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Editorial

Cardiovascular disease in diabetes: are we doing enough?

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Diabetes and Cardiovascular Disease

Diabetes mellitus (DM), the epidemic of the 21st century, carries a high risk of cardiovascular (CV) complications, which remain the main cause of mortlaity in this population. In 2011, 281 million men and 317 million women died worldwide with DM, the majority from vascular disease (www.diabetesatlas.org/content).

In addition to increased risk of first myocardial infarction [1,2], individuals with diabetes continue to have worse prognosis following cardiac ischaemia. Studies show that regardless of the type of intervention in the acute stage, mortality following a coronary event in diabetes remains significantly higher than individuals without diabetes. In particular, there has been little reduction in CV death following acute coronary syndrome in diabetes, despite improvement in clinical care. Comparing 1995 with 2003, mortality following acute coronary syndrome was reduced by 15% at 18 months in individuals without diabetes, but only a non-significant 4% reduction was documented in those with diabetes [3]. It could be argued that more up-to-date revascularisation strategies may have narrowed the difference between diabetes and non-diabetes subjects. However, diabetes individuals with myocardial infarction (MI) undergoing percutaneous coronary artery intervention (PCI) have significantly higher mortality than those without diabetes both at one month (7.4% vs 3.8%, respectively) and at 12 months (13.9% and 6.5%, respectively) [4]. The same applies to individuals treated with coronary artery bypass graft (CABG). In 10626 who have undergone CABG, mortality in individuals with diabetes was more than 50% higher at 1, 5 and 10 years compared with those having normal glucose metabolism [5]. Moreover, others have shown that drug eluting stents or CABG do not improve clinical outcome in diabetes after 5.6 years follow up, indicating the type of revascularisation has little effect on longer term prognosis [6].

Mechanisms for Poor Prognosis in Diabetes Following Cardiac Ischaemia

Several pieces of evidence indicate that the adverse clinical outcome in diabetes following coronary events is due to a combination of: i) more extensive vascular pathology, ii) increased thrombosis risk and iii) heart failure, related, at least in part, to vascular complications [7,8]. In addition to these modifiable pathologies, gender has also been implicated as women with diabetes faring less well than men following a vascular event, although this remains an area of debate [9-11].

Vascular pathology

Atherosclerotic disease is treated in the acute phase with revascularisation (PCI or CABG) followed by longer-term therapy to control risk factors including glycaemia, blood pressure and cholesterol. Although early treatment of elevated blood glucose is important to reduce longer term vascular complications, the role of strict glycaemic control in individuals with clinically established vascular disease is less clear, at least in the medium term [12]. In contrast, the beneficial effects of lowering blood pressure and cholesterol levels in these individuals is beyond doubt, although some caution is ought to be exercised. Current blood pressure targets are set at <140/85 mmHg (<130 mmHg systolic in high risk subjects) [12], but too aggressive lowering of blood pressure, particularly in older individuals, is to be avoided as it may have detrimental effects [13]. Therefore, the ideal blood pressure in this group of patients is yet to be determined and is likely to be affected by various factors including age and co-morbidities. Target cholesterol levels are currently set at low density lipoprotein cholesterol at <1.8 mmol/l [12], which should be achievable in the majority with currently available therapies. However, targets are seldom reached [14,15] and this is almost certainly contributing to increased CV mortality.

Thrombosis risk

Diabetes is associated with an increased thrombotic environment, characterised by increased reactivity of platelets and enhanced activity of coagulation proteins [16,17].

This increased thrombotic environment is managed with anti-platelet therapy and treatment of the acellular arm of coagulation is not currently advocated. Dual antiplatelet therapy is used following cardiac ischemia with the sole inhibitor of the thromboxane pathway, aspirin, and one of the P_2Y_{12} inhibitors (clopidogrel, prasugrel or ticagrelor). This treatment is continued for one year following the event followed by life-long antiplatelet monotherapy, usually with aspirin. Current guidelines recommend similar antiplatelet therapies in individuals with and without diabetes. However, there is limited evidence indicating differential response in diabetes. For example, prasugrel shows superior efficacy to clopidogrel following ACS in diabetes without an increase in bleeding, in contrast to individuals without diabetes, who suffer increased bleeding complications [18].

Heart failure

The close association between diabetes and heart failure has been recently emphasised by demonstrating that more than a quarter of individuals with diabetes have previously undiagnosed heart failure, which displays a gender difference (31% and 25% for women and men, respectively) [19]. Studies have shown that heart failure in diabetes increases the risk of mortality by up to 12 fold [8,20]. Deranged cardiac macro- and microcirculatory flow have been implicated as mechanisms for adverse cardiac remodelling following

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ACS in diabetes, which further contributes to the guarded clinical prognosis [21].

The role of gender

Women with diabetes lose CV protection and have higher vascular mortality than their male counterparts [9-11]. The relative risk of mortality from coronary artery disease has a male to female hazard ratio of 2.3 (CI 2.1-2.6) in those without diabetes, decreasing to 1.5 (CI 1.2-1.9), in individuals with diabetes [22]. A meta-analysis of 37 studies has shown significantly higher hazard ratio of mortality from CAD in women with diabetes at 3.5 (2.7-4.5) compared with men at 2.1 (1.8-2.3) [23].

Future directions

Despite the clear association between diabetes and CV disease, intervention studies in this population are rarely performed. Management decisions are usually based on data obtained from post hoc analysis of clinical trials that include a mixture of diabetes and non-diabetes subjects. Also, it should be appreciated that diabetes is not a single entity but a continuum of various conditions, with each subgroup having a different CV risk. For example, vascular risk of an individual with newly diagnosed and diet controlled diabetes is very different to someone with longer disease duration, on insulin therapy and with established micro vascular complications. Therefore, appropriate characterisation of diabetes patients in clinical vascular trials is paramount, which studies usually fail to address.

Another area that remains unclear is the best anti-thrombotic strategy in patients with diabetes. Until recently aspirin was advocated for primary CV protection in diabetes but this is not routine practice anymore. Current guidelines specify the use of aspirin for primary prevention in diabetes in higher risk subjects without clearly defining this group. Moreover, the role of aspirin in secondary prevention is not as clear as we are led to believe and requires further clarification [24]. In particular, recent evidence suggests that twice daily aspirin may be more effective in individuals with diabetes, although large-scale outcome studies are yet to be conducted [25].

The best glycaemic strategy in individuals with diabetes and established CV disease remains hotly debated [12]. The association between hypoglycaemia and CV mortality [26] further adds fuel to the fire and prospective studies are needed to establish the best glycaemic targets, at different time points following cardiac ischaemia and in patients with stable disease. An added difficulty is the varying effect of hypoglycaemic agents on vascular risk, which has become the focus of recent research, particularly with newer agents.

In contrast to glycaemia, lipid and blood pressure targets are relatively well established, although caution is required to avoid excessive lowering of blood pressure, particularly in the elderly [13].

Finally, the documented difference in clinical outcome between men and women following cardiac ischaemia requires more detailed analysis with the potential to develop gender-specific therapies.

References

1. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med. 1998; 339: 229-234.
2. Schramm TK, Gislason GH, Kober L, Rasmussen S, Rasmussen JN, et al. Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk: a population study of 3.3 million people. Circulation. 2008; 117: 1945-1954.
3. Cubbon RM, Wheatcroft SB, Grant PJ, Gale CP, Barth JH. Temporal trends in mortality of patients with diabetes mellitus suffering acute myocardial infarction: a comparison of over 3000 patients between 1995 and 2003. Eur Heart J. 2007; 28: 540-545.
4. Kahn MB, Cubbon RM, Mercer B, Wheatcroft AC, Gherardi G, et al. Association of diabetes with increased all-cause mortality following primary percutaneous coronary intervention for ST-segment elevation myocardial infarction in the contemporary era. Diab Vasc Dis Res. 2012; 9: 3-9.
5. van Straten AH, Soliman Hamad MA, van Zundert AA, Martens EJ, Schönberger JP. Diabetes and survival after coronary artery bypass grafting: comparison with an age- and sex-matched population. Eur J Cardiothorac Surg. 2010; 37: 1068-1074.
6. Kim YG, Park DW, Lee WS, Park GM, Sun BJ. Influence of diabetes mellitus on long-term (five-year) outcomes of drug-eluting stents and coronary artery bypass grafting for multivessel coronary revascularization. Am J Cardiol. 2012; 109: 1548-1557.
7. Puri R, Kataoka Y, Uno K, Nicholls SJ. The distinctive nature of atherosclerotic vascular disease in diabetes: pathophysiological and morphological insights. Curr Diab Rep. 2012; 12: 280-285.
8. Mercer BN, Morais S, Cubbon RM, Kearney MT. Diabetes mellitus and the heart. Int J Clin Pract. 2012; 66: 640-647.
9. Barrett-Connor EL, Cohn BA, Wingard DL, Edelstein SL. Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo Study. JAMA. 1991; 265: 627-631.
10. Juutilainen A, Kortelainen S, Lehto S, Rönnemaa T, Pyörälä K. Gender difference in the impact of type 2 diabetes on coronary heart disease risk. Diabetes Care. 2004; 27: 2898-2904.
11. Hu G, Jousilahti P, Qiao Q, Peltonen M, Katoh S. The gender-specific impact of diabetes and myocardial infarction at baseline and during follow-up on mortality from all causes and coronary heart disease. J Am Coll Cardiol. 2005; 45: 1413-1418.
12. Ryden L, Grant PJ, Anker SD, Berne C, Cosentino F, 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; 34: 3035-3087.
13. Moreno G, Mangione CM. Management of cardiovascular disease risk factors in older adults with type 2 diabetes mellitus: 2002-2012 literature review. J Am Geriatr Soc. 2013; 61: 2027-2037.
14. Ali MK, Bullard KM, Saaddine JB, Cowie CC, Imperatore G. Achievement of goals in U.S. diabetes care, 1999-2010. N Engl J Med. 2013; 368: 1613-1624.
15. Farkouh ME, Boden WE, Bittner V, Muratov V, Hartigan P. Risk factor control for coronary artery disease secondary prevention in large randomized trials. J Am Coll Cardiol. 2013; 61: 1607-1615.
16. Ferreiro JL, Cequier ÁR, Angiolillo DJ. Antithrombotic therapy in patients with diabetes mellitus and coronary artery disease. Diab Vasc Dis Res. 2010; 7: 274-288.
17. Alzahrani SH, Ajjan RA. Coagulation and fibrinolysis in diabetes. Diab Vasc Dis Res. 2010; 7: 260-273.
18. Wiviott SD, Braunwald E, Angiolillo DJ, Meisel S, Dalby AJ, et al. Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-Thrombolysis in Myocardial Infarction 38. Circulation. 2008; 118: 1626-1636.

19. Boonman-de Winter LJ, Rutten FH, Cramer MJ, Landman MJ, Liem AH. High prevalence of previously unknown heart failure and left ventricular dysfunction in patients with type 2 diabetes. Diabetologia. 2012; 55: 2154-2162.

20. Cubbon RM, Adams B, Rajwani A, Mercer BN, Patel PA. Diabetes mellitus is associated with adverse prognosis in chronic heart failure of ischaemic and non-ischaemic aetiology. Diab Vasc Dis Res. 2013; 10: 330-336.

21. Poornima IG, Parikh P, Shannon RP. Diabetic cardiomyopathy: the search for a unifying hypothesis. Circ Res. 2006; 98: 596-605.

22. Orchard TJ. The impact of gender and general risk factors on the occurrence of atherosclerotic vascular disease in non-insulin-dependent diabetes mellitus. Ann Med. 1996; 28: 323-333.

23. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ. 2006; 332: 73-78.

24. Cubbon RM, Gale CP, Rajwani A, Abbas A, Morrell C. Aspirin and mortality in patients with diabetes sustaining acute coronary syndrome. Diabetes Care. 2008; 31: 363-365.

25. Ajjan RA. Primary and secondary prevention of cardiovascular disease in diabetes with aspirin. Diab Vasc Dis Res. 2012; 9: 243-244.

26. Frier BM, Schernthaner G, Heller SR. Hypoglycemia and cardiovascular risks. Diabetes Care. 2011; 34 Suppl 2: S132-137.

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