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INVITED EDITORIAL

Is predicting the risk of incident diabetes useful in patients with cardiovascular disease?

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This editorial refers to 'Development and validation of a lifetime prediction model for incident type 2 diabetes in patients with established cardiovascular disease: the CVD2DM model', by M.A.G. Helmink *et al.*, https://doi.org/10.1093/eurjpc/zwae096.

The development of type 2 diabetes mellitus (T2D) is conditioned by genetic factors and the exposure to modifiable risk factors so, to some extent, T2D is a preventable disease.[1] Self-care is essential in reducing cardiovascular risk and preventing atherosclerotic cardiovascular disease (ASCVD) but also in preventing T2D. Low-risk lifestyle behaviours, such as reducing body weight excess, healthy diet, regular physical activity, and quit smoking, are effective measures to prevent the development of T2D.[2]

Prevention strategies can be implemented at different times of the disease. In general, preventive interventions should start as early as possible so low- to moderate-intensity programmes with little or no direct medical intervention can be implemented at all ages in a wide range of people with different T2D risks in the population, with lower costs. However, the later the disease risk is identified, the more intensive the intervention will have to be if we want to be effective. Public health strategies for diabetes prevention are key for early intervention while late interventions to correct unhealthy lifestyle patterns through individual or group counselling are particularly useful for people at higher risks of T2D, usually in the health care environment.[3]

Identifying individuals at risk for T2D to help them improve self-care as soon as possible to prevent the development of the disease is a logical strategy. The use of T2D risk scores allows identifying these individuals who, then, can be advised and invited to join lifestyle intervention programmes. Physician advice was identified early as a critical step in helping patients change lifestyle and adopt healthier behaviours.[4] Currently, this is often done by multidisciplinary teams, including other health professionals, such as nurses or nutritionists.

A definition of 'high risk' is essential for planning and implementing preventive strategies targeting individuals. However, defining 'high risk for T2D development' is not straightforward. There are several scores to predict incident T2D in populations without CVD, often with incomplete method reporting, not externally validated, including a wide variation of predictors. Interestingly, the correlation is higher among scores using only clinical variables compared with those including biomarkers.[5] These scores used different risk thresholds so there are large variations of people classified as high risk in different populations, ranging from 3.1%[6] to 47.1%.[7] Such variability may be explained, at least in part, by differences in the prevalence of risk factors, the prevalence of T2D, and the incidence rate of T2D among the different populations studied. The majority of these scores was developed to identify the risk of T2D in the general population, and only a few were developed for specific population subgroups, such as those with cancer[8] or human immunodeficiency virus.[9] However, no specific tool has been developed so far for the patients with already established ASCVD.

Helmink *et al.* in this issue of *EJPC* present an elegant study with the development and validation of the CVD2DM model, a prediction tool to estimate the future 10-year and lifetime risk of developing incident T2DM in patients with established ASCVD. Two versions, a core model including age, current smoking, family history of diabetes mellitus, body mass index, systolic blood pressure, fasting plasma glucose, and HDL-cholesterol and an extended model adding HbA1c and C-reactive protein, were developed derived from 19 281 participants with established CVD and without diabetes at baseline enrolled in the UK Biobank. The models were externally validated in 3481 patients from the UCC-SMART study followed up by a median of 12.2 years, predicting a 4.7% median 10-year incidence of T2D and a lifetime incidence of 9.3%.[10] The two models performed well for T2D prediction (*C*-statistics around 0.80 for both, although needed recalibration for risk underestimation in women) and acceptably for all-cause mortality (*C*-statistics around 0.70).

Some methodological aspects of this study deserve attention. First, the diagnosis of diabetes in the validation cohort during follow-up was self-reported and assessed retrospectively for the first years, which might be a source of bias. Second, the model was developed and validated in a largely white population. Although the utility of the inclusion of ethnicity in T2D predictive models is questionable, the differences in genetic aspects, risk factor prevalence, and incidence of T2D vary importantly between ethnic groups and countries, so the CVD2DM score should be confirmed in more diverse populations. Third, the lack of consideration of key aspects for T2D development and evolution,

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such as diet, physical activity, and medication, both at baseline and during follow-up, is relevant as these are important confounders that can accelerate or slow down the progression of the disease. These factors may have contributed to the baseline risk of T2D in the participants of both cohorts and their evolution over time. The lack of control for diet and physical activity is particularly relevant as these will be key recommendations for prevention, and the effect of the change to healthier patterns in each patient will likely depend on the starting point and the room for improvement. The intensity of the recommendations for a healthier life style will be different, for instance for a sedentary obese smoker with terrible diet habits compared with a person with an adequate life style. This aspect may influence as well the potential consideration of additional medical therapy for ASCVD prevention and, eventually, T2D prevention (i.e. with the use of glucagon-like peptide-1 receptor agonists).

Patients with ASCVD are already at very high cardiovascular risk so they are candidates for high-intensity secondary cardiovascular prevention.[11] If these patients are managed according to recommendations, they will be educated in the need of and engaged in quitting smoking, improving a healthy diet, or increasing physical activity. To what extent the knowledge of this additional risk can improve adherence to the recommended measures is unknown. The risk of developing T2D may be considered not of vital importance or, at least, less relevant than the shorter-time risk for cardiovascular complications by these patients. The score can help increasing their motivation to adhere to a healthy lifestyle and the visuals provided with the manuscript may be more engaging for patients to understand their risks and the potential benefits of improving self-care.

One additional methodological aspect with clinical relevance is the lack of exclusion of patients with pre-diabetes from the development and derivation cohorts. The CVD2DM score is designed to help guiding preventive measures for the patients at high risk for T2D development. If pre-diabetic patients are at high risk, what would change in terms of preventive recommendations? From this perspective, it would be interesting to know what proportion of non-pre-diabetic patients qualify as high risk and what would be the added value of more intensive preventive measures in them.

If we finally decide to use the CVD2DM score, what would be the best setting and moment to do it? Although most patients with chronic stable ASCVD are followed exclusively in primary care, it is unlikely that the score will be used in this setting, usually overwhelmed with clinical pressure and with hundreds of scores to estimate the risks of many diseases. It is also unlikely that it will be used during acute cardiovascular care given the number of variables to be considered for short-term risk stratification and secondary prevention planning, and the large number of confounders that may be present during the acute event, such as acute changes in glucose or cholesterol levels or in markers of inflammation. However, many patients after an acute coronary syndrome are intensively followed up during the next months. Probably the best settings for the use of the CVD2DM score are cardiac rehabilitation programmes, where there is intensive interaction between the members of the multidisciplinary teams and the patients, with ample time for specific education programmes directed to improve the understanding of the course of the disease and future risks, and the best ways to prevent these in the long-term, with specific measurable objectives based on self-care with lifestyle changes and the optimization of drug therapy.

In summary, it is uncertain if the prediction of the risk of incident T2D in patients with ASCVD is a useful strategy to improve its prevention given the overlap in the strategies based on life style changes to reduce future cardiovascular risk and T2D risk. The added value of the CVD2DM score will essentially depend on this utility. Time will tell if this tool will find its place in routine clinical practice.

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