Novel Diabetes Drugs and the Cardiovascular Specialist

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Abstract

Cardiologists have traditionally paid less attention to commencement of diabetes drugs in their patients. Recently, treatment with two newer classes of diabetes drugs were found to reduce events in patients with diabetes and cardiovascular (CV) disease, a group common in cardiology clinics. The sodium-glucose co-transporter (SGLT) 2 inhibitor, empagliflozin, markedly and rapidly reduced CV death and heart failure hospitalization, likely with hemodynamic/metabolic-driven mechanisms of action. More recently, glucagon-like peptide (GLP)-1 receptor agonists, liraglutide and semaglutide also reduced CV death and major adverse CV events, but did so more slowly, suggesting benefits on atherothrombosis and/or hypoglycemia avoidance. We will discuss drug therapy for diabetes relative to CV risk, briefly summarize key findings of CV benefit from recent trials, discuss potential mechanisms for benefits of SGLT2 inhibitors and GLP-1 agonists, and suggest how such drugs might be embraced by Cardiovascular specialists to reduce CV and mortality in their patients.

Key words: diabetes, cardiovascular disease, outcomes

Abbreviations

CI	Confidence interval
CV	Cardiovascular
CVOT	Cardiovascular outcomes trials
DKA	Diabetic ketoacidosis
DPP-4	Dipeptidyl peptidase
FDA	United States Food and Drug Administration
GLP	Glucagon-like peptide
HbA1c	Hemoglobin A1c (glycated hemoglobin)
HR	Hazard ratio
MACE	Major Adverse CV Events
MI	Myocardial infarction
RECORD	Rosiglitizone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes
RR	Risk ratio
SGLT	Sodium-glucose co-transporter
T2D	Type 2 diabetes
TZDs	Thiazolidinediones

Most cardiologists have focused their efforts on managing traditional risk factors and paid less attention to diabetes therapies whose primary role was to lower glucose. This may be because until recently diabetes therapies had little obvious impact on cardiovascular (CV) outcomes, the principal cause of morbidity and mortality in type 2 diabetes (T2D). Indeed for cardiologists the most common diabetes drug intervention was to stop drugs that may cause heart failure (for example glitazones); initiation or titration of drugs for diabetes care was most commonly relegated to primary caregivers or diabetes specialists. If anything, concerns about cardiovascular safety were more prevalent than potential benefits of these agents.

The rise of cardiovascular safety and outcome trials in diabetes care

In light of concerns regarding cardiovascular safety of new glucose lowering drugs being developed, the United States Food and Drug Administration and European Medicines Agency mandated new therapies for diabetes had to demonstrate CV safety in prospective, randomized controlled outcome trials. Current recommendations for trial design of new therapies for T2D have been recently reviewed (1) and include iterative assessment of drug safety, with initially liberal pre-approval statistical boundaries to exclude unacceptable CV risk, followed by more restrictive boundaries post-approval. For phase 4 post-marketing outcome trials, ultimately, the upper bound of the 95% confidence interval (CI) for any T2D treatment should not exceed 1.30 for major adverse CV events (MACE), while a 1.80 upper limit applies to phase 3 trials. Additionally, the recommendation was made that trials evaluating novel T2D therapies should focus on high-risk populations (such as those with vascular disease, with renal impairment, or at advanced age), should include long-term data, and all MACE events measured in such trials should be adjudicated by an independent committee.

Though designed to detect a risk signal, remarkably, results from recent "cardiovascular outcomes trials" (CVOTs) may lead to a meaningful change in how cardiologists might approach the patient with diabetes mellitus, as these CVOTs have shown not only CV safety but reduced CV and all-cause mortality in some studies (2–4). These trials include patients who are common to cardiologists' practice and the magnitude of the results compare favorably with the landmark cardiology trials that have shaped our international cardiology guidelines (5,6).

Clearly, cardiologists would do well to keep up with this evolving area of diabetes CVOT to ensure that their patients potentially benefit from newer therapies for diabetes care. In addition, a good understanding of the potential risks of diabetes drugs in treating patients with CV disease is also important. Before discussing newer therapies, reviewing experience of the CV effects of older drugs is helpful.

Diabetes drugs that have less favorable or uncertain cardiovascular or mortality risk benefits

Although meta-analyses of landmark glucose lowering trials suggest intensive glycemic control does reduce risk for CV disease events (7), improved CV outcomes as a function of intensive glucose control appear modest in comparison to the calculated CV benefits from lipid and blood pressure management (8). In addition, some concerning signals for risk from CV events have been associated with certain widely used diabetes medications, including sulfonylureas, thiazoladinediones, dipeptidylpeptidase 4 inhibitors, and insulin.

Sulfonylureas

Though widely used for care of T2D, drugs from the sulfonylurea class of drugs (though perhaps less so for the lesser used gliclazide) (9) have been associated with higher risk for CV events, notably

including a higher risk for non-fatal myocardial infarction (MI) or CV death relative to other diabetes drugs (10). For example, a meta-analysis of 72 small or modest sized randomized controlled trials found that all-cause mortality, CV mortality, and a composite of MI, stroke, and CV mortality were all increased in patients treated with glibenclamide, glipizide, and tolbutamide, compared to metformin (11). Based on these and other data, sulfonylurea medications carry a 'black box' CV warning from the FDA regarding heightened risk for CV events, although the same is not true in many non-US countries.

Thiazolidinediones

Thiazolidinediones (TZDs) are agonists for the peroxisome-proliferator-activated receptors that regulate gene expression, resulting in improved glucose utilization and reduced glucose production. TZDs improve a number of CV risk factors and became widely used at one point; however reports of significant CV risk increased following reports of fluid retention with incident heart failure, as well as a possible increased risk for incident MI (12), and earlier reports of excess bladder cancer risk now debated (13), led to reduction in their use. For example, the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial reported an adjusted risk for incident heart failure (hazard ratio [HR] 2.25; 95% CI= 1.27-3.97) (14), similar to findings in a meta-analysis (15). The MI risks for rosiglitazone have now been largely dispelled (16) whereas pioglitazone does have trial evidence to show net CV benefit (17) but the heightened HF risk as well as weight gain and potential risks for fractures with this class of drugs has led to a reduction in their use (18).

Dipeptidyl peptidase 4 inhibitors

Dipeptidyl peptidase 4 (DPP-4) is an enzyme that degrades many peptides, including glucagon-like peptide (GLP)-1; thus, pharmacologic inhibition of DPP-4 prolongs the half-life and biological activity of GLP-1. Inhibitors of DPP-4 have modest glucose lowering effects, but while three recent CVOTs did show evidence of CV safety according to FDA criteria, they did not demonstrate net CV benefits (19–21) contradicting an earlier meta-analysis (22). Furthermore, because of recent data suggesting a higher risk for incident heart failure associated with use of saxagliptin and alogliptin, recent regulatory warnings have been put in place for these two agents. While meta-analyses suggest the risk for incident heart failure to be significant with this class of drug (RR = 1.13; 95% CI = 1.01-1.26) (23), not all DPP-4 inhibitors have been linked to heart failure risk; for example, recent data suggest no increased risk for incident heart failure related to sitagliptin use (24).

Insulin

Insulin is effective for glucose lowering and is very widely used for the treatment of advanced T2D. Therapy with insulin commonly leads to increased body weight and is associated with greater hypoglycaemia risks. Thus, though insulin might improve glycemic control, its other effects may theoretically attenuate its clear glucose lowering benefits in subgroups with particular susceptibility to hypoglycemia or the adverse effects of hypoglycemia. There was also some expectation that exogenous insulin administration early in the course of T2D may have beneficial effects on CV outcomes, however the results of the ORIGIN trial failed to demonstrate any CV benefit (25).

Diabetes drugs recently reported to reduce cardiovascular and cardiovascular mortality risk

While numerous therapies for T2D have been associated with an increased risk of CV events, three recent CVOTs have shown benefit in terms of hard clinical end points (**Table 1)** (2–4). We discuss

first the results for the sodium-glucose co-transporter (SGLT) 2 inhibitor, empagliflozin, before discussing results for two GLP-1 receptor agonists.

Of course, before we discuss these drugs, it should be noted that up until these recent trials reported, metformin was the only drug with trial evidence for CV benefit, albeit modest: in the UKPDS trial metformin-treated patients had a 30% lower risk for macrovascular disease than did patients not given metformin (26). Importantly, metformin does not cause weight gain or increased risk for hypoglycemia, has many years of safety evidence, and is inexpensive; thus, it is widely used as a first-line therapy for the patient with CV disease.

SGLT2 inhibitors

SGLT2 is a low-affinity, high capacity glucose transporter located in the proximal tubule of the nephron; SGLT2 is responsible for 90% of glucose reabsorption. Inhibition of SGLT2 results in decrease of blood glucose due to glucosuria. Secondary effects of SGLT2 inhibition include a modest diuretic effect (sodium loss is also promoted), weight loss, and lowering of blood pressure.

The only available CVOT for SGLT2 inhibitors recently reported reduction in CV events following treatment with empagliflozin compared to placebo. The EMPA-REG OUTCOME trial included 7020 patients with established CV disease and randomized them to placebo, empagliflozin 10mg or empagliflozin 25mg. All study participants had established CV disease. The primary end point of EMPA-REG OUTCOME was 3-point MACE (CV mortality, non-fatal MI and non-fatal stroke). Patients randomized to empagliflozin had a modest reduction in the primary end point (HR 0.86; 95% CI 0.74-0.99, p=0.04 for superiority; absolute risk reduction 1.6%; **Figure 1**). The reduction in the primary end point was driven almost exclusively by a substantial reduction in CV death (HR 0.62; 95% CI 0.49-0.77, p<0.001; absolute risk reduction 2.2%), whereas non-fatal MI and stroke were not significantly altered; a 32% reduction in all-cause mortality was also observed. In recognition of the statistically robust impact on CV mortality, the US FDA recently granted an indication to empagliflozin to reduce risk for CV death (27).

Notably, in EMPA-REG OUTCOME, heart failure hospitalization was reduced by 35% (HR: 0.65; 95% CI 0.50-0.85, p=0.002; absolute risk reduction 1.4%), with a rapid separation in the survival curves suggesting acute benefit of the drug (**Figure 1**). The reduction in heart failure events was particularly clinically relevant as drugs from other classes of glucose-lowering drugs with very different mechanisms of action (in particular saxagliptin and rosiglitazone) had previously been found to be associated with an increase in hospitalizations for heart failure (15,19).

While compelling, there are several reasons heart failure outcome results should be interpreted cautiously. Although hospitalization for heart failure was a pre-specified outcome in EMPA-REG OUTCOME, it was not the primary outcome and did not have the rigor characteristic of heart failure trials. Patients could be recruited on the basis of investigator-reported heart failure, but there was no formal assessment of heart failure status or cardiac structure or function at baseline; for example, no natriuretic peptide measurement or echocardiography was performed. No understanding regarding forms of heart failure (e.g. preserved versus reduced ejection fraction) was established. Further, it is possible some of the 76% of patients included on the basis of coronary artery disease at baseline (including 47% with prior MI) may have had unrecognized left ventricular dysfunction.

In short, the finding of reduced hospitalization for heart failure is impressive but further detail documenting the patient characteristic and biomarkers of heart failure is unavailable. It is possible that in some cases empagliflozin prevented the onset of clinical heart failure in those with

unrecognised left ventricular dysfunction, but also that in some cases empagliflozin treated patients who already had unrecognised clinical heart failure. Mechanistic, or "bedside to bench", studies are now trying to clarify the mechanistic relationship between empagliflozin and heart failure while large outcome trials investigating the possible efficacy of SGLT2 inhibitors in treating heart failure, both preserved and reduced ejection fraction, are also underway (28,29).

Other benefits seen in EMPA-REG OUTCOME may help to understand the impact of empagliflozin on CV outcomes. For example, empagliflozin also had favorable effect on renal end points (30), with reduction in incident or worsening nephropathy and incident albuminuria. Whether these beneficial renal effects (thought to reflect reversal of maladaptive tubulo-glomerular renal feedback) are secondary to improved perfusion by cardiac or cardiovascular mechanisms or whether they are due to primary renal effects is unknown, although most consider renal effects to be critical.

The mechanism of benefit of empagliflozin is not fully known but several are speculated (**Figure 2**). As noted, empagliflozin has numerous possibly beneficial CV effects including the hemodynamic effects of a diuretic, as well as beneficial renal (reduction in intraglomerular pressure) (31), blood pressure, and weight effects as well as many others, as recently reviewed (32,33). Most experts believe the rapid reduction in CV death and heart failure hospitalizations seen in EMPA-REG OUTCOME is best explained by a rapid hemodynamic effect (33,34). Natriuresis, in combination with renal glucose losses, are thought to lead to a reduction in circulating volume and possibly extracellular fluid load with a consequent lowering of cardiac filling and pre- and after-load pressures. Supporting this concept was the rapid and sustained increase in hematocrit demonstrated in EMPA-REG OUTCOME (2), as well as preliminary evidence for empagaflozin-induced improvements in left ventricular mass and diastolic function (35).

In a more general sense, the data from EMPA-REG OUTCOME suggest many patients with diabetes and CV disease may have previously unrecognised excessive fluid overload, often in association with cardiac dysfunction, and that these patients benefit rapidly from intravascular decongestion. Some have suggested that less left ventricular stretch, arising from corrections in intravascular fluid load, might also decrease the incidence of atrial and ventricular arrhythmias. Another potential mechanism of benefit is that patients randomized to empagliflozin were less likely to receive other glucose-lowering therapies (e.g. insulin and sulfonylureas), drugs which increase weight and hypoglycemia risks. Possibly avoidance of these therapies in the treatment arm could have contributed to the positive outcome. A further proposed mechanism of benefit of empagliflozin, the ketone hypothesis, whereby slightly increased ketones with SGLT2 inhibitors serve as a better fuel supply for the failing heart, has been proposed.(36)

It is important to understand the potential side effects of SGLT2 inhibitors. The most notable adverse effect in EMPA-REG OUTCOME was an absolute 4.6% increase in genital infections; a greater incidence was noted in females. Fortunately, these infections are not generally serious and resolve with a course of anti-fungal agents. Once treated they uncommonly recur. From the perspective of a cardiologist, patients should be informed of this risk and shared care with primary care physicians (who manage these conditions on a regular basis) is recommended. It would not be prudent to use SGLT2 inhibitors in women or men with a history of recurrent genital infections. In EMPA-REG OUTCOME there was no increase in urinary tract infections, hypoglycemic episodes or diabetic ketoacidosis. Some concern does remain as to whether or not SGLT2 inhibitors can increase the risk of diabetic ketoacidosis outside the tightly monitored environment of a clinical trial, particularly in T2D individuals treated with insulin. It should be noted cases of ketoacidosis have been reported in

the off label use of SGLT2 inhibitors in patients with T1D (37). Patients given these agents should be educated about simple warning signs and symptoms of potential diabetic ketoacidosis.

It is worthwhile to emphasize EMPA-REG OUTCOME was not a primary prevention trial. Though tempting to speculate, it is impossible to conclude similar benefits would be seen in patients without CV disease. This makes the results of EMPA-REG OUTCOME all the more important to the practicing cardiovascular specialist, given high prevalence of T2D in those with established CV disease (38). Several other similar safety trials are being conducted with SGLT2 inhibitors with slightly differing pharmacology. However, these trials also differ in size and patient composition. For example, 60% of participants in DECLARE [https://clinicaltrials.gov/show/NCT01730534] do not have prior CVD, which is important. These trials will report over the next few years.

GLP-1 receptor agonists

Although empagliflozin was the first drug for T2D to be proven to reduce CV events, two other drugs, both from the GLP-1 receptor agonist family, have been shown to improve CV outcomes, albeit in a different pattern to EMPA-REG OUTCOME.

Liraglutide is a once daily injectable GLP-1 receptor agonist. It is also associated with weight loss and blood pressure lowering. In the recent Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, 9340 patients with an HbA1c of >7.0% (either aged >50 years of age with established CV disease or >60 with one or more CV risk factors) were randomized to liraglutide or placebo (3). The primary end point of MACE was reduced by 13% (HR 0.87 95% CI: 0.78-0.97; absolute risk reduction 1.9%; p for superiority p=0.01) (**Figure 3**). The components of the primary end point were all numerically in favor of liraglutide but only CV mortality was statistically significantly reduced (HR 0.78 95% CI 0.66-0.93, p=0.007; absolute risk reduction 1.3%); all-cause mortality was also reduced (HR 0.85 95% CI 0.74 to 0.97). Subgroup analysis did suggest a greater benefit in those with established CV disease rather than those with risk factors in the absence of clinically evident disease. Nephropathy events were less common with liraglutide (1.5 v 1.9/ 100 patient-years) but, in contrast to the widespread renal benefits with empagliflozin, liraglutide-driven renal benefits were largely driven by reduction in new-onset persistent macroalbuminuria with little discernible effects on other renal outcomes.

Subsequently, the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN)-6 trial investigated the safety of the once weekly GLP-1 receptor agonist, semaglutide. In this phase 3, randomized, placebo-controlled non-inferiority trial, 3297 study participants were treated with semaglutide or placebo. The inclusion criteria were very similar to those used in LEADER, as was the primary end point of three point MACE. Treatment with semaglutide reduced the primary end point by 2.3% (HR 0.74 95% CI 0.58-0.95, p<0.001 for non-inferiority; p=0.01 for superiority). The contribution of the components of MACE to the reduction in the primary end point was somewhat different to that seen in LEADER in that CV mortality was not affected by semaglutide, but non-fatal stroke was improved (ARR 1.1%; HR 0.61 95% CI 0.38-0.99) along with a non-significant trend toward lower rates of incident MI. It is important to draw an important distinction between LEADER and SUSTAIN-6, as the latter study was a much smaller non-inferiority design, increasing risk for Type 1 and Type 2 error due to underpowering.

It is not yet understood how GLP-1 receptor agonists may reduce CV events. Compared to trials of SGLT2 inhibitors, the relative benefit of GLP-1 agonists appeared at a later time following

randomization (note differences in divergence of Kaplan Meier curves in Figures 1 and 3); this slower appearance of CV benefits is more in line with atherothrombotic rather than hemodynamic effects. However, both MI and stroke were numerically but not statistically lower with liraglutide than placebo in LEADER. If this was the predominant mechanism of action explaining LEADER results, a more convincing reduction in MI or stroke might have been anticipated. Other possible mechanisms are blood pressure reduction, lessening of arterial stiffness (in keeping with lower SBP but higher DBP so narrowing of pulse pressure), weight loss and beneficial renal effects. The reduction in blood glucose was more pronounced in the early years in LEADER than in other recent diabetes CVOTs so one cannot rule out that glucose-lowering contributed to its beneficial effects; patients randomized to liraglutide were less likely to be exposed to insulin or sulphonylureas, prompting speculation that preventing exposure to these potentially harmful (or less "net" beneficial) drugs in such patients may also be a contributory mechanism. As well, severe hypoglycemia was significantly lower in patients randomized to liraglutide; emerging evidence indicates hypoglycemia may be more harmful in patients with existing CV disease, so less hypoglycemia could help explain the CV mortality reduction in LEADER. Other direct vascular or cardiac effects of GLP-1 receptor agonist have been proposed and could have contributed to the CV benefits seen (39).

Taken together and accepting the caveats mentioned above, the somewhat different pattern of CV benefits in LEADER versus SUSTAIN-6 suggests that a class effect of GLP-1 receptor agonists on CV outcomes cannot be assumed; rather, benefits and potential harms may differ between different GLP-1 receptor agonists. The results of Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL; testing once-weekly exenatide) are eagerly awaited (40). It should also be noted that the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) CVOT did not reduce MACE in T2D patients following acute coronary syndrome (41) but whether these results were due to the short acting nature of lixisenatide compared to other GLP-1 agonists requires further research.

As with the SGLT2 inhibitors, a good understanding of the potential side effects of GLP-1 receptor agonists should be known. In trials of these agents, more patients discontinued liraglutide or semaglutide than placebo due to adverse events. This was primarily due to gastrointestinal adverse effects, a known side effect of GLP-1 receptor agonist drugs. There was a slight numerical excess of retinopathy events with liraglutide versus placebo (0.6 v 0.5 per 100 patient years); rates of retinopathy events were higher in those treated with semaglutide (HR 1.76 95% CI 1.11-2.78), which is a concern, although the number of events is rather small. The more rapid glucose reduction seen with semaglutide is theorized to explain increased retinopathy but more work is needed to confirm findings, and if confirmed, examine the mechanisms. There was a concern prior to the trial that liraglutide might increase pancreatic conditions but these concerns were not realized.

Broader lessons learned from recent and prior CV outcome trials of drugs for diabetes

Diabetes is associated with a higher rates of incident CV disease which most have thought to be due to excess atherothrombotic risk with hyperglycemia adding fire to a background of hypertension, dyslipidemia and obesity. However, as MI and stroke rates have declined substantially (42), due in considerable part to much better treatments with statins and anti-hypertensives, heart failure and peripheral arterial disease have become the two commonest first presentations of CV disease in those with T2D (43). Moreover, once patients with T2D develop CV disease, their risk of premature mortality escalates substantially (44) and it is here that the unexpected and rapid CV mortality and heart failure benefits in the EMPA-REG OUTCOME trial have emerged. These benefits support far greater roles of cardiac structural abnormalities and excess fluid loads in driving premature death in such patients. Parallel improvements in renal, CV death and heart failure hospitalization also

emphasize the importance of cardio-renal interactions in patients with T2D and CV disease. Though cardiologists appreciate the role of kidney dysfunction in heart failure (45) a re-calibration towards appreciating overlapping mechanisms with the heart, kidney and T2D is worthwhile.

The recent positive CVOTs have also taught diabetologists that it is not necessarily lowering glucose *per se* (or even how much one lowers glucose) that only matters. In addition, the mechanism by which any particular diabetes drugs work and its associated multiple effects on other pathways may matter more to observed CVD benefits. EMPA-REG OUTCOME, LEADER and SUSTAIN-6 have shown blood glucose, CV and total mortality can be lowered in parallel with specific drugs that might improve hemodynamic status of patients or else lower glucose in conjunction with reduced weight, lower risk for hypoglycemia and improved blood pressure; possible direct beneficial direct effects on atherosclerosis may also be considered (**Figure 4**).

Clinical implications for the practicing cardiologist

It is impossible for cardiologists to assume full responsibility of blood glucose management; however, a change in thinking regarding initiation and titration of therapies with CV benefits is necessary, particularly since most patients with T2D develop CV disease and are frequently encountered in cardiology practice. As well, the patient with CV disease frequently has unrecognized or undertreated T2D: in the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) study, in addition to the 27% of patients with recognized T2D, 11% of patients with heart failure had unrecognized T2D (46).

In light of the new trial evidence of clinical benefit over and above existing therapies, and with the emergence of recent guidelines mentioning these CV benefits (47,48), it seems logical to suggest cardiologists perform routine, systematic measurement of hemoglobin A1c (HbA1c) in all those with established CV disease (**Figure 5; Central Figure**). Measurement of HbA1c should be performed both to diagnose T2D and to identify those that would have met the inclusion criteria for the positive CVOTs (e.g. HbA1c 7-10% in EMPA-REG OUTCOME and >7% in LEADER and SUSTAIN). Care of patients with T2D and CV disease should involve strong consideration for use of glucose lowering drugs that improve CV outcomes over and above existing therapies and not solely on the glucose-lowering abilities of therapies. In this regard, beyond their glucose lowering effects, empagliflozin, liraglutide or semaglutide (when available) might be considered for eligible patients for their proven CV benefits. Of course, one should also recognize identifying new diabetes in patients with CVD will also have other beneficial implications including, where relevant, the choice of revascularization (CABG vs. PCI), and the aggressiveness of management of other risk factors.

In analogy to the “heart team” approach used for those with other forms of heart disease, collaboration between cardiologists, primary care physicians and diabetologists will be necessary to achieve the goal of more widespread treatment of vulnerable patients with T2D. Management of adverse effects such as genital infections are an obvious example where this approach is likely to be beneficial. There is no reason that cardiologists cannot initiate SGLT2 inhibitors with the patient then monitored by colleagues in primary care or diabetology. While cardiologists might recommend GLP-1 receptor agonists, specialized teaching by primary care physicians and/or diabetologists might be needed. If the CV specialist does not feel comfortable prescribing these drugs, they should not only inform the patients but also the primary care physician (and other health care professionals involved in the patient's care) of the potential benefits of adding these drugs.

Clinical implications for the practicing diabetes specialist

Diabetologists have lowered CV risk by prescribing statins and anti-hypertensive for decades, but these have conventionally been started to lower cholesterol or blood pressure rather than because of recognition of CV disease. Based on present data, if a diabetes specialist recognizes a patient has CV disease, they have identified a patient who might benefit from therapy with newer agents such as SGLT2 inhibitors or GLP-1 receptor agonists. While numerous therapies exist to lower blood glucose, it will take a continued shift in philosophy towards using therapies that not only lower blood glucose modestly, but significantly reduce CV risk. Our view is that given empagaflozin is oral (rather than injectable) and has a more marked effect on CVD and total mortality, it should be the preferred choice (along with metformin) in most patients with CVD and diabetes. Of course, treatments need to be individualised and other factors such as renal function, and patient preference may mean a GLP-1 receptor agonist is prescribed.

The future

There are an array of ongoing safety CV outcome trials with DPP-4 inhibitors, GLP-1 receptor agonists and SGLT2 inhibitors in similar populations to the trials described in this manuscript, but also, importantly, including patients without CVD (49). The knowledge of the pros and cons of other agents in varying populations will evolve over the next 1-5 years. Trials with SGLT2 inhibitors are also underway in patients with heart failure, including those with T2D, pre-diabetes, as well as those without T2D. Trials of SGLT2 inhibitors in patients with chronic kidney disease are also underway. Trials of the combined effect of SGLT2 inhibitors and GLP-1 receptor agonists may also be reasonable, given the possible (and potentially additive) differences in mechanism of benefit of these agents.

Ultimately, studies of newer drugs for T2D must shift to focus on patients without prevalent CV disease (49). It is typically harder to prove CV benefit in such trials, given lower rates of incident events; enrichment of patient populations with tools to identify higher risk for CV events might be a way that can identify subgroups that potentially benefit. Circulating biomarkers might be such a tool. When measured in patients with T2D concentrations of amino-terminal pro-B type natriuretic peptide and highly sensitive troponin may be helpful to predict future CV events, including heart failure and atherothrombotic events (50–52). Thus it may be possible to envision a strategy of biomarker-guided screening and treatment of patients with T2D at high risk for CV events.

Conclusion

When the first few CVOTs of newer diabetes drugs began to report CV safety without reduction in CV risk, some started to question the value of these clinical trials. However, recent CVOTs have shown convincing evidence of CV benefit with an SGLT2 inhibitor and two classes of GLP-1 receptor agonists. Cardiologists should make note of the substantial reduction in CV events and CV mortality in these trials. If clinical experience follows the results of studies such as EMPA-REG OUTCOME (SGLT2 inhibitor) or LEADER (GLP-1 receptor agonist), a sizeable proportion of patients seen and managed by cardiologists on a daily basis might benefit from treatment with these novel agents. Consequently, cardiologists would do well to familiarize themselves with these drug classes as many of their patients (i.e. T2D plus CV disease) stand to benefit from their use. Cardiologists should also consider screening more widely for T2D, to identify patients who could benefit sooner from such drugs. By doing so it will be possible to better impact upon the rising burden of patients with both T2D and CV disease.

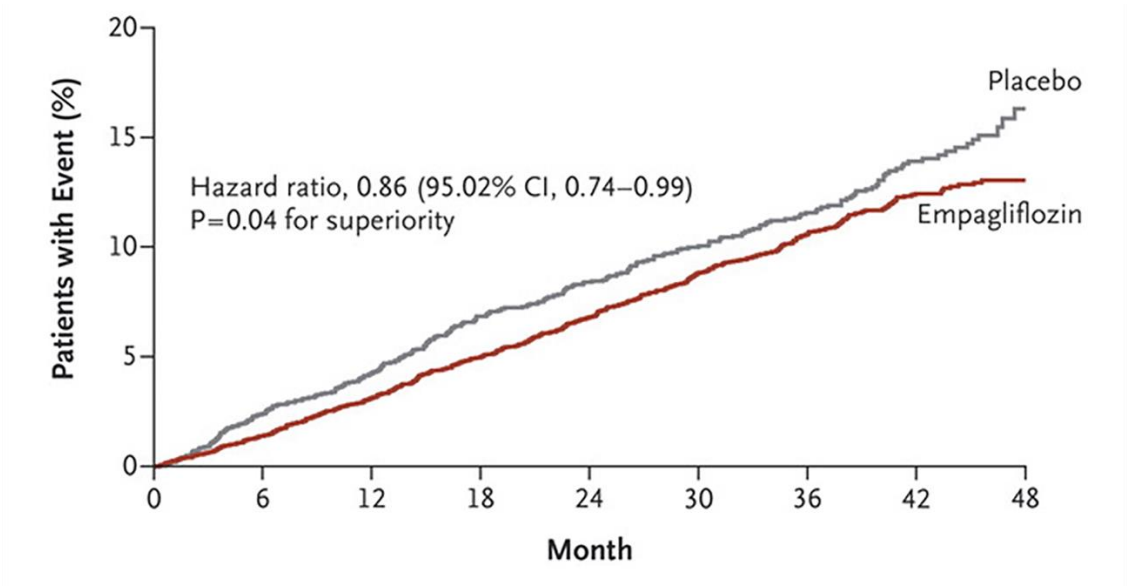
Table 1. Summary of the key findings of the three positive CVOT in diabetes. Adverse effects and broad beneficial mechanisms implicated for CV benefits are detailed.

Trial	**EMPAREG OUTCOME** (2)	**LEADER** (3)	**SUSTAIN-6** (4)
Agent	Empagliflozin (SGLT2 inhibitor)	Liraglutide (once daily GLP-1 agonist)	Semaglutide (once weekly GLP-1 agonist)
Duration of trial	3.1 years	3.8 years	2.05 years
Baseline HbA1c	8.1%	8.7%	8.7%
Primary end-point	↓ 14% (1 to 26%)	↓ 13% (3 to 22%)	↓ 26% (5 to 42%)
CV death	↓ 38% (23 to 51%)	↓ 22% (7 to 34%)	↓ 2% (-48 to 35%)
MI	↓ 13% (-9 to 30%)	↓ 12% (-3 to 25%)	↓ 26% (-8 to 49%)
Stroke	↑ 24% (-8 to 67%)	↓ 11% (-11 to 28%)	↓ 39% (1 to 72%)
HF hospitalization	↓ 35% (15 to 50%)	↓ 13% (-5 to 27%)	↑11% (-23 to 61%)
Noteworthy adverse effects	Genitourinary infections, no excess DKA	More gallstones, GI side effects	Higher retinopathy rates
Likely broad mechanisms of benefit	Rapid effects suggest a hemodynamic or metabolic benefit	Slower effects suggest benefits via less atherothrombosis and/or avoidance of hypoglycemia	Slower effects suggest benefits via less atherothrombosis

SGLT2 denotes: sodium-glucose cotransporter-2; GLP-1 denotes: glucagon-like peptide-1; HbA1c denotes: hemoglobin A1c; CV denotes: cardiovascular; MI denotes: myocardial infarction; HF denotes: heart failure; DKA denotes: diabetic ketoacidosis; GI denotes: gastrointestinal.

Figure 1: Cumulative incidence of A) major adverse cardiovascular events and B) hospitalization for heart failure in EMPAREG OUTCOME. Particularly rapid divergence of survival curves is noted. Hazard ratios are based on Cox regression analyses. Reproduced from reference (2) with permission.

A)



B)

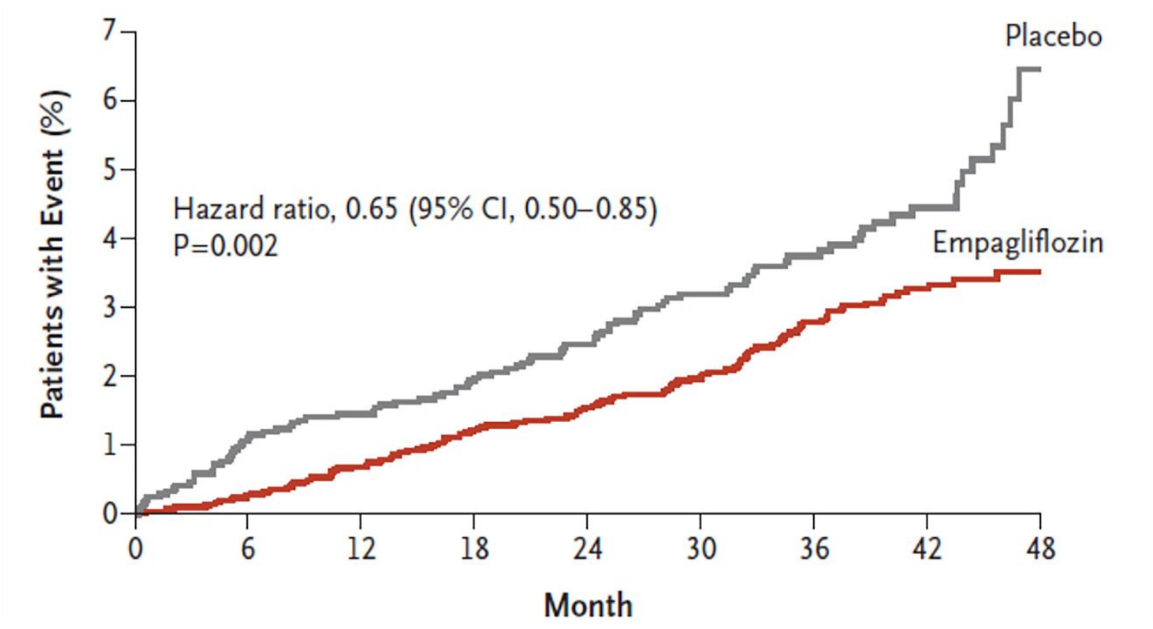


Figure 2: Potential pathway linking empagliflozin (and possibly other SGLT2 inhibitors) with lower risks for heart failure hospitalization and death due to cardiovascular disease. Adapted from reference (28). By increasing fluid losses via urinary glucose and sodium losses, intravascular volumes and systolic blood pressure are reduced, and there is a significant rise in haematocrit and modest weight loss. These changes in turn lessen cardiac stressors (pre- and afterload) and may help improve myocardial oxygen supply. The net result is a likely improvement in cardiac systolic and diastolic function, lessening chances of pulmonary congestion, thus lowering risks of hospitalization for heart failure and fatal arrhythmias. These cardiac function benefits could, in turn, feedback to improve renal function.

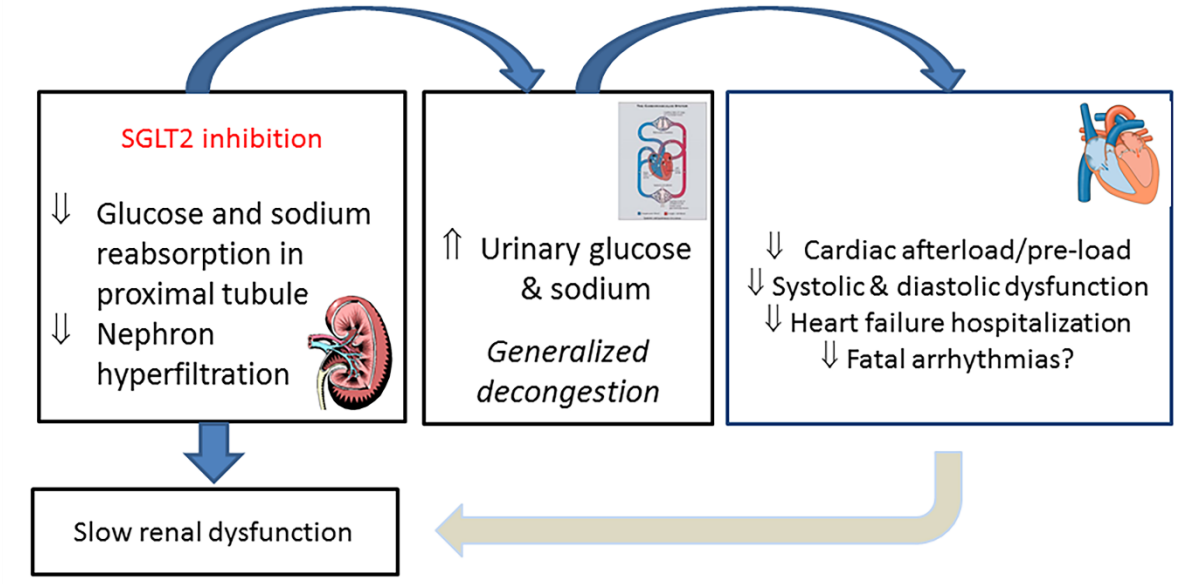
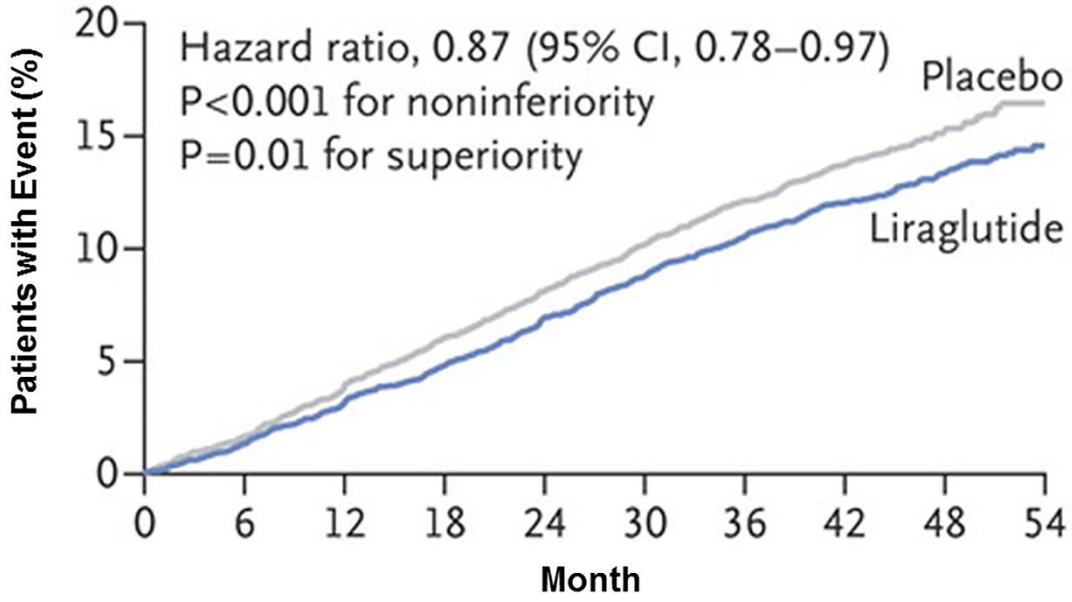


Figure 3: Cumulative incidence of A) major adverse cardiovascular events and B) CV death in the LEADER trial. In contrast to trials of SGLT2 inhibitors, the benefits of liraglutide were later in onset. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond this time point. Reproduced from reference (3) with permission.

A)



B)

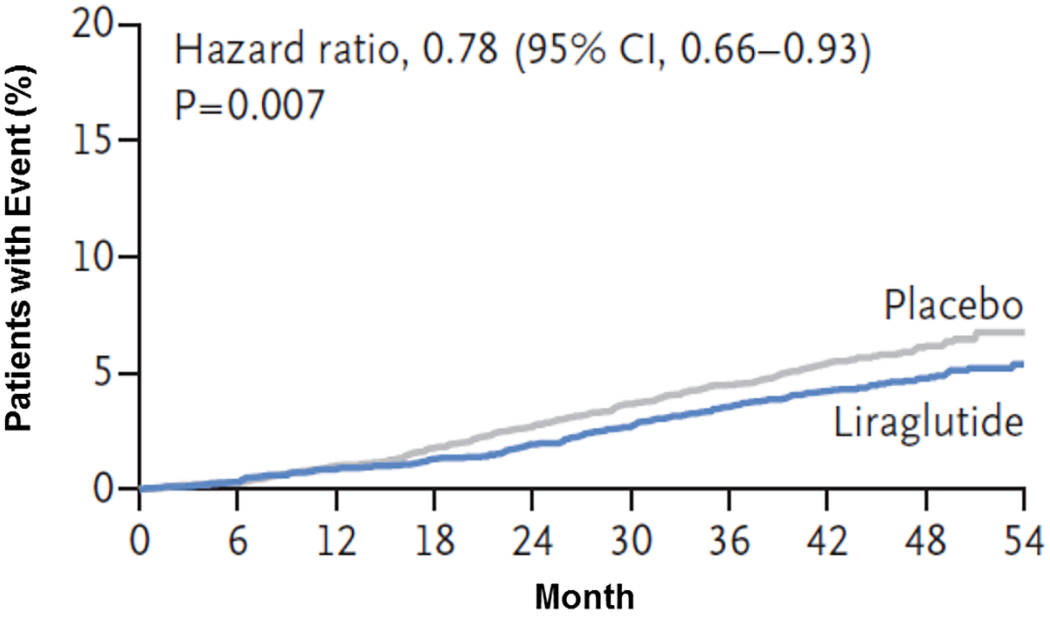


Figure 4: Summary of new diabetes drugs and patterns of CV benefits in patients with T2DM and CV disease. In patients with CV and T2DM, a combination of atherogenic and hemodynamic disturbances (the latter driven by combinations of renal disease, cardiac dysfunction and potentially obesity) likely contribute to accelerated CV and total mortality risks. If this is correct, SGLT2 inhibitors might be more likely to correct hemodynamic processes whereas GLP-1 receptors may act more to lessen atherogenic processes over time; both may aid hypoglycemia avoidance. This schematic also predicts the combination of SGLT2 inhibitors and GLP-1 receptor agonists may be yield additive benefits in patients with T2D and CV disease but further research is needed to test this supposition.

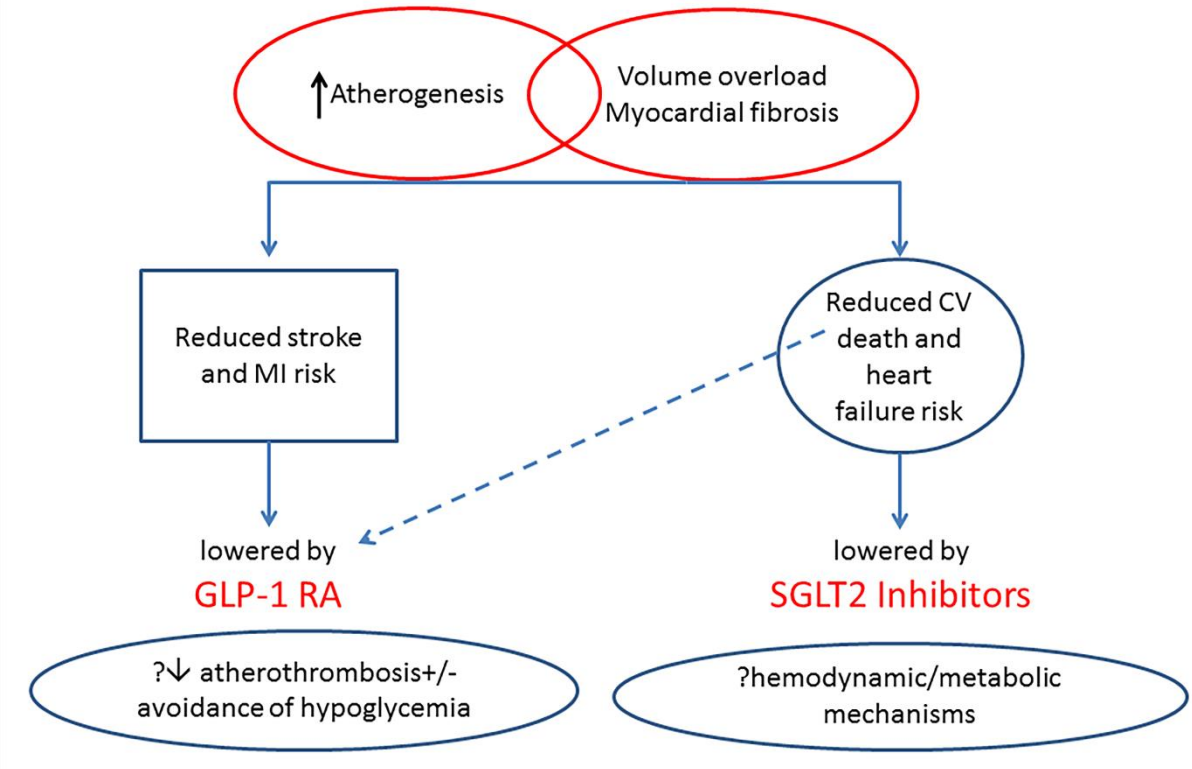
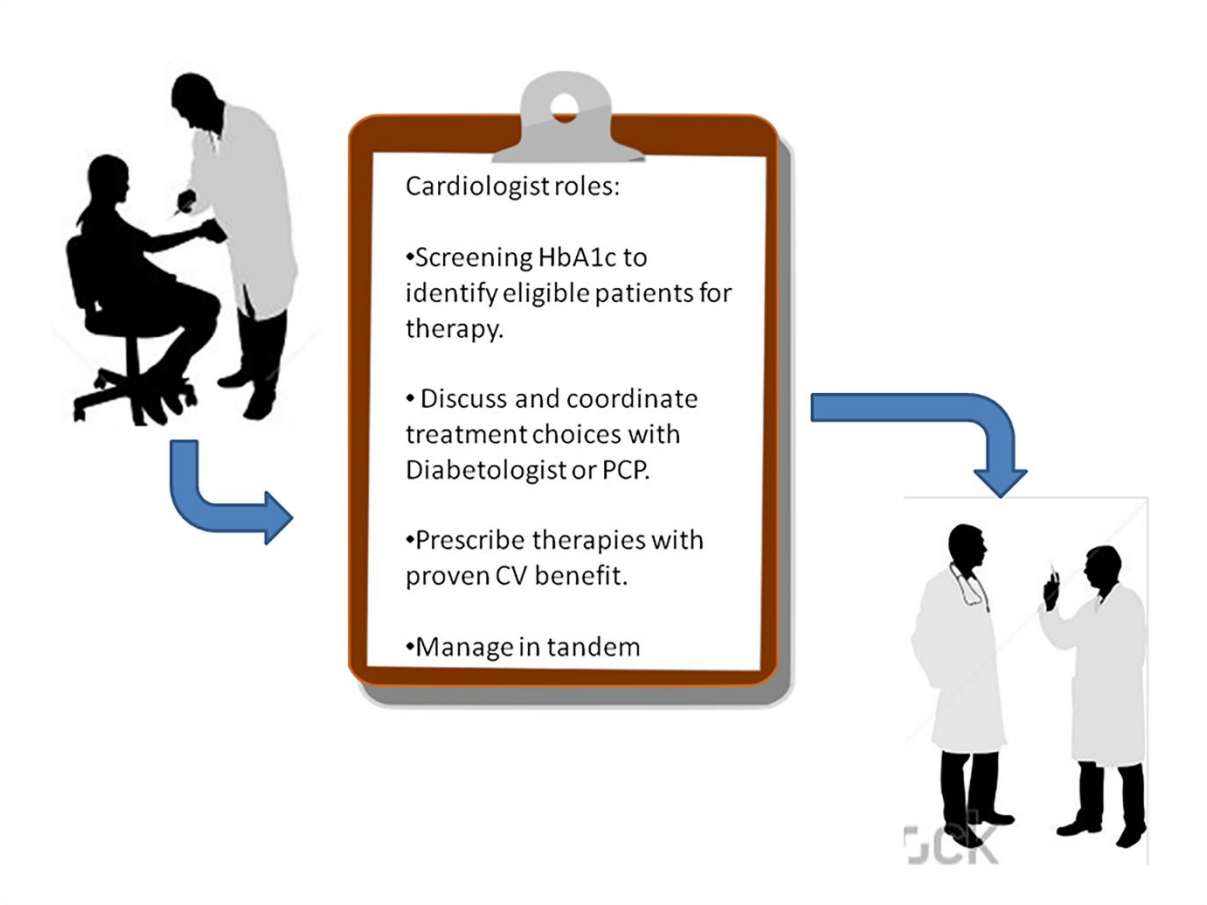


Figure 5 (Central Figure): The novel paradigm for care of the patient with CV disease and T2D. The cardiologist will need to take a more active role in patient care by more frequent testing for T2D using HbA1c in patients with CV disease to identify suitable patients for newer T2D therapies. Cardiologists should also prescribe T2D drugs with proven CV benefits and work more efficiently with diabetologists and primary care physicians to manage their patients.



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