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DIABETIC Medicine

LETTER

Cardiovascular disease risk stratification in type 2 diabetes

Khunti et al.[1] acknowledge that there are knowledge gaps regarding cardiovascular disease (CVD) risk factors and risk stratification in people with type 2 diabetes early in the course of their disease. Given the marked reduction in major adverse cardiovascular events (MACE) that can now be offered to people with type 2 diabetes at high cardiovascular risk, with the use of sodium-glucose co-transporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 receptor agonists, the identification of both CVD risk factors and accurate CVD risk stratification tools in this cohort must be a priority. It is increasingly recognised that cardiometabolic derangement can occur early in the course of type 2 diabetes and indeed, Khunti et al.[1] found that a large proportion of those without established CVD who were early in the course of their diabetes were at high cardiovascular risk, with an associated marked mortality (17%) over 6.4 years of follow up. The study, which examined 9 risk factors, provides insights into which risk factors were associated with MACE outcomes in this cohort. The study does not explain the rationale for the choice of the 9 risk factors assessed, which include the two diabetes-specific factors HbA1c, and duration of diabetes, and exclude measures of end of organ damage including retinopathy, proteinuria and left ventricular hypertrophy, which are associated with high cardiovascular risk.[2] This puts into sharp focus the question of how cardiovascular risk stratification should be approached in people with type 2 diabetes early on in their disease, and, therefore, albeit with the caveat that Khunti et al[1] did not seek to risk stratify, whether using cardiovascular risk stratification tools derived from the general population in this cohort are acceptable. In the UK, guidance from the National Institute for Health and Care Excellence (NICE) recommends that the population-based QRISK2 score is used to identify people with type 2 diabetes who are at increased risk of developing CVD in the next 10 years (>10% risk over 10 years), who should therefore initiate SGLT-2 inhibitor therapy as part of first-line treatment.[3] The QRISK2 assessment includes diabetes as a categorical variable and does not assess glycaemic control, or markers of end organ damage, except for chronic kidney disease, and only at stages 4–5. In contrast, the European Society of Cardiology states that population-based cardiovascular risk scores should not be used in people with diabetes,[4] and instead, stratifies patients with type 2 diabetes into very high, high, and moderate CVD risk. Those in the highest risk category are those with type 2 diabetes who have established CVD or other target organ damage (as evidenced by any of proteinuria, renal impairment defined as eGFR <30 ml/min/1.73 m^2, left ventricular hypertrophy or retinopathy), or three or more major risk factors (age, hypertension, dyslipidaemia, smoking, obesity).[2] Evaluation and validation of QRISK2 score and type 2 diabetes-specific cardiovascular risk tools in those with type 2 diabetes is limited. In 2014, Hippisley-Cox et al.[5] evaluated QRISK2 performance in people with type 2 diabetes but their approach to validation, whereby the performance of the model was assessed in a subset of the derivation cohort, is likely to have led to optimistic performance measures. In 2018, Read et al[6] in external validation of the QRISK2 in diabetes found that it performed poorly. The authors make two important observations: (a) inclusion of diabetes in the risk score as a categorical variable and interaction with age in QRISK2 is unlikely to sufficiently capture the complex relationship between diabetes and CVD and (b) prediction of CVD risk in people with type 2 diabetes is likely to be further complicated by the possible presence of type 2 diabetes subtypes with distinct disease trajectories. In early onset diabetes, which may represent a more aggressive type 2 diabetes phenotype[7], there is evidence that there is similar cardiovascular and mortality risk irrespective of cardiometabolic risk factor status at diagnosis.[8] Similarly Dziopa et al.[9] in their external validation of the QRISK2 tool found considerable attenuations in its discriminative ability when applied to individuals with type 2 diabetes, leading to poor performance. When they compared 22 cardiovascular risk scores in a primary care setting, all scores were found to perform universally poorly in diabetes, but diabetes-specific scores were not superior. Two areas are highlighted here that may advance CVD

risk assessment in type 2 diabetes. First, non-alcoholic fatty liver disease (NAFLD) is now recognised to be strongly associated with atherosclerotic CVD.[10] A recent American Heart Association statement[10] falls short of designating NAFLD as a cardiovascular risk factor but does describe it as a risk enhancer. This has widespread implications for those with type 2 diabetes given that there is a marked increase in the risk of CVD in people with type 2 diabetes with NAFLD in comparison to those without NAFLD, independent from traditional CVD risk factors.[10,11] Second, the field of cardio-metabolomics has facilitated insights into metabolomic phenotyping and identification of novel metabolomic- based biomarkers that may provide additional prognostic value in assessing cardiovascular risk. In the general population, there is sustained interest in how ceramide and phosphatidylcholine lipid species may enhance cardiovascular risk stratification.[12] In type 2 diabetes, studies in this field are small and generally case-control in nature. Larger prospective studies in this area are awaited with interest.

CONFLICT OF INTEREST

No conflict of interests from the authors.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Harriet Esdaile[1]
Jamil Mayet[2]
Neil Hill[3]

[1]*Department of Metabolism, Digestion and Reproduction, Faculty of Medicine, Imperial College London, Hammersmith Hospital, London, UK*
[2]*National Heart and Lung Institute, Imperial College London, London, UK*
[3]*Department of Metabolism, Digestion and Reproduction, Faculty of Medicine, Imperial College London, London, UK*

Correspondence
Harriet Esdaile, Department of Metabolism, Digestion and Reproduction, Faculty of Medicine, Imperial College London, Hammersmith Hospital, London W12 0NN, UK.
Email: h.esdaile@imperial.ac.uk

ORCID

Harriet Esdaile https://orcid.org/0000-0001-8906-4964
Neil Hill https://orcid.org/0000-0002-4359-2646

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