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Novel Anti-glycemic Drugs and Reduction of Cardiovascular Risk in Diabetes: Expectations Realized, Promises Unmet

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Abstract

Purpose of Review—To review evidence on cardiovascular risks and benefits of new treatments for type 2 diabetes mellitus.

Recent Findings—In response to guidance issued by the Food and Drug Administration, thousands of patients have been enrolled in large randomized trials evaluating the cardiovascular effects of the three newest diabetes drug classes: GLP-1 receptor agonists, SGLT-2 inhibitors, and DPP4 inhibitors. Two studies of GLP-1 receptor agonists – one of liraglutide, and one of semaglutide – have shown cardiovascular benefit relative to placebo, and one study of the SGLT-2 inhibitor empagliflozin has shown benefit. The other published cardiovascular outcomes studies of the newest drug classes have generally supported safety, apart from an as-yet unresolved safety concern about increased rates of heart failure with DPP-4 inhibitors. Recent research suggests the thiazolidinedione pioglitazone may have beneficial effects on some cardiovascular outcomes as well, but these are counterbalanced by a known increase of the risk of heart failure with this drug. In general, more prospective randomized trial data is now available regarding the cardiovascular effects of the newer diabetes drugs than on the older drug classes.

Summary—New evidence suggests that the newest diabetes drugs are safe from a cardiovascular perspective. Evidence on benefit from at least some members of the GLP-1 receptor agonist and SGLT-2 inhibitor classes is encouraging but not yet decisive.

Keywords

Type 2 Diabetes Mellitus; Novel anti-glycemic drugs; Cardiovascular Risk; Cardiovascular Outcomes; Cardiovascular Safety

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Compliance with Ethics Guidelines

Conflict of Interest

James H. Flory, Jenny K. Ukena, and James S. Floyd declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Intro

In addition to preventing and managing diabetes-specific microvascular complications, the care of patients with type 2 diabetes mellitus (T2DM) prioritizes the prevention and management of macrovascular disease, which includes coronary artery disease (CAD), myocardial infarction (MI), cerebrovascular disease, peripheral vascular disease (PVD), and heart failure (HF). Cardiovascular disease is the leading cause of death among patients with T2DM[1].

Guidance is relatively clear on how to apply common cardiovascular preventive measures, like aspirin and statin use and blood pressure control, in T2DM[2]. Beyond these measures, the selection of antidiabetic agent (ADA) might impact the risk of atherosclerotic cardiovascular disease (CVD), which include non-fatal MI, non-fatal stroke, and cardiovascular death, with some ADAs possibly superior to others. Plausible mechanisms include differing effects of ADAs on traditional cardiovascular risk factors such as glucose levels, blood pressure, and lipid profile, nontraditional risk factors such as insulin and glucagon levels, and off-target effects such as cardiovascular toxicity mediated through hypoglycemia (Figure 1).

Clinical trial data to study comparative cardiovascular effects from ADAs have been limited, largely because it was formerly possible to obtain United States Food and Drug Administration (FDA) approval for a new ADA once the drug is shown to lower blood sugar, without also needing to demonstrate effectiveness on clinical endpoints such as cardiovascular events. The resulting widespread use of new ADAs with sparse data on cardiovascular outcomes led to a protracted debate over the safety of rosiglitazone, a once widely used new diabetes drug. This was heightened by findings from the ACCORD study indicating that treatment strategies that focused on aggressively lowering HbA1c might result in increased cardiovascular mortality[3].

As a result, in 2008, the FDA issued guidance that future ADA approvals would be contingent on pooled results from Phase 2 and Phase 3 trials demonstrating no greater than an 80% increase in the risk of atherosclerotic CVD, with a requirement that post-marketing studies be conducted to exclude a 30% increase in the risk of cardiovascular events [3]. This change has led to an increase in the number of large, randomized placebo-controlled studies of new ADAs with primary cardiovascular outcomes: 17 such studies, with 140,000 total projected enrollees[4].

Seven of these studies have been completed. Four have shown no difference in the risk of cardiovascular events between drug and placebo, but three have reported statistically significant reductions in cardiovascular events from new drugs, relative to placebo. Editorialists have noted that these findings stood in need of replication before they could be considered definitive [4, 5].

This narrative review synthesizes the rapidly expanding evidence base about the cardiovascular safety and, to a lesser extent, efficacy of new ADAs for the treatment of T2D. We briefly review evidence on the commonly used older classes of oral drugs, before focusing on sodium glucose cotransporter 2 (SGLT-2) inhibitors, dipeptidyl peptidase-4

(DPP4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and thiazolidinediones.

Conceptual Framework

The question “do novel antidiabetes agents reduce cardiovascular risk?” raises several conceptual issues that need clarification.

First, it is conceivable that the newer drugs might increase cardiovascular risk. Indeed, much of the evidence reviewed here is from studies intended to establish cardiovascular safety, not benefit. The distinction can affect the way data are interpreted. First, there are sometimes subtle statistical implications when a study is designed to first exclude the possibility of harm before questions of benefit are examined [4]. Second, the standard for evidence needed to raise concerns about potential harms is lower than the standard needed to demonstrate benefit. As an example, evidence from secondary analyses indicating that DPP4 inhibitors might increase the risk of heart failure received far more attention than comparably weak evidence of benefit would.

Second, most of the new evidence about the cardiovascular safety of new ADAs comes from studies that compared them to placebo. These studies do not directly address the comparative effectiveness question of which drug to select from the many options available. As illustrated by the design of the Comparative Effectiveness Study of Major Glycemia-lowering Medications for Treatment of Type 2 Diabetes (GRADE) trial and current treatment guidelines [6 7], once metformin monotherapy has been initiated, there is little consensus about which drug therapy to choose for second- and third-line treatment. Comparisons of cardiovascular risks between these agents – particularly between the newer drugs and sulfonylureas – are more relevant to clinical decision-making than the comparisons with placebo in most of the large postmarketing studies conducted to date.

Third, cardiovascular outcomes are not the only consideration in choosing a diabetes drug. Clinicians and patients also care about differences in effectiveness lowering blood glucose, effects on weight, and side-effect profiles, as well as cost and convenience. But, it is reasonable to give special attention to a review of cardiovascular effects, because of their clinical importance and because of the lack of high-quality evidence.

Finally, this review follows the lead of regulators and professional societies in heavily emphasizing prospective, randomized controlled trials (RCTs) with primary cardiovascular outcomes. Other types of evidence, including meta-analyses of RCTs that lacked adjudicated primary cardiovascular outcomes and observational studies, are cited where they provide useful context.

Older agents

Metformin

Metformin, a biguanide that lowers blood glucose in large part by restraining hepatic gluconeogenesis, has been the consensus first-line drug for T2DM for over a decade due to advantages in its glucose-lowering effectiveness, cost, tolerability, and safety [7]. Evidence

that metformin prevents clinical complications of diabetes comes primarily from the UK Prospective Diabetes Study (UKPDS) RCT, which showed a reduced risk of cardiovascular events and mortality compared to the control group, which was treated primary with sulfonylureas and insulin[8]. The UKPDS findings were, until recently, the strongest evidence of cardiovascular benefit for a specific ADA, and this trial played a key role in establishing metformin as the first-line diabetes drug [9]. Additional supporting evidence comes from a controlled trial which randomly assigned 304 patients to either glipizide or metformin and found a significant reduction in a composite cardiovascular endpoint for the metformin group[10].

However, the totality of evidence supporting metformin's cardiovascular benefit is generally felt to be weak, as reflected by the absence of any claims for cardiovascular benefit in the FDA label. The mechanism of any putative benefit is unclear. A final consideration is whether the observed benefits are absolute or simply stand in contrast to potential harm from sulfonylureas, which were used extensively by the comparison groups in both of the RCTs that showed benefit.

Sulfonylurea

Sulfonylureas lower blood glucose by stimulating pancreatic beta-cell insulin secretion. In use since the 1940s, they are the most commonly prescribed class of oral therapy for T2DM after metformin; most patients in the United States take either glipizide, glyburide, or glimepiride[11]. The cost of sulfonylureas is low, they are well tolerated, and current guidelines support their use[12].

But, safety concerns related to sulfonylureas date back to the University Group Diabetes Program RCT, which over 40 years ago found higher mortality rates with the sulfonylurea tolbutamide than with either placebo or insulin[13]. While tolbutamide has long since been replaced with newer sulfonylureas, worries about this drug class persist, in part due to higher rates of cardiovascular events related to sulfonylureas compared with metformin in RCTs [14–16] and in part because observational studies suggest higher rates of cardiovascular events with this drug class compared to newer agents [17, 18].

A third reason for concerns about added cardiovascular risk from sulfonylureas is that they are mechanistically plausible. One potential mechanism is hypoglycemia, a common side effect of sulfonylureas that is associated with a cascade of negative consequences, including increases in heart rate and blood pressure, platelet aggregation and activation, inflammation, and vascular stiffness, which might precipitate both cerebral and myocardial ischemia[19–21]. Sulfonylureas may also have complex pro- and anti- arrhythmic effects mediated by their action on cardiac potassium channels [22], although these effects may not be uniform across the sulfonylurea drug class, since some sulfonylureas are more specific than others for pancreatic as opposed to cardiac potassium channels[23].

New agents

SGLT-2 Inhibitors

Sodium glucose co-transporter 2 (SGLT2) inhibitors are the newest class of drugs approved for the treatment of T2DM, in use since 2013. Empagliflozin, canagliflozin, and dapagliflozin are currently approved for use by the FDA. By decreasing renal glucose absorption, SGLT2 inhibitors lead to increased urinary glucose excretion resulting in a lower blood glucose level and thereby a reduction of glycated hemoglobin (HbA1c)[24].

In addition to improving glycemic control, SGLT2 inhibitors improve other potential cardiovascular risk factors, including blood pressure, body weight, visceral adiposity, hyperinsulinemia, albuminuria, serum uric acid, and oxidative stress. Further mechanisms for improving cardiac outcomes include osmotic diuresis and natriuresis, a direct cardiac or vascular effect (such as improved arterial stiffness), shifts in metabolism away from fat and glucose oxidation towards potentially more efficient energy sources such as ketones, and modulation of glucagon release [25–28].

A meta-analysis of 25 smaller trials comparing canagliflozin and dapagliflozin to placebo or an active comparator (17,181 patients with 283 events) included only 4 cardiovascular events and reported a HR of 0.89 (95% CI 0.70, 1.14) in favor of canagliflozin and dapagliflozin. [29]

The recent publication of the Empagliflozin Cardiovascular Outcome Event Trial (EMPA-REG OUTCOME) has increased enthusiasm about cardiovascular benefits from SGLT-2 inhibitors. This study randomized 7020 patients with T2DM and coexisting cardiovascular disease to one of three groups: empagliflozin 10 mg, empagliflozin 25 mg, or placebo. The primary outcome was a composite of death from cardiovascular causes, nonfatal MI, and nonfatal stroke. After a median 3.1 years of follow up, the primary endpoint occurred in 490 of 4687 patients (10.5%) in the empagliflozin groups and in 282 of 2333 patients (12.1%) in the placebo group. The hazard ratio for the pooled empagliflozin groups relative to placebo was 0.86 (95% CI 0.74–0.99, $p=0.04$). Patients on empagliflozin had a relative risk reduction of 38% for death from cardiovascular disease (3.7% in the pooled empagliflozin group vs. 5.9% in the placebo group), and 32% for death from any cause (5.7% and 8.3%, respectively). Heart failure hospitalizations were also significantly decreased (2.7% and 4.1%, respectively; 35% relative risk reduction).[30]

In subgroup analyses, there were interactions with age and HbA1c, but these were not significant after correction for multiple comparisons. With respect to surrogate endpoints, at study end, the adjusted mean HbA1c was 7.8% in the pooled empagliflozin group and 8.2% in the placebo group. Modest reductions in weight, uric acid level, and blood pressure were also seen[30].

Although the EMPA-REG findings persuasively support empagliflozin's safety from a cardiovascular standpoint, evidence for benefit stands in need of replication, and the mechanism of potential cardiovascular benefit is not yet understood. None of the array of novel potential mechanisms described above can be ruled in or out by the EMPA-REG

OUTCOME results. But, the difference in HbA1c-lowering observed between study arms is unlikely to be a significant contributor, based on both the small magnitude of the change seen and the fact that any effects HbA1c itself has on cardiovascular outcomes appears to be delayed, whereas the reduction in cardiovascular risk seen with empagliflozin occurred shortly after starting the drug [9, 31].

Some of the uncertainties left after the EMPA-REG OUTCOME trial should be addressed by additional ongoing randomized controlled studies designed to assess the cardiovascular effects of other SGLT-2 inhibitors, with three major studies expected to report results by 2020 (Table 1).

GLP-1 Receptor Agonists

Glucagon-like peptide 1 (GLP-1) and its receptor have been recognized as a potential target for diabetes treatment since the 1980s[32]. Injectable artificial agonists against the GLP-1 receptor, including albiglutide, exenatide, dulaglutide, liraglutide, lixisenatide, and semaglutide, have been developed for clinical use. By increasing insulin secretion, reducing glucagon levels, and delaying gastric emptying, all members of the class significantly lower blood glucose while also inducing weight loss, properties which have led to rapid increase in use.

There has long been optimism that GLP-1 receptor agonists (GLP-1 RA) might be cardioprotective through multiple possible mechanisms. In addition to glycemic control and weight loss, GLP-1 RAs improve other possible risk factors including blood pressure, inflammatory markers, insulin sensitivity, and lipid profile[33]. Animal studies have indicated that GLP-1 receptor activation in heart tissue may have benefits including improved left ventricular function [34] and protection from ischemic reperfusion injury[35]. Some of these mechanistic findings have been supported in pilot human studies [36].

Two recent large clinical trials have shown evidence of benefit from GLP-1 RAs for cardiovascular outcomes (Table 2). The first of these is the Liraglutide Effect and Action in Diabetes (LEADER) study, which randomized 9341 patients with T2DM and additional cardiovascular risk factors 1:1 to liraglutide versus placebo. The results significantly favored liraglutide on the primary outcome, a composite of cardiovascular death, nonfatal MI, and nonfatal stroke, with a hazard ratio of 0.87 (95% CI 0.66 to 0.93; $p = 0.007$). In addition, the rate of death from any cause was lower in the liraglutide group (HR 0.85, 95% CI 0.74–0.97). Subgroup analyses suggested potentially greater benefit in patients with $eGFR < 60$ ml/min/1.73 m² and, less convincingly, patients with pre-existing cardiovascular disease[37].

The second study was the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6), which randomized 3,927 patients with T2DM and additional cardiovascular risk factors to either once-weekly semaglutide or to placebo. Over two years of follow-up, the results significantly favored semaglutide on the same primary composite outcome used by LEADER, with a hazard ratio of 0.74 (95% CI 0.51 to 0.95). In contrast to LEADER, there was no difference seen in rates of death, either all-cause or cardiovascular. Differences in the primary composite outcome were instead driven by lower rates of nonfatal stroke and nonfatal MI in the semaglutide

treatment group. No subgroup analyses, including those by eGFR or by pre-existing cardiovascular disease, suggested any heterogeneity of effect [38].

In contrast to these two studies showing benefit, another large clinical trial of the GLP-1 RA lixisenatide enrolled 6,068 patients with a recent history of myocardial infarction or hospitalization for unstable angina and randomized them to drug or placebo. The primary outcome was a composite of cardiovascular death, myocardial infarction, stroke, or hospitalization for unstable angina. Study participants averaged 60 years of age, with a mean HbA1c of 6.6% and mean duration of diabetes of 9 years. Most had qualified for the study due to either non-ST elevation MI or ST elevation MI shortly prior to study enrollment. Median follow-up was 25 months, with a primary endpoint occurring in 13.4% of the exenatide group and 13.2% of the placebo group, yielding a hazard ratio of 1.02 (95% CI 0.89–1.17). [39]. Similar null results were seen in all pre-defined patient subgroups; for each component of the composite endpoint; and for a number of secondary outcomes, including hospitalization for heart failure.

The results of LEADER and SUSTAIN-6, while promising, must be interpreted in the context of the null result of the lixisenatide study. It is unclear at this point to what extent the cardiovascular benefits seen can be attributed to modestly lower blood pressure and HbA1c levels during follow-up in the intervention groups. In addition, it bears noting that the findings of these studies are restricted to high-risk groups.

Dipeptidyl-Peptidase 4 Inhibitors

DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin, and alogliptin), like GLP-1 receptor agonists, treat diabetes by modulating the incretin system. They are small-molecule inhibitors of an enzyme that breaks down endogenous incretins, can be dosed orally, and have become widely used since their introduction in 2006 [11, 32]. They increase insulin levels while decreasing glucagon but do not cause the same effect on gastric emptying as GLP-1 RAs, and are less potent in lowering HbA1c. The same arguments that GLP-1 RA's may confer cardiovascular benefit also apply to DPP-4 inhibitors, with increased levels of endogenous GLP-1 potentially acting on GLP-1 receptors on vascular endothelial cells and cardiomyocytes[40].

DPP-4 inhibitors have been the subjects of three large published placebo-controlled RCTs, which together enrolled a total population of 36,607 patients with type 2 diabetes and high cardiovascular risk and reported hazard ratios for primary composite cardiovascular outcomes of 0.96 (95% CI upper bound 1.16), 1.00 (95% CI 0.89–1.12), and 0.98 (95% CI 0.89–1.08), for alogliptin, saxagliptin, and sitagliptin, respectively (Table 3)[41–43]. Meta-analyses of smaller trials have similarly not shown consistent evidence of either increased or decreased cardiovascular risk of DPP-4 inhibitors compared to placebo[44]. In general, secondary and sensitivity analyses of these null findings have not been revealing.

However, the SAVOR-TIMI RCT showed, in secondary analysis, an increased risk of hospitalization for heart failure in users of saxagliptin compared to placebo (HR 1.27, 95% CI 1.07 to 1.51) [43]. A meta-analysis of SAVOR-TIMI, EXAMINE, and several smaller studies attenuated but did not eliminate the association (1.17, 95% CI 1.01–1.34)[45]. A

large multi-center observational study found no increased risk of heart failure with DPP-4 inhibitors, although it had limited ability to adjust for potential confounding[46]. The clinical significance of the original SAVOR-TIMI finding is unclear. But it is a useful reminder that there are many clinically important cardiovascular outcomes beyond those usually included in primary composite outcomes.

A final consideration is that observational studies have consistently shown superior cardiovascular outcomes with DPP-4 inhibitors relative to sulfonylurea, as have meta-analyses of small RCTs[17 46]. This observational evidence base is generally regarded as unconvincing, given the potential for confounding. But, plausible mechanisms, including decreased risk of hypoglycemia, might make DPP-4 inhibitors safer than sulfonylurea from a cardiovascular standpoint. DPP-4 inhibitors and sulfonylureas are the two most commonly used oral diabetes drugs after metformin, so this comparative effectiveness question is a particularly important one [11]. The majority of the published and ongoing cardiovascular safety studies of DPP-4 inhibitors are placebo controlled and therefore not informative for this question. One large study, CAROLINA, will compare DPP-4 inhibitor directly to sulfonylurea [4].

Thiazolidinediones

As PPAR-gamma agonists, thiazolidinediones act on a central metabolic regulatory gene[48]. Since their introduction in the late 1990s, initial optimism about cardiovascular benefit gave way to widespread concern about cardiovascular safety, including possible increases in risk of cardiovascular mortality and a substantial increase in the risk of heart failure exacerbation.

A meta-analysis published in 2006 that included over 40 trials, each of which had few or no cardiovascular events, showed an increased risk of cardiovascular mortality from rosiglitazone. This publication prompted a more comprehensive overview of the evidence by FDA, which led to changes in the drug label and a massive reduction in the use of rosiglitazone[3 49]. Subsequent completion of a major cardiovascular outcomes study showed that, although rosiglitazone does clearly increase the risk of heart failure, there was no statistically significant increased risk of MI or stroke from rosiglitazone (HR 0.99, 95% CI 0.85 to 1.16)[50], although it has been noted that the rate of cardiovascular events in this study was surprisingly low, raising concerns about the quality of outcome ascertainment[51, 52].

The one other marketed thiazolidinedione, pioglitazone, accounts for almost all modern thiazolidinedione use [11]. Unlike rosiglitazone, it has never been implicated in increasing rates of macrovascular adverse events, with a large cardiovascular outcome trial in patients with type 2 diabetes suggesting a possible benefit (HR 0.90, 95% CI 0.80 to 1.02) on a composite of MI and stroke[53]. But the same RCT also demonstrated an association between pioglitazone use and severe heart failure events (HR 1.41, 95% CI 1.10–1.80, $P < 0.007$). It remains controversial whether such events, when caused by pioglitazone, led to increased mortality or other long-term adverse consequences[54].

A notable recent development is the publication of the Insulin Resistance Intervention After Stroke (IRIS) trial, a study of pioglitazone in non-diabetic patients who had recently suffered stroke or TIA, with a primary outcome of a composite of fatal or non-fatal stroke or MI[55]. After up to 4.8 years of follow up in 3876 patients, rates of the primary outcome were significantly reduced in the pioglitazone arm (HR 0.76, 95% CI 0.62 to 0.93). While this trial in non-diabetic patients does not generalize in a straightforward way to decision-making in diabetes, it does fit into a consistent body of evidence that pioglitazone is a benign and possibly beneficial drug as far as composites of heart attack, stroke, and cardiovascular death are concerned, but potentially at the cost of an increased risk for heart failure.

For thiazolidinediones, there are potential mechanisms for both harm and benefit aside from the glucose-lowering effects of these drugs. For example, in IRIS, the use of pioglitazone was shown to improve risk factors, including insulin sensitivity, blood pressure, triglycerides, HDL cholesterol, and markers of inflammation, in addition to plasma glucose. But the highly pleiotropic effects of thiazolidinediones have also limited enthusiasm for their use: any possible cardiovascular benefit has to be balanced against known increases in weight, edema, heart failure, and fracture[56].

Relatively few major studies of cardiovascular outcomes from thiazolidinediones are in progress now. The major exception is the Thiazolidinediones or Sulphonylureas and Cardiovascular Accidents Intervention Trial (TOSCA-IT), which will compare pioglitazone to sulphonylurea in 3,371 patients with type 2 diabetes in relation to a composite outcome of all cause mortality, nonfatal MI, nonfatal stroke, and unplanned coronary revascularization (Table 4).

Conclusion

The past 20 years have seen a striking expansion in the options for drug treatment of T2DM. In that time, the field has evolved from an uneasy assumption that lowering blood glucose might reliably cause cardiovascular benefits, to a peak of concern that some glucose-lowering drugs cause adverse cardiovascular events, to a current climate of optimism that some newer agents may confer cardiovascular benefit.

Does the available evidence show convincingly that any of the novel antidiabetic agents confer cardiovascular benefit? One recent, public deliberation on this question was a recent FDA Advisory Committee meeting on whether empagliflozin could sustain a claim that it reduced cardiovascular mortality in selected patients. The final vote – yes, by a margin of a single vote – suggests that this is not an easy question. The materials for the meeting raised a number of serious critiques of EMPA-REG, related to outcome adjudication, the fact that the result was driven mainly by one component of a composite outcome, and perhaps most importantly that this was a single study that provided marginal statistical evidence of benefit [58]. A similar depth of public discussion of the LEADER study is not yet available, but several of these concerns are likely to recur – especially the fact that it is only a single study.

In addition to uncertainty about the validity of the findings from EMPA-REG and LEADER, questions about these drugs that have not yet been answered include whether the potential

cardiovascular benefits are drug-specific or class effects, and whether they are isolated to specific subgroups of patients. More importantly, comparative effectiveness research that compares the various second-line drugs is needed to address the clinical question about which drug to select once metformin monotherapy is no longer adequate to achieve glycemic control targets.

Perhaps the largest pragmatic evidence gap remaining is not whether the newer agents have cardiovascular benefit in and of themselves, but whether they are a better choice than sulfonylureas, which have been in use since the 1940s and remain the most commonly used class of oral drugs after metformin[11]. This point is particularly important because the existing research agenda is likely to contribute a reasonably large amount of data to inform questions about class effects and patient subgroups, but only two of the large cardiovascular outcome trials underway (one comparing pioglitazone and sulfonylurea, and another comparing DPP-4 inhibitor and sulfonylurea) are comparative effectiveness studies. The ongoing GRADE trial, which is comparing 4 second-line therapies used in combination with metformin – a sulfonylurea, a DPP-4 inhibitor, a GLP-1 agonist, and basal insulin - is underpowered to detect clinically important differences in cardiovascular risk, and results will not be available until at least 2020[57].

The paucity of high-quality studies with a sulfonylurea exposure group makes even network meta-analysis infeasible as a method of clearly answering the question of comparative effectiveness in preventing adverse cardiovascular events. The results of the TOSCA-IT and CAROLINA studies will be of great interest, since they will be the first large modern RCTs to directly compare sulfonylurea to an alternative.

What conclusions can providers draw now about novel drugs and cardiovascular effects? As far as benefits are concerned, it is reasonable to look at the current data on SGLT-2 inhibitors and GLP-1 RAs as encouraging but not decisive[5]. Ongoing studies may help to fill this gap in knowledge– for instance, if the reduction in cardiovascular events seen with empagliflozin is replicated for other SGLT-2 inhibitors, the likelihood of a genuine cardiovascular benefit would increase substantially, and an improved characterization of the types of patients who may stand to benefit would be possible.

But, from a safety perspective, the evidence is encouraging that liraglutide, semaglutide, lixisenatide, and empagliflozin do not have off-target effects the result in cardiovascular harm compared with placebo. For DPP-4 inhibitors, the situation remains more ambiguous. While the signal for an increased risk of heart failure from saxagliptin may turn out to be a false positive finding, there is not yet enough evidence to confidently dismiss it.

A final point from this review is that the new drugs are proving to be only as useful as the information provided about their effects. Some authors have argued that, since newer ADAs have consistently appeared to be safe, the current requirements for cardiovascular outcomes studies may be excessive [4]. But policies to encourage or fund future large cardiovascular outcome studies are important for reasons that now go beyond simply verifying drug safety. The recent publication of three studies indicating clinically relevant cardiovascular benefits from newer agents suggests that there may be real opportunities to improve the health of

patients, but only if extensive research is done to firmly establish and characterize these benefits.

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Figure 1.
Major classes of drugs to treat type 2 diabetes and primary mechanism(s) of antidiabetic effect

Table 1
Randomized controlled trials assessing cardiovascular outcomes with SGLT-2 Inhibitors

Study	Population	Active	Comparator	Size	Primary Outcome	Effect Estimate	Clinical Trials.gov registration
EMPA-REG	Diabetes Mellitus, Type 2, high risk for cardiovascular event	Empagliflozin	Placebo	7020	Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke	0.86 (95% CI 0.74–0.99)	NCT01131676
CANVAS	Diabetes Mellitus, Type 2, have a history of CV events or have a high risk for CV events	Canagliflozin	Placebo	4330	Major adverse cardiovascular events, including CV death, nonfatal myocardial infarction (MI), and nonfatal stroke	Anticipated 2017	NCT01032629
CREDENCE	Subjects with type 2 diabetes and elevated urine albumin/creatinine ratio	Canagliflozin	Placebo	4200	Composite of end-stage kidney disease, doubling of serum creatinine, renal or cardiovascular (CV) death	Anticipated 2020	NCT02065791
DECLARE- TIMI58	Diabetes Mellitus, Non-Insulin-Dependent, High Risk for Cardiovascular Event	Dapagliflozin	Placebo	17,150	Cardiovascular death, non fatal Myocardial infarction, non fatal ischemic stroke	Anticipated 2018	NCT01730534
VERTIS	Subjects with Type 2 Diabetes Mellitus and Established Vascular Disease	Ertugliflozin	Placebo	8000	Cardiovascular Death, Non- fatal Myocardial Infarction, or Non-fatal Stroke	Anticipated 2020	NCT01986881

Table 2

Cardiovascular outcome studies of GLP-1 Receptor Agonists

Study	Population	Active	Comparator	Size	Primary Outcome	Effect Estimate	Clinical Trials.gov registration
ELIXA	T2DM with hx of hospitalization for unstable angina in previous 180 days	Lixisenatide	Placebo	6068	Composite of CV death, MI, stroke, hospitalization for unstable angina	1.02 (95% CI 0.89–1.17)	NCT01147250
LEADER	DM + risk factors	Liraglutide	Placebo	9341	Composite of cardiovascular death, non-fatal MI, non-fatal stroke	0.87 (95% CI 0.66 – 0.93)	NCT01179048
SUSTAIN 6	DM + either age 50 + clinical evidence of CV disease, or age 60 + and subclinical evidence of CV disease	Semaglutide	Placebo	3,297	Composite of CV death, non-fatal MI, or nonfatal Stroke	0.74 (95% CI 0.59–0.95)	NCT01720446
PIONEER 5	DM + either age 50 + presence of CV disease, or age 60 + at least one CV risk factor	Semaglutide	Placebo	3,176	Composite of CV death, non-fatal MI, or non-fatal stroke	Anticipated 2018	NCT02692716
EXSCEL	DM	Weekly exenatide	Placebo	~9500	Composite of cardiovascular death, non-fatal MI, non-fatal stroke	Anticipated 2018	NCT01144338
FREEDOM CVO	DM + history of coronary, cerebrovascular, or peripheral artery disease	Continuous subcutaneous delivery of exenatide	Placebo	>4,000		Anticipated 2018	NCT01455896
REWIND	DM + risk factors	Dulaglutide	Placebo	~9600	Composite of cardiovascular death, non-fatal MI, non-fatal stroke	Anticipated 2019	NCT01394952
HARMONY OUTCOMES	DM + established CV disease with at least one of CAD, CVD, or PAD	Albiglutide	Placebo	9,400	Composite of cardiovascular death, MI, or stroke	Anticipated 2019	NCT02465515

Table 3
Randomized controlled trials assessing cardiovascular outcomes with DPP-4 Inhibitors

Study	Population	Active	Comparator	Size	Primary Outcome	Effect Estimate	Clinical Trials.gov registration
EXAMINE	T2DM+ recent hospitalization with acute MI or unstable angina	Alogliptin	Placebo	5380	CV death + MI + stroke	0.96 (upper bound 1.16)	NCT00968708
SAVOR- TIMI 53	T2DM + risk factors	Saxagliptin	Placebo	16,492	CV death + MI + ischemic stroke	1.00 (95% CI 0.89–1.12)	NCT01107886
TECOS	T2DM + known CVD	Sitagliptin	Placebo	14,735	CV death + nonfatal MI, nonfatal stroke, hospitalization for unstable angina	0.98 (95% CI 0.89–1.08)	NCT00790205
CAROLINA	T2DM + end- organ damage from diabetes or increased cardiovascular risk	Linagliptin	Glimepiride	6,000	CV death, nonfatal MI (excluding silent MI), nonfatal stroke and hospitalization for unstable angina pectoris	Anticipated 2018	NCT01243424
CARMELINA	T2DM + high risk of CV events	Linagliptin	Placebo	8,300	Composite endpoint of CV death, nonfatal MI, nonfatal stroke and hospitalization for unstable angina	Anticipated 2018	NCT01897532

Table 4
Randomized controlled trials assessing cardiovascular outcomes with thiazolidinediones

Study	Completion	Population	Active	Comparator	Size	Primary Outcome	Point	Clinical Trials.gov registration
RECORD	Date Complete	T2DM, no recent cardiovascular events	Rosiglitazone	Placebo	4447	CV death/CV hospitalization, MI, CV death	Estimate 0.99 (0.85-act 1.16)	NCT00379769
PROACTIVE	Complete	T2DM + evidence of macrovascular disease	Pioglitazone	Placebo	5238	T2DM/macrovascular disease	0.90 (0.80–1.02)	NCT00174993
IRIS	Complete	<i>Non-diabetic</i> patients with recent ischemic stroke or TIA	Pioglitazone	Placebo	3786	Fatal or nonfatal stroke or MI	0.76 (0.62–0.93)	NCT00091949
TOSCA IT	2018	T2DM	Pioglitazone	Various sulfonylureas	3371	Composite of all cause mortality, nonfatal MI (including silent MI), nonfatal stroke, unplanned coronary revascularization	Anticipated 2018	NCT00700856