

Spotlight on Antidiabetic Agents with Cardiovascular or Renoprotective Benefits

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ABSTRACT

Type 2 diabetes mellitus often goes hand in hand with cardiovascular and renal comorbidities. Stroke, myocardial infarction, heart failure, and chronic kidney disease are high-risk complications of type 2 diabetes that contribute to morbidity and mortality. Recent clinical trials have uncovered evidence that certain antidiabetic agents may confer cardiovascular and/or renal benefits such as reduced cardiovascular and all-cause mortality and reduced need for renal replacement therapy. Two landmark trials in particular, EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) and LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), demonstrated the cardioprotective and/or renoprotective effects of empagliflozin and liraglutide, respectively. These trials led to new US Food and Drug Administration indications for empagliflozin and liraglutide as risk reduction for major cardiovascular events in adults with type 2 diabetes and established cardiovascular disease. Other trials are under way to determine whether these benefits are class effects and what other agents may have a role in risk reduction for cardiovascular and renal disease. This review will summarize the evidence for noninsulin antidiabetic drugs with benefits beyond glycemic control, discuss proposed mechanisms for these effects, and consider their place in therapy.

INTRODUCTION

Type 2 diabetes mellitus is a known risk factor for cardiovascular disease (CVD) and chronic kidney disease (CKD), as well as a major contributor to morbidity and mortality. The alluring possibility of antidiabetic agents with protective cardiac and renal effects is the subject of several recent trials. Two landmark trials, EMPA-REG OUTCOME (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) and LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), demonstrated the cardiovascular (CV) and renal benefits of empagliflozin, a sodium-glucose cotransporter-2 (SGLT-2) inhibitor, and the CV benefits of liraglutide, a glucagon-like peptide-1 receptor (GLP-1) agonist. Table 1 (available online at: www.thepermanentejournal.org/files/2018/18-034-Table.pdf) summarizes the dosing, mechanisms, expected hemoglobin A_{1c} (HbA_{1c}) lowering, advantages and disadvantages, and evidence for cardiac and/or renal benefits of these 2 agents, as well as the other mainline noninsulin treatments of diabetes.

EMPA-REG OUTCOME TRIAL

The EMPA-REG OUTCOME trial assessed whether patients with type 2 diabetes at high risk of CV events may see a reduction in CV mortality, nonfatal myocardial infarction (MI), or nonfatal stroke when treated with empagliflozin added to standard care (statins, renin-angiotensin-aldosterone system inhibitors, and aspirin).¹ This multicenter, double-blind, placebo-controlled trial randomly assigned 7020 patients to receive empagliflozin, 10 mg; empagliflozin, 25 mg; or placebo daily for a 3.1-year follow-up period. Empagliflozin was associated with significant reductions in the composite of CV mortality, nonfatal MI, or nonfatal stroke (10.5% vs 12.1%; hazard ratio [HR] = 0.86, 95% confidence interval [CI] = 0.74-0.99; $p = 0.04$), CV mortality (3.7% vs 5.9%; HR = 0.62, 95% CI = 0.49-0.77; $p < 0.001$), heart failure hospitalization (2.7% vs 4.1%; HR = 0.65, 95% CI = 0.50-0.85; $p = 0.002$), and all-cause mortality (5.7% vs 8.3%; HR = 0.68, 95% CI = 0.57-0.82; $p < 0.001$). Empagliflozin did not reduce the risk of nonfatal MI or stroke individually. Compared with placebo, both empagliflozin groups had significantly higher rates of genital infections, a class effect stemming from SGLT-2 inhibitors' augmentation of the urinary excretion of glucose, which increases the risk of genital microorganism growth. A secondary outcomes analysis of the trial also found empagliflozin to be associated with a reduction in incident or worsening nephropathy (12.7% vs 18.8%; HR = 0.61, 95% CI = 0.53-0.70; $p < 0.001$), doubling of serum creatinine (1.5% vs 2.6%; HR = 0.56, 95% CI = 0.39-0.79; $p < 0.001$), and renal replacement therapy (0.3% vs 0.6%; HR = 0.45, 95% CI = 0.21-0.97; $p = 0.03$).²

LEADER TRIAL

The LEADER trial assessed similar CV endpoints for liraglutide added to the standard of care in patients with type 2 diabetes.³ This multicenter, double-blind, placebo-controlled trial randomly assigned 9340 patients with type 2 diabetes and high CV risk to liraglutide, 1.8 mg (or maximum tolerated dose), or placebo administered subcutaneously daily for a 3.8-year follow-up period. Liraglutide demonstrated reductions in the composite of first occurrence of CV mortality, nonfatal MI, or nonfatal stroke (13% vs 14.9%; HR = 0.87, 95% CI = 0.78-0.97; $p < 0.001$ for noninferiority; $p = 0.01$ for superiority), CV mortality (4.7% vs 6.0%; HR = 0.78, 95% CI = 0.55-0.93; $p = 0.007$), and all-cause mortality (8.2% vs 9.6%; HR = 0.85, 95% CI = 0.74-0.97; $p = 0.02$). Liraglutide was also associated

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with reduced nephropathy compared with placebo (5.7% vs 7.2%; HR = 0.78, 95% CI = 0.67-0.92; $p = 0.003$). Nonfatal MI, nonfatal stroke, and heart failure hospitalization rates were all nonsignificantly lower with liraglutide. In terms of adverse events, liraglutide had significantly higher rates of gastrointestinal side effects, acute cholecystitis, and injection site reactions compared with placebo.

MECHANISMS OF CARDIOVASCULAR AND RENOPROTECTIVE EFFECTS

The mechanisms behind these CV and renoprotective effects remain speculative. Empagliflozin's beneficial cardiac effects may in part be caused by a reduction in cardiac workload and myocardial oxygen consumption.^{4,5} The drug's capacity for modest blood pressure lowering, reduced arterial stiffness and vascular resistance, and its mild diuresis and natriuretic activity leading to weight loss are proposed hemodynamic explanations.^{4,8} Empagliflozin's renal benefits may be related to a reduction in glomerular hyperfiltration (which, in turn, reduces albuminuria), as well as improvements in intraglomerular hypertension through reduced vascular stiffness.^{4,5,7-9} Liraglutide's cardioprotective mechanism is even more elusive. It may be related to a reduced progression of atherosclerotic disease through the modulation of weight, blood pressure, lipids, and other metabolic factors.⁶ It is unclear from the LEADER findings alone whether liraglutide truly improves renal outcomes and, if so, by what mechanism.

OTHER DRUGS WITH CARDIOPROTECTIVE OR RENOPROTECTIVE EFFECTS

To date, empagliflozin and liraglutide are the only antidiabetic agents to earn US Food and Drug Administration indications for risk reduction of major CV events in adults with type 2 diabetes and established CVD. Trials are currently under way to determine whether these may be class effects and if antidiabetic agents from other classes confer similar benefits.

CANVAS (Canagliflozin Cardiovascular Assessment Study), a multicenter, placebo-controlled, randomized trial with 10,142 participants and a mean follow-up of 3.6 years, found that canagliflozin may reduce both CV and renal events in subjects with type 2 diabetes and high CV risk.¹⁰ In CANVAS, participants receiving canagliflozin had a risk reduction in the composite of death owing to CV causes, nonfatal MI, or nonfatal stroke (26.9% vs 31.5%; HR = 0.86, 95% CI = 0.75-0.97; $p < 0.001$ for noninferiority, $p = 0.02$ for superiority) compared with placebo. The prespecified criteria for renal outcomes did not meet statistical significance; however, there was the suggestion of a potential reduction in the progression of albuminuria (HR = 0.73, 95% CI = 0.67-0.79) and the composite outcome of sustained 40% reduction in estimated glomerular filtration rate, need for renal replacement therapy, or death owing to renal causes (HR = 0.60, 95% CI = 0.47-0.77). In addition to the previously described adverse effects associated with SGLT-2 inhibitors, canagliflozin recipients also experienced a higher rate of amputations, primarily of the toe or metatarsal, compared with placebo (6.3 vs 3.4 subjects per 1000 patient-years; HR = 1.97, 95% CI = 1.41-2.75). This finding led to a boxed warning of

lower limb amputation for canagliflozin. Empagliflozin and dapagliflozin have not been found to increase amputation risk and do not display this boxed warning.

A 2018 systematic review and meta-analysis included 35 randomized, placebo-controlled trials of SGLT-2 inhibitors (which included EMPA-REG OUTCOME and CANVAS) in nearly 35,000 subjects with type 2 diabetes. The review authors concluded that, as a class, SGLT-2 inhibitors reduce all-cause mortality (odds ratio [OR] = 0.79, 95% CI = 0.70-0.89; $p < 0.001$), major cardiac adverse events (OR = 0.8, 95% CI = 0.76-0.92; $p < 0.001$), nonfatal MI (OR = 0.85, 95% CI = 0.73-0.98; $p = 0.03$), and heart failure/hospitalization for heart failure (OR = 0.67, 95% CI = 0.59-0.76; $p < 0.001$) compared with placebo.¹¹ The review found no difference in risk reduction among all 3 SGLT-2 inhibitors tested (empagliflozin, canagliflozin, and dapagliflozin).¹¹

Evidence for CV and renal risk reduction as a possible class effect for GLP-1 agonists is less robust than for SGLT-2 inhibitors. To date, semaglutide, a recently approved GLP-1 agonist for the treatment of type 2 diabetes, is the only GLP-1 agonist with demonstrated CV and renal benefits.¹² In its preapproval noninferiority study, semaglutide demonstrated a lower risk of first occurrence of CV death, nonfatal MI, or nonfatal stroke compared with placebo (6.6% vs 8.9%; HR = 0.74, 95% CI = 0.58-0.95; $p < 0.001$). Semaglutide also lowered the risk of new or worsening nephropathy (3.8% vs 6.1%; HR = 0.64, 95% CI = 0.46-0.88; $p = 0.005$) compared with placebo. In randomized, placebo-controlled trials, 2 other GLP-1 agonists, exenatide and lixisenatide, did not demonstrate renal or CV benefits.^{13,14}

Pioglitazone, a thiazolidinedione, has also demonstrated a trend toward CV risk reduction in 2 trials, IRIS (Insulin Resistance Intervention After Stroke) and PROactive (PROspective pioglitazone Clinical Trial in macroVascular Events).¹⁵⁻¹⁷ In the IRIS trial, 3876 nondiabetic individuals with demonstrated insulin resistance and a recent stroke or transient ischemic attack were randomly assigned to receive either pioglitazone or placebo.¹⁵ Participants were allowed to use other CV risk-modifying therapies such as antihypertensive agents, antiplatelet agents, and statins in addition to their study drug. After a 4.8-year follow-up period, pioglitazone reduced the composite risk of fatal or nonfatal stroke or MI (9.0% vs 11.8%; HR = 0.76, 95% CI = 0.62-0.93; $p = 0.007$). There was no difference in all-cause mortality between pioglitazone and placebo. A secondary analysis of the IRIS trial also found that, compared with placebo, pioglitazone reduced the composite risk of acute coronary syndrome, defined as MI or unstable angina (4.3% vs 6.0% HR = 0.71; 95% CI = 0.54-0.94; $p = 0.02$).¹⁶ The study was not powered to detect whether pioglitazone reduced the risk of unstable angina or MI individually. Whether these findings are applicable to patients with type 2 diabetes—a population that was excluded from the IRIS trial—remains to be seen.

PROactive, a prospective, placebo-controlled, randomized trial of 5238 patients with type 2 diabetes and evidence of macrovascular disease, found that pioglitazone added to standard diabetes treatment (antidiabetic agents with or without insulin,

statins, antihypertensive agents, and antiplatelet agents) for a mean follow-up of 2.9 years did not reach statistical significance for its primary endpoint.¹⁷ The primary endpoint was a composite of all-cause mortality, MI, acute coronary syndrome, coronary intervention, major leg amputation, bypass surgery, or leg revascularization. However, pioglitazone did reduce the risk of the secondary endpoint, the composite of all-cause mortality, nonfatal MI, or nonfatal stroke (11.6% vs 13.6%; HR = 0.84, 95% CI = 0.72-0.98; $p = 0.02$). Antiatherogenic effects and improvements in insulin resistance are proposed mechanisms for pioglitazone's potential cardioprotective effects.^{16,17} More trials are needed to assess whether pioglitazone truly reduces CV risk and whether these results still apply in diabetic patients in whom macrovascular disease has not yet developed.

There are trends toward CV and/or renal protection seen with other antidiabetic agents, including metformin, sulfonylureas, and dipeptidyl peptidase-4 inhibitors. However, the data for these agents are mixed and would need further evaluation in clinical trials. Table 1 includes a summary of the possible cardiac and/or renal protective effects of these agents.

EMPAGLIFLOZIN AND LIRAGLUTIDE: PLACE IN THERAPY

The American Diabetes Association's 2018 Standards of Medical Care in Diabetes guidelines recommend metformin as the first-line treatment of type 2 diabetes.¹⁸ Clinicians are encouraged to consider insulin in patients with a new diagnosis of type 2 diabetes who are symptomatic and/or have a HbA_{1c} at or above 10%. Clinicians should also consider initiating dual therapy in patients with a new diagnosis and a HbA_{1c} of 9% or higher. The American Diabetes Association guidelines make a Level A (highest level) recommendation that patients with type 2 diabetes and established atherosclerotic CVD are treated first with metformin and lifestyle management, and subsequently with an antidiabetic agent that has demonstrated CV benefits (empagliflozin or liraglutide). Canagliflozin is named as an alternative to empagliflozin or liraglutide that can be considered for CV risk reduction, although this is a Level C recommendation, meaning that its evidence comes from poorly controlled or uncontrolled studies.

There are notable advantages and disadvantages to empagliflozin and liraglutide. In terms of HbA_{1c} lowering, empagliflozin and liraglutide are not the most potent antidiabetic agents. The SGLT-2 inhibitors lower HbA_{1c} by a mean 0.5% to 1%, and GLP-1 agonists lower HbA_{1c} between 0.5% and 1.5%. Metformin, sulfonylureas, and thiazolidinediones each produce, on average, a stronger HbA_{1c} lowering of 1% to 1.5%. Although SGLT-2 inhibitors carry a low risk of hypoglycemia and can confer modest weight loss and blood pressure-lowering effects, they also increase the risk of genitourinary infections, bone fractures (canagliflozin), amputations (canagliflozin), and diabetic ketoacidosis. They should be avoided in patients with existing moderate-to-severe renal impairment and are contraindicated when the estimated glomerular filtration rate is below 30. They carry a US Food and Drug Administration warning for acute kidney injury, which in EMPA-REG OUTCOME stabilized in about 4 weeks.¹ Such GLP-1 agonists as liraglutide also carry

a low risk of hypoglycemia and are sometimes used for their effects on weight loss. Most, such as liraglutide and semaglutide, can be used in patients with renal impairment, although data for their use in CKD Stages 4 and 5 are limited. The GLP-1 agonists carry a boxed warning for thyroid C-cell tumor risk (a finding seen in rats and mice) and are contraindicated in patients with a personal or family history of medullary thyroid carcinoma. Additionally, GLP-1 agonists may increase the risk of cholecystitis and pancreatitis.

Empagliflozin and liraglutide are high-cost agents. At the time of this writing, the average wholesale price of empagliflozin, whose formulary status varies by Kaiser Permanente Region, is roughly \$558 for a 30-day supply. Liraglutide, which is currently nonformulary for most Kaiser Permanente Regions, costs between \$645 and \$968 for a 30-day supply. Some pharmacoeconomic studies have suggested that both empagliflozin and liraglutide may be cost-effective adjuncts when added to standard care for type 2 diabetes.^{19,20} Using a Markov model, empagliflozin was estimated to result in higher total lifetime treatment costs (\$371,450 vs \$272,966) but greater quality-adjusted life-years (10.712 vs 9.419) compared with standard treatment without empagliflozin.¹⁹ This finding was based on a willingness-to-pay threshold of \$100,000 for each additional quality-adjusted life-year, which would make empagliflozin use for such patients cost-effective in 96% of 10,000 iterations. A systematic review of pharmacoeconomic studies of liraglutide as an adjunct for type 2 diabetes estimated liraglutide's probability of cost-effectiveness to be 58% compared with sitagliptin (a dipeptidyl peptidase-4 inhibitor) and 93% compared with glimepiride (a sulfonylurea).²⁰ It is difficult to conclude that liraglutide is a cost-effective adjunct across the board because not all studies included patients with high CV risk, the incremental cost-effectiveness ratios were based on projections of liraglutide's long-term benefits, and these studies hailed from health systems across the globe and had to be converted into US dollars for comparison.

Ultimately, we lack long-term data directly comparing the efficacy, safety, and cost-effectiveness of our many second-line antidiabetic agents (GLP-1 agonists, SGLT-2 inhibitors, sulfonylureas, thiazolidinediones, and dipeptidyl peptidase-4 inhibitors). GRADE (Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study), a randomized controlled trial of an estimated 5000 individuals with type 2 diabetes, is currently under way to compare long-term outcomes for people who are already receiving metformin and are randomly assigned to 1 of 4 add-on treatments: Glimepiride, sitagliptin, liraglutide, or insulin glargine.²¹ Participants will be followed-up for as long as 7 years to assess which of these agents, when added to metformin, confers the best glycemic control, is the most tolerable, and offers the best overall health benefits for people with type 2 diabetes. Unfortunately, the study does not include any SGLT-2 inhibitors in its analysis because they were not yet available in the US at study initiation. The estimated primary completion date is July 2021. In the meantime, formulary status and cost considerations of antidiabetic agents should be taken into consideration along with the projected risks vs benefits for individual patients.

CONCLUSION

At this time, empagliflozin and liraglutide are the antidiabetic agents with the most robust evidence for lowering CV and/or renal risk in patients with type 2 diabetes and established CVD. As this population ages, additional comorbidities will develop in many that will further elevate their risk of major CV events and CKD. In our stride toward individualized medicine, the opportunity to offer our patients diabetes treatments with potential morbidity benefits that transcend glycemic control is exciting. Depending on what ongoing and future trials uncover, it may be the way of the future. ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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References

- 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 Nov 26;373(22):2117-28. DOI: <https://doi.org/10.1056/NEJMoa1504720>.
- 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 Jul 28;375(4):323-34. DOI: <https://doi.org/10.1056/NEJMoa1515920>.
- Marso SP, Daniels GH, Brown-Frandsen K, et al; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016 Jul 28;375(4):311-22. DOI: <https://doi.org/10.1056/NEJMoa1603827>.
- Trujillo JM, Nuffer WA. Impact of sodium-glucose cotransporter 2 inhibitors on nonglycemic outcomes in patients with type 2 diabetes. *Pharmacotherapy* 2017 Apr;37(4):481-91. DOI: <https://doi.org/10.1002/phar.1903>.
- Kashiwagi A, Maegawa H. Metabolic and hemodynamic effects of sodium-dependent glucose cotransporter 2 inhibitors on cardio-renal protection in the treatment of patients with type 2 diabetes mellitus. *J Diabetes Investig* 2017 Jul;8(4):416-27. DOI: <https://doi.org/10.1111/jdi.12644>.
- Paneni F, Lüscher TF. Cardiovascular protection in the treatment of type 2 diabetes: A review of clinical trial results across drug classes. *Am J Cardiol* 2017 Jul 1;120(1S):S17-S27. DOI: <https://doi.org/10.1016/j.amjcard.2017.05.015>.
- Wanner C. EMPA-REG OUTCOME: The nephrologist's point of view. *Am J Cardiol* 2017 Jul 1;120(1S):S59-S67. DOI: <https://doi.org/10.1016/j.amjcard.2017.05.012>.
- Scheen AJ. Pharmacodynamics, efficacy and safety of sodium-glucose co-transporter type 2 (SGLT2) inhibitors for the treatment of type 2 diabetes mellitus. *Drugs* 2015 Jan;75(1):33-59. DOI: <https://doi.org/10.1007/s40265-014-0337-y>.
- Pecoits-Filho R, Perkovic V. Are SGLT2 inhibitors ready for prime time for CKD? *Clin J Am Soc Nephrol* 2018 Feb 7;13(2):318-20. DOI: <https://doi.org/10.2215/CJN.07680717>.
- Neal B, Perkovic V, Mahaffey KW, et al; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017 Aug 17;377(7):644-57. DOI: <https://doi.org/10.1056/nejmoa1611925>.
- Usman MS, Siddiqi TJ, Memon MM, et al. Sodium-glucose co-transporter 2 inhibitors and cardiovascular outcomes: A systematic review and meta-analysis. *Eur J Prev Cardiol* 2018 Mar;25(5):495-502. DOI: <https://doi.org/10.1177/2047487318755531>.
- Marso SP, Bain SC, Conzoli A, et al; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016 Nov 10;375(19):1834-44. DOI: <https://doi.org/10.1056/NEJMoa1607141>.
- Holman RR, Bethel MA, Mentz RJ, et al; EXSCEL Study Group. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2017 Sep 28;377(13):1228-39. DOI: <https://doi.org/10.1056/NEJMoa1612917>.
- Pfeffer MA, Claggett B, Diaz R, et al; ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med* 2015 Dec 3;373(23):2247-57. DOI: <https://doi.org/10.1056/NEJMoa1509225>.
- Kernan WN, Viscoli CM, Furie KL, et al. Pioglitazone after ischemic stroke or transient ischemic attack. *N Engl J Med* 2016 Apr 7;374(14):1321-31. DOI: <https://doi.org/10.1056/NEJMoa1506930>.
- Young LH, Viscoli CM, Curtis JP, et al; IRIS Investigators. Cardiac outcomes after ischemic stroke or transient ischemic attack: Effects of pioglitazone in patients with insulin resistance without diabetes mellitus. *Circulation* 2017 May 16;135(20):1882-93. DOI: <https://doi.org/10.1161/circulationaha.116.024863>.
- 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 Oct 8;366(9493):1279-89. DOI: [https://doi.org/10.1016/S0140-6736\(05\)67528-9](https://doi.org/10.1016/S0140-6736(05)67528-9).
- American Diabetes Association. Standards of medical care in diabetes—2018: Cardiovascular disease and risk management. *Diabetes Care* 2018 Jan;41 (Suppl 1):S86-S104. DOI: <https://doi.org/10.2337/dc18-S009>.
- Nguyen E, Coleman CI, Nair S, Weeda ER. Cost-utility of empagliflozin in patients with type 2 diabetes at high cardiovascular risk. *J Diabetes Complications* 2018 Feb;32(2):210-15. DOI: <https://doi.org/10.1016/j.jdiacomp.2017.10.006>.
- Zueger PM, Schultz NM, Lee TA. Cost effectiveness of liraglutide in type II diabetes: A systematic review. *Pharmacoeconomics* 2014 Nov;32(11):1079-91. DOI: <https://doi.org/10.1007/s40273-014-0192-4>.
- GRADE Study Group. A comparative effectiveness study of major glycemia-lowering medications for treatment of type 2 diabetes (GRADE). NCT01794143 [Internet]. Washington, DC: US National Library of Medicine; 2013 Feb 18 [updated 2018 Mar 30; cited 2018 May 25]. Available from: <https://clinicaltrials.gov/ct2/show/study/NCT01794143>.

Tomorrow

The church and the law deal with the yesterdays of life; medicine deals with the tomorrows.

— William J Mayo, MD, 1861-1939, American physician and surgeon, cofounder of the Mayo Clinic