

Pharmacotherapeutic Options for the Prevention of Cardiovascular Disease in Patients with Type 2 Diabetes

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Abstract: Type 2 diabetes is well recognized as an independent risk factor for cardiovascular disease (CVD). In turn, CVD is the leading cause of morbidity and mortality in patients with type 2 diabetes. The impact of glycemic control in reducing microvascular complications is now well accepted. Although improving glycemic control is also beneficial for the prevention of macrovascular diseases, adequate treatment of hypertension and hyperlipidemia is also essential. In fact, studies have repeatedly demonstrated the safety and efficacy of antihypertensive and antihyperlipidemic therapies for the prevention of CVD in patients with type 2 diabetes. This article reviews the impact of commonly used antidiabetic, antihyperlipidemic, antihypertensive and antiplatelet agents on reducing CVD risk in patients with type 2 diabetes.

Keywords: type 2 diabetes, cardiovascular disease, hyperlipidemia, hypertension

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Introduction

Diabetes is associated with an increased risk of cardiovascular disease (CVD).¹ A number of longitudinal epidemiological studies have shown that the risk of CVD-related mortality in diabetic patients is more than twice that of age-matched people.^{2,3} Moreover, among patients with type 2 diabetes, even after correcting for other known cardiovascular risk factors, the incidence of myocardial infarction (MI) or stroke is increased by 2–3-fold and the risk of death is increased by 2-fold,⁴ suggesting that some characteristics of diabetes confer an excessive propensity toward CVD.

Hyperglycemia is the main diagnostic feature of diabetes and is the target for antidiabetic therapy. Maintaining good glycemic control is associated with marked reductions in the risk of developing retinopathy, nephropathy and neuropathy in patients with type 1⁵ and type 2^{6,7} diabetes. Meanwhile, meta-analysis of randomized controlled trials reported before 2000, including Diabetes Control and Complications Trial (DCCT),⁸ UK Prospective Diabetes Study (UKPDS)^{6,9} and Kumamoto study,¹⁰ revealed that intensive diabetes therapy during the early stages of diabetes has long-term beneficial effects on the risk of macrovascular events in type 1 (RR 0.38, 95% CI 0.26–0.56) and type 2 diabetes (RR 0.58, 95% CI 0.38–0.89).¹¹

From epidemiological studies, there is ample evidence showing that the risk of cardiovascular mortality increases with the increasing plasma glucose and HbA_{1c} levels.^{12,13} Moreover, a direct association between glucose tolerance and cardiovascular events has been reported.^{14–17} Particularly in the Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE), the risk for CVD, coronary artery disease and stroke increased when moving from impaired fasting glucose (IFG) to impaired glucose tolerance (IGT) and overt diabetes.¹⁸ These observations support the view that hyperglycemia is a continuous risk factor for cardiovascular mortality.¹⁹ However, while the effects of hyperglycemia appear to be most apparent in determining microvascular risk, this does not seem to be the case for macrovascular complications. The UKPDS clearly showed that the incidence of MI is much greater than that of retinopathy at the same degree of HbA_{1c}.²⁰ This apparent paradox can be explained by acknowledging

the multifactorial nature of cardiovascular risk in patients with type 2 diabetes, and many of these factors have emerged in the UKPDS. In a ranking analysis, HbA_{1c} turned out to be the third most important factor in determining cardiovascular risk in patients with type 2 diabetes.⁶ The catalytic effect of diabetic hyperglycemia were also supported by the classic Multiple Risk Factor Intervention Trial (MRFIT).²¹ In that study, cardiovascular mortality increased with increasing number of coexisting cardiovascular risk factors, such as hypercholesterolemia, hypertension and smoking. Similar trends may be apparent in patients with diabetes, although the risk is magnified by concomitant hyperglycemia. More recently, re-analysis of the UKPDS results have revealed a powerful interaction between glycemic control and blood pressure (BP) control in increasing the risk for all-cause mortality, MI and stroke.²² Therefore, to prevent diabetic macroangiopathy, it is important to improve glycemic control concomitantly with other risk factors in patients with diabetes.

In this review, we discuss the synergistic effects of antidiabetic agents and commonly used risk management tools targeting atherosclerotic diseases in patients with type 2 diabetes.

Glycemic Control Prevention of CVD by polytherapy with antidiabetic agents

Although hyperglycemia increases the risk of macrovascular complications,²⁰ the impact of intensive glycemic control on macrovascular complications, including CVD, stroke, and peripheral vascular disease, remains uncertain. Generally, interventions that increase insulin supply (eg, insulin itself and sulfonylureas) have proven less promising for limiting cardiovascular complications than those that improve glucose utilization or reduce insulin resistance. Indeed, in one arm of the UKPDS, metformin monotherapy decreased the prevalence of MI by 39% in overweight individuals, a benefit not seen in patients given metformin plus a sulfonylurea or insulin.⁶ Since long-term follow up of 3,277 patients after the initial analysis of UKPDS⁶ revealed that, while differences in HbA_{1c} between the groups were lost within the first year after the trial ended, the intensive glycemic control group experienced significant reductions in the rates of MI and all-cause mortality in all treatment groups



(ie, sulfonylurea, insulin or metformin), as well as a sustained risk reduction of microvascular disease.²³ These results by UKPDS suggested that early and intensive antidiabetic therapy was recommended in patients with type 2 diabetes, especially those with a shorter duration of diabetes and without a history of CVD.²⁴ Three large randomized intervention trials were initiated to further examine the effects of intensive glycemic control on macrovascular outcomes in patients with type 2 diabetes: Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,²⁵ Action in Diabetes and Vascular Disease-Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) trial²⁶ and Veterans Affairs Diabetes Trial (VADT).²⁷ The main characteristics of these studies are summarized in Table 1. The primary outcomes of these trials differed. Intensive glycemic control resulted in a significant

change in the primary outcome in the ADVANCE trial, but not the other trials. In the ADVANCE trial, intensive glucose control reduced the incidence of combined major macrovascular and microvascular events [hazard ratio (HR): 0.90; 95% CI: 0.82–0.98]. However, the risk for macrovascular events alone was not significantly affected by intensive glucose control (HR: 0.94; 95% CI: 0.84–1.06). Notably, none of these three trials reported a significant reduction in cardiovascular mortality with intensive glycemic control. Moreover, despite the finding that intensive glycemic control was associated with a decreased risk of MI, the ACCORD trial was prematurely terminated because provisional analyses revealed a higher incidence of total and cardiovascular mortality in patients randomized to intensive glucose control (HR for cardiovascular death: 1.35; 95% CI: 1.04–1.76). Collectively, these

Table 1. Recent randomized cardiovascular outcome trials with standard glycemic control strategies in patients with type 2 diabetes.

	ACCORD	ADVANCE	VADT
Baseline characteristics			
N	10251	11140	1791
Gender (% of male)	61	57	97
Mean age (years)	62.2	65.8	60.4
Duration of diabetes (year)	10	7	10
History of macrovascular disease (%)	35.2	32.2	40.4
Mean HbA _{1c} (%)	8.3	7.5	9.4
Study protocol characteristics			
Goal of HbA _{1c} (%)	I: <6.0 S: 7.0–7.9	I: ≤6.5 S: target defined on basis of local guidelines	Absolute HbA _{1c} reduction of 1.5% in intensive group compared with standard group
Glycemic control strategy	Different glucose lowering agents and/or insulin by each physician	I: gliclazide (+ other treatment, if required) S: treatment by each physician without gliclazide	I: BMI > 27: maximal doses of metformin + rosiglitazone. BMI < 27: glimepiride + rosiglitazone. If HbA _{1c} ≥ 6.0, use insulin S: Half doses of intensive treatment. If HbA _{1c} ≥ 9.0, use insulin
On-study characteristics			
Median follow-up (year)	3.4	5.0	5.6
Median achieved HbA _{1c} (%)	I: 6.4, S: 7.5	I: 6.5, S: 7.3	I: 6.9, S: 8.4
On insulin at end point (%)	I: 77, S: 55	I: 41, S: 24	NS
Outcomes			
Primary outcome	Composite of non-fatal MI, non-fatal stroke and cardiovascular death	Composite of major macrovascular and microvascular events	Composite of major cardiovascular events
Risk for primary outcome (95% CI)	HR: 0.90 (0.78–1.04)	HR: 0.90 (0.82–0.98)	HR: 0.88 (0.74–1.05)
Risk for total mortality (95% CI)	HR: 1.22 (1.01–1.46)	HR: 0.93 (0.83–1.06)	HR: 1.07 (0.81–1.42)

Abbreviations: BMI, body mass index; FPG, fasting plasma glucose; HR, hazard ratio; I, intensive treatment arm; MI, myocardial infarction; NS, not stated; RR, relative risk; S, standard treatment arm.



results highlight the need for further clarification of the impact of glycemic control.^{24,28}

Prevention of CVD by monotherapy with antidiabetic agents

Several reports have shown beneficial effects of antidiabetic monotherapy on the risk of CVD in patients with type 2 diabetes. The UKPDS demonstrated that metformin monotherapy decreased the incidence of MI in overweight subjects with type 2 diabetes,⁶ suggesting that metformin has beneficial effects on CVD. In terms of newer agents, in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study, the thiazolidinedione pioglitazone reduced a secondary endpoint consisting of heart attack, stroke and cardiovascular death.²⁹ Moreover, a meta-analysis of trials of pioglitazone highlighted the possibility of an ischemic cardiovascular benefit of this drug.³⁰ This evidence suggests that the reduction of insulin resistance may be a practical therapy for the prevention of CVD in type 2 diabetes. However, in the absence of definitive prospective cardiovascular trials, several meta-analyses have demonstrated that another thiazolidinedione, rosiglitazone increased cardiovascular risk, which was not the case for pioglitazone.³¹⁻³³ This topic has drawn attention to the impact of antidiabetic therapies on cardiovascular safety.

Evidence from large clinical trials has also suggested a link between postprandial hyperglycemia (PPHG) and CVD risk in type 2 diabetes. The Diabetes Intervention Study in patients with newly diagnosed type 2 diabetes showed that PPHG predicted the risk of MI.³⁴ In that study, the baseline PPHG levels were significantly higher in patients who died during the follow-up than in the survivors. By contrast, fasting blood glucose (FBG) levels did not differ significantly between those who survived and those who died during the study. Effective PPHG management in individuals with IGT or type 2 diabetes can also reduce the risk of CVD endpoints. In the Study To Prevent Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM) trial, the α -glucosidase inhibitor acarbose, an agent that specifically reduces PPHG, reduced the risk of progression of IGT to diabetes by 25% over 3.3 years.³⁵ Furthermore, PPHG control with acarbose was associated with a 34% reduction in new cases of hypertension and a 49% reduction

in cardiovascular events during the same follow-up period.³⁶ Similar cardiovascular risk reductions in patients with type 2 diabetes were detected in a meta-analysis of seven long-term studies of acarbose.³⁷ Further evidence for the cardiovascular benefits of controlling PPHG comes from a trial of diabetes patients treated with the insulin secretagogues repaglinide and glyburide.³⁸ This study showed that PPHG control had a greater effect on carotid artery atherosclerosis regression than on reducing fasting hyperglycemia. On the other hand, in the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial, the short-acting insulin secretagogue nateglinide failed to reduce PPHG or reduce progression to overt type 2 diabetes or development of its complications, such as MI and stroke, in individuals with IGT.³⁹ Data from the Effects of Prandial versus Fasting Glycemia on Cardiovascular Outcomes in Type 2 Diabetes (Heart2D) trial demonstrated a lack of effectiveness of targeting PPHG with an insulin regimen in patients with type 2 diabetes following MI.⁴⁰ However, that study was underpowered, which may explain the absence of positive outcomes.

Based on the current evidence, it is not yet conclusive whether targeting PPHG has any real benefits, so further studies are needed to clarify the benefit of management of PPHG in patients with type 2 diabetes. Newer agents, particularly incretin-based therapies like glucagon-like peptide-1 analogues and dipeptidyl peptidase-IV inhibitors significantly lower PPHG, but cardiovascular endpoint data are not yet available for these drugs.

Antihyperlipidemic Agents

Dyslipidemia, an established risk factor for CVD, affects almost 50% of patients with type 2 diabetes.⁴¹ Similar to hyperglycemia and hypertension, dyslipidemia is a modifiable CVD risk factor that is commonly uncontrolled in patients with diabetes.⁴¹ HMG-CoA reductase inhibitors (statins) are known to reduce the incidence of cardiovascular events and death by inducing functional changes of atherosclerotic lesions.⁴²⁻⁴⁵ Moreover, because of these benefits, which were apparent in many clinical studies (summarized in Table 2),⁴⁶⁻⁵⁴ statin therapy is recommended as the initial pharmacological treatment for lowering low-density lipoprotein (LDL)-cholesterol

**Table 2.** Effects of primary or secondary prevention using statins on cardiovascular event in patients with diabetes.

Trial	Treatment	Number of patients	Type of event	Relative risk reduction (%)
4S ⁴⁴	Simvastatin vs. placebo	202	Secondary prevention (CHD-related death or nonfatal MI)	55 (<i>P</i> = 0.002)
4S reanalysis ⁴⁵	Simvastatin vs. placebo	483	Secondary prevention (CHD-related death or nonfatal MI)	45 (<i>P</i> = 0.01)
HPS ⁴⁶	Simvastatin vs. placebo	5,963	Primary and secondary prevention (Major coronary event, stroke, or revascularization)	22% (<i>P</i> < 0.0001)
CARE ⁴⁷	Pravastatin vs. placebo	586	Secondary prevention (CHD-related death or nonfatal MI)	25% (<i>P</i> = 0.05)
PPP project ⁴⁸	Pravastatin vs. placebo	1,444	Secondary prevention (CHD-related death, nonfatal MI, CABG or PTCA)	26% (<i>P</i> = 0.002)
LIPID ⁴⁹	Pravastatin vs. placebo	782	Secondary prevention (CHD-related death, nonfatal MI)	19% (<i>P</i> = 0.11)
LIPS ⁵⁰	Fluvastatin vs. placebo	202	Secondary prevention (CHD-related death, nonfatal MI, revascularization)	47% (<i>P</i> = 0.0088)
ASCOT-LLA ⁵¹	Atorvastatin vs. placebo	2,532	Primary prevention (Non-fatal MI and fatal CHD)	16% (<i>P</i> = 0.43)
CARDS ⁵²	Atorvastatin vs. placebo	2,838	Primary prevention (acute CHD events, stroke, or revascularisation)	37% (<i>P</i> = 0.001)

Abbreviations: 4S, Scandinavian Simvastatin Survival Study; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; CABG, coronary artery bypass grafting; CARDS, Collaborative Atorvastatin Diabetes Study; CARE, Cholesterol and Recurrent Events Trial; CHD, coronary heart disease; CHF, congestive heart failure; HPS, Heart Protection Study; LIPID, Long-Term Intervention with Pravastatin in Ischemic Disease Study; LIPS, Lescol Intervention Prevention Study; MI, myocardial infarction; PPP, Prospective Pravastatin Pooling Project; PTCA, percutaneous transluminal coronary angioplasty; UAP, unstable angina pectoris.

(LDL-C) levels in patients with type 2 diabetes.⁵⁵ Patients with diabetes are also at risk of other atherogenic lipid abnormalities including elevated smaller LDL particle, decreased high-density lipoprotein cholesterol (HDL-C) and increased triglyceride (TG) levels.⁵⁶ Therefore, an aggressive approach to control CVD risk factors, especially dyslipidemia, is essential in all patients with diabetes. However, clinical trial data related to the treatment of such patients (eg, high smaller LDL particles, low HDL-C and high TG) are less robust than those for the treatment of high LDL-C. Canner et al⁵⁷ reported that nicotinic acid can reduce CVD outcomes, although that study consisted of individuals without type 2 diabetes. Gemfibrozil was also reported to decrease rates of CVD events people without^{58,59} and with diabetes.⁵⁸ However, in a large trial of patients with diabetes, fenofibrate failed to reduce overall cardiovascular events.⁶⁰

According to the recommendations of the American Diabetes Association (ADA), the first priority of dyslipidemia management is to lower LDL-C levels to <100 mg/dL for primary prevention and <70 mg/dL for secondary prevention in patients with type 2 diabetes.⁵⁶ The Japanese Diabetes Society (JDS) recommends targets of <120 mg/dL for primary prevention and <100 mg/dL for secondary prevention.⁶¹ Both the ADA and JDS recommend the use of statins for initial pharmacotherapy.^{56,61} However, as described above, patients with type 2 diabetes often have multiple derangements in their lipid profile that require multiple treatments. If the HDL-C level is <40 mg/dL and LDL-C level is 100–129 mg/dL, gemfibrozil or niacin might be used for patients intolerant to statins.

Niacin is the most effective agent for raising HDL-C levels. At high doses, niacin can also substantially



increase blood glucose levels. However, recent studies have demonstrated that modest doses of niacin (750–2000 mg/day) substantially improve LDL-C, HDL-C and TG levels, but only modestly changes blood glucose levels, which are generally amenable to adjustment of the patient's antidiabetic medications.⁵⁶ Combination therapy (eg, statin plus fibrate or statin plus niacin) should be used with caution in patients with type 2 diabetes because the rate of adverse events is increased with the use of combination therapy, and the effects of combination therapy on CVD outcomes are unknown.⁵⁶ However, ACCORD-Lipid trial demonstrated that the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal MI, or nonfatal stroke, as compared with simvastatin alone. These results do not support the routine use of combination therapy with fenofibrate and simvastatin to reduce cardiovascular risk in the majority of high-risk patients with type 2 diabetes.⁶² Further studies are needed to clarify the benefit of combination therapy with statin and fibrate for the prevention of CVD in patients with type 2 diabetes.

Antihypertensive Agents

An epidemiological study of the general population has shown that the cardiovascular risk starts to increase above a BP of 115/75 mmHg, and then doubles for every 20 mmHg increase in systolic BP (SBP) and for every 10 mmHg increase in diastolic BP (DBP).⁶³ Each subsequent 20-mmHg increase in SBP or 10-mmHg in DBP also doubles the risk of cardiovascular-related death.^{63,64} Generally, BP lowering provides beneficial outcomes in patients with type 2 diabetes. The UKPDS⁶⁵ showed that tight control of BP (144/82 mmHg) compared with less aggressive BP control (154/87 mmHg) conferred an overall 24% risk reduction in fatal and nonfatal diabetes-related endpoints, including a 37% risk reduction in microvascular complications and a 32% risk reduction in diabetes-related deaths.⁶⁵

Current guidelines from the ADA,⁵⁶ the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7),⁶³ the National Kidney Foundation⁶⁶ and the JDS⁶¹ recommend that SBP and DBP should be reduced to <130 mmHg and <80 mmHg, respectively, in patients with type 2 diabetes.

Although most hypertension and renal guidelines suggest a BP target lower than 130/80 mmHg, the "optimal" BP target for patients with diabetes are widely debated, as several randomized controlled trials^{65,67,68} have demonstrated the preferable effects of "tight" BP control on cardiovascular outcomes, but the achieved SBP in the intervention groups was never <130 mmHg.⁶⁹ This issue is further complicated by (i) the results of recent observational studies,⁷⁰ which suggest that intensive BP lowering might cause an increased risk of cardiovascular events, the so-called J-curve; and (ii) the recently published ACCORD BP trial showed no improvements in the composite primary outcome of nonfatal MI, stroke or cardiovascular death in the intensive BP lowering group (target BP: <120 mmHg).⁷¹ Therefore, further prospective studies are needed to clarify the benefits of intensive BP control on diabetic macrovascular complications.

In clinical practice, multiple antihypertensive agents are often needed to achieve sufficient BP lowering.⁶³ BP reductions achieved with an inhibitor of the renin-angiotensin system (RAS) may show unique advantages for treating hypertension.⁶⁶ Angiotensin II has direct pathobiologic effects in many tissues, and affects the progression of CVD, as well as myocardial remodeling and heart failure in patients with hypertension.⁷² Lewis et al⁷³ reported that RAS inhibition with the angiotensin-converting enzyme inhibitor (ACEI) captopril slowed the progression of renal disease in patients with type 1 diabetes. Two other studies have since established the efficacy of the angiotensin receptor blockers (ARBs), namely losartan and irbesartan, in slowing the progression of renal disease in patients with type 2 diabetes.^{74,75} In the double-blinded, randomized, parallel-group Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study,^{76,77} involving patients with hypertension and left ventricular hypertrophy, losartan was more effective than atenolol in reducing the composite primary endpoint of cardiovascular mortality, stroke and MI. This finding was essentially due to the reduction in the risk of stroke in the losartan group.^{76,77} RAS inhibition also provides beneficial effects on cardiovascular outcomes,⁷⁸ heart failure^{79–82} and nephropathy⁸³ in patients with type 2 diabetes. In a meta-analysis of 12 randomized controlled trials evaluating the efficacy of RAS inhibition in the prevention of type 2 diabetes, the incidence of newly diagnosed type 2 diabetes was



reduced by 27% and 23% with an ACEI or ARB, respectively.⁸⁴ Most recently, the BP arm of the ADVANCE trial⁸⁵ demonstrated that routine administration of a fixed combination of the ACEI perindopril erbumine and the diuretic indapamide reduced the incidence of combined microvascular and macrovascular outcomes, as well as CVD risk and total mortality. Dihydropyridine calcium channel blockers (CCBs) are also relevant treatments for patients with hypertension. Beyond causing vasodilatation by inhibiting calcium channels, the dihydropyridine CCBs provide clinical benefits in patients with coronary artery disease that might be independent of BP reductions.^{86,87} Moreover, CCBs reduced the incidence of cardiovascular events in hypertensive patients with diabetes.^{67,88} Therefore, it is very important for the prevention of diabetic macroangiopathy to enforce anti-hypertensive therapy using an ACEI, ARB and/or CCB in patients with diabetes.

Antiplatelet Therapy

It is well understood that atherothrombosis is a leading cause of death in patients with type 2 diabetes. Platelets play a pivotal role in atherothrombosis, and patients with type 2 diabetes have a marked prothrombotic state that includes increased platelet reactivity (Table 3).^{89–91} Aspirin has been demonstrated to be effective in reducing cardiovascular morbidity and mortality in high-risk patients with MI or stroke (secondary prevention).⁹² However, the Food and Drug Administration in the United States has not approved aspirin for use in primary prevention, and its net benefit among patients with no previous cardiovascular events is more controversial, for both patients with and without diabetes.⁹² Several randomized trials have examined the effect of aspirin for primary prevention of cardiovascular events and have included patients with diabetes. In particular, the Anti-thrombotic Trialists' (ATT) collaborators recently reported an individual patient-level meta-analysis of the six large trials^{93–98} of aspirin for primary prevention in the general population.⁹² Overall, the meta-analysis found that aspirin reduced the risk of vascular events by 12% (RR 0.88, 95% CI 0.82–0.94), and the largest reduction was for the nonfatal MI (RR 0.77, 95% CI 0.67–0.89). On the other hand, the effect of aspirin on major vascular events was similar for patients with and without diabetes (RR 0.88, 95%

Table 3. Platelet abnormalities in patients with diabetes.

- Platelet activation via expression of surface adhesion molecules (eg, CD31, CD62P, CD63), vitronectin receptors and PAR-1 thrombin receptor
- Expression of platelet and endothelial cell adhesion molecules (eg, PECAM-1 and VCAM-1)
- Expression of platelet surface receptors (eg, P-selectin, GP Ib, GP IIB/IIIa)
- Expression of platelet mediated thrombin
- Platelet hypersensitivity to agonists (eg, ADP, collagen, thrombin, PAF)
- Downregulation of platelet sensitivity to PGI₂ and NO
- Reduction of PGI₂ and NO production in endothelial cells
- TXA₂ production
- Acceleration of thrombopoiesis or platelet turnover resulting in generation of fresh and hyper reactive platelets
- Production of proinflammatory and proatherogenic cytokines and chemokines (eg, PF4, IL-1 β , CD40L)
- Abnormal platelet calcium and magnesium homeostasis resulting in platelet hyperactivity, hyperaggregability, and adhesiveness

Abbreviations: ADP, adenosine diphosphate; GP, glycoprotein; IL-1 β , interleukin-1 β ; NO, nitric oxide; PAF, platelet activating factor; PAR-1, protease-activated receptor-1; PECAM-1, platelet endothelial cell adhesion molecule-1; PF4, platelet factor 4; PGI₂, prostaglandin I₂; TXA₂, thromboxane A₂; VCAM-1, vascular adhesion molecule-1.

CI 0.67–1.15, and RR 0.87, 95% CI 0.79–0.96, respectively) in the six trials examined by the ATT.⁹² However, these results showed that CI was wider for those with diabetes because of the smaller number of participants with diabetes and their smaller total numbers of CVD events. Under these limitations, Pignone M et al performed a new meta-analysis that added data from three trials^{99–101} performed specifically in patients with diabetes to the data from the subgroups of patients with diabetes from the six trials included in the ATT meta-analysis,¹⁰² and they demonstrated that aspirin was associated with a 9% decrease in risk of CVD events (nonfatal and fatal MI) that was not statistically significant (RR 0.91, 95% CI 0.79–1.05). Other recent meta-analyses also demonstrated the similar results.^{103–105} Therefore, further evidences are needed to clarify the benefit of aspirin usage for the prevention of CVD in patients with type 2 diabetes.

Guidelines from the ADA recommend aspirin therapy (75–162 mg/day) for primary prevention of atherothrombosis in patients with type 2 diabetes who are at increased CVD risk (10 year risk > 10%). These patients include most men > 50 years of age



and most women > 60 years of age who have at least one additional major risk factor for CVD (eg, family history of CVD, hypertension, smoking, dyslipidemia or albuminuria).^{56,106} The ADA guidelines also suggest that aspirin should not be used for CVD prevention in adults with diabetes at low CVD risk (10 year CVD risk < 5%), including men < 50 years of age and women < 60 years of age with no major additional CVD risk factors, because the potential adverse effects from bleeding likely offset the potential benefits.⁵⁶ In these age-groups of patients with multiple risk factors (eg, 10-year risk 5%–10%), clinical judgment is required.⁵⁶ Nevertheless, the ADA recommends the use of aspirin (75–162 mg/day) as a secondary prevention strategy in patients with diabetes and a history of CVD.⁵⁶

Conclusion

CVD is the most common cause of morbidity and mortality in patients with type 2 diabetes. Although good glycemic control may be an important factor for the prevention of diabetic macrovascular complications, the management of nonglycemic risk factors using antihypertensive, antihyperlipidemic and antiplatelet agents is far more important in determining CVD risk and outcomes than glucose lowering alone in patients with type 2 diabetes.

A number of ongoing clinical trials will deliver additional evidence on the impact of glycemic control and other factors. It is hoped that these trials will provide much needed information to improve the management of diabetic macrovascular complications.

Author Contributions

Conceived and designed the experiments: TM. Analysed the data: KT. Wrote the first draft of the manuscript: KT. Contributed to the writing of the manuscript: TM, NF, EA. Agree with manuscript results and conclusions: KT, TM, NF, EA. Jointly developed the structure and arguments for the paper: KT, TM, NF, EA. Made critical revisions and approved final version: KT, TM, NF, EA. All authors reviewed and approved of the final manuscript.

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Disclosures and Ethics

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