DIABETES MEDICATIONS AND CARDIOVASCULAR IMPACT

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Diabetes Medications and Cardiovascular Impact

Type 2 diabetes is a known risk factor for cardiovascular disease.[1,2] In addition, the combination of diabetes and cardiovascular disease increases the risk of death.[3] When considering glucose-lowering potential, side effects, cost, and outcomes; metformin remains the optimal first-line oral agent in the management of type 2 diabetes for most patients.[4,5] For a complete listing of available diabetes medications including expected A1C lowering and adverse effects see our charts, *Drugs for Type 2 Diabetes* (U.S.) and *Stepwise Treatment of Type 2 Diabetes* (Canada). In 2008, the FDA issued guidance for evaluating cardiovascular risk of medications used to manage type 2 diabetes.[19] Since then, studies are evaluating cardiovascular outcomes associated with diabetes medications. These studies will assist in prioritizing add-on medications choices for diabetes management. The chart below summarizes the existing cardiovascular outcome data for medications used to treat type 2 diabetes.

Cardiovascular impact definitions listed in the chart include:

- Unknown = cardiovascular outcome data is currently unavailable.
- Improves Outcomes = published data demonstrates cardiovascular benefit with use in the treatment of type 2 diabetes.
- Worsens Outcomes = published data demonstrates cardiovascular harm with use in the treatment of type 2 diabetes.
- Neutral = published data demonstrates neither benefit nor harm in cardiovascular endpoints with use in the treatment of type 2 diabetes.

Abbreviations: ACS = acute coronary syndrome; CV = cardiovascular; DM = diabetes mellitus; MI = myocardial infarction.

Medications[a]	Cardiovascular Impact	Cardiovascular Outcomes Data
Alpha-glucosidase inhibitors • Acarbose (e.g., *Precose* [U.S.], *Glucobay* [Canada]) • Miglitol (e.g., *Glyset* [U.S.])	Unknown: • Acarbose • Miglitol	• **Acarbose:** The ACE (Acarbose Cardiovascular Evaluation) trial (NCT00829660) is ongoing to evaluate if acarbose reduces CV morbidity and mortality in patients with impaired glucose tolerance and established coronary heart disease or ACS.[18]
Amylin analog • Pramlintide (*SymlinPen* [U.S.])	Unknown: • Pramlintide	• **Pramlintide**: Unable to identify any published or ongoing trials evaluating CV impact.

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Medications[a]	Cardiovascular Impact	Cardiovascular Outcomes Data
Biguanide • Metformin (e.g., *Glucophage*, *Glycon* [Canada])	Improves Outcomes: • Metformin	• **Metformin**: A subanalysis of the UKPDS trial found good glycemic control with metformin with about 10 years of use MAY reduce the risk of CV mortality, especially in obese patients, NNT = 14 [Evidence level A; high-quality RCT].[21] ○ Pooled data demonstrate possible reduced CV mortality with a NNT = 56, compared to other DM medications or placebo [Evidence level A; high-quality meta-analysis].[15]
Dipeptidyl peptidase-4 (DPP-4) inhibitors • Alogliptin (e.g., *Nesina*) • Linagliptin (e.g., *Tradjenta* [U.S.]; *Trajenta* [Canada]) • Saxagliptin (e.g., *Onglyza*) • Sitagliptin (e.g., *Januvia*)	Worsens Outcomes: • Alogliptin • Saxagliptin Neutral: • Sitagliptin Unknown: • Linagliptin	• **Alogliptin**: The EXAMINE trial found alogliptin use in patients with type 2 DM and a history of a recent ACS, did not increase major adverse CV events, compared to placebo [Evidence level A; high-quality RCT].[10] ○ Alogliptin is associated with an increased risk of heart failure-related admissions, NNH = 167 [Evidence level A; high-quality RCT].[10] • **Saxagliptin**: The SAVOR-TIMI 53 found saxagliptin use in patients with type 2 DM at high risk for CV events; neither reduced nor increased the risk of CV death, MI, or ischemic stroke, compared to standard therapy [Evidence level A; high-quality RCT].[11] ○ Saxagliptin was associated with an increased risk of heart failure-related admissions, NNH = 143 [Evidence level A; high-quality RCT].[11] • **Sitagliptin**: The TECOS trial found adding sitagliptin to existing DM therapy did not increase the major adverse CV events, hospitalization for heart failure, or other adverse events compared to placebo [Evidence level A; high-quality RCT].[12] • **Linagliptin**: CAROLINA, CARdiovascular Outcome study of LINAgliptin versus glimepiride in patients with type 2 DM (NCT01243424) is ongoing to evaluate the long-term impact of linagliptin versus glimepiride on CV morbidity and mortality.[14]
Glucagon-like peptide-1 (GLP-1) receptor agonists • Albiglutide (e.g., *Tanzeum* [U.S.]) • Dulaglutide (e.g., *Trulicity*) • Exenatide (e.g., *Byetta*) *Continued…*	Unknown: • Albiglutide • Dulaglutide • Exenatide Improves Outcomes: • Liraglutide	• **Albiglutide**: HARMONY Outcomes (NCT02465515) is ongoing to evaluate the effects of adding albiglutide to standard blood glucose lowering therapies on major cardiovascular events.[22] • **Dulaglutide**: The REWIND (Researching Cardiovascular Events with a Weekly Incretin in Diabetes) trial (NCT01394952) is ongoing to evaluate if dulaglutide can reduce major CV events in patients with type 2 diabetes.[23] • **Exenatide**: The EXSCEL (Exenatide Study of Cardiovascular Events Lowering Trial) trial (NCT01144338) is ongoing to evaluate if exenatide added to usual care

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Medications[a]	Cardiovascular Impact	Cardiovascular Outcomes Data
GLP-1 agonists, continued • Liraglutide (e.g., *Victoza*, *Saxenda*[b]) • Lixisenatide (pending FDA approval; *Lyxumia*)	Neutral: • Lixisenatide	impacts CV outcomes in patients with type 2 diabetes.[24] • **Liraglutide**: The LEADER trial [Evidence level A; high-quality RCT] found adding liraglutide to standard care in patients with type 2 DM with CV disease or at high CV risk over almost four years may reduce:[13] o Death from CV causes, nonfatal MI, or nonfatal stroke, NNT = 53. o Death from CV causes, NNT = 77. o Death from any cause, NNT = 71. o Liraglutide did not reduce the individual rates of MI, nonfatal stroke, or hospitalization for heart failure. • **Lixisenatide**: The ELIXA trial found adding lixisenatide to conventional therapy in type 2 DM patients with a recent ACS had a neutral effect on CV outcomes.[29]
Insulin	Neutral: • Glargine	• **Glargine**: The ORIGIN trial found use of basal insulin glargine for over six years had a neutral effect on CV outcomes [Evidence level A; high-quality RCT].[6]
Meglitinides • Nateglinide (e.g., *Starlix* [U.S.]) • Repaglinide (e.g., *Prandin* [U.S.], *GlucoNorm* [Canada])	Unknown: • Nateglinide • Repaglinide	• **Nateglinide**: No outcome data for inpatients with type 2 DM. However, the NAVIGATOR trial found nateglinide use in patients with **impaired glucose tolerance** and at high risk for CV events had a neutral effect on cardiovascular outcomes [Evidence level A; high-quality RCT].[25]
Sodium-glucose co-transporter 2 (SGLT2) inhibitors • Canagliflozin (e.g., *Invokana*) • Dapagliflozin (e.g., *Farxiga* [U.S.], *Forxiga* [Canada]) • Empagliflozin (e.g., *Jardiance*) *Continued…*	Unknown: • Dapagliflozin Improves Outcomes: • Canagliflozin • Empagliflozin	• **Canagliflozin**: CANVAS (CANagliflozin cardioVascular Assessment Study) [Evidence level A; high-quality RCT] found canagliflozin use for about 3.5 years when added to standard glucose-lowering therapy in patients with type 2 diabetes and very high CV risk (>70% of patients had atherosclerotic CV disease), may reduce the combined endpoint of CV mortality, nonfatal MI, or nonfatal stroke (NNT=333). However, when evaluated individually, these endpoints were no longer significantly reduced.[20] • **Dapagliflozin**: DECLARE-TIMI58 (NCT01730534) is ongoing to evaluate the impact of adding dapagliflozin to current DM therapy on MI, ischemic stroke, and CV death.[26] • **Empagliflozin**: The EMPAG-REG OUTCOME trial [Evidence level A; high-quality RCT] found empagliflozin use for about three years, when added to standard glucose-lowering therapy in patients with type 2 DM and underlying CV

Medications[a]	Cardiovascular Impact	Cardiovascular Outcomes Data
SGLT2 inhibitors, continued		disease, may reduce:[7] ○ Hospitalization due to heart failure (NNT = 71). ○ CV death rates (NNT = 45). ○ Overall death rates (NNT = 39). ○ Empagliflozin did not reduce the individual rates of MI or stroke.
Sulfonylureas (first generation) • Chlorpropamide • Tolazamide • Tolbutamide	Unknown: • Chlorpropamide • Tolazamide Worsens Outcomes: • Tolbutamide	• **Tolbutamide**: use has been associated with increased CV mortality compared to diet alone or diet plus insulin.[16]
Sulfonylureas (second generation) • Gliclazide (Canada) • Glipizide • Glimepiride • Glyburide	Unknown: • Gliclazide • Glipizide • Glimepiride • Glyburide	• **Glimepiride**: CAROLINA, CARdiovascular Outcome study of LINAgliptin versus glimepiride in patients with type 2 DM (NCT01243424) is ongoing to evaluate the long-term impact of glimepiride on CV morbidity and mortality.[14]
Thiazolidinediones • Pioglitazone (e.g., *Actos*) • Rosiglitazone (e.g., *Avandia*) *Continued…*	Improves Outcomes:* • Pioglitazone Neutral:* • Rosiglitazone *based on CV morbidity and mortality outcomes, but note increased risk of heart failure associated with use.	• **Pioglitazone**: The IRIS trial found use of pioglitazone for about five years in patients with prediabetes and a history of stroke (with mild impairment) or transient ischemic attack may reduce the risk of a future stroke or MI (NNT = 36) [Evidence level A; high-quality RCT].[8] • **Pioglitazone**: The primary endpoint in the PROactive trial was not improved with pioglitazone. A secondary endpoint found use of pioglitazone for about three years in patients with type 2 DM and macrovascular disease (e.g., MI, stroke, PCI) may reduce the risk of all-cause mortality, non-fatal MI, and stroke (NNT = 50) [Evidence level A; high quality RCT].[27] ○ Subgroup analysis found use of pioglitazone for about three years in patients with type 2 diabetes and a previous stroke may reduce the risk of recurrent fatal or nonfatal stroke (NNT = 22) [Evidence level A; high quality RCT].[28] • **Rosiglitazone**: The RECORD trial found adding rosiglitazone to metformin or a sulfonylurea for at least five years did not affect overall CV morbidity or mortality [Evidence level A; high-quality RCT].[9]

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Medications[a]	Cardiovascular Impact	Cardiovascular Outcomes Data
Thiazolidinediones, continued		• **Pioglitazone** and **Rosiglitazone** are known for their associated risk of heart failure with a meta-analysis determining an NNH of approximately 50 patients treated with either agent for approximately two years [Evidence level A; high-quality meta-analysis].[17]

a. Many of these are also available as combination products with other medications like metformin or pioglitazone with different brand names.
b. *Saxenda* contains the same active ingredient as *Victoza*, but at higher doses and is indicated for weight loss, NOT the treatment of diabetes.

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Levels of Evidence

In accordance with the trend towards Evidence-Based Medicine, we are citing the **LEVEL OF EVIDENCE** for the statements we publish.

Level	Definition
A	High-quality randomized controlled trial (RCT) High-quality meta-analysis (quantitative systematic review)
B	Nonrandomized clinical trial Nonquantitative systematic review Lower quality RCT Clinical cohort study Case-control study Historical control Epidemiologic study
C	Consensus Expert opinion
D	Anecdotal evidence In vitro or animal study

Adapted from Siwek J, et al. How to write an evidence-based clinical review article. *Am Fam Physician* 2002;65:251-8.

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References

1. Sarwar N, Gao P, Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010;375:2215-22.
2. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA* 2002;287:2570-81.
3. Di Angelantonio E, Kaptoge S, Wormser D, et al. Association of cardiometabolic multimorbidity with mortality. *JAMA* 2015;314:52-60.
4. 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;38:140-9.
5. Goldenburg R, Clement M, Hanna A, et al. Pharmacologic management of type 2 diabetes: 2016 interim update. *Can J Diabetes* 2016;40:193-5.
6. ORIGIN trial investigators, Gerstein HC, Bosch J, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med* 2012;367:319-28.
7. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373:2117-28.
8. Kernan WN, Viscoli CM, Furie KL, et al. Pioglitazone after ischemic stroke or transient ischemic attack. *New Engl J Med* 2016;374:1321-31.
9. Home PD, Pocock SJ, Beck-Nielsen H, et al. Rosiglitazone evaluated for cardiovascular outcomes in an oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomized, open-label trial. *Lancet* 2009;373:2125-35.
10. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med* 2013;369:1327-35.
11. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013;369:1317-26.
12. Green JB, Bethel A, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2015;373:232-42.
13. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016 Jun 13. [Epub ahead of print]. Doi: 10.1056/NEJMoa1603827.
14. ClinicalTrials.gov. CAROLINA: cardiovascular outcome study of linagliptin versus glimepiride in patients with type 2 diabetes. June 21, 2016. https://clinicaltrials.gov/show/NCT01243424. (Accessed June 29, 2016).
15. Selvin E, Bolen S, Yeh HC, et al. Cardiovascular outcomes in trials of oral diabetes medications: a systematic review. *Arch Intern Med* 2008;168:2070-80.
16. Meinert CL, Knatterud GL, Prout TE, Klimt CR. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. mortality results. *Diabetes* 1970;19:S789-830.
17. Singh S, Loke YK, Furberg CD. Thiazolidinediones and heart failure: a teleo analysis. *Diabetes Care* 2007;30:2148-53.
18. ClinicalTrials.gov. Acarbose cardiovascular evaluation trial (ACE). March 2016. https://clinicaltrials.gov/ct2/show/NCT00829660. (Accessed June 30, 2016).
19. FDA. Guidance for Industry. Diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. December 2008. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071627.pdf. (Accessed July 11, 2016).
20. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017 June 12. Doi: 10.1056/NEJMoa1611925. [Epub ahead of print].
21. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes. UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854-65.
22. ClinicalTrials.gov. Effect of albiglutide, when added to standard blood glucose lowering therapies, on major cardiovascular events in subjects with type 2 diabetes. March 2016. https://clinicaltrials.gov/ct2/show/NCT02465515?term

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=albiglutide+cardiovascular&rank=1. (Accessed July 12, 2016).
23. ClinicalTrials.gov. Researching cardiovascular events with a weekly incretin in diabetes (REWIND). May 2016. https://clinicaltrials.gov/ct2/show/NCT01394952?term=dulaglutide+cardiovascular&rank=1. (Accessed July 12, 2016).
24. ClinicalTrials.gov. Exenatide study of cardiovascular event lowering trial (EXSCEL): a trial to evaluate cardiovascular outcomes after treatment with exenatide once weekly in patients with type 2 diabetes mellitus. January 2016. https://clinicaltrials.gov/ct2/show/NCT01144338?term=exenatide+cardiovascular&rank=1. (Accessed July 12, 2016).
25. Holman RR, Haffner SM, McMurray JJ, et al. Effect of nateglinide on the incidence of diabetes and cardiovascular events. *N Engl J Med* 2010;362:1463-76.
26. ClinicalTrials.gov. Multicenter trial to evaluate the effect of dapagliflozin on the incidence of cardiovascular events (DECLARE-TIMI58). June 2016. https://clinicaltrials.gov/ct2/show/study/NCT01730534?term=dapagliflozin+cardiovascular&rank=1. (Accessed July 12, 2016).
27. Dormandy JA, Charbonnel B, Eckland DJ, et al. 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;366:1279-89.
28. Wilcox R, Bousser MG, Betteridge OJ, et al. Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04). *Stroke* 2007;38:865-73.
29. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med* 2015;373:2247-57.

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