The Euro Heart Survey on Diabetes and the Heart

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Abstract

Despite considerable improvements in the management of cardiovascular diseases, patients with diabetes mellitus have not benefited to the same extent as those without. Possible explanations are advanced atherosclerosis, inferior efficacy or insufficient use of evidence-based treatment, or inadequate glycemic control in these patients.

The Euro Heart Survey on Diabetes and the Heart (EHS) was a multicentre prospective observational study involving 110 centres in 25 European countries. The aims of the survey were to describe the prevalence of abnormal glucose regulation to assess clinical practice in relation to existing guidelines and to compare the impact of evidence-based medication and procedures on mortality and morbidity in patients with coronary artery disease (CAD). Patient enrolment was performed between February 2003 and January 2004. Consecutive patients with established CAD were recruited when admitted to hospital cardiology wards or visiting outpatient clinics. All patients were assessed, investigated and treated at the discretion of their physician according to the institution's practice.

The present review describes the main findings of the EHS and puts them into perspective.

Key words:
Coronary artery disease (CAD), diabetes, Euro Heart Survey on Diabetes and the Heart (EHS), guidelines, evidence-based medicine, glucose lowering medication

Introduction

Despite considerable therapeutic progress, cardiovascular disease (CVD) continues to have a substantial impact on outcome not least in patients with type 2 diabetes mellitus. The worldwide prevalence of diabetes is continuously increasing due to an ageing population, increasing overweight and lack of physical activity [1], and the number of people with diabetes is estimated to rise from 171 million in 2000 to 366 million in 2030 [2]. Because of this, diabetes has become a diagnosis of considerable and ominous importance in cardiovascular medicine.

The Euro Heart Survey on Diabetes and the Heart (EHS) was a multicentre prospective observational study carried out in 110 centres in 25 European countries *(Fig. 1)*. Patients were recruited between February 2003 and January 2004. During a period of 6 weeks, each centre screened consecutive patients >18 years age on admission to hospital wards or outpatient clinics for verified coronary artery disease (CAD). All patients were investigated and treated at the discretion of their physician. The database comprised 4961 patients with previously known (72%) or newly diagnosed (28%) CAD. Data were collected by means of a web-based case record form covering demography, conventional risk factors for CVD and diabetes, family history of premature CAD, family history of diabetes, medical history, performed or scheduled investigations, treatment and results of tests requested by the protocol. Patients were followed for 1 year with respect to cardiovascular events, survival, treatment and procedures.

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The strength of surveys like the EHS lies in the recruitment of patients seen in everyday clinical practice and not subject to exclusion criteria. Thus the EHS subjects should more truly reflect the type of patients seen in clinical prac-

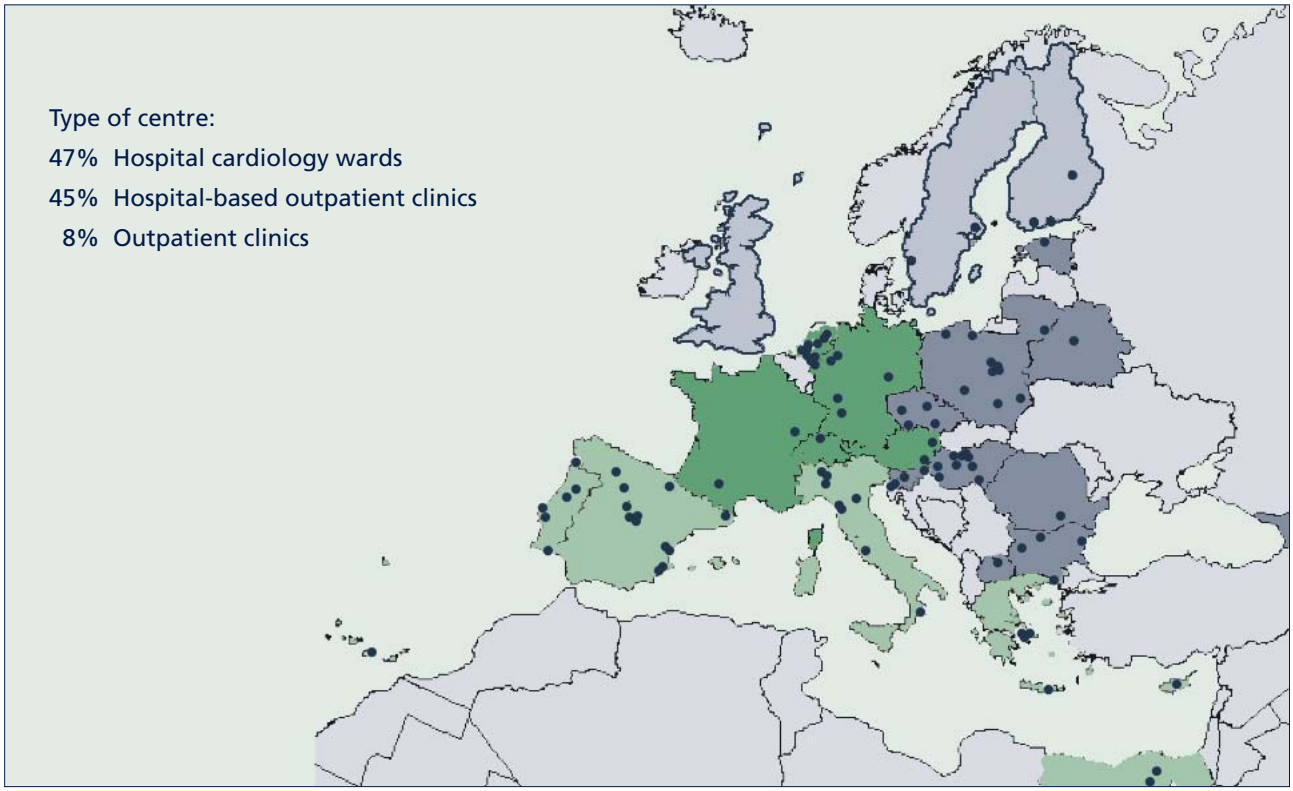


Fig. 1: *Location of the centres. The participating countries were divided into four regions: (1) West (Germany, Switzerland, Austria, France and the Netherlands); (2) Central (Bosnia and Herzegovina, Bulgaria, Belarus, Czech Republic, Estonia, Georgia, Hungary, Lithuania, Macedonia, Poland, Romania, Slovenia, Ukraine, and Serbia and Montenegro); (3) Mediterranean (Spain, Portugal, Italy, Cyprus, Greece and Egypt); and (4) North (Finland, Sweden and the UK). Adapted from [3].*

tice than those usually recruited to clinical trials. By necessity, trials are restricted to patients included on the basis of a study protocol that often has an age limit and excludes those with complex or concomitant diseases. In the EHS most patients were enrolled in hospital settings and it should be acknowledged that they may not be representative of those cared for in primary care. The size (almost 5000 patients) and the wide geographical recruitment area of the survey make it reasonable to assume that the disclosed patterns represent a true picture of the actual clinical situation among patients mainly recruited in a hospital setting.

Abnormal glucose metabolism in patients with CAD

Approximately one-third of the EHS patients had known type 2 diabetes. The protocol recommended that all patients without previously diagnosed diabetes should undergo an OGTT (75 g glucose in 250 ml water with plasma glucose measured before and 2 h after ingestion). An OGTT was performed in 1819 (54%) patients of the 3362 with unknown glucose abnormalities. Less than half were normal, while 37% had impaired glucose tolerance (IGT) and 18% had new diabetes [3], confirming the findings in the Glucose Tolerance in Patients with Acute Myocardial Infarction (GAMI) study [4]. In the GAMI study, which recruited patients with acute myocardial infarction (AMI) without known diabetes, an OGTT was performed at hospital discharge and repeated 3 months later. Abnormal glucose metabolism was detected in two-thirds of patients at hospital discharge (IGT 35%, new diabetes 31%). A similar prevalence was recorded 3 months later, suggesting that increased sympathetic drive induced by acute illness was not the main reason for the metabolic imbalance, and that testing before hospital discharge provides an accurate reflection of actual glucose metabolism. The subsequent China Heart Survey (CHS), mimicking the design of the EHS, enrolled 3513 Chinese patients with CAD. As in the EHS, diabetes was known in approximately one-third of the patients. Among those remaining, an OGTT diagnosed diabetes in 27% and IGT in 37% [5].

Together these three studies provide strong and universal evidence of a high prevalence of abnormal glucose metabolism among patients with CAD, highlighting the need for improved strategies for glucose screening and management.

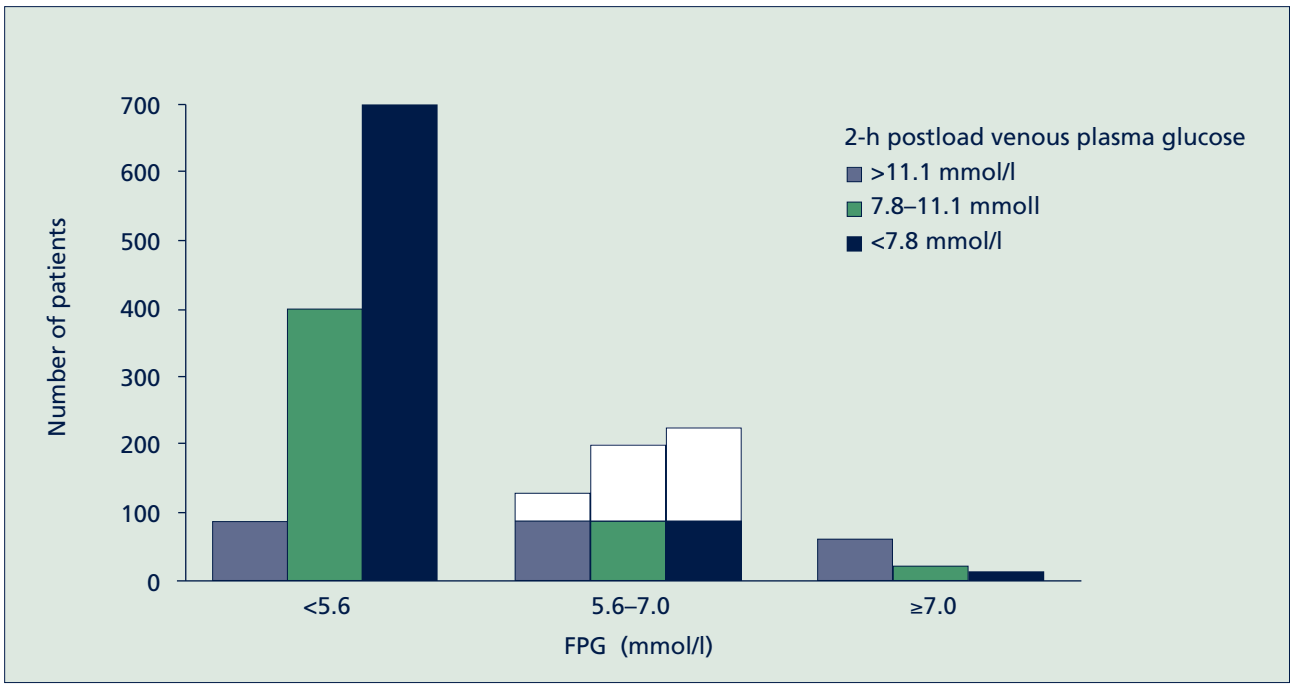


Fig. 2: *Fasting (FPG) (2004 ADA criteria) and postload plasma glucose (WHO criteria) in patients with CAD without any known glucose disturbances. The middle bars of the x-axis are divided into two parts: the lower part represents patients with FPG 6.1–7.0 mmol/l (impaired fasting glucose according to the WHO and 1997 ADA classifications); the upper part represents patients with FPG 5.6–6.1 mmol/l, transferred to the category of impaired fasting glucose, when the cut-off for normal fasting glucose was lowered by the ADA from 6.1 to 5.6 mmol/l in 2004.*

Cardiovascular risk and impaired glucose metabolism

Despite improved survival in CVD the prognosis for patients with diabetes has remained poor not only due to their more extensive coronary disease [6] but also to the lack of a comprehensive management strategy [7, 8]. Moreover macrovascular complications start to become manifest early in the dysglycemia disease continuum. A recent meta-analysis of prospective studies revealed that dysglycemia below the level of diabetes is a risk marker for future CVD and mortality [9]. A significant proportion of dysglycemic individuals develop vascular damage and the disturbed glucose metabolism often remains undetected until the first cardiovascular event [10].

Given its role as an independent predictor of adverse outcomes, screening for glucose abnormalities is strongly recommended in all patients with CAD

Given its role as an independent predictor of adverse outcomes [11], screening for glucose abnormalities is strongly recommended in all patients with CAD. The incidence of all-cause mortality in the EHS 1-year follow-up period was 2.2% in patients with CVD, 5.5% in patients with CVD and newly diagnosed diabetes and 7.7% in patients with CVD and known diabetes. In addition, the risk of experiencing an AMI during the 1-year follow-up was twice as high in patients with known diabetes compared with those with normal glucose metabolism (5.3% vs. 2.5%) [12].

Detecting abnormal glucose metabolism

Increasing awareness of dysglycemia within the medical community has not overcome the reluctance to diagnose prediabetes [13–15]. Screening for diabetes meets most of the recommended criteria. What remains to be shown in ongoing trials is that early detection and treatment of glucose perturbations will reduce morbidity and mortality. An OGTT is particularly useful in patients at high risk of glucose perturbations, including those with CVD [13]. Guidelines for the management of patients with diabetes, prediabetes and CVD state that all patients with CVD should be tested if their glucose homeostasis is unknown [16]. A diagnosis based on fasting plasma glucose (FPG) underestimates the true prevalence of dysglycemia. In the EHS, an FPG above the 1997 American Diabetes Association (ADA) threshold of >6.1 mmol/l or the 2004 threshold of >5.6 mmol/l was found, respec-

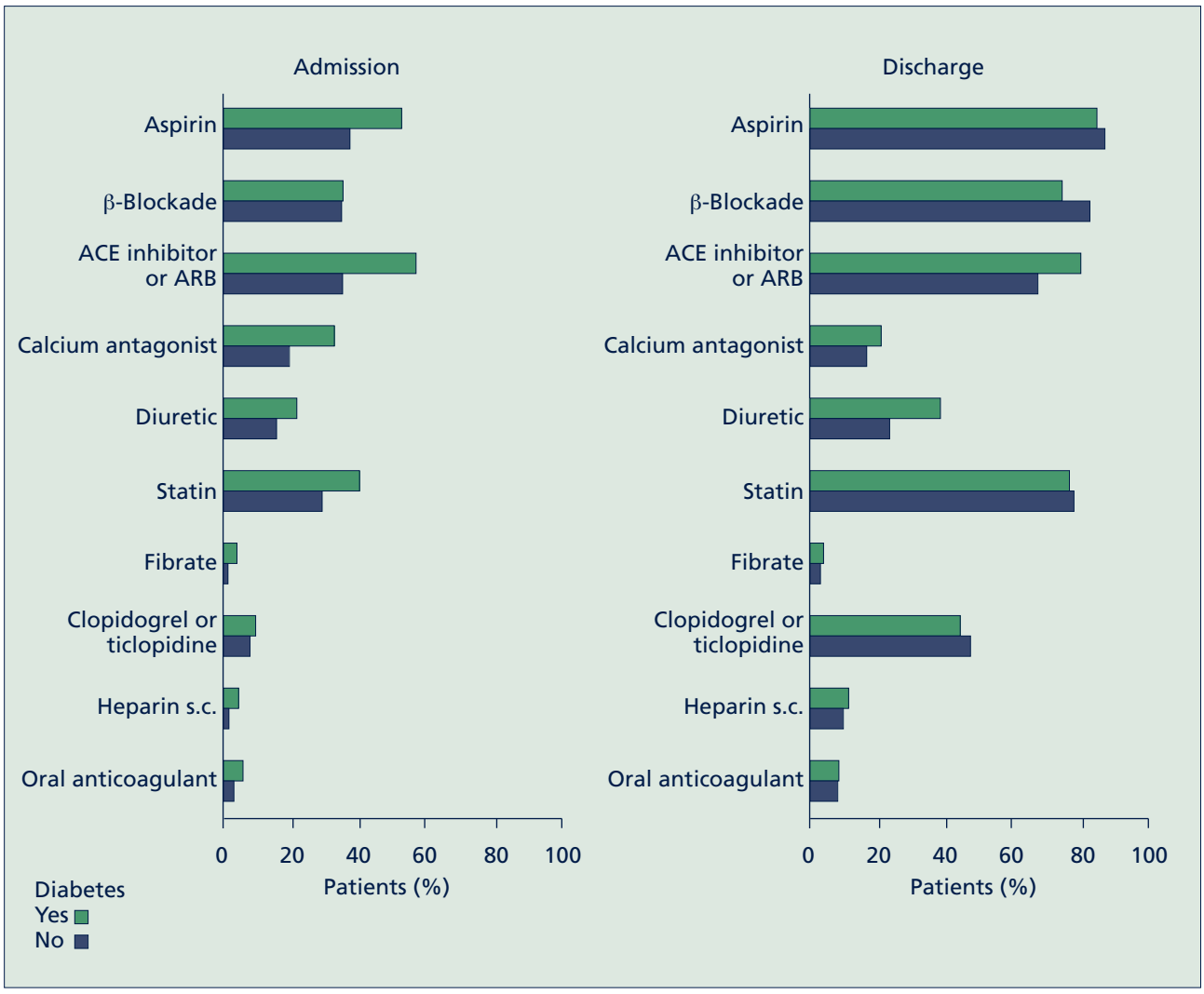


Fig. 3: *Treatment in relation to diabetic status at admission and as recommended at hospital discharge in the acute coronary syndrome cohort. ARB, Angiotensin II receptor blocker.*

tively, in 19% (n = 358) and 36% (n = 672) of patients, whereas abnormal glucose metabolism detected by OGTT was present in 53% (n = 997) of participants. The proportion of patients with IGT (n = 591) who had impaired FPG increased from 27% (n = 97) to 35% (n = 206) using the 1997 and 2004 ADA criteria. The proportion of underdiagnosed patients on the basis of the 1997 ADA criterion was 39%. Applying the 2004 ADA criterion, 33% of patients remained underdiagnosed and 8% would have been overdiagnosed, resulting in a total misclassification rate of 41% *(Fig. 2)* [17]. Importantly, patients with dysglycemia may have normal FPG levels but elevated postprandial blood glucose levels, which makes postload levels measured by OGTT a better predictor of dysglycemia than FPG and also a better risk predictor of subsequent cardiovascular complications [18, 19].

The OGTT has been criticized for lack of long-term reliability. In a recent report, OGTT-based classification of patients with AMI was performed on three occasions: before hospital discharge and 3 and 12 months after hospital discharge. At discharge, 34% were classified as normal, 31% as having IGT and 34% as having type 2 diabetes. Ninety-three percent of all patients with IGT or type 2 diabetes were still classified with these conditions after 12 months of follow-up [20].

Routine use of the OGTT in the cardiology setting is a simple and cost-effective approach that has the potential to significantly improve the detection of metabolic abnormalities in patients with CVD

The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Asia (DECODA) study showed that postload glucose was a better predictor of all-cause and cardiovascular mortality in comparison with FPG [21].

In summary, routine use of the OGTT in the cardiology setting is a simple and cost-effective approach that has the potential to significantly improve the detection of metabolic abnormalities in patients with CVD.

Current clinical practice

Of the 4961 patients enrolled in the EHS, 1872 (38%) received a preliminary diagnosis of acute coronary syndrome at admission. Somewhat surprisingly, accounting for differences in baseline characteristics, patients with diabetes received similar in-hospital pharmacological treatment and interventions to those of their non-diabetic counterparts [22]. At admission, diabetic patients tended more often to be on aspirin, renin-angiotensin-aldosterone system (RAAS) blockers, statins and combinations of blood pressure lowering agents. Drug therapy during hospitalization remained unchanged more frequently in patients with diabetes than in those without (7% vs. 11%; $p < 0.01$). Thus prescriptions of aspirin, β-blockers and statins became less frequent among patients with diabetes at the time of hospital discharge *(Fig. 3)*. In a multiple logistic regression analysis correcting for potential confounders, diabetes had a smaller impact on the choice of treatment and the use of interventions than did other baseline characteristics. Only the prescription of RAAS antagonists was influenced by diabetes (odds ratio 1.33, 95% CI 1.03–1.71; $p = 0.03$).

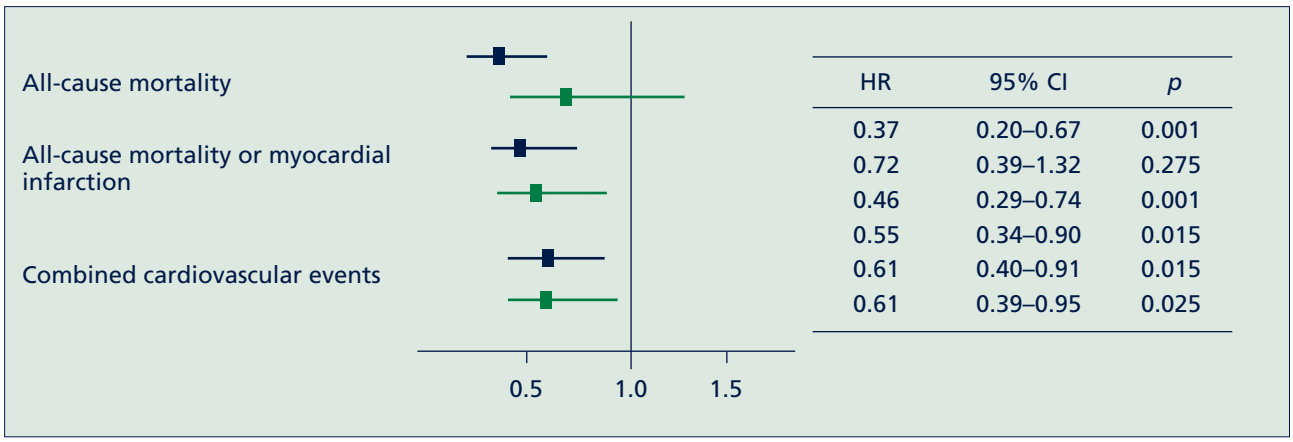
Underutilization of evidence-based drugs (heparins, intravenous β-blockers) and thrombolysis was highlighted in a large Swedish register (25,633 patients) of coronary care unit admissions for suspected AMI (Register of Information and Knowledge about Swedish Heart Intensive Care Admission [RIKS-HIA]) [23]. Different periods of EHS recruitment conducted 5 years later may explain the discrepancies particularly in the use of statins. Moreover prior heart failure and cerebrovascular and peripheral artery disease were not introduced as potential confounders in the RIKS-HIA multiple regression model. An underutilization of coronary angiography, percutaneous coronary intervention (PCI) and stenting described in the first Munich registry in 1999 had improved 2 years later [24].

Strategies for secondary prevention were investigated in 2854 patients with stable CAD [22], with reference to guidelines available at the time for patient recruitment [25, 26]. At admission, 1894 (66%) patients with stable CAD were on statins and 55% of those with and 47% of those without diabetes had total cholesterol levels (and 57% and 51% LDL cholesterol levels) above recommended targets of 5.0 mmol/l and 3.0 mmol/l, respectively. Regardless of the presence of diabetes, 35% had HDL cholesterol below the target of 1.0 mmol/l. A total of 2127 (75%) patients were on blood pressure lowering agents at admission, yet about 30% of these had a blood pressure above the recommended target of 140/90 mmHg. As far as glucose lowering treatment is concerned, about half of the diabetic patients with stable CAD on insulin ($n = 262$; 30%) or oral glucose lowering agents ($n = 492$; 57%) had fasting hyperglycemia (FPG >7.2 mmol/l).

The overall adherence to treatment targets was poor and would had been even worse if targets outlined in the most recent European guidelines for CVD prevention or for diabetes, prediabetes and CVD had been applied [16, 27]. The European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) I and II surveys reported similar findings with blood pressure ≥140/90 mmHg in, respectively, 57% and 49% and elevated total cholesterol >5.0 mmol/l in 55% and 59% of patients with established CAD. Concerning glucose control, 87% of diabetic patients in EUROASPIRE II had an FPG >6.0 mmol/l and 72% >7.0 mmol/l [28]. Referring to the glycemic targets recommended by the ADA in 2004 [29], a very low proportion reached optimal glucose control (59% of patients had an HbA_{1c} >7 mmol/l and 73% an FPG >7.2 mmol/l) [30].

Multifactorial evidence-based management

The management of patients with CVD has improved considerably. Patients with diabetes have, however, not benefited as much as those without [8], making it of particular interest to study the use and impact of evidence-based therapy in the EHS. Of the patients originally enrolled, 4676 (94%) were followed for 1 year with respect to treatment, survival and cardiovascular events. Patients who received polypharmacological treatment including RAAS inhibitors, β-blockers, statins and oral platelet stabilizing agents were classified as belonging to an evidence-based medicine group. Patients with declared contraindications to the use of one or more of these drugs were excluded. Thus patients classified as not receiving evidence-based medicine were those left untreated despite



	HR	95% CI	*p*
All-cause mortality	0.37	0.20–0.67	0.001
	0.72	0.39–1.32	0.275
All-cause mortality or myocardial infarction	0.46	0.29–0.74	0.001
	0.55	0.34–0.90	0.015
Combined cardiovascular events	0.61	0.40–0.91	0.015
	0.61	0.39–0.95	0.025

Fig. 4: *Adjusted hazard ratios (HR) for the interaction between the presence of diabetes and the prescribed treatment (blue denotes evidence-based treatment; green denotes revascularization).*

the absence of any contraindications. The revascularization group included patients treated with thrombolysis, PCI or coronary artery bypass grafting during the index hospitalization [31].

Diabetic patients on evidence-based medication had lower all-cause mortality (3.5% vs. 7.7%; $p = 0.001$) and fewer combined cardiovascular events (11.6% vs. 14.7%; $p = 0.05$) compared with those not receiving such treatment. Likewise, revascularized diabetic patients had lower all-cause mortality (5.7% vs. 8.6%; $p = 0.042$) and fewer cardiovascular events (9.9% vs. 16.9%; $p < 0.001$) compared with those who were not revascularized. As shown in *Figure 4*, the impact of evidence-based medication and revascularization was significant even after adjustment for potential confounders.

The prognosis after CAD is more severe in patients with than in those without diabetes and the reasons may be that evidence-based medication and revascularization are less commonly applied in this cohort of patients [32, 33] or that treatment modalities with proven efficacy in a population without diabetes is less efficient in diabetic patients. Controlled trials addressing well-defined groups of diabetic patients are not common. Accordingly the impact on the balance between benefit and harm attributable to many drugs and treatment strategies is not known [34]. Moreover the analyses commonly address single drugs rather than treatment strategies, in contrast to the results of the EHS which clearly indicate that it is multifactorial treatment that is effective. That high-risk patients with established type 2 diabetes and microalbuminuria benefit from a broad approach aimed at all modifiable risk factors is supported by the Steno-2 trial. In this trial, target-driven, multifactorial intervention significantly reduced the risk of CVD, nephropathy, retinopathy and autonomic neuropathy [35]. The intensive multifactorial therapy affected the prognosis even more strikingly in the extended 13-year follow-up of the trial, with an absolute mortality reduction of 20% [36].

The indications for revascularization were left in the hands of the physicians in charge, nevertheless allowing a comparison of efficacy between patients with and without diabetes. In this respect the EHS findings support the MONICA registry [37] that thrombolytic drugs were more powerful in reducing risk ratios in patients with diabetes (risk ratio 0.57 vs. 0.65, respectively).

A multifactorial management approach should be considered a priority in diabetic patients

In the light of these data a multifactorial management approach should be considered a priority in diabetic patients. The recently issued joint European Society of Cardiology and European Association for the Study of Diabetes guidelines on diabetes, prediabetes and CVD recommend increased collaboration between cardiologists and diabetologists to improve the management of CVD and dysglycemia [16]. The 'cardio-diabetologic' approach that hopefully will arise with this collaboration is expected to improve outcomes in this patient category. Their substantially elevated risks necessitate a comprehensive risk assessment followed by adequate multifactorial treatment of all modifiable risk factors.

Impact of glucose metabolism management on cardiovascular prognosis

The patients with known diabetes enrolled in the EHS were allocated into four groups based on

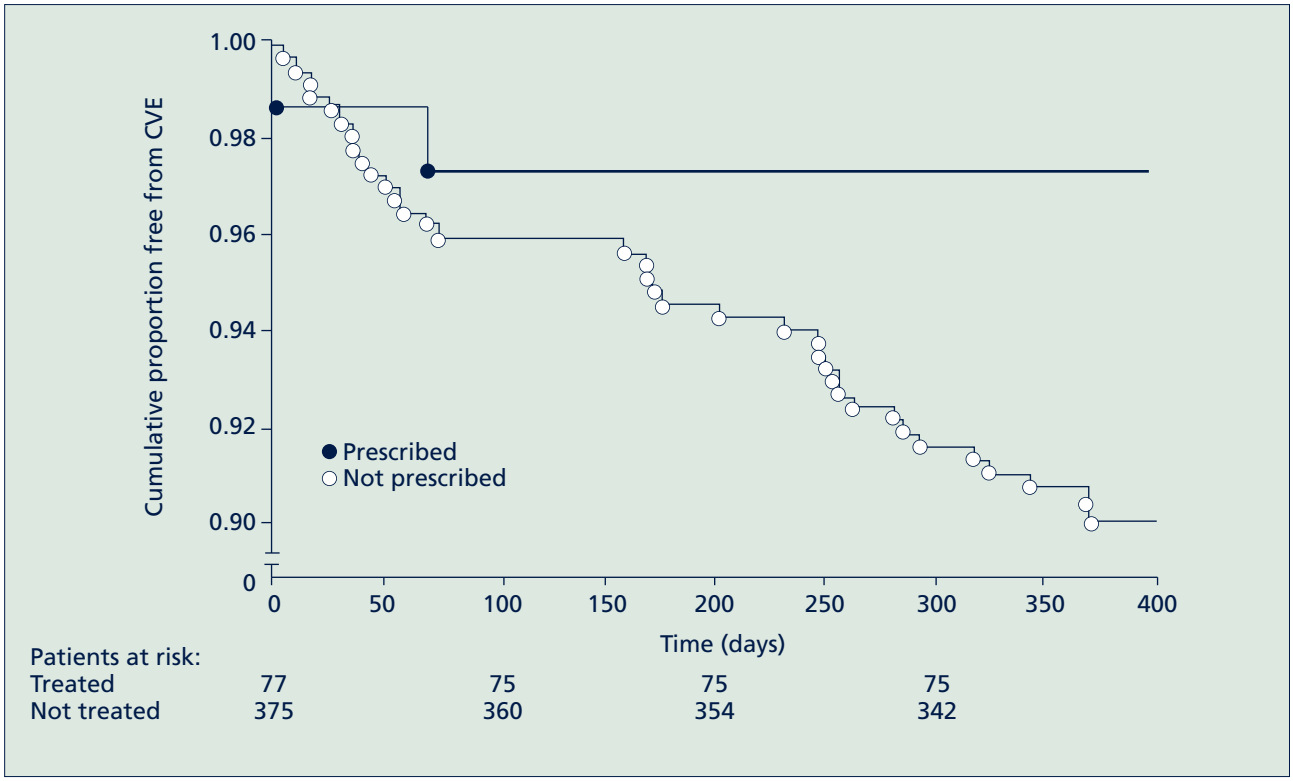


Fig. 5: *Kaplan-Meier curves for combined cardiovascular events (CVE) in patients with newly detected diabetes prescribed or not prescribed pharmacological glucose lowering treatment (log-rank test, p = 0.047).*

their glucose lowering treatment at follow-up: 378 (28%) were treated with insulin, 675 (54%) with oral glucose lowering agents, 76 (6%) with a combination of insulin and oral glucose lowering agents, and 152 (12%) with no pharmacological glucose lowering treatment [38]. Following adjustment for potential confounders, a proportional hazard (Cox) regression model disclosed a higher ratio for all-cause mortality (hazard ratio 2.23, 95% CI 1.24–4.03; p = 0.006) in the insulin compared with the oral glucose lowering group.

The Diabetes Mellitus, Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trials studied different glucose lowering modalities in patients with previously known diabetes and an AMI [39, 40]. 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 had also been described in critically ill patients with hyperglycemia in intensive care units [41]. By contrast, the DIGAMI 2 trial did not reveal any mortality advantages with insulin compared with oral glucose lowering therapy. The given explanation was that glucose control did not differ between patients on insulin and those on oral glucose lowering agents, indicating that insulin does not have any beneficial effects in itself. Patients on insulin usually have more advanced disease. Nonetheless seemingly harmful effects of insulin on cardiovascular mortality and morbidity have been reported in heart failure patients with diabetes [42, 43]. Johnsen et al. [44] performed a registry-based review of glucose lowering drugs given to patients hospitalized for a first AMI. Those prescribed insulin had a higher rate of infarctions than those on oral glucose lowering agents during follow-up. Similar observations emerged in a substudy of the DIGAMI 2 trial, reporting on an increased risk of non-fatal AMI and stroke (hazard ratio 1.73, 95% CI 1.26–2.37; $p < 0.001$) in insulin-treated patients compared with those on oral glucose lowering agents. The negative impact of insulin was still seen in patients not previously treated with insulin but randomized to it according to the study protocol [45]. These and the EHS findings should therefore be taken seriously and encourage clinical trials designed to clarify this particular subject.

Hitherto it has been uncertain whether the institution of pharmacological glucose lowering in patients with CAD and newly detected glucose perturbations may improve future prognosis. The EHS provides important indications that it may be beneficial. Out of the 452 patients with newly detected diabetes at follow-up, 77 (17%) had been prescribed pharmacological glucose lowering treatment. The vast majority (n = 72; 94%) were given oral glucose lowering agents, a few insulin or a combination of oral

agents and insulin, while the remaining 375 (83%) patients received no such drugs. During the year of follow-up none of the patients on glucose lowering treatment died compared with 25 of those who were untreated ($p = 0.002$), and 1 vs. 13 and 1 vs. 5 patients suffered from AMI and stroke, respectively *(Fig. 5)*. Patients on pharmacological glucose lowering treatment, compared with those without, had an adjusted 1-year hazard ratio for cardiovascular events of 0.22 (95% CI 0.05–0.97; $p = 0.041$) [38].

The EHS supports the usefulness of the early institution of pharmacological glucose lowering therapy in patients with newly detected diabetes and CAD

The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM), which was primarily designed to investigate the possibility of preventing the progression of patients with IGT towards diabetes by means of acarbose, demonstrated a 49% relative risk reduction in the 3-year risk of cardiovascular events compared with placebo [46]. In addition, data from this and six other long-term trials were assessed in the Meta-Analysis of Risk Improvement with Acarbose (MeRIA) study [47], which reported a 35% reduction in the risk of a cardiovascular event in type 2 diabetic patients receiving acarbose vs. placebo ($p = 0.0061$). The interesting and potentially very important findings of the EHS parallel these observations of the usefulness of the early institution of pharmacological glucose lowering therapy in patients with newly detected diabetes and CAD.

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