

Cardiovascular protection in type 2 diabetes: time to ADVANCE management ACCORDing to the evidence

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Abstract: Individuals with type 2 diabetes mellitus are at very substantial risk of cardiovascular disease, and most will succumb to complications from premature coronary artery events. At the same time, the diabetic myocardium undergoes unique phenotypic alterations as a consequence of multiple structural and cellular injuries, which together form “diabetic cardiomyopathy.” Attempts to curb risk through intensive modulation of glycemia and blood pressure have proven disappointing in preventing cardiovascular events, and potentially even dangerous. Conversely, prior to development of disease, there appears to be a linear relationship between risk parameters and events. These observations are likely the consequence of widespread vascular damage, which is present at the point that glycemic thresholds meet diagnostic criteria for diabetes. This is particularly true of the microcirculation. Interventions at the prediabetic stage have been consistent with this, where early intensive risk-factor modulation has been successful in preventing events and even regressing existing risk. Upstream, the force driving these pathologies is being overweight and obesity. High-risk individuals can be identified through simple body mass parameters, with confirmation of prediabetes/metabolic syndrome with further assessment of other metabolic parameters such as glucose and lipids. A number of novel pharmacotherapies may prove beneficial at this stage, and incretin-based therapies appear particularly promising in this respect. Similarly, bariatric procedures have shown remarkable improvements in metabolic and cardiovascular outcomes, but are clearly unsuitable as a population-wide strategy. Therapeutic lifestyle change and diet have consistently shown efficacy in reversing dysglycemia, lowering blood pressure, and optimizing cholesterol profiles. However, the longevity of these improvements is often limited, and alternative approaches therefore need to be considered. With an evolving and increasingly sophisticated evidence base for nutritional interventions, there is a clear window of opportunity to rescue these individuals from the clinical sequelae of diabetes and consequent cardiovascular complications.

Keywords: hypertension, diabetes, cardiovascular risk

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) continues to rise, with over 360 million affected worldwide in 2011 and forecast to reach 550 million by 2030.¹ The financial impact of this global epidemic is devastating, with approximately 10% of the entire UK National Health Service budget spent on diabetes.² Alarming, low/middle-income countries have the highest projected increase in prevalence, which threatens to rapidly overwhelm resource-deprived health care systems.¹ Complications from T2DM are broad and progressive. Microvascular injury begins early in the disease process, and causes substantial morbidity through retinopathy, neuropathy, and nephropathy, whilst macrovascular disease, most notably cardiovascular events,

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are responsible for the majority of deaths.^{3,4} Treatment of established coronary heart disease is challenging in these patients, with atypical or silent presentations of acute myocardial infarcts.⁵ Percutaneous coronary intervention is also typically more complex.⁶ The focus has therefore been on reducing cardiovascular risk, and adopting an empirical approach of more intensified treatment targets. In this review, we summarize some of the recent trials that have addressed the issue of optimal risk-factor control in diabetes, and provide potential explanations for their findings.

Mechanisms of risk and disease

The pathophysiology of T2DM involves both insulin resistance and reduced insulin production, through progressive pancreatic beta-cell dysfunction.⁷ Chronic insulin resistance demands increased activity of pancreatic beta cells to secrete insulin. These cells eventually decompensate, and hyperglycemia follows.⁷ There is an intermediary, or “prediabetic” stage between normoglycemia and overt DM, which can involve impaired fasting glucose (IFG), where fasting plasma glucose is 6.1–6.9 mmol/L, or impaired glucose tolerance (IGT), where plasma glucose 2 hours after a 75 g glucose load is 7.8–11.0 mmol/L.⁸ The cardiovascular risk associated with hyperglycemia exists across this spectrum, from early dysglycemia to prediabetes and T2DM. By the time a formal diagnosis is made, there is already significant cardiac risk.⁸ Indeed, one-third of patients with coronary artery disease have abnormal oral glucose-tolerance test results, and 22% with acute and 14% with stable coronary heart disease have newly diagnosed T2DM. As such, there is clear excess cardiovascular risk with IFG⁹ and IGT.¹⁰ The underlying mechanisms are legion. Diabetic individuals experience accelerated atherosclerosis,¹¹ which is itself multifactorial. Dyslipidemia plays a central role, typically including elevated triglycerides and decreased high-density lipoprotein (HDL) cholesterol.¹² Along with dysglycemia, this lipid profile is frequently seen in combination with obesity and high blood pressure, which together form metabolic syndrome, a highly atherogenic predisease condition. Diabetic individuals also exhibit elevated levels of small-dense, low density lipoprotein (LDL) cholesterol, which are more penetrating and particularly susceptible to oxidation.¹¹ Lipoproteins are also the subject of glycation with elevated blood sugars, which increases the half-life of LDL cholesterol but reduces that of HDL.^{13,14}

Microvascular injury develops as a consequence of a variety of molecular pathways, including alterations in redox and inflammatory states. Diabetes is independently associated

with endothelial dysfunction,¹⁵ tipping the balance of vasoactive agents in favor of vasoconstriction, with increased levels of endothelin 1 and other constricting factors, contributing to increased peripheral vascular resistance and hypertension.^{11,16} Angiotensin II type 1 (AT₁)-receptor activation is associated with increased free radical release and oxidative stress.^{17,18} We have previously shown that blocking the AT₁ receptors with an angiotensin-receptor blocker is associated with significant improvement in resistance-vessel endothelial function in patients with T2DM.¹⁸ Cardiac autonomic neuropathy is common in T2DM and an independent risk factor for cardiovascular events.^{11,19,20} Corneal confocal microscopy is a powerful tool for the early detection of small-fiber damage in diabetes and prediabetes.²¹ Autoregulation of the small arteries is also lost in diabetes. Schofield et al demonstrated impaired myogenic responsiveness in small arteries from individuals with T2DM,²² which is thought to be the trigger to arterial wall hypertrophy and structural detriment.²³ Hyperglycemia also leads to capillary basement-membrane thickening, resulting in impaired transport of metabolites and nutrients between the circulation and tissues.²⁴ Interestingly, in patients with T1DM, improved metabolic profiles can result in regression of maladaptive hypertrophic changes of small arteries to the more favorable eutrophic remodeling.²⁵ Many of these mechanisms – autonomic dysfunction, microvascular disease, alterations to reactive oxygen species, and intracellular calcium homeostasis – lead to cellular, structural, and functional injuries, which lead to diabetic cardiomyopathy. There are a number of dedicated reviews focusing on this subject.^{15,26,27}

Optimizing cardiovascular risk: glycemic control

The UK Prospective Diabetes Study (UKPDS) was a randomized, prospective, multicenter trial of intensive glucose therapy in subjects with newly diagnosed T2DM.²⁸ The trial reported significantly reduced risk of clinically evident microvascular complications in those receiving intensive intervention,²⁸ with macrovascular benefits becoming apparent with long-term follow-up.⁴ These findings have not been reproduced in recent randomized controlled trials (summarized in Table 1): the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation)²⁹ trial and VADT (Veterans Affairs Diabetes Trial)³⁰ failed to show improved outcomes in terms of cardiovascular disease, microvascular complications, and mortality with intensive glycemic control. Indeed the ACCORD (Action to Control Cardiovascular Risk in

Table I Comparison of glycemic targets on major diabetes-related and cardiovascular outcomes

Study	End point	Number of participants	Comparison	Adjustment for covariates	Result RR/HR (95% CI)	Statistical significance
UKPDS 33 ²⁸	Diabetes-related mortality	3,867	FPG <6 mmol/L vs FPG <15 mmol/L	Multivariate	HR 0.90 (0.89–1.27)	No
UKPDS 33 ²⁸	All-cause mortality	3,867	FPG <6 mmol/L vs FPG <15 mmol/L	Multivariate	HR 0.94 (0.90–1.20)	No
UKPDS 34 ⁹¹	Diabetes-related mortality	753	FPG <6 mmol/L vs FPG <15 mmol/L	Multivariate	HR 0.58 (0.37–0.91)	Yes
UKPDS 34 ⁹¹	All-cause mortality	753	FPG <6 mmol/L vs FPG <15 mmol/L	Multivariate	HR 0.66 (0.45–0.91)	Yes
ACCORD ³¹	All-cause mortality	10,251	HbA _{1c} <6.0% vs HbA _{1c} 7.0%–7.9%	Multivariate	HR 1.22 (1.01–1.46)	Yes
ACCORD ³¹	CVD-related mortality	10,251	HbA _{1c} <6.0% vs HbA _{1c} 7.0%–7.9%	Multivariate	HR 1.35 (1.04–1.76)	Yes
ADVANCE ²⁹	All-cause mortality	11,140	HbA _{1c} <6.5% vs control	Multivariate	HR 0.93 (0.83–1.06)	No
ADVANCE ²⁹	CVD-related mortality	11,140	HbA _{1c} <6.5% vs control	Multivariate	HR 0.88 (0.76–1.04)	No
VADT ³⁰	All-cause mortality	1,791	HbA _{1c} 6.9% vs HbA _{1c} 8.4%	Multivariate	HR 1.07 (0.81–1.42)	No
VADT ³⁰	CVD-related mortality	1,791	HbA _{1c} 6.9% vs HbA _{1c} 8.4%	Multivariate	HR 1.32 (0.81–2.14)	No

Abbreviations: RR, relative risk; HR, hazard ratio; CI, confidence interval; UKPDS, UK Prospective Diabetes Study; ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation; VADT, Veterans Affairs Diabetes Trial; CVD, cardiovascular disease; FPG, fasting plasma glucose; HbA_{1c}, glycosylated hemoglobin; vs, versus.

Diabetes)³¹ trial showed a trend towards increased mortality with intensive glycemic control, leading to premature termination of the trial. The reasons behind these findings are unclear, though a number of potential causes have been postulated. There was worse prognosis amongst intensively treated patients with one or more episodes of severe hypoglycemia, but secondary analysis of all patients suffering hypoglycemic events requiring assistance showed a nonsignificant trend to lower mortality risk with intensive therapy.³² Furthermore, only one of 451 deaths in the ACCORD trial were conclusively a consequence of hypoglycemia. The substantial weight gain in intensively treated patients is also concerning, but was not shown to be associated with mortality. Indeed, these findings have led to changes in the clinical recommendation for risk targets, though there is some discrepancy between guidelines. The American Diabetes Association (ADA), the American Heart Association (AHA), the American College of Cardiology (ACC) Foundation, and the Australian Diabetes Association still advise target glycosylated hemoglobin (HbA_{1c}) levels <7%, presumably due to evidence for protection from microvascular complications.³³ The National Institute of Clinical Excellence (NICE) has now altered HbA_{1c} targets from <6.5% to between 6.5% and 7.5%,³⁴ in conjunction with recent evidence. Similarly, the International Diabetes Federation has recently changed targets for HbA_{1c}

from <6.5% to <7%,³⁵ and the joint European Society of Cardiology (ESC) and European Association for the Study of Diabetes recommend targets between 6.5% and 7.0%.³⁶

Blood pressure control

The UKPDS showed intensive blood pressure lowering was associated with major reductions in important clinical end points, including a 32% reduction in diabetes-related death, 44% reduction in stroke, and 37% reduction in microvascular end points.^{33,37} At the same time, the Hypertension Optimal Trial (HOT) demonstrated a significantly lower rate of cardiovascular events and mortality in individuals with T2DM with intensively controlled blood pressure, compared with standard management.³⁸ In the ABCD (Appropriate Blood Pressure Control in Diabetes) trial,³⁹ intense blood pressure control was not associated with improved cardiovascular end points after 5 years of follow-up. The ACCORD trial randomized patients with T2DM to either intensive blood pressure control (BP <120 mmHg) or conventional therapy. Although an impressive reduction in blood pressure to 119/64 mmHg was achieved with intensive treatment, this was not associated with an improvement in cardiovascular end points compared with a blood pressure of 134/71 mmHg.⁴⁰ It should be noted that participants in the ACCORD trial were recruited 10 years after diagnosis, and as such there was a high prevalence of

preexisting cardiovascular disease.³³ These findings were further supported in ADVANCE⁴¹ and INVEST,⁴² which did not support blood pressure lowering below 130 mmHg systolic. There is now consensus for a U-shaped relationship between blood pressure control and cardiovascular-related end points in T2DM, with no evidence for a benefit in blood pressure reduction below 130 mmHg^{33,43} and potential for adverse hypotension, hypokalemia, bradycardia, and renal impairment. This is now reflected in major guidelines, with the AHA, ADA, NICE, and ESC no longer recommending blood pressure reduction <130/80 mmHg.³³ There are exception groups at particular risk of cerebrovascular accidents, such as those with transient ischemic attacks, or certain ethnic groups, such as African Caribbeans and South Asians,^{33,44} where a lower blood pressure target might be justified. Table 2 summarizes the main trials investigating blood pressure targets on cardiovascular outcomes in T2DM.

Taking the results from UKPDS, ADVANCE, VADT, and ACCORD together, there is a suggestion that intensive glycemic modification is beneficial in the early stages of diabetes, but that this opportunity is lost later in disease. Indeed, subgroup analysis of the VADT and ACCORD trials showed that patients free of cardiovascular disease and with a recent diagnosis of diabetes gained the most benefit from intensive glycemic control.³³ Indeed, the concept of a “legacy effect” has gained interest after extended follow-up of trials, where an early, transient phase of tight glycemic control may have benefit extending many years after the

intervention period. Following completion of the UKPDS, participants in the glycemic control arm were asked to attend annual UKPDS clinics for an additional five years, but no attempts were made to maintain their previously assigned therapies. A further 5 years of follow-up was established through annual questionnaires. One year after closure of the trial, between-group differences in glycemic control were lost, yet after 10 years of follow-up, those assigned to the intensive control arm with sulfonylurea and insulin had significantly reduced risks for microvascular disease (24%), myocardial infarction (15%), death from any cause (13%), and any diabetes-related end point (9%), compared with subjects assigned to conventional therapy.⁴⁵ Similar results were seen in those assigned to metformin compared to controls.

A similar post-trial follow-up of the hypertension arm of the UKPDS has also been performed. Between-group differences in blood pressure control were lost 2 years after closure of the trial. Surprisingly, 51% of the trial participants had died by the 10-year follow-up post-closure of the trial.⁴⁵ Additionally, the significant benefits in terms of diabetes-related end points, diabetes-related death, microvascular disease, and stroke established during the trial with tight blood pressure control were not sustained after the post-trial follow-up.⁴⁵ The evidence for a legacy effect of tight blood pressure control in diabetes is therefore lacking, and indeed for initial benefits to be sustainable, blood pressure control must be sustained consistently over time.

Table 2 Comparison of blood pressure targets on major diabetes-related and cardiovascular outcomes

Study	End point	Number of participants	Comparison; target blood pressures (mmHg)	Adjustment for covariates	Result RR/HR (95% CI)	Statistical significance
UKPDS 38 ⁹²	Diabetes-related mortality	1,148	150/85 vs 200/105 (180/105)*	Multivariate	HR 0.68 (0.49–0.94)	Yes
UKPDS 38 ⁹²	All-cause mortality	1,148	150/85 vs 200/105 (180/105)	Multivariate	HR 0.82 (0.63–1.08)	No
HOT ⁹³	CVD mortality	18,790	DBP <80 vs <90	Multivariate	RR 0.90 (0.68–1.21)	No
HOT ⁹³	Total mortality	18,790	DBP <80 vs <90	Multivariate	RR 0.91 (0.74–1.10)	No
ACCORD ⁴⁰	CVD related mortality	4,733	SBP <120 vs <140	Multivariate	HR 1.06 (0.85–1.52)	No
ACCORD ⁴⁰	All-cause mortality	4,733	SBP <120 vs <140	Multivariate	HR 1.07 (0.74–1.35)	No
INVEST ⁴²	All-cause mortality	6,400	SBP 110–115 vs 125–130	Multivariate	HR 1.63 (0.97–2.75)	No
INVEST ⁴²	All-cause mortality	6,400	SBP <110 vs 125–130	Multivariate	HR 2.18 (1.17–4.09)	Yes

Note: *Initial target of 200/105 mmHg, changed after 5 years to 180/105 mmHg.

Abbreviations: RR, relative risk; HR, hazard ratio; CI, confidence interval; UKPDS, UK Prospective Diabetes Study; HOT, Hypertension Optimal Treatment; ACCORD, Action to Control Cardiovascular Risk in Diabetes; INVEST, International Verapamil Sustained Release Trandolapril Study; CVD, cardiovascular disease; DBP, diastolic blood pressure; SBP, systolic blood pressure; vs, versus.

Primordial prevention

An increasingly overweight and obese population is the primary force responsible for the rising prevalence of T2DM. The Nurses' Health Study followed 84,941 females for up to 16 years, and reported a relative risk of diabetes of 38.8 and 20.2 for women with a body mass index (BMI) ≥ 35 and 30–34.9 kg/m², respectively, compared with women who had a BMI < 23 kg/m². Weight loss improves outcomes in T2DM and delays or prevents progression from IGT/IFG to diabetes. Epidemiological data from the Framingham study⁴⁶ have shown that sustained weight loss in overweight individuals can have a primary preventative effect on the incidence of T2DM. As a result, many strategies aimed at preventing T2DM have focused primarily on weight loss. The largest study to date was conducted by the Diabetes Prevention Program⁴⁷ (DPP) research group. This involved 3,234 nondiabetic (ethnically and racially diverse) individuals with IGT of mean age 51 years and BMI 34 kg/m² randomized to placebo, metformin, or lifestyle intervention. The lifestyle-intervention group were expected to maintain a weight reduction of 7% through dietary means and physical activity, performing at least 150 minutes of moderate-intensity activity per week. Lifestyle intervention was associated with an impressive 58% reduction in the incidence of diabetes when compared with placebo and was superior to metformin. Indeed, for every 1 kg reduction in weight, there was an associated 16% reduction in the incidence of diabetes. Follow-up studies have confirmed that this preventative or delaying effect persists at 10 years.⁴⁸ Similar outcomes have been shown in the Finnish Diabetes Prevention Study⁴⁹ and the Chinese Da Qing IGT and Diabetes Study⁵⁰ where intense weight-loss interventions in IFG/IGT delayed/prevented the onset of full-blown T2DM. Indeed, Gregg et al⁵¹ have recently shown that intense weight-loss interventions (limiting calorie intake to 1,200–1,800 kcal/day and 175 minutes of physical activity/week) resulted in a significant partial remission of diabetes, defined as transition from meeting diabetes criteria to a prediabetes level of glycemia. However, recently in a cohort of overweight or obese individuals with T2DM, the Look AHEAD (Action for Health in Diabetes) research group⁵² failed to show any reduction in cardiovascular events with intense intervention focusing on weight loss (through reduced calorie intake and increased physical activity), despite greater reduction in individual risk parameters. This emphasizes that nonpharmacological interventions may be less effective later in the course of diabetes. Looking beyond weight loss alone, data have begun to accrue reporting on the

efficacy of specific nutritional interventions in reducing risk factors and preventing hard cardiovascular end points.

Although nutritional evidence has been muddled by claims from pseudoscientific fad diets introduced by media figures and food corporations, powerful data and high-quality evidence do exist for effective dietary interventions. The Early ACTID (Early ACTivity In Diabetes trial) was a randomized controlled trial that investigated the effects of an intense dietary regime (the Diabetes UK dietary guidelines⁵³) on glycemic control in 593 T2DM patients. The study found that intensive dietary intervention when instituted soon after diagnosis improved glycemic control.⁵⁴ The DASH (Dietary Approaches to Stop Hypertension) trial demonstrated that a dietary pattern consisting of (potassium-rich) vegetables, fruit, nuts, seeds, whole grains, and low-fat dairy products and low in meat, poultry, eggs, salt, and overall fat diet was effective in reducing blood pressure.⁵⁵ The DASH diet was subsequently shown also to prevent or reverse the onset of T2DM.⁵⁶ More recently, the Mediterranean diet (consisting of plenty of fruit and vegetables, olive oil, seafood, oily fish, and wine) was tested in a multicenter randomized controlled trial (the PREDIMED [Prevención con Dieta Mediterránea] trial)⁵⁷ in 7,447 patients at high risk of cardiovascular complications, compared with a control arm that involved advice to reduce dietary fat. The primary end-point event was myocardial infarction, stroke, or death from cardiovascular causes. Multivariable-adjusted hazard ratios were 0.70 (95% confidence interval [CI] 0.54–0.92) and 0.72 (95% CI 0.54–0.96) in those assigned to a Mediterranean diet with extra-virgin olive oil (96 events) and the group assigned to a Mediterranean diet with nuts (83 events), respectively, versus the control group (109 events). There were no reports of diet-related adverse effects. A recent meta-analysis of 20 randomized controlled trials, involving 3,073 patients with T2DM, low-carbohydrate, Mediterranean, and high-protein diets all led to an improvement in glycemic control (HbA_{1c} reductions of -0.12% [$P=0.04$], -0.47% [$P<0.00001$], and -0.28% [$P<0.00001$], respectively) compared with their respective control diets, with the largest effect size seen in the Mediterranean diet, which was incidentally associated with the greatest weight loss.⁵⁸ Although yet to be tested in large trials, dietary sources rich in inorganic nitrates (eg, beetroot, rocket, and rhubarb) may provide an alternative source of nitric oxide that can be supplied by the serial conversion of inorganic nitrates to nitric oxide and other bioactive nitrogen oxides.^{59,60} Carlström et al⁵⁹ produced a near-complete compensation of nitric oxide in endothelial nitric oxide synthase-deficient mice through dietary supplementation with sodium nitrate. Early clinical

studies have been very promising in terms of blood pressure reduction,⁶¹ and further trials are in development. Table 3 summarizes some of the larger studies investigating the effects of nutritional and lifestyle interventions on major diabetes and cardiovascular outcomes.

We now know that the effects of vitamin D extend beyond traditional roles in bone metabolism and skeletal mineralization, and strong associations exist with cardiometabolic health and disease. In addition to numerous epidemiological studies linking vitamin D insufficiency/deficiency with diabetes,^{62–66} parallel mechanistic studies have shown the vitamin D receptor ubiquitously expressed. Experimental studies of animal models have shown high doses of active vitamin D to prevent diabetes,⁶⁷ with underlying mechanisms involving modification of dendritic cell phenotype, lymphocyte proliferation, and cytokine production,^{68,69} as well as direct effects of vitamin D on insulin action.^{70,71} Vitamin D promotes the action of insulin in skeletal muscle and adipose tissue, through its effect on calcium handling.^{72,73} Treatment with cholecalciferol has been shown to increase the disposition index (which reflects insulin action) in a population at risk of developing diabetes.⁷⁴ Further, recent analysis of the DPP data showed those individuals in the highest tertile of vitamin D levels had a hazard ratio of 0.74 for developing diabetes when compared with those in the lowest tertile. Meta-analysis data have also supported evidence for a relationship between low vitamin D status, calcium or dairy dietary intake, and prevalence of T2DM, metabolic syndrome,^{75,76} and obesity.^{77,78} Central to the mechanisms

proposed for the observed associations between vitamin D levels, hypertension, and diabetes is alterations to the renin–angiotensin–aldosterone system. A recent systematic review of the relationship between vitamin D levels and arterial hypertension by Pilz et al concluded that adequate levels of vitamin D are associated with lower arterial blood pressures, and that the antihypertensive effect of vitamin D is greatest in individuals with a combination of both vitamin deficiency and a previous diagnosis of hypertension.⁷⁹ Although there is evidence supporting the blood pressure-lowering effect of vitamin D from a number of other small trials,⁸⁰ there remains a paucity of adequately powered trials to prove a cause-and-effect relationship to support these observations, and the results of VITAL (VITamin D and OmegA-3 Trial) are eagerly anticipated.⁸¹

A number of pharmacological and surgical strategies have been effective at preventing diabetes and reducing associated cardiovascular risk. The gastrointestinal lipase inhibitor orlistat has been shown to significantly lower fasting plasma glucose and HbA_{1c} levels.⁸² Newer incretin-based therapies, such as glucagon-like peptide-1 agonists/analogues⁸³ and dipeptidyl peptidase-4 inhibitors,⁸⁴ form a particularly promising group of antidiabetic medications, with parallel benefits in weight reduction and possibly cardiovascular risk. For a comprehensive review, please see Khavandi et al.⁸⁵ Bariatric surgery achieves weight loss by restrictive or mal-absorptive mechanisms, and has shown some truly remarkable metabolic outcomes in tandem with weight reduction.

Table 3 Studies employing lifestyle or nutritional interventions as primary prevention strategies in relation to cardiovascular outcomes

Study	End point	Number of participants	Comparison	Adjustment for covariates	Result RR/HR (95% CI)	Statistical significance
Estruch et al ⁵⁷	Major cardiovascular events*	7,447	Mediterranean diet supplemented with EVOO vs control [§]	Multivariate	HR 0.70 (0.54–0.92)	Yes
Estruch et al ⁵⁷	Major cardiovascular events*	7,447	Mediterranean diet supplemented with nuts vs control [§]	Multivariate	HR 0.72 (0.54–0.96)	Yes
Estruch et al ⁵⁷	Primary end point*	7,447	Mediterranean combined vs control diet	Multivariate	HR 0.71 (0.56–0.90)	Yes
Williamson et al ⁹⁴	All deaths	4,970	Intentional weight loss	Multivariate	RR 0.75 (0.67–0.84)	Yes
Williamson et al ⁹⁴	CVD- and diabetes-related deaths	4,970	Intentional weight loss	Multivariate	RR 0.72 (0.63–0.82)	Yes
Wing et al ⁵²	All deaths	5,145	Lifestyle intervention [†] vs control	Multivariate	HR 0.85 (0.69–1.04)	No
Wing et al ⁵²	CVD-related deaths	5,145	Lifestyle intervention [†] vs control	Multivariate	HR 0.88 (0.61–1.29)	No

Notes: [§]Advice to reduce dietary fat; [†]reduced calorie intake and increased physical activity; *composite of myocardial infarction, stroke and death from cardiovascular causes.

Abbreviations: RR, relative risk; HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease; EVOO, extra-virgin olive oil; vs, versus.

The Roux-en-Y gastric bypass, a combination of the two, is associated with the best outcomes and is therefore accepted as the criterion standard.⁸⁶ Long-term outcomes in patients undergoing obesity surgery have confirmed a reduction in overall mortality when compared with conventional treatment for obesity.⁸⁷ Evidence suggests that bariatric surgery can also induce long-term remission of T2DM in both obese and morbidly obese patients.⁸⁸ It has become clear that these benefits extend beyond those explained simply by the reduced capacity for consumption, with a wide array of alterations to gut hormones.⁸⁹ Further mechanistic insights have been gained recently from investigation of the small arteries before and after bariatric interventions, which show alteration in the function of perivascular adipose tissue.⁹⁰

Conclusion

DM confers an exceptionally high risk of cardiovascular disease. The traditional strategy has been to intensify interventions and achieve greater reductions in risk parameters. Recent randomized control trial data have failed to show benefit in terms of cardiovascular end points with this approach in patients with established T2DM. At an earlier stage in the disease course, however, there is potential to improve risk and prevent cardiovascular events through aggressive modulation of blood pressure and glycemia. Given the now-epidemic proportion of diabetes, an optimal approach to this global problem should involve dual reduction in cardiac risk and prevention of diabetes itself. This can be achieved through appropriate diet and therapeutic lifestyle change. Whilst weight loss per se has antihypertensive and antidiabetic benefits, more specific nutritional interventions are accruing evidence for their powerful potential to reduce cardiovascular risk and improve metabolic profiles. Dietary modification can therefore achieve substantial reductions in the incidence of T2DM and improve the cardiovascular health of the population. This will clearly require engagement from policy-makers as well as the medical community. In specific cohorts, novel agents targeting gut hormones and bariatric interventions have the potential to improve metabolic profiles in conjunction with weight loss and cardiovascular risk reduction, to complement nonpharmacological strategies.

Disclosure

The authors report no conflicts of interest in this work.

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