

Cardiovascular Benefits and Risk Profiles of Oral Anti-Diabetic Agents: Current Evidence and Ongoing Trials

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Received: May 14, 2015

Revised: June 21, 2015

Accepted: June 25, 2015

Published online: October 10, 2015

ABSTRACT

Type 2 diabetes increases the risk of developing cardiovascular (CV) morbidity and mortality. Strict glycemic control may produce CV benefit in newly diagnosed or short duration diabetes, but not in long-standing complicated diabetic patients, especially in those with high risk of hypoglycemia. In 2008, the US Food and Drug Administration (FDA) revised regulations for the approval of medications for type 2 diabetes by requiring adequate CV safety evidences. Recently, major concerns have arisen about current oral anti-diabetic agents (OADs). This review will be focused on CV benefits and risk profiles of currently available OADs based on evidences from landmark randomized controlled trials and meta-analyses. Metformin, sulfonylureas (SUs), and alpha-glucosidase inhibitors have limited and/or controversial data on CV safety evaluation. Peroxisome proliferator-activated receptor gamma agonists or thiazolidinediones

(TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium-glucose co-transporter type 2 (SGLT2) inhibitors have been more extensively evaluated in well-designed CV outcome trials. A recently published randomized clinical trials demonstrated empagliflozin reduced CV risks and mortality in high CV risks type 2 diabetes patients. Ongoing trials will elucidate the CV safety for TZDs (pioglitazone), DPP-4 inhibitors, and SGLT2 inhibitors compared to SUs or placebo.

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Key words: Cardiovascular benefit; Cardiovascular risk; Cardiovascular safety; Diabetes; Oral anti-diabetic agent

Hua SC, Hwang JJ, Chang YC. Cardiovascular Benefits and Risk Profiles of Oral Anti-Diabetic Agents: Current Evidence and Ongoing Trials. *Journal of Cardiology and Therapy* 2015; 2(5): 386-392 Available from: URL: <http://www.ghrnet.org/index.php/jct/article/view/1204>

Abbreviation

CVD: cardiovascular disease, CV: Cardiovascular, OAD: oral anti-diabetic agent, SU: sulfonylurea, TZD: thiazolidinedione, DPP-4 inhibitor: dipeptidyl peptidase-4 inhibitor, SGLT2 inhibitor: sodium-glucose co-transporter type 2 inhibitor, RCT: randomized controlled trial, UKPDS: UK Prospective Diabetes Study, LDL: low-density lipoprotein-cholesterol, HDL: high-density lipoprotein-cholesterol, ACCORD: Action to Control Cardiovascular Risk in Diabetes, ADVANCE: Action in Diabetes and Vascular Disease, VADT: Veterans Affairs Diabetes Trial, AMI: acute myocardial infarction, MI: myocardial infarction, UGDP: University Group Diabetes Project, SUR1: sulphonylurea receptor type 1, SUR 2A: sulphonylurea receptor type 2A, SUR 2B: sulphonylurea receptor type 2B, TOSCA. IT: Thiazolidinediones or Sulfonylureas and Cardiovascular Accidents Interven-

tion Trial, CAROLINA: Cardiovascular Outcome Study of Linaagliptin versus Glimepiride in Patients with Type 2 Diabetes, Proactive study: PROspective pioglitAzone Clinical Trial In macroVascular Events study, CHICAGO trial: Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone trial, PERISCOPE study: Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation study, HF: heart failure, CHF: congestive heart failure, SAVOR-TIMI53: Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis In Myocardial Infarction 53, VIVVD: Vildagliptin in Ventricular Dysfunction Diabetes Trial, EXAMINE: Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care, STOP-NIDDM: Study to Prevent Non-Insulin Dependent Diabetes Mellitus, IGT: impaired glucose tolerance, DECLARE-TIMI58: Dapagliflozin Effect on Cardiovascular Events-TIMI Thrombolysis In Myocardial Infarction 58, CANVAS: Canagliflozin Cardiovascular Assessment Study

CV RISKS AND BENEFITS OF GLYCEMIC CONTROL

Type 2 diabetes has long been recognized as an independent risk factor for cardiovascular disease (CVD). Cardiovascular (CV) complications are the leading cause of comorbidity and death in the patient with diabetes. Although improved glycemic control in diabetic patients has been confirmed to reduce the incidence of microvascular complications, it has not been consistently shown to prevent macrovascular complications. The UK Prospective Diabetes Study (UKPDS), which is conducted in patients with newly diagnosed type 2 diabetes, demonstrated that hyperglycemia, as assessed by HbA1c levels, was a statistically independent and potentially modifiable risk factor for CVD, in addition to low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), blood pressure, and smoking^[1]. However, three other major trials including the Action to Control Cardiovascular Risk in Diabetes (ACCORD)^[2], Action in Diabetes and Vascular Disease (ADVANCE)^[3], and the Veterans Affairs Diabetes Trial (VADT)^[4], failed to show a significant reduction in macrovascular events in patients with long-standing diabetes (mean duration 8-11 years) and high CV risk using intensive glycemic control (hemoglobin A1c < 6-7 %). The ACCORD study was terminated at 3.5 years because of increased all-cause and CV mortalities in the intensive-therapy group^[2]. In the ADVANCE study, intensive control was not associated significant changes in major CV events, CV death, or all-cause mortality^[3]. In VADT trial, major CV event or all-cause mortality was not altered in the intensive-therapy group^[4]. However, hypoglycemia occurred significantly more frequently in the intensive- therapy group than control group in both ADVANCE and VADT trials. Hypoglycemia can be associated with cardiac ischemia, and unrecognized hypoglycemia can contribute to adverse CV outcomes^[5]. Collectively, current evidence indicates that glycemic control may produce CV benefit early in disease course, but not in long-standing complicated diabetes patients, especially those with high risk of hypoglycemia.

In mid-2007, a meta-analysis of 42 randomized controlled trials (RCTs) involving rosiglitazone reported a 1.4-fold increase in risk of acute myocardial infarction (AMI) compared with non-thiazolidinedione therapies^[6]. In addition to the CV risk associated with glucose-lowering effect, major concerns have recently arisen about the CV safety of individual oral anti-diabetic agent (OAD). The Food and Drug Administration (FDA) revised regulations for approval of medications for type 2 diabetes by requiring that enough CV events are

accrued prior to approval to rule out an upper 95% confidence interval for hazard ratio 1.8 for CV events, followed by ruling out an upper 95% confidence interval for hazard ratio 1.3 in the post-approval period since 2008. This review will be focused on CV safety of currently available OADs based on evidences from landmark RCTs and meta-analyses.

CV BENEFITS AND RISKS OF METFORMIN

The evidence of cardiovascular benefits of metformin therapy was first shown in the initial 10 year follow-up of UKPDS^[1]. In this study, overweight patients receiving metformin therapy had a 39% reduction in risk of myocardial infarction (MI) and a reduction of 36 % for death from any cause in comparison to conventional dietary therapy. A continued benefit of MI and death from any cause by metformin therapy among overweight patients was evident during 10 years of post-trial follow-up^[7]. However, systemic reviews and meta-analyses of cardiovascular effects of metformin have produced inconsistent results depending on the inclusion criteria used. A systemic review by Selvin *et al*^[8] found that metformin therapy associated with a decreased risk of cardiovascular mortality of 26% compared with any other OADs or placebo, but this systemic review did not include the results of non-overweight group. A meta-analysis by Lamanna *et al*^[9] showed that metformin was not associated with significant benefit or harm on cardiovascular events. Metformin had a significant cardiovascular benefit versus placebo or no therapy, but not in active comparator trials. However, this meta-analysis also included non-diabetic patients, HIV, and polycystic ovary syndrome patients. Another meta-analysis by Boussageon *et al*^[10] found that metformin did not significantly affect all-cause mortality or CV deaths. Collectively, the definite efficacy of metformin to prevent death or CV events has not been fully proven. However, among all OADs, metformin is one with least disadvantages. It does not cause hypoglycemia and weight gain.

CV BENEFITS AND RISKS OF SULFONYLUREA

SUs are divided into classes. The first-generation agents (carbutamide, tolbutamide, acetohexamide, tolazamide and chlorpropamide) were introduced in the 1950s. The second-generation agents (e.g., glibenclamide, glipizide, glibornuride and gliclazide) and the third-generation agents (glimepiride, gliclazide modified-release and glipizide gastrointestinal therapeutic system) have almost completely replaced the first-generation drugs. Historically, tolbutamide, a first-generation sulfonylurea is associated with increased cardiovascular events and all-cause mortality in the University Group Diabetes Project (UGDP) trial^[11]. Findings from several studies and meta-analyses suggest that SUs are associated with higher risk of mortality and adverse CV events than metformin and other OADs^[11,12-20]. The proposed mechanisms include cardiac ischemic conditioning interference and hypoglycemia. SUs bind to SU receptor type 1 (SUR1) on pancreatic β -cells and inhibit ATP-sensitive potassium channels which promotes insulin release. However, SUs also bind to receptors on myocardial (SUR2A) and vascular smooth muscle (SUR2B) cells which inhibit cardiac ATP-sensitive potassium channels^[21-22] and interfere with ischemic conditioning^[23]. The second mechanism is hypoglycemia, as well known side effects of SUs. Hypoglycemia can prolong the QT interval and is associated with cardiac ischemia^[24-25]. QT interval prolongation and cardiac ischemia increase the risk of adverse cardiovascular events^[26]. Among the second- and third-generation SUs, differences in SUR1 receptor affinity and pharmacokinetic properties create differences in the risk

of hypoglycemia, with glibenclamide, which has the highest affinity for SUR1^[27] having the highest risk among SUs^[28-29].

In contrast to first-generation SUs, second- and third-generation SUs seem to be associated with better safety profiles. A Cochrane systemic review and meta-analysis of randomized clinical trials by Hemmingsen *et al*^[30] showed that in comparison with metformin, the second- and third-generation SUs may not affect all-cause or CV mortality but may decrease the risk of nonfatal CV outcomes among patients with type 2 diabetes. Another recently published systemic review and network meta-analysis by Simpson *et al*^[31] to compare the relative risk of mortality and adverse CV events among SUs. The results showed that gliclazide and glimepiride were associated with a lower risk of all-cause and CV-related mortality compared with glibenclamide. The definite conclusions need to be answered by well-designed RCTs. The ongoing trials of Thiazolidinediones or Sulfonylureas and Cardiovascular Accidents Intervention Trial (TOSCA.IT) (NCT00700856)^[32] and CAROLINA (NCT01243424)^[33] trails will help answer some questions. Nevertheless, current evidence suggests a better CV risk profile of third-generation SUs compared to older-generation SUs.

CV BENEFITS AND RISKS OF THIAZOLIDINEDIONE (TZD)

TZDs are previously proposed to have protective effects on CVD. However, rosiglitazone have been shown to increase the risk of MI by 1.4-fold in a meta-analysis in 2007^[6] and subsequent analyses^[34,35]. In contrast, in the PROspective pioglitAZone Clinical Trial In macroVascular Events (PROactive) study, a large RCT investigating the effects of pioglitazone on macrovascular outcomes in 5,238 patients with type 2 diabetes and preexisting CVD, pioglitazone added to optimized standard care causes a significant reduction in a composite end point comprising CV death plus nonfatal MI plus nonfatal stroke [HR 0.82 (95% CI 0.70-0.97)] as compared to placebo, although the primary end point--a composite of all-cause mortality, nonfatal MI, acute coronary syndrome, stroke, major leg amputation, and coronary or leg revascularization was only nonsignificantly reduced by 10%^[36]. Furthermore, in patients with a previous MI, pioglitazone significantly reduced the risk of subsequent MI by 28% and acute coronary syndrome by 38%^[37]. In patients with a previous stroke, pioglitazone decreased the risk of a second stroke by 48%^[38]. Two additional RCTs also showed favorable effect of pioglitazone on the progression of atherosclerosis. In the Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone (CHICAGO) trial^[39], pioglitazone was observed to decrease progression of carotid intima-media thickness over an 18-month treatment period compared with glimepiride. In the Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE) study^[40], coronary intravascular ultrasonography was used to assess the change in percent atheroma volume in 360 patients with type 2 diabetes and coronary artery disease treated with either pioglitazone or glimepiride. Pioglitazone-treated patients had a significantly lower rate of progression of coronary atherosclerosis.

A report^[41] from the FDA analyzing the risk of CV events in 227571 patients aged more than 65 years who were treated with rosiglitazone, compared with pioglitazone, was associated with an increased risk of stroke, heart failure, and all-cause mortality and an increased risk of the composite of AMI, stroke, heart failure (HF), or all-cause mortality (HR 1.86, 95% CI 1.27-2.08). It has been

hypothesized that differing CV outcomes associated with different TZD may be due to their differential effects on lipid subfractions. Pioglitazone, compared with rosiglitazone was associated with significant improvements in triglycerides, HDL-cholesterol, non-HDL cholesterol, LDL particle size compared with rosiglitazone^[42-44].

The major adverse CV concern of all TZDs is congestive heart failure (CHF). Mouse models show that pioglitazone activation of peroxisome proliferator-activated receptor γ receptors in the distal nephron increases sodium reabsorption through the epithelial sodium channel^[45]. The underlying mechanism is due to fluid retention and plasma volume expansion. In the PROactive study, 5.7% and 4.1% of pioglitazone and placebo patients, respectively, were hospitalized for CHF; however, mortality rates due to CHF were similar. In conclusion, pioglitazone probably exert beneficial effect on MI and stroke while rosiglitazone may modestly increase the risk of MI and stroke. Both drugs are associated with substantial CHF risk.

CV BENEFITS AND RISKS OF DIPEPTIDYL PEPTIDASE-4 (DPP4) INHIBITORS

Up to date, four published trials including the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)–Thrombolysis in Myocardial Infarction (TIMI) 53 (SAVOR-TIMI 53), the Vildagliptin in Ventricular Dysfunction Diabetes Trial (VIVID), and Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care trial (EXAMINE), and Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin (TECOS) were appropriately designed and conducted to assess their effects on CV mortality and morbidity^[46-48]. In the SAVOR-TIMI 53^[46], 16,492 patients with type 2 diabetes and history or at risk of CV events were randomized to receive saxagliptin or placebo and were followed for 2.1 years. In this study, patients in the saxagliptin group were more frequently to be hospitalized for CHF, whereas no differences in all-cause and CV mortality and morbidity were observed. In EXAMINE trial^[48], 5,380 patients with type 2 diabetes with recent AMI or unstable angina were randomized to receive alogliptin or placebo and were followed-up for 1.5 years. No difference in the primary outcome (CV death, MI and stroke) was observed. However, a non-significant trend of increased risk for CHF was found for alogliptin. In VIVID study^[47], 254 patients with CHF (NYHA classes I to III) and type 2 diabetes were randomized to vildagliptin or placebo and followed for 52 weeks. Preliminary data from this trial showed no significant differences in change in ejection fraction and in brain natriuretic peptide values between two groups. However, patients taking vildagliptin experienced a two-fold increase in left ventricular end-diastolic volume, end-systolic volume and stroke volume compared to the control group. No differences in the number of patients reporting worsening CHF were observed. In TECOS trial^[49], 14,671 type 2 diabetes patients and established cardiovascular disease were randomly assigned to add either sitagliptin or placebo to their existing therapy. Adding sitagliptin to usual care did not appear to increase the risk of major adverse cardiovascular events, hospitalization for heart failure, or other adverse events^[49].

A meta-analysis by Agarwal *et al*^[50] assessed the CV safety of DPP-4 inhibitors, pooling 82 trials enrolling 73,678 patients and showing no benefit of DPP-4 inhibitors on CV death, MI or stroke, whereas no evaluation of CHF risk was performed in this study. Another meta-analysis by Monami *et al*^[51] reported DPP-4 inhibitors reduce the risk of CV events (particularly MI) and all-cause mortality. A weak

signal of increased CHF has been recently raised by another meta-analysis enrolling a smaller number of patients (55,141 participants)^[52]. A meta-analysis by Savarese *et al.* (53) showed that the benefits of DPP-4 inhibitors on MI risk in the short-term treatment (< 29 weeks) disappear with prolonged treatment, whereas the risk of CHF increases significantly with prolonged treatment (≥ 29 weeks).

It remains unclear how DPP-4 inhibitors affect risk of CHF. It has been reported that DPP-4 inhibitors increase heart rate and tend to lower blood pressure, which may be responsible for a chronic adrenergic activation potentially increasing the risk of CHF^[54]. Saxagliptin, alogliptin, and sitagliptin were tested in RCTs designed to assess CV outcomes, thus, more information is needed to assess whether increased CHF risk represents a class effect or is limited to specific drugs. Results of two ongoing RCTs: [Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus (CARMELINA) (NCT01897532) and Cardiovascular Outcome Study of Linagliptin versus Glimperide in Patients with Type 2 Diabetes (CAROLINA) (NCT01243424)]^[34] testing CV effects of DPP-4is are expected to clarify these aspects.

CV BENEFITS AND RISKS OF ACARBOSE

The CV benefits of acarbose treatment were first demonstrated by the Study to Prevent Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM) study^[55]. The study found that acarbose treatment in people with impaired glucose tolerance (IGT) was associated with a 49% reduction in the incidence of newly diagnosed CV events over a mean follow-up of 3.3 years. However, the CV events in STOP-NIDDM study is very limited (12 events vs. 1 event in each arm). In a meta-analysis of placebo-controlled studies of patients with type 2 diabetes treatment with acarbose reduced the risk of any CV event by 35% ($p = 0.006$)^[56]. However, in a substudy of patients with type 2 diabetes previously enrolled in the UKPDS (UKPDS 44), no effect of acarbose on CVD events was observed after 3 years of follow-up^[57]. In both studies^[56-57], no increase of any symptoms of CHF was observed in patients treated with acarbose. In summary, acarbose may have beneficial CV effects on prediabetes and diabetic patients, probably through lowering of post-prandial glucose.

CV BENEFITS AND RISKS OF SODIUM-GLUCOSE CO-TRANSPORTERTYPE 2 (SGLT2) INHIBITORS

Phase II–III RCTs demonstrate that SGLT2 inhibitors improve glucose control, body weight, visceral adiposity and blood pressure when used as monotherapy or add-on to other OADs. In a systematic review and meta-analysis, SGLT2 inhibitors significantly reduced both systolic and diastolic blood pressure from baseline^[58]. SGLT2 inhibitor also can lower serum uric acid, an independent CV marker, through alteration of uric acid transport activity in renal tubule by increased glucosuria^[59]. The other potential CV benefits included changes in arterial stiffness^[60], cardiac function, and cardiac oxygen demand^[60], cardiorenal effects^[60-61], and improvement in albuminuria^[62-63].

However, in another systematic review, a higher risk for hypotension was found with SGLT2 inhibitors than with other OADs^[64]. Orthostatic hypotension should be avoided in fragile elderly patients, especially in those receiving loop diuretics, even if it appears to be a rather rare event^[58]. The effects of SGLT2 inhibitors on lipid profile appear controversial^[65]. For example, canagliflozin

increased LDL-cholesterol by an average 8%^[66]. However, some beneficial lipid effects such as increased HDL-cholesterol and decreased triglycerides were also reported with canagliflozin^[67].

When added to a usual background regimen in an older population with advanced type 2 diabetes and pre-existing CV disease, dapagliflozin improved glycemic control without an increase in hypoglycemic risk, promoted weight loss and was well-tolerated^[68]. However, this trial was not designed to investigate the effects of dapagliflozin on CV events in this high-risk population. A meta-analysis of CV outcomes based on 14 trials, yielded an odds ratio of 0.73 (95 % CI 0.46–1.16) for dapagliflozin treatment compared with control^[59]. In this meta-analysis, canagliflozin was associated with neutral CV outcome (OR = 0.95; 95 % CI 0.71–1.26)^[63]. The recently published Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients trial (EMPA-REG OUTCOME) is a double-blind placebo-controlled trial designed to determine the CV safety of empagliflozin (10 or 25 mg once daily) in a cohort of patients with type 2 diabetes with high CV risk, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke and of death from any cause when the study drug was added to standard care^[69]. These benefits were observed in a population with established cardiovascular disease in whom cardiovascular risk factors, including blood pressure and dyslipidemia, were well treated with the use of renin–angiotensin–aldosterone system inhibitors, statins, and acetylsalicylic acid. There remain a number of large-scale prospective trials now ongoing to demonstrate the safety and possibly the efficacy of SGLT2 inhibitors on CV outcomes in type 2 diabetic patients at CV risk^[70]. The Dapagliflozin Effect on Cardiovascular Events-TIMI Thrombolysis In Myocardial Infarction 58 (DECLARE TIMI58) trial is a multicenter, randomized, double-blind, placebo-controlled trial to evaluate the effect of dapagliflozin 10 mg once daily on the incidence of CV death, myocardial infarction or ischemic stroke in patients with high risks for CV events type 2 diabetes^[71]. The Canagliflozin Cardiovascular Assessment Study (CANVAS) is a double-blind, placebo-controlled trial designed to evaluate the effects of canagliflozin (100 or 300 mg once daily) on the risk of CV disease and to assess safety and tolerability in patients with inadequately controlled type 2 diabetes and increased CV risk^[72]. Results of all these CV outcome trials will be available within the next few years.

CONCLUSION

In summary, current evidence support a possible beneficial CV effect of metformin. Although first-generation SUs are associated with adverse CV profiles, third-generation SUs seems to have safer CV profile than older-generation SUs. Rosiglitazone probably moderately increased CVD risk, while pioglitazone may lower CVD risk. Both TZDs substantially increase CHF. Limited data demonstrated a beneficial effect of acarbose on CVD. DPP-4 inhibitors seem be neutral with regard to CVD but concerns remained with the elevated risk for hospitalized CHF. As to SGLT2 inhibitors, the first published trials revealed empagliflozin reduced CV risks and mortality in type 2 diabetes patients with at high risk for CV events. It remains not yet a class effect for all SGLT2 inhibitors and waiting for large-scale CV outcome trials published. Several ongoing landmark CV outcome trials are listed and summarized in Table 1. The exact CV safety for TZDs (pioglitazone), DPP-4 inhibitors, and SGLT2 inhibitors compared to SUs or placebo will be answered in the next few years.

Table 1 Ongoing major randomized clinical trials for assessment of CV risk of oral anti-diabetic agents.

	Drug/comparator	Study design	Background	Baseline therapy	Composite primary endpoint	NCT number
TOSCA IT	Pioglitazone/SU	RCT, open label	No evidence of coronary or cerebrovascular events, no CHF	Metformin monotherapy	All-cause mortality, non-fatal MI, non-fatal stroke, unplanned coronary revascularization	NCT 00700856
CAROLINA	Linagliptin/glimepiride	RCT, double-blind	Evidence of CVD or high CV risk	Largely metformin and/or SU, glinides or acarbose	CV death, nonfatal MI, non-fatal stroke or hospitalized unstable angina	NCT 01243424
CARMELINA	Linagliptin/placebo	RCT	High risk for CV events	Anti-diabetic therapy	CV death, nonfatal MI, non-fatal stroke or hospitalized unstable angina	NCT 01897532
DECLARE-TIMI58	Dapagliflozin/placebo	RCT, double-blind	High risk for CV events	Anti-diabetic therapy	CV death, MI, ischemic stroke	NCT 01730534
CANVAS	Canagliflozin/placebo	RCT, double-blind	Vascular disease history, two or more risk factors	Anti-diabetic therapy	CV death, nonfatal MI, non-fatal stroke	NCT 01032629

CV: cardiovascular; CHF: congestive heart failure; CVD: cardiovascular disease; RCT: randomized clinical trial; SU: sulfonylurea; MI: myocardial infarction

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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