HHS Public Access

Author manuscript

Curr Opin Endocrinol Diabetes Obes. Author manuscript; available in PMC 2017 November 28.

Published in final edited form as:

Curr Opin Endocrinol Diabetes Obes. 2014 April ; 21(2): 109–120. doi:10.1097/MED.0000000000000044.

Type 2 diabetes and cardiovascular disease: what next?

Joshua J. Joseph[a] and **Sherita Hill Golden**[a,b]

[a]Division of Endocrinology, Diabetes and Metabolism, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

[b]Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, USA

Abstract

Purpose of review—Cardiovascular disease (CVD) is the leading cause of mortality in type 2 diabetes mellitus (T2DM), and modifying cardiovascular risk through lifestyle intervention and pharmacologic therapy is paramount. This review focuses on recent advances in treatment of classical (traditional) cardiovascular risk factors and highlights the impact of novel risk factors, including sleep disorders, socioeconomic status and chronic psychological stress on CVD in T2DM.

Recent findings—Obesity is a substantial cardiovascular risk factor, and recently, large trials of lifestyle and surgical (e.g. gastric bypass) interventions impact on CVD in overweight and obese patients have been reported. Lifestyle intervention including low calorie diet and exercise reduced individual cardiovascular risk factors but did not decrease the rate of long-term cardiovascular events. Bariatric surgery was beneficial in reducing cardiovascular risk factors and long-term cardiovascular events. Sleep insufficiency, poor sleep quality and obstructive sleep apnoea lead to higher CVD and further research is needed to characterize the benefit of treating sleep disorders on long-term cardiovascular events in T2DM. Lastly, socioeconomic status and chronic psychological stress independently have a major impact on increasing CVD in T2DM, and public health policies to reduce this burden will be important to address over the coming decade.

Summary—CVD in T2DM is multifactorial and requires a multifaceted approach in reducing known cardiovascular risks at the individual patient level through lifestyle, pharmacotherapy and surgical interventions and at the societal level through public health policies that support reduction in classical and novel cardiovascular risk factors.

Keywords

cardiovascular disease; neuroendocrine; risk factors; sleep disorders; stress; type 2 diabetes

Correspondence to Dr Sherita Hill Golden, Johns Hopkins University School of Medicine, Division of Endocrinology and Metabolism, 1830 E. Monument Street, Suite 333, Baltimore, MD 21287, USA. Tel: +1 410 502 0993; fax: +1 410 955 8172; sahill@jhmi.edu.

Conflicts of interest

There are no conflicts of interest.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in diabetes mellitus. Individuals with type 2 diabetes mellitus (T2DM) have a two-fold increase in all-cause mortality and a three-fold increase in cardiovascular mortality [1]. Reduction of cardiovascular risk in T2DM is thus paramount. In 1998, a study showed that diabetic patients without a previous myocardial infarction (MI) have as high a risk of MI as nondiabetic patients with a previous MI [2], which led to vigorous research over the last 16 years to aggressively treat known traditional risk factors and to define novel risk factors. In this review, we summarize recently published studies describing advances in treatment to reduce CVD risk and highlight novel CVD risk factors.

RECENT INNOVATION IN APPROACH TO GOALS AND TREATMENT OF TRADITIONAL RISK FACTORS OF CARDIOVASCULAR DISEASE

In the following sections, we summarize recent findings addressing traditional CVD risk factors in type 2 diabetes.

HYPERTENSION

The 2013 American Diabetes Association Clinical Practice Guidelines changed the SBP target to less than 140 mmHg, from the previous target of less than 130 mmHg [3]. This recommendation was changed on the basis of data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) [4] and Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trials [5], as well as two meta-analyses [6,7] that showed no statistically significant difference in treating to a target of less than 130 versus 130–140 mmHg.

In a recent Swedish cohort study involving 34 009 consecutive CVD-free T2DM patients followed for 11 years, the lowest risk of cardiovascular events was observed at a SBP of 135–139 mmHg and a DBP of 74–76 mmHg [8]. Another recent study evaluated over 15 000 individuals with T2DM recently diagnosed with hypertension and examined blood pressure control at 1 year after diagnosis and prospective cardiovascular risk. The rates of major cardiovascular events were lowest in those with mean 1-year blood pressure measurements of 130–139/80–89 mmHg [9]. Taken as a whole, these results indicate that SBP lowering is beneficial and 130–140 mmHg represents the middle of a U-shaped curve with increased cardiovascular risk outside of those ranges.

GLYCEMIC CONTROL

Both glycemic targets and glucose-lowering agents have potential implications in the prevention and treatment of CVD.

Glycemic targets and cardiovascular disease

The role of intensive glycemic control in the prevention of CVD in diabetes has been the focus of several clinical trials recently summarized in three meta-analyses. As shown in

Table 1 [10–12], the meta-analyses differed in the clinical trials they included, which resulted in slightly different findings. Ray *et al*. [10], conducting a meta-analysis of six studies, found that tight glycemic control was associated with a 17% reduction in nonfatal MI, 15% reduction in coronary heart disease (CHD) events, but no effect on stroke or all-cause mortality. In the meta-analysis by Kelly *et al*. [11], which included five trials and excluded the PROactive Study, there was a 16% reduction in nonfatal MI, no effect on cardiovascular or all-cause mortality and a two-fold higher risk of hypoglycemia in the intensive than in conventional arms. The study by Boussageon *et al*. [12] was inclusive of all trials (13) and found no effect of intensive glycemic control on cardiovascular or overall mortality but a two-fold higher risk of severe hypoglycemia and 47% increase in congestive heart failure. Collectively, these data suggest that any benefit of intensive glycemic control on CVD risk in T2DM is modest at best and very low HbA1c levels (<6.5%) are not beneficial in preventing diabetes-related CVD.

Oral hypoglycemic agents, insulin and cardiovascular risk

In a study of 304 Chinese T2DM patients with a history of coronary artery disease (CAD), individuals treated with metformin as compared with glipizide for 3 years had a 46% decrease in cardiovascular events [13]. This result is supported by previous research in the United Kingdom Prospective Diabetes Study 34 trial, showing decreased macrovascular events with metformin therapy [14] and a meta-analysis showing a 26% reduction in cardiovascular death with metformin therapy [15].

The controversy surrounding the potential adverse cardiovascular effects of rosiglitazone [16] led the Food and Drug Administration to require pharmaceutical companies to establish CVD risk of new glucose-lowering agents. Two new trials were recently published involving the dipeptidyl peptidase (DPP)-IV inhibitors saxigliptin [17▪] and alogliptin [18▪], which reported no effect of these agents on CVD outcomes (Table 2) [17▪,18▪,19,20▪▪,21–28]. But more patients in the saxagliptin than in the placebo group were hospitalized for heart failure [3.5 versus 2.8%; hazard ratio, 1.27; 95% confidence interval (CI) 1.07–1.51; $P = 0.007$] [17▪]. There was not a significantly higher risk of heart failure with alogliptin than with placebo [18▪]. It is well established that thiazolidinediones are associated with heart failure [16,29].

Finally, The Outcome Reduction with an Initial Glargine Intervention Trial [19], also recently published, compared glargine with placebo in individuals with impaired fasting glucose, impaired glucose tolerance or T2DM and found no difference in coprimary outcomes of nonfatal MI, nonfatal stroke or death from CVD at 6.2 years.

In summary, metformin seems to have proven benefit for CVD risk without significant risks of heart failure. Currently, there are no other oral hypoglycemic agents, which have proven CVD benefit without increasing risk of heart failure. Neither insulin nor one of the newest classes of incretin mimetics, DPP-4 inhibitors, appear to be associated with increased CVD risk or enhanced CVD benefit.

DYSLIPIDEMIA

Dyslipidemia is a critical component in the pathogenesis of vascular disease in T2DM. Statin therapy has been shown to resoundingly reduce cardiovascular events in individuals with T2DM in small trials [30,31] and was confirmed in the Cholesterol Treatment Trialist meta-analysis of 18 686 people with diabetes [32].

Recently, a meta-analysis of multiple trials showed a 9% increased risk of developing T2DM with statin therapy[33]. A comparison of those individuals who developed diabetes during those trials and those who did not showed a similar composite cardiovascular risk reduction of 37% at 4 years [34]. A recent analysis showed that the risk of hyperglycemia and T2DM was not the same with all statins, with pravastatin having the lowest risk and rosuvastatin having the highest risk, suggesting an association between potency and risk for incident T2DM [35]. A meta-analysis examining 26 trials with 3232 T2DM participants with five different statins found that overall statin therapy had no impact on HbA1c, BMI, fasting insulin or HOMA-IR. However, subgroup analysis showed a significant, detrimental effect of atorvastatin on HbA1c, whereas simvastatin improved HbA1c, suggesting a variable impact on glycemic control [36]. More research is needed to confirm these findings and elucidate the mechanisms, which could yield clinically relevant data on statin choice.

OBESITY

Overweight and obesity are the most important predictors of T2DM [37,38] and recent data suggest that the risk is specifically associated with visceral fat [39]. Obesity is also an independent predictor of clinical CVD [40–42]. The underlying relationship between obesity, CVD and diabetes has been reviewed extensively and is mediated through the adipokines released from visceral fat [43–46]. A reduction in weight is beneficial for cardiovascular risk and is reviewed in the following section.

Lifestyle intervention

The Look AHEAD trial is the first long-term study to examine the effect of lifestyle intervention on clinical CVD outcomes [20▪▪]. The study enrolled 5145 overweight or obese patients with T2DM and randomized them to intensive lifestyle intervention (ILI) or diabetes support and education (DSE). The primary outcome, a composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke or hospitalization from angina, was not significantly different at 9.6 years despite greater weight loss in the ILI group throughout the study. There were other benefits of the ILI including an improvement in glycemic control, depression, sleep apnea, quality of life, physical functioning and mobility [20▪▪]. There are some hypotheses about the lack of CVD benefit from the ILI. First, the ILI group used significantly less antihypertensive medications, insulin and statin therapy owing to lower LDL in the intervention group. Statin use is not only associated with a significant reduction in all-cause mortality and major vascular events [32] but is also associated with beneficial effects beyond low-density lipoprotein (LDL) lowering (e.g. stabilization of coronary plaques, improvement in endothelial dysfunction through enhanced nitric oxide bioavailability and inhibition of inflammatory responses) [47]. Finally, there is the question of maintenance of the ILI as weight increased in years 2–5 in the ILI group and the

estimated mean metabolic equivalents decreased precipitously after year one [48]. These data indicate that future research is needed to determine better approaches to weight loss maintenance and prevention of weight regain, which may impact CVD risk in diabetes. In addition, future ILI for CVD risk reduction in T2DM should consider not only caloric reduction but also dietary composition, as patients will likely derive benefit from increased amounts of vegetables, nuts, olive oil, fish and a reduction in red meat as evidenced by the PREDIMED [21] study and the Adventist Health Study 2 [22] (Table 2).

Bariatric surgery

Bariatric surgery is an effective method for weight loss demonstrated in many trials, the largest of which is the Swedish Obese Subjects (SOS) [49] trial, a nonrandomized prospective, contemporaneous matched-controls trial. In SOS, they showed an adjusted 29% reduction in all-cause mortality at 11 years mostly due to reduction in MI and cancer [49]. At 15 years, there was 83% reduction in incident T2DM [50], a 37% reduction in cardiovascular events and a 53% reduction in cardiovascular death with a postoperative mortality rate of 0.2% [51]. Within the last 2 years, there have been four trials of gastric bypass reporting results in patients with T2DM. The details of the most recent bariatric surgery trials examining the impact of surgical intervention on weight loss, diabetes risk and glycemic control are summarized in Table 2. A recent meta-analysis evaluated bariatric surgery for weight loss and glycemic control in nonmorbidly obese adults (BMI 30–35 kg/m^2) with T2DM and found that surgery was associated with greater weight loss and glycemic control than nonsurgical groups during 1–2 years of follow-up consistent with data from these four trials [52]. Only one study, a T2DM subgroup analysis of the SOS trial, has examined the impact of bariatric surgery on CVD outcomes among individuals with T2DM and found a significant 44% reduction in MI with no effect on stroke incidence at 13 years [23].

Improvement in insulin resistance and dyslipidemia following roux-en-y gastric bypass compared with simple gastric banding and reduction of stomach volume occur prior to weight loss [53]. The reasons for this are not entirely elucidated and it is an area of active investigation, but may be related to alteration in the incretin system or changes in gut microbiota. One recent trial of faecal transplant in 18 men with metabolic syndrome showed improved cholesterol and insulin sensitivity at 6 weeks in individuals who received faeces from a lean donor group compared with a group with reinfusion of their own feces [54]. Future understanding of these mechanisms might lead to development of novel CVD risk reduction interventions in T2DM.

SMOKING

Smoking remains a strong CVD risk factor. In 2013, a large meta-analysis [55] showed that in individuals with T2DM, smoking was associated with a significantly increased risk of total and cardiovascular mortality, CHD, stroke and MI compared with nonsmokers. Smoking cessation is beneficial, with studies showing a near return to baseline of diabetic cardiovascular risk following cessation [56]. One of the unanswered questions was whether the weight gain of 3–6 kg that occurs after smoking cessation would cause increased

cardiovascular risk in those with diabetes. A recent trial found that smoking cessation was still associated with decreasing the incidence of CHD despite a 3.6 kg weight increase [57]. Notably, the risk was not reduced back to nonsmoking baseline demonstrating the importance of public health policies for smoking prevention.

ANTI-PLATELET THERAPY: ASPIRIN FOR THE PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE?

The benefit of aspirin for secondary prevention of cardiovascular events in those with and without T2DM has been proven in both clinical trials and observation studies, but the role of aspirin in primary prevention remains speculative and inconclusive [58–61].

There are two trials underway, Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes [62] and A Study of Cardiovascular Events in Diabetes [63], with a combined enrollment of 15 000 patients to further answer the question regarding primary prevention in diabetes. Given that many of the other trials occurred prior to the time of uniform statin therapy, these trials should be more relevant to our current clinical practice.

NOVEL RISK FACTORS

It is known that classical cardiovascular risk factors do not account for all of the excess CVD risk in diabetes. It is therefore important to identify novel cardiovascular risk factors as potential targets for CVD prevention and intervention in T2DM.

SLEEP DISORDERS, DIABETES AND CARDIOVASCULAR DISEASE RISK

The understanding of the relationship between impairment in the quantity and quality of sleep and cardiovascular risk has expanded over recent years, and over the last year, there are more data on possible mechanisms and interventions for the increased cardiovascular risk of obstructive sleep apnea (OSA) and sleep insufficiency.

Obstructive sleep apnea

OSA is an important complication of obesity and is highly prevalent among individuals with T2DM [64]. In the Sleep AHEAD study, 86% of individuals with T2DM and obesity were diagnosed with OSA [65]. On the basis of these numbers, OSA in the primary care setting has been underrecognized and thus untreated with reported prevalences of 18% of all diabetic individuals and 23% in obese diabetic individuals [64]. A prospective study of 1889 individuals with treated and untreated OSA versus controls over 12 years showed that untreated sleep apnoea has a hazard ratio of 1.96 for hypertension compared with controls and that OSA treated with CPAP therapy was associated with a lower risk of hypertension with a hazard ratio of 0.71 [66].

A recent review [67] discusses some of the causes of increased CVD risk in OSA including hypoxia in adipose tissue leading to chronic inflammation, macrophage infiltration, reduction of adiponectin, elevation of leptin and mitochondrial dysfunction; worsening insulin resistance and beta cell dysfunction; impaired clearance of triglyceride rich

lipoproteins and inactivation of the lipoprotein lipase; endothelial dysfunction and elevated daytime and nocturnal blood pressure.

Sleep insufficiency

The Institutes of Medicine estimates that 50–70 million Americans chronically suffer from a disorder of sleep and wakefulness, hindering daily functioning and adversely affecting their health and longevity [68]. Insufficient sleep has been associated with worry [69], financial and home stress [70,71], smoking [71,72], meal timing [72], physical inactivity [71,73], obesity, heavy drinking [71,72,74] and electronics use prior to bedtime [75]. Sleep insufficiency has a higher prevalence among non-Hispanic blacks than among non-Hispanic whites [76] and among those of lower versus higher socioeconomic status in all races [77].

Sleep insufficiency has also been shown to cause dyslipidemia [low high-density lipoprotein (HDL) and elevated triglycerides] [78], total body [79] and adipocyte insulin resistance [80], hyperglycemia and incident T2DM [81,82], reduced leptin and elevated ghrelin levels [83], elevated afternoon and evening cortisol [79], weight gain [81,82,84], sympathetic nervous system activation and hypertension [85–88]. Short sleep duration has been linked directly to incident coronary calcification in a dose-dependent manner in nondiabetic individuals, with a 33% reduction in coronary calcification for every hour of sleep after 4h [89]. A prospective Japanese study [90] showed an increase in a composite endpoint of stroke, MI and cardiovascular death over 10 years in diabetic individuals with short sleep (<7.5 h) versus more than 7.5 h, but the short sleep group had higher smoking rates. These data correspond with a US multiethnic national analysis wherein self-reported insufficient sleep over the last month was associated with increased odds of CVD, CHD, stroke, diabetes and obesity [91].

Studies in the general population have shown not only that short sleep duration but also poor sleep quality is associated with incident CHD [92]. Sufficient sleep of more than 7 h, compared with insufficient sleep, had an added benefit of lower CVD risk when considered with other cardiovascular risk factors in the MORGEN study [93]. Although these data are from a general population, they demonstrate that sleep, which accounts for one-third of the normal human lifespan, is likely an important emerging frontier in combating CVD in all individuals, including patients with T2DM. Future studies should examine sleep disorders as risk factors for CVD specifically in individuals with T2DM and determine whether treatment interventions aimed at OSA, sleep insufficiency and poor sleep quality improve cardiovascular risk factors and lower CVD risk.

Melatonin: a possible sleep and cardiovascular disease link

Another possible novel causative agent linking T2DM and CVD is melatonin, which is secreted in a diurnal pattern peaking 3–5h after sleep onset in a dark environment. Both T2DM and CVD are mediated by inflammation and melatonin has known anti-inflammatory properties, as a direct free radical scavenger and indirect antioxidant activity. Its investigation in mitochondrial dysfunction and ischemia reperfusion in cell-based systems has proven beneficial [94–96] and it also has a beneficial effect on hypertension in humans [97]. From the T2DM perspective, recently genome-wide association studies with loss of function of the melatonin receptor have been associated with a high incidence of T2DM

[98]. A large nested case–control study showed that lower melatonin secretion was associated with a higher risk of developing T2DM [99]. Melatonin is a hormone in need of further study for its potential therapeutic application in the prevention and treatment of T2DM and CVD.

SOCIAL DETERMINANTS/SOCIOECONOMIC STATUS

National Health And Nutrition Examination Survey data from 1988 to 2008 showed improved cardiovascular risk factor reduction in T2DM, but these reductions were significantly greater in those with higher educational levels, and notably, there was no improvement in poor glycemic control and smoking rates in individuals with less than a high school degree [100]. In another study at community health centres of low SES individuals, those with diabetes had significantly increased mortality risk compared with nondiabetic individuals over 5.9 years [101]. A study examining managed care patients with T2DM from 2000 to 2007 showed stepwise increasing rates of total and cardiovascular mortality in individuals with low incomes and education compared with those at higher levels [102]. A third recent study [103] used a previously validated ‘social adaptability index’ (SAI) composed of a linear combination of indicators, including education, employment, income, marital status and substance abuse to quantify SES. In adults with T2DM, higher SAI score was significantly associated with improved survival in a dose-dependent manner [103]. Identifying the causative mechanisms linking low SES with higher cardiovascular risk in diabetes is an area ripe for further research. In nondiabetic populations, there is some evidence that lower SES is a risk factor for both higher levels of stress [104] and insufficient nocturnal blood pressure dipping [105], which could lead to higher cardiovascular risk.

CHRONIC PSYCHOLOGICAL STRESS

Various forms of chronic psychological stress, including work and home-related stress, financial stress and stressful life events (e.g. death of a child or spouse), are associated with an increased risk of MI worldwide [106,107]. Depression has also been associated with an increased risk of CVD in individuals with and without diabetes [107,108]. The concept of allostasis describes the capacity of an organism to adapt to a changing environment or stressful challenge to support homeostatic systems essential to life [109,110]. Allostatic load summarizes the cumulative impact of physiological wear and tear related to maladaptive stress patterns that predispose individuals to disease [109,111]. The biological systems involved in adaptation that mediate the link between stress and physiological functions are the hypothalamic-pituitary-adrenal (HPA) axis, autonomic nervous system and immune system [109,112] (Fig. 1). Allostatic load scores estimate stress-induced physiological dysfunction by summing the number of parameters within each system for which individuals fall into the highest-risk quartile [109]. Examples of physiological parameters include cardiovascular measures (lipids), metabolic measures (waist circumference, Hb_{A1c}), HPA axis function (dehydroepiandrosterone sulphate, cortisol), autonomic function (heart rate, urinary catecholamines) and immune function (C-reactive protein, interleukin-6) [109]. Various types of chronic psychological stress are associated with increased allostatic load [113–115], and in the MacArthur studies of ageing, high allostatic load scores predicted incident CVD and all-cause mortality, independent of SES and baseline morbidity [109].

MECHANISMS OF NOVEL CARDIOVASCULAR DISEASE RISK FACTORS IN CLINICAL CARDIOVASCULAR DISEASE IN DIABETES

Although there are many novel CVD risk factors being studied that have implications in the development of CVD in the setting of diabetes, the ones that we present in this review – sleep disorders, low SES and chronic psychological stress – share common pathways of neuroendocrine and immune system activation (Fig. 1). Activation of these pathways can enhance CVD risk in the setting of T2DM. Activation of the HPA axis and the resultant subclinical hypercortisolism lead to accumulation of visceral fat [116,117], which is a risk factor for T2DM, hypertension and CVD. A recent study in the Multi-Ethnic Study of Atherosclerosis demonstrated HPA axis dysfunction in the setting of T2DM with a blunted diurnal cortisol profile and higher daily cortisol exposure in women compared with women without T2DM, independent of depressive symptoms [118]. In addition to elevated cortisol levels and altered HPA axis dynamics in the setting of these physiological and psychological stressors, catecholamines and inflammatory markers are also elevated, inducing insulin resistance and enhancing CVD risk (Fig. 1) [119,120]. Inflammation, also associated with visceral adiposity [121], induces endothelial damage and dysfunction [122,123], leading to hypertension and atherosclerosis. Thus, activation of these interrelated stress systems can lead to CVD in the setting of T2DM and they deserve further study as potential intervention and prevention targets.

CONCLUSION

Control of CVD risk factors is known to prevent CVD, but unfortunately a large analysis has historically shown poor CVD risk factor control [124]. In 2010, 24% of individuals with T2DM met ADA goals for SBP, LDL-C and HbA1C [125], improved from 7.3% in 2000 [126], but still leaving three-quarters of individuals with T2DM uncontrolled for these three key risk factors. The picture is more grim for secondary CVD prevention, wherein risk factor control ranges from 8 to 23% [127]. These harrowing data indicate that in addition to focusing on novel therapies/targets, we must remain vigilant in aggressively treating known CVD risk factors and build on research into successful implementation of improved delivery of care targeting CVD risk factors in diabetes.

Acknowledgments

None.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. Taylor KS, Heneghan CJ, Farmer AJ, et al. All-cause and cardiovascular mortality in middle-aged people with type 2 diabetes compared with people without diabetes in a large U.K. primary care database. Diabetes Care. 2013; 36:2366–2371. [PubMed: 23435157]

2. Haffner SM, Lehto S, Rönnemaa T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med. 1998; 339:229–234. [PubMed: 9673301]

3. American Diabetes Association. Standards of medical care in diabetes – 2013. Diabetes Care. 2012; 36:S11–S66.

4. The ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010; 362:1575–1585. [PubMed: 20228401]

5. Patel A, Collaborative Group ADVANCE. MacMahon S, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet. 2007; 370:829–840. [PubMed: 17765963]

6. Cooper-DeHoff RM, Gong Y, Handberg EM, et al. Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. J Am Med Assoc. 2010; 304:61–68.

7. McBrien K. Intensive and standard blood pressure targets in patients with type 2 diabetes mellitus: systematic review and meta-analysis. Arch Intern Med. 2012; 172:1296. [PubMed: 22868819]

8. Sundström J, Sheikhi R, Östgren CJ, et al. Blood pressure levels and risk of cardiovascular events and mortality in type-2 diabetes: cohort study of 34 009 primary care patients. J Hypertens. 2013; 31:1603–1610. [PubMed: 23625112]

9. O'Connor PJ, Vazquez-Benitez G, Schmittdiel JA, et al. Benefits of early hypertension control on cardiovascular outcomes in patients with diabetes. Diabetes Care. 2012; 36:322–327. [PubMed: 22966094]

10. Ray KK, Seshasai SRK, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet. 2009; 373:1765–1772. [PubMed: 19465231]

11. Kelly TN, Bazzano LA, Fonseca VA, et al. Systematic review: glucose control and cardiovascular disease in type 2 diabetes. Ann Intern Med. 2009; 151:394–403. [PubMed: 19620144]

12. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, et al. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. BMJ. 2011; 343:d4169–d14169. [PubMed: 21791495]

13. Hong J, Zhang Y, Lai S, et al. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. Diabetes Care. 2012; 36:1304–1311. [PubMed: 23230096]

14. Turner RC, Holman RR, Stratton IM, et al. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998; 352:854–865. [PubMed: 9742977]

15. Selvin E, Bolen S, Yeh H-C, et al. Cardiovascular outcomes in trials of oral diabetes medications: a systematic review. Arch Intern Med. 2008; 168:2070. [PubMed: 18955635]

16. Dagenais GR, Gerstein HC, Holman R, et al. DREAM Trial Investigators. Effects of ramipril and rosiglitazone on cardiovascular and renal outcomes in people with impaired glucose tolerance or impaired fasting glucose: results of the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial. Diabetes Care. 2008; 31:1007–1014. [PubMed: 18268075]

17■. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013; 369:1317–1326. Saxagliptin was not associated with increased CVD. [PubMed: 23992601]

18■. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013; 369:1327–1335. Alogliptin was not associated with increased CVD. [PubMed: 23992602]

19. The ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med. 2012; 367:319–328. [PubMed: 22686416]

20■■. The Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med. 2013; 369:145–154. The Look AHEAD trial showed no decrease

in cardiovascular events with ILI as compared with DSE in individuals with T2DM. [PubMed: 23796131]

21. Estruch R, Ros E, Salas-Salvadó J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med. 2013; 368:1279–1290. [PubMed: 23432189]
22. Orlich MJ. Vegetarian dietary patterns and mortality in Adventist health study 2. JAMA Intern Med. 2013; 173:1230. [PubMed: 23836264]
23. Romeo S, Maglio C, Burza MA, et al. Cardiovascular events after bariatric surgery in obese subjects with type 2 diabetes. Diabetes Care. 2012; 35:2613–2617. [PubMed: 22855732]
24. Schauer PR, Kashyap SR, Wolski K, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med. 2012; 366:1567–1576. [PubMed: 22449319]
25. Kashyap SR, Bhatt DL, Wolski K, et al. Metabolic effects of bariatric surgery in patients with moderate obesity and type 2 diabetes: analysis of a randomized control trial comparing surgery with intensive medical treatment. Diabetes Care. 2013; 36:2175–2182. [PubMed: 23439632]
26. Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric surgery versus conventional medical therapy for type 2 diabetes. N Engl J Med. 2012; 366:1577–1585. [PubMed: 22449317]
27. Cohen RV, Pinheiro JC, Schiavon CA, et al. Effects of gastric bypass surgery in patients with type 2 diabetes and only mild obesity. Diabetes Care. 2012; 35:1420–1428. [PubMed: 22723580]
28. Ikramuddin S, Korner J, Lee W-J, et al. Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension and hyperlipidemia. J Am Med Assoc. 2013; 309:2240–2249.
29. Erdmann E, Dormandy JA, Charbonnel B, et al. The effect of pioglitazone on recurrent myocardial infarction in 2445 patients with type 2 diabetes and previous myocardial infarction. J Am Coll Cardiol. 2007; 49:1772–1780. [PubMed: 17466227]
30. Knopp RH. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN). Diabetes Care. 2006; 29:1478–1485. [PubMed: 16801565]
31. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004; 364:685–696. [PubMed: 15325833]
32. Trialists CT. Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008; 371:117–125. [PubMed: 18191683]
33. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet. 2010; 375:735–742. [PubMed: 20167359]
34. Ridker PM, Pradhan A, MacFadyen JG, et al. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. Lancet. 2012; 380:565–571. [PubMed: 22883507]
35. Navarese EP, Buffon A, Andreotti F, et al. Meta-analysis of impact of different types and doses of statins on new-onset diabetes mellitus. Am J Cardiol. 2013; 111:1123–1130. [PubMed: 23352266]
36. Zhou Y, Yuan Y, Cai R-R, et al. Statin therapy on glycaemic control in type 2 diabetes: a meta-analysis. Expert Opin Pharmacother. 2013; 14:1575–1584. [PubMed: 23826679]
37. Hu FB, Manson JE, Stampfer MJ, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med. 2001; 345:790–797. [PubMed: 11556298]
38. Narayan KMV, Boyle JP, Thompson TJ, et al. Effect of BMI on lifetime risk for diabetes in the U.S. Diabetes Care. 2007; 30:1562–1566. [PubMed: 17372155]
39. Neeland IJ, Turer AT, Ayers MCR, et al. Dysfunctional adiposity and the risk of prediabetes and type 2 diabetes in obese adults. J Am Med Assoc. 2012; 308:1150.
40. Rabkin SW, Mathewson FA, Hsu P-H. Relation of body weight to development of ischemic heart disease in a cohort of young North American men after a 26 year observation period: the Manitoba Study. Am J Cardiol. 1977; 39:452–458. [PubMed: 842466]
41. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. Circulation. 1983; 67:968–977. [PubMed: 6219830]

42. Wilson PWF, D'Agostino RB, Sullivan L, et al. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. Arch Intern Med. 2002; 162:1867–1872. [PubMed: 12196085]
43. Després J-P, Lemieux I. Abdominal obesity and metabolic syndrome. Nature. 2006; 444:881–887. [PubMed: 17167477]
44. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature. 2006; 444:840–846. [PubMed: 17167471]
45. Rosen ED, Spiegelman BM. Adipocytes as regulators of energy balance and glucose homeostasis. Nature. 2006; 444:847–853. [PubMed: 17167472]
46. Lau DCW. Adipokines: molecular links between obesity and atheroslcerosis. AJP Heart Circ Physiol. 2005; 288:H2031–H2041.
47. Davignon J. Beneficial cardiovascular pleiotropic effects of statins. Circulation. 2004; 109:III-39–III-43. [PubMed: 15198965]
48. The Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med. 2013; 369:145–154. [PubMed: 23796131]
49. Sjöström L, Narbro K, Sjöström CD, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med. 2007; 357:741–752. [PubMed: 17715408]
50. Carlsson LMS, Peltonen M, Ahlin S, et al. Bariatric surgery and prevention of type 2 diabetes in swedish obese subjects. N Engl J Med. 2012; 367:695–704. [PubMed: 22913680]
51. Sjöström L, Peltonen M, Jacobson P, et al. Bariatric surgery and long-term cardiovascular events. J Am Med Assoc. 2012; 307:56–65.
52. Maggard-Gibbons M, Maglione M, Livhits M, et al. Bariatric surgery for weight loss and glycemic control in nonmorbidly obese adults with diabetes. J Am Med Assoc. 2013; 309:2250–2261.
53. Stefater MA, Wilson-Perez HE, Chambers AP, et al. All bariatric surgeries are not created equal: insights from mechanistic comparisons. Endocr Rev. 2012; 33:595–622. [PubMed: 22550271]
54. Vrieze A, Van Nood E, Holleman F, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology. 2012; 143:913–916. e7. [PubMed: 22728514]
55. Qin R, Chen T, Lou Q, Yu D. Excess risk of mortality and cardiovascular events associated with smoking among patients with diabetes: meta-analysis of observational prospective studies. Int J Cardiol. 2013; 167:342–350. [PubMed: 22251416]
56. Al-Delaimy WK, Manson JE, Solomon CG, et al. Smoking and risk of coronary heart disease among women with type 2 diabetes mellitus. Arch Intern Med. 2002; 162:273–279. [PubMed: 11822919]
57. Clair C. Association of smoking cessation and weight change with cardiovascular disease among adults with and without diabetes. J Am Med Assoc. 2013; 309:1014.
58. Ogawa H, Nakayama M, Morimoto T, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes. J Am Med Assoc. 2008; 300:2134–2141.
59. Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ. 2008; 337:a1840–a11840. [PubMed: 18927173]
60. Colwell JA, Cushman M, Inzucchi SE, et al. ADA/AHA/ACCF scientific statement. Circulation. 2010; 121:2694–2701. [PubMed: 20508178]
61. De Berardis G, Sacco M, Strippoli GFM, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. BMJ. 2009; 339:b4531–b14531. [PubMed: 19897665]
62. De Berardis G, Sacco M, Evangelista V, et al. Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D): design of a randomized study of the efficacy of low-dose aspirin in the prevention of cardiovascular events in subjects with diabetes mellitus treated with statins. Trials. 2007; 8:21. [PubMed: 17725825]
63. Armitage, Jane M, BSc, MBBS, MRCP, FFPH. Clinical Trial Service Unit, University of Oxford. A study of cardiovascular events in diabetes [Internet]. http://clinicaltrials.gov/ct2/show/NCT00135226

64. Heffner JE. Prevalence of diagnosed sleep apnea among patients with type 2 diabetes in primary care. Chest J. 2012; 141:1414.
65. Foster GD, Borradaile KE, Sanders MH, et al. A randomized study on the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes: the Sleep AHEAD study. Arch Intern Med. 2009; 169:1619. [PubMed: 19786682]
66. Agusti A. Association between treated and untreated obstructive sleep apnea and risk of hypertension. J Am Med Assoc. 2012; 307:2169.
67. Drager LF, Togeiro SM, Polotsky VY, Lorenzi-Filho G. Obstructive sleep apnea. J Am Coll Cardiol. 2013; 62:569–576. [PubMed: 23770180]
68. Colten, HR., Altevogt, BM. Institute of Medicine (U.S.), Committee on Sleep Medicine and Research. Sleep disorders and sleep deprivation: an unmet public health problem [Internet]. Washington, DC: National Academies Press; 2006. http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=nap11617 [Accessed 11 October 2013]
69. Hamer M, Batty GD, Kivimaki M. Sleep loss due to worry and future risk of cardiovascular disease and all-cause mortality: the Scottish Health Survey. Eur J Prev Cardiol. 2011; 19:1437–1443. [PubMed: 21968572]
70. Mosca M, Aggarwal B. Sleep duration, snoring habits, and cardiovascular disease risk factors in an ethnically diverse population. J Cardiovasc Nurs. 2012; 27:263–269. [PubMed: 21743341]
71. Strine TW, Chapman DP. Associations of frequent sleep insufficiency with health-related quality of life and health behaviors. Sleep Med. 2005; 6:23–27. [PubMed: 15680291]
72. Nakade M, Takeuchi H, Kurotani M, Harada T. Effects of meal habits and alcohol/cigarette consumption on morningness-eveningness preference and sleep habits by Japanese female students aged 18–29. J Physiol Anthropol. 2009; 28:83–90. [PubMed: 19346668]
73. National Sleep Foundation. [Accessed 11 October 2013] Sleep and exercise in America 2013 [Internet]. http://www.sleepfoundation.org
74. Haario P, Rahkonen O, Laaksonen M, et al. Bidirectional associations between insomnia symptoms and unhealthy behaviours: Insomnia symptoms and unhealthy behaviours. J Sleep Res. 2013; 22:89–95. [PubMed: 22978579]
75. National Sleep Foundation. [Accessed 11 October 2013] Sleep in America 2011 [Internet]. http://www.sleepfoundation.org
76. Kingsbury JH, Buxton OM, Emmons KM, Redline S. Sleep and its relationship to racial and ethnic disparities in cardiovascular disease. Curr Cardiovasc Risk Reports. 2013; 7:387–394.
77. Stamatakis KA, Kaplan GA, Roberts RE. Short sleep duration across income, education, and race/ethnic groups: population prevalence and growing disparities during 34 years of follow-up. Ann Epidemiol. 2007; 17:948–955. [PubMed: 17855122]
78. Kaneita Y, Uchiyama M, Yoshiike N, Ohida T. Associations of usual sleep duration with serum lipid and lipoprotein levels. Sleep. 2008; 31:645. [PubMed: 18517035]
79. Buxton OM, Pavlova M, Reid EW, et al. Sleep restriction for 1 week reduces insulin sensitivity in healthy men. Diabetes. 2010; 59:2126–2133. [PubMed: 20585000]
80. Broussard JL, Ehrmann DA, Van Cauter E, et al. Impaired insulin signaling in human adipocytes after experimental sleep restriction: a randomized, crossover study. Ann Intern Med. 2012; 157:549–557. [PubMed: 23070488]
81. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. Diabetes Care. 2009; 33:414–420. [PubMed: 19910503]
82. Knutson KL, Ryden AM, Mander BA, Van Cauter E. Role of sleep duration and quality in the risk and severity of type 2 diabetes mellitus. Arch Intern Med. 2006; 166:1768. [PubMed: 16983057]
83. Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. Ann Intern Med. 2004; 141:846–850. [PubMed: 15583226]
84. Yaggi HK, Araujo AB, McKinlay JB. Sleep duration as a risk factor for the development of type 2 diabetes. Diabetes Care. 2006; 29:657–661. [PubMed: 16505522]

85. Altman NG, Izci-Balserak B, Schopfer E, et al. Sleep duration versus sleep insufficiency as predictors of cardiometabolic health outcomes. Sleep Med. 2012; 13:1261–1270. [PubMed: 23141932]

86. Tochikubo O, Ikeda A, Miyajima E, Ishii M. Effects of insufficient sleep on blood pressure monitored by a new multibiomedical recorder. Hypertension. 1996; 27:1318–1324. [PubMed: 8641742]

87. Lusardi P, Zoppi A, Preti P, et al. Effects of insufficient sleep on blood pressure in hypertensive patients: a 24-h study. Am J Hypertens. 1999; 12:63–68. [PubMed: 10075386]

88. Gangwisch JE, Feskanich D, Malaspina D, et al. Sleep Duration and risk for hypertension in women: results from The Nurses' Health Study. Am J Hypertens. 2013; 26:903–911. [PubMed: 23564028]

89. King CR, Knutson KL, Rathouz PJ, et al. Short sleep duration and incident coronary artery calcification. J Am Med Assoc. 2008; 300:2859–2866.

90. Eguchi K, Hoshide S, Ishikawa S, et al. Short sleep duration and type 2 diabetes enhance the risk of cardiovascular events in hypertensive patients. Diabetes Res Clin Pract. 2012; 98:518–523. [PubMed: 23020940]

91. Shankar A, Syamala S, Kalidindi S. Insufficient rest or sleep and its relation to cardiovascular disease, diabetes and obesity in a national, multiethnic sample. PLoS One. 2010; 5:e14189. [PubMed: 21152066]

92. Hoevenaar-Blom MP, Spijkerman AMW, Kromhout D, et al. Sleep duration and sleep quality in relation to 12-year cardiovascular disease incidence: The MORGEN Study. Sleep. 2011; 34:1487–1492. [PubMed: 22043119]

93. Hoevenaar-Blom MP, Spijkerman AM, Kromhout D, Verschuren WM. Sufficient sleep duration contributes to lower cardiovascular disease risk in addition to four traditional lifestyle factors: the MORGEN study. Eur J Prev Cardiol. 2013; 0:1–9.

94. Dayoub JC, Ortiz F, López LC, et al. Synergism between melatonin and atorvastatin against endothelial cell damage induced by lipopolysaccharide: melatonin improves atorvastatin effects. J Pineal Res. 2011; 51:324–330. [PubMed: 21585521]

95. Yang Y, Duan W, Jin Z, et al. JAK2/STAT3 activation by melatonin attenuates the mitochondrial oxidative damage induced by myocardial ischemia/reper fusion injury. J Pineal Res. 2013; 55:275–286. [PubMed: 23796350]

96. Tengattini S, Reiter RJ, Tan D-X, et al. Cardiovascular diseases: protective effects of melatonin. J Pineal Res. 2008; 44:16–25. [PubMed: 18078444]

97. Scheer FAJL, Van Montfrans GA, van Someren EJW, et al. Daily nighttime melatonin reduces blood pressure in male patients with essential hypertension. Hypertension. 2004; 43:192–197. [PubMed: 14732734]

98. Bonnefond A, Clément N, Fawcett K, et al. Rare MTNR1B variants impairing melatonin receptor 1B function contribute to type 2 diabetes. Nat Genet. 2012; 44:297–301. [PubMed: 22286214]

99. McMullan CJ, Schernhammer ES, Rimm EB, et al. Melatonin secretion and the incidence of type 2 diabetes. J Am Med Assoc. 2013; 309:1388–1396.

100. Chatterji P, Joo H, Lahiri K. Racial/ethnic- and education-related disparities in the control of risk factors for cardiovascular disease among individuals with diabetes. Diabetes Care. 2011; 35:305–312. [PubMed: 22190677]

101. Conway BN, May ME, Blot WJ. Mortality among low-income African Americans and whites with diabetes. Diabetes Care. 2012; 35:2293–2299. [PubMed: 22912421]

102. McEwen LN, Karter AJ, Waitzfelder BE, et al. Predictors of mortality over 8 years in type 2 diabetic patients: translating research into action for diabetes (TRIAD). Diabetes Care. 2012; 35:1301–1309. [PubMed: 22432119]

103. Goldfarb-Rumyantzev AS, Rout P, Sandhu GS, et al. Social adaptability index predicts overall mortality in patients with diabetes. J Diabetes Complications. 2012; 26:44–49. [PubMed: 22321220]

104. Gebreab SY, Diez-Roux AV, Hickson DA, et al. The contribution of stress to the social patterning of clinical and subclinical CVD risk factors in African Americans: The Jackson Heart Study. Soc Sci Med. 2012; 75:1697–1707. [PubMed: 22841454]

105. Hickson DA, Roux AVD, Wyatt SB, et al. Socioeconomic position is positively associated with blood pressure dipping among African-American adults: the Jackson Heart Study. Am J Hypertens. 2011; 24:1015–1021. [PubMed: 21654853]
106. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTER-HEART study): case-control study. Lancet. 2004; 364:937–952. [PubMed: 15364185]
107. Rosengren A, Hawken S, Ôunpuu S, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11 119 cases and 13 648 controls from 52 countries (the INTERHEART study): case-control study. Lancet. 2004; 364:953–962. [PubMed: 15364186]
108. Park M, Katon WJ, Wolf FM. Depression and risk of mortality in individuals with diabetes: a meta-analysis and systematic review. Gen Hosp Psychiatry. 2013; 35:217–225. [PubMed: 23415577]
109. Carlson ED, Chamberlain RM. Allostatic load and health disparities: a theoretical orientation. Res Nurs Health. 2005; 28:306–315. [PubMed: 16028266]
110. McEwen BS, Wingfield JC. The concept of allostasis in biology and biomedicine. Horm Behav. 2003; 43:2–15. [PubMed: 12614627]
111. McEwen BS. Sex, stress and the hippocampus: allostasis, allostatic load and the aging process. Neurobiol Aging. 2002; 23:921–939. [PubMed: 12392796]
112. Chrousos GP. Stress and disorders of the stress system. Nat Rev Endocrinol. 2009; 5:374–381. [PubMed: 19488073]
113. Flier JS, Underhill LH, McEwen BS. Protective and damaging effects of stress mediators. N Engl J Med. 1998; 338:171–179. [PubMed: 9428819]
114. Seeman TE, Singer BH, Ryff CD, et al. Social relationships, gender, and allostatic load across two age cohorts. Psychosom Med. 2002; 64:395–406. [PubMed: 12021414]
115. Mair CA, Cutchin MP, Kristen Peek M. Allostatic load in an environmental riskscape: the role of stressors and gender. Health Place. 2011; 17:978–987. [PubMed: 21543249]
116. Anagnostis P, Athyros VG, Tziomalos K, et al. The pathogenetic role of cortisol in the metabolic syndrome: a hypothesis. J Clin Endocrinol Metab. 2009; 94:2692–2701. [PubMed: 19470627]
117. Champaneri S, Xu X, Carnethon MR, et al. Diurnal salivary cortisol is associated with body mass index and waist circumference: The multiethnic study of atherosclerosis. Obesity. 2013; 21:E56–E63. [PubMed: 23404865]
118. Champaneri S, Xu X, Carnethon MR, et al. Diurnal salivary cortisol and urinary catecholamines are associated with diabetes mellitus: the Multi-Ethnic Study of Atherosclerosis. Metabolism. 2012; 61:986–995. [PubMed: 22209664]
119. Golden SH. A review of the evidence for a neuroendocrine link between stress, depression and diabetes mellitus. Curr Diabetes Rev. 2007; 3:252–259. [PubMed: 18220683]
120. Champaneri S, Wand GS, Malhotra SS, et al. Biological basis of depression in adults with diabetes. Curr Diab Rep. 2010; 10:396–405. [PubMed: 20878274]
121. Lam YY, Mitchell AJ, Holmes AJ, et al. Role of the gut in visceral fat inflammation and metabolic disorders. Obesity. 2011; 19:2113–2120. [PubMed: 21881620]
122. Tousoulis D, Kampoli A-M, Papageorgiou N, et al. Pathophysiology of atherosclerosis: the role of inflammation. Curr Pharm Des. 2011; 17:4089–4110. [PubMed: 22204371]
123. Kampoli A-M, Tousoulis D, Briasoulis A, et al. Potential pathogenic inflammatory mechanisms of endothelial dysfunction induced by type 2 diabetes mellitus. Curr Pharm Des. 2011; 17:4147–4158. [PubMed: 22204375]
124. Ford ES. Trends in the control of risk factors for cardiovascular disease among adults with diagnosed diabetes: findings from the National Health and Nutrition Examination Survey 1999–2008*: cardiovascular risk factor control. J Diabetes. 2011; 3:337–347. [PubMed: 21767347]
125. Wong ND, Patao C, Wong K, et al. Trends in control of cardiovascular risk factors among US adults with type 2 diabetes from 1999 to 2010: comparison by prevalent cardiovascular disease status. Diab Vasc Dis Res. 2013; 10:505–513. [PubMed: 23975724]
126. Saydah SH. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. J Am Med Assoc. 2004; 291:335.

127. Farkouh ME, Boden WE, Bittner V, et al. Risk factor control for coronary artery disease secondary prevention in large randomized trials. J Am Coll Cardiol. 2013; 61:1607–1615. [PubMed: 23500281]

KEY POINTS

- Metformin is the only oral hypoglycemic agent associated with decreased cardiovascular disease risk in T2DM.
- Bariatric surgery improves cardiovascular risk factors and long-term cardiovascular events in type 2 diabetes, whereas intensive lifestyle intervention improves cardiovascular risk factors but does not lower the risk of long-term clinical cardiovascular events in T2DM.
- Novel cardiovascular risk factors, sleep disorders, low socioeconomic status and chronic stress increase cardiovascular risk in type 2 diabetes through interrelated neuroendocrine and inflammatory pathways.
- Despite studies showing a benefit of cardiovascular risk factor control in lowering cardiovascular events in type 2 diabetes, risk factor control remains poor and it is thus imperative to remain vigilant in aggressively treating known risk factors to prevent CVD in type 2 diabetes.

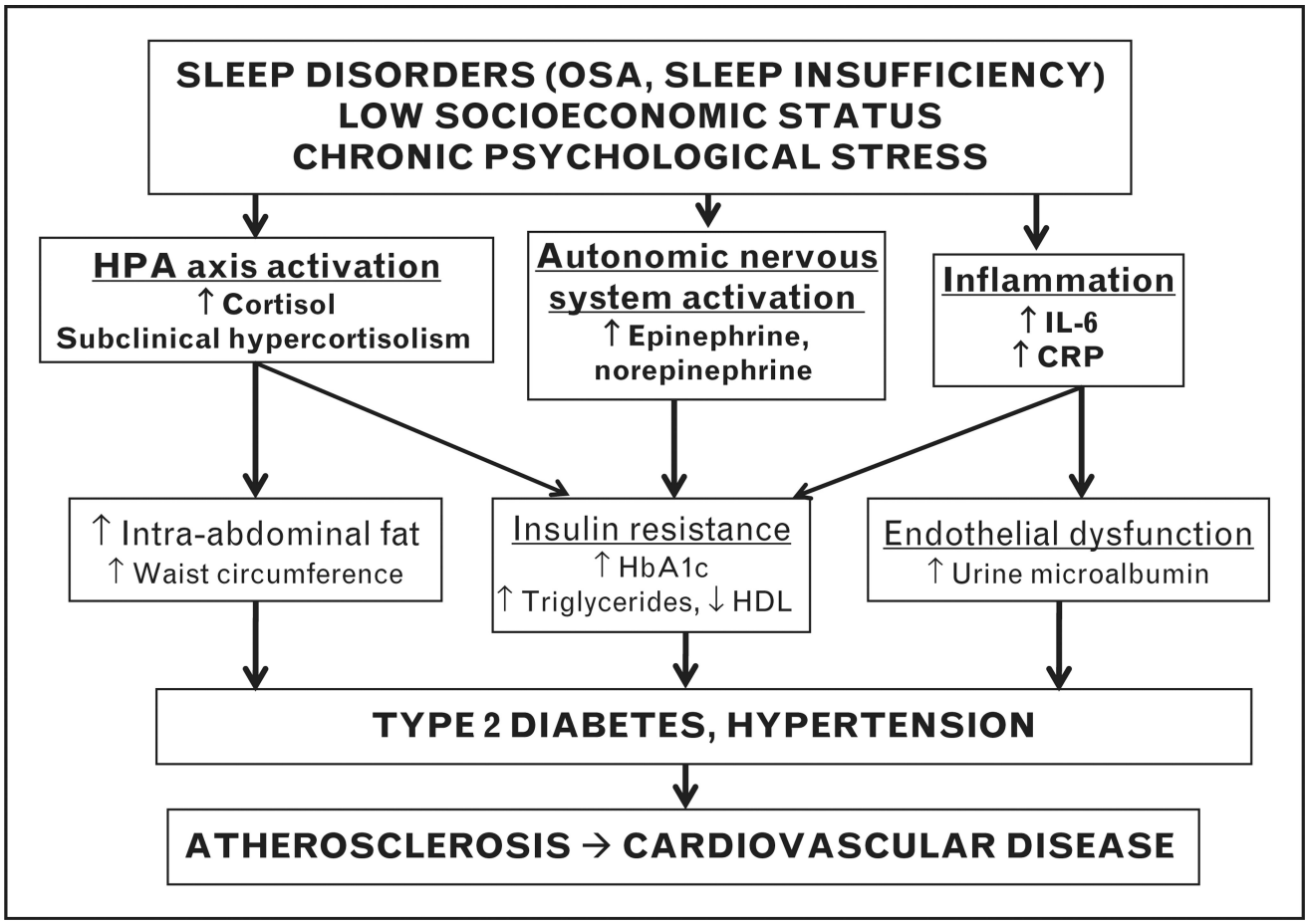

FIGURE 1.

A hypothesized relationship between novel cardiovascular risk factors and clinical cardiovascular disease in type 2 diabetes.

Table 1

Meta-analyses of trials of glycemic control and cardiovascular outcomes in type 2 diabetes mellitus

Study	Trials included in meta-analysis	Number of patients	Results
Ray *et al.* [10]	UKPDS, ACCORD, ADVANCE, VADT, PROactive ($n = 6$)	33 040	17% decrease in nonfatal MI; 15% decrease in CHD events; No effect on stroke or all-cause mortality
Kelly *et al.* [11]	UKPDS, ACCORD, ADVANCE, VADT ($n = 5$)	27 802	16% decrease in nonfatal MI; No effect on CVD or all-cause mortality; 2-fold increase in severe hypoglycemia
Boussageon *et al.* [12]	Above as well as UGDP studies, PROactive, Kumamoto Study, HOME Study ($n = 13$)	34 533	No significant effect on CVD or overall mortality; Slight decrease in nonfatal MI; 2-fold increase in severe hypoglycemia and 47% increase in CHF

ACCORD, Action to Control Cardiovascular Risk in Diabetes Trial; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation trial; CVD, cardiovascular disease; HOME, Hyperinsulinemia: the Outcome of its Metabolic Effects; MI, myocardial infarction; PROactive, The PROspective pioglitAzone Clinical Trial In macroVascular Events; UGDP, University Group Diabetes Program; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

Table 2

Summary of new studies focusing on cardiovascular disease in type 2 diabetes mellitus: 2012–2013

Category study	Study	Population characteristics	Study design/interventions	Summary of primary findings
Glycemia treatment	SAVOR-TIMI 53 [17▪]	16 492 patients with T2DM with a HbA1C of 6.5–12.0%, and either a history of established cardiovascular disease or multiple risk factors for vascular disease.	Individuals randomized to saxagliptin daily versus placebo, in addition to existing hypoglycemic/CV agents and followed for a median of 2.1 years for the primary endpoint of a composite of cardiovascular death, myocardial infarction or ischemic stroke.	Primary endpoint occurred in 7.3% in saxigliptin group versus 7.2% in placebo. No difference in CVD events.
	EXAMINE [18▪]	5380 patients with T2DM and either an acute myocardial infarction or unstable angina requiring hospitalization.	Individuals randomized to alogliptin or placebo in addition to existing hypoglycemic and CV drug therapy within 15–90 days of AMI or UA and followed for a median of 1.5 years for primary endpoint of a composite of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke.	The primary endpoint event occurred in 11.3% of patients assigned to alogliptin and in 11.8% patients assigned to placebo. HBA1C 0.36% lower in alogliptin group.
	ORIGIN [19]	12 537 people with CV risk factors along with impaired fasting glucose, impaired glucose tolerance or T2DM.	Patients received insulin glargine (with a target fasting blood glucose level of ≤95 mg per decilitre) or standard care. The coprimary outcomes were nonfatal myocardial infarction, nonfatal stroke or death from cardiovascular causes and these events along with revascularization or hospitalization for heart failure over a median of 6.2 years.	The first coprimary outcome occurred in 5.52 (glargine) and 5.28 (standard care groups with a hazard ratio, 1.02 $P = 0.63$) and the second coprimary outcome occurred in 5.52 and 5.28 per 100 person-years HR 1.04, ($P = 0.27$). No difference in CV events with addition of glargine to standard care.
Lifestyle interventions	Look AHEAD [20▪▪]	5145 overweight or obese patients with T2DM.	Patients randomized to either intensive lifestyle intervention that promoted weight loss through decreased caloric intake and increased physical activity (intervention group) or received diabetes support and education (control group) and followed a median of 9.6 years for the development of the primary outcome of a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke or hospitalization for angina.	The primary outcome occurred at a rate of 1.83 (intervention) and 1.92 events per 100 person-years (control) with a hazard ratio in the intervention group of 0.95 ($P = 0.51$).
	PREDIMED [21]	7447 persons in Spain at a high cardiovascular risk with either T2DM or at least three of the following major risk factors: smoking, hypertension, elevated LDL cholesterol, low HDL cholesterol	Patients were randomized to one of the three diets: a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts or a control diet	The primary endpoint occurred in 96 patients with Mediterranean diet with extra-virgin olive oil (multivariable-adjusted HR 0.70 and 83) patients in the

Category study	Study	Population characteristics	Study design/interventions	Summary of primary findings
		levels, overweight or obesity or a family history of premature coronary heart disease but with no known CVD.	(advice to reduce dietary fat) and were followed until trial stopped early at 4.8 years for the development of the primary endpoint of major cardiovascular events (myocardial infarction, stroke or death from cardiovascular causes).	group assigned to a Mediterranean diet with nuts (multivariable adjusted HR 0.72), versus 109 patients in the control group.
	Adventist Health Study 2 [22]	73 308 Seventh-day Adventist participants with no history of cancer or CVD.	Participants were followed prospectively to assess the association between vegetarian dietary patterns and mortality over a median of 5.79 years. The primary endpoint was all-cause mortality with a secondary endpoint of CVD mortality.	The adjusted hazard ratio (HR) for all-cause mortality in all vegetarians combined versus nonvegetarians was 0.88 (95% CI 0.80–0.97). The adjusted hazard ratio (HR) for CVD mortality in male vegetarians combined versus nonvegetarians was 0.71 (95% CI 0.57–0.90).
Bariatric surgery interventions	SOS Substudy [23]	A subset of 607 T2DM patients in SOS trial, 345 individuals in the surgery group and 262 individuals in the control group.	Participants were followed for a mean of 13.3 years for all cardiovascular events.	Bariatric surgery was associated with an adjusted HR of 0.56 ($P = 0.025$) for CHD. There was no significant difference in stroke incidence with adjusted HR 0.73 ($P = 0.29$).
	STAMPEDE Trial [24]	150 individuals with uncontrolled type 2 diabetes (HbA1c 9.7%) and moderate obesity [BMI 36.6 kg/m^2 27–43)].	Randomized in a nonblinded fashion to intensive medical therapy (IMT) alone, IMT along with Roux-en-Y gastric bypass or IMT along with sleeve gastrectomy and followed for 5 years for a primary endpoint of HgbA1C <6% at 1 year.	The primary endpoint at 1 year was reached in 12% IMT alone group versus 42% in gastric bypass group and 37% in the sleeve-gastrectomy group. The mean A1C was 7.5% in the IMT group versus 6.4% in gastric bypass and 6.6% in the sleeve gastrectomy group with reduced CV and T2DM medications in surgical groups.
	STAMPEDE Trial Substudy [25]	60 individuals from the STAMPEDE trial.	Evaluated at 1 and 2 years for assessment of beta-cell function (mixed-meal tolerance testing) and body composition.	At 2 years, A1C 8.4% for IMT versus 6.7% for gastric bypass and 7.1% for sleeve gastrectomy with greater insulin sensitivity, beta-cell function and reduction in truncal fat in the gastric bypass group, but not in the sleeve gastrectomy group.
	Mingrone *et al.* [26]	60 Italian individuals with BMI >35 kg/m^2 and A1C >7%.	Individuals were randomized to conventional medical therapy versus Roux-en-Y gastric bypass or biliopancreatic diversion with a primary endpoint of diabetes remission (A1C <6.5%) at 2 years in the absence of pharmacologic	At 2 years, T2DM remission occurred in no patients in the medical-therapy group (mean HbA1C 7.69%) versus 75% in the gastric-bypass group (mean HbA1C 6.35%) and 95% in the

Category study	Study	Population characteristics	Study design/interventions	Summary of primary findings
			therapy (diabetes remission).	biliopancreatic diversion group (mean HbA1C 4.95%) ($P <$ 0.001 for both comparisons).
	Cohen *et al.* 2012 [27]	66 consecutive individuals in Brazil with uncontrolled T2DM (HbA1C >8%) and BMI 30–35 with no control group.	Individuals underwent Roux-en-Y gastric bypass and were prospectively studied for a median of 5 years for safety of procedure and the percentage of patients experiencing diabetes remission (HbA1c, 6.5% without diabetes medication).	Durable diabetes remission occurred in 88% of cases, with glycemic improvement in 11%. Mean HbA1c fell from 9.7 to 5.9% ($P <$ 0.001). There was no mortality, major surgical morbidity or excessive weight loss.
	Diabetes Surgery Study [28]	120 individuals with T2DM and BMI 30–39.9.	Individuals underwent intensive lifestyle-medical treatment (ILMT) along with Roux-en-Y gastric bypass (60) versus ILMT alone (60) with a primary composite outcome of HgbA1C <7%, LDL <100mg/dl and SBP <130 mmHg.	At 1 year, they reported the primary outcome occurring in 49% of individuals in the surgery/ILMT versus 19% in the ILMT group with an odds ratio of 4.8, but notably there were 22 serious adverse events in the gastric bypass group compared with 15 in the ILMT alone group.

EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care study; ORIGIN, The Outcome Reduction with an Initial Glargine Intervention Trial; PREDIMED, Prevención con Dieta Mediterránea; SAVOR-TIMI 53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI) 53; SOS, Swedish Obese Subjects; STAMPEDE, Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently trial; T2DM, type 2 diabetes mellitus.