Combination therapy for the improvement of long-term macrovascular and microvascular outcomes in type 2 diabetes: rationale and evidence for early initiation

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ABSTRACT

Diabetes is a leading cause of macrovascular and microvascular complications that can increase the risk of mortality if not properly managed. Proper glucose control can reduce the incidence of these complications, in particular those of the microvasculature. Over the last ~10 years, the cardiovascular safety of glucose-lowering drugs has come to the forefront of diabetes management and clinical trial design. While early combination therapy improves glycemic control, its impact on long-term outcomes, is not as clearly understood. The objective of this review is to examine the evidence of early combination therapy for the treatment of type 2 diabetes mellitus as it relates to studies of long-term macrovascular and microvascular outcomes.

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1. Introduction

Diabetes is a leading cause of death, cardiovascular disease (CVD), and microvascular complications among U.S. adults (CDC, 2014b). Although rates of myocardial infarction (MI) and stroke have declined in the last two decades (Gregg et al., 2014), CVD death rates in 2003–2006 were 1.7 times higher among adults with versus without diabetes (CDC, 2014b). Similarly, the incidence of end-stage renal disease (ESRD) related to diabetes decreased from 1995–2008 (CDC, 2014a), however, 44% of all new cases of kidney failure in the U.S. in 2011 listed diabetes as the primary cause.

For the management of patients with type 2 diabetes mellitus (T2DM) focus on treatment of hyperglycemia, and continue to evolve as new evidence emerges on microvascular and macrovascular complications. In addition, recommendations were issued in 2008 by the U.S. Food and Drug Administration (FDA) to ensure that new glucose-lowering agents do not exceed pre-specified CV risk limits (upper bound of the 2-sided 95% confidence interval [CI] for the estimated risk ratio ≤1.3) (U.S. Department of Health and Human Services, Food and Drug Administration, & Center for Drug Evaluation and Research (CDER), 2008). The relationship between glucose levels and vascular risk factors has been established in several prospective and observational studies (Barr et al., 2007; Juutilainen, Lehto, Rönnemaa, Pyörälä, & Laakso, 2008; Sarwar et al., 2010; Stratton et al., 2000). In one study, pre-diabetes (glycated hemoglobin [HbA1c] 5.7%–6.4%) and T2DM were associated with an increased relative risk (RR) for incident levels of elevated cardiac troponin, a measure of subclinical myocardial damage (Selvin et al., 2014), suggesting that hyperglycemia negatively impacts the myocardium before the diagnosis of T2DM. Similarly, diabetic retinopathy can develop as early as 7 years before diagnosis of T2DM (Fong, Aiello, Ferris, & Klein, 2004), and microalbuminuria has been identified in up to 7% of patients with T2DM at the time of diagnosis (Adler et al., 2003).

1.1. Initiation and management of T2DM treatment

The American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) (Inzucchi et al., 2015) and the American Association of Clinical Endocrinologists (AACE) (Garber et al., 2016) recommend an HbA1c level of <7.0% and ≤6.5%, respectively, for reducing the risk of diabetic complications in most patients. Metformin has been a first-line treatment for T2DM since it was shown to decrease all-cause mortality compared with diet alone in the United Kingdom Prospective Diabetes Study (UKPDS) (UKPDS Group, 1998), and is considered the optimal drug for monotherapy because of its “low cost, proven safety record, weight neutrality, and possible benefits on cardiovascular outcomes” (Inzucchi et al., 2015). Both ADA/EASD and AACE algorithms outline a stepwise progression from lifestyle changes, to monotherapy, and to combination therapy

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within ~3 months if metformin alone cannot adequately control glycemia. However, recommendations for add-on therapy choices and the prerequisite for initiating dual therapy differ between algorithms. Initial combination therapy is suggested for HbA1c levels ≥7.5% (AACE) and ≥8% (ADA/EASD). Because of the progressive nature of T2DM, many patients will need to intensify therapy to achieve glycemic control (UKPDS Group, 1995).

The rationale for early therapy has been demonstrated in a pooled analysis of patients with pre-diabetes, where assessments of insulin secretion and insulin resistance showed that subjects in the upper tertile of normal glucose tolerance had lost two-thirds of their β-cell function, whereas those in the upper tertile of impaired glucose tolerance (IGT), had lost 80%–85% (Defronzo, 2009). Thus, by the time a diagnosis of T2DM was made, the majority of β-cell function was lost. These key findings emphasize the need for early intervention in the treatment of T2DM.

2. Objective and methods

This review examines the evidence of early combination therapy for the treatment of T2DM as it relates to long-term microvascular and macrovascular outcomes. Despite significant advances in pharmacologic approaches to treat hyperglycemia, the timing of combination therapy and its impact on the prevention of long-term outcomes requires further investigation.

A search of PubMed (through to March 2015) for clinical trials evaluating combination glucose-lowering agents and long-term outcomes for the treatment of T2DM was conducted. Search terms included “type 2 diabetes macrovascular outcomes trial” or “type 2 diabetes MACE” (major adverse cardiac events) or “type 2 diabetes microvascular outcomes trial.” The results were reviewed qualitatively based on treatment initiation time, duration of T2DM diagnosis, and use of monotherapy, combination therapy, or multifactorial therapy. The U.S. National Institutes of Health database of clinical trials (ClinicalTrials.gov) was used to search for ongoing trials of combination glucose-lowering agents and long-term outcomes. Updates to several clinical trials subsequently published, including the cardiovascular (CV) outcome trial with empagliflozin, are included. Because a limited number of studies have evaluated long-term outcomes with early combination T2DM therapy, evidence for intensive versus conventional glycemic control strategies and combination therapy in patients with long-standing T2DM are included in this narrative review.

3. The past: what have we learned from outcomes trials of intensive versus conventional and combination glucose-lowering therapy?

3.1. Intensive versus conventional glycemic therapy in patients with long-standing T2DM

Landmark outcomes trials – the Action to Control Cardiovascular Risk in Diabetes (ACCORD) (Gerstein et al., 2008, 2011); Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) (Patel et al., 2008; Zoungas et al., 2014); and the Veterans Affairs Diabetes Trial (VADT) (Duckworth et al., 2009; Hayward et al., 2015) – assessed the effect of intensive glucose lowering on CV risk in patients with long-standing diabetes. These trials were not designed to evaluate the effects of individual agents or combination treatment on macrovascular outcomes; however, combinations of glucose-lowering drugs (intensive and standard therapy) were utilized in an attempt to achieve glycemic targets (mean HbA1c 6.3%–6.9% for intensive therapy). The ACCORD trial was discontinued prematurely because of an increased risk of all-cause mortality (hazard ratio [HR], 1.22 [95% CI 1.01, 1.46]; P = 0.04) in the intensive versus standard-therapy arm (Gerstein et al., 2008). In an additional 5-year follow-up exploratory analysis of intensive therapy, there was a reduced risk for the combined endpoint of MI, coronary revascularization, and unstable angina [overall HR 0.87 [95% CI 0.79, 0.96]; P = 0.006] (Gerstein et al., 2014); however, this benefit was offset by the earlier increased CV mortality risk (Gerstein et al., 2008). The initial results of ADVANCE (Patel et al., 2008) and VADT (Duckworth et al., 2009) also failed to demonstrate a significant benefit of intensive glycemic control on macrovascular outcomes, although intensive glycemic control improved microvascular outcomes in ADVANCE (Patel et al., 2008) and slowed the progression of albuminuria in VADT (Duckworth et al., 2009). In a 6-year, post-trial follow-up of ADVANCE, tight glucose control resulted in significant improvements in ESRD (HR 0.54 [95% CI 0.34, 0.85]; P = 0.007). However, no improvements in the composite for CV death, MI, or stroke (HR 1.00 [95% CI 0.92, 1.08]; P = 0.93) or CV mortality (HR 0.97 [95% CI 0.86, 1.10]; P = 0.63) were observed (Zoungas et al., 2014). The ~10-year follow-up that showed intensive therapy reduced the risk of the primary composite CV outcome of MI, stroke, new or worsening congestive heart failure (HF), death from CV causes, or amputation (ischemic gangrene) (HR 0.83 [95% CI 0.70, 0.99]; P = 0.04). It did not show any difference in CV-related mortality (HR 1.05 [95% CI 0.89, 1.25]; P = 0.54) (Hayward et al., 2015). Taken together, these studies suggest that the CV benefits of intensive glucose-lowering therapy may be slow to manifest, and may also depend on individual patient characteristics such as short duration of diabetes, lower baseline HbA1c, prior to intensive therapy, and lack of concomitant CVD (Duckworth et al., 2011; Gerstein et al., 2008; Skyler et al., 2009).

3.2. Combination therapy in patients with long-standing T2DM

The Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral agent combination therapy for type 2 Diabetes (RECORD) (Home et al., 2009) and PROspective PioglitAzone Clinical Trial In macroVascular Events (PROactive) (Dormandy et al., 2005) studies assessed the effect of thiazolidinedione (TZD) add-on therapy on macrovascular and microvascular outcomes in patients with a T2DM duration of 6–10 years. In RECORD, addition of rosiglitazone to metformin or sulfonylurea (SU) increased the rate of HF (HR 2.10 [95% CI 1.35, 3.27]; P = 0.0010) and was inconclusive about MI risk (HR 1.14 [95% CI 0.80, 1.63]; P = 0.47) and CV mortality (HR 0.84 [95% CI 0.59, 1.18]; P = 0.32) (Home et al., 2009). The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) study showed similar rates of ischemic CV events and congestive HF in patients with T2DM and coronary artery disease with rosiglitazone versus patients not receiving a TZD during 4.5 years of follow-up (Bach et al., 2013). In patients with T2DM and a history of macrovascular disease in the PROactive study, addition of pioglitazone to current diabetes and CV medications did not significantly reduce the time to the primary composite endpoint. This primary composite endpoint included death from any cause, nonfatal MI, stroke, acute coronary syndrome (ACS), leg amputation, coronary revascularization, or revascularization of the leg (HR 0.90 [95% CI 0.80, 1.02]; P = 0.095). However, addition of pioglitazone reduced the risk of the composite secondary endpoint (death from any cause, nonfatal MI or nonfatal stroke (HR 0.84 [95% CI 0.72 to 0.98]; P = 0.027) (Dormandy et al., 2005).

Bromocriptine mesylate is a quick-release (QR) dopamine receptor agonist that reduces glucose slightly without a risk of hypoglycemia (Garber et al., 2016). In a placebo-controlled, randomized, 1-year safety trial, patients (n = 3070) had an average baseline HbA1c of 7.0%, a mean T2DM duration of 8 years, and most were receiving background therapy with additional oral agents or insulin. Compared with placebo plus usual care, treatment with bromocriptine QR significantly reduced the composite CV endpoint of MI, stroke, hospitalization for unstable angina, congestive HF, or revascularization surgery (HR 0.60 [95% CI 0.35, 0.96]) (Gazziano et al., 2010). A post hoc analysis that included CV mortality in the composite also showed
reduced risk (HR 0.61 [95% CI 0.38, 0.97]), as did an analysis that restricted the composite to MACE (CV mortality, MI, and stroke [HR 0.48; 95% CI 0.23, 1.00]) (Gaziano et al., 2012).

In summary, the PROactive trial and the bromocriptine safety trial suggest that pioglitazone and bromocriptine QR, respectively, may reduce CV event rates, but these analyses did not have the full rigor of a prospective cardiovascular outcomes study.

3.3. Early glucose-lowering and intensive therapy

Evidence for long-term outcomes with early glucose-lowering combination therapy is limited. The landmark UKPDS randomized newly diagnosed patients with T2DM to intensive or conventional therapy (UKPDS Group, 1998). After a median 10 years, the intensive arm had a significantly lower risk for any diabetes-related endpoint (RR, 0.88; P = 0.029), most of which was due to a 25% risk reduction in microvascular endpoints (RR, 0.75; P = 0.099). However, macrovascular endpoints, such as diabetes-related deaths (RR, 0.9; P = 0.34), all-cause mortality (RR, 0.94; P = 0.44), or MI (RR, 0.84; P = 0.052) were not significantly reduced versus standard therapy (UKPDS Group, 1998). The CV benefits of intensive glucose control, including a significant reduction in MI (15%; P = 0.01) and death from any cause (13%; P = 0.007), became evident only after an additional 10 years post trial and was subsequently termed the “legacy effect” (Holman, Paul, Bethel, Matthews, & Neil, 2008). The findings suggest that early intensive glucose-lowering therapy may offer long-term protection from CV events; however, these changes may take a long time to manifest.

The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial included patients with prior CVD or at high risk of a CV event, and impaired fasting glucose (IFG), IGT, or newly diagnosed or established T2DM (mean duration = 5 years); baseline median HbA1c was 6.4%. Patients received insulin glargine or standard therapy alone for a median of 6.2 years. Results showed no significant reduction in the composite co-primary endpoint of CV death, nonfatal MI, and nonfatal stroke. However, insulin glargine reduced incident diabetes in patients with IFG and IGT (Gerstein et al., 2012).

Taken together, the difference in outcomes between UKPDS and ORIGIN may relate to the patient populations and timing of the intervention. Whereas ORIGIN included a mixed population with pre-diabetes, early disease, or established T2DM; older age (mean 63.5 years); and established CVD or high CV risk, the UKPDS population was younger (median 54 years) with newly diagnosed disease and lower CV risk. Results from the Study To Prevent Non-insulin-Dependent Diabetes Mellitus (STOP–NIDDM), although not a trial of intensive glucose control involving combinations of therapies in T2DM, further support the importance of early intervention (Chiasson et al., 2002). This trial evaluated the efficacy of acarbose 100 mg three times daily versus placebo in preventing progression from IGT to T2DM, as assessed by a yearly postprandial oral glucose tolerance test. Among the analyzed population (mean age 54 years; n = 1368), acarbose delayed the progression from IGT to T2DM over 3.3 years by 25% (Chiasson et al., 2002). The study was not powered to examine CV outcomes but analyzed the composite of coronary heart disease, CV death, congestive HF, cerebrovascular events, and peripheral vascular disease as a secondary endpoint. Based upon a small number of patients with composite CV outcome events (acarbose, n = 15; placebo, n = 32), a reduced risk of CV events was shown (HR, 0.51 [95% CI 0.28, 0.95]; P = 0.03) (Chiasson et al., 2003).

4. The present: recent evidence of improvements in clinical outcomes with combination therapy

4.1. Initial combination therapy and glycemic control

A meta-analysis of 15 randomized controlled trials (N = 6693) assessed whether initial combination therapy with metformin plus another agent (TZD, sulfonylureas/glinides, dipeptidyl peptidase-4 [DPP-4] inhibitors or sodium glucose cotransporter 2 [SGLT2] inhibitors) improved glycemic control in treatment-naïve patients with T2DM (mean diabetes duration, 1.6–4.1 years; baseline mean HbA1c, 7.2%–9.9%). When compared with metformin monotherapy, combination treatment reduced HbA1c (weighted mean difference, −0.43% [95% CI −0.56, −0.30]) but increased the risk of hypoglycemia (RR, 1.56 [95% CI 1.08, 2.26]) (Phung, Sobieraj, Engel, & Rajpathak, 2014). Table 1 summarizes results for the newer glucose-lowering therapies versus metformin included in the meta-analysis.

Since then, another study has demonstrated the efficacy of canagliflozin 100 mg and 300 mg in combination with metformin in significantly reducing HbA1c versus metformin in treatment-naïve patients with T2DM (Rosenstock et al., 2016) (Table 1). Other recent studies have evaluated the efficacy of initial combination therapies with DPP-4 inhibitors. For example, initial combination of lixagliptin and metformin in patients with T2DM was assessed in a 24-week trial (Haak et al., 2012), followed by a 1-year extension study (Haak et al., 2013). Results demonstrated lower mean standard deviation (SD) reductions in HbA1c levels in patients who continued to receive lixagliptin 2.5 mg plus metformin 500 mg twice a day (bid) or 1000 mg bid than with metformin 1000 mg bid alone, with a low risk of hypoglycemia (Haak et al., 2013) (Table 1). In treatment-naïve T2DM patients with baseline HbA1c ≥9.5%, initial therapy with lixagliptin plus metformin showed marked improvements in adjusted mean standard error (SE) changes from baseline in HbA1c after 24 weeks (−2.8% ± 0.1%) versus lixagliptin monotherapy (−2.0% ± 0.1%) (treatment difference, −0.8% [95% CI −1.1, −0.50]; P < 0.0001) (Ross et al., 2015).

The initial combination of alogliptin and metformin (12.5 mg/500 mg or 12.5 mg/1000 mg bid) provided significantly greater reductions in HbA1c, levels from baseline to week 26 versus metformin 500 and 1000 mg bid (Table 1) (Pratley et al., 2014). In addition, the efficacy of the initial combination of alogliptin 25 mg and pioglitazone 30 mg on β-cell function and glycemic control was evaluated in patients with T2DM (N = 71) (Van Raalte et al., 2014). After 16 weeks, mean (SD) improvements in HbA1c were significantly greater with combination therapy (−0.9% ± 0.1%) than with alogliptin monotherapy (−0.4% ± 0.2%; P < 0.001) or placebo (0.4% ± 0.1%; P < 0.001). The combination of a DPP-4 inhibitor and TZD also improved β-cell glucose sensitivity versus placebo, supporting the concept of combination therapy to address multiple pathophysiological defects.

Unlike in the aforementioned studies of metformin-based oral combination, treatment-naïve patients were randomized to dual-inhibitor combination therapy (SGLT2/DPP-4) of empagliflozin 25 mg/linagliptin 5 mg, or empagliflozin 10 mg/linagliptin 5 mg, or monotherapy with empagliflozin 25 mg, empagliflozin 10 mg, or linagliptin 5 mg (Lewin et al., 2015). After 24 weeks, reductions in HbA1c were significantly greater for empagliflozin 25 mg/linagliptin 5 mg versus linagliptin 5 mg (−1.08% vs. −0.67%; P < 0.001), but not versus empagliflozin 25 mg (−0.95%; P = 0.179), and were significantly greater for empagliflozin 10 mg/linagliptin 5 mg versus the individual components (−1.24% vs. −0.83% and −0.67%, respectively; P < 0.001 for both). Efficacy was maintained over 52 weeks. Modest reductions in systolic blood pressure from baseline were observed with empagliflozin/linagliptin combination therapies and empagliflozin alone at week 52, but these changes were not significantly different between the combination therapies and their individual components. In conclusion, initial combination therapy studies provide evidence of improved glycemic control but lack evidence regarding long-term macrovascular and microvascular outcomes.

4.2. Macrovascular and microvascular outcomes with newer T2DM therapies in patients with long-standing diabetes

The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial
Infarction (SAVOR-TIMI) 53 (Scirica et al., 2013) and the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) (White et al., 2013) trials were the first prospective studies of a DPP-4 inhibitor or placebo added to standard of care completed in accordance with FDA guidance regarding exclusion of unacceptable CVD risk. Subsequently, the results of the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) (Green et al., 2015), the Evaluation of Cardiovascular Outcomes in Patients with Type 2 Diabetes after Acute Coronary Syndrome During Treatment with Lixisenatide (ELIXA) (Pfeffer et al., 2015), and the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) were reported (Zinman et al., 2015).

The SAVOR-TIMI 53 trial (N = 16,492) assessed CV outcomes with saxagliptin treatment added to existing glucose-lowering and CV therapy in patients with a history or heightened risk of CV events (Table 2) (Scirica et al., 2013). Saxagliptin treatment (median 2.1 years) plus standard care did not increase the risk of the primary MACE endpoints (HR, 1.00 [95% CI 0.89, 1.12]; P = 0.001 for non-inferiority; P = 0.99 for superiority) versus placebo. However, saxagliptin did increase the risk of hospitalization for HF (HR, 1.27 [95% CI 1.07, 1.51]; P = 0.007) versus placebo (Scirica et al., 2013, 2014). Patients with prior HF and estimated glomerular filtration rate ≤60 mL/min and/or increased N-terminal-pro-B-type natriuretic peptide levels at baseline were at greater risk of HF (Scirica et al., 2014). In a subsequent analysis, saxagliptin reduced progressive albuminuria (Udell et al., 2015).

The EXAMINE trial (White et al., 2013) (N = 5380) assessed MACE with alogliptin added to existing diabetes and CV therapy in patients with a recent history of ACS. Alogliptin treatment (median 18 months) did not increase the risk of MACE versus placebo (HR, 0.96 [95% CI upper boundary, 1.16]; P = 0.001 for non-inferiority; P = 0.32 for superiority). A post hoc analysis of the EXAMINE trial revealed that alogliptin did not significantly increase the risk of the first hospitalization occurrence for HF (HR, 1.07 [95% CI 0.79, 1.46]; P = 0.657) (Zannad et al., 2015).

TECOS (N = 14,671) assessed CV outcomes with sitagliptin or placebo added to an existing CV and diabetes regimen for a median 3 years (Green et al., 2015). For the primary composite CV outcome, sitagliptin was non-inferior to placebo (HR, 0.98 [95% CI 0.88, 1.09]; P < 0.001). In contrast to SAVOR-TIMI 53, the risk of hospitalization for HF did not differ significantly between sitagliptin and placebo (HR, 1.00 [95% CI 0.83, 1.20]; P = 0.98).

The results of the trials mentioned in this section demonstrate similar composite CV outcomes among patients with T2DM treated with DPP-4 inhibitors or placebo plus usual care, supporting CV safety of this class among patients with a high risk for CVD. The risk of hospitalization for HF was heterogeneous among these three CV outcomes trials, perhaps because of differences in patient enrollment and background care provided, variations in how HF was defined, pharmacologic differences among DPP-4 inhibitors (Green et al., 2015), or differences in the length of follow-up or the level of HF severity in each study. Data from these trials suggest that increased risk of hospitalization for HF is not a class effect of DPP-4 inhibitors.
Nonetheless, according to the updated ADA/EASD 2015 position statement, which was published before the results of the TECOS trial, this class of drugs “should probably be used cautiously, if at all, in patients with pre-existing heart failure” (Inzucchi et al., 2015).

The ELIXA trial (N = 6086) is the first to report the safety and efficacy of a glucagon-like peptide-1 (GLP-1) receptor agonist in a patient population with T2DM and a recent ACS event (Bentley-Lewis et al., 2015). After 2.1 years (median), lixisenatide was non-inferior to placebo for the primary CV composite (HR, 1.02 [95% CI 0.98, 1.17]; P = 0.81) (Sanofi, 2015). Risks of hospitalization for HF were similar for both groups (HR,0.96 [95% CI 0.75, 1.23]; P = 0.75). When combined with the evidence from the three DPP-4 inhibitor trials, the data support a neutral effect on incretin-based therapy on composite MACE.

Finally, EMPA-REG OUTCOME is the first CV outcomes trial to report a decreased risk of MACE and CV mortality with a glucose-lowering agent, specifically the SGLT2 inhibitor empagliflozin, in patients with T2DM and high CV risk (Zinman et al., 2015). Overall, 7020 patients received treatment with empagliflozin 10 mg or 25 mg or placebo once daily (plus standard of care) for a median of 2.6 years; the median observation period was 3.1 years. Significantly fewer patients in the pooled empagliflozin versus placebo group (10.5% vs. 12.1%) experienced the primary composite outcome (HR, 0.86 [95% CI 0.74, 0.99]; P < 0.001 for non-inferiority; P = 0.04 for superiority) (Fig. 1A) (Zinman et al., 2015). The authors indicated that the reduction in CV death drove the difference between treatments for the primary outcome; empagliflozin treatment provided a 38% RR reduction in death from CV causes (HR, 0.62 [95% CI 0.49, 0.77]; P < 0.001). However, no significant between-group differences in the rates of nonfatal MI or stroke were observed. The key secondary composite endpoint (4-point MACE, including hospitalization for unstable angina) met the test for non-inferiority (HR, 0.89 [95% CI 0.78, 1.01]; P < 0.001), but empagliflozin was not superior to placebo for this outcome (P = 0.08). Also, empagliflozin treatment versus placebo significantly reduced all-cause mortality (5.7% and 8.3%, respectively; 32% RR reduction) (Fig. 1B). The absolute risk reduction in all-cause mortality was 2.6%, thus, to prevent one death, 39 patients need to be treated for 3 years. Although not a component of the primary or key secondary endpoints, empagliflozin treatment provided a 35% RR reduction in the rate of hospitalization for HF (HR, 0.65 [95% CI 0.50, 0.85]; P = 0.002) (Fitchett et al., 2016).

4.3. Multifactorial therapy

The Steno-2 study evaluated multifactorial therapy with intensive antihyperglycemic therapy, antihypertensives, aspirin, and lipid-lowering agents in patients with T2DM and microalbuminuria (Gaede, Lund-Andersen, Parving, & Pedersen, 2005; Gaede, Vedel, Parving, & Pedersen, 1999; Gaede et al., 2003). Patients had a mean HbA1c of 8.4%–8.8% and median disease duration of 5.5–6.0 years (Gaede et al., 1999). During the first 3.8 years of follow-up, intensive versus conventional therapy reduced the risk of nephropathy (odds ratio [OR], 0.27 [95% CI 0.10, 0.75]; P = 0.01, retinopathy (OR, 0.45 [95% CI 0.21, 0.95]; P = 0.04), and autonomic neuropathy (OR, 0.31 [95% CI 0.12, 0.78]; P = 0.01) (Gaede et al., 1999). Reductions were maintained after a mean 7.8 years of additional follow-up (nephropathy HR, 0.39 [95% CI 0.17, 0.87]; P = 0.003 and retinopathy HR, 0.42 [95% CI 0.21, 0.86]; P = 0.02). After 7.8 years, intensive therapy decreased the risk of the primary composite macrovascular endpoint (unadjusted HR 0.47 [95% CI 0.24, 0.74]; P = 0.008) (Gaede et al., 2003). After a mean follow-up of 17 years, the original intensive-therapy group had an absolute risk reduction of 2.8% for composite CV endpoints (Gaede et al., 2008). The authors concluded that the use of statins and antihypertensive drugs may have had the largest effect on long-term CV risk.
Patients had a mean HbA1c of 7.0% and endpoints and non-traumatic amputation for a mean of 5.3 years. The Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes (ADDITION-Denmark) trial included patients with early T2DM and directly compared linagliptin to an active comparator, glimepiride, primarily when added to metformin. The CARMELINA trial will examine CV and renal microvascular outcomes of linagliptin in high-risk individuals with T2DM.

5. Conclusion

Based on current knowledge, providing combination therapy in the form of metformin with one additional agent as soon as possible after diagnosis results in improved glycemic control (Phung et al., 2013). Therefore, it may be advisable to initiate combination therapy with one or two glucose-lowering agents to the standard of care and are assessing macrovascular outcomes, microvascular outcomes, or both.

5.1. GLP-1 receptor agonists

The clinical trials EXSCEL (NCT01144338), REWIND (NCT01394952), LEADER (NCT01179048), and SUSTAIN 6 (NCT01720446) are evaluating the impact of exenatide once-weekly, dulaglutide, liraglutide, and semaglutide, respectively, on CV and/or microvascular outcomes in patients with T2DM.

5.2. DPP-4 inhibitors

Two trials of DPP-4 inhibitor therapy are ongoing in patients with T2DM and CVD or high CV risk. The CAROLINA (Rosenstock et al., 2013) trial includes patients with early T2DM and directly compares linagliptin to an active comparator, glimepiride, primarily when added to metformin. The CREDENCE trial will examine CV and renal microvascular outcomes of linagliptin in high-risk individuals with T2DM.

5.3. SGLT2 inhibitors

The clinical trials DECLARE-TIMI 58 (NCT01730534) and CANVAS (Neal et al., 2013) are evaluating the impact of dapagliuzin and canagliflozin, respectively, in patients with T2DM and high risk of CV complications. Two other ongoing trials are primarily designed to address renal outcomes with canagliflozin use — the CANVAS-R (NCT01989754) trial, with the change in albuminuria as the primary outcome, and the CREDENCE (NCT02065791) trial, which will evaluate treatment in patients with diabetic nephropathy.

5.4. TZD and SUs

In the PROactive trial (Section 3.2), pioglitazone significantly reduced the risk of the composite secondary endpoint (Dormandy et al., 2005). Patients were on a wide range of glucose-lowering medications, including insulin. In contrast, a comparison of add-on pioglitazone versus add-on SU in high CV-risk patients inadequately controlled with metformin is underway in the TOSCA.IT trial (Vaccaro et al., 2012). In the final analysis, which is expected in 2018, both CV and microvascular endpoints will be considered after at least 48 months of treatment (Vaccaro et al., 2012).

5.5. Comparative effectiveness

Selecting the appropriate combination from an armamentarium of glucose-lowering drugs can be challenging for physicians. Although T2DM algorithms recommend various treatment combinations, few studies have directly compared these combinations. The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness (GRADE) study is an ongoing comprehensive examination of four classes of glucose-lowering drugs (SUs, DPP-4 inhibitors, GLP-1 receptor agonists, and insulin) in addition to metformin (Nathan et al., 2013). GRADE will compare the long-term effectiveness of each drug combination with respect to glycemic control over time, CVD risk factors, and microvascular complications in 5000 patients recently diagnosed with T2DM (duration <5 years), and will also evaluate the phenotypic differences that contribute to the efficacy and safety of each combination. The results of this study will help guide physicians in establishing individualized regimens for their patients.
2014). Whether initial combination therapy improves long-term outcomes compared with a more traditional stepwise approach remains unknown. Indeed, early-onset pathophysiologic damage induced by hyperglycemia and worsening metabolic control, a consequence of this progressive disease, substantiates the use of early combination therapy.

The current clinical trial evidence includes a number of combination therapies in patients with long-standing diabetes, and permits assessment of the effect of intensive glycemic control on microvascular and macrovascular outcomes. Evidence from ADVANCE (Patel et al., 2008; Zoungas et al., 2014) and VADT (Duckworth et al., 2009) indicate long-term benefits of intensive glycemic control on microvascular outcomes. However, these two studies and ACCORD (Gerstein et al., 2008) found no significant reduction in the risk of macrovascular outcomes with intensive versus standard glycemic control within the first 3.5–5.6 years of follow-up. Interestingly, improvements in CV outcomes became apparent after an additional –5 years in ACCORD (Gerstein et al., 2014) and ~10 years in VADT (Hayward et al., 2015), similar to the findings of the UKPDS (Holman et al., 2008), but not after 6 years of follow-up in ADVANCE (Zoungas et al., 2014). These differences may reflect heterogeneity among the trials.

The recent CV outcome trials, EXAMINE (White et al., 2013), SAVOR-TIMI 53 (Scirica et al., 2013, 2014; Udell et al., 2015), and TECOS (Green et al., 2015) were primarily designed to examine CV safety, and included patients who already had a CV event or were at high risk of CVD. Although SAVOR-TIMI 53 and TECOS enrolled a sufficient number of patients for a superiority analysis, improvements in CV outcomes remained elusive. Possible explanations include short treatment duration (~3 years) and a population with long-standing, or advanced disease, thus, the intervention may have been too late. In contrast, the EMPA-REG OUTCOME trial was the first trial of a glucose-lowering agent plus standard of care to show a reduction in CV risk in a population with T2DM and existing CVD (Zinman et al., 2015). A reduction in the rate of CV and all-cause death occurred early and was maintained for the duration of the trial. Further investigation is needed to elucidate the mechanism(s) underlying the mortality benefits of empagliflozin. Non-glycemic effects of empagliflozin, including changes in arterial stiffness, cardiac function, cardiac oxygen demand (in the absence of sympathetic-nerve activation), cardio–renal effects, reductions in albuminuria and uric acid, and effects on weight, visceral adiposity, and blood pressure have been proposed (Zinman et al., 2015).

Support for improvement in microvascular and macrovascular outcomes with early, aggressive therapy is conflicting. UKPDS (Holman et al., 2008) supports the use of intensive therapy to improve long-term microvascular and macrovascular outcomes, although significant improvements in MI and death from any cause did not materialize until 10 years post-trial. The ORIGIN (Gerstein et al., 2012) trial was the first key evaluation of long-term CV outcomes in patients with T2DM. Participants had IFG, IGT, or newly diagnosed T2DM, but insulin glargine therapy targeting near-normal FPG levels did not significantly reduce the risk of macrovascular outcomes. The ADDITION (Charles et al., 2011; Griffin et al., 2011) trial used a unique strategy to assess CV and microvascular outcomes with multifactorial early intervention in a population with screen-detected diabetes. Conflicting results of the ADDITION (Charles et al., 2011; Griffin et al., 2011) studies are similar to previous studies of the impact of intensive glycemic control on the incidence of diabetic nephropathy (UKPDS, ACCORD, and Steno-2) (Gaede et al., 2008; Ismail-Beigi et al., 2010; UKPDS Group, 1998).

The rationale for early combination treatment in adults with T2DM is straightforward, and studies clearly support a glycemic benefit. However, evidence of long-term improvements in macrovascular outcomes with early combination therapy is limited. Early intensive combination therapy may be a way to offset early pathophysiologic damage resulting from hyperglycemia, therefore reducing the period in which patients are exposed to hyperglycemia.

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