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REVIEW

Importance of cardiovascular disease risk management in patients with type 2 diabetes mellitus

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Abstract: Type 2 diabetes mellitus (T2DM) is commonly accompanied by other cardiovascular disease (CVD) risk factors, such as hypertension, obesity, and dyslipidemia. Furthermore, CVD is the most common cause of death in people with T2DM. It is therefore of critical importance to minimize the risk of macrovascular complications by carefully managing modifiable CVD risk factors in patients with T2DM. Therapeutic strategies should include lifestyle and pharmacological interventions targeting hyperglycemia, hypertension, dyslipidemia, obesity, cigarette smoking, physical inactivity, and prothrombotic factors. This article discusses the impact of modifying these CVD risk factors in the context of T2DM; the clinical evidence is summarized, and current guidelines are also discussed. The cardiovascular benefits of smoking cessation, increasing physical activity, and reducing low-density lipoprotein cholesterol and blood pressure are well established. For aspirin therapy, any cardiovascular benefits must be balanced against the associated bleeding risk, with current evidence supporting this strategy only in certain patients who are at increased CVD risk. Although overweight, obesity, and hyperglycemia are clearly associated with increased cardiovascular risk, the effect of their modification on this risk is less well defined by available clinical trial evidence. However, for glucose-lowering drugs, further evidence is expected from several ongoing cardiovascular outcome trials. Taken together, the evidence highlights the value of early intervention and targeting multiple risk factors with both lifestyle and pharmacological strategies to give the best chance of reducing macrovascular complications in the long term.

Keywords: cardiovascular risk, hypertension, obesity, dyslipidemia

Introduction

A seemingly relentless increase in the incidence of diabetes[1] finds us in the midst of a global diabetes epidemic. More than 382 million people are currently affected worldwide, and this number is expected to rise to 592 million by 2035.[2] The latest statistics for the US indicate that over 25 million people, or 8.3% of the population, are affected,[3] and another 79 million with prediabetes are at increased risk of developing the disease. The dynamics of the diabetes epidemic are also changing rapidly. Once a disease of the West and the affluent, type 2 diabetes mellitus (T2DM) has now spread to every country in the world and is increasingly common among the less wealthy. Notably, Asia's large population and rapid economic development have made it an epicenter of the epidemic. Furthermore, rising rates of childhood obesity have resulted in T2DM becoming more common in children and adolescents, particularly in certain ethnic groups.[2]

Diabetes is a major risk factor for cardiovascular disease (CVD), and CVD is the most common cause of death in people with diabetes. Various studies have indicated

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that, relative to those without diabetes, the presence of diabetes significantly increases the risk (two- to fourfold) for developing CVD,[4–9] and of dying when CVD is present.[9–13] In the US in 2004, heart disease was noted on 68% of diabetes-related death certificates among people aged 65 years or older, and stroke was noted on 16%.[3] Although rates of death attributable to CVD have declined in people with and without diabetes,[14] the burden of CVD in those with diabetes remains high, and implementation of preventive strategies is frequently not adequate.[15–17] Individuals with prediabetes also have an increased risk of CVD. Indeed, it has been suggested that CVD risk reduction and prevention of diabetes in the prediabetes population may do more to reduce the CVD burden than aggressive treatment of CVD risk factors once diabetes has fully developed.[18]

T2DM is associated with clustered risk factors for CVD. Adults with diabetes have a 77%–87% prevalence of hypertension, a 74%–81% prevalence of elevated low-density lipoprotein cholesterol (LDL-C), and a 62%–67% prevalence of obesity.[19] The increased risk of CVD in patients with diabetes is related in part to this high prevalence of other CVD risk factors. The management of modifiable CVD risk factors, including hyperglycemia, hypertension, dyslipidemia, obesity, cigarette smoking, and physical inactivity, is therefore critical to minimizing the risk of macrovascular complications of diabetes.

Although critically important, these traditional risk factors do not fully explain the excess risk for CVD in people with diabetes, and there have also been efforts to identify and understand the link between diabetes and other "nontraditional" CVD risk factors, such as endothelial dysfunction, impaired fibrinolysis, inflammation, microalbuminuria, increased homocysteine levels, and vascular wall abnormalities. An assessment of the clinical utility of such nontraditional risk factors by the US Preventive Services Task Force concluded that there was insufficient evidence to recommend using them to assess CVD risk in the general population.[20,21] Although there is some evidence regarding their role in diabetes,[22–24] it has not been conclusively determined whether it is of clinical benefit to screen for or therapeutically target these nontraditional risk factors, and their management has not been incorporated into diabetes guidelines. This article will therefore focus on how the modification of traditional risk factors impacts CVD risk in patients with T2DM, and discuss current guidelines in this regard.

Lifestyle interventions

Lifestyle management is universally advocated for prevention as well as management of T2DM. Lifestyle interventions generally include healthy eating, increased physical activity, and cessation of smoking. Such interventions have several beneficial effects, and can also have an impact on CVD risk.

Weight loss

Weight loss is advised for all overweight or obese patients with T2DM. Recommended strategies to reduce weight include regular physical activity and maintaining a healthy eating pattern.[25–27] An association between overweight/obesity and an increased risk of CVD is well established in the general population.[28] Furthermore, studies have shown that overweight and obesity, particularly visceral obesity, increase the risk of developing T2DM.[29,30] The presence of inflammation leading to insulin resistance has been proposed as the mechanistic link between obesity and diabetes.[31,32] In the context of T2DM, the relationship between weight change and CVD risk is complicated by the issue of how to adjust for such confounding factors as hypertension, dyslipidemia, and hyperglycemia, and conflicting results have made it difficult to conclusively state that weight loss is linked with a reduction in CVD risk. Nevertheless, other benefits of weight loss have been clearly demonstrated (eg, improvements in quality of life, insulin resistance, and other CVD risk factors), and clinical guidelines therefore continue to recommend weight loss for overweight or obese individuals with T2DM.

Look AHEAD (Action for Health in Diabetes; see Table 1 for full trial names) tested the hypothesis that weight loss in patients with T2DM could reduce the risk of CV events.[33] Participants were randomized to an intensive lifestyle-modification program of caloric restriction combined with 175 minutes per week of moderate-intensity physical activity, or to a standard program of diabetes education. Although intensive lifestyle intervention was associated with significant weight loss and improvements in several CVD risk factors, there was no effect on the rate of CV events during long-term follow-up, and the trial was stopped for reasons of futility after a median follow-up of almost 10 years.[33] The authors proposed the possibility that a sustained weight loss of more than that achieved in the intervention group may be required to reduce the risk of CVD. Furthermore, the mean loss of 3.5% of body weight in the control group is not typical of routine care, and may have contributed to the lower-than-expected CV event rate. The difference between groups may also have been reduced by an increased use of potentially cardioprotective drugs in the control group, as well as the provision of educational sessions. It may also be possible that any effect of lifestyle interventions on CV outcomes requires more than 10 years to become apparent, and would therefore not

Table 1 Trials and titles

Trial	Title	Registration (if available)
ACCEPT-D	Aspirin and simvastatin combination for cardiovascular events prevention trial in diabetes	ISRCTN48110081
ACCOMPLISH	Avoiding cardiovascular events through combination therapy in patients living with systolic hypertension	NCT00170950
ACCORD	Action to control cardiovascular risk in diabetes	NCT00000620
ACE	Acarbose cardiovascular evaluation trial	NCT00829660
ADVANCE	Action in diabetes and vascular disease: Preterax and Diamicron – modified release controlled evaluation	NCT00145925
AleCardio	A study with aleglitazar in patients with a recent acute coronary syndrome and type 2 diabetes mellitus	NCT01042769
AlePrevent	A study of aleglitazar in patients with stable cardiovascular disease and glucose abnormalities	NCT01715818
ALLHAT	Antihypertensive and lipid-lowering treatment to prevent heart attack trial	NCT00000542
ASCEND	A study of cardiovascular events in diabetes	NCT00135226
CANVAS	Canagliflozin cardiovascular assessment study	NCT01032629
CARMELINA	Cardiovascular and renal microvascular outcome study with linagliptin in patients with type 2 diabetes mellitus at high vascular risk	NCT01897532
CAROLINA	Cardiovascular outcome study of linagliptin versus glimepiride in patients with type 2 diabetes	NCT01243424
DCCT	Diabetes control and complications trial	NCT00360815
DECLARE-TIMI 58	Multicenter trial to evaluate the effect of dapagliflozin on the incidence of cardiovascular events	NCT01730534
EDIC	Epidemiology of diabetes interventions and complications	NCT00360893
ELIXA	Evaluation of cardiovascular outcomes in patients with type 2 diabetes after acute coronary syndrome during treatment with AVE 0010 (lixisenatide)	NCT01147250
EMPA-REG OUTCOME	Empagliflozin cardiovascular outcome event trial	NCT01131676
EXAMINE	Examination of cardiovascular outcomes with alogliptin versus standard of care in patients with type 2 diabetes mellitus and acute coronary syndrome	NCT00968708
EXSCEL	Exenatide study of cardiovascular event lowering trial	NCT01144338
GRAND 306	Study of tak-875 in adults with type 2 diabetes and cardiovascular disease or risk factors for cardiovascular disease	NCT01609582
LEADER	Liraglutide effect and action in diabetes: evaluation of cardiovascular outcome results – a long term evaluation	NCT01179048
Look AHEAD	Look AHEAD: action for health in diabetes	NCT00017953
MRFIT	Multiple risk factor intervention trial	NCT00000487
ONTARGET	Ongoing telmisartan alone and in combination with ramipril global endpoint trial	NCT00153101
ORIGIN	Outcome reduction with initial glargine intervention	NCT00069784
PLATO	The platelet inhibition and patient outcomes trial	NCT00391872
REWIND	Researching cardiovascular events with a weekly incretin in diabetes	NCT01394952
SAVOR-TIMI 53	Saxagliptin assessment of vascular outcomes recorded in patients with diabetes mellitus – thrombolysis in myocardial infarction 53 study	NCT01107886
Steno-2	Intensified multifactorial intervention in patients with type 2 diabetes and microalbuminuria	NCT00320008
SUSTAIN 6	Trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes	NCT01720446
TECOS	Trial evaluating cardiovascular outcomes with sitagliptin	NCT00790205
T-emerge 8	A study of taspoglutide in patients with inadequately controlled diabetes mellitus type 2 and cardiovascular disease	NCT01018173
TIDE	Thiazolidinedione intervention with vitamin D intervention study	NCT00879970
TOSCA IT	Thiazolidinediones or sulphonylureas and cardiovascular accidents intervention trial	NCT00700856
TRITON-TIMI 38	Trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel – thrombolysis in myocardial infarction	NCT00097591
UKPDS	United Kingdom prospective diabetes study	
VADT	Veterans Affairs and diabetes trial	NCT00032487

have been detected.[34] Nevertheless, several other benefits of intensive lifestyle intervention were reported, including reductions in urinary incontinence,[35] sleep apnea,[36] and depression,[37] and improvements in quality of life,[38] physical functioning,[39] and mobility.[40] Therefore, even though significant effects on CV morbidity and mortality were not demonstrated, this finding will not change the recommendation of weight loss for overweight and obese patients with T2DM.

On the topic of weight loss, it is also important to note that all the major diabetes guidelines refer to bariatric surgery.[25–27]

The American Diabetes Association (ADA) guidelines state that bariatric surgery may be considered for adults with T2DM and a body mass index (BMI) >35 kg/m², especially if the T2DM or associated comorbidities are difficult to control with lifestyle and pharmacological therapy.[25] Similarly, the American Association of Clinical Endocrinologists (AACE) guidelines state that bariatric surgery should be considered for patients with a BMI ≥35 kg/m² and comorbidities, especially if therapeutic goals have not been reached using other strategies.[26] European diabetes guidelines mention that in obese individuals, bariatric surgery causes long-term weight loss and reduces the rate of incidence of T2DM and mortality.[27] Several studies have shown that bariatric surgery leads to near-normalization of hyperglycemia or remission of T2DM in 40%–95% of patients, although the mechanisms underlying these metabolic effects of bariatric surgery are unclear.[41–48] Some evidence also suggests that bariatric surgery is associated with reduced cardiovascular events and mortality. However, this is based on results from a nonrandomized study in which the control group was contemporaneously matched and differed by several characteristics at baseline.[49,50] Therefore, the impact of bariatric surgery on cardiovascular risk is unclear, and appropriately controlled studies are required to clearly assess any impact.

Physical activity

Physical activity is recommended as part of weight-loss strategies, and the effects of weight loss on CVD risk were discussed in the previous section. However, physical activity is also thought to influence CVD risk independently of weight loss. The potential mechanisms underlying this link include decreased systemic inflammation, improved early diastolic filling, improved endothelial vasodilator function, and decreased abdominal visceral fat accumulation.[51] Most studies have shown a significant relative reduction in the incidence of CV events in participants who are physically active and/or aerobically fit, with a recent prospective meta-analysis of 12 cohort studies concluding that higher levels of total physical activity were associated with a lower CV mortality risk in individuals with diabetes.[52] Although there is considerable variation in the range of benefits reported, the recommendation to incorporate at least 150 minutes per week of moderate (to vigorous)[27] aerobic physical activity, in addition to resistance training at least twice a week, remains a cornerstone of T2DM management and prevention of CVD in T2DM.[25,27]

Smoking

A large body of evidence has established a causal link between cigarette smoking and health risks in the general population.

In patients with T2DM, studies also consistently demonstrate that smoking is a risk factor for mortality and coronary heart disease, and to a lesser extent for stroke.[53–59] MRFIT (Multiple Risk Factor Intervention Trial) quantified an independent and increasing risk of coronary heart disease mortality based on the number of cigarettes smoked per day.[60] Although several studies have shown the benefits of quitting smoking in patients with diabetes, the potential consequence of weight gain may discourage patients from attempting to quit. A recent study investigating the link between smoking cessation and weight gain demonstrated CV benefits of smoking cessation in adults without diabetes, despite subsequent weight gain. The same trend was demonstrated for patients with diabetes, although it did not reach statistical significance, possibly because of limited study power.[61] Diabetes guidelines universally recommend that all patients should be advised not to smoke, and that smoking-cessation counseling and other forms of treatments should be included as routine components of diabetes care.[25,27]

Glucose control

In the context of elevated blood glucose, the function of the vascular endothelium is altered in ways that promote atherosclerosis (reviewed in Bornfeldt and Tabas[62]). While epidemiological and pathophysiological studies clearly support the hypothesis that hyperglycemia is associated with an increased risk of CVD, they do not directly address whether interventions to improve hyperglycemia reduce this risk.[63] Historically, one of the most contentious issues in the diabetes field is whether improved glycemic control is associated with a reduction in CVD, and following on from that, where glycated hemoglobin (HbA_{1c}) targets should be set.

In type 1 diabetes mellitus, DCCT (Diabetes Control and Complications Trial) showed a trend towards a lower risk of CV events with intensive glucose control, but the number of events was small and the result was not statistically significant.[64] However, EDIC (Epidemiology of Diabetes Interventions and Complications), a 9-year follow-up of the DCCT cohort, showed that participants who were initially randomized to the intensive glucose-control arm had a 42% reduction of CV outcomes (95% confidence interval [CI] 9%–63%) and a 57% reduction in the risk of nonfatal myocardial infarction, stroke, or CV death (95% CI 12%–79%).[65] These findings demonstrate that an initial period of intensive glucose control had a sustained beneficial effect on CVD risk. The mechanisms underlying this legacy effect are not fully understood. A follow-up of the EDIC cohort 15 years after the study stopped found no significant difference between

the intensive- and standard-care groups in terms of cardiac function or remodeling assessed by cardiac magnetic resonance imaging.[66]

Such remarkable CV benefits have not been demonstrated in T2DM. On the one hand, in UKPDS (United Kingdom Prospective Diabetes Study), a study begun in the 1970s to compare intensive glucose control with the conventional treatment of the time in patients with newly diagnosed T2DM, there was evidence, albeit inconclusive, of a CV benefit of intensive glucose control, with a 16% reduction in the risk of myocardial infarction.[67] The aim of intensive treatment was fasting plasma glucose <6 mmol/L (108 mg/dL), making it difficult to compare this study with more recent investigations that used HbA_{1c} targets. Nevertheless, a legacy effect, as seen in DCCT/EDIC, was demonstrated in the 10-year follow-up of UKPDS, with patients who were originally randomized to receive intensive glucose therapy achieving a significant reduction in the risk of myocardial infarction and all-cause mortality.[68]

On the other hand, two large CV outcome trials, ADVANCE (Action in Diabetes and Vascular disease: PreterAx and Diamicron – MR Controlled Evaluation)[69] and VADT (Veterans Affairs and Diabetes Trial),[70] which prospectively examined the effects of intensive glucose control on macrovascular outcomes, showed no significant reduction in CVD risk with intensification of glucose control. A third trial, ACCORD (Action to Control Cardiovascular Risk in Diabetes),[71] was prematurely terminated, due to increased mortality in participants randomized to an intensive glucose-control strategy.

Although several meta-analyses have explored this controversial relationship between glucose control and CVD, these studies are not strictly comparable, making it impossible to draw firm conclusions. In summary, improved glucose control in patients with T2DM has not been definitively shown to reduce CVD, although a trend toward benefit has been observed. Based on ACCORD, ADVANCE, and VADT, Skyler et al suggest that glucose control plays a greater role before macrovascular disease is well developed and a minimal role when it is advanced, and that significant benefit is only seen in subsets of patients with shorter T2DM duration, lower baseline HbA_{1c}, and/or absence of known CVD.[63] Furthermore, any benefit of glucose control on CVD risk in T2DM is likely to be modest compared with treatment of other CVD risk factors, and therefore difficult to demonstrate in their presence.[63] This resonates with the Look AHEAD weight-loss trial, where potential CV benefits in the intervention group may have been masked by efficient treatment

of other risk factors in the control group, and highlights an ongoing difficulty with the design of CV outcome trials.

Current guidelines suggest a target $HbA_{1c} \leq 6.5\%$ (AACE) or <7.0% (ADA) for patients with short diabetes duration, long life expectancy, no significant CVD, and at low hypoglycemia risk.[25,27] However, all guidelines emphasize the importance of individualization of targets, especially for patients with concurrent illness and at risk for hypoglycemia. The AACE guideline suggests a target HbA_{1c} of >6.5% if lower targets cannot be achieved without adverse outcomes.[26] The ADA suggests a less stringent goal (than their general target of <7.0%) for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with long-standing diabetes.[25] Furthermore, all guidelines recognize that any comprehensive diabetes-care plan should include modification of other CVD risk factors and also provide recommendations to this effect.

Although beneficial effects of glucose control on CVD risk have not been conclusively demonstrated, the benefits of good glucose control on microvascular outcomes are unequivocal, and antihyperglycemic agents therefore remain a cornerstone of T2DM treatment. There are many such agents to choose from and several factors for the physician to consider, including safety. The CV safety of certain antihyperglycemic drugs, particularly rosiglitazone and some sulfonylureas, has been called into question.[72,73] This has led to much debate and controversy, although recent studies demonstrated that rosiglitazone did not increase the risk of CV overall morbidity and mortality any more than other standard glucose-lowering agents.[74,75] Nevertheless, partly as a result of the rosiglitazone experience, the US Food and Drug Administration (FDA) recognized the need for safety data and issued guidance in 2008 making it essential for manufacturers to demonstrate that a new antidiabetes therapy is not associated with an unacceptable increase in CV risk.[76] As a result of this change in the regulatory landscape, several large CV-outcome trials are ongoing or have recently been completed (Table 2).

The FDA guidance applies to drugs approved since 2008, and thus many of these trials involve incretin-based therapies (dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 agonists) and sodium glucose cotransporter (SGLT)-2 inhibitors, as these are the most recently developed antihyperglycemic drug classes. There has been cautious optimism that incretin-based therapies may have CV benefits beyond those attributed to reducing hyperglycemia, with evidence of cardioprotective actions in preclinical models

Table 2 Cardiovascular outcomes trials in diabetes

Clinical Trial.gov ID	Drug	Trial short name[a]	Sample size	Start date
Sodium glucose cotransporter 2 (SGLT2) inhibitors				
NCT01032629[83]	Canagliflozin	CANVAS	4,330	Dec 2009
NCT01131676	Empagliflozin	EMPA-REG OUTCOME	7,000	Jul 2010
NCT01730534	Dapagliflozin	DECLARE-TIMI 58	17,150	Apr 2013
NCT01986881	Ertugliflozin		3,900	Nov 2013
Dipeptidyl peptidase-4 (DPP-4) inhibitors				
NCT00790205	Sitagliptin	TECOS	14,000	Dec 2008
NCT00968708[80]	Alogliptin	EXAMINE	5,380	Oct 2009[b]
NCT01107886[81]	Saxagliptin	SAVOR-TIMI 53	16,492	May 2010[b]
NCT01243424[84]	Linagliptin	CAROLINA	6,000	Oct 2010
NCT01703208	MK-3102		4,000	Oct 2012
NCT01897532	Linagliptin	CARMELINA	8,300	Jul 2013
Glucagon like peptide-1 (GLP-1) agonists				
NCT01018173	Taspoglutide	T-emerge 8	2,118	Jan 2010[c]
NCT01147250	Lixisenatide	ELIXA	6,000	Jun 2010
NCT01144338	Exenatide	EXSCEL	14,000	Jun 2010
NCT01179048[85]	Liraglutide	LEADER	9,340	Aug 2010
NCT01394952	Dulaglutide	REWIND	9,622	Jul 2011
NCT01720446	Semaglutide	SUSTAIN 6	3,260	Feb 2013
NCT01455896	ITCA 650		2,000	Mar 2013
Others				
NCT00700856[86]	Pioglitazone versus SU	TOSCA IT	3,371	Sep 2008
NCT00879970[87]	Rosiglitazone/pioglitazone	TIDE	1,332	May 2009[c]
NCT01042769[88]	Aleglitazar	AleCardio	7,228	Jan 2010[c]
NCT01715818	Aleglitazar	AlePrevent	1,999	Dec 2012[c]
NCT00069784[89]	Insulin glargine	ORIGIN	12,537	Aug 2003[b]
NCT01959529	Insulin degludec		7,500	Oct 2013
NCT00829660	Acarbose	ACE	7,500	Feb 2009
NCT01609582	Fasiglifam (TAK-875)	GRAND 306	5,000	Jun 2012

Notes: [a]For full trial names see Table 1; [b]completed; [c]terminated.

of CV dysfunction and beneficial effects on cardiac function in short-term clinical studies of ischemic heart disease.[77–79] However, this optimism has been tempered by results of SAVOR-TIMI (Saxagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus – Thrombolysis in Myocardial Infarction) 53 and EXAMINE (EXamination of cArdiovascular outcoMes with alogliptIN versus standard of carE in patients with type 2 diabetes mellitus and acute coronary syndrome), which demonstrated the safety of saxagliptin and alogliptin, respectively, but failed to show a benefit on CV outcomes in either case.[80,81] Therefore, while early studies for SGLT2 inhibitors also suggest they may have beneficial effects on CVD risk (in particular, as they are associated with lowering blood pressure and inducing weight loss),[82] the ongoing CV-outcome trials are essential to provide conclusive information on clinical outcomes (see Table 2).

Blood pressure control

The pathophysiological relationship between hypertension and diabetes is complex and not well understood.

Evidence suggests that insulin resistance plays a significant role in the interplay between diabetes, hypertension, and CVD, but such comorbidities as obesity and dyslipidemia make it difficult to decipher the common pathological mechanisms. Nevertheless, various studies indicate that the presence of hypertension is a very strong driver of CV outcomes in individuals with diabetes.[90,91] Further evidence suggests that CVD risk starts to increase above a blood pressure of 115/75, and is then doubled for every 20 mmHg increase in systolic blood pressure, or for every 10 mmHg increase in diastolic blood pressure.[92] In contrast to hyperglycemia, several clinical investigations have shown that lowering blood pressure in patients with hypertension and diabetes reduces the risk of cerebrovascular accidents and congestive heart failure.[93–98] In spite of this evidence, hypertension is reportedly the most poorly controlled of the cardiac risk factors in this population.[15–17]

Furthermore, the treatment of hypertension has also raised controversies in the context of choosing blood pressure targets, with some arguments for targets of 130/80 or even lower,[99,100] and others for targets below 140/80 mmHg.[101–105]

This controversy is reflected in the targets recommended by different clinical practice guidelines. Until recently, various guidelines and position statements were strikingly consistent in setting a target blood pressure level at 130/80 mmHg. However, recent guidelines on hypertension management for patients with diabetes issued by the ADA and European Society of Hypertension/European Society of Cardiology/European Association for the Study of Diabetes include a systolic blood pressure target of <140 mmHg.[25,27] On the other hand, the AACE algorithm maintains its recommendation of a target in the region of 130/80 mmHg.[26] Table 3 shows only major US and international guidelines issued in the last three years, as these were able to take into account the most recent investigations. Although there are discrepancies between the recommendations, what is clear is that patients with diabetes should be treated to a target blood pressure of at least <140/80 mmHg, but the physician will need to consider the individual's overall health when setting any further targets.

Intensive lifestyle intervention may be sufficient to lower blood pressure in patients with mild hypertension.[25–27] However, additional pharmacological intervention will be required for most patients. A wide variety of blood pressure-lowering agents, including angiotensin-converting enzyme inhibitors (ACE-Is), angiotensin-receptor blockers (ARBs), β-blockers, diuretics, and calcium-channel blockers, have been shown to be effective in reducing the risk of CV events. The *Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* recommended a thiazide diuretic as the first line of treatment.[108] This guidance was based on the findings of ALLHAT

(Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), which showed that chlorthalidone was superior to other agents in preventing heart failure.[109] However, many other studies provide evidence that blockade of the renin–angiotensin–aldosterone system (RAAS) with an ACE-I or an ARB is particularly valuable for the treatment of hypertension in T2DM patients with high CVD risk.[110–118]

The most up-to-date diabetes guidelines recommend an ACE-I or ARB as the first line of therapy.[25–27] Multiple drug therapy is generally required to achieve blood pressure targets, although ACE-I/ARB combinations are not recommended, as ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) showed they are associated with an increased risk of renal failure and hyperkalemia.[119] The AACE algorithm for CVD risk-factor modification recommends dual therapy with an RAAS blocker and a thiazide, calcium-channel blocker, or β-blocker when blood pressure is >150/100 mmHg, or when goals are not met.[26] RAAS blockade is usually the cornerstone of combination therapy, with a thiazide diuretic or a calcium-channel blocker often recommended as an add-on. ACCOMPLISH (Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension) compared these combinations, and showed superiority of an ACE-I/calcium-channel blocker combination over an ACE-I/thiazide diuretic combination.[120] In light of these findings, a combination of an RAAS blocker and a calcium-channel blocker is often proposed as a first choice.[121] However, this should not imply that other combinations are ineffective or harmful.[122] Indeed, there is such an array of antihypertensive options that the choice may be bewildering; however, a meta-analysis of 27 randomized trials concluded that all of the major classes of blood pressure-lowering agents are likely to substantially reduce CV risk.[123] This emphasizes the priority of blood pressure lowering per se, regardless of the choice of drug class. Nevertheless, individualization is always appropriate, eg, patients with heart failure could benefit from β-blockers, those with proteinuria from RAAS blockade, those with prostatism from α-blockers, and those with coronary artery disease from β-blockers or calcium-channel blockers.[26]

Dyslipidemia

Dyslipidemia is strikingly common in patients with T2DM. The altered lipid profile associated with T2DM is most commonly attributed to insulin resistance,[124,125] and is generally characterized by a high concentration of plasma triglycerides, low concentration of high-density lipoprotein cholesterol (HDL-C), and increased concentration of

Table 3 Recommended blood pressure targets

Issuing organization	Blood pressure target (mmHg)
American Diabetes Association[25]	<140/80 <130/80 may be appropriate for certain individuals, such as younger patients, if achievable without undue treatment burden
American Association of Clinical Endocrinologists[26]	~130/80
European Society of Cardiology/ European Association for the Study of Diabetes[27]	<140/85
European Society of Hypertension/ European Society of Cardiology[106]	<140/85
International Diabetes Federation[107]	≤130/80 Revise target upward in elderly or if there is significant risk of postural hypotension and falls

small dense LDL-C particles. A multivariate analysis from UKPDS found that an increased concentration of LDL-C was the strongest independent predictor of CVD, followed by decreased concentrations of HDL-C.[55] Indeed, several studies have shown that lowering LDL-C (usually with statins) reduces the risk of major CV events in patients with diabetes.[126–132] While HDL-C is a strong CVD risk predictor, numerous studies of pharmacological interventions to raise HDL-C have not found evidence of a beneficial effect on CV risk.[133–137] Similarly, although there is an association between elevated triglycerides and CVD, the degree to which triglycerides directly promote CVD has long been debated. Currently, very little clinical evidence exists to show that lowering triglycerides leads to a reduction of CVD risk,[138] although in the ACCORD lipid trial, a subgroup of patients who had the highest baseline triglyceride level and lowest HDL-C baseline level appeared to benefit from combination therapy with a statin plus a fibrate.[135]

In 2004, the US National Cholesterol Education Panel Adult Panel III guidelines emphasized the importance of lowering elevated levels of LDL-C as the most effective treatment to reduce the incidence of coronary heart disease mortality and morbidity.[139] Management of LDL-C concentrations remains a major goal of diabetes treatment, with current guidelines emphasizing lowering LDL-C to a target goal of <100 mg/dL for T2DM patients without overt CVD.[25–27] Lifestyle interventions along with improved glycemic control may allow some patients to reach this lipid goal; however, pharmacological agents should be added if there is an inadequate response to lifestyle modifications, or in cases of high CVD risk. In patients with overt CVD or older than 40 years with other CVD risk factors, pharmacological treatment should be added to lifestyle therapy regardless of baseline lipid levels; an LDL-C target of <70 mg/dL is appropriate for such high-risk patients.[25–27] If statin-treated patients do not reach targets on maximum tolerated doses, the ADA guideline suggests a 30%–40% LDL-C reduction from baseline as an acceptable alternative target, while other guidelines recommend at least a ≥50% reduction if goals cannot be reached.[27] Statins are the drug of choice for lowering LDL-C; however, the ADA guideline also mentions additional LDL-C-lowering agents, including niacin, fenofibrate, ezetimibe, and bile-acid sequestrants, and these are included in the AACE CVD risk factor-modification algorithm as options to be used in combination with a statin to lower LDL-C.[26] However, without evidence that such combination therapy provides any significant improvement in CVD risk reduction, this approach is not broadly recommended by the ADA.

Although it is unclear whether modifying HDL-C and triglyceride levels impacts CVD risk, target goals for these parameters have nevertheless been incorporated into ADA and AACE guidelines, with both recommending lifestyle modifications and referring to the use of omega-3 fish oil, fibrates, and niacin to achieve target triglyceride levels <150 mg/dL.[25,26] The ADA guideline states that HDL-C targets of >40 mg/dL in men and >50 mg/dL in women are desirable, and mentions the use of niacin and fibrates to increase HDL-C levels, even though their effect on CVD outcomes in patients with diabetes is unclear. The AACE CVD risk factor-modification algorithm proposes a non-HDL-C (total cholesterol minus HDL-C) level of <130 mg/dL, and also identifies fibrates, niacin, and omega-3 fish oil as treatment options.

Although it is encouraging to note that the proportion of patients meeting LDL-C goals has improved over time, recent analyses indicate that LDL-C levels remain uncontrolled in over 45% of patients with T2DM.[140,141] Intensification of efforts to achieve lipid goals in clinical practices therefore provides an opportunity to have an impact on overall CV risk in patients with diabetes.

Antiplatelet therapy

Prothrombotic and fibrinolytic mechanisms are tightly regulated under normal circumstances, such that there is protection from bleeding without the formation of pathological thrombosis. However, in patients with diabetes, this regulation is disrupted, and there is an increased thrombotic tendency, due to platelet hyperreactivity, decreased fibrinolysis, and increased activation of prothrombotic coagulation factors (eg, tissue factor, factor VIII, thrombin, fibrinogen, plasminogen-activator inhibitor 1).[142,143] A number of antiplatelet agents have been shown to be of benefit for the prevention of CV events in certain groups, with aspirin being the most commonly used. Aspirin inhibits thromboxane A_2-dependent platelet activation and aggregation by way of its irreversible inhibition of cyclooxygenase 1, and a number of studies have demonstrated that treatment with low-dose aspirin resulted in a significant reduction of serious vascular events in patients with diabetes and CVD.[144–146]

The evidence regarding the use of aspirin for primary prevention of CV events in adults with diabetes is more controversial. For example, two recent randomized controlled trials did not show a significant CV benefit of aspirin in patients with diabetes.[147,148] These trials were included in a recent meta-analysis that also incorporated data from seven other trials, either performed specifically in patients with diabetes, or that

included subgroups of patients with diabetes.[149] Across trials, aspirin was associated with a 9% decrease in risk of coronary events and a 10% reduction in the risk of stroke; however, the decrease in risk for both outcomes did not reach statistical significance. These results are consistent with the findings of other meta-analyses,[150–154] and together they suggest that aspirin may produce a modest reduction in the risk of CV events in patients with diabetes. However, aspirin use is also associated with a significant increase in the risk of intracranial and extracranial hemorrhage, and the relative trade-off between CV events prevented by aspirin and bleeding events caused by aspirin therefore needs careful consideration.[149] Further studies are required to assess more reliably the benefit-to-risk ratio of aspirin in primary prevention in T2DM patients at moderate CV risk. To address this, ACCEPT-D (Aspirin and simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes)[155] and ASCEND (A Study of Cardiovascular Events iN Diabetes) are two large ongoing trials that collectively will include more than 15,000 participants with diabetes. These investigations will provide important information about the role of aspirin for primary prevention in patients with diabetes, and may help identify which patients are at greatest risk, and therefore which patients stand to derive a net benefit from aspirin therapy.

Platelet $P2Y_{12}$-receptor blockers are an alternative class of antiplatelet agents that include clopidogrel, prasugrel, and ticagrelor. Clopidogrel inhibits adenosine diphosphate-dependent platelet function by irreversible inhibition of the platelet $P2Y_{12}$ receptor, and has proven clinical efficacy in reducing CV events in patients with diabetes.[156] However, its inhibition is less predictable than the inhibition of thromboxane A_2-dependent platelet activation by aspirin, and genetic variation of relevant liver enzymes, as well as drug–drug interactions with proton-pump inhibitors, can affect clopidogrel's mechanism of action, leading to a variable clinical response to treatment.[157] Furthermore, various studies suggest a clinically relevant suboptimal clopidogrel response in at least some patients with diabetes.[158]

Prasugrel also exerts its antiplatelet effect by irreversible inhibition of the $P2Y_{12}$ receptor; however, it leads to platelet inhibition more rapidly and with less variability compared with clopidogrel. It is currently indicated for the reduction of thrombotic CV events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with percutaneous coronary intervention. TRITON-TIMI (TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibitioN with prasugrel – Thrombolysis In Myocardial Infarction)

38 demonstrated that prasugrel produced a greater reduction in ischemic events than clopidogrel, but was associated with an increased risk of bleeding in patients with acute coronary syndrome undergoing percutaneous coronary intervention.[159] Interestingly, a subgroup of patients with T2DM derived the highest benefit from prasugrel without an increased risk of major bleeding.[160] On the other hand, another study that compared prasugrel with clopidogrel in the context of acute coronary syndromes without revascularization did not demonstrate an increased benefit of prasugrel for reducing ischemic events in the general cohort or in a diabetes subgroup; furthermore, similar risks of bleeding were observed with both antiplatelet agents.[161]

Ticagrelor also inhibits $P2Y_{12}$ receptors, but differs from clopidogrel and prasugrel by virtue of its direct and reversible mechanism of action. PLATO (Platelet Inhibition And Patient Outcomes) demonstrated that ticagrelor was more effective than clopidogrel in reducing death from CV causes and total mortality in a general postacute coronary syndrome cohort,[162] and decreased ischemic events in diabetes patients without increasing the risk of bleeding.[163] In a recent small study (30 patients) that compared ticagrelor and prasugrel in acute coronary syndrome patients with diabetes, ticagrelor achieved a significantly higher platelet inhibition than prasugrel;[164] however, no clinical relevance of these findings has so far been demonstrated.

Current guidelines recommend aspirin therapy as a potential primary prevention strategy in those with diabetes who are at increased CVD risk and who are not at increased risk for bleeding.[25,27] However, a net benefit of aspirin use for the primary prevention of CVD has not been unequivocally demonstrated, and thus aspirin is no longer recommended for those with diabetes at low CVD risk.[25,27,149] Low-dose aspirin therapy (75–162 mg/day) is recommended as a secondary prevention strategy in those with diabetes with a history of CVD, and clopidogrel as an alternative therapy in aspirin-intolerant patients.[25,27] Use of a $P2Y_{12}$-receptor antagonist in combination with aspirin for at least 1 year in patients following acute coronary syndrome is recommended by the ADA. The ADA guideline also draws attention to the fact that evidence supports the use of either ticagrelor or clopidogrel if no percutaneous coronary intervention was performed, and the use of clopidogrel, ticagrelor, or prasugrel if percutaneous coronary intervention was performed.[25] The prescribing information for both ticagrelor and prasugrel contains a boxed warning regarding bleeding risk,[165,166] and caution is therefore urged in patients with a high risk for bleeding.

Multifactorial approaches

Evidence suggests that targeted multifactorial intervention is of benefit for reducing CVD in the context of T2DM. In Steno-2 (Intensified Multifactorial Intervention in Patients with Type 2 Diabetes and Microalbuminuria), patients with T2DM and persistent microalbuminuria were randomized to receive either conventional intervention involving multiple risk factors, or intensified, targeted, multifactorial intervention involving a combination of medications and focused behavior modification.[167] Targets for HbA_{1c}, systolic and diastolic blood pressure, and fasting values of serum total cholesterol, LDL-C, and triglycerides were lower in the intensified-intervention group than with conventional intervention. Although only 15% of patients in the intensive arm reached the HbA_{1c} target of <6.5%, the risk of vascular complications was approximately halved in this group after a mean follow-up of 7.8 years. Few patients achieved all treatment goals (approximately 70% reached the total cholesterol target of <175 mg/dL, approximately 58% reached the triglyceride target of <150 mg/dL, almost 50% reached the systolic blood pressure goal of <130 mmHg, and approximately 70% reached the diastolic blood pressure goal of <80 mmHg).[167] Nevertheless, for most patients, the treatment goals for lipids and blood pressure were achievable without undue difficulties.[168]

At the end of this study, all patients in both groups were informed in detail about the benefits of intensified multifactorial treatments, and the primary care providers to whom the patients were referred were educated about this approach. Patients were subsequently followed observationally for a mean of 5.5 years. This follow-up analysis demonstrated that the intensified multifactorial approach had sustained beneficial effects with respect to vascular complications: absolute mortality was reduced by 20%, and CV mortality was reduced by 13% in patients originally assigned to the intensively managed group, compared with those who received conventional therapy.[169] A recent study aiming to address the feasibility of a multifactorial intensive intervention in patients with T2DM of at least 2 years' duration and no previous CV events demonstrated that such an approach is feasible and effective in clinical practice, and is associated with significant and durable improvements in CVD risk profile.[170]

Conclusion

Early intervention has the greatest impact on micro- and macrovascular complications of T2DM. Glycemic control therapies should be started as soon as diabetes is detected, and early intervention for blood pressure and lipids is vital.

Treatment strategies for these patients will evolve as new drugs are continually being developed. However, lifestyle changes are also essential to any management plan, and although many patients may need pharmacological therapy to reach targets, the benefits of a healthy lifestyle should not be underestimated. For a newly diagnosed patient, the range of risk factors requiring consideration may seem overwhelming. Integrated care teams incorporating diabetes educators can greatly help in this respect, providing the support patients need to make lifestyle changes, as well as adhere closely to treatment regimens. Working with the patient to target multiple risk factors with both lifestyle and pharmacological strategies needs time and effort, but gives the best chance of reducing the likelihood of microvascular and macrovascular complications in the long term.

Disclosure

Dr Lorber is a board member of Biodel; has served as a consultant for Merck, Novo Nordisk, and Janssen; has received grants from MannKind, Eli Lilly, and Boehringer Ingelheim; has received payments for lectures from Novo Nordisk and Janssen; and owns stock in Biodel.

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