DIABETES MEDICATIONS AND CARDIOVASCULAR IMPACT

Chart from Prescriber’s Letter
December 2017
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.

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

<table>
<thead>
<tr>
<th>Medications(^a)</th>
<th>Cardiovascular Impact</th>
<th>Cardiovascular Outcomes Data</th>
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<tr>
<td><strong>Alpha-glucosidase inhibitors</strong></td>
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<tr>
<td>Acarbose (e.g., Precose [U.S.], Glucobay [Canada])</td>
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<tr>
<td>Miglitol (e.g., Glyset [U.S.])</td>
<td>Unknown:</td>
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<tr>
<td></td>
<td>Acarbose</td>
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<tr>
<td></td>
<td>Miglitol</td>
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<tr>
<td><strong>Amylin analog</strong></td>
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<tr>
<td>Pramlintide (SymlinPen [U.S.])</td>
<td>Unknown:</td>
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<td></td>
<td>Pramlintide</td>
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**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.\(^18\)

**Pramlintide:** Unable to identify any published or ongoing trials evaluating CV impact.
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| **Biguanide**    | Improves Outcomes:    | **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].\(^{21}\)  
  • Metformin  
    (e.g., *Glucophage*, *Glycon* [Canada]) |
|                  | Worsens Outcomes:    | **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  
    (e.g., *Nesina*)  
  • Linagliptin  
    (e.g., *Tradjenta* [U.S.]; *Trajenta* [Canada])  
  • Saxagliptin  
    (e.g., *Onglyza*)  
  • Sitagliptin  
    (e.g., *Januvia*) |
|                  | Neutral:              | **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  
    (e.g., *Onglyza*) |
|                  | Unknown:              | **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].\(^{12}\)  
  • Sitagliptin  
    (e.g., *Januvia*) |
|                  |                       | **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.\(^{14}\) |
| **Dipeptidyl peptidase-4 (DPP-4) inhibitors** |                       | **Albiglutide:** HARMONY Outcomes (NCT02465515) is ongoing to evaluate the effects of adding albiglutide to standard blood glucose lowering therapies on major cardiovascular events.\(^{22}\)  
  • Albiglutide  
    (e.g., *Tanzeum* [U.S.])  
  • Dulaglutide  
    (e.g., *Trulicity*)  
  • Exenatide  
    (e.g., *Byetta*) |
| **Glucagon-like peptide-1 (GLP-1) receptor agonists** | Improves Outcomes:    | **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.\(^{23}\)  
  • Dulaglutide  
  • Exenatide  
  • Liraglutide |
|                  | Unknown:              | **Exenatide:** The EXSCEL (Exenatide Study of Cardiovascular Events Lowering Trial) trial (NCT01144338) is ongoing to evaluate if exenatide added to usual care... |

\(^a\) Please note that this table may contain incomplete or outdated information. Always consult the most recent and authoritative sources for the most accurate and up-to-date data.
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<td><strong>GLP-1 agonists, continued</strong></td>
<td>Neutral: - Liraglutide (e.g., Victoza, Saxenda&lt;sup&gt;b&lt;/sup&gt;) - Lixisenatide (pending FDA approval; Lyxumia)</td>
<td>impacts CV outcomes in patients with type 2 diabetes.&lt;sup&gt;24&lt;/sup&gt; - <strong>Liraglutide</strong>: 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:&lt;sup&gt;13&lt;/sup&gt; - 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. - Liraglutide did not reduce the individual rates of MI, nonfatal stroke, or hospitalization for heart failure. - <strong>Lixisenatide</strong>: 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.&lt;sup&gt;29&lt;/sup&gt;</td>
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<td><strong>Insulin</strong></td>
<td>Neutral: - Glargine</td>
<td>- <strong>Glargine</strong>: 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].&lt;sup&gt;6&lt;/sup&gt;</td>
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<td><strong>Meglitinides</strong></td>
<td>Unknown: - Nateglinide (e.g., Starlix [U.S.]) - Repaglinide (e.g., Prandin [U.S.], GlucoNorm [Canada])</td>
<td>- <strong>Nateglinide</strong>: 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].&lt;sup&gt;25&lt;/sup&gt;</td>
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<td><strong>Sodium-glucose co-transporter 2 (SGLT2) inhibitors</strong></td>
<td>Unknown: - Dapagliflozin</td>
<td>- <strong>Canagliflozin</strong>: 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 (&gt;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.&lt;sup&gt;20&lt;/sup&gt; - <strong>Dapagliflozin</strong>: DECLARE-TIMI58 (NCT01730534) is ongoing to evaluate the impact of adding dapagliflozin to current DM therapy on MI, ischemic stroke, and CV death.&lt;sup&gt;26&lt;/sup&gt; - <strong>Empagliflozin</strong>: 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...</td>
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</table>
| **SGLT2 inhibitors, continued** | | disease, may reduce:7  
  o Hospitalization due to heart failure (NNT = 71).  
  o CV death rates (NNT = 45).  
  o Overall death rates (NNT = 39).  
  o 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) | Improves Outcomes:*  
  • Pioglitazone  
  Neutral:*  
  • Rosiglitazone | **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  
  o 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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<td>Thiazolidinediones, continued</td>
<td></td>
<td>• 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]&lt;sup&gt;17&lt;/sup&gt;</td>
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</table>

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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Users of this resource are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.
Levels of Evidence

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

<table>
<thead>
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<th>Level</th>
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| 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 |


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References


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