Anticoagulation therapy in diabetic patients

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Introduction

Diabetic patients have a high risk of developing arterial disease (coronary artery, cerebrovascular and peripheral arterial disease) and are therefore often given antiplatelet therapy.

Although only retrospective studies[1,2] suggest that diabetic patients are also prone to venous thrombo-embolism, many comorbid factors in the diabetic patient, such as heart failure, physical inactivity and atrial fibrillation increase the risk of venous thrombosis. A recent sub-analysis of the RECORD study[3] examined the risk of hyperglycaemia during hip replacement, as a risk factor for postoperative venous thrombo-embolism. For these reasons, diabetic patients are also often given anticoagulant therapy.

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Pathophysiology of vascular disease in diabetic patients

Endothelial cell dysfunction, smooth muscle cell migration and platelet hyper-reactivity play an important role in arterial disease. Virchow's triad of endothelial injury, endothelial dysfunction and hypercoagulability (hyper-reactive platelets and increased clotting factors) are important factors in venous thrombosis.

Endothelial cells produce important active substances that lead to decreased vascular tone and blood flow, increased fibrinolysis, activation of endogenous anticoagulants, decreased leucocyte diapedesis and decreased platelet activation. The nitric oxide (NO) produced by endothelial cells also prevents vascular smooth muscle proliferation and migration (thus protecting the cell from atherosclerosis).

Endothelial dysfunction in diabetic patients is due to metabolic abnormalities such as hyperglycaemia, insulin resistance and increased serum free fatty acid levels.

Platelet function in the diabetic patient is also abnormal due to increased GPIb receptors (increased platelet interaction with the 'glue' von Willebrand factor) and increased GPIIb/IIIa receptors (increased platelet interaction with fibrin and fibrinogen). Calcium homeostasis is abnormal and NO production decreased in the platelets.

Increased levels of procoagulants (clotting factors) such as FIII (tissue factor), FVII and FII, and a decrease in naturally occurring anticoagulants (thrombomodulin on the endothelial surface activates some of the anticoagulants) lead to hypercoagulability. The fibrinolytic pathway is also abnormal, with decreased fibrinolysis due to the increased production of plasminogen activator inhibitor-1 (PAI-1).

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Atrial fibrillation and diabetes mellitus

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and is more prevalent in older patients and men. Risk factors include coronary artery disease and hypertensive heart disease. Since atrial fibrillation is an important risk for stroke and thrombo-embolism, many of these patients are given anticoagulant therapy.

It is important to realise that stroke risk in asymptomatic or paroxysmal AF patients is comparable with that seen in patients with permanent AF. Management of these patients also includes control of heart rate or rhythm.

The decision to give anticoagulation must be weighed against the risk of bleeding. Either aspirin (antiplatelet effect) or warfarin (anticoagulant) has been used. A risk-scoring system, the $CHADS_2$ score,[4] considers congestive heart failure, hypertension, age over 75 years, diabetes mellitus and previous stroke/TIA. A new scoring system (CHA_2DS_2VASc)[5] adds vascular disease (myocardial infarction, peripheral arterial disease or aortic plaque), female gender and an altered age stratification. The HASBLED[6] score has been developed to evaluate the risk of bleeding in AF patients.

Taking this latest CHA_2DS_2VASc scoring system into consideration, the 2010 European Society of Cardiology (ESC) guidelines[7] recommend that any patient with AF and diabetes (without any other added risk) should receive either anticoagulation therapy or aspirin (and preferably anticoagulation). If any one other risk factor (e.g. female, 65 years and older, hypertension) is present, oral anticoagulation is definitely recommended. The reason for this is the superiority of warfarin and the newer oral anticoagulants over aspirin. It is also suggested that patients with a CHA_2DS_2VASc score of 0 receive no antithrombotic therapy.

Warfarin has been used successfully for many years, but most strokes occur in AF patients on warfarin during under-anticoagulated periods. Due to the narrow therapeutic index (INR between 2 and 3), control of oral anticoagulation can be challenging, especially due to the wide variety of drug–drug and drug–food interactions.

Newer oral drugs, the anti-FII drug (acting against clotting factor II) dabigatran (Pradaxa) and the anti-FX drug (acting against clotting factor FX) rivaroxaban (Xarelto) have been extensively tested for stroke prevention in atrial fibrillation patients. In the RE-LY study,[8] dabigatran was shown to be more effective than warfarin, with a similar risk of bleeding in dosages of 150 mg twice a day. The 110 mg bd dose of dabigatran showed significantly less bleeding than warfarin, with a similar efficacy. In 2010 the USA Food and Drug Administration (FDA) approved the use of the 220-mg bd dose of dabigatran for atrial fibrillation.

Rivaroxaban (the ROCKET-AF study[9]) has also been shown to be non-inferior to warfarin, with comparable rates of bleeding but significantly lower rates of intracranial bleeding compared to warfarin. In 2011 the FDA approved rivaroxaban 20 mg once daily for use in patients with AF in the USA. Recently, the results of a

study of rivaroxaban in acute coronary syndromes[10] were published, showing reduced risk of the composite end-point of death from cardiovascular causes, myocardial infarction or stroke with the use of this new drug, although it increased the risk of major bleeding and intracranial haemorrhage, but not the risk of fatal bleeding.

In the AVERROES study, apixaban (another anti-FX drug) was compared with aspirin in patients with AF.[11] Apixaban 5 mg twice daily was superior to aspirin, with a similar rate of major bleeding, and was better tolerated than aspirin.

These drugs have not been approved in South Africa yet for use in AF, but have been approved and successfully used as prophylactic agents against deep-vein thrombosis in orthopaedic patients. In view of the newer guidelines worldwide and experience in other countries, many patients with AF and diabetes will probably receive them in the future.

No laboratory testing is necessary with these two new drugs, but routine laboratory assays may be used to determine the presence of the drugs in cases of bleeding. With dabigatran, activated partial thromboplastin time (PTT) and thrombin time (TT) may be used, and in the case of rivaroxaban, prothrombin time (PT) may be used. Specific assays to determine the level of the drug in the blood have been developed, but in view of the predicted response and lack of need for monitoring, these assays are not available in routine laboratories.

No specific antidote is available for these drugs yet, but fortunately both have a short half-life. Fresh, frozen plasma and activated FVII (Novo VII) have been suggested as antidotes in a patient who is bleeding and needs urgent reversal. Ideally, a fast-acting antidote for these newer drugs would be welcomed.

Dabigatran may need dose adjustment if used with amiodarone, and use is not recommended concomitant with quinidine. It should also be used with caution with verapamil, clarithromycin, rifampicin and other potent P-gp inducers. Rivaroxaban should not be used with ketoconazole, itraconazole and HIV protease inhibitors, and should be used with caution with fluconazole, phenotoin, carbamzepine and other strong CUYP3A4 inducers. Considering the many warfarin–drug interactions, these drug interactions are few in number.

Combination therapy with antiplatelet and anticoagulation drugs

The risk of bleeding increases with dual therapy consisting of anticoagulants and antiplatelet drugs. It is even greater with triple therapy where two antiplatelet drugs (aspirin and clopidrigel) and an anticoagulant are used. There are however patients who need this combination of the antiplatelet effect of aspirin (e.g. underlying ischaemic heart disease) with anticoagulant therapy (e.g. valve replacement, high-risk AF patients).

The ESC working group on thrombosis recommends that in patients with atrial fibrillation who are on oral anticoagulants and present with acute coronary syndrome and possibly stenting, the following applies: with a $CHADS_2$ score of 0, patients should receive dual therapy, and with a $CHADS_2$ score of 1 or more, triple therapy is indicated. INR control must be kept between 2.0 and 2.5 with triple therapy. The duration of triple therapy depends on the HASBLED bleeding risk, as well as type of procedure that has been done.[12]

The North American perspective[13] further suggests that aspirin, if used in combination with oral anticoagulants, should be less than 100 mg and that a proton pump inhibitor (such as pantoprazole) be given for the duration of therapy. It is also suggested that if the newer drug dabigatran is used in combination with antiplatelet therapy, the 110-mg instead of the 150-mg dosage be used. It is recommended that the newer antiplatelet drugs such as prasugrel and ticagrelor not be used with oral anticoagulant therapy.

Conclusion

Many new anticoagulant therapies have been developed and have undergone testing in atrial fibrillation. New antiplatelet drugs have also been developed. Many other novel drugs are at present being tested in clinical trials. The time may come when more specific therapy, tailored to each individual patient's circumstances, will be recommended.

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