Does using HbA1c inform diagnosis of diabetes in patients with coronary artery disease?

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This editorial refers to ‘Screening for dysglycaemia in patients with coronary artery disease as reflected by fasting glucose, oral glucose tolerance test, and HbA1c: a report from EUROASPIRE IV—a survey from the European Society of Cardiology’1, by V. Gyberg et al. on page 1171.

In recent years, using easy, quality-certified, and accurate glycated haemoglobin (HbA1c) measurements has become a globally accepted, if not recommended part of our everyday practical armamentarium in diagnosing diabetes mellitus (DM), although controversy continues over its precise position in the diagnostic algorithm.1–4 On the other hand, the very high and, in fact, increasing number of both diagnosed and undiagnosed cases of DM (besides other established cardiovascular risk factors) in patients with coronary artery disease (CAD) has also emerged as a worldwide phenomenon, and prompted the first joint guidelines in ‘cardio-diabetology’ released by the European Society of Cardiology and the European Association for the Study of Diabetes.5 Indeed, the view has been put forward in those guidelines that DM and CAD may represent the two sides of a coin, which was also maintained in the recent update.4

The publication in this issue based on the EUROASPIRE IV survey and aiming to compare the performance of the three different available biochemical tests, i.e. fasting plasma glucose (FG), 2 h glucose after an oral glucose tolerance test (2hPG), and HbA1c, in diagnosing previously unknown DM in patients with chronic CAD provides important and practically highly relevant new information in this context.6 First, it confirms the high prevalence of known diabetes, i.e. 27% or 2164 out of 7998 patients enrolled from 79 centres in 24 European countries during May 2012 to April 2013. Secondly, it finds another 29% of new DM cases in the finally investigated cohort of 4004 patients, after exclusion of patients not appropriately fasting or with insufficient or missing data. Allowing for extrapolation, this would add some 21% of new DM cases to the 27% cases of known DM in the EUROASPIRE IV cohort as a whole, i.e. close to 50% of a contemporary European CAD cohort has co-existing DM one way or the other, a figure similar to that reported recently from the German SWEETHEART registry evaluating 2767 consecutive patients presenting with acute myocardial infarction.7 Thirdly, it showed that using HbA1c measurements on top of FG determinations informed diagnosing diabetes in this CAD patient cohort at high risk for DM rather little, as the additional yield over and beyond the 75% of DM cases already identified by FG amounted to only 6%. Moreover—and this is of concern—the majority of these additional HbA1c-defined cases might actually represent a misclassification, not only since their corresponding FG was in the non-diabetic glucose range, but also because so was their 2hPG. In contrast, fourthly, it demonstrated that an oral glucose tolerance test (OGTT) was by far the better second diagnostic test in this cardiology population, identifying another 21% cases of previously undiagnosed diabetes, whereas relying exclusively on HbA1c measurements would have left 83% of patients with overt diabetes undetected in the current EUROASPIRE IV database.

The rationale of using HbA1c measurements to monitor glycaemic control in persons with DM and—more recently—to diagnose DM is based on the fact that glycosylation of haemoglobin, i.e. attachment of glucose and irreversible transformation to HbA1c, is a result of the average glucose exposure of the haemoglobin molecules in the circulating blood during the previous 6–8 weeks.8,9 So, an increase in HbA1c is the end-result of prior increasing blood glucose concentrations, but short-lived glucose spikes as in the post-prandial state may not be sufficient to induce a lasting effect on HbA1c.9,10 It is a widely held concept that DM often first develops post-prandially, followed by an increase of FG, the rise in HbA1c being a rather late event.7 In line with this, HbA1c-detected DM represented by far the smallest group of new cases of DM in EUROASPIRE IV. At the same time, there is very robust evidence that the surge in post-prandial glucose signals increased cardiovascular (CV) complications in the future, so it should be captured when it comes to CV risk stratification.10 For example, at the 3-year follow-up of the SWEETHEART registry, the patients with OGTT-detected DM, and—emerging—the group with impaired glucose tolerance, showed a significantly adverse prognosis both for mortality and for MACCE (major adverse cerebrovascular and cardiovascular events), compared with non-diabetic patients at baseline.7

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These pathophysiological considerations seem to be relevant in the care of CAD patients as in EUROASPIRE IV, as their DM—albeit so common—is often short term or even undiagnosed. For example, in ORIGIN, one of the large-scale randomized intervention trials seeking to evaluate the effect of diabetes therapies on CV outcomes in patients with prior CV disease or at very high risk for it, participants showed a mean duration of known DM of 5 years at baseline or DM was screen detected in a substantial subgroup. Baseline mean HbA1c in those with known DM was 6.4%, i.e. below the diagnostic cut-off level of 6.5% for overt DM. The findings in EUROASPIRE IV are in accordance, for example, with observations made in the SWEETHEART registry, where HbA1c in patients with new DM based on FG/2hPG was 5.9% [95% confidence interval (CI) 5.5–6.4%], or in the Silent Diabetes Study in 1015 patients with CAD undergoing angiography without pre-diagnosed diabetes. The angiographic severity of CAD was very closely related to 2hPG in the latter study, whereas it was not closely related to HbA1c. Furthermore, as in EUROASPIRE IV, HbA1c detected only a minority of all new cases of DM. At 3-year follow-up, the surge of 2hPG over FG at baseline was found to be closely related to mortality—in addition to CAD severity and levels of high sensitivity C-reactive protein and N-terminal pro brain natriuretic peptide at baseline—in contrast to no such association whatsoever with HbA1c. So, HbA1c measurements were not helpful for stratification of 3-year mortality risk in this CAD cohort; indeed, as in EUROASPIRE IV, half of the HbA1c-defined DM cases might have represented a misclassification, since their FG and 2hPG were in the non-diabetic range.

In aggregate, there seems to be an evolving theme that using HbA1c measurements might be less suitable in CAD patients for the diagnosis of new DM, including the risk of misclassification in those patients. The reasons for the latter can only be speculated on, since neither the Silent Diabetes Study nor EUROASPIRE IV were able to inform the specifics of patients with an isolated increase of HbA1c into the diabetic range (i.e. >6.5%) much further. The 49 patients with isolated ‘diabetic’ HbA1c or 4% of all new cases of DM in EUROASPIRE IV were reported to exhibit a lower level of education, more obesity, and a lower level of physical activity, perhaps also a preponderance of males. It is unknown whether one or more of these factors do affect the life span of the haemoglobin-carrying red blood cells in the circulation. It is textbook knowledge that reduced survival of erythrocytes, e.g. due to blood loss or forms of anaemia, is associated with lower HbA1c levels, whereas prolongation of erythrocyte life span generates higher HbA1c values. Clearly, there is individual biological variation in red blood cell survival as there are ethnic-specific differences in the relationship between mean blood glucose levels and the corresponding HbA1c levels. African American people with DM, for example, show a 0.3% higher HbA1c for the same glucose concentration. So, ethnic-specific information in a European-wide CAD cohort might be relevant. In addition, it might be worthwhile to explore whether heart disease-related aspects, such as heart failure or haemo-concentration on therapy, or kidney function, especially in the elderly, might play a role in modulating HbA1c concentrations. Finally, larger groups of people with isolated ‘diabetic’ HbA1 might also be subjected to evaluation on the genetic level, to see whether they show the typical gene variants associated with DM, FG, HbA1c, or CAD, etc.

In light of the findings in EUROASPIRE IV and recent evidence discussed in this Editorial, the diagnostic algorithm of screening for DM might be worth revisiting in the context of known CAD and also appreciating the differences compared with the normal population.

**Figure 1** Screening for diabetes mellitus (DM): context with co-existing coronary artery disease (CAD). Pts, patients; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; 2hPG, plasma glucose 2 h post-load.
provides an attempt to adapt the present ESC/EASD guideline algorithm for patients with CAD to the new evidence, i.e. by shifting measuring HbA1c to a new box for use with more caution, away from a joint position together with FG in the mainstream diagnostic pathway, as in the algorithm for the general population. Measurements of HbA1c certainly are to be kept, as they may be informative regarding the control and duration of previously unrecognized DM in patients with CAD, but diagnosis of DM should not be solely based on those measurements for the time being. This is notwithstanding the fact that HbA1c measurements are often readily available at reliable quality and without much preparation time on the part of the patients. Performing OGTTs requires more organizational skills and also resources, but seems to be currently indispensable in identifying all cases of co-existing DM in CAD patients, since these patients clearly are at increased risk for fatal and non-fatal CV complications.4,5,7

How does the algorithm put forward in Figure 1 work then for CAD patients at ‘high risk for developing DM’ according to the different criteria, i.e. ranges of FG + HbA1c recommended by the American Diabetes Association (ADA) vs. of FG + 2hPG suggested by the World Health Organization (WHO)?13 Again, there is little substance to using HbA1c criteria in this ‘at DM risk’ category. Due to the wide HbA1c range from 5.7% to 6.4% in the at-risk ADA definition, nearly 95% of the total EUROASPIRE IV cohort is labelled as being at high DM risk or having DM (known or newly diagnosed). So, there is little gain in terms of risk stratification in a group who by the diagnosis of CAD is already known to be at high risk both for DM and for further CV complications. Moreover, evidence is lacking on what precisely the CV risk is in CAD patients with an HbA1c ranging from 5.7% to 6.4%. So, much more data are needed to assess the role of HbA1c measurements in this regard and it would be very helpful if the EUROASPIRE IV investigators could provide results based on follow-up examinations of the cohort in the future. On the other hand, we already know from the Silent Diabetes Study that HbA1c levels were not associated with mortality risk at 3-year follow-up.13 Looking at the mean HbA1c levels in the SWEET-HEART registry for differences between the ‘at DM risk’ (based on OGTT) and the normal glucose-tolerant group, the numbers were virtually identical (5.6%; 95% CI 5.4–5.8% in the at-risk category and 5.7%; 95% CI 5.3–5.8% in the normal group). The WHO report has actually discouraged using an HbA1c range from 5.7% to 6.4% to define people being at high DM risk, as the corresponding results from OGTTs may be all the way from normal to diabetic, i.e. no formal recommendation can be made to interpret HbA1c levels <6.5%. In contrast, OGTT-based risk categories appear to be much better established, both for risk of developing DM and for CV complications.5,6,7,10–16,17 although also for the latter measure evidence is needed regarding the further risk of CV complications in CAD patients with impaired glucose tolerance. The ongoing ACE trial seeking to intervene in impaired glucose tolerance in patients with prior CV disease might shed some more light on this.22 In EUROASPIRE IV, some 30% of the total cohort was categorized as having impaired glucose tolerance or being at risk for DM and would be amenable for assessment of CV outcomes at follow-up examinations.

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References