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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Received 24 June 2007; revised 10 October 2007; accepted 18 October 2007; Online publish-ahead-of-print 21 December 2007

See page 141 for the editorial comment on this article (doi:10.1093/eurheartj/ehm595)

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).¹ 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.² Regarding glucose lowering (GL) therapy, the
cornerstone should be lifestyle modification, based on recommenda-
tions of increased physical activity, and improved diet.1 Recom-
mendations from the American Diabetes Association7 and more recently from the European Society of Cardiology and the
European Association for the Study of Diabetes2 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 treat-
ment 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 possi-
bility 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.1,6 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
defined as that recorded at follow-up. Patients were followed with
respect to treatment, survival, CVE, and procedures.

Definitions
Glucometabolic state
Patients with known DM were those reporting on an established diag-
nosis or those on GL drugs (n = 1425). The study protocol asked for
an OGTT in patients with unknown glucometabolic state. Such test
was performed in 1819 and FPG was available in another 696 patients,
respectively. In 736 (16%) of the patients with unknown gluco-
metabolic state neither FPG nor OGTT was available. These patients
were excluded from further analyses. The glucometabolic classifi-
cation, performed at the index hospitalization, in normal glucose regu-
lation, impaired glucose regulation (impaired fasting glucose and/or
impaired glucose tolerance), and newly detected DM was based on
OGTT or FPG according to definitions given by the WHO.7

Measurements
Glucose concentrations at enrolment were measured according to
local routines while follow-up values were self-reported by the
patients. When needed, conversion to venous plasma glucose in
mmol/L was performed as established by the European Diabetes
Epidemiology Group.8

Geographic regions
The 25 participating countries were divided into four regions: West
(Germany, Switzerland, Austria, France, and The Netherlands),
Central (Bosnia and Herzegovina, Bulgaria, Belarus, Czech Republic,
Estonia, Georgia, Hungary, Lithuania, Macedonia, Poland, Romania,
Ukraine, and Serbia and Montenegro), Mediterranean
(Spain, Portugal, Italy, Cyprus, Greece, and Egypt), and North
(Finland, Sweden, and UK).

Statistical methods
Continuous variables are expressed as medians with lower and upper
quartiles (Q1–Q3) and categorical variables as counts and percents.
Continuous variables were compared between strata by means of the
Wilcoxon–Mann–Whitney test, and categorical vari-
ables in two-way tables by means of the Fisher exact test. Tables
with more entries (degree of freedom >1) were analysed with ordin-
ary $\chi^2$ test. Kaplan–Meier curves were computed for all-cause
mortality and the composite endpoint of CVE (including all-cause
mortality, myocardial infarction, and stroke). The log-rank test was
used to test for differences in the unadjusted survival curves. Since
the number of patients on combinations of GL drugs or on no pharma-
cological treatment at all was low, comparisons between groups were
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 age, sex, and
baseline characteristics (Table 1; variables with P < 0.05), index diagno-
sis, interventions, and medications at follow-up. Results are reported as
hazard ratios (HR) and 95% confidence intervals (95% CI).

The final model testing the 1 year impact of receiving insulin or an
OGLD in patients with known DM was adjusted for age, sex, 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).

The final model testing the 1 year impact of receiving or not a GL
treatment in patients with newly detected DM was adjusted for
age, sex, previous history of CAD, previous heart failure and
use at follow-up of evidence-based treatments (β-blockers, renin–
angiotensin–aldosterone system blockers, oral anti-aggregants, and
statins).

These models were found by combining stepwise forward and back-
ward analyses to avoid multicollinearity problems. The assumption of
proportional hazards was assessed and satisfied by visual inspection
of the log–log survival curves for the categorical variables. The con-
tinuous variables were classified and a graphical approach was
applied to verify the linearity assumption.

A two-sided P-value <0.05 was considered statistically significant.
All analyses were performed with STATISTICA (v 7.1, Stat Soft, Inc.).

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. 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. 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.

### Table 1 Baseline characteristics, index diagnosis, performed interventions, and medications at follow-up by glucose lowering therapy in patients with known diabetes mellitus

<table>
<thead>
<tr>
<th>Variable (%)</th>
<th>Insulin (n = 378)</th>
<th>OGLD (n = 675)</th>
<th>P-value</th>
<th>Combination (n = 76)</th>
<th>No (n = 152)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>224 (59.3)</td>
<td>457 (67.7)</td>
<td>0.006</td>
<td>42 (55.3)</td>
<td>96 (63.1)</td>
</tr>
<tr>
<td>Age (years; median, Q1–Q3)</td>
<td>68 (60–75)</td>
<td>68 (59–74)</td>
<td>0.687</td>
<td>65 (59–71)</td>
<td>69 (61–75)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>31 (8.5)</td>
<td>81 (12.3)</td>
<td>0.004</td>
<td>8 (10.8)</td>
<td>16 (10.7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>284 (75.1)</td>
<td>534 (79.1)</td>
<td>0.209</td>
<td>63 (82.9)</td>
<td>115 (75.7)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>253 (66.9)</td>
<td>449 (66.5)</td>
<td>0.764</td>
<td>45 (59.2)</td>
<td>99 (65.1)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>76 (20.1)</td>
<td>118 (17.5)</td>
<td>0.478</td>
<td>9 (11.8)</td>
<td>16 (10.5)</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>98 (25.9)</td>
<td>164 (24.3)</td>
<td>0.557</td>
<td>13 (17.1)</td>
<td>30 (19.7)</td>
</tr>
<tr>
<td><strong>Previous</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>84 (22.2)</td>
<td>145 (21.5)</td>
<td>0.789</td>
<td>13 (17.1)</td>
<td>27 (17.8)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>203 (53.7)</td>
<td>307 (45.5)</td>
<td>0.010</td>
<td>28 (36.8)</td>
<td>62 (40.8)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>158 (41.8)</td>
<td>212 (31.4)</td>
<td>&lt;0.001</td>
<td>16 (21.1)</td>
<td>39 (25.7)</td>
</tr>
<tr>
<td>PCI</td>
<td>94 (24.9)</td>
<td>131 (19.4)</td>
<td>0.037</td>
<td>12 (15.8)</td>
<td>23 (15.1)</td>
</tr>
<tr>
<td>CABG</td>
<td>102 (27.0)</td>
<td>138 (20.4)</td>
<td>&lt;0.001</td>
<td>13 (17.1)</td>
<td>26 (17.1)</td>
</tr>
<tr>
<td>Diabetes complications</td>
<td>180 (47.6)</td>
<td>226 (33.7)</td>
<td>&lt;0.001</td>
<td>28 (36.8)</td>
<td>37 (24.3)</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>139 (37.2)</td>
<td>166 (23.5)</td>
<td>0.383</td>
<td>22 (27.6)</td>
<td>26 (20.3)</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>78 (21.3)</td>
<td>63 (27.9)</td>
<td>0.001</td>
<td>11 (13.9)</td>
<td>14 (10.5)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>88 (24.9)</td>
<td>119 (52.7)</td>
<td>0.451</td>
<td>12 (42.9)</td>
<td>24 (46.9)</td>
</tr>
</tbody>
</table>

| Medication at follow-up           |                  |                |         |                     |              |
| β-blockers                        | 276 (73.6)       | 507 (75.1)     | 0.590   | 61 (80.3)           | 95 (62.9)    |
| ACE-inhibitors/ARBs               | 302 (80.5)       | 535 (79.2)     | 0.623   | 65 (86.7)           | 96 (63.6)    |
| Oral anti-aggregants              | 343 (90.7)       | 622 (92.1)     | 0.429   | 72 (94.7)           | 127 (84.1)   |
| Statins                           | 279 (74.6)       | 494 (73.2)     | 0.618   | 54 (71.1)           | 102 (67.6)   |
| Coronary angiography              | 251 (66.4)       | 434 (64.3)     | 0.492   | 48 (63.2)           | 86 (56.6)    |
| PCI                               | 120 (31.8)       | 166 (24.6)     | 0.012   | 18 (23.7)           | 43 (28.5)    |
| CABG                              | 67 (17.7)        | 118 (17.5)     | 0.921   | 15 (19.7)           | 25 (16.6)    |

| Fasting plasma glucose (mmol/L)   |                  |                |         |                     |              |
| At enrolment (median, Q1–Q3)      | 8.7 (6.8–12.2)    | 7.4 (6.4–9.7)  | <0.001  | 9.6 (7.3–12.4)      | 7.3 (6.2–9.2) |
| at follow-up (median, Q1–Q3)      | 7.5 (6.7–8.7)    | 6.9 (6.1–7.8)  | 0.024   | 7.8 (6.8–9.4)       | 6.7 (5.8–7.6) |

Data shown as counts and percentages if not indicated otherwise. Wilcoxon–Mann–Whitney (continuous) or Fisher exact (categorical) test P-values were used for the comparison of patients on insulin vs. oral glucose lowering drugs. PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ARBs, angiotensin receptor blockers.

### Figure 1 Patterns of glucose lowering therapy (shown as %) at enrolment and at follow-up in patients with known diabetes (dotted, insulin only; striped, oral agents only; filled, insulin and oral; open, no pharmacological therapy)
and a combination of both in the Northern region, respectively (Figure 2).

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 glucometabolic 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)

**Figure 2** Proportion of various glucose lowering therapy (%) in patients with known diabetes at the time of follow-up in four European regions (dotted, insulin only; striped, oral agents only; filled, insulin and oral; open, no pharmacological therapy)

**Table 2** Crude events, numbers and within brackets proportions, by glucose lowering therapy during the 1 year follow-up period

<table>
<thead>
<tr>
<th>Glucose lowering treatment</th>
<th>All-cause mortality</th>
<th>Myocardial infarction</th>
<th>Stroke</th>
<th>CVE</th>
<th>PCI/CABG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin (n = 378)</strong></td>
<td>37 (9.8)</td>
<td>23 (6.1)</td>
<td>13 (3.4)</td>
<td>65 (17.2)</td>
<td>63 (16.7)</td>
</tr>
<tr>
<td>OGLD (n = 674)</td>
<td>28 (4.1)</td>
<td>39 (5.8)</td>
<td>27 (4.0)</td>
<td>83 (12.3)</td>
<td>91 (13.5)</td>
</tr>
<tr>
<td>Combination (n = 76)</td>
<td>0 (0)</td>
<td>2 (2.6)</td>
<td>2 (2.6)</td>
<td>4 (5.3)</td>
<td>11 (14.5)</td>
</tr>
<tr>
<td>No (n = 155)</td>
<td>11 (7.2)</td>
<td>7 (4.6)</td>
<td>5 (3.3)</td>
<td>19 (12.5)</td>
<td>23 (15.1)</td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>&lt;0.001</td>
<td>0.560</td>
<td>0.901</td>
<td>0.014</td>
<td>0.579</td>
</tr>
<tr>
<td><strong>Insulin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal (n = 150)</td>
<td>8 (5.3)</td>
<td>5 (3.3)</td>
<td>2 (1.3)</td>
<td>14 (9.3)</td>
<td>23 (15.3)</td>
</tr>
<tr>
<td>Short acting (n = 56)</td>
<td>3 (5.4)</td>
<td>2 (3.6)</td>
<td>4 (7.1)</td>
<td>8 (14.3)</td>
<td>8 (14.3)</td>
</tr>
<tr>
<td>Combination (n = 192)</td>
<td>23 (12.0)</td>
<td>16 (8.3)</td>
<td>7 (3.7)</td>
<td>40 (20.8)</td>
<td>34 (17.7)</td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>0.058</td>
<td>0.103</td>
<td>0.113</td>
<td>0.012</td>
<td>0.759</td>
</tr>
<tr>
<td><strong>OGLD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfonylureas (n = 313)</td>
<td>11 (3.5)</td>
<td>16 (5.1)</td>
<td>15 (4.8)</td>
<td>38 (12.1)</td>
<td>36 (11.5)</td>
</tr>
<tr>
<td>Metformin (n = 124)</td>
<td>3 (2.4)</td>
<td>5 (4.0)</td>
<td>7 (5.6)</td>
<td>13 (10.5)</td>
<td>12 (9.7)</td>
</tr>
<tr>
<td>Combination (n = 202)</td>
<td>10 (4.9)</td>
<td>17 (8.4)</td>
<td>6 (3.0)</td>
<td>28 (13.9)</td>
<td>35 (17.3)</td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td>0.478</td>
<td>0.194</td>
<td>0.441</td>
<td>0.656</td>
<td>0.081</td>
</tr>
</tbody>
</table>

*P*-values relate to overall differences between the various glucose lowering treatments. CVE, death or myocardial infarction or stroke; OGLD, oral glucose lowering drugs.
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 whereof 72 (94%) were on OGLD and five on insulin or a combination (6%). The remaining 375 (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 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 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 who, irrespective of geographical region, 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. More than 50% of physicians in charge of 2600 Canadian diabetic patients left them with inadequate glucose control. 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 did, however, report on a reduction of macrovascular events by tight glycemic 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. 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. 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—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. and Smooke et al. Johnsen et al. performed a registry-based review of GL drugs given to patients hospitalized for a first myocardial infarction.

Figure 4 Kaplan–Meier curves for combined cardiovascular events in patients with newly detected diabetes prescribed (filled circle) or not (open circle) pharmacological glucose lowering treatment.
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 opens 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 that a high insulin concentration may cause harm, these two therapeutic modalities were compared in UKPDS 33,20 All-cause mortality and morbidity after 10 years did, however, not differ. Another direct comparison of sulfonylureas and insulin was reported in UKPDS 35;21 CVE and all-cause mortality did only relate to the magnitude of the reduction in updated HbA1c, strongly indicating that glucose control rather than the tool used to accomplish this carries the prognostic benefit. Overweight patients with DM were randomly assigned to diet alone, insulin, or OGLD and followed for 10 years in UKPDS 43,22 Metformin caused a significantly lower number of DM-related endpoints, all-cause mortality, and stroke. This observation is supported by the present survey, in which metformin treated patients had a trend towards lower 1 year mortality, combined CVE, and revascularization procedures while sulfonylureas were neutral in this respect.

A fair proportion of patients with CAD has abnormal glucose regulation, and an OGTT is needed to accurately categorize these patients.1 Their prognosis is impaired already at glycaemic levels just slightly above those labelled as normal.21,22 The reason driving the decision of responsible physicians to institute pharmacological GL therapy was not asked for by the survey. That untreated patients presented with post-prandial glucose levels in the diabetic range more frequently than in the fasting state supports that European practice regarding these high risk patients has room for improvement. Post-prandial hyperglycaemia is one of the earliest indicators of impaired glucose control and a stronger risk factor for cardiovascular disease than FPG.24 Regarding patients with newly detected DM and CAD, the present survey strongly suggests early institution of OGLD. Still it must be admitted that there is a lack of randomized trials addressing the possibility to improve future prognosis by pharmacological GL treatment in DM patients with CAD. The STOP NIDDM trial, primarily designed to study the possibility to prevent patients with impaired glucose tolerance to progress toward DM by means of acarbose, demonstrated a 49% relative risk reduction of the 3 year risk for CVE compared with placebo.25 The present findings parallel these observations of the usefulness of the early institution of pharmacological GL therapy in patients with newly detected DM and CAD.

Study limitations
The recruited patients were, as in previous Euro Heart Surveys, A3B2 show [sr]26–28 chosen to be as representative as possible for a general population of patients with CAD. The period of recruitment was kept short and the number of patients asked for from each centre modest to simplify consecutive recruitment and ensure collection of high quality data. Strength with surveys of the present kind is the enrolment of patients seen in everyday practice without any exclusion criteria. However, since most patients originated from hospitals it should be acknowledged that they may not be representative for those in primary care. With this potential limitation, the size and wide geographical recruitment area make it reasonable to assume that patterns disclosed by the survey represent a reasonable picture of the actual situation.

Glucometabolic classification was, according to WHO, based on OGTT and FPG values obtained at the index hospitalization. The investigators were not asked to declare the glucometabolic state in the case record forms. The physician in charge may therefore not have paid attention to the outcome of the OGTT, a reason to abstain from GL treatment. This does, however, not weaken the observation that an early institution of GL therapy improved the prognosis in CAD patients with newly detected diabetes compared with those without such treatment. No data on the prescription of lifestyle advice, the cornerstone in GL treatment, were recorded in the survey. Even if patients with newly detected DM received at least some counselling, this was obviously not sufficient from a prognostic perspective.

An important shortcoming is that FPG at follow-up was self-reported and available only in two-thirds of the known DM patients on insulin or OGLD. This limited the possibility to introduce follow-up glucose levels in the multiple proportional hazards model. Glycosylated haemoglobin at follow-up was not demanded by the survey and could therefore not be used as a measure of glucometabolic control. Despite these limitations, the present findings deserve attention and should certainly stimulate further research.

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.

Conflict of interest: none declared.

Funding
This report was supported by unconditional grants from the Swedish Heart and Lung Foundation, AFA Insurance, and Sanofi-Aventis. None of these providers of research funds had any role in the analyses, interpretation of data, or in the preparation of the manuscript.

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