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DIABETES AND CARDIOVASCULAR DISEASE (N WONG, SECTION EDITOR)

The Importance and Role of Multiple Risk Factor Control in Type 2 Diabetes

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Abstract

Purpose of Review The importance of composite risk factor control for reducing CVD risk in type 2 diabetes (T2DM) has gained increased attention and here we review the latest findings in the field.

Recent Findings The Steno-2 study was the first to show that early intensive risk factor control could improve risk factor status and halve the CVD risk in patients with diabetes with lasting impact. A range of observational studies have added further insight to the importance of multiple risk factor control showing an incremental association between number of risk factors controlled and reduction in CVD risk. Noteworthy, a Swedish population-based study recently showed that optimal risk factor status in patients with T2DM was associated with a CVD risk similar to the general population.

Summary Early intensive intervention to achieve optimal risk factor control reduces CVD risk and should be of principal focus in T2DM management.

Keywords Risk factor control · Cardiovascular disease · Type 2 diabetes

Introduction

Type 2 diabetes (T2DM) is a complex metabolic disorder, which predisposes individuals with T2DM to cardiovascular (CV) complications and mortality at higher rates compared to the general population. To that end, an unprecedented rise in T2DM to nearly half a billion cases worldwide is making T2DM a global health crisis [1]. Despite the long-standing recognized link between diabetes and cardiovascular disease (CVD) [2], there has been inertia in shifting focus from controlling glucose alone towards multiple risk factor control as a strategy to improve patient outcomes. T2DM is often accompanied by other CV risk factors, which increased the risk of cardiovascular complications, and it has recently been estimated that almost 40% of coronary heart disease events among patient with T2DM within the next 10 years could be prevented if all modifiable risk factors were brought to target levels [3]. Here, we mention CVD-related risk factors to be considered among patients with T2DM. We then briefly review the most recent studies on multiple risk factor control in

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T2DM and summarize the value and recent status of risk factor control. Finally, we discuss the relative importance of risk factors and barriers to achieving risk factor control in T2DM.

Cardiovascular Risk Factors

A multitude of CV risk factors exist, and while these are not restricted to diabetic individuals, T2DM being a recognized independent risk factor for CVD makes risk factor assessment critical in these individuals [4–6]. Well-established modifiable risk factors include elevated systolic and diastolic blood pressure, obesity (including visceral adiposity), elevated HbA1c (including insulin resistance and hyperinsulinemia), dyslipidemia (high low-density lipoprotein cholesterol (LDL-C), low high-density lipoprotein cholesterol (HDL-C), high triglycerides), and inflammation. Generally, these risk factors can be improved through life style interventions that include a healthy diet, physical activity, smoking cessation, stress and sleep management, patient education, and psychosocial care [7], as well as pharmacotherapy. Importantly, lifestyle interventions extend beyond reducing CVD risk laying the foundation for all non-communicable disease prevention [8]. Non-modifiable risk factors include advanced age, gender, family history, ethnicity, and genetics. A range of more non-traditional risk factors are emerging in the risk factor landscape, such as microalbuminuria, hematologic and thrombogenic factors, inflammatory markers, epigenetics, and gut microbiota-host interactions [9, 10], and these will likely play a larger role in our future understanding and evaluation of CVD risk.

Importance of Cardiovascular Risk Factors in T2DM

Lifestyle Modifications

The massive burden of T2DM and CVD is largely preventable as these predominantly result from prolonged suboptimal behavioral patterns closely linked to urbanization and modern lifestyle, including sedentary behavior, poor diet quality, excess caloric intake, and smoking [11, 12]. Thus naturally, targeting the root causes of T2DM and CVD constitutes the first and primary approach to halt the progressive nature of T2DM and reducing the risk of CVD. Nevertheless, results from the largest randomized trial evaluating lifestyle intervention to reduce CVD events in T2DM have been disappointing [13], possibly due to the limited weight reduction and type of dietary intervention in the intervention group as well as the greater use of cardioprotective drugs in the control group.

There is evidence that diet and exercise-mediated weight loss and lifestyle intervention can prevent type 2 diabetes [14]. Overweight and obesity are the most important predictors of T2DM and is associated with increased mortality in T2DM [15–17]. Hence, increasing daily physical activity and eating a healthful diet, including consumption of fruits, vegetables, whole grains, legumes, non-tropical vegetable oils, and healthy protein sources [1, 12, 18–21], are imperative aspects in improving overall health status, achieving weight loss, and reducing CVD risk [7].

Smoking

Smoking is one of the most hazardous life style choices and it is both an independent predictor for developing T2DM, while it markedly increases the risk of CVD mortality in those with T2DM [22–25]. Nonetheless, smoking is a widely undertreated modifiable risk factor [26]. As an example, less than half of diabetic smokers in the GUIDANCE study reported being given advice on smoking cessation within the past 12 months [27]. Every health care provider should use evidence-based strategies such as the US Public Health Service five-step model the "5As" (Ask, Advice, Assess, Assist, Arrange) to support smoking cessation [28]. For better outcomes, smoking deserves to be managed as intensively as other CV risk factors and requires more attention and pharmacotherapeutic efforts in clinical practice [29].

Glycemic Control

Although observational studies have reported a strong correlation between poor glucose control in patients with T2DM and CVD events, they do not address whether improving hyperglycemia reduces this risk.

Findings from randomized controlled trials on glucose control have not been conclusive, which may be due to the timing of the interventions. Large glycemic control trials, counting the VADT, ADVANCE, and ACCORD, included patients with longer duration of T2DM and found no improvement in CV events. However, subset analyses indicated that patients without established atherosclerotic disease and shorter-duration diabetes might benefit from intensive glucose control [30–32]. By the 5-year post-trial follow-up mark in the Steno-2 study, the previously significant differences in level of risk factors, including HbA1c, between the study groups had disappeared, but the difference in CV events between groups kept growing larger with time [33, 34••]. This phenomenon was also demonstrated in the UKPDS, which focused on glycemic interventions in newly diagnosed diabetes patients [35], and is known as the "legacy effect" or "metabolic memory, implying that timely efforts to decrease the exposure of early hyperglycemia imprints at the molecular level and has lasting impact, even after the intervention has stopped, for lowering the risk of future CVD complications [36, 37]. The promise of the legacy effect should encourage glucose control without delay

in patients with newly diagnosed T2DM, yet it is important to take an individualized, considering a range of patient and disease features, when defining targets for glucose control [38]. Furthermore, new glucose-lowering agents, specifically the SGLT2 inhibitors and GLP-1 analogs, suggest an exciting future for CVD prevention in T2DM, as agents from these drugs classes recently have been shown to be the first to lower the CVD risk and mortality in T2DM [39, 40].

Blood Pressure Control

Hypertension has long been recognized as a major risk factor that dramatically increases the risk of CVD among T2DM patients [41, 42]. Furthermore, hypertension is a very common and often poorly controlled risk factor; for example, around 49–54% of patients with incident T2DM, and 36–54% of patients with prevalent T2DM were found to have hypertension in the Tromsø study [43]. Results from large trials, including UKPDS, HOT, and ADVANCE, showed that lowering blood pressure in patients with T2DM is beneficial and supported a blood pressure ≤ 140/90 mmHg for T2DM patients [44–46]. The ACCORD BP Trial, however, found no CV benefits in lowering blood pressure < 120 mmHg (mean attained blood pressure: 119.3 mmHg) versus < 140 mmHg (mean attained blood pressure: 133.5 mmHg), except from stroke [47]. Meta-analyses suggest that more intensive blood pressure lowering is beneficial, especially in high-risk patients [48–50]. Consequently, blood pressure treatment thresholds in patients with T2DM remain controversial, and guidelines differ to this day [51]. Trials evaluating blood pressure-lowering therapy among hypertensive and non-hypertensive T2DM patients would help elucidate whether added benefits are achieved with a goal of 120–130 mmHg versus 130–140 mmHg.

Lipid Control

Like hypertension, dyslipidemia is one of the CV risk factors which is more common in patients with T2DM than in the general population, and is characterized by higher levels of atherogenic LDL-C and triglycerides, and lower levels of protective HDL-C, which are all associated with increased CVD risk [52, 53]. There is evidence that lipid-lowering medication reduces the risk of CVD events in patients with T2DM, as shown in the CARDS trial and MRC/BHF Heart Protection Study [54, 55], and the most recent US cholesterol guidelines suggests that all T2DM patients aged 40–75 and a LDL-C ≥ 70 mg/dL (≥ 1.8 mmol/L) should initiate moderate-intensity statin therapy without estimating 10-year atherosclerotic CVD risk, and that high-intensity statin therapy can be used in those with multiple risk factors or aged 50–75 to reach at least 50% reduction in LDL-C levels.

Value and Recent Status of Multiple Risk Factor Control

Composite risk factor control has been shown to reduce CVD risk and mortality. Yet, studies testing multiple risk factor control interventions are scarce and observational studies differ with respect to design, and the population, risk factors, and outcomes studied. Here we summarize the key and most recent studies for multiple risk factor control in T2DM, with an overview presented in Table 1.

The Steno-2 study was the first clinical trial to quantify the effect of multifactorial intensive risk factor control, consisting of behavior modification and poly-pharmacologic therapy, in patients with newly diagnosed T2DM. After 8 years of follow-up, patients in the intensive treatment group had a 53% risk reduction in CV events compared to patients in the conventional therapy group [60]. At this time, use of statin, aspirin, angiotensin-converting-enzyme (ACE) inhibitor, and angiotensin-receptor blocker (ARB) therapy had increased in the intensive group, and was used significantly more than in the conventional therapy group. Furthermore, there was a significantly larger decline in HbA1c, systolic and diastolic blood pressure, cholesterol, and triglyceride levels and dietary fat intake (including saturated fatty acids) in the intensive-therapy group.

During post-trial follow-up period, the investigators found sustained benefits, including a 57% reduction in CV mortality and 59% reduction in CV events after 13 years [33], and that a median of 7.9 years of life was gained among patients randomized to the intensive therapy group versus the conventional therapy group after 21 years [34••]. The MIND.IT study supported the effectiveness and feasibility of an intensive therapy approach to improve risk factor control in T2DM. This cluster-randomized trial tested intervention with multifactorial intensive risk factor control against conventional diabetes care in 1461 CVD-free T2DM patients in a clinic-based setting. After 2 years, a larger proportion in the intensive-therapy group used antihypertensive, statin, and aspirin therapy and reached not only target levels for BMI, HbA1c, cholesterol, and triglyceride levels, but also had significant and lasting improvement of these factors, compared to the conventional care group [66].

Similarly, the cluster-randomized ADDITION-Europe trial tested an intensive stepwise lifestyle and therapy regimen inspired by the Steno-2 study, or conventional diabetes care in newly screen detected T2DM patients at primary care practices in Northern Europe. After 5 years, the intervention to promote early intensive management was associated with a non-significant 17% reduction in the incidence of CVD events. However, only slightly yet significantly more patients in the intensive-therapy group received pharmacotherapies and reached target levels for HbA1c, cholesterol, and blood pressure [56•]. The lack of difference between groups should

Table 1 Recent studies examining multiple risk factor control in type 2 diabetes with CVD and mortality outcomes

Study name, author, and year	Study design and follow-up	Intervention	Studied population	Risk factors assessed	Primary outcome	Country	MRFC success
ADDITION-Europe, Griffin et al. (2011) [56•]	Cluster-randomized, parallel group trial (5-year follow-up)	Intervention group: intensive treatmentof multiple risk factors. Control group: routine diabetes care	3.057 screen-detected T2DM patients from 343 general practices	HbA1c, BP, total cholesterol	Composite of CV disease, CV death, revascularization, and non-traumatic amputation	Denmark, the Netherlands, UK	No
Shi et al. (2013) [57]	Retrospective cohort study (4.5-year follow-up)	–	75,646 Veterans with T2DM	HbA1c, LDL-C	Composite of death from CV events, non-fatal MI, and non-fatal stroke	USA	Yes
BARI 2D Trial, Bittner et al. (2015) [58]	Protocol-guided study (5-year follow-up)	Protocol-guided intensive medical therapy	2265 T2DM patients with CHD	HbA1c, BP, smoking status, TG, non-HDL-C	Death, composite of death, MI, and stroke	USA, Canada, Brazil, Mexico, the Czech Republic, and Austria	Yes
Wan et al. (2017) [59]	Retrospective cohort study (5.5-year follow-up)	–	144,271 CVD-free T2DM patients	HbA1c, BP, LDL-C	Total CVD (coronary heart disease, stroke, and heart failure)	China	Yes
Steno-2 Study, Gæde et al. (2003) [60]; Gæde et al. (2008) [33]; Gæde el al. (2016) [34••]	Clinical trial (8-year randomization, 13–21-year observational follow-up)	Behavior modification and intensive pharmacologic therapy directed at hyperglycemia, hypertension, dyslipidemia, and microalbuminuria, secondary prevention of CVD with aspirin	160 T2DM patients.	HbA1c, BP, total cholesterol, HDL-C, triglycerides	Composite of death from CV causes non-fatal MI, non-fatal stroke, revascularization, and amputation	Denmark	Yes
TECOS trial, Pagidipati et al. (2017) [61]	Clinical trial with secondary analysis of baseline risk factors in the intention-to-treat group (3 years of follow-up)	–	13,616 T2DM patients with prior CVD and well-controlled hyperglycemia treated with sitagliptin	BP, LDL-C, smoking status, ACEI or ARB use, aspirin use	Composite of CV death, non-fatal MI, and non-fatal stroke	38 countries	Yes
Wong et al. (2016) [62]	Retrospective cohort study (11 years of follow-up)	–	2018 diabetes patients from the Atherosclerosis Risk in communities (ARIC) study, Multi-Ethnic Study of Atherosclerosis (MESA), and Jackson Heart Study (JHS)	HbA1c, BP, LDL-C	Incident CVD (MI, CHD death, cardiac procedure, stroke, or HF) and CHD (MI, CHD death, cardiac. or procedure)	USA	Yes
Saydah et al. (2017) [63]	Retrospective cohort study (5.4–year follow-up)	–	3335 diabetes patients from the National Health and Nutrition Examination Survey 1999–2001	HbA1c, BP, non-HDL-C	Death	USA	Yes
Hamada et al. (2018) [64]	Retrospective population-based cohort study (5.7-year follow-up)	–	11,431 T2DM patients with CKD	HbA1c, BP, total cholesterol, smoking	All-cause death, CV death. CV events (CHD and stroke)	UK	Yes
Rawshani et al. (2018) [65••]	Retrospective population-based cohort	–			Death, MI, stroke, HF	Sweden	Yes

Table 1 (continued)

Study name, author, and year	Study design and follow-up	Intervention	Studied population	Risk factors assessed	Primary outcome	Country	MRFC success
	study (5.7-year follow-up)		433,619 T2DM patients (2,168,095 matched controls)	HbA1c, BP, LDL-C, smoking, albuminuria			

ACEI angiotensin-converting enzyme inhibitor, ARB angiotensin-receptor blocker, BP blood pressure, CHD coronary heart disease, CKD chronic kidney disease, CV cardiovascular, CVD cardiovascular disease, HbA1c hemoglobin A1c, HDL-C high-density lipoprotein cholesterol, HF heart failure, LDL-C low-density lipoprotein cholesterol, non-HDL-C non-high-density lipoprotein cholesterol, TG triglycerides, MI myocardial infarction, MRFC multiple risk factor control

be seen in light of a lower than expected CVD outcome rate in the control group presumably owing to the early and high quality of delivered care in both groups, combined with a suboptimal adherence to treatment algorithms in the intensive-therapy group.

Despite significant improvement in risk factors in all three trials, the proportion of patients reaching target levels in the intensive-therapy groups varied greatly, to which the trial duration and target levels also must be considered. In the Steno-2 study > 70% reached the cholesterol target, which also was the most commonly achieved risk factor target in the ADDITION-Europe trial with more than > 80% at target. Less than 50% reached the cholesterol target in the MIND-IT trial, but > 50% of patients reached HbA1c levels. In contrast, HbA1c was reached by less than 20% in the Steno-2 study but > 70% in the ADDITION-Europe trial. Blood pressure targets were reached by < 50% in all three trials. Thus, cholesterol seems to be the risk factor most often at target after multifactorial therapy intervention. This observation was supported by a recent study from Denmark, which looked at patients with high-risk T2DM referred to a specialized diabetes center for a short-term treatment program directed at HbA1c, blood pressure, and cholesterol levels. The goal for cholesterol was reached by 65% versus 52% at baseline, HbA1c by 58% versus 31% at baseline, and blood pressure by 34% versus 24% at baseline. Overall, 24% (starting at 8%) reached target levels of both HbA1c, blood pressure, and LDL-C [67]. Consequently, efforts to improve composite risk factor in clinical practice lead to improvements, but some risk factors are more difficult to control and risk factor status seem to vary greatly with the studied population. For example, in the USA, even though there seems to have been a modest improvement in risk factor control over time, only 24% of diabetes patients met target levels for HbA1c, blood pressure, and LDL-C in 2010. Overall, HbA1c and blood pressure control was achieved by 42% and LDL-C by 32% [68]. In Europe, only 6.5% met target levels for HbA1c, blood pressure, and LDL-C in 2009–2010. Overall, LDL-C and HbA1c was achieved by 55% and 54%, whereas blood pressure control was achieved by only 19% [27].

In summary, despite progress in CV risk factor management for patients with T2DM, it seems that optimal control of targeted risk parameters remains difficult to achieve without a structured treatment plan.

Since the Steno-2 study there has been paucity in trials studying the effects of multiple risk factor control. Further insight into the importance of risk factor control for CVD must be extracted from observational studies.

The largest and most recent observational study by Rawshani et al. explored the value of multiple risk factors at target in the Swedish population including 433,619 T2DM patients. Those with T2DM and all five risk factors (HbA1c, LDL-C, albuminuria, smoking, and blood pressure) at target

were found to have similar risks of death, myocardial infarction, and stroke as matched controls without T2DM, although there was still a 45% increased risk of heart failure despite control of these risk factors. The study, however, did not consider changes in risk factors during follow-up, and whether medical therapy was used prior to baseline to improve risk factors. Thus, the study highlights the predictive value of diagnostic metabolic status for future CVD risk rather than the impact of controlling multiple risk factors. Only 5% of those with T2DM were free of all five investigated risk factors, with 23% having one risk factor outside target range. Furthermore, the study found that there was a stepwise increase in CVD events and death for each risk factor not at target [65••]. This incremental association between risk factor status and CVD risk has been reported in numerous other studies, as mentioned below.

In a pooled US cohort, Wong et al. found among 2018 T2DM patients with no prior CVD that only 7% were at target for HbA1c, blood pressure, and LDL-C. In multivariable analyses patients with optimal risk factor status had a 60% lower risk of coronary heart disease and 62% lower risk of CVD events compared to patients with no risk factors at target over 11 years of follow-up [62]. Furthermore, data from the National Health and Nutrition Examination Survey (NHANES) showed that being at target for HbA1c, blood pressure, and LDL-C was associated with a 37% reduction in mortality over a 5-year period compared to those with no risk factors at target [63]. Shi et al. found among 75,646 Veterans with T2DM that having both HbA1c and LDL-C at target was associated with an approximately 20% lower risk of the composite CV endpoint compared to having neither risk factor at target over a 4.5-year follow-up period [57]. In a large Chinese cohort of 141,271 primary care patients, Wan et al. found that achieving target levels for HbA1c, blood pressure, and LDL-C were associated with an incremental risk reduction, including a 55% decrease in CVD events among patients with all three factors at target compared to those with suboptimal control of all targets [59]. In a study from the UK, Hamada et al. found among 11,431 T2DM patients with chronic kidney disease that 13% met all risk factor targets for HbA1c, blood pressure, total cholesterol, and smoking status, and that this was associated with a risk reduction of 40% for all-cause and CV mortality, 27% for coronary heart disease, and 37% for stroke, compared to having one or no factors controlled [64].

Importantly, multiple risk factors control has also been shown to be effective in secondary prevention.

Among T2DM patients with prior CVD in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), there was an incremental association between the number of preventive parameters (blood pressure, LDL-C, smoking status, ACE inhibitor or ARB use, aspirin use) achieved at baseline and secondary CVD prevention, with 40% CVD reduction among those meeting all five parameters compared to those with two or less [61]. Furthermore, the Bypass Angioplasty Investigation Revascularization 2 Diabetes (BARI 2D) trial, which tested protocol-guided intensive medical therapy for risk factor control in patients with T2DM and coronary heart disease, found that having up to six CV risk factors at target, including HbA1c, blood pressure, smoking status, triglycerides, and non-HDL-C during follow-up, was incrementally associated with improved survival in a selected group of patients with T2DM and coronary heart disease [58]. More precisely, having all six risk factors controlled during follow-up, which pertained to 7% at baseline and 15% after 5 years, was associated with half the risk of death, compared to having only 0–2 risk factors controlled. After 5 years significant improvement in risk factor control compared to baseline was observed for the following: HbA1c (46% versus 40%), systolic blood pressure (62% versus 49%), diastolic blood pressure (77% versus 68%), non-HDL-C (82% versus 54%), and triglycerides (64% versus 50%), whereas improvement in smoking cessation only was observed the first year of the study.

Collectively, current evidence in this field overwhelmingly favors the concept of composite risk factor control to reduce the risk of CVD in T2DM in both primary and secondary prevention; however, many studies concomitantly report that the majority of patients exhibit suboptimal or poor levels of risk factor control. Hence, ways to ensure further improvement in risk factor profiles translating into better outcomes in patients with T2DM should be widely encouraged.

Relative Importance of Risk Factors

With the importance and recent status of multiple risk factor control established, the question of what risk factor is the most important one continue to be a common and relevant clinical question surrounding diabetes management. Mixed results have appeared in the quest to elucidate this. In a meta-analysis of from 2001, Huang et al. found that blood pressure and lipid control was associated with a, respectively, 27% and 25% relative risk reduction in CVD risk, whereas glucose lowering was associated with a non-significant 14% risk reduction [69]. Additionally, Yudkin and colleagues compared the effect of HbA1c, blood pressure, and lipid control on CVD events among T2DM patients by combining findings from epidemiological and meta-analyses and concluded, using the 5-year number needed to treat (NNT), that the order of importance was blood pressure (NNT: 33.6), lipids (NNT: 44.4), and HbA1c (NNT: 118.5) [70]. Wan et al. found the order of importance for CVD events to be lipids, blood pressure, and HbA1c [59], which was in agreement with an analysis from the Tehran Lipid and Glucose Study, which followed 1198 T2DM patients for 10 years [71].

Although the design on the Steno-2-study did not allow for conclusions to be drawn regarding this question, a secondary analysis based on estimations from the UKPDS risk engine, indicated that lipid control accounted for 73% of the observed decrease in CVD, with HbA1c accounting for 16%, and blood pressure control 11% [72]. Also using the UKPDS risk engine, Wong et al., estimated based on the 2007–2012 NHANES, that 13.7% of coronary events within 10 years could be prevented with optimal cholesterol control, whereas the numbers were 11.6% for HbA1c control and 6.7% for blood pressure [3]. Rawshani et al. found that the strongest predictor of death was smoking, however that HbA1c was the strongest predictor of stroke and acute myocardial infarction. Smoking was also the most important risk factor for CVD in women with T2DM in the Million Women Study [6].

To sum, the difference in design, population, follow-up, interventions, and outcomes assessed impede direct comparisons of studies. As of now, there is no consensus on what risk factor is most important and neither that focusing on just a single risk factor is beneficial, especially since the individual risk factors influence on the natural history of T2DM is poorly understood. Crucially, current evidence suggests that HbA1c control is important, but not necessarily the principal factor in preventing CVD, and that T2DM should be treated as a cardiovascular disease rather than merely a disorder of blood glucose control.

Barriers to Risk Factor Control

The reasons for poor risk factor control and unsatisfactory outcomes in T2DM are broad and multifaceted. Based on the results from the recent International Diabetes Federation (IDF) multi-country survey, "Taking Diabetes to Heart," 25% of patients with T2DM have never discussed CV risk factors with a health care professional and one in three reported that they could only do what their doctor would tell them in relation to T2DM and CVD. Moreover, although two out of three had CV risk factors or experienced a CVD event, one in four considered themselves to be at no or low risk of CVD [73]. These findings suggest that many T2DM patients underestimate their own CVD risk and that health care providers play a key role for information and advice. A study from Northern California including 161,697 T2DM patients sought to elucidate some overall mechanisms for not reaching risk factor targets and found that both patient non-adherence and lack of therapy intensification by clinicians occurred in 53–68% of patients with above-target levels of HbA1c, blood pressure, or LDL-C, with lack of therapy intensification being more common [74].

Patient adherence is fundamental for improving risk factor control but is not straightforward as the degree of adherence may differ substantially depending on the targeted component in diabetes management, such as glucose monitoring, administration of medication, diet, and physical activity. Important negative correlates for adherence behaviors are complex treatment, long duration of disease, high out-of-pocket costs, and perceived barriers of care, as well as a multitude of intrapersonal and interpersonal factors, and environmental aspects [75].

Therapeutic inertia has been demonstrated for both HbA1c [76], blood pressure [77], and lipid control [78]. The gap between evidence-based best practice and implementation by health care providers is widely recognized but may not be surprising given the complexity of diabetes management, including the coordination of care between primary care physicians and multiple sub-specialty providers. A meta-analysis by Tricco et al. showed that quality improvement strategies are important for improvement in diabetes care. Nonetheless, such strategies were only found effective when baseline HbA1c was above 8.0% when targeting health care providers, whereas strategies targeted at patients were found beneficial regardless of baseline HbA1c. Promotion of self-management, team changes, and patient education were all strategies associated with significant reductions in both HbA1c, blood pressure, and LDL-C after the strategy intervention had ended [79]. Furthermore, a systematic review focusing on primary care interventions to improve CV risk factors found that multidisciplinary team collaborations combined with various interventions were more effective that single interventions aimed at primary or community care professionals in improving HbA1c [80].

Even with proven effectiveness of various quality improvement strategies and use of multidisciplinary teams for risk factor optimization, the approach of how to deliver care in an integrated manner targeted at the right patients at the right time remains a challenge. Effective integration of advances made in technology, monitoring, and treatment strategies is crucial to overcome such challenges and move towards a more dynamic and individualized model of diabetes care. Yet, despite advances in the field of diabetes care, societal factors such as health care systems and financial models play an integral role in responding to these [81].

Conclusion

Composite risk factor control in T2DM constitutes a critical approach to mitigating CVD risk amidst a global diabetes crisis. Current evidence suggests that a holistic approach aiming to optimize all modifiable CV risk factors early on through intensive and sustained lifestyle changes supported by individualized polypharmacotherapeutic interventions can have a dramatic influence on the disease trajectory for patients with T2DM. These findings should strongly encourage health care systems to promote the use of well-functioning

multidisciplinary care teams and empower clinicians and patients alike to engage in patient-centered diabetes care with the perspective to improve quality of life and reduce CV morbidity and mortality. Furthermore, efforts to address and tackle factors for patient non-adherence, clinical inertia, and ineffective care models are important steps towards improving risk factor control in T2DM.

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Compliance with Ethical Standards

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- • Of importance
- •• Of major importance

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