Cardiodiabetology: Reducing Risks to Optimize Cardiovascular Disease Outcomes

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Summary

- Atherosclerotic cardiovascular diseases, including coronary heart disease, stroke, heart failure, and peripheral arterial disease, along with microvascular disease (retinopathy, neuropathy and chronic kidney disease), are principal causes of morbidity and mortality in persons with diabetes.
- Diabetes is associated with great heterogeneity in cardiovascular disease risk, warranting cardiovascular risk assessment, including global risk scoring and consideration of risk-enhancing factors and subclinical atherosclerosis.
- Few persons with diabetes are at recommended targets for all major cardiovascular risk factors, including LDL-cholesterol, blood pressure, HbA1c, nonsmoking status, and body mass index.
- The treatment approach for diabetes involves consideration of cardiovascular risk assessment, lifestyle modifications: diet and exercise, weight control and avoidance of cigarette smoking; cholesterol, blood pressure, and glucose management; and for higher risk patients, antiplatelet therapy.
- Newer medications for diabetes, including SGLT2 inhibitors and GLP-1 receptor agonists, also reduce cardiovascular events independent of glycemic control. Both classes prevent further kidney function deterioration while the SGLT2 inhibitors reduce heart failure hospitalizations.
- A multidisciplinary team is required to address the myriad of cardiovascular risks in persons with diabetes.

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1 Introduction

Diabetes mellitus (DM), in particular type 2 DM, is increasing in prevalence worldwide, fueled largely by the obesity epidemic as well as unhealthy lifestyles. Nearly 500 million adults have diabetes, a number expected to increase to 700 million by 2045. Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in persons with DM, due principally to coronary heart disease, stroke, heart failure, and peripheral arterial disease. While type 2 DM has traditionally been referred to as a coronary heart disease (CHD) risk equivalent, it actually presents with a great heterogeneity in CHD and CVD risk which is dependent on many factors such as severity of accompanying risk factors, duration of diabetes, and the presence of risk-enhancing factors and subclinical atherosclerosis, thus warranting the importance of risk assessment. However, while DM is not necessarily a CHD risk equivalent, those with DM do have a markedly higher risk for CVD events. Persons at recommended levels and/or treatments for blood pressure, lipids, and glucose, as well as at non-smoking status and ideal body weight, have significantly lower rates of adverse cardiovascular outcomes than those who are not. Few persons with type 2 DM, however, are at target recommendations for all these measures, warranting the need for improved coordination of care to ensure that not only microvascular complications are minimized by glucose control, but also CVD risks are managed aggressively to prevent adverse CVD outcomes. Thus, cardiovascular risk assessment, blood pressure, cholesterol, glucose management, as well as proper dietary and exercise strategies and weight control, smoking cessation, and, as appropriate, antiplatelet therapy for people at higher risk, comprise the key strategies to manage CVD risk in persons with DM.

This chapter will review the epidemiology of DM and CVD, approaches for CVD risk assessment, the role of composite risk factor control, and the key strategies for CVD risk reduction in DM, including the evidence and recommendations for newer therapies aimed to reduce CVD risk in DM.

2 Epidemiology of Diabetes and Cardiovascular Disease

Latest estimates from 2019 indicate 463 million (9.3%) adults worldwide aged 20–79 years are living with diabetes, a number expected to rise to 578 million (10.2%) by 2030 and to 700 million (10.9%) by 2045. Current annual deaths due to complications from diabetes are estimated to be 4.2 million and annual healthcare expenditures exceed 750 billion US dollars [1]. China, India, and the United States have the greatest number of cases of diabetes with 116.4 million, 77.0 million, and 31.0 million cases, respectively [1].

Cardiovascular disease is the most common cause of death among patients with diabetes, according to data from death certificates. Heart disease accounts for approximately 55% of all deaths and cerebrovascular disease is responsible for another 10% of deaths [2].

Acute diabetes-related complications are the next most common cause of death, accounting for 13% of deaths. Pneumonia/influenza, malignant neoplasms, and other causes account for the remaining deaths [2]. Data from the Emerging Risk Factors Collaboration shows diabetes to confer a 2.0-fold increased risk of coronary heart disease, while the risks for ischemic and hemorrhagic stroke are increased 2.3- and 1.6-fold [3]. Recent data from a population of 1.9 million persons demonstrated the most common initial manifestations of CVD in adults with diabetes mellitus (DM) were peripheral arterial disease (16.2%) and heart failure (14.7%), followed by stable angina, nonfatal myocardial infarction, and stroke [4]. Moreover, among cardiovascular patients, data from the Glucose Tolerance in Patients with Acute Myocardial Infarction study, Euro Heart Survey, and the China Heart Survey show 34–45% have diabetes and another 35–37% have prediabetes, indicating the vast majority of cardiovascular patients have abnormal glucose tolerance [5]. It has also been shown that upon admission for an acute coronary syndrome approximately 15% of patients are newly diagnosed with T2DM [6] and some two-thirds of patients meeting criteria for DM based on fasting glucose are discharged from hospital inappropriately undiagnosed for DM [7].

We previously showed among US adults from the National Health and Nutrition Examination Survey mortality from CHD, CVD, and all causes to increase in a stepwise gradient among those who were disease free, or had metabolic syndrome, diabetes, and prior CVD, with the highest rates seen for those who had both DM and CVD, indicating this combination to be a very high-risk condition (Fig. 1). Of interest, however, all-cause mortality is similar in those with DM without CVD compared to those with CVD without DM, suggesting these conditions to be risk equivalents for all-cause mortality [8]. The Framingham Heart Study demonstrated that diabetes is a stronger risk factor for CVD outcomes in women compared to men. While diabetes is associated with a 2.2-fold greater risk of all CVD outcomes in men (absolute rate 76/1000), the respective increase in risk was 3.7-fold in

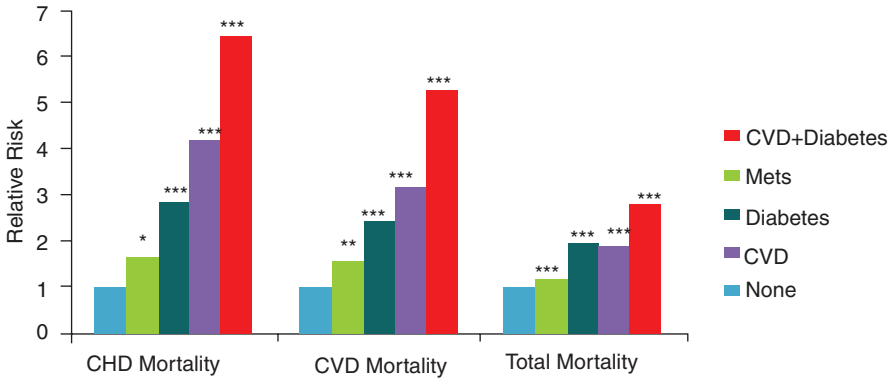

Fig. 1 Metabolic syndrome and diabetes in relation to CHD, CVD, and total mortality: US men and women ages 30–74. * $p < .05$, ** $p < .01$, **** <.0001 compared to none. (Based on data from Ref. [8])

women (absolute rate 65/1000). In particular, the sex difference for the relative risk associated with DM was substantial for peripheral artery disease (3.4 in men and 6.4 in women; absolute rate 18/1000 for both) and heart failure (4.4 in men and 7.8 in women; absolute rate 23 and 21/1000, respectively) [9]. The presence of chronic kidney disease (CKD) with diabetes increases the risk of many cardiovascular complications (myocardial infarction, stroke, heart failure, peripheral arterial disease, and death) by at least another twofold [10].

3 Cardiovascular Risk Assessment in Diabetes

The work of Haffner and colleagues [11] showing that among Finnish men those with DM without a prior myocardial infarction (MI) had a similar risk of future MI as those with a prior MI but without DM helped promulgate the concept that DM was a risk equivalent for CHD. This was also adopted by the Third Adult Treatment Panel of the National Cholesterol Education Program in 2001 [12]. However, several years later, a meta-analysis of over a dozen studies examining this issue showed that those with DM without a prior MI had a 43% lower risk of future CHD compared to those with a prior MI without DM [13]. In an analysis of US adults [8], it was shown that DM (without CVD) carried a lower risk of CHD and CVD mortality than those with preexisting CVD (without DM). Moreover, it has been shown utilizing global risk assessment with the Framingham risk equations that among US adults with DM from NHANES, nearly a third of men and half of women did not reach CVD risk equivalent status and were at intermediate or lower risk (<20% 10-year risk of CVD events) [14]. Finally, data from the Multiethnic Study of Atherosclerosis examining CHD and CVD event rates, according to levels of coronary calcium in adults with DM or metabolic syndrome, show a tenfold variation in event rates (Fig. 2). For example, in those with DM with a 0 calcium score, CHD event rates were 0.4% per year, compared to 4% per year in those with calcium scores of 400 or greater [15]. Most recently, Rana and colleagues showed, among a large registry of DM patients from Kaiser Permanente, DM patients with a duration of DM of 10 years or more to have a risk similar to those with preexisting CHD [16]. Thus, while those with DM are clearly at higher risk of CVD events than those without DM, some are at clearly higher risk than others, warranting quantitative risk stratification.

Key risk factors in persons with DM that promote CHD risk include elevated low-density lipoprotein cholesterol (LDL-C), low high-density lipoprotein cholesterol (HDL-C), elevated blood pressure, and elevated triglycerides. The UKPDS showed among 2693 persons with DM, important predictors (of a first CVD event) were in order of importance: LDL-C, HDL-C, A1c, systolic blood pressure, and cigarette smoking [17]. Thrombogenic and inflammatory factors include C-reactive protein, intereukin-1, fibrinogen, and PAI-1, all of which are increased in DM [18]. Diet, physical activity, tobacco smoking, obesity, and excess alcohol consumption can also influence risk. Nonmodifiable factors include age, sex, and family and

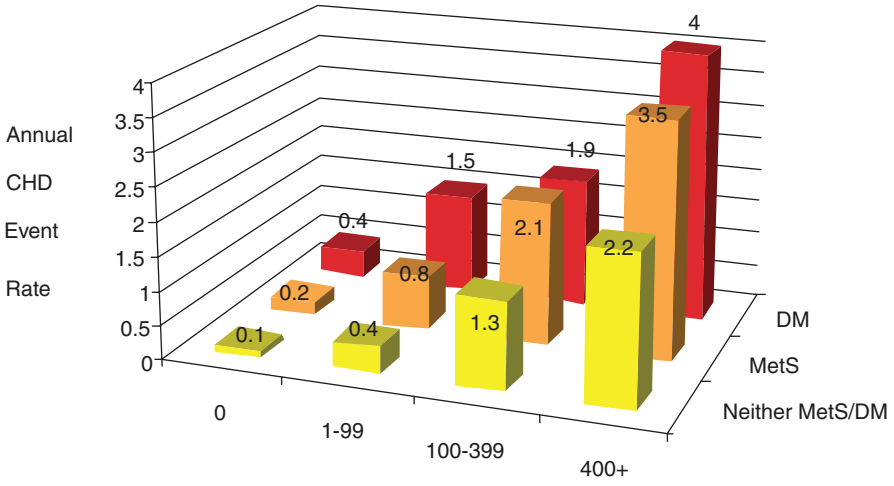

Fig. 2 Annual CHD Event Rates (in %) by Calcium Score Events by CAC Categories in Subjects with DM, MetS, or Neither Disease [15]. (Courtesy of Nathan D. Wong, PhD)

personal history of CVD [19]. In the Swedish National Diabetes Register a glycated hemoglobin level outside the target range was the strongest predictor of stroke and acute myocardial infarction, and patients who were younger than 55 years had the highest excess risk [20] Patients with type 1 DM are also at risk for ASCVD. The strongest predictors for death and cardiovascular outcomes were glycohemoglobin, albuminuria, duration of DM, systolic blood pressure, and LDL-C [21]. Risk factors frequently cluster together and in persons with DM, among those with hypertension, hyperlipidemia, and obesity, over 35% have two of these factors and another 21% have all three [22]. Long ago the MRFIT study showed risk of mortality varies fourfold (from 31 to 125 per 10,000 person years) comparing those with DM who have no risk factors to those who smoke and have elevated cholesterol and blood pressure [23].

The 2018 AHA/ACC Multisociety Guideline for Management of Blood Cholesterol [24] recognizes the importance of risk stratification in persons with DM. The following "risk-enhancing factors" can be used to inform the treatment decision regarding initiating or intensifying statin therapy: long duration (≥10 years for type 2 diabetes mellitus or ≥20 years for type 1 diabetes mellitus), albuminuria ≥30 mcg of albumin/mg creatinine, eGFR <60 mL/min/1.73 m^2, retinopathy, neuropathy, and an ankle brachial index of <0.9. While at least a moderate-intensity statin is recommended for those with DM aged 40 and over, it is recommended the Pooled Cohort Risk Calculator be used to determine the 10-year ASCVD risk, which if over 20%, recommends the use of a high-intensity statin with ezetimibe if needed to reduce the LDL-C by at least 50%. However, neither this risk calculator nor the Framingham risk calculators were derived from exclusive DM samples and treat DM as a binary factor in the equation, without consideration for other factors such as HbA1c or duration of DM. Specifically, the UKPDS risk score (Fig. 3),

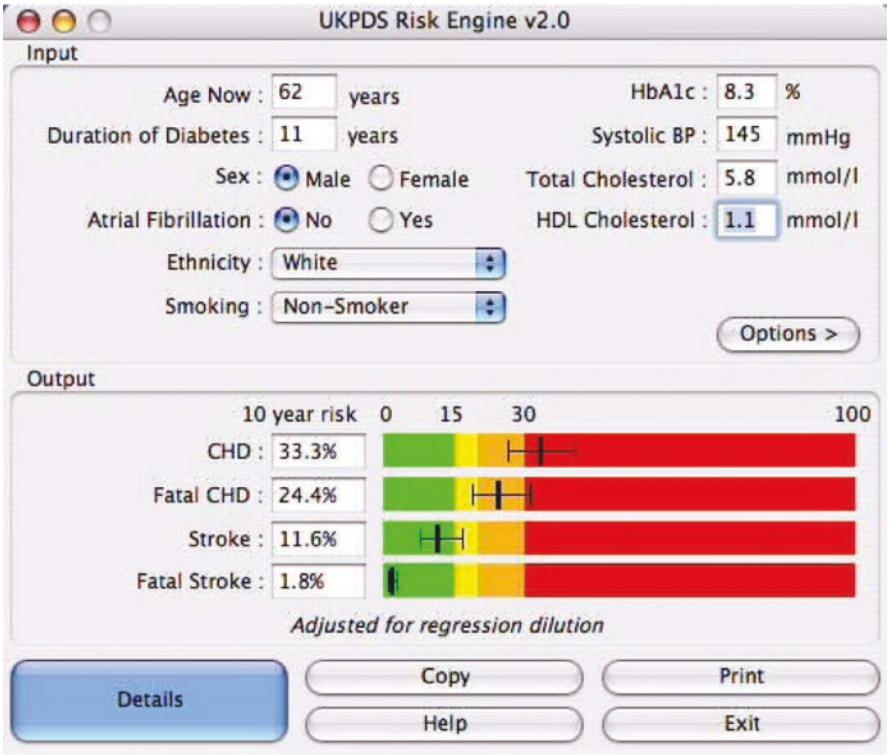

Fig. 3 UKPDS risk engine. T2DM specific risk calculator. Based on 53,000 patients years of data from the UK Prospective Diabetes Study. Risk estimates and 95% confidence intervals in individuals with type 2 diabetes not known to have heart disease. (Based on data from: http://www.dtu.ox.ac.uk/riskengine [24])

which was derived from the large UKPDS diabetes sample, does calculate the 10-year risk of fatal and nonfatal MI and stroke and includes factors such as duration of DM, HbA1c, and even the presence of atrial fibrillation [25]. There have also been attempts to develop other risk scores for those with DM in the United States, such as from the ACCORD cohort [26]. There is a need for a DM Pooled Cohort Risk Score for calculating the risk of total CVD and its major components which will help to more precisely quantify CVD risks in patients with DM in the future.

4 Evidence for Multiple Risk Factor Control to Reduce Cardiovascular Risk

Glycemic and cardiovascular risk factor control in persons with DM remains suboptimal. Studies examining composite control of multiple risk factors note this remains poor with little improvement over the past decade. A recent report from

the US Diabetes Collaborative Registry Analysis of 74,393 US adults with DM [27] showed 74% of patients have a HbA1C <7% (<8% if with ASCVD), 40% had blood pressure <130/80 mmHg), 49% to have an LDL-C <100 mg/dL (<70 mg/dL if with ASVD), and 85% were nonsmoking. Only 13% of patients, however, were at target for all four measures. Moreover, an analysis of NHANES 2013-2016 [28] showed similar results with 56%, 51%, and 49% at targets for HbA1c, blood pressure, and LDL-C cholesterol, respectively, but only 17% at guideline target for all three. With the addition of proportion nonsmoking (84%) and with BMI <25 kg/m^2 (9%), fewer than 10% were at all five targets. Moreover, composite target achievement tended to be worse for those with preexisting CVD compared to those without (20% and 10%, respectively, for HbA1c, LDL-C, and BP control together).

The Intensified Multifactorial Intervention in Patients With Type 2 Diabetes and Microalbuminuria (STENO-2) trial is among the few trials designed specifically to examine the impact of comprehensive risk factor control (lipids, blood pressure, glucose, diet, exercise) on cardiovascular and mortality outcomes. The primary trial involving 7.8 years of follow-up showed a 53% reduction in the composite CVD endpoint of CVD death, myocardial infarction, stroke, revascularization, and amputation by the end of the trial [29]; however, of note, a further 13-year follow-up report showed mortality to be 40% lower in the intensively treated group [30], suggesting a possible legacy effect beyond the original trial from comprehensive CV risk factor management that occurred during the trial. Moreover, in the Bypass Angioplasty Revascularization Investigation 2 (BARI 2D) trial of DM subjects with CAD, those who had a greater number of risk factors controlled to optimal levels (nonsmoking, blood pressure, non-HDL-cholesterol, HbA1c, and triglycerides) had a decreased risk of MI, stroke, and death [31] (Fig. 4). Finally an analysis from a pooled cohort of more than 2000 subjects with DM without CVD at baseline from the MESA, Jackson, and Atherosclerosis Risk in Communities (ARIC) prospective studies [32] showed lower CHD and CVD event

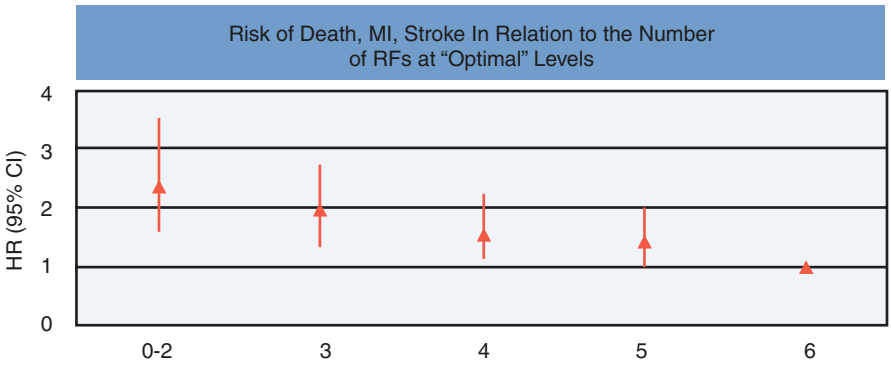

Fig. 4 Risk of death, myocardial infarction, and stroke in relation to the number of risk factors at optimal levels: BARI-2D study. (Reprinted from Bittner et al. [31]. With permission from Elsevier)

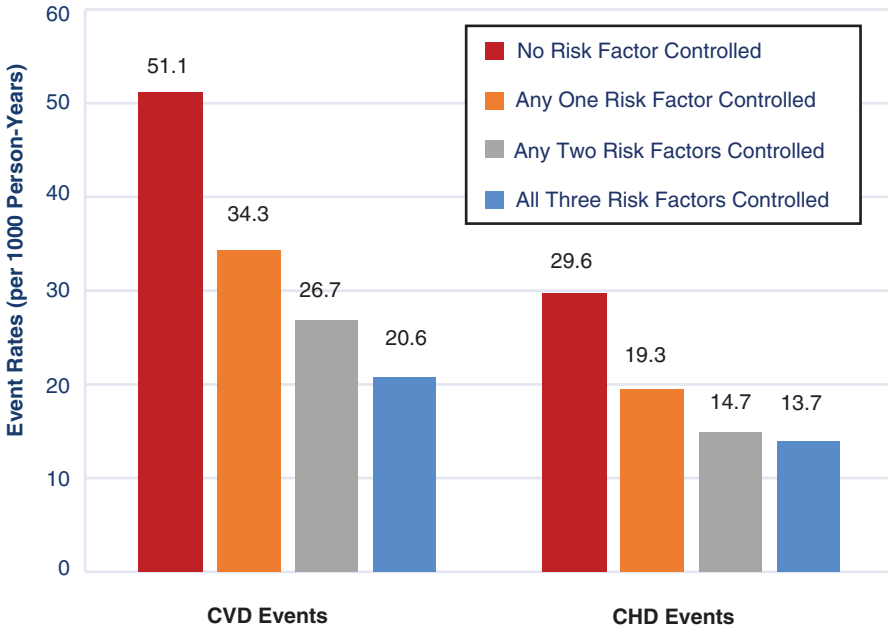

Fig. 5 CVD and CHD event rates by number of risk factors at target among HbA1c, LDL-C, and blood pressure: pooling of ARIC, JACKSON, and MESA study DM subjects. (Courtesy of Nathan D. Wong, PhD)

rates the more the number of risk factors at target (Fig. 5), and that those who had HbA1c <7%, blood pressure <130/80 mmHg, and LDL-C <100 mg/dl had a 62% lower CVD event risk and a 60% lower CHD event risk after adjustment for age, sex, ethnicity, and other risk factors. Findings were also robust in African Americans who comprised about half of the cohort. These data together show the importance of composite risk factor control in persons with DM in optimizing CVD risk reduction. Improved efforts to coordinate control of these multiple risk factors are needed given the currently poor state of risk factor control among US adults with DM.

5 Cardiovascular Risk Management in Diabetes

The management of CVD risks in persons with DM involves a comprehensive approach addressing: (a) assessment of CVD risks (as discussed above), (b) lifestyle management, (c) statins and other lipid-lowering drugs, (d) blood pressure management, (e) hyperglycemia management, and (f) aspirin therapy for those at highest risk. Each of these will be addressed in the following sections, including the most recent recommendations for management.

6 Lifestyle Management

The Diabetes Prevention Program (DPP) was highly successful in showing a lifestyle program involving diet to reduce weight by 7% and physical activity of 150 minutes per week resulted in a 58% reduction in risk of developing DM among persons with pre-DM, which was even more effective than the 31% risk reduction provided with metformin therapy over usual care [33]. Lifestyle management of DM was examined in the LOOK AHEAD trial to reduce CVD events in persons with established DM and after 9 years of follow-up there was no macrovascular or death benefit seen. However, there was improvement in systolic blood pressure, LDL-C, and HDL-C, although with diminishing group differences over time [34].

Diet and Weight Management Importantly, the PREDIMED trial in more than 8000 persons with DM or multiple risk factors for CVD implemented a Mediterranean diet intervention and showed a striking 30% reduction in risk of future CVD events in those who consumed such a diet supplemented by either extra virgin olive oil or nuts, compared to a standard low-fat diet [35]. The importance of weight loss in reducing cardiometabolic risk factors cannot be overemphasized; a 15% weight loss resulted in substantial improvements in many risk factors including systolic (10.5%) and diastolic (9.3%) blood pressure, serum glucose (16.5%), triglycerides (44.8%) and total cholesterol (11.8%). These results indicated that generally a 5–10% weight loss is sufficient to improve CV risk factors [36]. The ACC/AHA Guideline on Lifestyle Management [37] is in line with other medical societies (the ADA and AACE), and recommends a dietary pattern that emphasizes intake of vegetables, fruit, and whole grains; includes low-fat dairy products, poultry, fish, legumes, non-tropical vegetable oils and nuts; and limits the intake of refined sugar, sugar-sweetened beverages, and red meats.

Physical Activity It is also recommended that persons with or without diabetes perform at least 150 min/week of moderate-intensity aerobic physical activity (50–70% of maximum heart rate), spread over at least 3 days per week with no more than 2 consecutive days without exercise, and in the absence of contraindications, adults with type 2 diabetes should be encouraged to perform resistance training at least twice per week.

Cigarette Smoking Cessation Both in those with and without DM, cigarette smoking is an important risk factor for CVD events. The methodology for smoking cessation is similar for those with and without DM and focuses on the 5As [38], which should be addressed at each patient visit by the provider and involves: (1) Asking and documenting current tobacco use, and if a user, (2) Advising in providing a strong personalized message to quit, (3) Assessing readiness to quit in the next 30 days, and if ready (4) Assisting in negotiating a plan to quit, which should involve the STAR plan which involves setting a quit date, telling family, friends, and coworkers, anticipating challenges: withdrawal, breaks, and removing tobacco from the house, car, etc., and may also involve pharmacotherapy, providing social support

and educational materials, and (5) Arranging follow-up to check the plan and adjust medications if necessary, which may involve calling the patient before and after the quit date, weekly follow-up for 2 weeks then monthly, asking about difficulties, building upon successes, and seeking a commitment to remain tobacco free. In a recent quitter, it is important to prevent relapse by congratulating the patient, providing encouragement, discussing benefits experienced by patient, and addressing weight gain, negative mood, and lack of support. If the patient is not yet ready to quit, increase motivation relevant to the personal situation, address short and long-term environmental risks, potential benefits of quitting, identify barriers and solutions, repeat motivational intervention, and reassess readiness to quit. Finally, avoidance of second-hand smoke, which can substantially increase CVD risks in a nonsmoker, as well as other nicotine-based products (e.g., vaping products and chewing tobacco) should be a priority in all patients.

7 Blood Pressure Control

The UKPDS [39] showed the importance of tighter blood pressure control (then defined as <150/85 mmHg) compared to less tight control (then defined as <180/105 mmHg) in reducing both microvascular and macrovascular events, resulting in a significant 37% reduction in microvascular disease, 34% reduction in retinopathy progression, 37% reduction in vision deterioration, 44% reduction in stroke, and 56% reduction in incident heart failure; the composite of any diabetes-related endpoint and all-cause mortality was reduced a significant 32%. The UKPDS and other studies led guidelines committees to recommend a target blood pressure of <130/80 mmHg for persons with DM, which was lower than that for the general population (<140/90 mmHg) for many years. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Blood Pressure Trial [40] involving 4733 patients with DM, however, found that more intensive BP control with a target of <120 mmHg systolic compared to <140 mmHg systolic did not provide incremental benefit for the primary composite CVD endpoint of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death; however, there was a 41% relative risk reduction in stroke, although stroke event rates were low. This study prompted some societies to recommended treatment initiation and target levels of BP to <140/90 mmHg in those with DM.

More recently, while the SPRINT trial of persons without ASCVD or DM who had a systolic blood pressure of ≥130 mmHg showed 25% reductions in CVD events in high risk persons without DM, a recent sub-analysis of SPRINT-eligible persons in ACCORD with DM, while a post-hoc analysis, did show a significant and similar 21% reduction in CVD events [41]. Other recent meta-analyses of persons with DM showing lower BP levels are related to lower risks for CVD outcomes motivated the most recent 2017 ACC/AHA blood pressure guideline committee to recommend a universal target of <130/80 mmHg for most persons, including those with DM [42–44]. They note initial therapy may consist of most classes of

hypertensive medication, including diuretics, ACE inhibitors, angiotensin receptor blockers, and calcium channel blockers.

8 Cholesterol and Lipid Management

The Cholesterol Treatment Trialists Collaboration involving a meta-analysis of 14 statin trials comprising 18,686 persons with DM showed a 21% reduction in CVD events per mmol/l (39 mg/dl) reduction in LDL-C [45], which is similar to those without DM. Clinical trials of fibrate therapy, including the Bezafibrate Intervention Program (BIP), FIELD (evaluating fenofibrate), and finally ACCORD Lipid (evaluating the addition of fenofibrate to statin therapy) failed to meet their primary endpoint (though showing trends of benefit in subjects with atherogenic dyslipidemia, which is appropriate for fibrates – namely, high triglycerides and low HDL-C) [46]. Thus, there have been limited recommendations for the use of fibrate therapy in persons with DM to reduce CVD risks; the AACE suggests reducing elevated triglycerides to 150–200 mg/dl (1.6–2.2 mmol/l) [47], although such therapy is still indicated for those with very high TG to reduce the risk of pancreatitis. Also, while the IMPROVE-IT trial including participants within 10 days of an ACS randomized to ezetimibe or placebo in addition to simvastatin met its primary endpoint [48], a post-hoc analysis showed that the entire benefit was attributed to those with DM who had a significant 14% reduction in risk from the addition of ezetimibe, whereas those without DM showed no benefit [49]. In the FOURIER trial involving evolocumab assigned to persons with prior ASCVD, while showing similar relative risk reductions in those with and without DM (17% and 13%, respectively), there was a greater absolute risk reduction in those with DM (2.7%) resulting in a very favorable number needed to treat of 37 [50]. Most recently, the REDUCE-IT trial of icosapent ethyl (IPE- pure eicosapentaenoic acid) showed persons with either preexisting CVD or DM plus at least one additional CVD risk factor showed a 25% lower risk of subsequent CVD events over nearly 5 years of follow-up, on top of statin therapy in those with higher triglycerides (135 mg/dL or higher) and relatively well-controlled LDL-C levels (40–99 mg/dL). There was a similar reduction in risk in those with (23%) and without (27%) DM [51].

The recent 2018 AHA/ACC – Multisociety Cholesterol Management guidelines [24] recommend for adults with DM aged 40–75 years treatment with a moderate intensity statin. In those persons with DM who have two or more other risk factors, a high-intensity statin is recommended, and if 10-year ASCVD risk exceeds 20%, a high-intensity statin combined with ezetimibe is recommended to reduce LDL-C levels by at least 50%. In those persons with preexisting CVD who also have DM and other high-risk conditions (such as CKD, hypertension, cigarette smoking, or coronary revascularization), or multiple CVD conditions, if despite maximally tolerated statin and ezetimibe the LDL-C still remains at 70 mg/dL or higher, the addition of a proprotein convertase/subtilisin kexin type 9 (PCSK9) monoclonal antibody can be considered. Other guidelines such as those of the American Association of Clinical

Endocrinologists (AACE) [47] and the ESC-EAS 2019 Lipid Guidelines [52] have LDL-C goals which are <100 mg/dL for lower risk persons with DM, <70 mg/dL for those with DM who have multiple risk factors alone, and <55 mg/dL for those with DM who have established ASCVD. Also, for those with DM who have triglycerides of 135 mg/dL or higher and other risk factors for CVD, who have well-controlled LDL-C on statin therapy, the American Diabetes Association [53] and the AACE have recently recommended IPE- icosapent ethyl to further reduce ASCVD risk [47].

9 Newer Diabetes Therapies and CVD Risk Reduction

Epidemiologic studies show that for every 1% lower HbA1c level, there is a 14% lower risk of myocardial infarction, 21% lower risk of diabetes-related death, 37% lower risk of microvascular complications, and 43% lower risk of amputation or peripheral arterial disease-related death [54] Until 2015, cardiovascular outcomes trials involving glucose-lowering therapy in persons with DM had failed to meet their primary endpoints. The well-known UKPDS trial of intensive glucose control resulted in a borderline no-significant reduction in CVD events, except for the metformin subgroup in overweight and obese individuals where there was a significant reduction [55]. Moreover, neither the ACCORD [56], ADVANCE [57], nor VADT [58], all trials examining intensive versus standard glucose control, showed significant reductions in CVD outcomes; in fact, the ACCORD trial showed a significantly higher risk of cardiovascular mortality, despite a reduction in risk of nonfatal myocardial infarction. ADVANCE [57] or VADT [58], however, showed neither benefit nor increased risk for any endpoint. The adverse outcomes in ACCORD were later attributed to those who were assigned to intensive control but failed to respond in lowering their A1c. Outcomes trials of the thiazolidinediones rosiglitazone and pioglitazone failed to reduce their composite CVD endpoints; however, a principal secondary MACE endpoint was significantly reduced in the PROACTIVE trial involving pioglitazone [59]. Of interest, however, a meta-analysis of UKPDS, ACCORD, VADT, ADVANCE, and PROACTIVE showed an overall significant 15% reduction in CHD events in the intensive compared to standard treatment groups [60].

An increased risk of myocardial infarction from a meta-analysis of trials involving the thiazolidinedione rosiglitazone [61], while later refuted in the RECORD outcome trial [62], prompted the Food and Drug Administration in 2008 to require that manufacturers of newer diabetes medications would need to demonstrate cardiovascular safety within certain point estimates and limits of uncertainty [63]. This fueled the design and execution of numerous cardiovascular safety and outcomes trials of newer diabetes drugs over the past decade. The first of these contemporary trials involved the DPP4 inhibitors, which showed overall cardiovascular safety, though failed to show benefits in cardiovascular outcomes. An unanticipated finding in one of the DPP4i studies (saxagliptin) showed an increased risk of developing heart failure hospitalization [64].

Newer DM therapies include the sodium glucose co-transporter 2 (SGLT2) inhibitors which reduce glucose reabsorption in the proximal tubule thereby increasing urinary excretion, as well as the GLP1 receptor agonists, which stimulate insulin release and inhibit glucagon release, thus reducing blood glucose. These therapies also reduce weight and improve blood pressure. The SGLT2 inhibitors appear to have hemodynamic and diuretic effects and the GLP1 receptor agonists seem to impact the vasculature, specifically the endothelium. Both classes have anti-atherosclerotic benefits, reduce intrahepatic fat, and have favorable effects on the kidneys. The SGLT2i class reduces, in particular, heart failure hospitalization [65].

The breakthrough in cardiovascular outcomes trials of DM therapies came with the release of the EMPA-REG trial [66] involving randomization of over 7000 patients with DM to empagliflozin versus placebo in addition to usual care therapies in persons with known CVD. This trial demonstrated a 14% reduction in the primary composite outcome of MACE-CVD death, nonfatal myocardial infarction, and stroke. The result was primarily driven by a dramatic 38% reduction in CVD death. Other secondary outcomes were a 32% reduction in all-cause mortality, and a 35% reduction in hospitalization for heart failure. As a result, the FDA approved empagliflozin to reduce CV death in people with DM and established CVD, independent of glycemic levels and/or goals. The second SGLT-2 CVD outcomes trial to report was CANVAS involving canagliflozin versus placebo on top of standard of care administered to over 4200 patients with DM both with and without CVD, but with elevated risk due to other risk factors [67]. CANVAS, like EMPA-REG, showed a 14% reduction in the primary composite CVD outcome, and while not showing significant reductions in each individual MACE component, it received an FDA indication to reduce MACE: nonfatal MI or stroke and CV death, also independent of glucose level. Further, CANVAS demonstrated a significant 32% reduction in hospitalization for heart failure and prevention of renal function deterioration. Finally, the largest of the SGLT-2 CVD outcomes trials, DECLARE [68], involving over 17,000 patients with DM (about two-thirds being primary prevention with other risk factors but not CVD), had two co-primary endpoints for which the composite of heart failure hospitalization (HHF) and CVD death was significantly reduced by 17%, but the composite MACE outcome showed a nonsignificant 7% risk reduction. As a result, dapagliflozin is now indicated to reduce HHF in both primary and secondary prevention.

The LEADER trial [69] involving liraglutide was the first GLP-1 receptor agonist trial to report on CVD outcomes. This trial enrolled over 9000 patients randomized to liraglutide versus placebo on top of standard of care and included patients both with and without preexisting CVD and with other risk factors. The trial showed an overall 13% reduction in the primary composite endpoint of 3 point MACE: nonfatal MI, nonfatal stroke, and CV death; there were no statistically significant reductions in individual endpoints of myocardial infarction or stroke, but cardiovascular and all-cause mortality were significantly lower in the liraglutide group. The results of LEADER led the FDA to indicate liraglutide to reduce 3 point MACE in people with DM and established CVD. SUSTAIN-6 evaluated the efficacy of semaglutide and included a similar study population of DM patients with and without

known CVD and was designed as a CV safety trial; however, it showed a 24% reduction in the primary composite CVD outcome driven primarily by a 39% reduction in nonfatal stroke, without significant reductions in nonfatal myocardial infarction or CVD death. However, as all these three components of MACE trended positively, the FDA approved semaglutide to reduce 3 point MACE in persons with DM and established CVD [70]. The PIONEER-6 trial [71] also evaluated semaglutide but in its oral form (both liraglutide used in LEADER and semaglutide used in SUSTAIN-6 were injectable preparations), which had similar entry criteria and endpoints as SUSTAIN-6. Again, a safety trial, PIONEER-6, with a 21% relative risk reduction met its primary endpoint safety but not for superiority. While nonfatal MI or nonfatal stroke were not reduced significantly, the component of CVD death was significantly reduced by 51%.

Without a doubt, there is great interest in these therapies, particularly the SGLT2-inhibitors, as a new class of therapies for heart failure and for chronic kidney disease, irrespective of DM status. There are numerous ongoing trials involving these therapies both for patients with heart failure with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF). The first of these trials, DAPA HF, involving dapagliflozin, recently reported a significant 26% reduction in risk of the composite of cardiovascular death, subsequent HF hospitalization, or urgent HF visit with a 4.9% absolute risk reduction, translating to a number needed to treat of 21 [72]. Finally, the CREDENCE trial involving canagliflozin showed among patients with CKD (eGFR of 30–89 ml/min/1.73 m^2 and albuminuria >300 mg/24 hours, all treated with renin angiotensin system blockade) a 30% reduction in the composite of end stage renal disease, doubling of serum creatinine, or renal or CVD death [73]. Also, in the DECLARE trial in patients with DM (described above) there was a significant 24% reduction in the composite renal outcome (≥40% decrease in estimated glomerular filtration rate, new end-stage renal disease, or death from renal or cardiovascular causes) [68]. Both empagliflozin and dapagliflozin are in further trials to evaluate their efficacy in patients with medium to severe CKD, with or without diabetes.

10 Guidelines for Glycemic Control

The American Diabetes Association Standards of Diabetes Care [74] has noted that a reasonable HbA1c target for most adults with diabetes is <7% with a target of <6.5% which may be considered if it can be done without undue side effects or adverse events. A less stringent target of 7.5% or even 8% may be appropriate for those with a history of advanced microvascular or macrovascular complications, severe hypoglycemia, or anticipated short life span. Targets can be more stringent than 7%; in fact, the AACE [75] recommends a target of 6.5% or less if it can be achieved safely, especially without hypoglycemia, and where there is a short disease duration, long life expectancy, absence of important comorbidities or vascular complications, a positive patient attitude, good resources, and an adequate support system.

For persons with DM with established ASCVD, heart failure, kidney disease, or with multiple risk factors, the American College of Cardiology published a consensus decision pathway [65], whereby along with guideline-directed medical therapy, the addition of an SGLT-2 inhibitor or GLP-1 receptor agonist with proven CVD benefit can be considered part of the clinician-patient treatment decision. An SGLT2 inhibitor may be preferred in cases where there is a desire to reduce heart failure hospitalization or reduce blood pressure, whereas a GLP1 receptor agonist is preferred if weight loss is desired or when the eGFR is under 45 ml/min/1.73 m^2. However, neither of these drugs are approved to reduce blood pressure or promote weight loss. There are also other considerations where an alternative agent might be considered (Table 1). Other recent guidelines include those from the American Heart Association, noting that a GLP-1 receptor agonist or SGLT-2 inhibitor may be considered in patients with DM and multiple risk factors in addition to metformin therapy [76]. Most recently, the American Diabetes Association Standard of Medical Care 2020, although still requiring metformin as first line, noted that one of these therapies can be considered irrespective of current or target HbA1c level since the benefit does not depend on this [53]. Other guidelines including the 2019 ESC-EASD CVD in DM [52] and the 2020 AACE DM management algorithm [75] state that patients with DM and risk factors or established CVD have to be on one of these agents not only independent of A1C but also independent of background antihyperglycemic medications. In other words, they can be prescribed directly on top of diet and exercise. The AACE also recommends the SGLT2i dapagliflozin and others once they have data to manage patients with HF and reduced ejection fraction, and the SGLT2i canagliflozin and others once they have available data to manage people with DM and moderate to severe kidney disease. Per AACE,

Table 1 Patient and clinician preferences and priorities for considering SGLT2 inhibitors with demonstrated CV benefit versus GLP-1Ras with demonstrated CV benefit

Consider using an SGLT2 inhibitor first when patient and clinician priorities include:	Consider using a GLP-1RA first when patient and clinician priorities include:
Reducing MACE and CV death	Reducing MACE and CV death
Preventing heart failure hospitalization	Substantial weight loss
Reducing blood pressure	Once weekly (subcutaneous) dosing[a]
Orally administered therapies	Therapy when eGFR consistently <45 ml/min/1.73m^2
Consider alternative agents if: Significant CKD History of prior amputation, severe peripheral arterial disease, neuropathy, or diabetic foot ulcers (avoid canagliflozin) History of recurrent genital candidiasis History of diabetic ketoacidosis History of osteoporosis (avoid canagliflozin)	Consider alternative agents if: Persistent nausea, even at low doses History of pancreatitis History of gastroparesis History of MEN2 or medullary thyroid cancer History of proliferative retinopathy (semaglutide)

Adapted from Das et al. [65]. With permission from Elsevier

[a]Semaglutide administration recently available in the USA; MEN2 = multiple endocrine neoplasia type 2

based on all SGLT2i & GLP1-RA cardiovascular outcome trials, these drugs may improve or at least prevent reduction in kidney function. Of note, although the contemporary GLs focus on CVD prevention independent of glycemic levels, the ADA, AACE, and EASD all continue to recommend management of hyperglycemia to goal to prevent short-term microvascular and long-term macrovascular complications.

11 Aspirin Therapy

While prior analyses of subgroups of DM subjects from earlier clinical trials showed beneficial effects of aspirin therapy on reducing CVD events [77–79], other clinical trials did not [80–83]. Most recently, the ASCEND trial [84] of over 15,000 persons with DM but without prior CVD showed 100 mg of daily aspirin to result in a significant 12% reduction in the primary CVD endpoint; however, this was largely counterbalanced by a 29% relative risk increase in bleeding, with the resulting net clinical benefit essentially null. Even those at higher (>10% CVD risk in 10 years) did not derive greater clinical benefit. The American Diabetes Association guidelines note that aspirin may be used in higher-risk primary prevention DM, but serious consideration should be given to the possible risks of serious bleeding and the overall net clinical benefit [74]. Lower-risk patients with DM are not recommended for aspirin therapy.

12 The Cardiodiabetes Care Team

In order to maximize opportunities for CVD risk reduction in patients with diabetes, a comprehensive cardiodiabetes care team (Fig. 6) is needed [85]. While the primary care provider cares for most patients with diabetes, it is critical that there first be sufficient resources for proper lifestyle management, including having registered dietitians and/or exercise physiologists in particular on the team to manage the often complex lifestyle issues common in these patients. The endocrinologist should be consulted when challenges are faced with glycemic control and when questions arise about whether to add to or replace existing therapies with newer agents proven to reduce CVD risk. Also, since approximately a third of patients with DM have some form of CVD, consultation with the cardiologist, neurologist, or other specialists as appropriate is needed to ensure adherence to cardiovascular therapies along with those aimed to control DM.

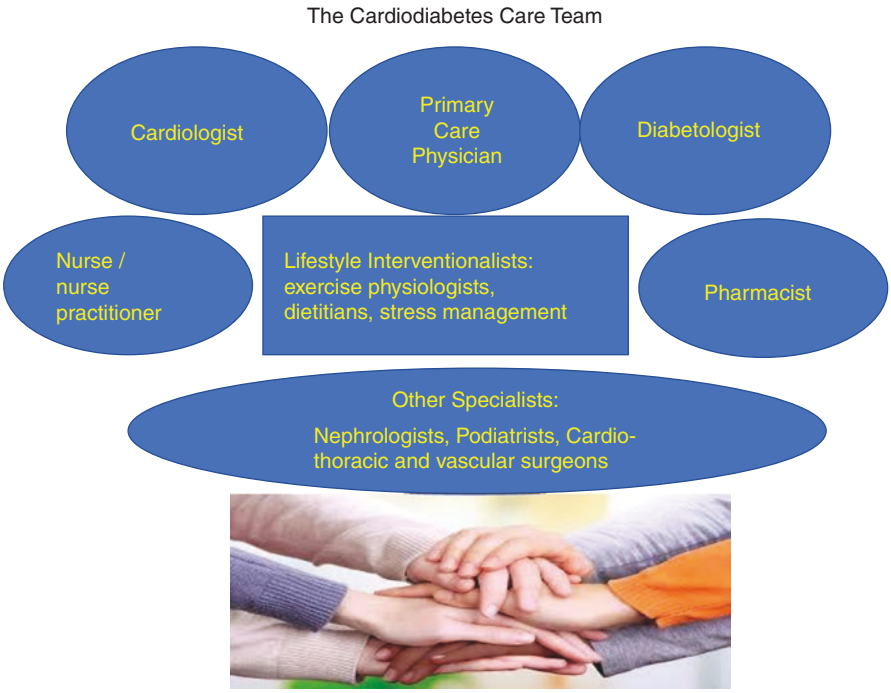

Fig. 6 The cardiodiabetes care team [85]. (Courtesy of Nathan D. Wong, PhD)

13 Conclusions

The prevalence of DM continues to increase both in the United States and worldwide, warranting greater efforts not only to prevent its rapid rise, but also to reduce the complications resulting from it. With ASCVD the major cause of morbidity and mortality in persons with DM, and the continuing poor state of control of the multiple risk factors associated with CVD in patients with DM, there is a continuing urgent need to better coordinate the identification and management of these risks. With more aggressive recommendations for blood pressure control, specific guidelines focusing on statin therapy and consideration for newer nonstatin therapies in higher-risk patients, as well as newer diabetes medications that have been proven to improve cardiovascular outcomes, in particular heart failure, there are significant opportunities to enhance our ability to optimize CVD risk reduction in such persons. Finally, a coordinated multidisciplinary team of healthcare providers focusing on the common goal of reducing CVD and other complications in patients with DM is essential.

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