Is Coronary Artery Disease Inevitable in Type 2 Diabetes? From a Glucocentric to a Holistic View on Patient Management

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Type 2 diabetes represents a major threat to global health mainly because of its strong link to atherosclerotic vascular disease. From position 15 among the 20 leading causes of loss of disability-adjusted life-years in 2000, type 2 diabetes climbed to position 8 in 2016. The fact that ischemic heart disease and stroke, conditions for which diabetes is a major risk factor, hold the two leading positions confirms that diabetes is an important threat to health (1). Combining this information with a predicted increase in adults living with diabetes from 9.3% of the global population (463 million) in 2019 to 10.9% (700 million) in 2045, the majority with type 2 diabetes, further underlines that this menace is truly of an immense magnitude. In addition, impaired glucose tolerance (IGT) has been shown to be a risk factor for cardiovascular disease. The proportion of IGT is estimated to increase from 7.5% (374 million) of the adult population in 2019 to 8.6% (548 million) in 2045, with the largest increase in low- to middle-income countries. Of great concern is that about one-half of people with type 2 diabetes are undiagnosed, varying from 38% in high-income countries to 67% in low-income countries, limiting the possibility to prevent the development of diabetes-related complications. Diabetes already puts a strain on health economics; diabetes-related expenditure was estimated to be US$760 billion in 2019 and is expected to increase to US$845 billion in 2045 (2), with costs associated with cardiovascular complications dominating (3).

HISTORICAL NOTES

Cardiovascular complications of diabetes were unknown until the Nobel Prize–awarded discovery of insulin a century ago allowed people with diabetes to survive longer (4). Not until the 1960s–1970s did the first reports on an increased cardiovascular risk associated with diabetes make their appearance from several research groups (5–8). One of the first long-term observations on the relation between diabetes and cardiovascular disease came from Denmark, where Deckert et al. (9) followed 307 patients diagnosed with type 1 diabetes between 1907 and 1932 until death or by the end of 1972. These patients' mortality was two to six times higher than that of control subjects without type 1 diabetes, and 50% of the patients who developed diabetes before the age of 30 years did not reach age 50. Thirty-one percent died as a result of uremia and 26% as a result of myocardial infarction, while 30% became blind or developed severely impaired vision and 12% suffered amputation or gangrene of a lower limb (i.e., manifestations of micro- and macrovascular disease). Experimental (10) as well as human (11) studies verified the relation between microvascular disease, in particular retinopathy, and glycemic control, reporting that old age, long diabetes duration, and high levels of glycated hemoglobin A_{1c} (HbA_{1c}) were associated with a more dismal outcome. This association between long-standing hyperglycemia and cardiovascular disease in a more general sense was subsequently confirmed in several populations (12–14).

It was not until 1993 that evidence of the beneficial effects of a reduction of hyperglycemia was presented for the first time in patients with type 1 diabetes. The Diabetes Control and Complications Trial (DCCT) reported on a decreased frequency and severity of complications, including retinopathy and neuropathy, after insulin-based glucose control (15). This observation was followed by long-term reports on the

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reduction of a composite of cardiovascular death, myocardial infarction, angina pectoris or coronary revascularization (16), and nephropathy (17). The beneficial impact of glucose lowering in patients with type 2 diabetes was first reported by the UK Prospective Diabetes Study (UKPDS) in 1998 (18). Intensified early glycemic control in newly diagnosed diabetes by means of insulin, sulfonylurea, or metformin compared with conventional treatment (diet at that time) led to a decrease of microvascular complications and seemed to decrease macrovascular events during extended periods of follow-up, even after the study intervention had stopped, an impact that was labeled the legacy effect (19). Both DCCT and UKPDS must be considered as landmark investigations. That insulin is mandatory in patients with type 1 diabetes is undoubted. Today, the UKPDS findings should be interpreted in consideration of the conditions in which this trial was conducted. Back then, available background treatment did not comprise statins and modern blood pressure–reducing drugs, and acetylsalicylic acid had not been introduced as an antithrombotic agent in patients with cardiovascular disease. Thus, improved control of hyperglycemia was the only available preventive pharmacological alternative. In light of the observed association between increasing HbA_{1c} levels and cardiovascular complications, it was appealing to counteract the most apparent perturbation in patients with type 2 diabetes: hyperglycemia. However, subsequent attempts to decrease cardiovascular complications by means of strict glucose control in addition to a contemporary background therapy in patients with type 2 diabetes failed to protect from premature mortality and macrovascular complications, besides a small decrease in myocardial infarctions in one study, as reviewed by Turnbull et al. (20), Rodríguez-Gutiérrez and Montori (21), and Rydén et al. (22). Over time, we learned that the relation is more complex and still only partly understood.

ON THE RELATION BETWEEN TYPE 2 DIABETES AND CARDIOVASCULAR DISEASE

Acute Coronary Syndromes

That hyperglycemia could be a link between diabetes and myocardial infarction was suggested by Levine (23) and Cruickshank (24) in 1929 and 1931, respectively. Before the introduction of enzymatic indicators of myocardial injury, an increase in blood glucose was used as a diagnostic criterion of myocardial infarction as a cause of acute chest pain. The association between high blood glucose and acute myocardial infarction has since been confirmed in several studies. As summarized by Opie and Stubbs (25) in 1976, the degree of hyperglycemia was considered to be related to the severity of the infarction and the underlying hormonal changes as a result of stress, inducing an increased secretion of catecholamines and glucagon. That elevated plasma glucose during acute coronary syndromes may be a marker of disturbed glucose metabolism in need of treatment was originally not suspected for several reasons, such as limited-size populations, the lack of established diagnostic criteria, and the short-lived observations (26). By studying the impact of an elevated admission plasma glucose in patients with myocardial infarction without known diabetes, Norhammar et al. (27) concluded that glucose level seemed to be an independent predictor of long-term outcome, favoring the assumption that admission hyperglycemia might be not only a consequence of acute stress conditions but also an indicator of abnormal glucose tolerance.

Unrevealed Glucose Perturbations and Cardiovascular Disease

This observation led to the Glucose Tolerance in Patients with Acute Myocardial Infarction (GAMI) study, which tested the hypotheses that glucose abnormalities are common in patients with an acute myocardial infarction, that the glucometabolic condition can be identified early after the acute event, and that newly detected glucose abnormalities predict long-term prognosis. Patients with a myocardial infarction without known diabetes ($n = 168$) and control subjects ($n = 185$) without myocardial infarction and diabetes were subjected to an oral glucose tolerance test (OGTT). This revealed that 33% of the patients had type 2 diabetes and 34% had IGT, leaving 33% with a normal glucose metabolism. The corresponding proportions in the control population were 11%, 24%, and 65% (28,29). These results were subsequently confirmed in other populations, including patients with both acute and stable coronary artery disease (e.g., from Europe and China). The Euro Heart Survey (30), in which 4,901 patients with acute and stable coronary artery disease were investigated with an OGTT, revealed that a minority (29%) were normoglycemic, while 43% had diabetes (known 31%, newly detected 12%), IGT (25%), or impaired fasting glucose (3%). In China, Hu et al. (31) performed an OGTT in 2,263 patients with stable coronary artery disease of whom 36% were normoglycemic, 27% had newly detected diabetes, and 37% had IGT. Similar proportions of unrevealed glucose perturbations have also been documented in patients with peripheral and cerebral artery disease (32). The GAMI population was followed over a median time of 11.6 years (33): both newly detected type 2 diabetes and IGT were associated with a considerably worse cardiovascular prognosis than that seen among patients with a normal glucose metabolism. The dismal prognostic implication of newly detected IGT among patients with acute coronary syndromes (Fig. 1) has also been confirmed by George et al. (34) and Chattopadhyay et al. (35).

Prognostic Implications

The first reports of an accumulation of acute myocardial infarctions and the unfavorable prognosis in patients with diabetes were published by Biorck et al. (36) in 1958 and Sievers et al. (37) in 1961. They noted that diabetes was about five times more common in patients with myocardial infarction than in the general population, irrespective of age and sex, and that these patients had a poor prognosis. Kannel and McGee (38) are usually referred to as the pioneers in this field, but their data from the Framingham study appeared 25 years later. Several investigators confirmed the dismal prognosis of patients with diabetes and myocardial infarction in scattered populations in the precoronary care era. In the 1980s, Malmberg and Rydén (39) presented an unselected, consecutive series of 341 patients with myocardial infarction of whom 24% had a history of diabetes. They concluded that both in-hospital (25% vs. 16%; $P < 0.02$) and 1-year (53% vs. 28%; $P < 0.001$) mortality were higher in patients with diabetes than in those without. Thus, patients with myocardial infarction were common and had a poor prognosis despite the by-then-introduced improvements in coronary care. The gap in 1-year mortality between patients with and without diabetes was 52%. As can be exemplified by data from the Swedish coronary care

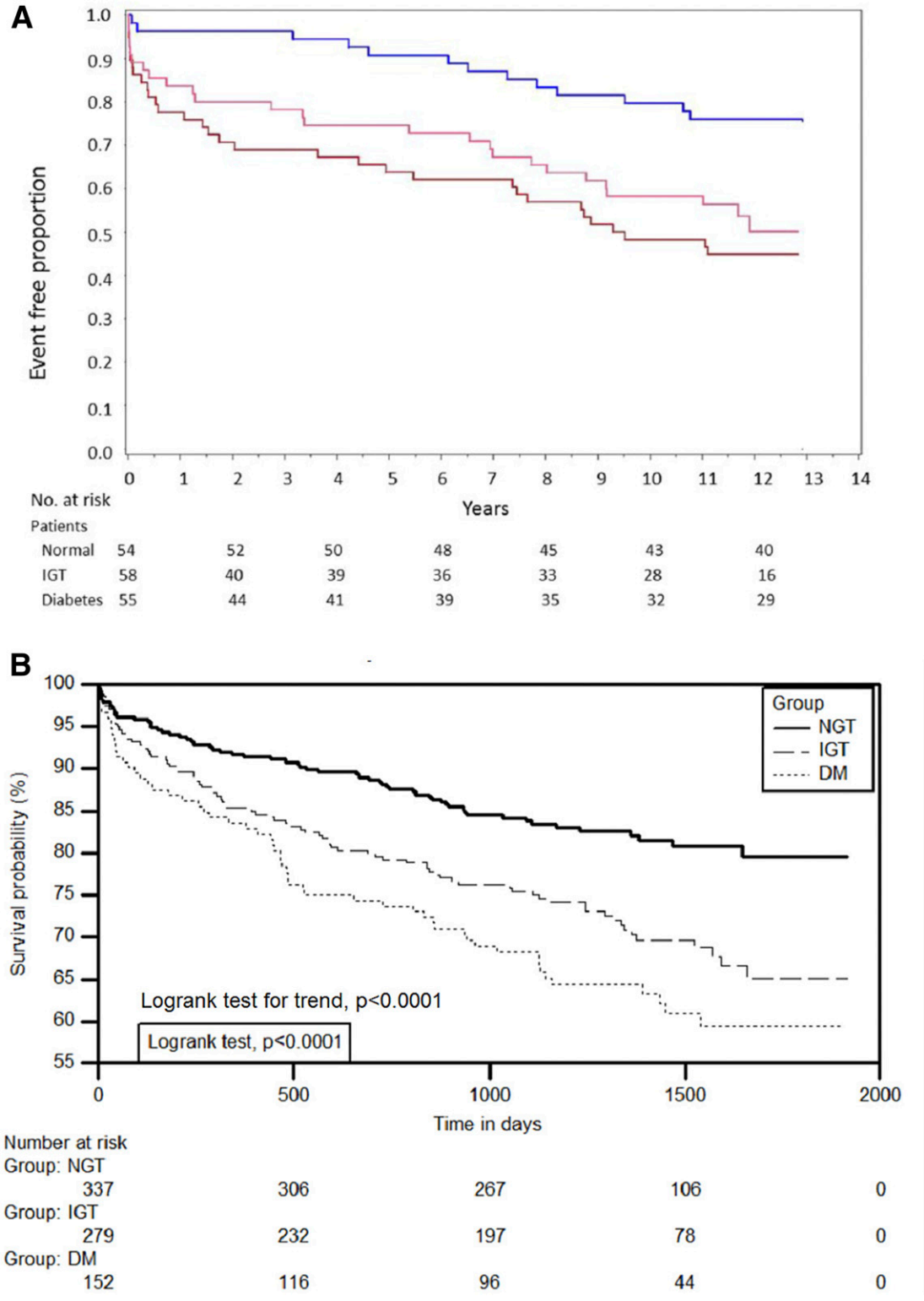

Figure 1—Kaplan-Meier curves. *A*: The GAMI trial showing time to a first major adverse cardiovascular event (cardiovascular death, nonfatal myocardial infarction, stroke, and severe heart failure) in patients by glucose tolerance group (normal glucose tolerance [NGT], blue; IGT, brown; diabetes [DM], pink) (log-rank overall $P = 0.0046$). Reprinted with permission from Ritsinger et al. (33). *B*: The Yorkshire study showing time to a first major adverse cardiovascular event. Reprinted with permission from George et al. (34).

unit registry (40), there has been a substantial improvement in 1-year survival for patients with and without diabetes, but the gap is still of the same magnitude (48% in 2018) (Fig. 2). This gap, which does not seem to be inevitable, is probably explained by three major factors: insufficient knowledge of the glycemic state in populations at risk, insufficient management of people with dysglycemia, and remaining gaps in knowledge, including a lack of the perfect

tool to normalize insulin resistance and dysglycemia.

INADEQUATE SCREENING

Macrovascular disease develops during several years before the diagnosis of type 2 diabetes according to the concept of a dysglycemic cardiovascular continuum (Fig. 3). Thus, it is reasonable to consider hyperglycemia as a continuously increasing cardiovascular risk factor that commences before the fasting and postprandial thresholds for overt diabetes (41–43). On the basis of this assumption, contemporary guidelines recommend screening for glucose perturbations in patients with cardiovascular disease (44). This recommendation is based on the fact that dysglycemia is harmful before the onset of diabetes, that dichotomizing a continuous risk variable is incorrect, and that previously undetected dysglycemia is common among patients with cardiovascular disease.

As it seems from Swedish (40) and U.S. data (45), we are facing an increasing number non–ST elevation myocardial infarctions in our coronary care units. Many of them are in overweight patients with insulin resistance, dysglycemia, and dyslipidemia. The GAMI study revealed that the metabolic profile of the patients with acute coronary syndromes differed significantly from that seen in matched control subjects without myocardial infarction in the following respects: lower HDL, higher triglycerides, higher fasting and postload plasma glucose, higher leptin, higher adiponectin and proinsulin levels, and a compromised β-cell function with an attenuated first phase of insulin release (29,46). This underlines the necessity to screen patients who have suffered an acute coronary syndrome for dysglycemia. Unrevealed dysglycemia is also common in other cardiovascular conditions, such as cerebral and peripheral artery disease (32) and heart failure (47,48).

The prevalence of dysglycemia varies among different populations, something that has to be taken into consideration when choosing the screening tool and the most appropriate screening method. An OGTT is presently the only method that is able to detect both IGT and diabetes. The use of a fasting glucose, and especially of HbA_{1c} alone, is insufficient since a negative result does not rule out dysglycemia, which might prolong the time until the dysglycemic condition is discovered, thereby postponing the establishment of preventive strategies to forestall complications (49,50). Moreover, the postload glucose provides important prognostic information with regard to the risk for future cardiovascular events beyond that based on fasting glucose or HbA_{1c} (50). The OGTT has been criticized since it necessitates an overnight fast and is considered to be time-consuming and lacking reproducibility (51). This seems hard to embrace in light of the magnitude of the information obtained. Such information not only makes it possible to discover previously unrevealed IGT and diabetes but also offers patients with diabetes access to glucose-lowering agents with a cardioprotective effect (52,53). The repeatability of the OGTT has been tested over a period of 1 year in the GAMI cohort and was very high. Of all patients with myocardial infarction diagnosed with type 2 diabetes after an OGTT at the time of hospital discharge, 93% were still classified as such or as having IGT after 12 months. In the same manner, 60% of the patients classified with normal glucose tolerance at discharge remained normal after 12 months, although 12% had developed type 2 diabetes (54). Screening can be simplified by the use of accurate point-of-care equipment, such as the HemoCue (55), which provides an immediate answer, thereby saving time and costs.

In populations with a lower risk for glucose perturbations, screening can be initiated by means of a risk score questionnaire, such as the Finnish Diabetes Risk Score (FINDRISC), adding a fasting glucose in cases of a high score and an OGTT when still in doubt about glycemic state (56). Especially, one should consider screening people with a high risk of dysglycemia, such as those with a strong family history of type 2 diabetes, gestational diabetes mellitus (52), and periodontitis (57).

There are major differences in the access of the recommended screening tests for diabetes globally (58), but even in countries with unlimited access to testing facilities, screening is not at all practiced as recommended. According to experiences from the European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) V, which recruited 8,261 patients with coronary artery disease from 27 countries from 2016 to 2017, 30% had a history of diabetes. Screening for glucose perturbations as recommended by the guidelines had often not been performed as part of the clinical routine in patients unaware of their glucometabolic state. As a part of the study, when 4,440 patients without known diabetes were subjected to an OGTT, the presence of dysglycemia (known plus newly detected IGT or diabetes) increased to

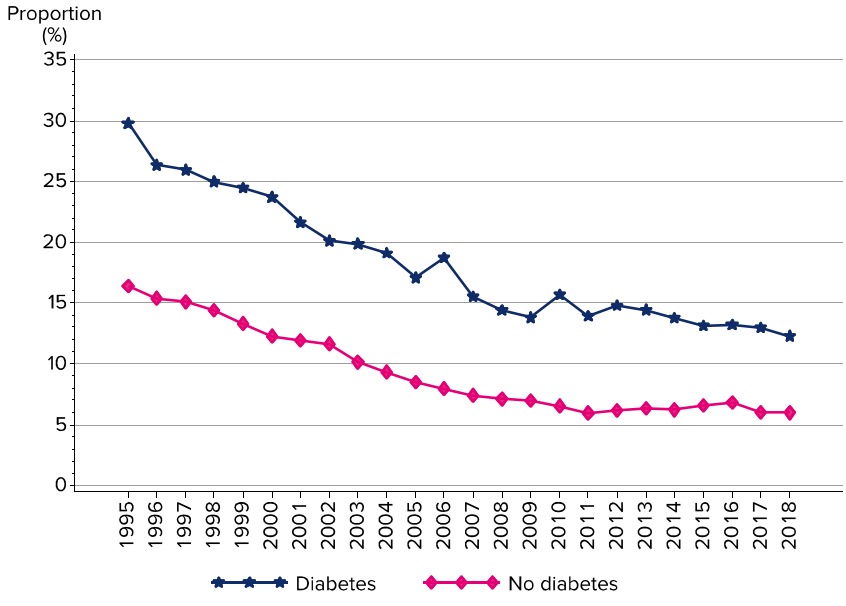

Figure 2—Trend in 1-year mortality in Swedish patients with myocardial infarction in relation to the presence of diabetes or not. All ages 1995–2018. Reprinted with permission from SWEDEHEART (40).

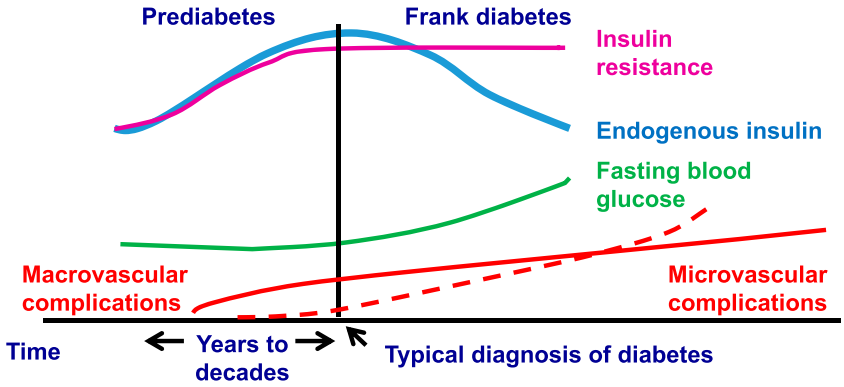

Figure 3—Progression of dysglycemia in relation to macro- and microvascular complications. Adapted with permission from Laakso and Kuusisto (41).

60%, leaving only one-third of the total population with a normal glucose metabolism. Thus, without the OGTT, which should have been performed as a routine part of patient management (52,56) but was not, 70% of all patients with IGT and 30% of those with newly detected diabetes would have remained undetected (59) and deprived of the opportunity for available, life-saving therapy. Sadly enough and despite a similar survey that included OGTT in 2012–2013 and medical reports on the high proportions of undetected dysglycemia, EUROASPIRE V showed no increased undertaking of this screening method. A probable explanation is the scant interest in diabetes among cardiologists. Hopefully, this low engagement will be amended with the diffusion of the novel cardioprotective glucose-lowering agents (49). In conclusion, it is reasonable to assume that appropriate screening would contribute to improved treatment of unrevealed dysglycemia in populations at risk, thereby contributing to closing the prognostic gap between coronary patients with and without diabetes.

INADEQUATE MANAGEMENT

The relation between type 2 diabetes and cardiovascular disease is complex, involving multiple possibilities for an interaction (Fig. 4). Already, UKPDS had postulated that a quintet of potentially modifiable risk factors for coronary artery disease exists in patients with type 2 diabetes: increased concentrations of LDL cholesterol, decreased concentrations of HDL cholesterol, raised blood pressure, hyperglycemia, and smoking (60). An early indication that careful management could contribute to improved survival of patients with type 2 diabetes and myocardial infarction came with a registry-based Swedish study. It was, however, also evident that such patients were less often offered revascularization therapy, acetylsalicylic acid, and lipid-lowering treatment at discharge (61). That early introduction of a comprehensive, evidence-based pharmacological treatment, including renin-angiotensin-aldosterone system inhibitors, β-blockers, statins, oral antiplatelet therapy, and early revascularization, associated with a lower 1-year mortality in coronary patients with type 2 diabetes approaching the level of coronary patients without type 2 diabetes was shown by observational analyses of the Euro Heart Survey (62). Further proof of the very beneficial impact of a multifactorial treatment has subsequently been demonstrated by the randomized controlled Intensified Multifactorial Intervention in Patients With Type 2 Diabetes and Microalbuminuria (Steno-2) trial (63) and by observational analyses in the Swedish Diabetes Registry. In the latter, patients with type 2 diabetes with all five risk factor variables within recommended target ranges appeared to have little or no excess risk of death, myocardial infarction, and stroke compared with the general population (64,65).

International guidelines on how to manage patients with type 2 diabetes with and without coronary artery disease have been issued by major professional organizations since 2007. These recommendations have been updated at several occasions to reflect progress in knowledge and experience. The most recent from Europe and the U.S. were released in 2019 and 2020 (52,66,67). Not in the least, the 2013 European guidelines were widely distributed, endorsed by 28 national societies, and translated into 7 languages in the full version and 12 languages in the pocket version (L.R., personal communication).

The EUROASPIRE surveys address the compliance with guidelines in clinical practice in Europe. The most recent EUROASPIRE V was conducted at 131 centers in 27 European countries during 2016–2017 (59). A total of 8,261 patients with an established coronary artery disease (myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft) were investigated 6–24 months after the event. This delay was chosen to enable the initiation and/or refinement of required management. A combination of drugs from all cardioprotective classes were prescribed to 58% of the patients with known type 2 diabetes. Only 55% had a blood pressure <140/90 mmHg, 37% an LDL cholesterol level <1.8 mmol/L (69.6 mg/dL), and 55% an HbA_{1c} <7% (53 mmol/mol), which must be seen as far from satisfactory. Only one-third had been advised to attend a diabetes clinic.

A comparison with the preceding EUROASPIRE IV survey, conducted 2012–2013, did, if anything, reveal a slight deterioration in the adherence to guideline-recommended management and treatment targets (68). As already described, screening for dysglycemia among high-risk coronary patients with an unknown glucometabolic state was poor. It was concluded that urgent action is required for management of patients with coronary artery disease and dysglycemia, with the expectation of a substantial reduction in risk of further cardiovascular events and complications of diabetes as well as a longer life expectancy.

The experiences from the EUROASPIRE IV and V surveys are not unique. Similar observations of an unsatisfactory secondary prevention in patients with cardiovascular diseases have been reported from many parts of the world (69–73). Especially concerning is the poor access to medications and interventions in low-income countries, which makes it impossible to reach recommended targets (2,58).

FUTURE PERSPECTIVES

To come to grips with the unsatisfactory management of dysglycemia as a risk factor for cardiovascular disease manifestations, there are, above all, three factors that must be improved in the

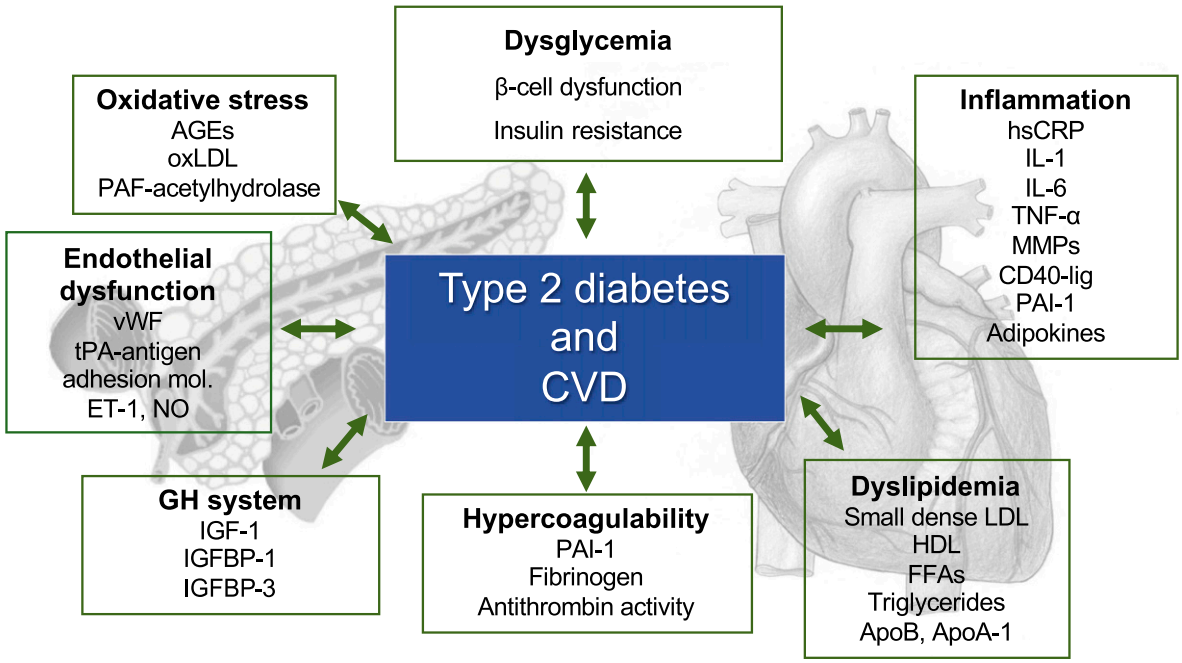

Figure 4—A schematic presentation of possible pathways between type 2 diabetes and enhanced risk of cardiovascular disease. AGE, advanced glycoxidation end product; Apo, apolipoprotein; CVD, cardiovascular disease; ET-1, endothelin-1; FFAs, free fatty acids; GH, growth hormone; IGFBP, IGF binding protein; IL, interleukin; lig, ligand; MMP, matrix metalloproteinase; mol., molecule; NO, nitrogen oxide; oxLDL, oxidized LDL; PAF, platelet-activating factor; PAI-1, plasminogen activator inhibitor-1; TNF-α, tumor necrosis factor α; tPA, tissue plasminogen activator; vWF, von Willebrand factor.

future: guideline adherence, increased attention to people at risk, and simplified and hopefully better screening tools.

Guideline Adherence

It is obvious that further efforts have to be invested in distributing knowledge of the best available practice for patients with cardiovascular disease and dysglycemia. One obstacle is diversified care, at least in Europe. According to EUROASPIRE V, the study participants were seen by cardiologists (80%) and/or general practitioners (63%) or diabetologists (34%). Only 24% had attended a diabetes school or a diabetes educational program. Physician-guided, nurse-led programs have been reported as successful at least when it comes to lifestyle-oriented adaptation, the cornerstone in all management of the current patient population (74–76).

Educational activities must be directed toward professionals in different segments of the health care sector. It is often hospital-based specialists, not just cardiologists, who initiate diagnostic and therapeutic activities, but subsequently, patients are often referred to specialists in primary care. Referral notes should be explicit with regard to treatment goals that, to be successful, have to be based on good communication among the various care providers, including nurses. The patients must be informed about what they should expect with regard to treatment targets and be a central part of the managing team.

Increased Attention to People at Risk

The metabolic syndrome, defined as the presence of three of five abnormal findings (elevated waist circumference, elevated triglycerides, reduced HDL cholesterol, elevated blood pressure, and elevated fasting plasma glucose), predicts cardiovascular disease and type 2 diabetes, as reviewed by Nilsson et al. (77). Early identification and lifestyle adjustments, sometimes supplemented by pharmacological treatment, of patients with prediabetes (IGT) can prevent or postpone the development of type 2 diabetes and, in the long run, cardiovascular disease. Examples of such studies are the Da Qing Study in China, the Malmö Feasibility Study in Sweden, the Diabetes Prevention Study in Finland, and the Diabetes Prevention Program in the U.S. (78–81). Yet, the best lifestyle intervention seems not to be established, as suggested by the overall outcome of the Look AHEAD (Action for Health in Diabetes) trial (82), which randomized overweight or obese patients with type 2 diabetes to an intensive lifestyle intervention or just ordinary pharmacological therapy. On the other hand, in the Look AHEAD study, there was a significant reduction (hazard ratio 0.79 [95% CI 0.64–0.98]; $P = 0.034$) of cardiovascular events among the participants who succeeded in reducing their body weight by at least 10 kg during the first year of follow-up (83). The solution is likely individually tailored and differentiated patient advice followed up by the same health care professional.

Shahim et al. (84) tested the hypothesis that if appropriately screened, the prevalence of dysglycemia is high in people without known diabetes and free from cardiovascular disease on treatment for hypertension and/or dyslipidemia. A total of 2,395 individuals from the EUROASPIRE IV primary care cohort recruited in 14 European countries in 2014–2015 were subjected to an OGTT. Thirty-nine percent of them were dysglycemic, whereof 19% had type 2 diabetes and 20% IGT. An attempt to simplify the screening by starting with the FINDRISC questionnaire failed since already a high proportion among those with a low to moderate risk of developing type 2 diabetes were dysglycemic according to the OGTT. Among various tests, a single HbA_{1c} was the least efficient, with a

limited ability to detect type 2 diabetes and inability to diagnose IGT. Fasting plasma glucose was the best option for detecting type 2 diabetes but could naturally not disclose IGT. Screening with fasting plasma glucose in all patients, followed by an OGTT in patients with impaired fasting glucose, was recommended as a pragmatic approach. An ad hoc–designed outcome trial would offer people with dysglycemia to be detected through screening lifestyle-oriented treatment and randomizing them to a cardioprotective glucose-lowering drug or placebo, with future cardiovascular events as outcome measures. An alternative would be to test standard care versus novel lifestyle approaches, such as special dietary advice and effective exercise activities that engage lower-extremity muscles, inhibiting sarcopenia. Such an approach theoretically makes more sense than, as presently, starting treatment after a first cardiovascular event.

Simplified Screening

That hyperglycemia became a primary target for treatment of patients with diabetes is easy to understand. The more-or-less linear relation between an increasing HbA_{1c} and cardiovascular complications was convincing. As an example, an increase of 1% in updated mean HbA_{1c} was associated with a 21% increase in any diabetes-related end point, a 21% increase in deaths, and a 14% increase of myocardial infarction (85). This finding led to a glucocentric approach—the lower, the better—which, however, failed at least with regard to decreasing macrovascular complications, as already discussed. The understanding that type 2 diabetes is a multifactorial disease in which multifactorial treatment turned out to be beneficial (52), together with access to new glucose-lowering drugs, such as glucagon-like peptide 1 receptor agonists and sodium–glucose cotransporter 2 inhibitors, with cardioprotective capabilities, changed this paradigm (22,86). Pleiotropic effects of the new agents are considered important, in fact even more important than their glucose-lowering capabilities (87).

The concept of insulin resistance as an important part of type 2 diabetes was launched by Reaven (88), who suggested that this condition might be the link between dysglycemia and the increased risk of myocardial infarction and stroke. The rationale behind this hypothesis is appealing since insulin resistance is associated not only with dysglycemic conditions but also with a plethora of known cardiovascular risk factors, such as hypertension, dyslipidemia, endothelial dysfunction, inflammation, and enhanced thrombogenesis (89–91). The concept that a decrease in insulin resistance can reduce cardiovascular events has been tested with lifestyle measures, including increased physical activity (78), and by the use of the insulin-sensitizing drug pioglitazone (92–94).

The HOMA index is widely used to quantify insulin resistance and β-cell function (95). It is based on basal plasma glucose and basal insulin levels, both obtained through a single blood sample. It is therefore attractive to further explore whether insulin resistance expressed by the HOMA index will diagnose glucose perturbations as well or even delineate particularly unfavorable abnormalities with greater precision than tests like HbA_{1c} and fasting and postload glucose. An important question is whether insulin resistance expressed by the HOMA index is a better predictor of future cardiovascular events in patients with established cardiovascular disease or at high risk for such disorders than HbA_{1c}, fasting plasma glucose, and a postload glucose. If these assumptions are corroborated, screening and treatment of such patients will be much simplified and reasonably more assimilated in daily clinical practice. A future aspiration would be to find an even easier accessible marker of early-onset insulin resistance than the HOMA index, which is proven predictive for both the development of cardiovascular disease and type 2 diabetes.

CONCLUDING REMARKS

The present detection and management of dysglycemia in people with or at high risk for cardiovascular events is truly unsatisfactory. Globally, there are major differences. Relatively simple and affordable measures can improve this situation. These are all reasons to believe that if screening and guideline adherence are improved, cardiovascular complications of dysglycemia would be considerably reduced and possibly not inevitable.

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