

Diagnosing diabetes in patients with cardiovascular disease: why HbA1c should  
be the preferred test in the majority of patients and why the OGTT fails to  
make the grade

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Optimal, cost-effective and pragmatic screening for and diagnosis of important health disorders remains a key aspect of clinical care. With this in mind, the American Diabetes Association formally accepted the use of HbA1c as a diagnostic test for type 2 diabetes (T2DM) in January 2010<sup>1</sup>. Whilst this decision was opposed by some, acceptance of HbA1c as a diagnostic test by key organisations followed. HbA1c was subsequently added to the T2DM diagnosis algorithm in the joint ESC/EASD guidelines on the management of diabetes and cardiovascular disease (CVD)<sup>2</sup>. Choice of diagnostic tests for diabetes remains a hotly debated issue, however, with major healthcare implications. For example, a recent analysis of the EURO-ASPIRE IV study led the authors to recommend that all patients with CVD should have an oral glucose tolerance test (OGTT) performed<sup>3</sup>. In this commentary we consider the options for diagnosing T2DM with particular emphasis on those with CVD.

Before deciding between potential options for diabetes screening, it is crucial to first be aware of their respective performances in detecting or predicting the risk of diabetes-related morbidities given that it is the prevention of such complications that is the priority. With regard to microvascular complications, the basis of diabetes diagnostic criteria, the results of the Evaluation of Screening and Early Detection Strategies for Type 2 Diabetes and Impaired Glucose Tolerance (DETECT-2) collaboration remain critical<sup>4</sup>. DETECT-2 compared cross-sectional associations of the three diagnostic candidates (HbA1c, fasting plasma glucose [FPG], 2 hour glucose) with prevalent retinopathy in 44,623 participants pooled from nine studies, and showed that 2 hour glucose levels demonstrated only a relatively weak association. By contrast, FPG and HbA1c demonstrated clear inflection points (at 6.5mmol/L and 6.5% [48mmol/mol] respectively) above which the prevalence of retinopathy clearly rose. These modest results for 2 hour glucose are highly likely to be even

worse in real-life settings due to variability in how OGTTs are conducted compared to research study situations, along with the test's inherent considerable intra-individual variation (coefficient of variation up to 20%)<sup>5</sup>, weaknesses not easily addressed.

There is no doubt that the combination of established CVD and T2DM escalates mortality risk well beyond that observed with only one of these conditions. However, there is no clear evidence that 2 hour glucose in patients with CVD, but without known diabetes, meaningfully reclassifies risk of a subsequent CVD event beyond other established risk factors. Moreover, even if such evidence existed, it would be necessary to show that reclassification on the basis of 2 hour glucose is better or more cost-effective than alternatives like HbA1c. To prove the latter would require demonstrating that patients with CVD and newly diagnosed T2DM on the basis of OGTT (but not HbA1c) derived greater risk reduction from any potential interventions; such evidence does not exist. What we do know, albeit from patients without CVD and without known diabetes, is that of the three glycaemic tests, improvement in CVD risk prediction beyond established risk factors that was provided by HbA1c measurement, albeit modest, was equal to or better than estimated improvements in prediction offered by FPG, random, or post-load plasma glucose levels<sup>6</sup>. This major study involved analyses of individual-participant data from 294,998 individuals without a history of diabetes or CVD from 73 prospective studies, and it thus provides the best current evidence on this topic.

Despite increasing acceptance of HbA1c as a diagnostic measure for T2DM, some colleagues in the cardiovascular community continue to argue that OGTTs should be routinely conducted in patients with CVD. Using data from EUROASPIRE IV, a cross-sectional survey of

4,004 patients aged 18-80 years with coronary artery disease but no reported diabetes in 24 European countries, Gyberg et al recommended that OGTT should be the preferred diagnostic test for T2DM in such individuals based on the rationale that OGTT labelled many more patients with T2DM than FPG or HbA1c testing<sup>3</sup>. They reported that a positive OGTT (either FPG  $\geq 7.0$  mmol/l or 2 hour glucose  $\geq 11.1$  mmol/l) occurred in 1,054 (~26%), 867 (~22%) could be diagnosed based on FPG while only 193 patients (~5%) had an HbA1c  $\geq 6.5\%$ , the diagnostic threshold for T2DM. These 5.4 to 1 or 4.4 to 1 ratios (for OGTT and FPG respectively vs. HbA1c as diagnostic measures) appear remarkable and comfortably exceed published reports of other studies conducted in various populations where the ratio of 'undiagnosed diabetes' identified by OGTT/FPG versus HbA1c is typically somewhat less and, not infrequently, reversed<sup>7-10</sup>. For example, the recent NCD collaboration which pooled data from 27 studies demonstrated that the prevalence of undiagnosed diabetes was broadly similar when using HbA1c or FPG, even if the overlap of identified patients was modest<sup>11</sup>.

While EUROASPIRE IV is one of the largest studies to address the question of the comparative performance of various approaches to diagnosing T2DM in patients with CVD<sup>3</sup>, over-estimation of newly identified T2DM cases by OGTT is a major possibility in our view. Importantly, EUROASPIRE IV used point-of-care analysers to measure whole blood (not plasma) glucose in each participating centre, rather than one central lab, introducing the issue of between-site variation; by contrast, HbA1c was analysed centrally. The approach for estimating plasma glucose also required two mathematical adjustments, one to account for cholesterol levels and the second for conversion of whole blood glucose to plasma levels, all of which introduce variance. These points are important since even a slight positive bias in

glucose can substantially over-estimate undiagnosed diabetes diagnoses given its Gaussian distribution. Furthermore, even if the results were accurate, it is important to stress that the key metric is not how many individuals are diagnosed by a test but how much the test, and its associated diagnosis, improve prediction of morbidity and mortality overall.

Having established that microvascular disease appears to be best indicated by either FPG or HbA1c (not 2 hour glucose) and CVD risk by HbA1c, it is now appropriate to decide what the optimal approach is for diabetes screening in real-life settings. Where performance of diagnostic or screening tests is broadly similar, pragmatic considerations are crucial in determining which approaches will be most readily adopted. For each of these questions, HbA1c is better than, or at least as good as, OGTT and it also has advantages over FPG alone (**Table 1**). In addition, individuals with HbA1c 6.0 to 6.4% are at elevated diabetes risk and they can then be advised regarding lifestyle changes. In some patients in whom HbA1c may not be suitable due to altered red cell turnover, FPG is an obvious alternative. Based on the aforementioned arguments, we suggest that the vast majority of patients with CVD can have their diabetes status robustly checked using HbA1c (**Figure 1**, Appendix).

In summary, the introduction of HbA1c as a routine test into diabetes diagnostic algorithms has been a welcome development in clinical care and we have argued why it is clearly a superior option to the OGTT in patients with CVD for both predictive and pragmatic reasons, advantages which apply to those without CVD also. We therefore suggest that, rather than mandating that all CVD patients have OGTT performed as has been suggested based on EUROASPIRE IV data<sup>3</sup>, health care workers should rather check HbA1c when other blood samples are being taken anyway. As most bloods tests (including lipids, kidney and liver

function tests) are valid when non-fasting, HbA1c will be the best option in most cases which will allow it to dovetail easily with routine care, thereby offering the best option for improving health at a population level.

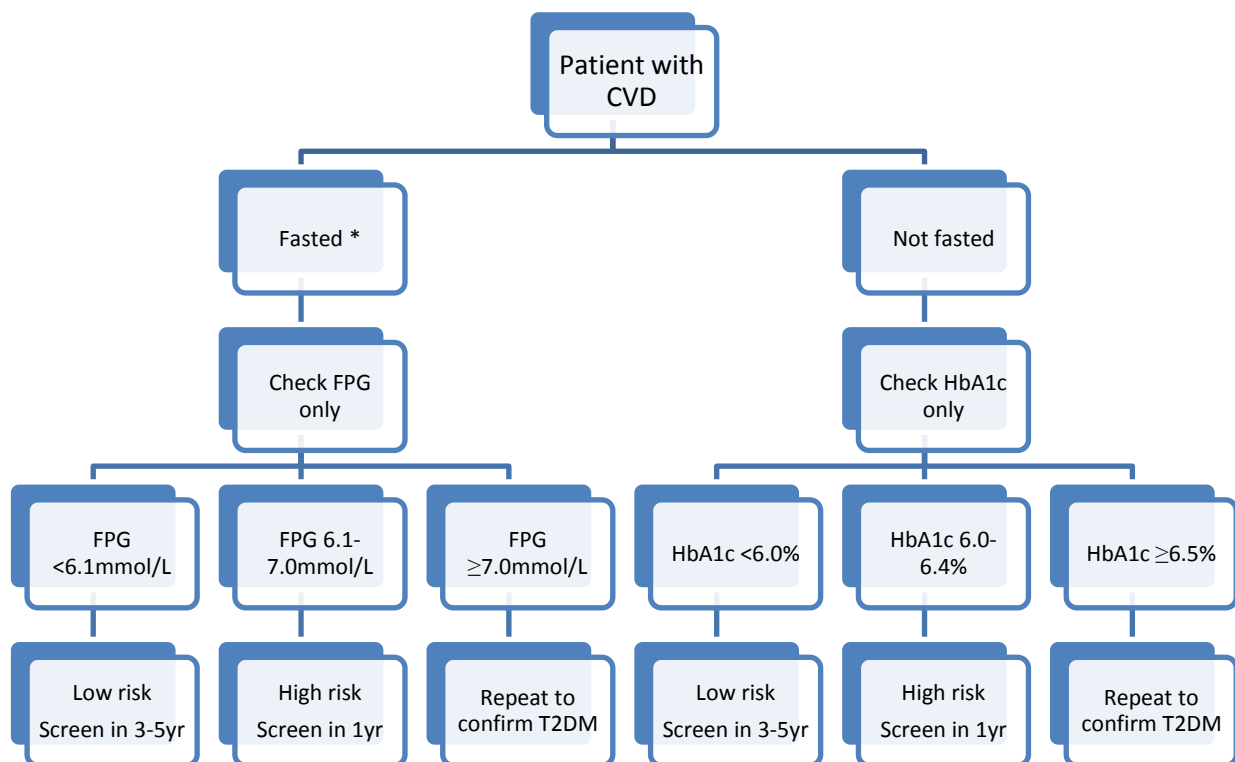
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**Table 1.** Why HbA1c and fasting plasma glucose, but not OGTT, make the grade for diagnosing diabetes in patients with or without cardiovascular disease

Criteria	Current evidence base
Microvascular risk	HbA1c (and FPG) appear at least as good as, and potentially better than, 2 hour glucose for identifying patients with retinopathy
Macrovascular risk	<p>In non-diabetic individuals, HbA1c is more strongly linked to CVD risk than other glucose-based tests (though no glycaemia test meaningfully reclassifies CVD risk beyond other established risk factors).</p> <p>Robust evidence that 2 hour glucose meaningfully reclassifies risk of subsequent CVD events or mortality over and above other established risk factors, and beyond HbA1c levels, in patients with CVD is lacking.</p>
Pragmatic considerations	<p>HbA1c does not require fasting and can be done at any time of the day and along with any other blood tests. It can also be done any time after an acute event unlike fasting plasma glucose which should only be measured 4 days post MI to account for the acute phase response.</p> <p>By contrast, the OGTT is cumbersome, time-consuming, more expensive and has poor reproducibility.</p>
Signalling high diabetes risk	While impaired glucose tolerance identified by OGTT indicates high risk of developing T2DM, HbA1c 6.0-6.4% also signals multiple-fold higher risk for T2DM so that patients at elevated risk can be targeted for lifestyle intervention.

**Figure 1 (For appendix).** Suggested algorithm for screening for type 2 diabetes in patients with cardiovascular disease.



\*patients will not be fasted in the vast majority of situations but if a patient attends having fasted, FPG is a cheap and effective alternative; if there is legitimate concern over the validity of HbA1c as a diagnostic measure (e.g. abnormal full blood count), FPG should be measured when possible