

Diabetes Screening in Patients with Macrovascular Coronary Disease: Are the New European Guidelines a Step Backwards?



Rastreio da Diabetes em Doentes com Doença Macrovascular Coronária: As Novas Guidelines Europeias são um Retrocesso?

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ABSTRACT

Background: The new European guidelines on diabetes mellitus and cardiovascular diseases propose that the FINnish Diabetes Risk Score should be used to evaluate the risk of diabetes mellitus and that diabetes mellitus screening in coronary artery disease patients should be based on fasting glucose and HbA1c. The 2 hour oral glucose tolerance test, recommended for all pts in the previous guidelines, is now only recommended for 'inconclusive' cases. We aimed to evaluate this new strategy.

Material and Methods: Fasting glucose, HbA1c and glucose tolerance test (75 g, 2h) were prospectively evaluated in a consecutive group of pts with coronary artery disease. ADA criteria (both glucose tolerance test and HbA1c) were used to define diabetes mellitus and pre-diabetes mellitus. Diabetes mellitus risk was evaluated according to the FINnish Diabetes Risk Score.

Results: A total of 135 patients were included (mean age 62.3 +/- 13.1 years, 99 males). Glucose tolerance test and HbA1c together diagnosed 18 (13.3%) new cases of diabetes mellitus and 77 (57.0%) patients with pre-diabetes mellitus. Fasting glucose + HbA1c (guidelines strategy) identified 12/18 patients with diabetes mellitus (Sens 66.7%; negative predictive value 95.1%; Kappa 0.78; $p < 0.0001$) and 83/95 patients with glucose anomalies (pre- diabetes mellitus + diabetes mellitus) (Sens 87.4%; negative predictive value 76.9%). Performing glucose tolerance test in the 29 patients with an elevated FINnish Diabetes Risk Score would allow identifying 15/18 patients with diabetes mellitus (Sens 83.3%; negative predictive value 97.5%; Kappa 0.85; $p < 0.0001$) and 86/95 patients with glucose anomalies (Sens 90.5%; negative predictive value 81.6%).

Discussion: Although this strategy improved the screening accuracy, one in each six patients with diabetes mellitus would still remain undiagnosed, as compared to measuring HbA1c and performing an glucose tolerance test in all patients.

Conclusion: Using the FINnish Diabetes Risk Score to select candidates to additional glucose tolerance test improves the accuracy for identifying diabetic patients, as compared with fasting glucose + HbA1c alone. However, 1/6 patients diabetes mellitus is still left undiagnosed with this strategy proposed by the current guidelines.

Keywords: Coronary Artery Disease; Diabetes Mellitus, Type 2; Glucose Tolerance Test; Hemoglobin A, Glycosylated; Mass Screening

RESUMO

Introdução: As novas recomendações europeias de diabetes *mellitus* tipo 2 e doença cardiovascular sugerem que o risco de diabetes *mellitus* tipo 2 deve ser avaliado através do *score* de risco *FINnish Diabetes Risk Score* e que o rastreio de diabetes *mellitus* tipo 2 na população com doença arterial coronária deve ser efetuado apenas com a glicemia plasmática em jejum e a HbA1c, remetendo a prova de tolerância oral à glicose para os casos 'inconclusivos'. Pretendemos avaliar os resultados desta estratégia, que difere da previamente defendida nas *guidelines*.

Material e Métodos: A glicemia plasmática em jejum, HbA1c e a prova de tolerância oral à glicose (75 g, 2 horas) foram avaliadas prospectivamente num grupo de doentes consecutivos submetidos a intervenção coronária percutânea, sendo usada a classificação da ADA para pré-diabetes *mellitus* tipo 2 e diabetes *mellitus* tipo 2. O risco de diabetes foi avaliado de acordo com o *FINnish Diabetes Risk Score*.

Resultados: Foram incluídos 135 doentes (idade média 62,3 +/- 13,1 anos; 99 homens). Usando a prova de tolerância oral à glicose e a HbA1c, foram diagnosticados 18 (13,3%) novos casos de diabetes *mellitus* tipo 2 e 77 (57,0%) casos de pré-diabetes *mellitus* tipo 2. A glicemia plasmática em jejum + HbA1c identificou 12/18 doentes com diabetes *mellitus* tipo 2 (Sens 66,7%; valor preditivo negativo 95,1%; Kappa 0,78; $p < 0,0001$) e 83 do total (pré-diabetes *mellitus* tipo 2/ diabetes *mellitus* tipo 2) de 95 doentes com distúrbios da glicose (Sens 87,4%; valor preditivo negativo 76,9%). Realizar adicionalmente prova de tolerância oral à glicose nos 29 doentes com um *FINnish Diabetes Risk Score* elevado permitiu diagnosticar 15/18 doentes com diabetes *mellitus* (Sens 83,3%; valor preditivo negativo 97,5%; Kappa 0,85; $p < 0,0001$) e 86/95 dos doentes com distúrbios da glicose (Sens 90,5%; valor preditivo negativo 81,6%).

Discussão: Apesar da melhoria diagnóstica, um em cada seis doentes com diabetes *mellitus* tipo 2 não seria diagnosticado por esta estratégia.

Conclusão: A utilização do *FINnish Diabetes Risk Score* como forma de selecionar os doentes candidatos a rastreio com prova de tolerância oral à glicose melhora a capacidade diagnóstica, quando comparada com a simples avaliação da glicemia plasmática em jejum e da HbA1c. No entanto, um em cada seis doentes com diabetes *mellitus* tipo 2 não é identificado com esta metodologia.

Palavras-chave: Diabetes Mellitus Tipo 2; Doença da Artería Coronária; Hemoglobina A Glicosilada; Rastreio; Teste de Tolerância a Glucose

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INTRODUCTION

Despite the ever-increasing number of patients with diabetes, an estimated 30% of the population with type-2 diabetes mellitus (DM) remains undiagnosed and 25% of these patients already have overt retinopathy or micro-albuminuria at the time of diagnosis.^{1,2} Despite DM has been defined according with the level of hyperglycaemia corresponding to an increased risk of glucose-induced microvascular disease (including retinopathy, nephropathy or neuropathy), the presence of macrovascular complications, particularly related to coronary heart disease (CHD) is very relevant in patients with diabetes and their outcome is greatly affected.³

On the other hand, the disorders of glucose metabolism are very prevalent, even though they frequently remain unnoticed in these patients.^{4,5} This is also a very relevant issue, as these disorders are associated with poorer outcome in patients with CHD, when compared with normoglycaemic patients.⁶⁻⁹

In line with this mutual impact between CHD and DM, the European Society of Cardiology – ESC and the European Association for the Study of Diabetes – EASD have for the first time issued in 2007 their recommendations on the diagnosis of diabetes in the presence of cardiovascular disease.¹⁰ The need for a screening program for disorders of glucose metabolism (including diabetes, impaired fasting glucose and impaired glucose tolerance) in all the patients with CHD was for the first time assumed by these guidelines as well as the assessment of fasting plasma glucose levels supplemented with an oral glucose tolerance test (OGTT) in all the patients with CHD not previously diagnosed with diabetes.

A new evidence has emerged and the HbA1c level became a diagnostic criterion for diabetes.¹¹⁻¹⁴ The European guidelines were reviewed in 2013 and aimed at the inclusion of this new evidence³ with the recommendation for the use of fasting plasma glucose (FPG) and HbA1c levels in patients with established cardiovascular disease. According with this new document, the OGTT has only an indication for patients with an inconclusive diagnosis, whose identification has not been clearly defined. The new guidelines have also recommended that the risk of diabetes in patients with overt CHD should be based on the FINnish Diabetes RiSk SCORE (FINDRISC) which in fact has not yet been validated for the population of patients with CHD.¹⁵ This is a different approach and the percentage of patients who would remain undiagnosed should the OGTT not been systematically carried out in patients with CHD has still not been clearly established.

This study aimed at: 1) The assessment of the diagnostic capability of the approach recommended by the European guidelines for the identification of new cases of DM in a population of patients with overt CHD; 2) The assessment of the FINDRISC score in patients with CHD with an indication for the use of OGTT.

MATERIAL AND METHODS

Study design and group of patients

This was a prospective observational study involving consecutive patients who underwent coronary angioplasty and attended the Cardiology outpatient clinic at a single hospital between Jan 2013 and Jul 2014. The following data were obtained, including epidemiological (age, gender) physical (body mass index and waist circumference) and clinical characteristics (including cardiovascular risk factors: high blood pressure, dyslipidaemia and smoking) and those related to coronary heart disease (number of affected arteries, history of myocardial infarction or revascularization). The risk for the development of diabetes has been assessed by the FINDRISC score for each patient and the presence of disorders of glucose metabolism by FPG, OGTT and HbA1c level was obtained from all the patients.

FINDRISC

The FINDRISC score¹⁵ was obtained for each patient, including the following variables: patient's age, waist circumference, BMI, physical exercise habit, dietary habit, history of high blood pressure, previously known disorders of glucose metabolism and family history of DM (Fig. 1). The overall risk was calculated by adding the individual scores and is shown in terms of the chance of developing DM over the following 10 years:

- Low risk: Score < 7 (1/100 patients will develop DM);
- Slightly elevated: Score 7-11 (1/25 will develop DM);
- Moderate: Score 12-14 (1/6 will develop DM);
- High: Score 15-20 (1/3 will develop DM);
- Very high: Score > 20 (estimated that 1 in 2 will develop DM).

Laboratory assessment and diabetes diagnostic criteria

Laboratory tests were performed to all the patients with no known diabetes (approximately two months upon hospital discharge) on the first medical examination upon coronary angioplasty, between the fourth and the fifth month upon discharge from hospital, including FPG, OGTT and HbA1c. The OGTT was carried out according with the WHO recommendations (FPG, followed by a 2-h 75 g OGTT). The HbA1c level was determined by high-resolution liquid chromatography at the time of the first blood sampling for OGTT. Disorders of glucose metabolism have been diagnosed according with the recommendations of the American Diabetes Association (Table 1)¹⁶ and prediabetes was defined in patients with impaired fasting glucose (IFG) and with impaired glucose tolerance (IGT).

Statistical analysis

Normally-distributed continuous variables were represented by the mean and standard deviation. Non-normally distributed continuous variables were represented by the median and interquartile range. Normality has been assessed by using the Kolmogorov-Smirnov test and visual

FINish Diabetes Risk Score (FINDRISK) for the assessment of the 10-year risk of type-2 diabetes in adult patients.

(Available at: www.diabetes.fi/english)

Type-2 diabetes assessment form

Circle the right alternative and add up your points.

1. Age

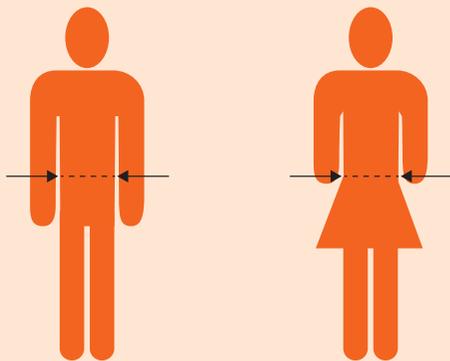
- 0 p. Under 45 years of age
- 2 p. 45 - 54 years
- 3 p. 55 - 64 years
- 4 p. Over 64 years

2. Body mass index

- 0 p. Lower than 25 kg/m²
- 1 p. 25 - 30 kg/m²
- 3 p. Higher than 30 kg/m²

3. Waist circumference measured below the ribs (usually at the level of the navel)

- | MEN | | WOMEN | |
|------|------------------|-------|-----------------|
| 0 p. | Less than 94 cm | 0 p. | Less than 80 cm |
| 3 p. | 94 - 102 cm | 3 p. | 80 - 88 cm |
| 4 p. | More than 102 cm | 4 p. | More than 88 cm |



4. Do you usually have daily at least 30 minutes of physical at work or during leisure time (including normal daily activity)?

- 0 p. Yes
- 2 p. No

5. How often do you eat vegetables, fruit or berries?

- 0 p. Every day
- 1 p. Not every day

6. Have you ever taken antihypertensive medication regularly?

- 0 p. No
- 2 p. Yes

7. Have you ever been found to have high blood glucose (eg. in a health examination, during an illness or during pregnancy)?

- 0 p. No
- 5 p. Yes

8. Have any of the members of your immediate family or other relatives been diagnosed with diabetes (type 1 or type 2)?

- 0 p. No
- 3 p. Yes: grandparent, aunt, uncle or first cousin (but no own parent, brother, sister or child)
- 5 p. Yes: parent, brother, sister or own child

Total risk score

The risk of developing type-2 diabetes within 10 years is:

- < 7 **Low:** estimated 1 in 100 will develop disease
- 7 - 11 **Slightly elevated:** estimated 1 in 25 will develop disease
- 12 - 14 **Moderate:** estimated 1 in 6 will develop disease
- 15 - 20 **High:** estimated 1 in 3 will develop disease
- > 20 **Very high:** estimated 1 in 2 will develop disease

Test designed by Professor Jaakko Tuomilehto, Department of Public Health, University of Helsinki and by Dr. Jaana Lindström, MFS, National Public Health Institute.

Figure 1 – FINish Diabetes Score (FINDRISC)³

Table 1 - Diagnostic criteria for diabetes (American Diabetes Association, 2016)¹⁶

	Fasting plasma glucose (mg/dL)	2-h. blood glucose (mg/dL)	HbA1c
Normal	< 100	< 140	< 5.7
Prediabetes	Impaired fasting glucose (IFG)	100 – 126	< 140
	Impaired glucose tolerance (IGT)	< 126	140 – 200
Diabetes	> 126	> 200	≥ 6.5

assessment of quantile-quantile plots. Discrete variables were represented by percentages. Comparisons were established between the variables of the different groups (classification of disorders of glucose metabolism and risk groups according with the FINDRISC score) by using Chi-square test for categorical variables, Student’s t-test or one-way ANOVA test for normally-distributed continuous variables or the Kruskal-Wallis test for non-normally distributed continuous variables. The agreement between the different techniques for the assessment of disorders of glucose metabolism was assessed through the value of kappa. For all the comparisons, a *p*-value < 0.05 has been considered as statistically significant. The statistical analysis has been carried out using SPSS® Statistics version 19.0 (SPSS Inc., Chicago, IL) IBM® software.

RESULTS

Characteristics of the study population

Fifty (27.0%) patients from an initial group of 185 with overt CHD were excluded from the study, as these were previously diagnosed with DM (Fig. 2). The main characteristics of the study population, including their cardiovascular risk factors, major cardiovascular history data, patient’s lipid profile and the analysis of diabetes diagnosis are shown in Table 2.

Results according with the presence of disorders of glucose metabolism

The overall assessment of OGTT and HbA1c led to the identification of 77 (57%) patients with prediabetes and 18 (13%) patients with DM. Only 40 (30%) patients did not show any disorder of glucose metabolism (Fig. 2). Apart from the 50 patients who were excluded from the analysis due to having been previously diagnosed with diabetes, 18 additional patients with diabetes were identified, showing an overall 36.8% prevalence of diabetes (68/185) in our group of patients. The characteristics of our group of patients according with the presence of disorders of glucose metabolism are shown in Table 2. Newly diagnosed patients with DM showed higher BMI and a tendency for higher waist circumference and no other significant differences were found, namely as regards patient’s age and the presence of cardiovascular risk factors. As regards laboratory tests, the patients with DM and pre-diabetes showed higher triglyceride levels and no other differences were found as regards the remaining parameters included in patient’s lipid profile. Progressively higher FPG, 2-h glucose and HbA1c

levels were found in patients with DM when compared with patients with prediabetes and with normoglycaemic patients.

Results according with the FINDRISC score

A low risk of developing diabetes according with the FINDRISC score has been found in 17 (13%), slightly

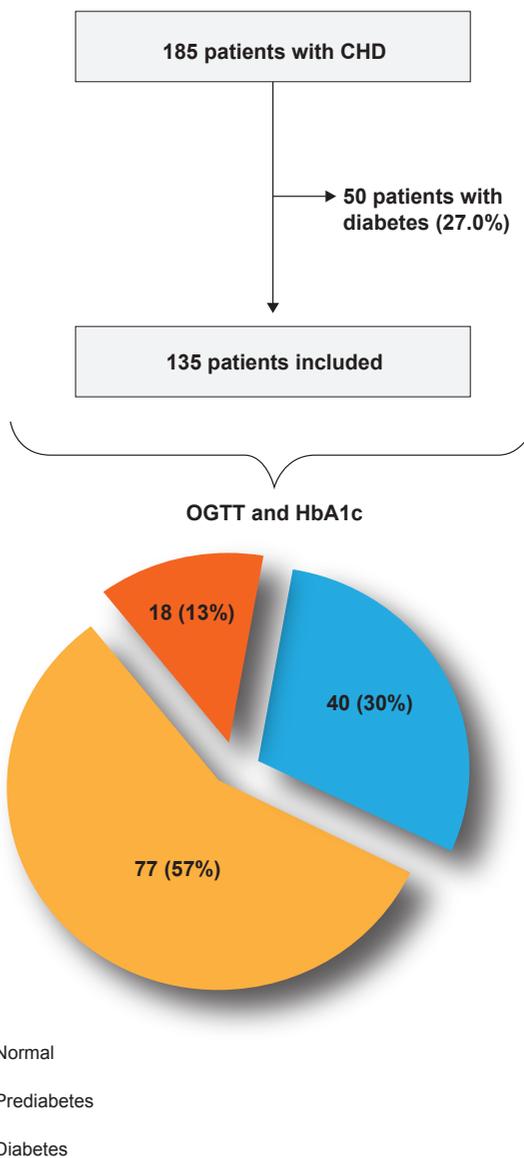


Figure 2 – Patient inclusion flowchart. Prevalence of disorders of glucose metabolism (according with the determination of HbA1c levels and the oral glucose tolerance test).

CHD – coronary heart disease

Table 2 - Characteristics of our group of patients according with the presence of disorders of glucose metabolism

	Total population (n = 135)	Normal blood glucose (n = 40)	Prediabetes (n = 77)	Diabetes (n = 18)	p-value
Age	62.3 ± 13.1	61.3 ± 13.0	63.0 ± 13.4	61.4 ± 12.1	0.755*
Male gender	99 (73.3)	30 (75.0)	55 (71.4)	14 (77.8)	0.826**
Cardiovascular risk factors					
Body mass index	27.6 ± 4.1	26.5 ± 3.8	27.8 ± 4.2	29.3 ± 2.8	0.041*
Waist circumference	98.7 ± 11.9	96.6 ± 12.1	98.4 ± 11.0	104.2 ± 13.8	0.076*
High blood pressure	91 (67.4)	28 (70.0)	48 (62.3)	15 (83.3)	0.212**
Dyslipidaemia	67 (49.6)	21 (52.5)	34 (44.2)	12 (66.7)	0.208**
Smoking	54 (40.0)	22 (55.0)	27 (35.1)	5 (27.8)	0.059**
History					
Previous myocardial infarction	21 (15.6)	7 (17.5)	8 (10.4)	6 (33.3)	0.050**
Previous PCI	22 (16.3)	6 (15.0)	10 (13.0)	6 (33.3)	0.106**
Coronary heart disease					
Ejection fraction < 40%	13 (9.7%)	2 (5.0)	10 (13.2)	1 (5.6)	0.301**
Multi-vessel disease	82 (60.7)	21 (52.5)	49 (63.6)	12 (66.7)	0.433**
Lipid profile (mg/dL)					
Total cholesterol	160 ± 82	153 ± 34	164 ± 45	162 ± 42	0.406*
HDL-cholesterol	46 ± 11	49 ± 11	45 ± 11	43 ± 9	0.148*
LDL-cholesterol	90 ± 36	86 ± 29	92 ± 40	92 ± 32	0.658*
Triglyceride	124 ± 65	96 ± 36	136 ± 75	133 ± 51	0.004*
Blood glucose and HbA1c					
Fasting plasma glucose (mg/dL)	99 ± 17	88 ± 6	100 ± 13	120 ± 26	< 0.001*
2-hour blood glucose test (mg/dL)	135 ± 50	94 ± 24	139 ± 34	222 ± 39	< 0.001*
HbA1c (%)	5.7 ± 0.5	5.3 ± 0.2	5.7 ± 0.3	6.4 ± 0.015	< 0.001*

Numbers represent mean ± standard deviation or n (%); * One-way ANOVA test; ** Chi-square test; PCI: percutaneous coronary intervention

elevated in 51 (38%), moderate in 38 (28%) and high/very high in 29 (21%) patients. The characteristics of the population according with the FINDRISC score are shown in Table 3. Apart from the parameters included in the score (BMI, waist circumference and history of high blood pressure), no other significant differences were found between populations, namely as regards other risk factors, the presence of cardiovascular history, the characteristics of coronary heart disease or the lipid profile. No significant differences were found between the groups as regards the FPG levels, unlike what was found regarding the 2-h OGTT and HbA1c, that progressively and significantly showed higher levels as the FINDRISC score increased.

Diagnostic approach to the disorders of glucose metabolism (diabetes and prediabetes)

The results of the different approaches to DM in patients with overt CHD are shown in Fig. 3A. The approach recommended by the current European guidelines showed a 66.7% sensitivity and a 95.1% negative predictive value (NPV) for the identification of new patients with DM (Kappa 0.78; $p < 0.0001$, for the comparison with OGTT + HbA1c approach). A percentage of 33% of new patients with DM would remain undiagnosed should this approach had been used.

On the other hand, a 83.3% sensitivity and 97.5% NPV (Kappa 0.85; p -value <0.0001) would have been found should the approach involving the OGTT only performed in patients in high risk of developing DM according with the FINDRISC score had been used. Even so, 17% of the new patients with DM would remain undiagnosed should this approach had been used, when compared with the OGTT + HbA1c approach performed in all the patients.

As regards the patients with disorders of glucose metabolism (prediabetes and DM), the approach that was recommended by the guidelines showed an 87.4% sensitivity and a 76.9% NPV, while the additional use of OGTT in patients with high FINDRISC score increased the sensitivity to 90.5% and the NPV to 81.6% and 10% of the patients with disorders of glucose metabolism would remain undiagnosed, when compared to the OGTT + HbA1c approach performed in all the patients.

DISCUSSION

In short, the main results of the study were: 1) a very high prevalence of disorders of glucose metabolism and particularly of diabetes has been found in patients with CHD; 2) the diagnostic approach recommended by the new European guidelines provides for the identification of only part of these new patients with diabetes and prediabetes; 3)

Table 3 - Characteristics of our group of patients according with the FINDRISC score

	Low (n = 17)	Slightly elevated (n = 51)	Moderate (n = 38)	High (n = 29)	p-value
Age †	59.8 ± 14.2	61.3 ± 13.0	62.2 ± 13.2	65.8 ± 12.2	0.390*
Male gender	16 (94.1)	37 (72.5)	28 (73.7)	18 (62.1)	0.130**
Cardiovascular risk factors					
Body mass index †	23.8 ± 1.8	26.7 ± 3.7	28.3 ± 4.1	30.5 ± 3.5	< 0.001**
Waist circumference †	86.2 ± 7.6	96.9 ± 12.4	102.2 ± 10.0	104.4 ± 9.3	< 0.001**
High blood pressure †	4 (23.5)	29 (56.9)	31 (81.6)	27 (93.1)	< 0.001**
Dyslipidaemia	6 (35.3)	21 (41.2)	22 (57.9)	22 (62.1)	0.128**
Smoking	7 (41.2)	21 (41.2)	19 (50.0)	7 (24.1)	0.198**
History					
Previous myocardial infarction	1 (5.9)	6 (11.8)	8 (21.1)	6 (20.7)	0.358**
Previous PCI	1 (5.9)	8 (15.7)	6 (15.8)	7 (24.1)	0.444**
Coronary heart disease					
Ejection fraction < 40%	1 (5.9)	3 (6.0)	7 (18.4)	2 (6.9)	0.202**
Multi-vessel disease	9 (52.9)	29 (56.9)	23 (60.5)	21 (72.4)	0.491**
Lipid profile (mg/dL)					
Total cholesterol	155 ± 45	163 ± 38	170 ± 51	146 ± 28	0.124*
HDL-cholesterol	49 ± 10	46 ± 11	45 ± 11	44 ± 12	0.500*
Triglyceride	93 ± 35	132 ± 77	137 ± 65	111 ± 47	0.063*
Blood glucose and HbA1c					
Fasting plasma glucose (mg/dL)	97 ± 11	96 ± 14	101 ± 21	103 ± 18	0.21*
2-hour blood glucose test (mg/dL)	116 ± 36	124 ± 42	144 ± 50	155 ± 60	0.01*
HbA1c (%)	5.5 ± 0.4	5.6 ± 0.4	5.8 ± 0.5	5.9 ± 0.6	0.007*

Numbers represent mean ± standard deviation or n(%); † Included into the risk score; * One-way ANOVA test; ** Chi-square test; PCI: percutaneous coronary

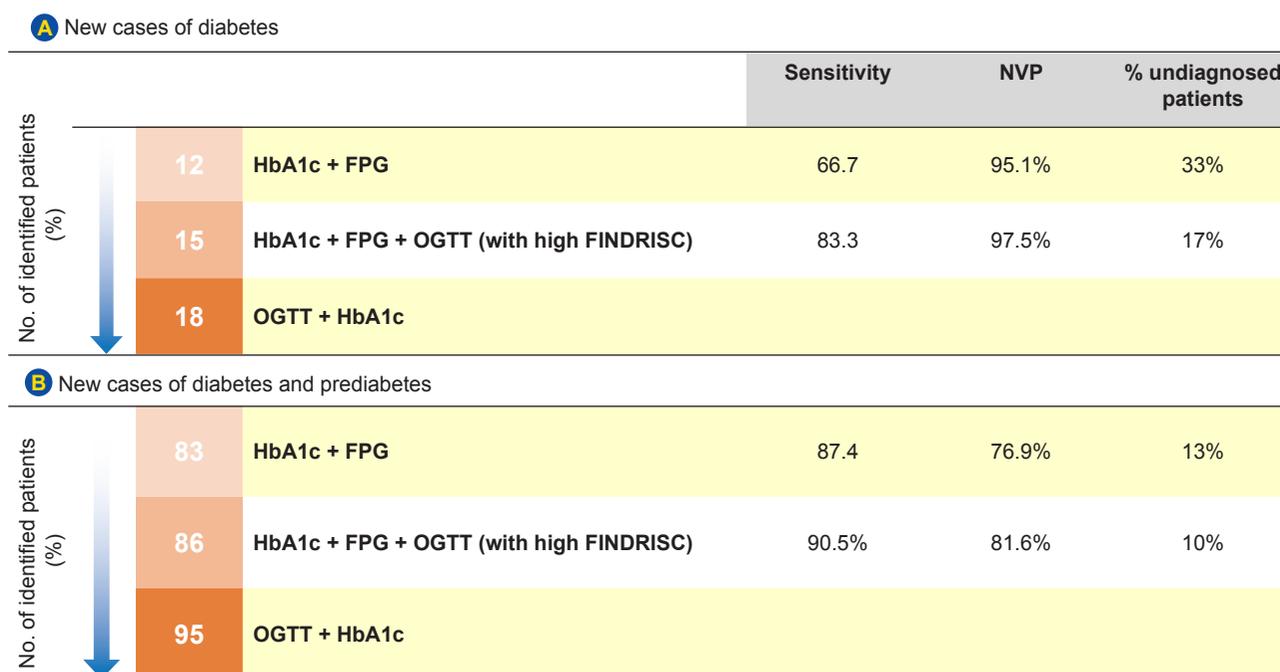


Figure 3 - Diagnostic capability of the different approaches to the identification of (A) new cases of diabetes and (B) new cases of disorders of glucose metabolism (diabetes and prediabetes)

the diagnostic capability of the approach recommended by the guidelines is improved by the inclusion of the FINDRISC score in the selection of the patients with an indication for the use of OGTT, even though it still does not allow for the identification of a significant number of patients with diabetes (one in six).

Prevalence of diabetes/prediabetes in patients with CHD

The high prevalence of disorders of glucose metabolism was clearly shown in the Euro Heart Survey on Diabetes.⁴ The use of the OGTT in all the patients with stable or acute CHD with no previously diagnosed diabetes was recommended in this international multicentric study. A 14 and 37% incidence of de novo diabetes or prediabetes in clinically stable patients who underwent this test have been found, respectively, while a 22 and 36% incidence, respectively, were found in patients with acute CHD. These numbers were added to the 31% percentage of patients already diagnosed with diabetes at the time of study inclusion. The authors found that most of the patients with CHD had an abnormal glucose metabolism and have recommended the use of OGTT in all the patients with no previously diagnosed diabetes. We have also confirmed these results in our study: only 40 from the initially assessed 185 patients (21.6%) showed a normal glucose metabolism and 68 (36.8%) patients had diabetes (including 50 patients previously diagnosed with diabetes and 18 patients with previously unknown diabetes) and 77 (41.6%) had prediabetes. It should be mentioned that, according with what has been described by the Euro Heart Survey on Diabetes,⁴ the prevalence of diabetes found in our study is much higher than the prevalence described in the Portuguese population (13.1%, according with the most recent results).¹⁷ These results have confirmed the crucial need for the screening of disorders of glucose metabolism in all the patients with CHD, considering the impact on patient's outcome produced by this metabolic disorder in this population. Even though there are no published data allowing for the assessment of the percentage of patients with CHD in whom this screening is carried out, the general feeling is that this is probably a very small percentage and that most physicians (including cardiologists) following these patients are not aware of the problem.

Diabetes diagnostic approach to patients with CHD

The most recent European recommendations (2013)³ have introduced a very relevant change when compared to the previous recommendations as regards the diagnostic approach to disorders of glucose metabolism in patients with CHD: diagnosis became only based on FPG and on HbA1c levels and OGTT was reserved for 'doubtful' cases. This has been a somewhat surprising change, considering that previous recommendations were based on the already mentioned Euro Heart Survey on Diabetes, in which OGTT was a crucial element.¹⁰ The inclusion of HbA1c levels as diagnostic criterion seems obvious, taking into account that

it became a diagnostic criterion in general population;^{16,18,19} however, the limitation of the use of OGTT for 'doubtful' cases has not been clearly reasoned in the new guidelines. In fact, a 'doubtful' case is not clearly defined in recommendations and may be interpreted as involving patients with inconclusive laboratory results or eventually patients in higher risk of developing diabetes. The recommendations have suggested the FINDRISC score for the assessment of the risk of diabetes, even though considering that this is a score that has been developed in populations with no known CHD.

In our study, the approach recommended by the guidelines allowed for the identification of only 66% of new patients with diabetes, when compared to the systematic use of OGTT + HbA1c in all the patients. Even when selecting the 'doubtful' patients – defined as those with a risk of developing diabetes (high or very high FINDRISC score) – for the use of OGTT, only 83.3% of the patients with diabetes were correctly identified, meaning that 1 in 6 patients remained undiagnosed.

Obviously, it should not be expected that different diagnostic strategies would identify exactly the same patients with diabetes. All techniques involve advantages and disadvantages and, while the OGTT involves the use of an oral glucose load and a second blood sampling and is not absolutely reproducible, the level of HbA1c, even though allowing for a more reliable assessment of the chronic exposure to glucose, is a more expensive test and may be influenced by some pathologies.¹⁹

In a previous study, at the time when the European recommendations only suggested the use of OGTT, we showed that diagnostic capability was improved with the use of HbA1c level, allowing for the identification of approximately 15% of new patients who were not identified by the OGTT.¹⁴ In the present study, we have also confirmed that the opposite also occurs: the use of OGTT allows for the identification of around 17% of patients with diabetes who were not identified by the level of HbA1c and by FPG. In addition, the use of OGTT allows for the identification of 13% more patients with disorders of glucose metabolism (diabetes and prediabetes), when compared with the approach recommended by the guidelines (HbA1c + FPG).

The discussion around the use of OGTT in patients with CHD is not confined to its capability for the identification of different populations of patients with diabetes, rather regarding its capability for the identification of patients with increased insulin resistance and subsequently in higher risk for cardiovascular events.²⁰

Current diagnostic criteria, defined for the general population, are based on the levels of blood glucose and HbA1c that are associated with an increased risk for developing microvascular disease.¹⁶ Macrovascular disease and its consequences were not correctly taken into account for the definition of diabetes diagnostic criteria and recent trials (ACCORD,²¹ ADVANCE²²) were not able to show any reduction in macrovascular events with the intensive reduction in the levels of blood glucose. However, these

results must be analysed considering that microvascular disease seems to be mainly associated with the decreased function of pancreatic beta-cells, while macrovascular disease (such as coronary heart disease) seems to mainly relate to a decreased sensitivity to insulin.²³ Knowing that the studies ACCORD and ADVANCE have assessed the events according with the levels of HbA1c (mainly corresponding to the function of pancreatic beta-cells), a closer relationship with microvascular disease should be expected and the fact that no reduction in macrovascular events has been shown is not surprising.

In addition, sensitivity to insulin is better assessed by the use of OGTT: postprandial status requires a quick and high release of insulin, which is reduced in patients resistant to insulin. In patients with CHD, this fact is associated with an increased risk of macrovascular events and is not assessed by FPG or by HbA1c levels.^{20,24} In addition, the analysis of the levels of HbA1c does not allow for the assessment of another relevant aspect of glucose metabolism – the fluctuations that occur during the postprandial period in patients with insulin resistance. These fluctuations in blood glucose levels have shown a deleterious action at different levels: activation of the protein kinase C pathway, induction of the production of different inflammatory markers and induction of deeper endothelial dysfunction, when compared with higher yet more stable levels of blood glucose.²⁵⁻²⁷

In patients with predominant macrovascular disease, the levels of HbA1c may therefore underestimate the risk associated with disorders of glucose metabolism, explaining for the routine use of OGTT in this population. Considering the high prevalence and the impact of disorders of glucose metabolism in the outcome of patients with CHD,^{6,7} it is at the very least questionable that the information provided by this technique would be overlooked, even considering the inconvenience associated with the use of a glucose load and the need for a second blood sampling. The early identification of DM and prediabetes stages is particularly important in these patients, allowing for pharmacological approaches as well as over patient's lifestyle^{28,29} in preventing or delaying the progression to diabetes and reducing the risk of macrovascular complications. Finally, it should be mentioned that a small additional cost is involved with the systematic use of OGTT, as supported in our study: according with the current price chart of the Portuguese Ministry of Health,³⁰ the assessment of blood glucose has a cost of €1.20 (when compared to €7.30 for the determination of HbA1c) and this would be the additional cost per patient, when compared to the diagnostic approach recommended

by the current guidelines (FGP + HbA1c).

Limitations

This has been a monocentric study and involved a selected small population with clinically relevant coronary heart disease – with an indication for angioplasty and therefore the results must be considered within this background. In addition, diagnostic tests for diabetes were not repeated, as recommended by the guidelines, suggesting that diagnosis should not be based on a single determination of blood glucose or HbA1c levels.

CONCLUSION

The approach recommended by the new guidelines only allows for the identification of 66.7% new patients with DM and a significant percentage of patients remains undiagnosed. The use of the FINDRISC score for the selection of patients with an indication for screening with OGTT allows for an improvement in diagnostic capability, when compared with the simple use of FPG together with the HbA1c level. However, 17% of these patients remained undiagnosed with the use of this approach, meaning that 1 in 6 patients remains undiagnosed. According with the results of this study and considering the impact of DM in the outcome of CHD, the identification of all the patients is crucial and the systematic use of the OGTT in all the patients with CHD and not previously diagnosed with DM should continue to be recommended.

HUMAN AND ANIMAL PROTECTION

The authors declare that they followed procedures were according to regulations established by the Ethics and Clinical Research Committee and according to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

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