Is It Time to Change the Type 2 Diabetes Treatment Paradigm? No! Metformin Should Remain the Foundation Therapy for Type 2 Diabetes

Silvio E. Inzucchi

Diabetes Care 2017;40:1128–1132 | https://doi.org/10.2337/dc16-2372

Most treatment guidelines, including those from the American Diabetes Association/European Association for the Study of Diabetes and the International Diabetes Federation, suggest metformin be used as the first-line therapy after diet and exercise. This recommendation is based on the considerable body of evidence that has accumulated over the last 30 years, but it is also supported on clinical grounds based on metformin's affordability and tolerability. As such, metformin is the most commonly used oral antihyperglycemic agent in the U.S. However, based on the release of newer agents over the recent past, some have suggested that the modern approach to disease management should be based upon identification of its etiology and correcting the underlying biological disturbances. That is, we should use interventions that normalize or at least ameliorate the recognized derangements in physiology that drive the clinical manifestation of disease, in this circumstance, hyperglycemia. Thus, it is argued that therapeutic interventions that target glycemia but do not correct the underlying pathogenic disturbances are unlikely to result in a sustained benefit on the disease process. In our field, there is an evolving debate regarding the suggested first step in diabetes management and a call for a new paradigm. Given the current controversy, we provide a Point-Counterpoint debate on this issue. In the point narrative that precedes the counterpoint narrative below, Drs. Abdul-Ghani and DeFronzo provide their argument that a treatment approach for type 2 diabetes based upon correcting the underlying pathophysiological abnormalities responsible for the development of hyperglycemia provides the best therapeutic strategy. Such an approach requires a change in the recommendation for first-line therapy from metformin to a GLP-1 receptor agonist. In the counterpoint narrative below, Dr. Inzucchi argues that based on the medical community's extensive experience and the drug's demonstrated efficacy, safety, low cost, and cardiovascular benefits, metformin should remain the "foundation therapy" for all patients with type 2 diabetes, barring contraindications.

—William T. Cefalu
Chief Scientific, Medical & Mission Officer, American Diabetes Association

Within a few years of its introduction to the U.S. market in 1995, the biguanide metformin became considered the favored initial therapy in patients with type 2 diabetes. This distinction was owed to the combination of a paucity of long-term side effects, weight neutrality or modest weight loss, effectiveness in reducing HbA_{1c} without increasing the risk of hypoglycemia, and evidence for cardiovascular benefits. Despite its popularity, however, metformin's precise mechanism of action still remains incompletely

Yale School of Medicine, New Haven, CT

Corresponding author: Silvio E. Inzucchi, silvio.inzucchi@yale.edu.

See accompanying article, p. 1121.

POINT-COUNTERPOINT

understood. Over the years, several lines of evidence have supported multiple mechanisms, as shown in Table 1. The most consistent finding is that the drug reduces hepatic glucose production (HGP), mainly through inhibition of hepatic gluconeogenesis (1). Recently, elegant studies in murine models have clearly demonstrated that the specific target of metformin is likely to be inhibition of the mitochondrion-specific isoform of glycerophosphate dehydrogenase, leading to an increase in the cytosolic redox state and, as a consequence, decreased conversion of lactate and glycerol to glucose (2). There is also growing evidence that at least some of the drug's metabolic effects may involve the enteroendocrine axis, including gut activation culminating in the release of GLP-1 and peptide YY (3). Because patients with type 2 diabetes express both increased HGP and derangements in the incretin system, metformin's mechanism(s) of action could also be considered to be pathophysiologically based.

The cardiovascular benefits of this drug were initially demonstrated in 1998, with publication of the results from a small, prespecified subinvestigation of overweight patients within the UK Prospective Diabetes Study (UKPDS). This demonstrated strikingly better macrovascular outcomes in those randomized to metformin versus conventional diet therapy (myocardial infarction: hazard ratio [HR] 0.61 [95% CI 0.41, 0.89], diabetes-related death: 0.58 [0.37, 0.91], and all-cause mortality: 0.64 [0.45, 0.91]) (4). In contrast, in the main UKPDS comparing sulfonylurea or insulin versus diet, there was no such cardiovascular advantage (5). Moreover, when metformin-treated patients were compared directly to those on sulfonylureas or insulin, they experienced fewer diabetes-related end points ($P = 0.003$) and less all-cause mortality ($P = 0.02$) and stroke ($P = 0.03$) (2). In two subsequent trials, Hyperinsulinaemia: the Outcome of its Metabolic Effects (HOME) (6) and Study on the Prognosis and Effect of Antidiabetic Drugs on Type 2 Diabetes Mellitus With Coronary Artery Disease (SPREAD-DIMCAD) (7), the risk reductions related to cardiovascular end points were remarkably consistent at about 40% (Table 2).

Table 1—Major proposed mechanisms of action of metformin

- Reduction in HGP
- Enhanced release of GLP-1 and other gut peptides
- Improvement in peripheral insulin sensitivity
- Decrease in gut carbohydrate absorption
- Increase in enteric glucose extraction
- Increased fatty acid oxidation

More recently, several large observational studies have buttressed the notion of cardiovascular benefits from metformin, showing improved outcomes with the biguanide as compared with sulfonylurea monotherapy both for cardiovascular events and all-cause mortality (8–10). Admittedly, it cannot be known from such data whether event rates are decreased by metformin or increased by sulfonylureas, which are, of course, associated with hypoglycemia. Mechanistic studies over the years, however, seem to support the former conclusion, with this biguanide having protean benefits on cardiovascular risk factors, including body weight, blood pressure, lipid levels, inflammatory markers, hypercoagulability, platelet dysfunction, and microvascular reactivity (11).

This body of evidence, along with metformin's low cost and general good tolerability, catapulted the drug in less than a decade to be the most commonly used oral antihyperglycemic agent in the U.S. (12). Most treatment guidelines, including those from the American Diabetes Association/European Association for the Study of Diabetes (13) and the International Diabetes Federation (14), suggest metformin be used as the first-line therapy after diet and exercise, barring any prevailing contraindications. The drug is also endorsed by professional organizations for diabetes prevention in those with mild hyperglycemia, attesting to its excellent safety profile (15). This recommendation and growing use by the medical community stems from the impressive findings of the Diabetes Prevention Program (DPP), a study involving 3,234 overweight patients with impaired glucose tolerance and fasting plasma glucose 95–125 mg/dL who were randomized to intensive lifestyle change, metformin, or placebo (16). Patients in the metformin arm experienced a 31% reduction in the incidence of type 2 diabetes over 2.8 years relative to placebo. In the long-term follow-up component of the DPP, known as the Diabetes Prevention Program Outcomes Study (DPPOS), those initially randomized to metformin experienced an 18% reduction in the incidence of diabetes versus the original placebo group at the end of a full decade (17). This was despite the fact that placebo patients were offered additional lifestyle support and good adherence to metformin was achieved by only 57% patients.

The value of metformin was recently indirectly suggested by the U.S. Food and Drug Administration's revision of its proviso for use in those with chronic kidney disease (CKD) (18), which, when severe, can result in drug accumulation and increased risk of lactic acidosis. The updated guidelines now allow therapy in those with stable, mild to moderate CKD, thereby expanding its use in the U.S. by, potentially, more than a million individuals (19).

In fact, so pervasive is metformin's clinical use that every recent drug development program for new glucose-lowering agents routinely tests its investigational agent in combination with metformin. It is also the most common therapeutic ingredient in fixed-dose combination drugs, now available in conjunction with sulfonylureas, glinides, thiazolidinediones, DPP-4 inhibitors, and SGLT2 inhibitors.

Despite these now widely recognized advantages of metformin, a rapidly growing pharmacopeia for type 2 diabetes has led to the emergence of an important but controversial question: should any of the newer medications replace metformin as first-line therapy? Until recently, there was no solid evidence that any specific glucose-lowering drug or drug category had any definitive long-term benefit over other agents. During the past year, however, members of two categories of diabetes medications, the SGLT2 inhibitors (specifically empagliflozin) (20) and the GLP-1 receptor agonists (GLP-1 RAs) (specifically the daily injectable liraglutide [21] and the weekly and still investigational injectable semaglutide [22]) have now been shown to have clear cardiovascular benefits over the standard of care. Two of these (empagliflozin [23] and liraglutide [21]) were also found to improve renal outcomes. Both benefits are extremely important and also likely to be, at least in part, distinct from the drugs' glucose-lowering effects. Based on these new data, should either of these agents

Table 2—Randomized clinical trials involving metformin and CVD outcomes

Trial/year	Comparison	Study population	*N*	Main CVD outcome(s)	HR (95% CI)	*P*
UKPDS 34 (4) (1998)	Metformin vs. diet Metformin vs. SU/insulin	Overweight, newly diagnosed T2D patients	1,704	All-cause mortality Myocardial infarction	0.64 (0.45, 0.91) 0.61 (0.41, 0.89)	NR 0.010
HOME (6) (2009)	Metformin vs. placebo	T2D patients on insulin	390	Expanded MACE*	0.61 (0.40, 0.94)	0.02
SPREAD-DIMCAD (7) (2013)	Metformin vs. glipizide	T2D patients with CAD	304	Expanded MACE†	0.54 (0.30, 0.90)	0.026

CAD, coronary artery disease; MACE, major adverse cardiovascular events; NR, not reported; SU, sulfonylurea. *Myocardial infarction, acute coronary syndrome, coronary or peripheral revascularization, electrocardiogram changes, heart failure, stroke/transient ischemic attack. †Cardiovascular cause, death from any cause, nonfatal myocardial infarction, nonfatal stroke, or arterial revascularization.

supplant metformin's long-held position as the favored initial therapy for type 2 diabetes? Might the answer differ when addressing it in the context of patients with versus without overt cardiovascular disease (CVD)? In this writer's view, based on the available evidence, the answers are the same: a resounding "No."

In order to be preferred over metformin as initial monotherapy for type 2 diabetes, a glucose-lowering drug must at the very least demonstrate some tangible advantage, whether it be greater potency, enhanced durability of effectiveness, or a clear benefit on the incidence of long-term complications, either microvascular or macrovascular. No category has thus shown this convincingly. Metformin, with perhaps the exception of insulin, has unsurpassed efficacy for HbA_{1c} reduction, typically in the 1–1.5% range, influenced to some degree by baseline glycemia (24). Whenever it has been compared head-to-head with other drugs, equivalent glycemic reductions have been measured or, in some studies, an actual advantage to metformin has been found (24). Admittedly, however, the degree of HbA_{1c} reduction may not necessarily be the most important outcome from a medication used for diabetes.

The recently demonstrated cardiovascular benefits of the newer agents have also been measured versus placebo, not versus metformin, and, moreover, upon a background of contemporary treatment, which commonly included metformin. For example, in the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), 74% of patients were already on metformin at baseline (20). Corresponding figures from Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long Term Evaluation (LEADER) and Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6) were 76% and 73%, respectively (21,22). Accordingly, it can be said that the benefits to the cardiovascular system of the newer agents have only been demonstrated, largely, on top of widespread metformin use.

Most importantly, extending the findings from these trials to the primary prevention setting—the most common scenario when prescribing initial glucose-lowering therapy—is very premature. In the EMPA-REG OUTCOME trial, a main inclusion criterion was a prior history of CVD (20). It is impossible to know whether empagliflozin might have benefits in those without overt macrovascular complications. Given the prominent effects of empagliflozin in this trial on heart failure hospitalization rates (HR 0.65 [95% CI 0.50, 0.85]) and its recognized diuretic actions, some have proposed that the drug exerts its benefits on cardiovascular mortality by simply offloading the left ventricle in those with known and even perhaps yet unrecognized ventricular dysfunction (25). In LEADER (21) and SUSTAIN-6 (22), eligibility criteria included those over age 50 years with overt CVD but also a smaller cohort (about 1 in 5 to 6 participants) over age 60 years with cardiovascular risk factors only. Notably, in both studies, the point estimates for the primary outcome were $\geq$1.00 for those without overt CVD (LEADER: HR 1.20 [95% CI 0.86, 1.67], *P* for interaction = 0.04 [21]; SUSTAIN-6: 1.00 [0.41, 2.46], *P* for interaction = 0.49 [22]) (Fig. 1). These data also suggest that the GLP-1 RAs may exert their cardiovascular outcome benefits solely in those with prevalent macrovascular disease. Even the thiazolidinedione pioglitazone, which has been shown to have favorable effects on atherosclerotic end points in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) (26) and Insulin Resistance Intervention after Stroke (IRIS) (27) trial, has been tested solely in those with preexisting macrovascular complications. Accordingly, it can be confidently stated that metformin remains the only diabetes drug with clear cardiovascular benefits demonstrated in individuals without known CVD. Therefore, its fundamental position as the preferred initial glucose-lowering therapy for patients with type 2 diabetes remains deeply rooted.

Another concern is the adverse effect profile of any medication, particularly those used in chronic disease management. Other than metformin's well-recognized gastrointestinal side effects, which are typically self-limited and often mitigated by use of extended-release formulations (28), it is exceedingly well tolerated and, as mentioned, has been in widespread use for more the two decades in the U.S. The very rare complication of lactic acidosis is likely to occur only in those taking the drug in spite of prevailing contraindications, especially renal failure (29). Additionally, as mentioned, the drug is now being proposed as a diabetes prevention agent (15) and prescribing guidelines in those with mild to moderate CKD have recently been relaxed (Fig. 2) (18), which both attest to the safety of this compound.

In contrast, with newer agents, by definition, there is less information available concerning long-term toxicities. SGLT2 inhibitors appear to be reasonably well tolerated except for genitourinary infections, but they have been in wide use for less than 5 years. They now appear to increase the risk of diabetic ketoacidosis, a rare but potentially serious complication that we are still trying to understand (30). The

LEADER	*N*	Liraglutide	Placebo	HR (95% CI)	*P* for interaction
≥50 years old with established CVD	7,598	536/3,831 (14.0%)	629/3,767 (16.7%)	0.83 (0.74, 0.93)	0.04
≥60 years old and CVD risk factors	1,742	72/837 (8.6%)	65/905 (7.2%)	1.20 (0.86, 1.67)	
SUSTAIN-6	*N*	Semaglutide	Placebo	HR (95% CI)	*P* for interaction
≥50 years old with established CVD	2,735	98/1,353 (5.4%)	137/1,382 (9.9%)	0.72 (0.55, 0.93)	0.49
≥60 years old and CVD risk factors	562	10/295 (3.4%)	9/267 (3.4%)	1.00 (0.41, 2.46)	

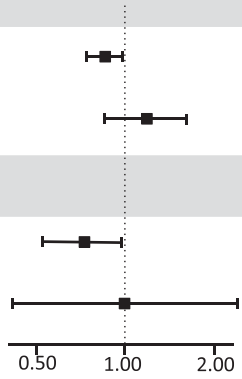

Figure 1—Point estimates for primary outcome treatment effect in LEADER and SUSTAIN-6 by subgroups of baseline CVD status. HRs for the primary outcome were >1.00 in participants enrolled with CVD risk factors only (i.e., no established CVD) in these trials. Such data suggest that the cardiovascular benefits of these GLP-1 RAs (liraglutide in LEADER and semaglutide in SUSTAIN-6) were restricted to those participants with established CVD, calling into question their role in primary prevention.

GLP-1 RAs have been available for nearly a decade but in more limited use and are associated with substantial rates of nausea. Initial concerns about carcinogenesis appear to be diminishing (31), but additional long-term safety data are still needed.

Finally, the current relative annual cost differences between metformin (<$50), SGLT2 inhibitors (~$4,800), and GLP-1 RAs (~$9,300) are striking (32). With hundreds of billions of dollars already spent in the U.S. on the management of diabetes, it is critical that we favor the most cost-effective options in the absence of compelling data dictating a different approach. Were these newer categories to be used as initial therapy for all 29 million Americans with diabetes (admittedly an extreme case used for illustrative purposed only), costs to the health care system might range up to $139 to $270 billion dollars—clearly unreasonable. If both categories were used in tandem, as some have proposed, the combined costs could easily exceed the total expenditures for all retail prescription drugs in the U.S. as of 2014 (33)! Our group recently reported that while spending on diabetes medications has increased dramatically over the past decade, the mean HbA_{1c} and rates of hypoglycemia have not changed appreciably (12). These data suggest, at the very least, that the value of diabetes therapy must be carefully considered, especially if any major changes in traditional strategies are being contemplated.

Instead, as endorsed by the American Diabetes Association and European Association for the Study of Diabetes (13), SGLT2 inhibitors and GLP-1 RAs are reasonable options after metformin monotherapy no longer adequately controls HbA_{1c}. Indeed, some members of these drug categories may be the preferred agents in this setting in patients with established CVD, as suggested by the aforementioned trials.

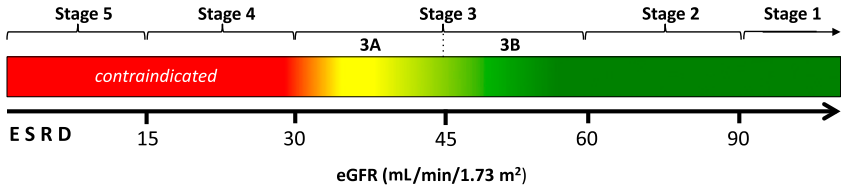

Figure 2—Recently updated U.S. Food and Drug Administration guidelines for the use of metformin in CKD. Metformin may now be used in patients with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 but is contraindicated in those with an eGFR <30 mL/min/1.73 m^2. If eGFR falls <45 mL/min/1.73 m^2, the benefits and risks of continuing treatment should be assessed. Starting metformin in patients with an eGFR between 30 and 45 mL/min/1.73 m^2 is not recommended. ESRD, end-stage renal disease.

In order to replace metformin as the preferred initial drug in type 2 diabetes, a head-to-head trial with the proposed agent would need to be conducted, assessing the relative effects on glycemia and both macrovascular and microvascular outcomes. Given the likely underlying cardiovascular benefits of metformin, however, such a study would probably need to involve tens of thousands of patients and extend well beyond 5 years. Some trialists would view this as impractical from both a cost and logistical standpoint. The majority of the long-term diabetes treatment trials currently underway consist of other cardiovascular outcome studies of similar design to EMPA-REG OUTCOME, LEADER, and SUSTAIN-6, testing the investigational agent versus placebo upon background therapy (34). They therefore will not provide relevant information as to the preferred monotherapy for type 2 diabetes. One exception is a trial comparing the DPP-4 inhibitor linagliptin to the sulfonylurea glimepiride, but also upon background glucose-lowering therapy that will likely commonly involve metformin (35). The National Institutes of Health's Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) trial is testing mainly the durability of several options added to metformin (glimepiride, sitagliptin, liraglutide, and insulin glargine) (36). By definition, all GRADE participants, per protocol, will already be on metformin monotherapy. The study is also not powered to adequately assess for important long-term complications, such as CVD. Notably, an important second-line category, SGLT2 inhibitors, a member

of which is now indicated for the prevention of cardiovascular death in patients with type 2 diabetes and CVD, are not represented because they became available in the U.S. after the trial had started. Thus, GRADE will also not be able to inform on this specific debate.

In summary, based on the medical community's extensive experience and the drug's demonstrated efficacy, safety, low cost, and cardiovascular benefits, metformin should remain the "foundation therapy" for all patients with type 2 diabetes, barring contraindications. There is no convincing evidence at the present time to consider any other approach.

Duality of Interest. S.E.I. reports serving on clinical trial steering/executive/publications committees for AstraZeneca, Boehringer Ingelheim, and Daiichi Sankyo; serving on data-monitoring committees for Novo Nordisk and Intarcia; and serving as a consultant to Janssen, Lexicon, Merck, Sanofi, and vTv Therapeutics. No other potential conflicts of interest relevant to this article were reported.

References

1. Hundal RS, Krssak M, Dufour S, et al. Mechanism by which metformin reduces glucose production in type 2 diabetes. Diabetes 2000;49:2063–2069
2. Madiraju AK, Erion DM, Rahimi Y, et al. Metformin suppresses gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase. Nature 2014;510:542–546
3. Buse JB, DeFronzo RA, Rosenstock J, et al. The primary glucose-lowering effect of metformin resides in the gut, not the circulation: results from short-term pharmacokinetic and 12-week dose-ranging studies. Diabetes Care 2016;39:198–205
4. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998;352:854–865
5. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–853
6. Kooy A, de Jager J, Lehert P, et al. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. Arch Intern Med 2009;169:616–625
7. Hong J, Zhang Y, Lai S, et al.; SPREAD-DIMCAD Investigators. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. Diabetes Care 2013;36:1304–1311
8. Roumie CL, Hung AM, Greevy RA, et al. Comparative effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events in type 2 diabetes mellitus: a cohort study. Ann Intern Med 2012;157:601–610
9. Johnson JA, Majumdar SR, Simpson SH, Toth EL. Decreased mortality associated with the use of metformin compared with sulfonylurea monotherapy in type 2 diabetes. Diabetes Care 2002; 25:2244–2248
10. Claesen M, Gillard P, De Smet F, Callens M, De Moor B, Mathieu C. Mortality in individuals treated with glucose-lowering agents: a large, controlled cohort study. J Clin Endocrinol Metab 2016;101:461–469
11. Anabtawi A, Miles JM. Metformin: nonglycemic effects and potential novel indications. Endocr Pract 2016;22:999–1007
12. Lipska KJ, Yao X, Herrin J, et al. Trends in drug utilization, glycemic control, and rates of severe hypoglycemia, 2006–2013. Diabetes Care 2017; 40:468–475
13. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140–149
14. International Diabetes Federation. Global guideline for type 2 diabetes. Available from https://www.idf.org/e-library/guidelines/79-global-guideline-for-type-2-diabetes.html. Accessed 6 November 2016
15. American Diabetes Association. Prevention or delay of type 2 diabetes. Sec. 5. In *Standards of Medical Care in Diabetes—2017*. Diabetes Care 2017;40(Suppl. 1):S44–S47
16. Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403
17. Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. Lancet Diabetes Endocrinol 2015;3:866–875
18. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA revises warnings regarding use of the diabetes medicine metformin in certain patients with reduced kindey function [Internet]. Available from http://www.fda.gov/Drugs/DrugSafety/ucm493244.htm. Accessed 29 October 2016
19. Flory JH, Hennessy S. Metformin use reduction in mild to moderate renal impairment: possible inappropriate curbing of use based on Food and Drug Administration contraindications. JAMA Intern Med 2015;175:458–459
20. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128
21. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and CV outcomes in type 2 diabetes. N Engl J Med 2016;375:311–322
22. Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834–1844
23. Wanner C, Inzucchi SE, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375:323–334
24. Maruthur NM, Tseng E, Hutfless S, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2016;164:740–751
25. Sattar N, McLaren J, Kristensen SL, PreissD, McMurray JJ. SGLT2 inhibition and CV events: why did EMPA-REG Outcomes surprise and what were the likely mechanisms? Diabetologia 2016; 59:1333–1339
26. Dormandy JA, Charbonnel B, Eckland DJ, et al.; PROactive Investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005;366:1279–1289
27. Kernan WN, Viscoli CM, Furie KL, et al.; IRIS Trial Investigators. Pioglitazone after ischemic stroke or transient ischemic attack. N Engl J Med 2016;374:1321–1331
28. Ali S, Fonseca V. Overview of metformin: special focus on metformin extended release. Expert Opin Pharmacother 2012;13:1797–1805
29. Inzucchi SE, Lipska KJ, Bailey CJ, McGuire DK. Metformin in type 2 diabetes patients with kidney disease: a systematic review. JAMA 2014;312: 2668–2675
30. Goldenberg RM, Berard LD, Cheng AY, et al. SGLT2 inhibitor-associated diabetic ketoacidosis: clinical review and recommendations for prevention and diagnosis. Clin Ther 2016; 38:2654–2664.e1
31. Nauck MA, Friedrich N. Do GLP-1–based therapies increase cancer risk? Diabetes Care 2013;36 (Suppl. 2):S245–S252
32. GoodRx. Stop paying too much for your prescriptions [Internet]. Available from https://www.goodrx.com. Accessed 6 November 2016
33. U.S. Centers for Medicare & Medicaid Services. National health expenditures 2015 highlights [Internet]. Available from https://www.cms.gov/research-statistics-data-and-systems/statistics-trends-and-reports/nationalhealthexpenddata/downloads/highlights.pdf. Accessed 6 November 2016
34. Holman RR, Sourij H, Califf RM. Cardiovascular outcome trials of glucose-lowering drugs or strategies in type 2 diabetes. Lancet 2014;383: 2008–2017
35. Marx N, Rosenstock J, Kahn SE, et al. Design and baseline characteristics of the CARdiovascular Outcome Trial of LINAgliptin Versus Glimepiride in Type 2 Diabetes (CAROLINA®). Diab Vasc Dis Res 2015;12:164–174
36. The George Washington University Biostatistics Center. Glycemia Reduction Approches in Diabetes: A Comparative Effectiveness Study (GRADE) [Internet]. Available from https://portal.bsc.gwu.edu/web/grade. Accessed 6 November 2016