAC	non-vitamin K antagonist oral anticoagulant
OAC	oral anticoagulant
PAD	peripheral artery disease
PAR	protease-activated receptor
PCI	percutaneous coronary intervention
PGI_2	prostacyclin
RCTs	randomized controlled trials
RRR	relative risk reduction
SAPT	single antiplatelet therapy
TIMI	thrombolysis in myocardial infarction
TP	thromboprostanoid
TXA_2	thromboxane A_2
UA	unstable angina
VKA	vitamin K antagonist
vWF	von Willebrand factor

INTRODUCTION

Despite a century of advances in understanding and management of diabetes mellitus (DM), it continues to increase in prevalence and, furthermore, remains an independent risk factor for atherosclerotic cardiovascular disease (ASCVD), leading to a significant burden of premature mortality and morbidity (1).

ASCVD includes a spectrum of clinical syndromes. This can include acute presentations such as acute coronary syndromes (ACS, including myocardial infarction [MI] or unstable angina [UA]), thrombotic stroke, or acute limb ischemia (ALI) (Figure 1). Similarly, ASCVD can lead to chronic conditions such as chronic coronary syndromes (CCS, for example those with stable angina or a history of MI >1 year previously) or chronic lower extremity arterial disease (LEAD) (2).

Most acute events in ASCVD are caused by thrombosis. The hemostatic response has an important physiological role in the response to trauma

but, if it becomes activated inappropriately, thrombosis can be triggered (3). The clinical effects of thrombosis arise primarily from its location, such as in the coronary arteries leading to acute coronary syndrome (ACS, including myocardial infarction [MI] and unstable angina [UA]), cerebral arteries leading to thrombotic stroke, peripheral arteries leading to acute limb ischemia or deep limb veins leading to deep vein thrombosis (DVT). Alternatively, a thrombus formed at a site can embolize, leading to presentations such as acute pulmonary embolism (typically embolism of a DVT to the pulmonary arteries) or embolic stroke (typically left atrial thrombus to the cerebral arteries) (2,4). In addition to atherosclerotic diseases, individuals with DM who have atrial fibrillation are at higher risk of stroke, secondary to atrial thrombosis and subsequent cardioembolic events (5).

There are clear links between pathological processes associated with DM and those responsible for atherogenesis and thrombosis, including inflammation, platelet activation, and coagulation (6,7). Alongside control of glucose levels and optimization of other risk factors, such as dyslipidemia, hypertension, and smoking cessation, antithrombotic therapy (ATT), including antiplatelet therapy (APT) and oral anticoagulation (OAC), has become a key component of the treatment and prevention of atherothrombotic and cardioembolic events. ATT has evolved greatly in the last decades, both in terms of the range of drugs available but also our understanding of how best to deploy them (8).

Whilst ATT reduces thrombotic risk, in particular reducing the composite of major adverse cardiovascular events (MACE, typically defined as cardiovascular death, stroke or MI), it also leads to an increased risk of bleeding. Balancing these risks is central to interpretation of clinical trial data and development of treatment recommendations, including in those with DM (9).

In this chapter, we will review the underlying pathophysiological mechanisms of thrombosis and the pharmacology of commonly prescribed drugs during ATT. With specific reference to individuals with DM, we will appraise evidence for ATT in a broad range of clinical settings, highlighting current treatment recommendations and particular areas in which more data are needed.

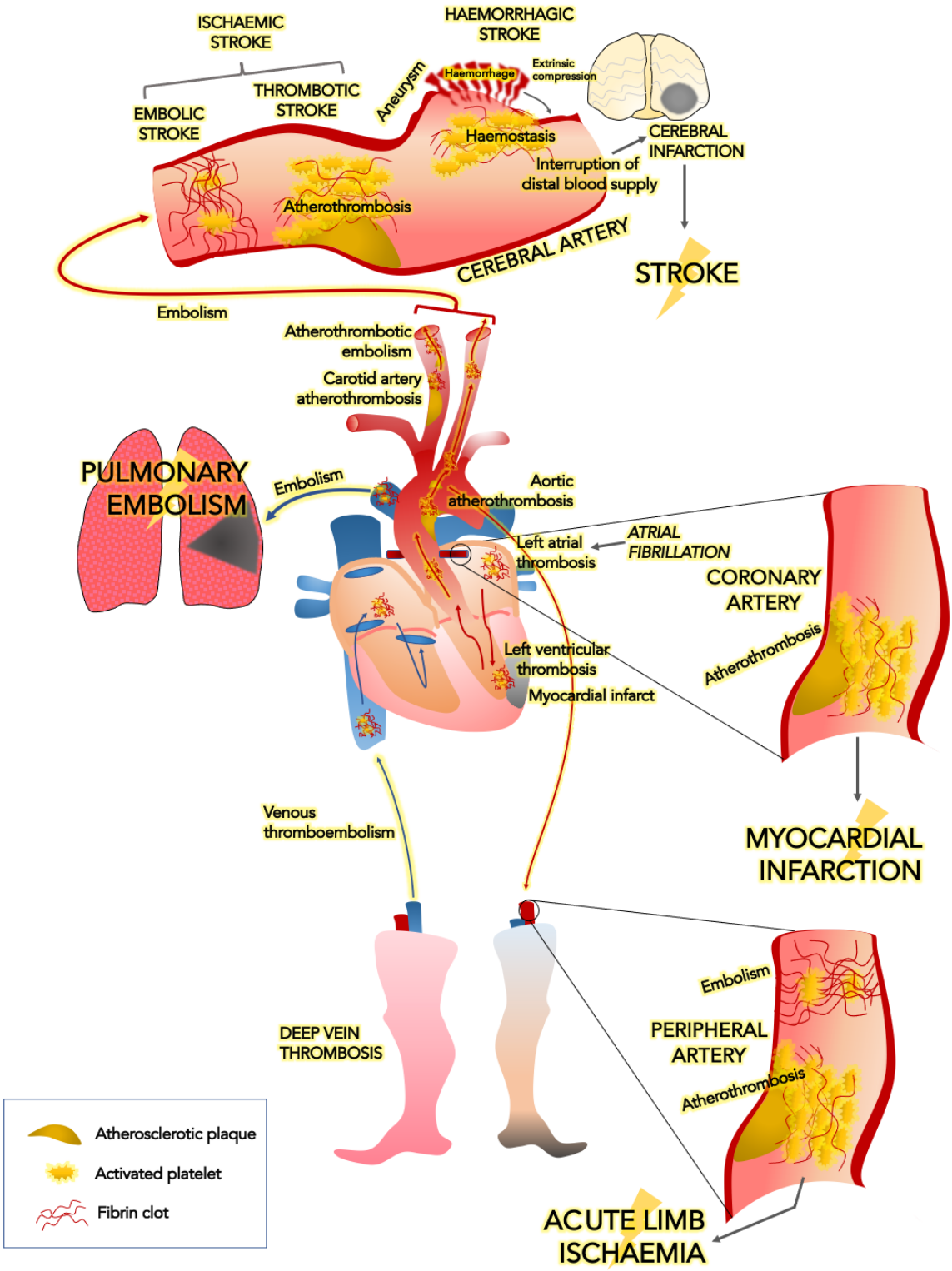

Figure 1. The spectrum of acute cardiovascular events relating to thrombosis and hemostasis in DM.

THE THROMBOTIC RESPONSE AND ITS PHARMACOLOGY

As described in Virchow's triad, prothrombotic changes in the blood flow, constituents and/or vessel wall can trigger thrombosis (10). Broadly, thrombosis involves the activation of platelets and the coagulation cascade (Figure 2). Understanding these processes provides insights into how pharmacological modulation may improve ischemic risk and increase bleeding risk as well as how the individual components of combination ATT interact, including in those with DM.

Platelet Activation

Platelet activation typically occurs upon endothelial injury and atherosclerotic plaque rupture or erosion, resulting in exposure of blood constituents to prothrombotic substances such as collagen. Collagen exposure leads to platelets adhering to the vessel wall via the glycoprotein (GP) Ia receptor and activation via GPVI (11,12). GPIb forms a complex with clotting factors IX, V and von Willebrand Factor (vWF), strengthening adhesion (13).

Platelet activation involves several key processes. Alterations in the cytoskeleton lead to shape change with the formation of filopodia, which increase surface area to volume ratio and may facilitate mechanical adhesion to the vessel wall, other platelets and fibrin strands (14). Platelet activation also involves the release of arachidonic acid from the cell membrane, which is then locally converted to thromboxane A_2 (TXA_2) by cyclo-oxygenase (COX) 1 and TXA_2 synthase. TXA_2, via the platelet TP-α receptor, contributes further to platelet activation (15). Aspirin (acetylsalicylic acid) irreversibly inhibits COX1, thereby blocking the downstream release of TXA_2 for the platelet's lifespan (around 8-10 days in healthy individuals) as, unlike nucleated cells, platelets cannot regenerate the enzyme (8). Endothelial COX1 and 2 generate the antiplatelet and vasodilatory substance prostacyclin (PGI_2). The facts that aspirin is short-lived in the systemic circulation, that platelets are exposed to higher levels of aspirin than endothelium, due to travel through the portal circulation, and that aspirin has relative selectivity for COX1 over COX2 leads to aspirin's net antiplatelet effect at low doses (16).

Platelets also undergo degranulation on activation; α granules contain procoagulant and proinflammatory factors, including platelet P-selectin (also known as CD62P), the surface expression of which is therefore increased. P-selectin mediates platelet-leukocyte aggregation and therefore contributes to an associated inflammatory response (17). Dense granules contain adenosine triphosphate (ATP), adenosine diphosphate (ADP) and 5-hydroxytryptamine (5HT, also known as serotonin). In particular, ADP stimulates platelet activation via $P2Y_1$ and, most significantly, $P2Y_{12}$ receptors (18,19).

Stimulation of the $P2Y_{12}$ receptor leads to central amplification of the response to a range of agonists and contributes significantly to activation of platelet surface GPIIb/IIIa receptors, the final pathway of platelet aggregation (20). Via vWF and fibrinogen bridges, GPIIb/IIIa mediates platelet-platelet interaction (21).

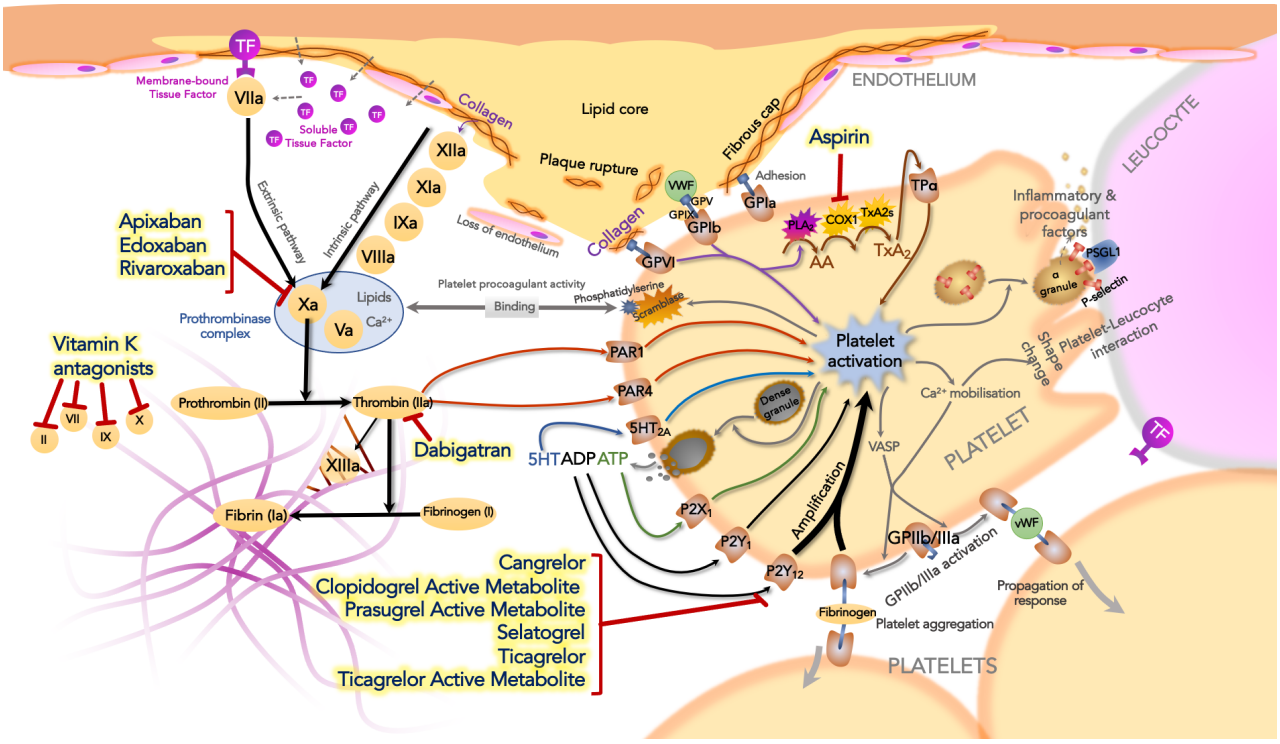

Figure 2. Pathophysiology of the thrombotic response showing targets for antithrombotic drugs discussed in this chapter. 5HT, 5-hydroxytryptamine (serotonin); AA, arachidonic acid; ADP, adenosine diphosphate; ATP, adenosine triphosphate; Ca^{2+}, calcium; COX1, cyclo-oxygenase 1; GP, glycoprotein; IXa, activated factor IX; $P2X_1$, platelet ATP receptor; $P2Y_1$/$P2Y_{12}$, platelet ADP receptors; PAR, protease activated receptor; PLA_2, phospholipase A_2; PSGL1, P-selectin glycoprotein ligand 1; TF, tissue factor; TPα, thromboxane receptor α; TXA_2, thromboxane A_2; TXA_2s, thromboxane A_2 synthase; Va, activated factor V; VIIa, activated factor VII; VIIIa, activated factor VIII; VASP, vasodilator-stimulated phosphoprotein; vWF, von Willebrand factor; Xa, activated factor X; XIa, activated factor XI; XIIa, activated factor XII; XIIIa, activated factor XII. Modified from (22).

Several oral platelet $P2Y_{12}$ receptor antagonists ('$P2Y_{12}$ inhibitors') are currently available (23). Clopidogrel and prasugrel are irreversibly-binding thienopyridines (8). As pro-drugs, they require hepatic metabolism to be activated. In the case of prasugrel this pathway is reliable, whereas there is interindividual variation in the metabolism of clopidogrel meaning around one-third of recipients have poor response when assessed using aggregometry (22). Ticagrelor is a reversibly-binding cyclopentyl-triazolopyrimidine that does not require metabolism to be active. Prasugrel or ticagrelor provide more potent and reliable platelet inhibition compared with clopidogrel (24).

Parenterally administered $P2Y_{12}$ inhibitors have also been developed. Cangrelor is a reversibly-binding ATP analogue that is potent and has rapid onset and offset (25). Selatogrel is a novel, parenterally-active, reversibly-binding $P2Y_{12}$ inhibitor formulated for subcutaneous administration, but has not yet completed phase III trials and is yet to be marketed (26).

Activation of the Coagulation Cascade

Although likely an oversimplification of the in vivo state, the coagulation cascade can be summarized as

two key pathways made up of factors that converge on a final pathway (27).

Loss of endothelium leads to exposure of subendothelial extracellular matrix and contact activation of factor XII, triggering the chain of clotting factor activation known as the intrinsic pathway (28). Tissue factor, expressed on subendothelial cells and released in microparticles from atheromatous plaques, can activate factor IX when in a complex with factor VII: this is the extrinsic pathway (29).

Initiation of either pathway can lead to activation of factor X, which associates with activated factor V, calcium (released from damaged tissue) and phospholipids to form the prothrombinase complex (30). Prothrombin (II) is thus broken down to thrombin (IIa), which completes the process through cleavage of fibrinogen to fibrin, the latter being insoluble and forming strands. Tissue factor pathway inhibitor and antithrombin limit this response, but, as recruitment of activated platelets contributes to higher levels of thrombin generation, this endogenous inhibition is quickly overwhelmed (31). Once fibrin is formed, factor XIIIa, activated by thrombin, stabilizes the structure of clot by forming crosslinks between strands and by crosslinking anti-fibrinolytic proteins into the clot (32).

Fibrin is lysed by plasmin, a proteolytic enzyme that degrades into variously termed fragments (33). Plasmin is cleaved from its precursor, plasminogen, by tissue plasminogen activator, and is endogenously inhibited by antiplasmin.

A number of drugs target the coagulation cascade. During chronic administration, vitamin K antagonists (VKA) such as warfarin reduce the biological activity of prothrombotic vitamin-K-dependent factors (II, VII, IX, X) more than antithrombotic factors (e.g., proteins C and S) (34). Non-vitamin K antagonist oral anticoagulants (NOACs) include the Xa inhibitors apixaban, edoxaban and rivaroxaban and the thrombin inhibitor dabigatran (35).

Crosstalk Between Platelets and the Coagulation Cascade

Despite the fact that platelets and coagulation are often considered separately when discussing physiology and pharmacology, there is significant crosstalk between the two. Thrombin is generated upon activation of coagulation, and is able to stimulate platelet activation via action on protease-activated receptor (PAR) 1 and, at higher concentrations, PAR4 (36). Conversely platelets can contribute to thrombin generation, increasing coagulability, via scramblase activity that leads to greater surface expression of phosphatidylserine, supporting the assembly of prothrombinase complex on the activated platelet surface, which potentiates thrombin generation (37).

SPECIAL PATHOPHYSIOLOGICAL CONSIDERATIONS IN DIABETES

DM is an independent risk factor for atherothrombosis and also thrombosis after vascular interventions (38). Individuals with DM have greater average atherosclerotic plaque burden than those without (39), and onset is at an earlier age (40). There is also some evidence that atherosclerosis in people with DM is more likely to involve distal vessels than those without DM (41). The reasons for this are not completely understood and are likely multifactorial, but a number of relevant pathological processes such as hyperglycemia, chronic inflammation, and oxidative stress are prominent in DM. These contribute to both endothelial injury/dysfunction and increased platelet reactivity, resulting in a prothrombotic milieu (42-44).

Platelet activation markers are enhanced in people with DM (45). Effects of hyperglycemia on platelets include increased expression of GPIbα, GPIIb/IIIa, and $P2Y_{12}$, and reduced platelet membrane fluidity (46,47). Hyperglycemia-induced changes in intracellular magnesium and calcium signaling increase sensitivity of platelets to agonists such as ADP, epinephrine and thrombin (48). TXA_2 and F2-isoprostane synthesis is increased, the latter via

oxidative stress, leading to increased TPα receptor stimulation (49). Reduced sensitivity to PGI_2, nitric oxide and insulin, which inhibit platelet activation, also contributes to hyper-reactivity (50,51).

Platelet turnover is accelerated in those with DM compared to those without (52). This increased activity in the creation and destruction of circulating platelets means a higher proportion of immature platelets, which are hyper-reactive, are present at any time (53). As well as increasing baseline platelet reactivity, the more frequent appearance of aspirin-naïve platelets in the circulation means more have uninhibited COX1 between doses (54).

There is also evidence that DM affects expression of platelet-associated microRNAs (miR-223, miR-26b, miR-126, miR-140), which play a role in the expression in a wide range of genes including those encoding the $P2Y_{12}$ receptor and P-selectin, though the significance of this remains to be fully established (55,56).

As well as platelet activation, DM may affect coagulation and fibrinolysis (57). Changes include increased levels of tissue factor, prothrombin, factor VII and fibrinogen leading to impaired anticoagulant and fibrinolytic activity (58). Increased levels of fibrinogen and its levels of glycation and oxidation lead to more compact, densely-packed fibrin networks and reduced fibrinolysis (59). Hyperglycemia inhibits the fibrinolytic activity of plasminogen through inducing qualitative changes (60). Fibrinolysis is further impaired by elevated levels of plasminogen activator inhibitor 1 and thrombin-activatable fibrinolysis inhibitor as well as incorporation into clot of complement C3 and plasmin inhibitor (59,61).

DM also appears to enhance the crosstalk between platelets and clotting factors, leading to tendency to more externalization of phosphatidylserine in the outer platelet membrane, promoting clotting factor assembly and tissue factor activation (62).

Finally, individuals with DM frequently have other metabolic conditions such as obesity, dyslipidemia, and increased systemic inflammation. These may interact with diabetes to further enhance platelet reactivity and impair fibrinolysis (59).

CURRENT EVIDENCE AND TREATMENT RECOMMENDATIONS FOR ANTITHROMBOTIC THERAPY IN DIABETES

The Need for Therapeutic Oral Anticoagulation

Broadly, when considering the need for antithrombotic therapy (ATT), including in people with DM, it is helpful to make first a distinction between those with an indication for therapeutic anticoagulation and those without. The most common indication is for prevention of cardioembolic stroke in those with current or previous atrial fibrillation (AF). Individuals with atrial flutter are typically regarded as having similar thrombotic risk to those with AF so similar recommendations are followed (63).

DM increases the risk of developing AF by around 40% (64,65). Whilst difficult to completely exclude the effects of confounders such as obesity and hypertension, epidemiological data suggest a causal association between DM and AF, including that poor glycemic control and longer diabetes duration increase AF risk (66). A raised level of HbA1c is also associated with a higher chance of AF recurrence after catheter ablation (67). Hyperglycemia and glycemic fluctuations may contribute to the development of AF though exact mechanisms remain to be determined. Disappointingly, however, there is no clear evidence that intensive glycemic control reduces AF risk, though prospective trials are lacking (66). Treatment with metformin, thiazolidinediones, or dapagliflozin is associated with lower AF risk, suggesting that hypoglycemia avoidance may play a role but adequately designed studies to investigate this possibility are lacking (68-71). AF is often clinically silent and screening with simple pulse checking or

using wearable devices should be considered in those over 65 years old (72).

Presence of DM is incorporated into the CHA_2DS_2VASc score used to assess stroke risk when determining whether to recommend oral anticoagulation in people with AF (Table 1 and 2) (73). Long-term oral anticoagulation is strongly recommended in those with AF/atrial flutter and a CHA_2DS_2VASc score of ≥2 (if male) or ≥3 (if female), and should be considered when the score is 1 (male) or 2 (female). Individuals with DM, technically defined for the purposes of calculating the score as treatment with oral hypoglycemic drugs and/or insulin or fasting blood glucose >7.0 mmol/L (126 mg/dL), will have a score of at least 1 (males) or 2 (females), therefore OAC should be considered in all people with DM and concurrent AF (63). Bleeding risk should also be considered when weighing the benefits and risks of OAC, but there is no concrete evidence that DM itself increases this, including in those with complications such as retinopathy (74). For people with non-valvular AF (i.e., those without at least moderate mitral valve stenosis or a mechanical valve prothesis), there is now good evidence that, unless contraindicated, a NOAC should be preferred over a VKA, offering better stroke prevention whilst leading to less bleeding, including in individuals with DM (75).

Components of the CHA2DS2VASc score are shown in Table 1 and the relation of the score with stroke risk is shown in table 2 (76-78).

Table 1. Components of the CHA_2DS_2VASc Score

Abbreviation	Criterion	Contribution to score	Details
C	Congestive heart failure	1	LVEF ≤40%
H	Hypertension	1	Includes patients receiving antihypertensive medication
A	Age ≥75 years	2	
D	Diabetes	1	Treatment with oral hypoglycemic drugs and/or insulin or fasting blood glucose >7.0 mmol/L (126 mg/dL)
S	Stroke/TIA/thromboembolism	2	
V	Vascular disease	1	Atherosclerotic disease e.g., prior MI, PAD or aortic plaque
A	Age 65-74	1	
Sc	Sex category female	1	

LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral artery disease; TIA, transient ischemic attack.

Table 2. Relation of CHA2DS2VASc Score with Stroke Risk	
Total CHA_2DS_2VASc score	**Adjusted stroke risk (% per year)**
0	<1
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

When choosing between individual non-vitamin K antagonist oral anticoagulants (NOACs), beyond considering specific drug interactions, there is little evidence to support the use of one agent over another as these have never undergone head-to-head clinical outcome-driven randomized controlled trials (RCTs), although observational data have emerged to provide some insights. In a large retrospective observational study of 434,046 participants with non-valvular AF comparing treatment with apixaban, dabigatran, rivaroxaban and warfarin, apixaban led to a lower risk of stroke against both dabigatran (HR 0.72 [95% CI 0.60-0.85]) and rivaroxaban (0.80 [0.73-0.89]), whilst also leading to less bleeding (major bleeding: vs. dabigatran 0.78 [0.70-0.87]; vs. rivaroxaban 0.80 [0.55-0.59]) (79). These findings remain hypothesis-generating, however, and prospective trials would clarify this issue more definitively.

Although not discussed in detail in this chapter, OAC may also be indicated for the treatment and prevention of venous thromboembolism. Whilst DM is regarded as a weak risk factor for VTE, beyond this there are no particular considerations relating to DM and usual clinical guidelines as for non-DM individuals should generally be followed (4). Of specific note, however, is that people with DM who are experiencing hyperosmolar states such as ketoacidosis or hyperosmolar hyperglycemic syndrome are at particular risk of VTE. There is ongoing debate around the intensity of anticoagulation that is appropriate for thromboprophylaxis in this group. Consensus is that at least prophylactic doses of low molecular weight heparin, for example, are warranted, with others advocate therapeutic doses (80,81). A robustly-powered clinical outcomes-driven RCT would be welcome to definitively address this issue.

Where indications for both anti-platelet therapy (APT) and therapeutic levels of oral anticoagulant therapy (OAC) exist, the general principle is to prioritize continuation of OAC. Co-prescription of APT and OAC should in general be reserved for those with acute coronary syndrome (ACS), recent percutaneous coronary intervention (PCI) or indication for long-term therapy in selected individuals with chronic coronary syndromes (CCS) where ischemic risk is felt to significantly outweigh bleeding risk (22).

Treating Acute Atherothrombotic Events

ACUTE CORONARY SYNDROMES (ACS)

Current guidelines recommend 12 months of dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor, including in those with DM, as the default antithrombotic strategy for ACS (72,82-84).

There is robust evidence for aspirin therapy in ACS. For example, ISIS-2 demonstrated that aspirin led to an odds reduction in 30-day vascular mortality of 23% in those with acute MI (85). Current recommendations advise a loading dose of around 300 mg followed by maintenance therapy with 75 mg once daily, including in those with DM. However, because of higher platelet turnover in people with DM, 24-hour platelet inhibition is greater with twice-daily compared with once-daily aspirin administration (86-88). Any effects of clinical outcomes are yet to be determined, but are being studied in the ANDAMAN trial that aims to recruit 2573 participants (NCT02520921) and is estimated to finish in December 2023.

In ACS, the newer $P2Y_{12}$ inhibitors prasugrel and ticagrelor are recommended in preference to clopidogrel due to their greater pharmacodynamic and clinical efficacy (83,84). Post-hoc analysis of the TRITON-TIMI trial suggested an impressive benefit of prasugrel over clopidogrel in people with DM (89). Similar findings were noted with regards to ticagrelor over clopidogrel in the PLATO trial, for which post-hoc analysis showing that the absolute benefit of was greatest in individuals with both DM and chronic kidney disease (90).

Table 3. Key Double-Blinded Randomized Controlled Trials of Dual Antiplatelet Therapy in Acute Coronary Syndrome, Including in People with Diabetes.

Trial	n	ACS group included	Group 1	Group 2	Primary efficacy endpoint – whole trial population	Number with DM	Primary efficacy endpoint – DM subgroup
CURE (91)	12,562	NSTE-ACUTE CORONARY SYNDROME	Aspirin + Clopidogrel	Aspirin + Placebo	CV death/MI/stroke:11.4% vs. 9.3%, HR 0.80 [95% CI 0.72-0.90], p<0.001), ARR 2.1%.	2840 (23%)	CV death/MI/stroke:14.2 % vs. 16.7%. RR 0.85. ARR 2.5%.
CLARITY (92)	3491	STEMI	Aspirin + Clopidogrel	Aspirin + Placebo	Occluded infarct-related artery/death/recurrent MI: 15.0% vs. 21.7%, odds reduction 36% [95% CI 24-47], p<0.001, ARR 6.7%.	575 (16%)	NR
COMMIT (93)	45,852	STEMI	Aspirin + Clopidogrel	Aspirin + Placebo	Death/reinfarction/stroke: 9.2% vs. 10.1%, OR 0.91 [95% CI 0.86-0.97], p=0.002, ARR 0.9%.	NR	NR

TRITON-THROMBOLYSIS IN MYOCARDIAL INFARCTION 38 (94)	13,608	ACUTE CORONARY SYNDROME with scheduled PCI	Aspirin + Prasugrel	Aspirin + Clopidogrel	CV death/MI/stroke: 9.9% vs. 12.1%, HR 0.81 [95% CI 0.73-0.90], p<0.001, ARR 2.2%.	3146 (23%)	CV death/MI/stroke: 12.2% vs. 17.0%, HR 0.70, ARR 4.8%.
TRILOGY ACUTE CORONARY SYNDROME (95)	7243	NSTE-ACUTE CORONARY SYNDROME with medical management	Aspirin + Prasugrel	Aspirin + Clopidogrel	CV death/MI/stroke: 13.9% vs. 16.0%, HR 0.91 [95% CI 0.79-1.05], p=0.21, ARR 2.1%.	2811 (39%)	CV death/MI/stroke: 17.8% vs. 20.4%, HR 0.90 [95% CI 0.73 to 1.09]), ARR=2.6%, interaction-p for DM status 0.71, ARR 2.6%.
PLATO (96)	18,624	All ACUTE CORONARY SYNDROME (STEMI patients included only if for PPCI)	Aspirin + Ticagrelor	Aspirin + Clopidogrel	CV death/MI/stroke: 9.8% vs. 11.7%, HR 0.84 [95% CI 0.77-0.92], p<0.001, ARR 1.9%.	4662 (25%)	CV death/MI/stroke: 14.1% vs. 16.2, HR 0.88 [95% CI 0.76-1.03], interaction-p for DM status 0.49, ARR 2.1%.

ACS, acute coronary syndrome; ARR, absolute risk reduction; CV, cardiovascular; DM, diabetes mellitus; HR, hazard ratio; MI, myocardial infarction; NR, not reported; NSTE-ACS, non-ST elevation ACS; OR, odds ratio; PCI, percutaneous coronary intervention; PPCI, primary PCI; PPM, permanent pacemaker; RR, relative risk; STEMI, ST elevation MI; NR, not recorded

The recent ISAR-REACT-5 study demonstrated superiority of a prasugrel-based strategy over a ticagrelor-based strategy in reducing cardiovascular events in ACS patients but was an open-label trial with limited power (97,98). Furthermore, data from the pre-specified subgroup with DM suggested there was no difference between the drugs (99).

Early de-escalation from dual antiplatelet therapy (DAPT) to ticagrelor monotherapy after PCI, including for ACS, has recently been trialed as an alternative strategy. In the TWILIGHT study, de-escalation from aspirin and ticagrelor to ticagrelor monotherapy at 3 months after PCI for ACS or stable coronary artery disease (CAD) was compared with continued DAPT in 7,119 participants (100). De-escalating to ticagrelor monotherapy led to a lower incidence at 12 months of

the primary end point of Bleeding Academic Research Consortium type 2, 3, or 5 bleeding compared with DAPT (4.0% vs 7.1%, HR 0.56 [95% 0.45-0.68], p<0.001). This finding appeared similar regardless of DM status. There was no evidence of an increase in the secondary combined endpoint of death, MI or stroke. Conversely, 1 month of DAPT followed by ticagrelor alone for 23 months was not superior to 12 months of standard DAPT followed by 12 months of aspirin alone in reducing the primary endpoint of all-cause mortality or new Q-wave MI following PCI in the GLOBAL LEADERS trial, in which 47% of participants had ACS (101). Antiplatelet strategy had no significant effect on BARC type 3 or 5 bleeding in those with and without DM (102). Currently, de-escalation of DAPT may be an option for individuals with high bleeding risk and relatively low risk of vascular re-occlusion but guidelines are yet to recommend more widespread adoption.

In summary, following ACS in individuals with diabetes, DAPT for 12 months with aspirin and prasugrel or aspirin and ticagrelor is recommended by the majority of guidelines/experts and early de-escalation should be reserved to those at high bleeding risk. Longer term DAPT should be considered in those at high thrombosis/low bleeding risk, which is further detailed below.

ACUTE ISCHEMIC STROKE

If no contraindications exist, the first-line treatment for significant acute ischemic stroke is thrombolysis with an intravenous tissue plasminogen activator, or percutaneous mechanical thrombectomy (103). Antiplatelet therapy (APT), typically aspirin monotherapy, is then administered from 24 hours later (104,105).

In those with minor stroke (National Institutes of Health Stroke Score $\leq$3), high-risk transient ischemic attack (TIA) (Age, blood pressure, clinical feature, duration and presence of diabetes score$\geq$4) or TIA not requiring thrombolysis or thrombectomy, APT can be initiated as soon as hemorrhagic stroke is excluded. The current regimen of choice may be dual antiplatelet therapy (DAPT) with aspirin 75-100 mg once daily and clopidogrel 75 mg once daily, based on findings from the CHANCE and POINT trials (106,107). After 21 days, DAPT should be de-escalated to clopidogrel monotherapy (105).

Both ticagrelor monotherapy and aspirin plus ticagrelor have also been compared to aspirin alone after acute non-severe ischemic stroke or high-risk TIA. The SOCRATES trial narrowly failed to demonstrate statistically-significant difference in the primary endpoint of stroke, MI or death (6.7% vs. 7.5%, HR 0.89 [95% CI 0.78-1.01], p=0.07) between participants receiving ticagrelor vs. aspirin (108). However, exploratory analysis suggested those who received both aspirin and ticagrelor in the peri-event period appeared to gain more benefit compared to individuals not having aspirin pre-randomization (HR 0.76 [95% CI 0.61-0.95], p=0.02; vs. 0.96 [0.82-1.12]). This was explored further in the THALES trial, which demonstrated a significant reduction in the primary composite endpoint of stroke or death at 30 days (5.5% vs. 6.6%, HR 0.83 [95% CI 0.71-0.96, p=0.02) when receiving aspirin plus ticagrelor compared to aspirin alone, but at the expense of more frequent severe bleeding (0.5% vs. 0.1%, HR 3.99 [95% CI 1.74-9.14], p=0.001), defined using the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries trial criteria (109). Findings from SOCRATES appeared similar in the subgroups with and without DM, whereas in THALES there was less signal of benefit of DAPT in those with DM vs. those without (HR 0.93 [95% CI 0.72-1.20] vs. 0.78 [0.64-0.94]).

In summary, following major stroke requiring thrombolysis or thrombectomy, aspirin monotherapy should be administered 24 hours later. In minor stroke or high-risk TIA, DAPT should be initiated as soon as intracerebral bleeding is ruled out and continued for 21 days with aspirin then withdrawn and individuals treated with long-term clopidogrel monotherapy.

Preventing Atherothrombotic Events in Individuals with Diabetes and Established Cardiovascular Disease

CORONARY ARTERY DISEASE

In those with established CAD, even without an ACS event in the last 12 months, the benefits of antiplatelet therapy (APT) are well-established. Robust evidence for vs. against use of APT in patients with ASCVD, including CAD comes, for example, from the Antithrombotic Trialists Collaboration, who performed a meta-analysis including 135,000 individuals (110). This demonstrated clear benefit, mainly with aspirin as single-antiplatelet therapy (SAPT), in reducing MACE by around a quarter (110). The incidence of diabetes in these studies, many of which are now several decades old, was relatively low, however.

There is evidence from trials with both pharmacodynamic and clinical outcomes that increasing daily aspirin dose beyond 75-100 mg in patients with DM leads to neither greater platelet inhibition nor improved outcomes (111,112).

Daily doses of aspirin in the range 75-100 mg and no higher are recommended for use as APT. Recent data on clinical outcomes relating to aspirin dosing comes from the ADAPTABLE trial, in which the regimens 81 mg OD and 325 mg OD were compared in 15,076 patients with ASCVD (113). After a median of 26 months, there was no significant difference in the rates of a composite primary endpoint of all-cause death, hospitalization for myocardial infarction or hospitalization for stroke (7.28% [81 mg] vs. 7.51% [325 mg], HR 1.02, 95% CI 0.91-1.14; p=0.75). Furthermore, this finding appeared replicated in the subgroup (n=5676) with diabetes (HR 0.99 [0.84-1.17]). This is supported by pharmacodynamic data showing that, whilst individuals with DM have reduced response to aspirin 75 mg once daily compared with healthy controls, increasing the dose to 300 mg does not alter the response (111).

In the CAPRIE study, clopidogrel 75 mg once daily was compared with aspirin 325 mg once daily (114). There was a slightly lower rate of MI, ischemic stroke or CV death with clopidogrel (5.32% vs. 5.83%, RRR 8.7% [95% CI 0.3-16.5], p=0.043) as well as less gastrointestinal bleeding. A fifth of participants in CAPRIE had diabetes and a retrospective subgroup analysis suggested an amplified benefit of clopidogrel over aspirin compared to those without diabetes. Clopidogrel monotherapy is currently recommended in those people with chronic coronary syndromes (CCS) who are unable to take aspirin, or, based on pre-specified subgroup analyses of CAPRIE suggesting particular benefit, as a first-line agent in those with either concurrent CAD and cerebrovascular disease or PAD.

Beyond single antiplatelet therapy (SAPT), there is good evidence for intensification of antithrombotic therapy in select people with CAD who are at high risk of ischemic events but without high risk of bleeding. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study randomized 19,185 stable aspirin-treated individuals with established atherothrombotic disease or multiple risk factors to receive clopidogrel 75 mg once daily or placebo (115). Though the point estimate of the hazard ratio was below 1, there was no significant reduction in the primary efficacy endpoint of MACE when receiving dual antithrombotic therapy (DAPT) vs. aspirin alone (HR 0.93, [95% CI 0.83-1.05], p=0.22). However, in the subgroup with prior MI, prior stroke or PAD, there was some evidence of benefit (0.77 [0.61-0.98], p=0.031) (116). Around 30% of the participants in CHARISMA had DM and there was in fact a trend towards less benefit of DAPT over SAPT in this group compared to those without DM.

The DAPT study similarly showed that 30 vs. 12 months of clopidogrel (65%) or prasugrel (35%) given to aspirin-treated individuals undergoing PCI

significantly reduced death, MI or stroke in those with prior MI (HR 0.56 [95% CI 0.42-0.76], p<0.001), but not those without (0.83 [0.68-1.02], p=0.08) (117). Like CAPRIE, there was some evidence that those in the trial with DM gained less benefit in reduction of MACE from continued thienopyridine vs. placebo, when compared to those without DM (6.6% vs. 7.0% in those with DM, p=0.55; 3.3% vs. 5.2% in those without, p<0.001; interaction-p=0.03). Conversely, DM did not appear to be an interacting factor with regards to stent thrombosis or bleeding.

There is perhaps more convincing evidence, particularly in those with DM, for use of long-term ticagrelor-based DAPT. In the PEGASUS-TIMI 54 study, DAPT with aspirin plus ticagrelor, either 60 mg or 90 mg twice-daily, reduced MACE vs. aspirin alone (e.g. 60 mg twice-daily vs. placebo: HR 0.84 [95% CI 0.74-0.95], p=0.008) in participants with prior MI (>1 year ago) and an additional risk factor (age ≥65 years, DM, recurrent MI, multivessel CAD or non-end stage CKD) (118). Thrombolysis In Myocardial Infarction (TIMI)-major bleeding was significantly more frequent in ticagrelor-treated individuals, but serious events such as intracranial hemorrhage, hemorrhagic stroke or fatal bleeding showed no increase. In contrast to the thienopyridine trials, the 6806 participants with diabetes demonstrated a significant benefit of DAPT over SAPT in reducing MACE (HR 0.84 [95% CI 0.72-0.99], p=0.035) with a greater absolute risk reduction than in the cohort without diabetes (1.5% vs. 1.1%) (119). Patients without a history of anemia or hospitalization for bleeding, important risk factors for bleeding, appeared to derive greater benefit from long-term DAPT (120).

As well as in those with prior MI, ticagrelor-based DAPT has also been tested against aspirin alone in people with type 2 DM and chronic coronary syndromes (CCS) but without prior MI. THEMIS included 19,220 participants randomized to receive ticagrelor (90 mg twice daily, reduced to 60 mg during the trial) or placebo, on a background of aspirin treatment (121). After an average follow-up of 40 months, there was a lower incidence of MACE in those receiving ticagrelor when compared to placebo (HR 0.90 [95% CI 0.81-0.99], p=0.04). Notably, however, there was a relatively greater increase in TIMI-major bleeding (2.32 [1.82-2.94], p<0.001). Whilst meeting its primary endpoint, the net clinical benefit has not supported adoption in European practice, although subgroup analysis has suggested this may have been more favorable in those patients with prior PCI (122). Furthermore, based on the THEMIS data, the US Food and Drug Administration has recently extended the licensed indication for ticagrelor to include the prevention of a first MI or stroke in people with CCS at high risk of MI or stroke, including in those with DM (123).

An alternative to long-term DAPT is low-dose dual antithrombotic therapy (DATT) with aspirin 75-100 mg once daily and rivaroxaban 2.5 mg twice daily. The COMPASS trial included randomization of 27,395 participants with prior MI or multivessel CAD (38% with DM) or PAD to receive either low-dose DATT, rivaroxaban 5 mg twice daily alone or aspirin alone (124). Compared to aspirin alone, low-dose DATT led to a significantly reduced incidence of MACE [4.1% vs 5.4%, HR 0.76 [95% CI 0.66-0.86], p<0.001], people with DM gaining an even greater absolute net benefit.

Current guidelines recommend long-term DAPT or low-dose dual antithrombotic therapy (DATT) in those individuals with CCS without an indication for therapeutic oral anticoagulant (OAC) who are at high ischemic risk but not high bleeding risk (22).

In those undergoing PCI for stable CAD, including in those individuals with DM, the standard DATT regimen is DAPT with aspirin and clopidogrel for 6 months (125).

In summary, individuals with DM who have CCS should be treated with at least one antiplatelet agent, usually aspirin, although clopidogrel can be used if aspirin is contraindicated. However, more recent

evidence indicates that those with a previous MI benefit from long-term DAPT (aspirin and ticagrelor) or a combination of antiplatelet and anticoagulant (DATT with aspirin and rivaroxaban) provided they have a low bleeding risk. Individuals with significant CAD but without a previous MI may also benefit from DAPT or DATT, which is best reserved for people with high vascular risk but low bleeding risk.

CEREBROVASCULAR DISEASE

There is good evidence for use of APT with aspirin, clopidogrel, ticlopidine or aspirin and dipyridamole in combination for secondary prevention in people with cerebrovascular disease, including those who also have DM (126). Aspirin plus dipyridamole offers better long-term protection than aspirin alone, but has a frequent adverse effect of headache that can limit its use (127). Clopidogrel monotherapy, without this side effect, offers similar levels of secondary prevention to aspirin plus dipyridamole and is the current preferred agent. In the first 3 months after an ischemic stroke, if reperfusion therapy has been given, aspirin alone is typically prescribed. In cases where reperfusion therapy has not been given, there is good evidence for using either aspirin and clopidogrel or aspirin and ticagrelor over aspirin alone (128,129). After 3 months, typically clopidogrel monotherapy is then given long-term, though aspirin and dipyridamole or aspirin alone are used instead at some centers (127,130,131).

PERIPHERAL ARTERY DISEASE

The effectiveness of APT for secondary prevention of ASCVD, including in those with symptomatic PAD, was established by the Antithrombotic Trialists' Collaboration as discussed above. Similarly, in the CAPRIE trial, $P2Y_{12}$ inhibitor monotherapy with clopidogrel was compared with aspirin, including in people with PAD (114). Whilst in the overall trial population there was only a modest reduction in MACE, there was evidence of greater efficacy in the subgroup with PAD, meaning clopidogrel may be preferred to aspirin. Current ESC guidelines recommend either aspirin or clopidogrel for patients with symptomatic PAD and/or those who have required revascularization, including in individuals with DM (132).

In those with symptomatic PAD, ticagrelor monotherapy has also been compared with clopidogrel in the EUCLID trial (133). There was no significant difference in the primary composite endpoint of MACE during a median follow-up period of 30 months and therefore ticagrelor monotherapy is not licensed for use in PAD. Prasugrel monotherapy has not been well tested in clinical-outcome studies but may offer pharmacodynamic advantages over clopidogrel, including in individuals with DM (134).

Comparison of DAPT (aspirin plus clopidogrel) with aspirin alone in people with PAD was included in CHARISMA (n=3,096 with PAD, 36.2% with DM). There was no significant difference in MACE (7.6% vs 8.9%, HR 0.85 [0.66–1.08], p=0.18) (135).

Conversely, there is good evidence for intensification of aspirin monotherapy to low-dose DATT with aspirin 75-100 mg once daily and rivaroxaban 2.5 mg twice daily in people with PAD, supported by the analysis of 7,470 participants with PAD in the COMPASS trial (136). The combination of rivaroxaban and aspirin reduced incidence of MACE over a median follow up of 21 months versus aspirin alone [5.1% vs 6.9%, HR 0.72 (0.57-0.90); p=0.0047]. Particularly important benefits observed included a lower incidence of major adverse limb events [1% vs 2%, HR 0·63 [95% CI 0.41–0.96], p=0·032], and lower incidence of major amputation [0.30 [0.11–0.80], p=0.011].

Subsequently, the evidence base for low-dose DATT in people PAD has been enhanced by the results of the VOYAGER-PAD trial, which randomized 6564 individuals with PAD treated by revascularization to receive either low-dose DATT or aspirin alone (137). After a median follow-up of 28 months (interquartile

range 22-34), the primary composite endpoint of acute limb ischemia, amputation, MI, ischemic stroke or CV death occurred in 17.3% vs. 19.9% (HR 0.85 [0.76-0.96], p=0.009) without a significant increase in the incidence of TIMI major bleeding (2.65% vs. 1.87%, HR 1.43 [0.97-2.10, p=0.07). Forty percent of the trial population had DM with a similar response observed in this group.

It should be noted that DM individuals with symptomatic PAD are likely to have extensive vascular pathology and therefore DATT is likely to offer benefit in more than one vascular bed. Discussion of antithrombotic therapy for those people with DM and asymptomatic PAD is included in the next section.

Preventing First Atherothrombotic Event in Patients with Diabetes and No Symptomatic Atherosclerotic Cardiovascular Disease

It is rational to hypothesize that antithrombotic therapy (ATT) therapy may reduce the chance of a first atherothrombotic event or limit its severity by preventing thrombosis or reducing its impact. ATT in several distinct groups with DM but without symptomatic ASCVD have been investigated in a number of trials. The largest individual-level meta-analysis was performed in 2009 and included 95,000 participants from 6 trials (138). In individuals with DM, though aspirin led to a 12% proportional reduction in the rate of serious vascular events, this did not reach statistical significance. However, the point estimate was consistent with the statistically significant benefit of aspirin in the non-DM population and the DM population showed an identical trend. Three further trials have been added to the literature since this meta-analysis was performed. Two, JPAD (n=2539) and POPADAD (n=1276) were not adequately powered to draw firm conclusions (139,140). However, most recently ASCEND provided data from 15,480 individuals with DM but without symptomatic ASCVD who were randomized to receive aspirin 100 mg once daily or placebo (141). After a mean follow up of 7.4 years, those randomized to aspirin had a significantly reduced rate of serious vascular events (MI, stroke or TIA, or vascular death excluding intracranial hemorrhage) (RR 0.88 [95 % CI 0.79-0.97], p=0.01). However, major bleeding was significantly more frequent when receiving aspirin (1.24 [1.09-1.52], p=0.003), the majority being gastrointestinal. The investigators concluded that the absolute benefits were largely counterbalanced by the risks, despite a favorable, albeit modest, risk-benefit ratio.

Antiplatelet drugs other than aspirin have not been widely studied for primary prevention in individuals with DM and this remains an area for future research.

CONCLUSIONS

DM leads to a prothrombotic milieu that increases the risk of atherothrombotic and thromboembolic events compared to the non-DM population. Changes in platelets, coagulation, and inflammation appear central to this increased risk. Antithrombotic therapy (ATT) can help treat or prevent thrombotic events but increases bleeding risk. In those with a history of symptomatic ASCVD, long-term antiplatelet therapy (APT) with aspirin or clopidogrel is indicated. Intensification to long-term dual antiplatelet therapy (DAPT) or low-dose dual antithrombotic therapy (DATT) should be considered in those with chronic coronary syndromes (CCS) who have high ischemic risk but not high bleeding risk. Low-dose DATT can also be beneficial to people with symptomatic PAD. Therapeutic levels of oral anticoagulant (OAC) should be considered in all individuals with DM who develop AF. Accurately assessing and balancing a patient's risk of ischemic and bleeding events is key to making rational treatment recommendations for ATT in DM (Figure 3).

Looking to the future, further work to determine more precisely an individual's thrombotic and bleeding risk would greatly enhance our ability to make the best treatment recommendations for patients with DM.

Whether this is achieved by more complex statistical modelling, novel imaging techniques, and/or better appreciation of circulating biomarkers remains to be determined. This would allow a greater move towards personalized strategies in order to more appropriately balance the benefits and risks of ATT. People with DM often have complex co-morbidities meaning choosing the best regimen is difficult, but is at the same time crucial to ensure an optimal outcome.

Emerging strategies such as early de-escalation of DAPT are encouraging new tools giving more options for subtle adjustment of ATT intensity, but require definitive proof they lead to no significant ischemic penalty and ratification by guideline committees before wider adoption can be recommended. No doubt further clarity will follow in the coming years.

The lack of an ability of ATT to meaningfully improve net clinical outcomes in those with DM without established ASCVD is a source of disappointment and demands future attention. Trials have focused on aspirin but it is clear that people with DM may have a poor response (111). As well as trials exploring novel regimens of aspirin, trials testing $P2Y_{12}$ inhibitor monotherapy, which may offer pharmacodynamic advantages over aspirin in this group, are warranted (134).

Finally, targeting the pathological abnormalities that cause hypofibrinolysis in diabetes, such as inhibition of PAI-1 activity, may offer an alternative management strategy to further reduce vascular occlusive disease in diabetes, while keeping the risk of bleeding to a minimum.

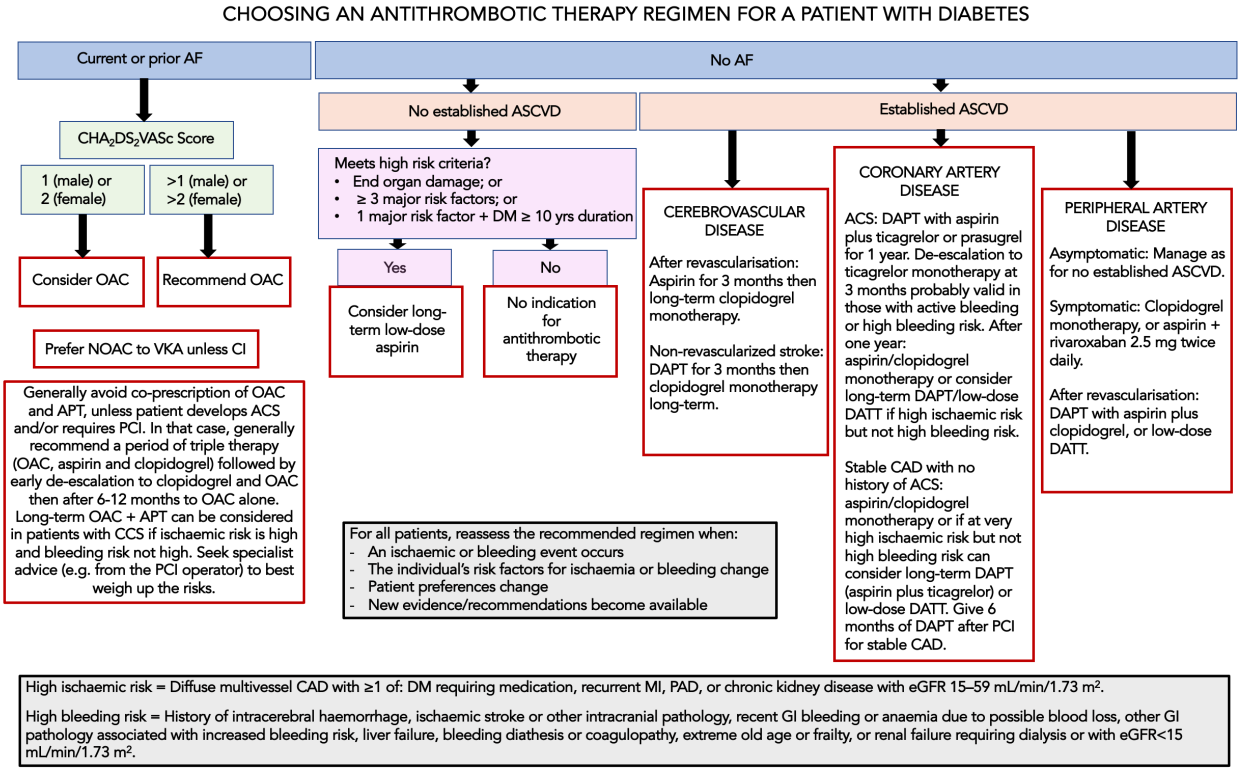

Figure 3. Principles to consider when deciding on the optimal regimen of antithrombotic therapy in a person with diabetes. ACS, acute coronary syndrome; AF, atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CI, contraindication; DAPT, dual antiplatelet therapy; DATT, dual antithrombotic therapy; DM, diabetes mellitus; eGFR, estimated glomerular filtration

rate; GI, gastrointestinal; OAC, oral anticoagulation; PAD, peripheral artery disease; PCI, percutaneous coronary intervention.

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