After 10 Years and 26 CVOTs, Where do We Stand on CV Safety in Diabetes?

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Washington, DC
Financial Disclosure

Consultant: Adocia, Novo Nordisk, Virta

Stock Holdings: J & J, Abbott, Abbvie
“...sponsors should demonstrate that the therapy will not result in an unacceptable increase in CV risk.”

Guidance for Industry
Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

Pre-marketing Analyses
Upper CL of 95% CI < 1.8
For a HR=1.0 \( \Rightarrow \approx 122 \) events

Post-marketing Analyses
Upper CL of 95% CI < 1.3
For a HR=1.0 \( \Rightarrow \approx 611 \) events

1.0 1.3 1.8
Hazard Ratio

- Meta-analysis strategy using Phase 2/3 data
- Blinded central adjudication of CVD events in Phase 2/3
- Inclusion of high-risk subjects: advanced CVD, elderly, CKD
- Minimum exposure of 2 years in large CVOT
- Approximately 15,000 pt-yrs
Over 130,000 subjects with diabetes are entered into placebo-controlled clinical trials to prove the absence of a problem.

These patients must be at very high risk for cardiovascular outcomes so that the trial can be undertaken in a reasonable period of time, with an achievable number of subjects.

These patients also do not reflect the ‘typical’ patient with T2D.

These safety studies do not test a hypothesis.

Are we asking the correct questions?
**CVOTs**

<table>
<thead>
<tr>
<th>Year</th>
<th>Trial Name</th>
<th>Treatment</th>
<th>Phase</th>
<th>Duration</th>
<th>Enrollment</th>
<th>Status</th>
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<tbody>
<tr>
<td>2013</td>
<td>ELIXA³</td>
<td>Lixisenatide, GLP-1RA</td>
<td>6068</td>
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<td>Q1 2015</td>
<td>RESULTS</td>
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<tr>
<td>2015</td>
<td>SUSTAIN 6⁰</td>
<td>Semaglutide, QW GLP-1RA</td>
<td>3297</td>
<td>duration – 2.4 yrs</td>
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<td>RESULTS</td>
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<td>2016</td>
<td>CANVAS⁰</td>
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<td>4418</td>
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<tr>
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<td>2018</td>
<td>DECLARE-TIMI 58</td>
<td>Dapagliflozin, SGLT-2i</td>
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<td>duration – 6 yrs</td>
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<tr>
<td>2019</td>
<td>PIONEER 6</td>
<td>Oral semaglutide, GLP-1RA</td>
<td>3176</td>
<td>duration – 1.5 yrs</td>
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<tr>
<td>2020</td>
<td>SCORED</td>
<td>Sotagliflozin, SGLT-1i &amp; SGLT-2i</td>
<td>10,500*</td>
<td>duration – 4.5 yrs</td>
<td>Q1 2022</td>
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<tr>
<td>2021</td>
<td>TOSCA IT13</td>
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<td>3028</td>
<td>duration – 10 yrs</td>
<td>Q4 2017</td>
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<tr>
<td>2022</td>
<td>TECOS4</td>
<td>Sitagliptin, DPP-4i</td>
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<td>Insulin degludec, insulin</td>
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</tr>
<tr>
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<td>CARDEIA 12</td>
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<td>7141</td>
<td>duration – 4.5 yrs</td>
<td>Q2 2018</td>
<td>RESULTS</td>
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<tr>
<td>2022</td>
<td>CARMELINA</td>
<td>Linagliptin, DPP-4i</td>
<td>7003</td>
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<td>2022</td>
<td>CAROLINA</td>
<td>Linagliptin, DPP-4i vs SU</td>
<td>6072</td>
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<tr>
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<td>4462</td>
<td>duration – 5.5 yrs</td>
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<td>Aleglitazar, PPAR-αγ</td>
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<td>6522</td>
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<td>REWIND</td>
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<td>duration – 6.5 yrs</td>
<td>Completion Q3 2018</td>
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<td>Ertugliflozin, SGLT-2i</td>
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<td>Exenatide ER, QW GLP-1RA</td>
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</table>

*Estimated enrolment; †Stopped early after a median follow-up of 57.4 months following futility analysis.

Trials with filled boxes are completed. Trials with a white background are ongoing.

AGI, alpha-glucosidase inhibitor; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase-4 inhibitor; ER, extended release; GLP-1RA, glucagon-like peptide 1 receptor agonist; ITCA 650, continuous subcutaneous delivery of exenatide; PPAR-αγ, peroxisome proliferator-activated receptors-α and γ; QW, once weekly; SGLT-1i, sodium-glucose co-transporter 1 inhibitor; SGLT-2i, sodium-glucose co-transporter 2 inhibitor; SU, sulphonylurea; TZD, thiazolidinediones.

What Have We Learned From CVOTs

• CVOTs have demonstrated that the tested diabetes drugs do not show increased CV risk
• Some CVOTs have demonstrated reduced CV risk
• Pancreatic safety for DPP-4i and GLP-1RA has been demonstrated
• Safety signals of CHF for DPP-4i and amputations for SGLT2i have been seen
• CVOTs have been valuable additions to our knowledge base
Should CVOTs Continue to be Mandatory?

• Is there a signal of harm?
Summary of Major CVOTs in T2DM

- **Saxagliptin (SAVOR TIMI 53)**
  - HR = 1.00
  - (95% CI: 0.89-1.12)

- **Alogliptin (EXAMINE)**
  - HR = 0.96
  - (one-side CI: 1.16)

- **Sitagliptin (TECOS)**
  - HR = 0.98
  - (95% CI: 0.88-1.09)

- **Lixisenatide (ELIXA)**
  - HR = 1.02
  - (95% CI: 0.89-1.17)

- **Liraglutide (LEADER)**
  - HR = 0.87
  - (95% CI: 0.78-0.97)

- **Semaglutide (SUSTAIN-6)**
  - HR = 0.74
  - (95% CI: 0.58-0.95)

- **Exenatide (EXSCEL)**
  - HR = 0.91
  - (95% CI: 0.83-1.00)

- **Empagliflozin (EMPA-REG Outcome)**
  - HR = 0.86
  - (95% CI: 0.74-0.99)

- **Canagliflozin (CANVAS-program)**
  - HR = 0.86
  - (95% CI: 0.75-0.97)

Should CVOTs Continue to be Mandatory?

• Is there a signal of harm?
• Are current CVOTs generalizable?
Prevalence and Co-prevalence of Comorbidities in T2DM (Q-EMR) (N=1.39 million)

- Total CKD: 24.1%
- Total CVD: 21.6%
- CVD: 13.0%
- CKD: 15.5%
- CVD + CKD: 8.6%
- T2DM: 62.9%

Results of GLP-1 CVOTs are Not Generalizable to the T2D Population

<table>
<thead>
<tr>
<th>Trial</th>
<th>Individuals Likely to Have a Diagnosis of T2D</th>
<th>Individuals Who Would Meet All Trial Inclusion Criteria</th>
<th>% of Individuals with T2D Who meet Trial Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELIXA</td>
<td>23,941,512</td>
<td>1,538,856</td>
<td>6.4%</td>
</tr>
<tr>
<td>LEADER</td>
<td>23,941,512</td>
<td>3,063,663</td>
<td>12.8%</td>
</tr>
<tr>
<td>SUSTAIN-6</td>
<td>23,941,512</td>
<td>2,815,927</td>
<td>11.8%</td>
</tr>
<tr>
<td>EXSCEL</td>
<td>23,941,512</td>
<td>11,347,155</td>
<td>47.4%</td>
</tr>
</tbody>
</table>

Adapted from Wittbrodt ET, et al. Generalizability of GLP-1 RA Cardiovascular Outcomes Trials Enrollment Criteria to the US Type 2 Diabetes Population. Poster presented at the America Diabetes Association 77th Scientific Sessions; June 9-13, 2017; San Diego, CA.
## Proportion of “Primary Prevention” participants in DM CVOTs

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Without Known CVD at Baseline n (%)</th>
<th>HR</th>
<th>With CVD</th>
<th>Without CVD</th>
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</thead>
<tbody>
<tr>
<td><strong>LEADER</strong></td>
<td>9340</td>
<td>1742 (18.7)</td>
<td></td>
<td>0.83 (0.74–0.93)</td>
<td>1.20 (0.86–1.67)</td>
</tr>
<tr>
<td><strong>SUSTAIN-6</strong></td>
<td>3297</td>
<td>562 (17.0)</td>
<td></td>
<td>0.72 (0.55-0.93)</td>
<td>1.00 (0.41-2.46)</td>
</tr>
</tbody>
</table>

Should CVOTs Continue to be Mandatory?

- Is there a signal of harm?
- Are current CVOTs generalizable?
- Is it now ethical to withhold empagliflozin, liraglutide, canagliflozin, or albiglutide from the control arm?
Consider important comorbidities that should influence the choice of a particular glucose-lowering medication

Among patients with type 2 diabetes with established atherosclerotic cardiovascular disease (ASCVD), sodium-glucose cotransporter 2 (SGLT2) inhibitors or glucagon-like peptide 1 (GLP-1) receptor agonists with proven cardiovascular benefit are recommended as part of glycaemic management

Diabetes Care 2018;41:1-33 https://doi.org/10.2337/dc18-0033
If ASCVD Predominates:

GLP-1 receptor agonist with proven cardiovascular benefit
- Liraglutide > semaglutide > exenatide LAR

SGLT2 inhibitor with proven cardiovascular benefit
- Empagliflozin > canagliflozin

1. Proven CVD benefit means a non-inferiority trial of reducing CVD events, the SGLT2 inhibitors included in this recommendation (canagliflozin = emeglabiflozin = empagliflozin = liraglutide) had a cardio-protective effect compared to placebo.
2. The American Diabetes Association recommends the use of SGLT2i in combination with GLP-1 RA in patients with chronic kidney disease.
3. Basal insulin can be added to GLP-1 RA or SGLT2i, depending on patient needs.
4. Basal insulin is the preferred initial therapy in patients with type 2 diabetes and a high likelihood of development of CVD.
5.TZD and SU are considered as last-line therapy in type 2 diabetes patients with CVD.

Diabetes Care 2018;41:1-33 https://doi.org/10.2337/dci18-0033
Caveats

No evidence of CVD benefit in those at lower cardiovascular risk

The combination of SGLT2-i and GLP-1 RA has not been tested in cardiovascular outcome trials

Diabetes Care 2018;41:1-33 https://doi.org/10.2337/dci18-0033
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• Are current CVOTs generalizable?
• Is it now ethical to withhold empagliflozin, liraglutide, canagliflozin, or albiglutide from the control arm?
• What is the impact of allowing use of proven effective therapy in the comparison arm?
T2DM + ASCVD

Randomize

Standard of Care with Liraglutide, Albiglutide or Semaglutide or Empagliflozin or Canagliflozin vs New (or Old) Drug With or without another effective agent
Impact on Sample Size Moving from Placebo to Active Control

- For placebo control, somewhat arbitrary non-inferiority margins set by regulators
  - T2DM: 1.8 and 1.3

<table>
<thead>
<tr>
<th>NI Margin</th>
<th>#Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
<td>87</td>
</tr>
<tr>
<td>1.8</td>
<td>122</td>
</tr>
<tr>
<td>1.4</td>
<td>371</td>
</tr>
<tr>
<td>1.3</td>
<td>611</td>
</tr>
</tbody>
</table>

Darren McGuire, presented at ADA Scientific Sessions, June, 2018, Orlando, FL
Impact on Sample Size from Placebo to Active Control

- Moving to active controlled trials, standard non-inferiority margin determination is quantitative
  - Margin is $1/UCL$ of meta-analysis vs. placebo
  - $\frac{1}{2}$ of the treatment effect vs. placebo

- For 3-point MACE versus GLP1-RAs or SGLT2i yields NI margin $\sim 1.1$

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Impact on Sample Size from Placebo to Active Control

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  - Margin is $1/UCL$ of meta-analysis vs. placebo OR
  - $\frac{1}{2}$ of the treatment effect vs. placebo

- For 3-point MACE versus GLP1-RAs or SGLT2i yields NI margin ~1.1

- required sample sizes increased ~3-fold

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<td>611</td>
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<tr>
<td>1.1</td>
<td>~1800</td>
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• Is there a signal of harm?
• Are current CVOTs generalizable?
• Is it now ethical to withhold empagliflozin, liraglutide, canagliflozin, or albiglutide from the control arm?
• What is the impact of allowing use of proven effective therapy in the comparison arm?
• Should CVOTs be undertaken for primary prevention?
GLP1s: Patients Without Prior CV Events Did Not Benefit

Comparison of Patients With and Without Prior CVD

LEADER
≥ 50 yrs of age with established CVD: 7598, 536/3831 (14.0), 629/3767 (16.7), 0.83 (0.74-0.93)
≥ 60 yrs of age with risk factors for CVD: 1742, 72/837 (8.6), 65/905 (7.2), 1.2 (0.86-1.67)

SUSTAIN-6
≥ 50 yrs of age with established CVD: 2735, 98/1353 (5.4), 137/1382 (9.9), 0.72 (0.55-0.93)
≥ 60 yrs of age with risk factors for CVD: 562, 10/295 (3.4), 9/267 (3.4), 1.0 (0.41-2.46)

EXSCEL
Prior CV event: 10782, 722/5394 (13.4), 786/5388 (14.6), 0.9 (0.82-1.0)
No Prior CV event: 3970, 117/1962 (6.0), 119/2008 (5.9), 0.99 (0.77-1.28)
## Primary CV Prevention

<table>
<thead>
<tr>
<th></th>
<th>SAVOR TIMI 53</th>
<th>LEADER</th>
<th>DEVOTE</th>
<th>CANVAS Program</th>
<th>SUSTAIN 6</th>
<th>EXCSEL</th>
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</thead>
<tbody>
<tr>
<td>n (%) 1º prevention</td>
<td>3533 (21.4%)</td>
<td>1742 (18.7%)</td>
<td>1105 (14.5%)</td>
<td>3486 (34.4%)</td>
<td>562 (17.0%)</td>
<td>3970 (26.9%)</td>
</tr>
<tr>
<td>2º Prevention Results</td>
<td>0.96 (0.86, 1.09)</td>
<td>0.83 (0.74, 0.93)</td>
<td>0.89 (0.76, 1.04)</td>
<td>0.82 (0.72, 0.95)</td>
<td>0.72 (0.55, 0.93)</td>
<td>0.90 (0.82, 1.00)</td>
</tr>
<tr>
<td>1º Prevention Results</td>
<td>1.34 (0.95, 1.90)</td>
<td>1.20 (0.86, 1.67)</td>
<td>1.03 (0.62, 1.72)</td>
<td>0.98 (0.74, 1.30)</td>
<td>1.00 (0.41, 2.46)</td>
<td>0.99 (0.77, 1.28)</td>
</tr>
<tr>
<td>1º Prevention Annualized 3P MACE</td>
<td>1.3%</td>
<td>1.9%</td>
<td>2.7%</td>
<td>1.6%</td>
<td>1.7%</td>
<td>1.8%</td>
</tr>
</tbody>
</table>
Trends in age-standardized rates of diabetes-related complications among U.S. adults with diabetes, 1990-2010

Figure 2. Major Cardiovascular Outcomes in Patients with Type 2 Diabetes and Matched Controls.

A. Death from Any Cause

B. Death from Cardiovascular Disease

C. Death from Coronary Heart Disease

D. Hospitalization for Cardiovascular Disease

Where Should the FDA Go From Here?

- Return to the pre-2008 regulatory approach.
- Demand Outcome Trials whenever a safety signal is noted in Ph 2 or 3 trials.
- Require Outcome Trials if the sponsor desires a label indication.
How Can Outcome Trials be Modified to be more feasible?

• Different trial designs
## Attributes of Different Clinical Trial Designs

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Relative Cost</th>
<th>Design and Data Collection</th>
<th>Patient Populations</th>
<th>Potential for Bias</th>
<th>Advantages and Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observational studies (including registry studies)</td>
<td>$</td>
<td>Retrospective or prospective; variable data quality</td>
<td>Typically unselected</td>
<td>Without randomization, comparative effectiveness cannot be performed</td>
<td>Large population; often many unmeasured variables or unexplained factors</td>
</tr>
<tr>
<td>Traditional RCTs</td>
<td>$$$$$-$$$$$$</td>
<td>Prospective; data collection occurs at specialized study centres</td>
<td>Highly selected; may lead to non-generalizable results</td>
<td>Randomization eliminates confounding bias</td>
<td>Current gold standard for comparative-effectiveness studies</td>
</tr>
<tr>
<td>Registry-based RCTs</td>
<td>$$-$$$$</td>
<td>Prospective; data collection often at diverse sites</td>
<td>Typically a specific population (e.g. undergoing PCI)</td>
<td>Randomization eliminates confounding bias</td>
<td>Large number of outcomes; harnesses power of already established clinical registry</td>
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<td>Large, pragmatic clinical trials</td>
<td>$$-$$$$$$</td>
<td>Prospective; data is collected ubiquitously as part of clinical care</td>
<td>Broad or selective (dependent on electronic infrastructure); can incorporate enrichment criteria</td>
<td>Randomization eliminates confounding bias</td>
<td>Simple design; large number of outcomes; requires infrastructure that can facilitate easy and quick enrollment</td>
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ADAPTABLE Study Design

Patients with known ASCVD + ≥1 "Enrichment Factor"

- Identified through EHR/direct patient contact in clinics and hospitals through CDRNs/PPRNs (PPRN patients would need to connect through a CDRN to participate)

- Patients contacted via email, mail, and in clinic with trial information and e-Consent Treatment assignment will be provided directly to patient

*Enrichment Factors
- Age > 65 years
- Creatinine > 1.5 mg/dL
- Diabetes mellitus (type 1 or 2)
- Known 3-vessel CAD
- Current CVD or PAD
- Known EF<50% by echo, cath, nuclear study
- Current smoker

- ASA 81 mg QD n=10,000
- ASA 325 mg QD n=10,000

- Randomized Electronic Follow-Up: 3 vs 6 months Supplemented with EHR/CDM Data

- Duration: Enrollment over 24 months; maximum follow up of 30 months

- Primary Endpoint: Composite of all-cause mortality, hospitalization for MI, or hospitalization for stroke
- Primary Safety Endpoint: Hospitalization for major bleeding

How Can Outcome Trials be Modified to be more feasible?

• Different trial designs
• Different statistical approaches
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<th>NNT</th>
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Bayes theorem: posterior odds = prior odds × evidence (Bayes factor). Bayes factor = probability (data|H₁)/probability (data|H₀) (likelihood ratio); H₀ = null hypothesis; H₁ = alternative hypothesis. Minimum Bayes factor = exp(−0.5z²). Odds = probability/(1 − probability). Probability = odds/(1 + odds). NNT to prevent one event over 3 years, calculated as inverse of absolute risk difference based on Kaplan-Meier curve estimates, is only reported for statistically significant differences. NE, not estimated because of lack of statistically significant difference.
How Can Outcome Trials be Modified to be more feasible?

- Different trial designs
- Different statistical approaches
- Incorporate outcomes important to people with diabetes
Patient Priorities for Diabetes Drugs

Type 1 (n=1,016)
1. Time in Range
2. Unexpected blood glucose numbers
3. Dosing insulin
4. Hypoglycemia
5. A1C

Type 2 on insulin (n=1,141)
1. Time in Range
2. A1C
3. Non-diabetes health issues
4. Dosing insulin
5. Unexpected blood glucose numbers

Type 2 no insulin (n=1,266)
1. Time in Range
2. A1C
3. Non-diabetes health issues
4. Unexpected blood glucose numbers
5. Symptoms of Complications

Glucose-Lowering Medication in Type 2 Diabetes: Overall Approach

**Consensus Recommendation:**
The choice of medication added to metformin is based on patient preference and clinical characteristics. Important clinical characteristics include the presence of established ASCVD, other co-morbidities such as HF or CKD, and risk for specific adverse medication effects, particularly hypoglycaemia and weight gain, as well as safety, tolerability, and cost.

**Consensus Recommendation:**
Intensification of treatment beyond dual therapy to maintain glycaemic targets requires consideration of the impact of medication side effects on co-morbidities, as well as the burden of treatment and cost.

Diabetes Care 2018;41:1-33 https://doi.org/10.2337/dci18-0033
Figure 2

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH

FIRST-LINE THERAPY IS METFORMIN AND COMPREHENSIVE LIFESTYLE (INCLUDING WEIGHT MANAGEMENT AND PHYSICAL ACTIVITY)
IF HbA1c ABOVE TARGET PROCEED AS BELOW

ESTABLISHED ASCVD OR CKD

NO

WITHOUT ESTABLISHED ASCVD OR CKD

ASCVD PREDOMINATES

GLP-1 RA with proven CVD benefit[1]

SGLT2i with proven CVD benefit[1], if GLP-1 RA inadequate[1]

PREFERABLY SGLT2i with evidence of reducing HF and/or CVD progression in CVOTs

IF HbA1c above target

IF further intensification is required or patient is non-acceptable to tolerate

GLP-1 RA, and/or SGLT2i, choose agents demonstrating CVD safety:

- Consider adding the other class GLP-1 RA or SGLT2i with proven CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin
- TZD
- SU

HP OR CKD PREDOMINATES

SGLT2i with evidence of reducing HF and/or CVD progression in CVOTs

GLP-1 RA with proven CVD benefit[1]

IF HbA1c above target

COMPELLING NEED TO MINIMISE HYPOGLYCAEMIA

DPPI-4i

GLP-1 RA

SGLT2i

TZD

IF HbA1c above target

COMPELLING NEED TO MINIMISE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

GLP-1 RA with good efficacy for weight loss

GRAPES-4: if not on GLP-1 RA

SGLT2i

IF HbA1c above target

COST IS A MAJOR ISSUE[8]

EITHER OR

IF HbA1c above target

DPPI-4i

GLP-1 RA

SGLT2i

TZD

IF HbA1c above target

SU

TZD[10]

IF HbA1c above target

SU

TIZD

IF HbA1c above target

TIZD[11]

SU

IF HbA1c above target

- Insulin therapy: basal insulin with lowest acquisition cost
- Consider DPPI-4i or SGLT2i with lowest acquisition cost

IF triple therapy required or SGLT2i and/or GLP-1 RA not tolerated or contraindicated use regimen with lowest risk of weight gain

PREFERABLY

DPPI-4i if not on GLP-1 RA

Based on weight neutrality

IF DPPI-4i not tolerated or contraindicated or patient already on GLP-1 RA cautiously add:

- SU
- TZD
- Basal insulin

1. Proven CVD benefit means it has label indications of reducing CVD events. For GLP-1 RA-choosing evidence of ISCHEMIA = semaglutide = exenatide. For SGLT2 evidence mostly design for microalbuminuria - canagliflozin - canagliflozin.
2. Beware that SGLT2 may require regular and individual advice with regard to indications of DPP4 inhibitors to continue and reconsider dose.
3. Both semaglutide and exenatide have shown reductions in HF and reduction in CV morbidity in CVOTs.
4. Empagliflozin or canagliflozin has demonstrated CVD safety.
5. Low doses may be safer. Avoid or stop oral agents when appropriate.
6. Consider later generation SU with lower doses of thiazolidinediones.
7. Empagliflozin/Canagliflozin = pioglitazone = metformin.
8. Frequent and regular follow-up (i.e., established ASCVD, low risk of hypoglycaemia and low priority to avoid weight gain) are not weighted in the scoring.
10. Consider DPP-4i or SGLT2i with lowest acquisition cost.
Final Thoughts

• Diabetes is a chronic disease with people living with the disorder for 25-70 years.

• All-cause mortality and CV mortality are falling among people with diabetes, with life expectancy significantly increasing.

• Increased time living with diabetes puts a premium on Quality of Life issues.

• The goal is to improve the lives of people with diabetes, not just their longevity.