ESC SUM: uncovering the mechanisms of GLP-1 RA in T2D

2019 ESC guidelines on diabetes, pre-diabetes and cardiovascular diseases

Expert insights and rationale

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Disclosures

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Advisory board/speaker: AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Mundipharma, Novo Nordisk, Pfizer
Reclassification of CV risk in diabetes
New treatment algorithms with glucose-lowering agents for management/prevention of CVD
New recommendations regarding the role of aspirin and NOACs in diabetes
Duration of DAPT post ACS in diabetes
New lipid targets relating to severity of CV risk / new recommendations for the use of PCSK9 inhibitors
Individualised blood pressure targets
# Cardiovascular risk categories in patients with DM

<table>
<thead>
<tr>
<th>Very high-risk</th>
<th>Patients with DM and established CVD or other target organ damage(^a) or three or more major risk factors(^b) or early onset T1DM of long duration (&gt;20 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk</td>
<td>Patients with DM duration ≥10 years without target organ damage(^a) plus any other additional risk factor(^b)</td>
</tr>
<tr>
<td>Moderate-risk</td>
<td>Young patients (T1DM &lt;35 years; T2DM &lt;50 years) with DM duration &lt;10 years, without other risk factors</td>
</tr>
</tbody>
</table>

\(^a\) proteinuria, renal impairment defined as eGFR≥30mL/min/1.73m\(^2\).  
\(^b\) age, hypertension, dyslipidemia, smoking, obesity.
Glucose-lowering agents
new evidence from cardiovascular outcome trials

2013

ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

2019

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD
Cardiovascular outcome trials with newer glucose-lowering agents

### SGLT2 inhibitors

<table>
<thead>
<tr>
<th>Trial</th>
<th>EMPA-REG OUTCOME</th>
<th>CANVAS</th>
<th>DECLARE–TIMI 58</th>
<th>CREDENCE</th>
<th>ELIKA</th>
<th>LEADER</th>
<th>SUSTAIN–6</th>
<th>EXSCEL</th>
<th>Harmony Outcome</th>
<th>REWIND</th>
<th>PIONEER 6</th>
<th>SAVOR–TIMI 53</th>
<th>EXAMINE</th>
<th>TEOS</th>
<th>CARMINA</th>
<th>CAROLINA</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>7020</td>
<td>10 142</td>
<td>17 156</td>
<td>4401</td>
<td>6068</td>
<td>9340</td>
<td>3297</td>
<td>14 753</td>
<td>9463</td>
<td>9901</td>
<td>3182</td>
<td>16 492</td>
<td>5400</td>
<td>14 671</td>
<td>6979</td>
<td>6033</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63</td>
<td>63</td>
<td>63</td>
<td>63</td>
<td>60</td>
<td>64</td>
<td>64</td>
<td>62</td>
<td>64</td>
<td>66</td>
<td>66</td>
<td>65</td>
<td>61</td>
<td>66</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>DM (years)</td>
<td>57% &gt; 10</td>
<td>13.5</td>
<td>11.8</td>
<td>15.8</td>
<td>9.3</td>
<td>12.8</td>
<td>13.9</td>
<td>12.0</td>
<td>14.1</td>
<td>10.5</td>
<td>14.9</td>
<td>10</td>
<td>7.2</td>
<td>9.4</td>
<td>14.7</td>
<td>6.2</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>30.6</td>
<td>22.0</td>
<td>22.1</td>
<td>31.3</td>
<td>30.1</td>
<td>22.5</td>
<td>32.8</td>
<td>37.8</td>
<td>32</td>
<td>22.3</td>
<td>21.1</td>
<td>21</td>
<td>20</td>
<td>33.3</td>
<td>30.1</td>
<td></td>
</tr>
<tr>
<td>Insulin (%)</td>
<td>48</td>
<td>59</td>
<td>-40</td>
<td>65</td>
<td>39</td>
<td>44</td>
<td>58</td>
<td>46</td>
<td>60</td>
<td>24</td>
<td>61</td>
<td>41</td>
<td>20</td>
<td>23</td>
<td>58</td>
<td>0</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.1</td>
<td>8.2</td>
<td>8.3</td>
<td>8.3</td>
<td>7.7</td>
<td>8.7</td>
<td>8.7</td>
<td>8.0</td>
<td>8.7</td>
<td>7.2</td>
<td>6.2</td>
<td>8.0</td>
<td>8.0</td>
<td>7.3</td>
<td>7.9</td>
<td>7.2</td>
</tr>
<tr>
<td>Previous CVD (%)</td>
<td>99</td>
<td>65</td>
<td>40</td>
<td>50.4</td>
<td>100</td>
<td>-81</td>
<td>-83</td>
<td>73</td>
<td>100</td>
<td>31</td>
<td>35</td>
<td>78</td>
<td>100</td>
<td>74</td>
<td>57</td>
<td>42</td>
</tr>
<tr>
<td>CV risk inclusion criteria</td>
<td>MI, CHD, CVD, or PVD</td>
<td>MI, CHD, CVD, or PVD</td>
<td>CVD or at least one CVRF</td>
<td>CKD</td>
<td>ACS ≤ 60 days</td>
<td>Age ≥ 50 years and CVD, 4 or CKD, or age ≥ 60 years and at least one CVRF</td>
<td>CHD, or PVD 7 days ago previous CVD event</td>
<td>MI, CHD, or CVD, or PVD</td>
<td>Age ≥ 50 years and CVD or CVRFs</td>
<td>Age ≥ 50 years and CVD, 4, or CKD, or age ≥ 40 years and at least one CVRF</td>
<td>ACS ≤ 90 days</td>
<td>MI, CHD, CVD, or PVD</td>
<td>CVD and/or CKD</td>
<td>CVD evidence of vascular-related end-organ damage, or age ≥ 70 years, or at least two CVRFs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>94</td>
<td>89</td>
<td>89</td>
<td>96.8</td>
<td>76</td>
<td>92</td>
<td>92</td>
<td>90</td>
<td>86</td>
<td>93</td>
<td>94</td>
<td>81</td>
<td>83</td>
<td>86</td>
<td>95</td>
<td>90</td>
</tr>
<tr>
<td>Follow-up (years)</td>
<td>3.1</td>
<td>2.4</td>
<td>4.5</td>
<td>2.6</td>
<td>2.1</td>
<td>3.8</td>
<td>2.1</td>
<td>3.3</td>
<td>1.6</td>
<td>5.4</td>
<td>1.3</td>
<td>2.1</td>
<td>1.5</td>
<td>2.8</td>
<td>2.2</td>
<td>6.3</td>
</tr>
</tbody>
</table>

European Heart Journal 2019 doi/10.1093/eurheartj/ezh486
CVOTs with DPP-IV inhibitors
(MACE endpoint and hospitalisation for heart failure)

3P-MACE

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SAVOR-TIMI 53</strong>¹</td>
<td>1.00 (0.89, 1.12)</td>
<td></td>
<td>0.99</td>
</tr>
<tr>
<td><strong>EXAMINE²,³</strong></td>
<td>0.96 (n/a, 1.16)</td>
<td></td>
<td>0.32*</td>
</tr>
<tr>
<td><strong>TECOS⁴</strong></td>
<td>0.99 (0.89, 1.10)</td>
<td></td>
<td>0.84</td>
</tr>
<tr>
<td><strong>CARMELINA⁵</strong></td>
<td>1.02 (0.89, 1.17)</td>
<td></td>
<td>0.74</td>
</tr>
</tbody>
</table>

Hospitalisation for heart failure⁵,⁶

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SAVOR-TIMI 53</strong>¹</td>
<td>1.27 (1.07, 1.51)</td>
<td></td>
<td>0.007</td>
</tr>
<tr>
<td><strong>EXAMINE²,³</strong></td>
<td>1.19 (0.89, 1.59)</td>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td><strong>TECOS⁴</strong></td>
<td>1.00 (0.83, 1.20)</td>
<td></td>
<td>0.98</td>
</tr>
<tr>
<td><strong>CARMELINA⁵</strong></td>
<td>0.90 (0.74, 1.08)</td>
<td></td>
<td>0.26</td>
</tr>
</tbody>
</table>

Favours DPP-4 inhibitor
Favours placebo

CVOTs with GLP-1 receptor agonists
(3P-MACE endpoint)

3. Hernandez AF et al. *Lancet* 2018
CVOTs with GLP-1 receptor agonists (all-cause mortality)

CVOTs with SGLT2 inhibitors (3P-MACE endpoint)

CVOTs with SGLT2 inhibitors
(HF hospitalization and CV death)

CVOTs with SGLT2 inhibitors
(all cause mortality)

HR 0.68
(95% CI 0.57, 0.82)
p<0.0001

NNT: 39

# Glucose-lowering agents and CVD

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
</table>
| **SGLT2 inhibitors**<br>Empagliflozin, canagliflozin, or dapagliflozin**<br>are recommended in patients with T2DM and CVD or at very high/high CV risk to reduce CV events.**<br>**IAS**<br>Empagliflozin is recommended in patients with T2DM and CVD to reduce the risk of death.**<br>**IB**<br>**GLP1-RAs**<br>Liraglutide, semaglutide or dulaglutide are recommended in patients with T2DM and CVD or at very high/high CV risk to reduce CV events.**<br>**IAB**<br>Liraglutide is recommended in patients with T2DM and CVD or at very high/high CV risk to reduce the risk of death.**<br>**IB**<br>**Biguanides**<br>Metformin should be considered in overweight patients with T2DM without CVD and at moderate CV risk.**<br>**IIa**<br>C

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Treatment algorithm in drug-naïve patients with Type 2 Diabetes

ASCVD, or high/very high CV risk (target organ damage or multiple risk factors)

SGLT2i or GLP-1 RA Monotherapy

Metformin Monotherapy

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Treatment algorithm in patients with Type 2 Diabetes - on Metformin

ASCVD, or high/very high CV risk (target organ damage or multiple risk factors)

Add SGLT2i or GLP-1 RA

Continue Metformin Monotherapy

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