Microvascular complications in diabetes as simple indicators of risk for cardiovascular outcomes and heart failure

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Once in a while a paper comes along which, while reinforcing established wisdom, does so in a manner which is potentially clinically impactful. The paper by Brownrigg et al (1), which takes advantage of the excellent Clinical Practice Research Datalink (CPRD) to examine the associations of microvascular complications with cardiovascular risk, heart failure hospitalisation and all-cause mortality in patients with type 2 diabetes, does just this. Its simple message is that the presence of any microvascular disease, namely neuropathy, retinopathy and/or nephropathy, signals risk for cardiovascular disease which is sufficient to warrant robust preventative therapy; indeed, individual microvascular complications appeared to better indicate cardiovascular risk than did individual classical risk factors. More notably, cardiovascular risk appeared to escalate in a graded, almost linear, fashion with increasing numbers of microvascular complications such that the simultaneous presence of retinopathy, nephropathy and neuropathy was associated with twice the risk for cardiovascular events compared to those with no such complications in analyses adjusted for not only classical risk factors but also lipid-lowering and anti-hypertensive therapy (1). Multiple microvascular complications signalled even higher risks for both cardiovascular death and heart failure hospitalisation, a finding which in itself deserves further study. The authors cogently argue that the presence of multiple microvascular complications should encourage intensification of cardiovascular protective therapies. Such findings are not surprising if we consider that microvascular complications typically develop over several years (although the findings were robust to adjustment for the duration of diabetes) and that hypertension is also a strong risk factor for both diabetic retinopathy and renal disease. Nor should the results be a surprise on mechanistic grounds as there is now ample evidence that pathophysiological processes leading to microvascular damage in part mirror, or directly contribute to, macrovascular damage (2).

A key question with any such evidence is whether the findings can truly improve clinical practice. With this in mind, it is notable that statin in CPRD use was above 70% in subjects with any microvascular complications while more than 85% were receiving blood pressure treatment, and corresponding cholesterol and blood pressure levels were excellent. These treatment figures are high in CPRD since NICE guidelines recommend statins to all adults above 40 years of age with type 2 diabetes, and that SBP should be <140 to lessen CVD risks, the latter target supported by a recent meta-analysis (3). Only in England and Wales have the health authorities (National Institute of Clinical Excellence) recently recommended reverting to cardiovascular risk scoring to determine which diabetic patients should receive statins for primary prevention (4). In this latter case, as well as the US-based ACC/AHA cardiovascular risk score (5) (used to determine which diabetic patients should be escalated to more intensive statin therapy), Brownrigg et al (1) show that adding information on microvascular complications could meaningfully improve allocation of moderate or intensive dose statins. The caveat to this is that primary prevention cardiovascular risk scores commonly used in most countries do not include diabetes-specific factors such as HbA1c or duration of diabetes, and though diabetes specific risk scores do exist (6), it appears that such risk scores are unlikely to gain widespread clinical use because of their complexity and the widening use of generically available statins.

Rather, we suggest the current findings may help in three simpler ways. Firstly, the findings should strongly reinforce the need to commence statin therapy and aggressively pursue recommended blood pressure targets in any patients not already on such therapies with any microvascular damage, particularly patients younger than 40 years of age in whom guidelines are often less prescriptive. Secondly, microvascular disease in more than one vascular bed (e.g. retinopathy plus neuropathy) should prompt consideration of more intensive lipid-lowering therapy to achieve lower LDL-c (or non-HDL-c) targets. Notably, the recently

published European Society of Cardiology cardiovascular prevention guidelines (7) already categorise “diabetes with target organ damage such as proteinuria” as conveying very high risk for cardiovascular disease and thus supporting lower LDL-c targets. Of all the microvascular complications, the present paper in conjunction with prior studies (8) reinforces the notion that diabetes plus microalbuminuria is commensurate with markedly elevated cardiovascular risk. Thirdly, the paper’s findings could help those designing trials in patients with diabetes looking to enrich their population in terms of cardiovascular risk or, more specifically, cardiovascular death and heart failure risks.

Finally, it must be borne in mind that while cardiovascular event rates in patients with diabetes in high income countries have decreased sharply in the last two decades, concerns remain with respect to complications like end-stage renal failure and heart failure (9). To mitigate against these will require more aggressive management of microvascular damage per se which would mean aiming for: i. Lower SBP targets (<130mmHg) in selected groups, ii. Earlier detection of diabetes and more aggressive glycaemia management early after diagnosis, and iii. The earlier use of drug classes proven to do more than just lower glucose levels. Fortunately, though higher costs will limit their usage, two more recent additions to the diabetes armoury (GLP-1 receptor antagonists and SGLT2 inhibitors) fulfil this latter characteristic and thus meaningfully add to the tool box of diabetes medications.

Conflicts of interest

NS reports having received honoraria for advisory boards or lectures for Amgen, Sanofi, Boehringer Ingelheim, Novo Nordisk, Merck, Janssen and Astrazeneca. DP reports consulting for Sanofi during previous employment.

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