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Coronary thrombosis in diabetes: are we doing enough?

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Introduction

Despite advances in treatment, mortality of individuals with diabetes remains higher than the general population, mainly due to increased risk of cardiovascular (CV) events (1). The higher CV mortality in diabetes, often secondary to coronary artery disease (CAD), is mainly related to two factors: i) premature and advanced atherosclerosis and ii) increased thrombosis potential. The former is usually treated with revascularisation following an acute event (provided the affected vessel is accessible) followed by multifactorial medical therapy to optimise blood pressure and lipid parameters together with appropriate management of glycaemia (2). Despite the enhanced thrombotic environment in diabetes, anti-thrombotic therapy in this population appears to be largely similar to those with normal glucose metabolism, posing the question: is this practice clinically justified?

Antithrombotic treatment in diabetes can be divided into primary prevention in those without previous history of CV disease and secondary prevention in individuals who previously sustained a vascular event.

Primary prevention

Earlier guidelines advocated initiation of antiplatelet therapy, usually using aspirin, in individuals with diabetes and no cardiovascular history. This advice was mainly based on data from post hoc analysis of historical studies, conducted in the pre-statin era (3;4). However, this practice has changed after some high profile, if woefully underpowered, studies suggested that aspirin is not an effective primary prevention agent in diabetes (5;6). A number of subsequent meta-analyses failed to show a clinically favourable benefit/risk ratio for aspirin in diabetes, dampening any residual enthusiasm for widespread use of this agent in primary prevention (7-11). The relatively recent ESC/EASD and ADA guidelines quite rightly emphasised the lack of robust evidence for or against such a practice and adopted a pragmatic approach by advocating that antiplatelet therapy for primary prevention in diabetes *can be* offered to higher risk patients (level of evidence IIbC) without clearly defining this subgroup (2;12). The simple truth is that adequately powered studies to address the role of aspirin, or any other antiplatelet therapy, in primary CV protection in diabetes have not been undertaken until

recently and results of these trials, such as ASCEND (NCT00135226) and ACCEPT-D (ISRCTN48110081), are eagerly awaited. Until these data become available, routine use of antiplatelet agents for primary vascular protection should be avoided.

Secondary prevention

This can be divided into medium and long term prevention following the vascular event. It can be argued that a third category exists related to antithrombotic treatment during the acute vascular event but this is beyond the scope of the current editorial.

Medium term treatment usually lasts for 12 months following a coronary event and relies on dual antiplatelet therapy (DAT) employing two agents that modulate different pathways in platelet activation. These consist of an inhibitor of the thromboxane pathway, aspirin, and one of the P_2Y12 inhibitors clopidogrel, prasugrel or ticagrelor. Long-term therapy, beyond one year, employs a single antiplatelet agent, usually aspirin, which is continued for life. However, the best treatment strategy in diabetes is far from clear despite a number of recent large multicentre trials.

In the TRITON-TIMI 38 study, involving 13608 patients with acute coronary syndrome, the composite primary end point (PEP) of CV mortality, non-fatal myocardial infarction or stroke was lower with the combination of prasugrel and aspirin (9.9%) than clopidogrel and aspirin (12.1%; p<0.001) but the increase in bleeding events cancelled out the clinical benefit (2.4% and 1.8%, respectively; p=0.03). However, analysis of the diabetes subgroup (n=3146) showed a greater reduction in PEP with prasugrel and aspirin compared with clopidogrel and aspirin (17.0% and 12.2%, respectively; p<0.001) without an increased risk of bleeding (13). The PLATO study (n=18624) showed superiority of ticagrelor and aspirin compared with clopidogrel and aspirin following acute coronary syndrome, an observation that was maintained in diabetes patients (n=4662), although strictly speaking the difference in this subgroup failed to reach statistical significance (14).

These studies strongly suggest that clopidogrel is not the best P_2Y12 inhibitor when used in combination therapy in patients with diabetes.

Unfortunately, a specific and adequately powered DAT study in diabetes patients with ACS is yet to be conducted and current data have been obtained following subgroup analysis of trials including a combination of diabetes and non-diabetes individuals. The ESC/EASD guidelines highlighted the superiority of modern P_2Y12 inhibitors and encouraged the use of these agents for DAT in diabetes (2). It should be noted that the beneficial effect of prasugrel is mainly evident in patients undergoing percutaneous coronary intervention (PCI) and therefore this treatment is not recommended for patients who do not undergo revascularisation (15). A recent metaanalysis further suggested that DAT with prasugrel may be the best option in patients with diabetes, particularly those undergoing PCI, emphasising superiority of this agent compared with clopidogrel (16).

What about long-term secondary CV prevention in diabetes? Current practice dictates lifelong antiplatelet monotherapy, usually with aspirin, after the initial phase of DAT in those sustaining a coronary event (class of evidence IA according to EASD/ESC guidelines). However, several pieces of evidence suggest that this treatment is suboptimal in patients with diabetes. Almost 15 years ago, Bhatt and colleagues demonstrated that long-term monotherapy with clopidgrel is superior to aspirin in diabetes, particularly in those with longer diabetes duration requiring insulin therapy (17). Naturally, this was not a definitive study, as it was based on a post hoc analysis, but it is surprising that this was not investigated further at the time in a definitive trial. This will be rectified to some extent by investigating the effects of ticagrelor monotherapy following acute coronary syndrome and PCT in the LEADERS-GLOBAL trial, which is ongoing and includes a decent sized population of diabetes patients (18).

Others have suggested that once daily aspirin is less effective than twice daily dosing in diabetes, given the short half-life of aspirin and the high platelet turnover in this condition (19). Outcome studies investigating the role of twice daily aspirin in diabetes would be of interest but funding to undertake such work may prove to be difficult. More recently, a study has shown that longer term therapy with aspirin and ticagrelor in 6806 diabetes patients with established CAD (for a median of 33 months) reduced major adverse cardiac events compared with aspirin alone (20), suggesting that DAT should be continued beyond 12 months of the coronary event, adding yet another dimension to long-term antiplatelet therapy in diabetes.

Is it all about antiplatelet therapy?

In the absence of cardiac arrhythmias and valvular heart disease, prevention of coronary thrombosis mainly relies on antiplatelet therapy. However, coagulation proteins are affected in diabetes resulting in fibrin networks (the backbone of blood clots) that are compact and difficult to breakdown, contributing to an enhanced thrombotic environment (21). Clinical studies targeting fibrin networks as a way of preventing CAD have been scarce and used in combination of DAT, failing in the process to show a benefit, largely due to increased bleeding events [summarised in (22)]. Current agents targeting coagulation proteins have a relatively broad inhibitory activity by modulating FX or thrombin activity, consequently resulting in profound inhibition of fibrin network formation that in turn increases bleeding risk. A more targeted approach may prove to be both safer and more effective. For example, studies have shown increased incorporation of antifibrinolytic proteins into clots from patients with diabetes. Plasmin inhibitor and complement C3 incorporation into fibrin clots of patients with diabetes is increased, which in turn compromises fibrin clot lysis and predisposes to thrombosis (23;24). Targeting the interaction between fibrinogen and anti-fibrinolytic proteins may offer an alternative antithrombotic strategy in diabetes that is disease specific and perhaps safer than the broad inhibition of fibrin network formation by agents targeting FX and thrombin.

Future directions

There are a number of measures to be considered in order to optimise antithrombotic therapy in diabetes. Firstly, adequately powered clinical studies in individuals with diabetes are needed, rather than drawing conclusions from subgroup analysis of large studies, including mixed populations of diabetes and non-diabetes patients. Carefully designed diabetes studies, conducted in collaboration between cardiologists and diabetologists, will allow appropriate characterisation of patients with the possibility of identifying diabetes subgroups who would most benefit from a particular intervention. Secondly, more studies are required to understand the best strategy for long-term antithrombotic therapy in diabetes. This is likely to encompass a large programme of work that includes alternative dosing of existing agents, use of low dose combination antiplatelet

therapies and low dose combination of anti-platelet and anticoagulant therapies. The latter is a particularly attractive concept as "mild" inhibition of both the cellular and protein phase of coagulation may prove to be more effective at reducing thrombosis risk while limiting bleeding complications. Thirdly, research into alternative antithrombotic therapies offers another avenue to control the enhanced thrombosis risk in diabetes. For instance, FXII inhibitors have been claimed to offer protection from thrombosis with minimal risk of bleeding (25). Such an approach may be particularly useful in clinical scenarios involving activation of the intrinsic pathway (such as stent thrombosis) but perhaps less effective in conditions involving plaque rupture (which involves activation of the extrinsic pathway). Diabetes-specific therapies involving modulation of antifibrinolytic protein incorporation into fibrin networks offer the novel possibility of tackling head on one of the pathophysiological mechanisms in diabetes that enhances the thrombotic milieu.

Finally, we are in desperate need of a measure that accurately identifies thrombosis potential in individuals at risk of coronary artery disease. We regularly measure response to antihypertensive or lipid therapies with subsequent modification of treatment according to the response of each patient. In contrast, antithrombotic therapy is given to patients and the prescribing physician simply "hopes for the best" without properly assessing response to these agents. It is well accepted that platelet reactivity can predict future ischaemic events but modification of treatment according to platelet function testing failed to improve outcome in a large study (26), leading some to conclude that such an approach is not clinically viable. Collet and colleagues should be applauded for their efforts but the study is far from conclusive; thrombosis risk should not rely on a single measurement and more work is needed to identify a reliable marker of the thrombotic milieu, which is likely to include multiple measures of thrombosis.

Conclusions

Although modulation of thrombosis risk in individuals with CAD has been fundamental at reducing future ischaemic events and mortality, current therapies are yet to be optimised, particularly in patients with diabetes. The enhanced thrombotic environment in diabetes calls for alternative antithrombotic treatment

strategies in this group both in primary and secondary vascular protection. An often overlooked difficulty is that diabetes is not a single disease entity but a continuum of different conditions with variable vascular risk dependent on a number of factors such as diabetes duration, type of hypoglycaemia therapy and presence of microvascular complications. Therefore, the benefit of antithrombotic therapy, particularly in primary prevention, is likely to be different according to the individual vascular risk of each patient. Therefore, treatment to reduce thrombosis risk may need to be varied in subgroups of diabetes patients in order to achieve the best benefit/risk ratio.

A combination of basic, translational and clinical research studies to identify accurate markers of thrombosis and develop novel antithrombotic compounds will help to effectively control the thrombotic environment in diabetes. Moreover, studies investigating different doses of existing agents and various antithrombotic combination therapies is perhaps necessary to maximise benefits in this high risk group. One thing for sure, there is still a long way to go in order to optimise antithrombotic therapy in patients with diabetes and we have thus far merely scraped the surface of this highly complex area.

Reference List

(1) Di AE, Kaptoge S, Wormser D, Willeit P, Butterworth AS, Bansal N, et al. Association of Cardiometabolic Multimorbidity With Mortality. JAMA 2015 Jul 7;314(1):52-60.

(2) Ryden L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J 2013 Oct;34(39):3035-87.

(3) Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. N Engl J Med 1989 Jul 20;321(3):129-35.

(4) Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study report 14. ETDRS Investigators. JAMA 1992 Sep 9;268(10):1292-300.

(5) Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ 2008;337:a1840.

(6) Ogawa H, Nakayama M, Morimoto T, Uemura S, Kanauchi M, Doi N, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. JAMA 2008 Nov 12;300(18):2134-41.

(7) Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009 May 30;373(9678):1849-60.

(8) Pignone M, Alberts MJ, Colwell JA, Cushman M, Inzucchi SE, Mukherjee D, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes. J Am Coll Cardiol 2010 Jun 22;55(25):2878-86.

(9) De Berardis G, Sacco M, Strippoli GF, Pellegrini F, Graziano G, Tognoni G, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. BMJ 2009;339:b4531.

(10) Zhang C, Sun A, Zhang P, Wu C, Zhang S, Fu M, et al. Aspirin for primary prevention of cardiovascular events in patients with diabetes: A meta-analysis. Diabetes Res Clin Pract 2010 Feb;87(2):211-8.

(11) Kunutsor SK, Seidu S, Khunti K. Aspirin for primary prevention of cardiovascular and all-cause mortality events in diabetes: updated meta-analysis of randomized controlled trials. Diabet Med 2016 Apr 17.

(12) Standards of medical care in diabetes--2014. Diabetes Care 2014 Jan;37 Suppl 1:S14-S80.

(13) Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007 Nov 15;357(20):2001-15.

(14) James S, Angiolillo DJ, Cornel JH, Erlinge D, Husted S, Kontny F, et al. 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 Dec;31(24):3006-16.

(15) Roe MT, Armstrong PW, Fox KA, White HD, Prabhakaran D, Goodman SG, et al. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. N Engl J Med 2012 Oct 4;367(14):1297-309.

(16) Rossington JA, Brown OI, Hoye A. Systematic review and meta-analysis of optimal P2Y12 blockade in dual antiplatelet therapy for patients with diabetes with acute coronary syndrome. Open Heart 2016;3(1):e000296.

(17) Bhatt DL, Marso SP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus. Am J Cardiol 2002 Sep 15;90(6):625-8.

(18) Vranckx P, Valgimigli M, Windecker S, Steg PG, Hamm C, Juni P, et al. Long-term ticagrelor monotherapy versus standard dual antiplatelet therapy followed by aspirin monotherapy in patients undergoing biolimus-eluting stent implantation: rationale and design of the GLOBAL LEADERS trial. EuroIntervention 2015 Nov 23;11(7).

(19) Dillinger JG, Drissa A, Sideris G, Bal Dit SC, Voicu S, Manzo SS, et al. Biological efficacy of twice daily aspirin in type 2 diabetic patients with coronary artery disease. Am Heart J 2012 Oct;164(4):600-6.

(20) Bhatt DL, Bonaca MP, Bansilal S, Angiolillo DJ, Cohen M, Storey RF, et al. Reduction in Ischemic Events With Ticagrelor in Diabetic Patients With Prior Myocardial Infarction in PEGASUS-TIMI 54. J Am Coll Cardiol 2016 Jun 14;67(23):2732-40.

(21) Alzahrani SH, Ajjan RA. Coagulation and fibrinolysis in diabetes. Diab Vasc Dis Res 2010 Oct;7(4):260-73.

(22) Park Y, Franchi F, Rollini F, Angiolillo DJ. Antithrombotic Therapy for Secondary Prevention in Patients With Diabetes Mellitus and Coronary Artery Disease. Circ J 2016 Mar 25;80(4):791-801.

(23) Agren A, Jorneskog G, Elgue G, Henriksson P, Wallen H, Wiman B. Increased incorporation of antiplasmin into the fibrin network in patients with type 1 diabetes. Diabetes Care 2014 Jul;37(7):2007-14.

(24) Hess K, Alzahrani SH, Mathai M, Schroeder V, Carter AM, Howell G, et al. A novel mechanism for hypofibrinolysis in diabetes: the role of complement C3. Diabetologia 2012 Apr;55(4):1103-13.

(25) Baeriswyl V, Calzavarini S, Chen S, Zorzi A, Bologna L, Angelillo-Scherrer A, et al. A Synthetic Factor XIIa Inhibitor Blocks Selectively Intrinsic Coagulation Initiation. ACS Chem Biol 2015 Aug 21;10(8):1861-70.

(26) Collet JP, Cuisset T, Range G, Cayla G, Elhadad S, Pouillot C, et al. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. N Engl J Med 2012 Nov 29;367(22):2100-9.