Glucose lowering treatment in patients with coronary artery disease is prognostically important not only in established but also in newly detected diabetes mellitus: a report from the Euro Heart Survey on Diabetes and the Heart

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Aims Glucose lowering (GL) therapy in patients with diabetes mellitus (DM) and coronary artery disease (CAD) is prognostically important. This report from the Euro Heart Survey on Diabetes and the Heart describes present practice in relation to 1 year prognosis.

Methods and results The survey enrolled 4676 patients with CAD from 110 centres out of whom 1425 had known and 452 newly detected DM. The impact of different GL modalities on cardiovascular events (CVE: death, myocardial infarction, or stroke) was followed. Insulin treated patients with known DM (n = 378) had an adjusted 1 year hazard ratio (HR) for mortality of 2.23 (95% CI 1.24–4.03; P = 0.006) and for CVE of 1.27 (95% CI 0.85–1.87; P = 0.230) compared with those on oral GL drugs (n = 675). Of patients with newly detected DM 77 (17%) were started on GL drugs. None of them died compared with 25 (P = 0.002) among those without such treatment and their 1 year CVE HR was 0.22 (95% CI 0.05–0.97; P = 0.041) compared with untreated subjects.

Conclusion Insulin therapy may relate to a more serious prognosis in CAD-patients with DM. There was a pronounced decrease in cardiovascular events in patients with newly detected DM prescribed GL drugs compared with those not receiving such treatment.

Keywords Coronary artery disease • Diabetes mellitus • Newly detected diabetes • Insulin • Oral glucose lowering drugs • Mortality • Cardiovascular endpoints

Introduction The Euro Heart Survey on Diabetes and the Heart reported that abnormal glucose regulation is very common in patients with coronary artery disease (CAD). Moreover, it was noted that patients with known or newly detected diabetes mellitus (DM) were at a particularly high risk for mortality and cardiovascular events (CVE) during 1 year of follow-up. There is clear evidence that a multifactorial intervention directed towards the traditional risk factors for CAD effectively reduces micro- and macro-vascular complications in patients with type 2 DM. Regarding glucose lowering (GL) therapy, the
cornerstone should be lifestyle modification, based on recommendations of increased physical activity, and improved diet. Recommendations from the American Diabetes Association and more recently from the European Society of Cardiology and the European Association for the Study of Diabetes highlight the importance of strict glycaemic control. There is, however, no firm evidence favouring one pharmacological treatment before another to obtain this goal. Accordingly, the choice of GL treatment has been driven by the physician’s assessment of the stage of the disease and the general condition of and preferences expressed by the patient. So far no studies addressed the possibility to improve future prognosis by GL therapy in patients with newly detected DM screened due to CAD.

This study reports on the present GL practice and its impact on CVE in CAD-patients with known or newly detected DM within the framework of the Euro Heart Survey on Diabetes and the Heart.

Methods

The Euro Heart Survey on Diabetes and the Heart is a multi-centre observational study involving 110 centres in 25 European countries. A total of 4676 patients, recruited February 2003 to January 2004, were followed during 1 year. Detailed descriptions of the survey and the follow-up have been given elsewhere. In brief, consecutive CAD patients were screened for their glucometabolic state when admitted to a cardiology ward or outpatient clinic. They were assessed, investigated, and treated at the discretion of the responsible physicians. Clinical characteristics, interventions, and test results—e.g. fasting plasma glucose (FPG) or oral glucose tolerance test (OGTT)—were collected in a web-based case record form. The GL therapy that was the basis for group allocation in the present study [insulin, oral glucose lowering drugs (OGLD), a combination or none] was limited to patients on oral GL drugs and insulin (Table 1).

Multiple Cox proportional hazard modelling was performed to analyse the relation of the glucometabolic state and GL therapeutic modalities to 1 year outcome. In order to control for prognostically confounding variables, the models were adjusted for sex, age, previous history of CAD, previous heart failure, smoking (ever/never), FPG at baseline, and use at follow-up of evidence-based treatments (β-blockers, renin–angiotensin–aldosterone system blockers, oral anti-aggregants, and statins).

Ethical consideration

Ethical permission was obtained in each country. Patients were enrolled following oral and/or written informed consent according to local rules.

Results

Of the 4961 patients originally enrolled in the survey, 4676 (94%) were followed for at least 1 year (median 374 days; Q1–Q3, 366–397). Apart from a somewhat higher proportion of males (78 vs. 70%) clinical characteristics of patients lost to follow-up (n = 285) did not differ importantly (median age 67 vs. 65 years, DM 33 vs. 30%) from the total population.
Of the 3940 patients with known glucometabolic state, 947 (24%) had normal glucose regulation. Baseline characteristics, including and medications at follow-up, by glucometabolic category have been presented in detail elsewhere. In brief, the 1425 (36%) patients with known DM were older, more often females and more frequently presented with hypertension, hyperlipidaemia, cerebrovascular and peripheral artery disease (P-values, 0.001). Compared with patients with normal glucose metabolism, a higher proportion of those with DM were treated with inhibitors of the renin–angiotensin–aldosterone system while they less frequently were on β-blockers (P-values, 0.001).

In patients with known DM, the patterns of GL therapy changed from hospital admission to discharge, with the use of insulin somewhat increasing while the opposite was found for OGLD. The treatment pattern returned towards that at enrolment by the end of follow-up (Figure 1). Mono therapy with insulin was more frequent in the Western, OGLD in the Mediterranean.
Patients with known DM were divided into four groups in relation to GL treatment at follow-up: 378 (28%) were treated with insulin only, 675 (54%) with OGLD only, 76 (6%) with combination of both while 152 (12%) did not receive any pharmacological GL treatment. Data on treatment were missing in 144 (10%) patients. As can be seen from Table 1, presenting pertinent patient characteristics at follow-up, patients on insulin were more often of female sex, had a more frequent history of cardiovascular disease and DM complications (P-values < 0.001), and had undergone more percutaneous coronary interventions (P = 0.012) compared with OGLD patients. Both at enrolment (measured in 1009 patients) and at follow-up (self reported by 738 patients), FPG levels were less well controlled in patients on insulin compared with those on OGLD, respectively. The glucomeabolistic control did, however, improve significantly from enrolment to follow-up in both groups (Table 1).

All-cause mortality, non-fatal myocardial infarction, stroke, combined CVE, and revascularization procedures (PCI and CABG) by GL therapy are presented as crude numbers and proportions in Table 2. Kaplan–Meier curves comparing patients on insulin with those on OGLD reveal a higher mortality (Figure 3) and more combined CVE (not shown) among those on insulin. In contrast, patients with a combination of insulin and OGLD had lower all-cause mortality (none) and fewer combined CVE. Following adjustment for baseline confounders, index diagnosis, coronary interventions, therapy at follow-up, and FPG levels at enrolment, a proportional hazard (Cox) regression model confirmed a higher hazard ratio for all-cause mortality (HR 2.23, 95% CI 1.24–4.03; P = 0.006) in the insulin compared with OGLD group. Insulin treated patients had a non-significant trend towards higher all-cause mortality and myocardial infarction (HR 1.33, 95% CI 0.85–2.03; P = 0.206) and combined CVE (HR 1.27, 95% CI 0.85–1.87; P = 0.230). Other models analysing the impact of GL therapy on 1 year events (e.g. the seemingly protective effect of the combination of insulin and OGLD) did not remain significant following adjustment.

When analysing details as regards the insulin and/or OGLD treatments, (Table 3) patients with a combination of basal and short-acting insulin (43%) presented a more dismal CVE rate (Table 2) compared with those on basal (33%) or short-acting (12%) insulin only (P = 0.012). Patients on metformin (16%) had lower all-cause mortality, myocardial infarction, combined CVE, and revascularization rates than patients on sulfonylureas (41%) or a combination of both (27%), but these differences did not reach statistical significance.

![Figure 2](https://academic.oup.com/eurheartj/article-abstract/29/2/177/434608)
Newly detected diabetes mellitus

Of the 3940 patients with known glucometabolic state, 452 (11%) had newly detected DM. These patients did less often present with a previous history of cardiovascular disease but more frequently with a diagnosis of myocardial infarction compared with patients in other glucometabolic states. At follow-up, 77 (17%) of these patients were on pharmacological GL treatment whereas 72 (94%) were on OGLD and five on insulin or a combination (6%). The remaining 373 (83%) patients did not receive any GL drugs. Clinical characteristics of patients with or without GL drugs did not reveal any major differences, except for a slightly higher proportion of males (86 vs. 71%, P = 0.005). FPG levels at enrolment were less well controlled in patients given pharmacological GL treatment compared with those without such drugs (8.6 vs. 7.1 mmol/L; P > 0.001). Patients who received GL treatment more frequently presented FPG values in the diabetic range (48 vs. 38%; P < 0.001) compared with the untreated group while the diagnosis of DM was more often based on an elevated post-prandial glucose in the latter group (52 vs. 30%; P < 0.001).

None of the patients on GL drugs died compared with 25 among those without such treatment (P = 0.002) and myocardial infarction and stroke occurred in 1 vs. 13 and 1 vs. 5 patients, respectively. Kaplan–Meier curves for combined CVE are shown in Figure 4. Following adjustments, as outlined above, patients on pharmacological GL treatment had a 1 year HR for CVE of 0.22 (95% CI 0.05–0.97; P = 0.041) compared with those without such therapy.

Discussion

This report from the Euro Heart Survey on Diabetes and the Heart indicates that the choice of GL modality could be prognostically important in patients with CAD and known DM and that GL is not well practiced. A new and important observation is that early institution of GL drugs seems to be beneficial in patients with newly detected DM.
The present study describes the GL treatment pattern in a large population of CAD patients from everyday practice. Although it is reasonable to assume that the investigators were alerted by the subject studied, the general impression is that patients with CAD and DM are inappropriately managed. Regardless of an often poor glucometabolic control at the time for recruitment, GL therapy was rarely and inconsistently improved. One explanation may be that cardiologists neglect or are inexperienced as regards GL treatment, which usually is handled by representatives for other medical specialties such as general practice, internal medicine, or endocrinology. The recent European guidelines on diabetes and cardiovascular disease\textsuperscript{5} call for a close collaboration between cardiologists and diabetologists, a recommendation that is heavily supported by the present data. A noteworthy finding was the substantial proportion of DM patients, irrespective of geographical region, who were handled without any pharmacological GL treatment (known DM = 152; new DM = 375; overall 28%). These findings relate to what has been described as a ‘clinical inertia’, both among specialists and primary care physicians.\textsuperscript{9} More than 50% of physicians in charge of 2600 Canadian diabetic patients left them with inadequate glucose control.\textsuperscript{10} It should also be acknowledged that lack of adequate pharmacological tools to achieve recommended glucometabolic targets may contribute to a poor glucose control, especially in patients with long-standing diabetes. Finally, compelling evidence for the reversibility of macrovascular complications by intensive GL treatment may be experienced as lacking. A recent meta-analysis\textsuperscript{11} did, however, report on a reduction of macrovascular events by tight glycaemic control in type 1 (HR 0.38, 95% CI 0.26–0.56) although somewhat less impressive in type 2 DM (HR 0.81, 95% CI 0.72–0.91).

The DIGAMI trials studied different GL modalities for post myocardial infarction patients with DM.\textsuperscript{12,13} The first trial showed beneficial long-term mortality effects of intensive, insulin-based glucose control. A beneficial short-term effect of normalization of FPG by intensive insulin has also been described in critically ill patients with hyperglycaemia in intensive care units.\textsuperscript{14} In contrast, the second DIGAMI trial did not reveal any mortality advantages by insulin compared with OGLD-based therapy. The given explanation was that glucose control did not differ between patients on insulin and OGLD, indicating that insulin does not have any beneficial effects in itself. The present observation on an unfavourable impact of insulin on the prognosis of DM patients with CAD is therefore of interest. However—as discussed in more detail in a previous report from the survey\textsuperscript{15}—FPG, at enrolment and follow-up, was less well controlled in patients on insulin than in those on OGLD. Still the negative impact of insulin compared with other GL alternatives remained after the introduction of glucose and other potentially misleading variables in the adjusted proportional hazards model. Despite this, the present observations must be taken with great caution. They may still express that patients on insulin are at a more advanced disease state, and that the excess of pre-existing heart failure, myocardial infarction, and nephropathy accelerates cardiovascular diseases. The present findings are, however, not the only indicating unfavourable effects of insulin. Harmful effects on cardiovascular mortality and morbidity have been discussed by Nichols et al.\textsuperscript{16} and Smooke et al.\textsuperscript{17} Johnsen et al.\textsuperscript{18} performed a registry-based review of GL drugs given to patients hospitalized for a first myocardial infarction. Those prescribed insulin had a higher rate of myocardial infarction

![Figure 4](https://academic.oup.com/eurheartj/article-abstract/29/2/177/434608/182)
than those on OGLD during follow-up. Similar observations emerged in the DIGAMI 2 trial, reporting on an increased risk for non-fatal myocardial infarction and stroke (HR 1.73 95% CI 1.26–2.37; \( P < 0.001 \)) in insulin treated patients compared with those on OGLD (Mellbin et al.19). The present findings should, not the least in the light of previous reports in a similar direction, be taken as important observations encouraging clinical trials designed to clarify this particular subject. It may be speculated that insulin-based therapy leaving patients with poor glucose control open for potentially harmful effects of this compound while an accurate glycaemic control would be beneficial. This assumption may gain support by the UKPDS findings. With the concern that sulfonylureas increase cardiovascular mortality in type 2 DM and that a high insulin concentration may cause harm, these two therapeutic modalities were neutral in this respect.24 Regarding patients with newly detected DM and CAD, an early pharmacological approach seems to be rewarding. These concepts definitely deserve confirmation in randomized clinical trials.

Concluding remarks
GL treatment for patients with CAD and known or newly detected DM influences 1 year prognosis. The finding that insulin may not be the best GL option needs further consideration. In newly detected DM patients, an early pharmacological approach seems to be rewarding. These concepts definitely deserve confirmation in randomized clinical trials.

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