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EDITORIAL

Cardiovascular risk in type 1 and type 2 diabetes: Differences, similarities and insights

Riesgo cardiovascular en diabetes tipo 1 y tipo 2: Diferencias, similitudes y reflexiones

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Cardiovascular disease (CVD), particularly coronary artery disease, cerebrovascular disease and peripheral arterial disease, as well as heart failure, are common complications and the primary cause of mortality among diabetics. Thanks to improvements made to health systems, pharmacotherapy and other advances in the social setting, overall and cardiovascular (CV) mortality are consistently falling, particularly among individuals with type 1 diabetes (T1DM).[1,2] The roll-out of insulin therapy plus physiological therapy (basal-bolus), accessibility to safer insulin analogues, and the growing availability of continuous glucose monitoring systems in patients with T1DM may be contributing to this decrease, as they provide for better blood glucose control. How could the impact of hyperglycaemia (or its microangiopathic complications) on CV disease not be less if we compare the mean baseline HbA1c (8.8%) of participants in the Diabetes Control and Complications Trial (DCCT) with the mean baseline value of our patients today (7.9%)?[3] Yet quite the opposite is true, as the growing number of people with type 2 diabetes mellitus (T2DM) and the fact that they are being diagnosed at a younger age may buck this trend in T2DM.[3]

However, the diabetic patients that attend our clinic today still have a 2—3-fold (T2DM) or a 3—10-fold (T1DM) greater risk of suffering a CV event than their non-diabetic counterparts of the same age and gender,[4,5] highlighting the need to devise a more thorough and personalised prevention strategy. In T2DM, the greatest inequality and the greatest burden of CVD falls on those who develop diabetes before the age of 50.[5] In T1DM, this manifest inequality seems less dependent on age at diagnosis, although there is still a disproportionate impact on life expectancy when the onset of diabetes is before 10–15 years of age.[4] As well as age, simple precision medicine also dictates the need to more thoroughly assess women and their possible CV symptoms, and to disabuse the medical community of the notion that women possess greater CV protection, in order to treat them with at least the same intensity as their male counterparts.[6] There is also a need to analyse in more detail the potential pathophysiological differences between CV complications experienced by men and women.

Evidence of CV prevention in T1DM is very limited.[7] This means that the preventive actions and strategies applied to T1DM tend to be devised on the basis of the wealth of evidence coming from T2DM. There is high-level evidence

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recommending that people with diabetes follow a heart-healthy lifestyle (Look-Ahead and PREDIMED), implement intensive blood glucose control, particularly at the onset of T2DM (UKPDS, ACCORD/ADVANCE/VADT), ensure optimal blood pressure control (''always'' <140/90 mmHg) (UKPDS, ACCOMPLISH, HOPE/MICRO-HOPE, ACCORD-BP, ADVANCE), and achieve a marked decrease in LDL cholesterol regardless of the baseline value (CARDS, HPS, IMPROVE-IT, ODYSSEY OUTCOMES and FOURIER). Cardiovascular value and benefit can be attributed to GLP-1 receptor agonists and SGLT2 inhibitors, and probably to metformin and pioglitazone, each with their own levels of evidence, peculiarities, exceptions and gaps.[8] The use of antiplatelet drugs in primary prevention continues to be subject to debate (ASCEND). Finally, the multifactorial approach (STENO type) is widely viewed to be the optimal prevention strategy, and it has been shown that control of the five main risk factors in patients with T2DM reduces their risk of CVD to the same level as their non-diabetic counterparts, although the same cannot be said for heart failure.[9]

In T1DM, intensive blood glucose control (DCCT/EDIC), the prevention of recurrent and/or severe hypoglycaemia[10] and taking into account existing chronic microangiopathic complications[11] are the most important clinical determinants of the disease when it comes to devising a prevention strategy. Otherwise, the guidelines to be followed pertaining to smoking cessation and the administration of intensive lipid-lowering drugs and blood pressure therapy are similar to those for patients with T2DM. These last two risk factors, together with kidney disease and time since onset of diabetes, are the main determinants of CV events and mortality in individuals with T1DM.[12] As stated at the beginning, improved mean blood glucose control and greater life expectancy may mean that the impact of chronic poor control or its consequences (microangiopathic complications) leaves more room for the CV disease of our time to assert itself, including in T1DM: atherogenic dyslipidaemia, obesity and a sedentary lifestyle, together with the classic risk factors.[3] It is estimated that up to 50% of individuals with T1DM are overweight or obese,[3] which, along with the determinants or consequences thereof (insulin resistance and hepatic steatosis), promotes the onset of atherogenic lipid characteristics despite seemingly normal cholesterol and triglyceride concentrations.[13] Finally, in this elusive search for normal blood glucose levels, recurrent or undetected hypoglycaemia emerges as a CV risk factor of increasing significance.[10]

How can we apply the myriad studies, publications, guidelines and recommendations to benefit patients? Should we measure everyone with diabetes with the same yardstick? Answering these questions requires a three-pronged approach: assessment of the overall risk; establishment and agreement of targets and goals; and clinical follow-up. Clinical follow-up in CV patients is required before and after the risk assessment. A focussed anamnesis should be performed at every visit, and a targeted or focussed examination conducted every 1–2 years. Clinical symptoms indicative of impaired arterial function in various organs and systems, whether classic or otherwise (more typical of women and of individuals with diabetes in general) should be evaluated systematically, and detecting arterial murmurs, indices (ankle-brachial index) or cutaneous manifestations of insufficient arterial blood flow should alert us to the presence of already advanced disease.

When assessing cardiovascular risk from a simplified standpoint, there are two alternatives: the a priori consideration of T1DM or T2DM as a disease of high or very high risk; or the assessment of individuals with diabetes using personalised or adapted risk scales. For patients with T2DM, the risk scales tend to lack precision and discriminatory power. In T1DM, the best of these scales is the Steno T1 Risk Engine, the main drawback of which is its lack of external validity, in terms of clinical events, outside of the North-European populations in which it was initially developed.[14] Nevertheless, it is still a helpful tool as it brings together and reminds clinicians of all the relevant factors that must be considered when evaluating cardiovascular risk (CVR) in people with T1DM. Finally, in this assessment it is important to remember that the detection of concomitant kidney disease or diabetic nephropathy arguably represents the greatest risk for people with T1DM or T2DM.

The second step entails establishing and agreeing goals and targets with the patient. For arterial hypertension (particularly in conjunction with renal complications), the recommendation to stop smoking, the promotion of moderate or intense physical activity, the adoption of a heart-healthy diet and selecting drugs (in T2DM) with added value are practices that are widely agreed upon. The lipid target and the use of lipid-lowering drugs remain subject to much debate. The new guidelines on cardiovascular disease prevention in clinical practice issued by the European Atherosclerosis Society and the European Society of Cardiology recommend a two-step intensification process, in which achieving the first (STEP-1) would already constitute a necessary advance if we consider the current LDL cholesterol goal attainment results, while the second step (STEP-2) would consist of individualised treatment goals agreed with the patient.[15] Finally, aiming to achieve T2DM disease remission should be a non-negotiable goal, particularly in people with early-onset diabetes. The best form of CV disease prevention should be considered to be the cure, or at least prolonged remission, of diabetes and its associated risk factors. Bariatric surgery, intensive medical weight loss programmes (the DIRECT study[16]) and the potency of new agonists with single or dual incretin action open the door to a little-trodden path towards CV disease prevention mediated by weight loss, and prompt us to imaginatively deliver this evidence to patients.

We shall end with two insights. Firstly, the need for an individualised care plan in CV disease prevention in general is becoming increasingly pressing. Detecting atherosclerosis and its burden,[17] a mandatory substrate and powerful and independent predictor of clinical events, clinical genetics and the individualised use of the many pharmacological alternatives of value in CV disease prevention will drive the growth of this clinical subspeciality. Various drugs, such as SGLT2 inhibitors, GLP-1 receptor agonists, statins, ezetimibe, PCSK9 inhibitors, eicosapentaenoic acid, ApoC3 inhibitors and anti-inflammatory therapy, are options that have already been shown to reduce CV events or are in the process of demonstrating their effect. Should we simply prescribe all these to our highest risk diabetes patients? In T1DM, unlike in T2DM, the early and continuous optimisation of intensive insulin therapy is unquestionably the best strat-

egy for CV disease prevention in this disease: from the onset, sustained and avoiding recurrent hypoglycaemia. Secondly, unlike the assessment and screening of microangiopathic complications, CV disease prevention in diabetics should be standardised as part of specific programmes, rather than simply adopting an opportunistic approach. In our case, and in T1DM, we have standardised the way CV risk is assessed by integrating the insights proposed in this article into a care protocol that encompasses the time, cadence and expertise that the problem and the patient deserve.[18] In T2DM, we have chosen to proactively specify and materialise the evidence in order to reach those patients with early-onset diabetes who are at greatest risk.[5] This is achieved through standardised and specific initiatives and programmes, both in coordination with Primary Care and by means of a multidisciplinary approach, which combine face-to-face care with digital healthcare and give weight loss the importance it deserves.

Conflicts of interest

Emilio Ortega has received fees for consultancy or participation in training sessions sponsored or funded by AKCEA, AMGEN, AstraZeneca, Daiichi-Sankyo, GlaxoSmithKline, Lilly/Boehringer-Lilly, MSD, NovoNordisk, Pfizer and Sanofi. He has received unrestricted funding for clinical research projects or the implementation of care programmes from AKCEA-Sobi, AMGEN, AstraZeneca, Lilly and NovoNordisk. He has worked as a consultant for the evaluation of medicinal products for the Servei Català de la Salut (Catalan Health Service). Clara Viñals has received sponsorships for continuing medical education and fees for conferences, medical consultations or research from AstraZeneca, NovoNordisk, Sanofi, Medtronic, MSD, Akcea Therapeutics and Lilly.

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