Early Detection and Integrated Management of Dysglycemia in Cardiovascular Disease: A Key Factor for Decreasing the Likelihood of Future Events

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Dysglycemia is widespread among patients with coronary artery disease. It is indeed more common than normoglycemia in these patients. Coexistence of cardiovascular disease and dysglycemia presents significant health risks, and evidence suggests that both conditions should be treated early to reduce the development of complications. Guidelines recommend testing for prediabetes and type 2 diabetes in the cardiology setting and highlight the use of therapies that treat metabolic and cardiovascular risk factors. Blood glucose levels have previously been the interest of diabetologists, but modern integrated management approaches should include assessment by a cardiologist. We propose that postprandial blood glucose testing be carried out routinely in all patients with coronary artery disease, and that newly diagnosed dysglycemia be actively managed.

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Key words: • Dysglycemia • Diabetes • Prediabetes • Oral glucose tolerance test • Glucose-lowering drugs • Cardiovascular disease risk

A high percentage of patients with cardiovascular disease (CVD) have impaired glucose metabolism,[1-3] also known as dysglycemia. This progressive condition ranges from prediabetes to advanced type 2 diabetes, and often remains undiagnosed until it is exposed by serious complications.[4] However, all stages of dysglycemia are associated with an increased risk of cardiovascular morbidity and mortality,[5-6] making it important to identify dysglycemia as early as possible. Collaboration between cardiologists and diabetologists is essential to

achieve this objective, to increase awareness of the coexistence of these diseases and to provide realistic treatment targets. This review will discuss the growing evidence for an association between CVD and dysglycemia, the tools available to aid the cardiologist in the early diagnosis of dysglycemia, and the recent guidelines that recommend integration of treatments to achieve a "cardiodiabetologic" approach.

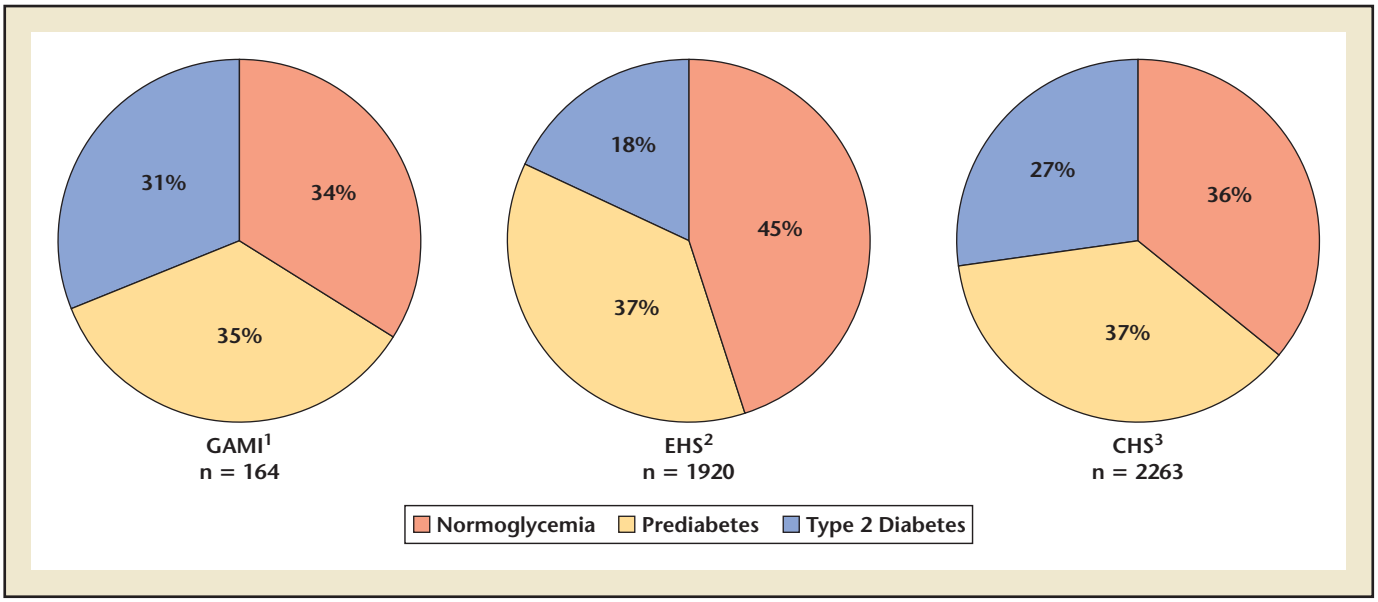
Prevalence of Dysglycemia in Patients With CVD

Three prospective studies have indicated that dysglycemia—including prediabetes and type 2 diabetes—is more common than normoglycemia in patients with CVD (Figure 1).[1-3] The Glucose Tolerance in Patients with Acute Myocardial Infarction (GAMI) study was designed to detect the prevalence of dysglycemia in patients admitted to the hospital with acute myocardial infarction (MI).[1] An oral glucose tolerance test (OGTT; for technical details, see below) was performed according to World Health Organization (WHO) recommendations[7] at hospital discharge, about 4 to 5 days after the MI (n = 164), and again 3 months later (n = 144). Dysglycemia was detected in approximately two-thirds of patients at hospital discharge—35% had prediabetes and 31% had newly diagnosed type 2 diabetes (Figure 1). A similar prevalence was recorded 3 months later, suggesting that the increased sympathetic drive induced by the acute illness was not the main reason for the metabolic imbalance, and that testing before hospital discharge provided an accurate reflection of the glucometabolic status.

Similar findings were reported in 2 larger studies, the 25-country Euro Heart Survey[2] and the China Heart Survey.[3] The Euro Heart Survey collected data on European patients (N = 3444) with acute and stable coronary artery disease (CAD).[2] Approximately one-third of these patients (n = 1524) had known diabetes at the study start. An OGTT was performed in 1920 of the patients without known diabetes, which revealed that fewer than half of those tested had normoglycemia, 37% had prediabetes (impaired glucose tolerance), and 18% had newly diagnosed type 2 diabetes (Figure 1).[2] Overall, 75% of the 3444 patients in the study had dysglycemia. The China Heart Survey,[3] conducted in Chinese patients, had the same study design as the Euro Heart Survey and enrolled 3513 patients with CAD.[3] Type 2 diabetes was known in approximately one-third of those recruited for the study. An OGTT was performed in the remaining 2263 patients, which revealed type 2 diabetes in 27% and prediabetes in another 37%.[3] Overall, dysglycemia was detected in more than three-quarters of the study population (Figure 1).

Together, the GAMI, Euro, and China Heart Surveys provide evidence of a high prevalence of dysglycemia among patients with CVD, highlighting the need for improved strategies for glucometabolic health

Figure 1. *Dysglycemia, including prediabetes and type 2 diabetes, was more common than normoglycemia in 3 studies of patients admitted to the hospital with cardiovascular disease. Figures reflect patient cohorts who were not diagnosed with diabetes at the study start, but who underwent an oral glucose tolerance test (OGTT). GAMI, Glucose Tolerance in Patients with Acute Myocardial Infarction study; EHS, Euro Heart Survey; CHS, China Heart Survey.* www.medreviews.com



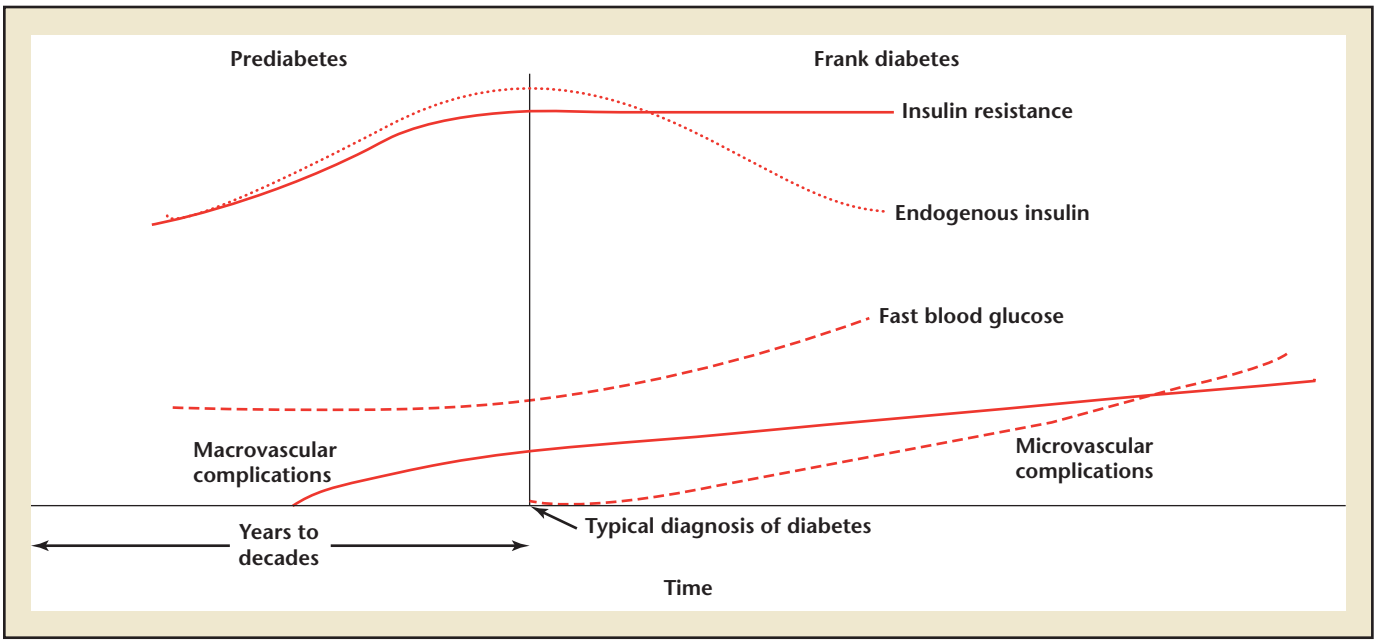


Figure 2. *Insulin resistance, impaired insulin secretion, and fasting blood glucose in relation to microvascular and macrovascular disease. Reprinted from Laakso M, Kuusisto J. Understanding patient needs: diabetology for cardiologists.* Eur Heart J. *2003;5(suppl B):B5-B13*[15] *with permission of the European Society of Cardiology.* www.medreviews.com

assessment and management in these patients. Furthermore, these studies indicate that undetected dysglycemia in patients with CAD is a universal problem and presents an important medical opportunity for both cardiologists and diabetologists.

Risks Associated With Dysglycemia

Despite increasing survival rates for patients with CVD, the prognosis for those who also have diabetes remains poor, not only because of the greater extent of their coronary disease[8] but also because of the failure of current strategies to effectively treat the diabetes component.[9,10] Dysglycemia alone is a major risk factor for macrovascular[11] and microvascular[12-14] complications that impair quality of life and diminish survival, and the coexistence of CVD and dysglycemia in the same individual increases this risk considerably. Moreover, macrovascular complications start to manifest early in the dysglycemia disease continuum. A significant proportion of dysglycemic individuals develop vascular damage during the prediabetes stage, although the glucometabolic perturbations often remain undetected until the first cardiovascular event.

Postprandial hyperglycemia is a major underlying cause of the pathology of dysglycemia complications. Postprandial hyperglycemia occurs in dysglycemic individuals when the pancreatic β-cells fail to release enough insulin to overcome the enhanced peripheral insulin resistance and plasma glucose excursions become elevated (Figure 2).[15]

The resulting glucotoxicity activates pathological processes such as oxidative stress, which causes dysfunction of the pancreatic β-cells[16] and atherogenic pathways.[17] Such processes have clinical implications for the patient as demonstrated in the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study. This landmark study found postprandial hyperglycemia to be an independent risk factor for premature mortality, with CVD the most common cause of death.[18] Numerous other studies have contributed to the considerable body of evidence supporting a close association between postprandial hyperglycemia and cardiovascular mortality.[5,6,19,20]

Progression of the dysglycemia continuum is associated with worsening cardiovascular health. The incidence of all-cause mortality in the Euro Heart Survey 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 (Figure 3).[21,22] In addition, the risk of experiencing an MI during the 1-year follow-up was twice as high in patients with known diabetes compared with patients with normoglycemia (5.3% vs 2.5%).[21] Estimates predict that 40% to 50% of individuals with prediabetes will develop type 2 diabetes within 10 years,[23] highlighting the importance of early detection of dysglycemia to prevent

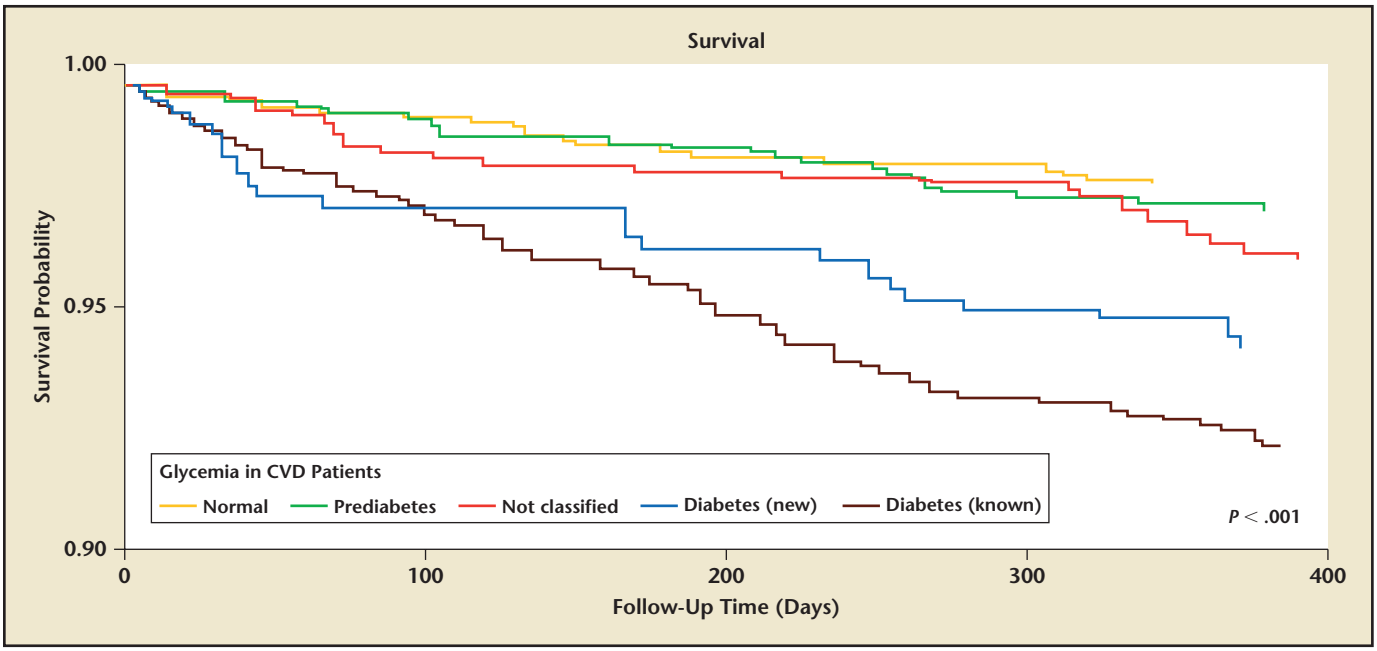


Figure 3. *Patients with CVD and known diabetes had the lowest survival probability in the 1-year follow-up period of the Euro Heart Survey. CVD, cardiovascular disease. Reprinted from Lenzen M, Ryden L, Ohrvik J, et al. Diabetes known or newly detected, but not impaired glucose regulation, has a negative influence on 1-year outcome in patients with coronary artery disease: a report from the Euro Heart Survey on diabetes and the heart.* Eur Heart J. *2006;27:2969-2974*[21] *with permission of the European Society of Cardiology.* www.medreviews.com

the progression of prediabetes to type 2 diabetes.

Economic Implications

Effective management of dysglycemia is of economic as well as medical importance. The increased health risks associated with the late stages of dysglycemia incur expensive treatment procedures.[24] A study conducted in the German healthcare system (N = 3268) found that the costs associated with type 2 diabetes increased 2.7-fold between the first and eighth years following diagnosis,[24] owing mostly to the development of complications during the interim period. Furthermore, the proportional cost of complications increased from approximately 40% of total costs in the first year after diagnosis to approximately 70% in the eighth year. Early diagnosis and management of dysglycemia reduces the incidence of complications, and is therefore a cost-effective strategy in the long term.[25]

Table 1
Diagnosis of Normoglycemia and Different Stages of Dysglycemia According to WHO/IDF[31] and ADA[32] Criteria

Glucometabolic State	Source	Classification Criteria mmol/L (mg/dL)*
Normal	WHO/IDF	FPG < 6.1 (110) + 2hPG < 7.8 (140)
	ADA	FPG < 5.6 (100)
Impaired fasting glucose	WHO/IDF	FPG ≥ 6.1 (110) and < 7.0 (126) + 2hPG < 7.8 (140)
	ADA	FPG ≥ 5.6 (100) and < 7.0 (126)
Impaired glucose tolerance	WHO	FPG < 7.0 (126) + 2hPG ≥ 7.8 and < 11.1 (200)
Diabetes mellitus	WHO	FPG ≥ 7.8 (126) or 2hPG ≥ 11.1 (200)
	ADA	FPG ≥ 7.0 (126)

WHO, World Health Organization; IDF, International Diabetes Federation; ADA, American Diabetes Association; FPG, fasting plasma glucose; 2hPG, 2-hour post-challenge plasma glucose.
*Conversion factor: 1 mmol/L = 18 mg/dL.

Diagnosing Dysglycemia in Patients With CVD

Despite cardiologists' increasing awareness of dysglycemia, there has been a reluctance to diagnose the prediabetes stage, due to a lack of complete understanding of the condition.[26-28] Criteria to diagnose dysglycemia are provided in Table 1.

Fasting plasma glucose (FPG) levels are measured after the patient has

not eaten for 8 hours, whereas postprandial plasma glucose levels are measured 2 hours following a standardized meal. The OGTT is used in the clinic to measure 2-hour postchallenge plasma glucose (2hPG) levels, which correspond closely with postprandial levels.[29] The OGTT involves a glucose challenge, in which patients drink 75 g of glucose dissolved in water, with blood sampling at baseline (FPG level) and after 2 hours (2hPG level).[29,30] The OGTT is recommended for the diagnosis of dysglycemia.[31,32] The OGTT is particularly useful in patients at high risk for glucometabolic perturbations, such as those with CVD.[26] Guidelines for managing patients with diabetes, prediabetes, and CVD state that all patients with CVD should be tested if their glucometabolic condition is not already known.[31,33] A diagnosis based on fasting glycemia alone would underdiagnose the prevalence of dysglycemia. The Euro Heart Survey reported that two-thirds of patients with positive OGTTs would have remained undiagnosed if only FPG levels had been considered.[34] Similarly, in the China Heart Survey, more than 80% of the patients with dysglycemia would have remained undiagnosed if FPG levels had been considered instead of OGTT 2hPG levels.[3]

Elevated FPG levels indicate fasting hyperglycemia, whereas elevated 2hPG levels indicate postprandial hyperglycemia. Impaired fasting glycemia and impaired glucose tolerance are forms of prediabetes characterized by fasting and postprandial hyperglycemia, respectively (Table 1). Individuals may have both fasting and postprandial hyperglycemia. However, patients with dysglycemia may have normal FPG levels but elevated postprandial blood glucose levels. Thus, a 2hPG level measured by OGTT is a better predictor of the dysglycemic state than FPG and also a better risk predictor for subsequent cardiovascular complications.[5,6,18,35,36] For example, the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Asia (DECODA) trial analyzed the effect of including 2hPG and FPG levels in models to predict all-cause and cardiovascular mortality.[37] The inclusion of 2hPG levels in an FPG-level model significantly improved the predictability ($P < .001$), but inclusion of FPG levels in a 2hPG-level model had no such effect.[20]

These epidemiology studies support the routine use of OGTTs in the cardiology setting. This test is a straightforward, noninvasive, and cost-effective approach that has the potential to significantly improve the detection of metabolic abnormalities in patients with CVD.

. . . patients with dysglycemia may have normal FPG levels but elevated postprandial blood glucose levels.

Integrating Therapies for Dysglycemia and CVD

Guidelines recommend increased collaboration between cardiologists and diabetologists to improve the management of CVD and dysglycemia.[38] The European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD) have recently published joint guidelines that present an algorithm for the diagnosis of dysglycemia in patients with CVD, and for the diagnosis of CVD in patients with type 2 diabetes (Figure 4). These guidelines outline appropriate diagnostic tests for detecting dysglycemia and CVD.[33]

The "cardiodiabetologic" approach that will arise from closer collaboration between cardiologists and diabetologists is necessary to improve care for patients with CVD and dysglycemia. The elevated health risks in these patients necessitate that they undergo extensive risk assessment and are provided with a comprehensive, multifactorial management plan, taking all risk factors into account. The ESC/EASD guidelines provide an investigational algorithm to aid the diagnostic component of this plan, as well as specific treatment goals for patients with CVD and dysglycemia. Diabetology and cardiology specialists should aim to help patients achieve these treatment targets in a timely fashion to optimize patient outcomes.

Treating Dysglycemia in Patients With CVD

The European guidelines recommend that the postprandial plasma glucose level be below 7.5 mmol/L (135 mg/dL) and the FPG level be below 6.0 mmol/L (108 mg/dL).[33] The guidelines state that routine care of people at high risk of type 2 diabetes and CVD should always be based on lifestyle modifications.[33] Studies have shown that structured counseling regarding a healthy diet and regular exercise can improve glycemic control and prevent—or at least delay—the development of overt diabetes in patients with prediabetes, and thus reduce the risk of CVD-linked mortality.[39-42] However, additional therapy is usually required to help the diabetic patient achieve glucometabolic targets.

Special consideration must be given to treatment options for patients with dysglycemia and CVD, to allow selection of appropriate oral glucose-lowering drugs that also provide cardiovascular benefits. A number of trials have investigated the

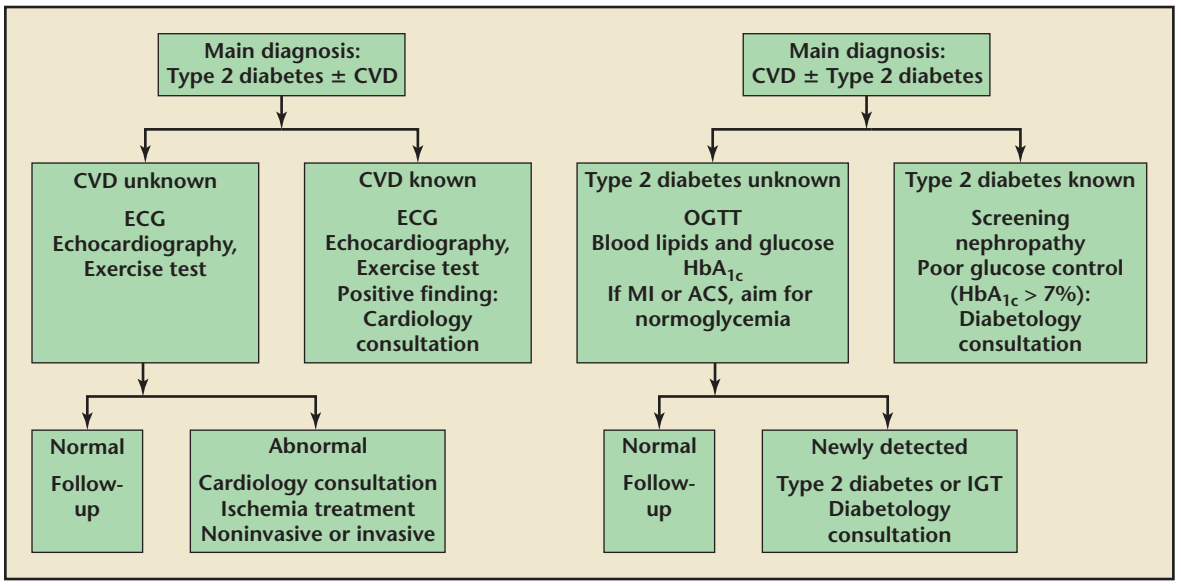


Figure 4. *Investigational algorithm for patients with CVD and/or diabetes, adapted from European Society of Cardiology/European Association for the Study of Diabetes joint guidelines on diabetes, prediabetes, and cardiovascular diseases. T2D, type 2 diabetes; CVD, cardiovascular disease; ECG, electrocardiogram; OGTT, oral glucose tolerance test; HbA_{1c}, glycosylated hemoglobin; MI, myocardial infarction; ACS, acute coronary syndrome; IGT, impaired glucose tolerance. Adapted with permission from Rydén L et al.*[33] www.medreviews.com

effects of such drugs on the risk of cardiovascular events in patients with prediabetes and type 2 diabetes, and have produced varying results. In addition, there is potentially a need to treat dysglycemia during the early stages of the disease continuum. However, so far only one oral drug—acarbose—is approved for the treatment of prediabetes.

Two trials have investigated the effects of metformin on cardiovascular health in dysglycemic patients. The UK Prospective Diabetes Study (UKPDS) reported that metformin was associated with lower risks of MI and all-cause mortality compared with conventional dietary advice (both $P = .01$) in patients with type 2 diabetes.[43] This observation gained further support with a recent report from the DIGAMI 2 trial that recruited patients with type 2 diabetes and MI. After controlling for confounders, including glycemic control, there was no significant difference in long-term mortality among patients treated with sulphonylureas, metformin, and insulin. The risk for nonfatal myocardial reinfarction and stroke did, however, increase with insulin treatment, whereas metformin was protective and sulphonylureas were neutral.[44] The Diabetes Prevention Program (DPP) failed to show cardiovascular benefits with metformin in individuals with prediabetes, but did demonstrate that metformin reduces the incidence of diabetes in this population (31%; $P < .001$ vs placebo).[39]

Presently, the use of the thiazolidinedione (TZD) class of glucose-lowering drugs is the subject of much controversy. Safety data from a pooled analysis of controlled clinical trials demonstrated a significant, although small, increase in the risk of heart attack in patients taking rosiglitazone. There was an increase in cardiovascular mortality in patients taking rosiglitazone, but the trend missed statistical significance ($P = .06$).[45] Another meta-analysis of studies with at least 12 months of follow-up presented similar results regarding the risk for MI, although not for mortality.[46] The trials included in these meta-analyses provide contradictory evidence about the risk of ischemic cardiovascular events in patients treated with rosiglitazone. The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial, which enrolled 5269 patients with prediabetes and no history of CVD, reported that rosiglitazone reduced progression to type 2 diabetes over 3 years (62%; $P < .0001$ vs placebo).[47] The incidence of cardiovascular events, assessed as a secondary endpoint, was not significantly different in the rosiglitazone and placebo groups, although heart failure was more common among patients in the rosiglitazone group than in the placebo group ($P = .01$). Another TZD, pioglitazone, was investigated in the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) of 5238 type 2 diabetes patients with macrovascular disease.[48] There was no significant

difference between the pioglitazone and placebo groups for the primary composite endpoint of all-cause mortality, cardiovascular events, and vascular morbidity; the incidence of all-cause mortality, nonfatal MI, or stroke, a secondary endpoint, was lower in the pioglitazone group (P = .027). A subsequent meta-analysis of pioglitazone trials concluded that this drug is associated with a lower risk of death and cardiovascular events among patients with diabetes. Serious heart failure was, however, increased, without an associated increase in mortality.[49] Based on these and other studies, both rosiglitazone and pioglitazone are currently contraindicated in patients with heart failure or a history of heart failure.[50,51] Whether there is a true difference in outcome between these 2 glitazones will be further evaluated in several ongoing controlled clinical trials. Whatever the outcome may be, the recent controversy has highlighted the fact that treating diabetes without addressing CVD may institute an unfavorable balance between the risk and benefit of glucose control.

The α-glucosidase inhibitor acarbose is approved globally for the treatment of type 2 diabetes and in 25 countries for the treatment of prediabetes. As the only oral glucose-lowering drug approved for prediabetes therapy to date, acarbose is suitable for the treatment of patients at all stages of the dysglycemic disease continuum. This drug lowers postprandial plasma glucose levels,[52-55] targeting the postprandial plasma glucose spikes that are considered important for the pathology of dysglycemia and contribute to the atherogenic process. Progression of dysglycemia to overt type 2 diabetes is reduced in individuals with prediabetes who use acarbose,[56-58] and there is some evidence for the usefulness of this agent in primary prevention of cardiovascular events.[59] The multicenter, randomized Study to Prevent Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM; N = 1429) reported that acarbose reduced the relative risk of developing type 2 diabetes by 36% over 3 years. Diabetes was diagnosed in 105 out of 682 patients in the acarbose group versus 165 out of 686 patients in the placebo group (P = .0003).[57] In addition, secondary endpoint analyses demonstrated that acarbose reduced the risk of cardiovascular events by 49%. Cardiovascular events occurred in 15 out of 682 patients in the acarbose group versus 32 out of 686 patients in the placebo group (P = .03). This reduction includes a 91% decrease in the risk of clinical MI (which occurred in 1 out of 682 patients in the acarbose group vs 12 out of 686 patients in the placebo group [P = .02]).[60] Acarbose was also associated with a significant reduction in new cases of hypertension: 115 new diagnoses were made in the placebo group compared with 78 in the acarbose group, a risk reduction of 34%.[60] Data from 7 long-term trials were assessed in the Meta-Analysis of Risk Improvement with Acarbose (MeRIA), which reported a 35% reduction in the risk of a cardiovascular event in type 2 diabetes patients receiving acarbose (P = .0061 vs placebo).[61]

Acarbose has a good safety profile.[62-65] The adverse effects associated with this drug are initial mild-to-moderate gastrointestinal reactions, many of which can be prevented by a stepwise approach to increasing dosage.[62,66] Unlike many other glucose-lowering therapies, acarbose is not associated with weight gain or hypoglycemia, and it has few contraindications.[62,67] These data must be confirmed by randomized trials that investigate cardiovascular health as a primary endpoint in a large population.

The idea that early institution of glucose-lowering therapy may be beneficial in patients with CAD and newly detected type 2 diabetes has recently been underlined by observations made in the Euro Heart Survey on Diabetes and the Heart, which recruited patients with CAD. Among 452 patients with newly detected diabetes, 77 (17%) were started on glucose-lowering drugs. During the first year of follow-up, no deaths were seen among patients on the study drugs, as compared with 25 deaths in patients not receiving the drugs. During the same period, the hazard ratio for a cardiovascular event was 0.22 in treated subjects as compared with untreated subjects (95% confidence interval [CI], 0.05-0.97; P = .041).[68]

Considering the promising results with the early institution of glucose-lowering therapy shown by the STOP-NIDDM trial and the Euro Heart Survey, it is obvious that there is a need for further information from prospective clinical trials addressing the potential of various treatment modalities. One such trial is the Acarbose Cardiovascular Evaluation (ACE) trial. This randomized, placebo-controlled trial is investigating the effect of acarbose, with secondary prevention of cardiovascular events as a primary endpoint. The trial commenced in 2007, and will follow approximately 7500 patients with established CVD and prediabetes for a minimum of 4 years.[69] Another trial of interest in this area is the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) study. This trial includes patients with evidence of CVD and with impaired glucose tolerance and newly detected or established diabetes, who are randomized to either one daily injection of insulin glargine with the dose titrated to achieve normoglycemia or to standard glycemic

care. The primary outcome is cardiovascular death and CVD events.[70] Thus, the ORIGIN trial will determine whether early institution of insulin will reduce CVD morbidity or mortality. This study has recruited 12,612 patients across 40 countries, and the results are expected in 2011.

Conclusion

Greater awareness of the prevalence of dysglycemia in patients with CVD will help to improve diagnosis and treatment and reduce the associated health risks. Just as diabetologists are familiar with the threat of CVD in patients with diabetes, cardiologists should encourage testing for dysglycemia in all patients with CVD. Early intervention is essential to prevent progression of dysglycemia. Routine OGTTs are advised for all patients with CAD, and such testing is feasible for use in the clinic as part of ongoing CVD management. Patients diagnosed with dysglycemia and CVD should be treated appropriately to achieve strict glucose targets, using effective drugs such as acarbose when diet and exercise alone fail to improve cardiometabolic health. Most importantly, close collaboration with diabetologists is required to achieve a fully integrated treatment strategy that effectively manages both diseases. ■

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Main Points

- All stages of dysglycemia are associated with an increased risk of cardiovascular morbidity and mortality, making it important to identify dysglycemia as early as possible.
- Three prospective studies have indicated that dysglycemia—including prediabetes and type 2 diabetes—is more common than normoglycemia in patients with cardiovascular disease (CVD).
- Despite increasing survival rates for patients with CVD, the prognosis for those who also have diabetes remains poor, not only because of the greater extent of their coronary disease but also due to the failure of current strategies to effectively treat the diabetes component.
- A significant proportion of dysglycemic individuals develop vascular damage during the prediabetes stage, although the glucometabolic perturbations often remain undetected until the first cardiovascular event.
- Special consideration must be given to treatment options for patients with dysglycemia and CVD, to allow selection of appropriate glucose-lowering drugs that also provide cardiovascular benefits.

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