Targeting risk in patients with CVD, Diabetes or CKD: new guidelines and risk management approaches

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Professor John Deanfield: Disclosures

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- No conflicts of interest for this presentation
- Member of SOUL and SELECT Study Steering Committees for Novo Nordisk
Healthy Ageing?

CV Disease is the Major Cause of Morbidity and Mortality
On average, a 50-year old with diabetes but no history of vascular disease is ~6 years younger at time of death than a counterpart without diabetes.

Diabetes UK: The Impact of Diabetes Today

Almost 3.7 million people have been diagnosed with diabetes in the UK.

12.3 million people are at increased risk of Type 2 diabetes.

4.6 million people are living with diabetes in the UK.

90% are Type 2 Diabetes (T2DM), 10% are Type 1 Diabetes (T1DM).
DM and 1-yr Composite Outcome and All-cause Mortality for ASIAN-HF Men and Women


4 X Hospitalization for Heart Failure in Diabetes

Major Diabetes Complications in USA

Hyperglycaemic Deaths

CVD Admissions
Management should be targeted at reducing / delaying CV complications in patients with T2DM with and without clinical CVD

Not just icing on the cake!!!
Insulin Resistance: An Inflammatory Atherothrombotic Syndrome

- Insulin Resistance
  - Hyperglycaemia
  - Hyperinsulinaemia
  - Hypertension
  - Smoking
    - Fibrinogen
    - Factor VII
    - Factor XII
    - PAI-1
    - tPA
  - Triglyceride
  - Cholesterol
  - PAI-1
  - tPA
  - Factor VII
  - Factor XII
  - CRP
  - Monocytes
  - Cytokines
  - Adhesion Molecules
  - Fibrinogen

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Risk Factors for CVD in patients with T2DM

271,174 pts with T2DM matched to 1,355,870 controls
Median F/U = 5.7 years with 175,345 deaths

Benefit of different interventions per 200 patients with diabetes treated for 5 years

Using traditional glucose lowering treatments

Per 4mm Hg lower SBP

Per 1mmol/L lower LDL-C

Per 0.9% lower HbA1c

CV Events

Diabetes Medications and Increased CV Risk

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Rosiglitazone Group</th>
<th>Control Group</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small trials combined</td>
<td>44/10,285 (0.43)</td>
<td>22/6106 (0.36)</td>
<td>1.45 (0.88–2.39)</td>
<td>0.15</td>
</tr>
<tr>
<td>DREAM</td>
<td>15/2,635 (0.57)</td>
<td>9/2634 (0.34)</td>
<td>1.65 (0.74–3.68)</td>
<td>0.22</td>
</tr>
<tr>
<td>ADOPT</td>
<td>27/1,456 (1.85)</td>
<td>41/2895 (1.42)</td>
<td>1.33 (0.80–2.21)</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td>1.43 (1.03–1.98)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Death from cardiovascular causes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small trials combined</td>
<td>25/6,845 (0.36)</td>
<td>7/3980 (0.18)</td>
<td>2.40 (1.17–4.91)</td>
<td>0.02</td>
</tr>
<tr>
<td>DREAM</td>
<td>12/2,635 (0.46)</td>
<td>10/2634 (0.38)</td>
<td>1.20 (0.52–2.78)</td>
<td>0.67</td>
</tr>
<tr>
<td>ADOPT</td>
<td>2/1,456 (0.14)</td>
<td>5/2895 (0.17)</td>
<td>0.80 (0.17–3.86)</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td>1.64 (0.98–2.74)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Diabetes Medications and Possible Increased CV Risk

FDA / EMA requirements:

- New diabetes drugs should demonstrate CV safety with meta-analysis and CV outcome trial
GLP-1RA CV Outcome Trials

**LEADER**

Time to first occurrence of CV death, non-fatal MI or non-fatal stroke

- **Liraglutide**
  - HR: 0.87
  - (95% CI: 0.78; 0.97)
  - p<0.001 for non-inferiority
  - p=0.01 for superiority

- **Placebo**

- **SUSTAIN 6**
  - **Semaglutide**
  - HR: 0.74
  - (95% CI: 0.58; 0.95)
  - p<0.001 for non-inferiority
  - p=0.02 for superiority
Empagliflozin, CV Outcomes and Mortality in T2DM

Primary Outcome

Death from Cardiovascular Causes

Death from Any Cause

Hospitalization for Heart Failure

CVD-REAL 2: Lower CV Risk Associated With SGLT-2 in 6 Countries: Asia Pacific, Middle East, North America - 27% established CVD

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Number of Events</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Cause Death (ACD)</td>
<td>5,216</td>
<td>0.51 [0.37, 0.70]</td>
</tr>
<tr>
<td>Hospitalization for Heart Failure (HHF)</td>
<td>5,997</td>
<td>0.64 [0.50, 0.82]</td>
</tr>
<tr>
<td>HHF+ACD</td>
<td>9,788</td>
<td>0.60 [0.47, 0.76]</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>2,249</td>
<td>0.81 [0.74, 0.88]</td>
</tr>
<tr>
<td>Stroke</td>
<td>6,439</td>
<td>0.68 [0.55, 0.84]</td>
</tr>
</tbody>
</table>

Diabetes Treatment for CVD Reduction

SGLT-2 Inhibitors

- Preload
- Afterload
- Epicardial Fat

GLP-1R Agonists

- Satiety
- Nausea

Hemodynamic Effect

- Major Adverse Cardiovascular Events
- Nephropathy
- Weight
- Blood Pressure

Anti-Atherogenic Effect

- Gastric motility
- Chylomicrons

Post-prandial Glucose

Insulin

Vasodilation

Glycosuria

Natriuresis

Uricosuria

Four weeks of liraglutide inhibits progression of atherosclerotic lesions in ApoE−/− mice


Lesion development

Lipid deposition

Intima–media ratio (IMR)

Haemotoxylin and eosin staining in the aortic arch

Oil red O staining performed in the aorta

IMR analysis performed in the aortic arch
## Meta-analysis of SGLT2i trials on hospitalisation for Heart Failure and CV death by established Atherosclerotic CV disease

<table>
<thead>
<tr>
<th>Patients with atherosclerotic cardiovascular disease</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>Treatment (n)</td>
<td>Placebo (n)</td>
<td>Treatment</td>
<td>Placebo</td>
</tr>
<tr>
<td>4645</td>
<td>2323</td>
<td>152</td>
<td>6.3</td>
<td>11.5</td>
</tr>
<tr>
<td>CANTAS Program</td>
<td>Treatment (n)</td>
<td>Placebo (n)</td>
<td>Treatment</td>
<td>Placebo</td>
</tr>
<tr>
<td>3756</td>
<td>2900</td>
<td>179</td>
<td>6.4</td>
<td>10.5</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>Treatment (n)</td>
<td>Placebo (n)</td>
<td>Treatment</td>
<td>Placebo</td>
</tr>
<tr>
<td>3474</td>
<td>3500</td>
<td>183</td>
<td>4.7</td>
<td>8.6</td>
</tr>
<tr>
<td>Fixed effects model for atherosclerotic cardiovascular disease (p&lt;0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients with multiple risk factors</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANTAS Program</td>
<td>Treatment (n)</td>
<td>Placebo (n)</td>
<td>Treatment</td>
<td>Placebo</td>
</tr>
<tr>
<td>2039</td>
<td>1447</td>
<td>70</td>
<td>4.1</td>
<td>6.6</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>Treatment (n)</td>
<td>Placebo (n)</td>
<td>Treatment</td>
<td>Placebo</td>
</tr>
<tr>
<td>5108</td>
<td>5078</td>
<td>182</td>
<td>3.0</td>
<td>5.9</td>
</tr>
<tr>
<td>Fixed effects model for multiple risk factors (p&lt;0.0001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Zelniker, T et al., Lancet 2019; 393: 31–39
Meta-analysis of SGLT2i trials on the composite of Renal Worsening, ESRD, or Renal Death by established Atherosclerotic CV disease

<table>
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<th>Weight (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment (n)</strong></td>
<td><strong>Placebo (n)</strong></td>
<td><strong>Treatment</strong></td>
<td><strong>Placebo</strong></td>
<td></td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>4687</td>
<td>2333</td>
<td>463</td>
<td>19.7</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>3756</td>
<td>2900</td>
<td>524</td>
<td>21.0</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>3474</td>
<td>3500</td>
<td>597</td>
<td>19.9</td>
</tr>
</tbody>
</table>

Fixed effects model for atherosclerotic cardiovascular disease (p<0.0001)

<table>
<thead>
<tr>
<th>Patients with multiple risk factors</th>
<th>Events</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td><strong>Treatment (n)</strong></td>
<td><strong>Placebo (n)</strong></td>
<td><strong>Treatment</strong></td>
<td><strong>Placebo</strong></td>
<td></td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>2039</td>
<td>1447</td>
<td>128</td>
<td>8.9</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>5108</td>
<td>5078</td>
<td>316</td>
<td>7.0</td>
</tr>
</tbody>
</table>

Fixed effects model for multiple risk factors (p=0.0634)

Source: Zelniker, T et al., Lancet 2019; 393: 31–39
Meta-analysis of SGLT2i trials on the composite of Myocardial Infarction, Stroke, and CV death (major adverse CV events) by Heart Failure

<table>
<thead>
<tr>
<th>Patients with history of heart failure</th>
<th>Events</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (n) Placebo (n)</td>
<td>Treatment Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPA-REG OUTCOME 462 244</td>
<td>124</td>
<td>63.6</td>
<td>23.6</td>
<td>0.72 (0.50-1.04)</td>
<td></td>
</tr>
<tr>
<td>CANVAS Program 803 658</td>
<td>203</td>
<td>35.4</td>
<td>34.1</td>
<td>0.61 (0.46-0.80)</td>
<td></td>
</tr>
<tr>
<td>DECLARE-TIMI 58 852 872</td>
<td>314</td>
<td>45.1</td>
<td>42.4</td>
<td>0.79 (0.63-0.99)</td>
<td></td>
</tr>
</tbody>
</table>

Fixed effects model for history of heart failure (p<0.0001)

<table>
<thead>
<tr>
<th>Patients with no history of heart failure</th>
<th>Events</th>
<th>Events per 1000 patient-years</th>
<th>Weight (%)</th>
<th>HR</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (n) Placebo (n)</td>
<td>Treatment Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPA-REG OUTCOME 4225 2089</td>
<td>339</td>
<td>15.5</td>
<td>30.0</td>
<td>0.63 (0.51-0.78)</td>
<td></td>
</tr>
<tr>
<td>CANVAS Program 4992 3689</td>
<td>449</td>
<td>13.6</td>
<td>32.4</td>
<td>0.87 (0.72-1.06)</td>
<td></td>
</tr>
<tr>
<td>DECLARE-TIMI 58 7730 7706</td>
<td>599</td>
<td>8.9</td>
<td>37.6</td>
<td>0.84 (0.72-0.99)</td>
<td></td>
</tr>
</tbody>
</table>

Fixed effects model for no history of heart failure (p<0.0001)

Source: Zelniker, T et al., Lancet 2019; 393: 31–39
Diabetes is very common in Heart Failure

<table>
<thead>
<tr>
<th>Medical History</th>
<th>HF-REF (%)</th>
<th>HF-PEF (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHD</td>
<td>48.4</td>
<td>37.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>49.1</td>
<td>40</td>
<td>0.857</td>
</tr>
<tr>
<td>MI</td>
<td>30.7</td>
<td>18.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Valve disease</td>
<td>23.9</td>
<td>31.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>52.1</td>
<td>59.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>33.3</td>
<td>33.5</td>
<td>0.577</td>
</tr>
<tr>
<td>Asthma</td>
<td>8.4</td>
<td>9.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>COPD</td>
<td>16.7</td>
<td>18.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
NHE-dependent Pathways That May Underlie the Interplay of Pathogenesis of HF and DM

Novel ‘Diabetes’ Drugs: Unanswered Questions

- Which patients benefit most from each drug? e.g. patients with HF or kidney disease
- Mechanisms by which drugs mediate CV benefit? ‘Bedside to Bench!’
- Are these drugs equally effective in patients without CVD or without DM (primary prevention)?

Heart failure
Nephropathy
Obesity

Future CVOTs

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The Ticking Clock: ↑ CV Risk Before ↑ Glucose
(Nurses’ Health Study)

20 yr F/U of 117,629 women: n=1,508 diabetes at B/L; n=5,894 developed diabetes; n=110,227 free from diabetes

Source: Hu et al, Diabetes Care 2002; 25: 1129-1134
SGLT2i In Different Patient Populations

Cardiorenal efficacy of SGLT2i

- **Renal protection**
- **Hospitalisation for heart failure**
- **Major adverse cardiovascular events**

**Diabetes and established cardiovascular disease**

**Secondary prevention population**
SGLT2i prevent heart failure and renal disease, and reduce atherosclerotic events (major adverse cardiovascular events)

**Diabetes and multiple risk factors**

**Primary prevention population**
SGLT2i prevent heart failure and renal disease but may not reduce major adverse cardiovascular events

In patients with type 2 diabetes and established atherosclerotic cardiovascular disease, antihyperglycemic therapy should begin with lifestyle management and metformin and subsequently incorporate an agent proven to reduce major adverse cardiovascular events and cardiovascular mortality (currently, empagliflozin and liraglutide), after considering drug-specific and patient factors (Table 8.1).

Exciting New Era for CVD Management in DM

- Opportunity to improve outcomes in millions of patients with diabetes
- Likely to be benefits beyond current evidence from trials
- Transform clinical care including the preclinical phase of cardiometabolic risk
Evidence Based CV Risk Reduction

- Statins
- BP Lowering
- Metformin

GLP1-RA

SGLT2-i
How to Organize Best Care for Patients with Diabetes?

Diabetologists, Cardiologists, Nephrologists, Primary Care physicians need to **work together in** care plan
Diabetes Treatment for CVD Reduction

SGLT-2 Inhibitors

- Preload
- Afterload
- Epicardial Fat

GLP-1R Agonists

- Satiety
- Nausea

Hemodynamic Effect

- Major Adverse Cardiovascular Events
- Nephropathy
- Weight
- Blood Pressure

Anti-Atherogenic Effect

- Gastric motility
- Chylomicrons

Vasodilation

Outcome Benefits in EMPA-REG OUTCOME, LEADER, and SUSTAIN 6 Trials

Source: Sattar J Am Coll Cardiol 2017;69:2646–2656
ASCVD predominates

GLP-1 RA with proven CVD benefits\(^1\)

OR

SGLT2-i with proven CVD benefit if eGFR adequate\(^1-2\)

If HbA\(_{1c}\) above target

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2-i, choose agents demonstrating CV safety:

- Consider adding the other class with proven CVD benefit
- DDP-IVi if not on GLP-1 RA
- Basal insulin\(^4\)
- TZD\(^5\)
- SU\(^6\)

Heart failure (HF) predominates

SGLT2-i with evidence of reducing HF in CVOT trials if eGFR adequate\(^2-3\)

OR

GLP-1 RA with proven CVD benefit\(^1\)

If HbA\(_{1c}\) above target

- Avoid TZD
- Choose agents demonstrating CV safety:
  - Consider adding the other class with proven CVD benefit\(^1\)
  - DDP-IVi (not Saxagliptin) if not on GLP-1 RA
  - Basal Insulin\(^4\)
  - SU\(^6\)
Outcomes by LVH subgroup: Empagliflozin vs Placebo

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR (95% CI)</th>
<th>Treatment by subgroup interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CV death</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients*</td>
<td>0.59 (0.46, 0.76)</td>
<td></td>
</tr>
<tr>
<td>LVH: Yes</td>
<td>0.40 (0.16, 1.01)</td>
<td>$P = 0.40$</td>
</tr>
<tr>
<td>LVH: No</td>
<td>0.60 (0.47, 0.78)</td>
<td></td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients*</td>
<td>0.65 (0.54, 0.80)</td>
<td></td>
</tr>
<tr>
<td>LVH: Yes</td>
<td>0.32 (0.13, 0.78)</td>
<td>$P = 0.11$</td>
</tr>
<tr>
<td>LVH: No</td>
<td>0.67 (0.55, 0.83)</td>
<td></td>
</tr>
<tr>
<td><strong>3-point MACE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients*</td>
<td>0.87 (0.74, 1.02)</td>
<td></td>
</tr>
<tr>
<td>LVH: Yes</td>
<td>0.39 (0.19, 0.81)</td>
<td>$P = 0.03$</td>
</tr>
<tr>
<td>LVH: No</td>
<td>0.89 (0.76, 1.05)</td>
<td></td>
</tr>
</tbody>
</table>

Source: Verma, S. et al, Diabetes Care Volume 42, March 2019; page e42-e44
Empagliflozin Impact after CABG: EMPA-REG Outcome Trial

CV death after CABG

CV death no CABG

All Cause Mortality after CABG

All Cause Mortality no CABG

Source: Verma Diabetologia 2018; 61:1712-1723
SGLT2i and GLP1-RAs: Give together?

- Complimentary Actions
- Both reduce blood glucose
- Both classes are naturetic
- Improve NO endothelial function
- SGLT2i can counteract adverse GLP1-RA cardiac effects?
GLP-1 RA in combination with SGLT2-i better than monotherapy in diabetic patients (on HbA1c)

52 weeks results of the DURATION-8 study

Percentage of patients achieving their glycemic and weight targets

Source: Jabbour et al, Diab Care July 2018, pub ahead of print, doi:10.2337/dc18-0680/-DC1
NHE-dependent Pathways That May Underlie the Interplay of Treatments of HF and DM

Blood pressure lowering and natriuresis in diabetes

Hypoglycemic drugs for diabetes
- GLP-1 agonists
- DPP-4 inhibitors
- SGLT2 inhibitors

Inhibition of NHE3 in kidney

Drugs for heart failure
- ACE inhibitors
- ANG receptor blockers
- MR antagonists
- Certain β-blockers
- Neprilysin inhibitors

Inhibition of NHE1 in heart and vasculature

Reduction in the risk of major adverse heart failure outcomes

Despite all of the Evidence for SGLT2i and GLP1-RAs…
their use is still low compared with OADs
Limitations and conclusions: “…The reductions in CVD events in T2DM patients reported for both CANVAS and EMPA-REG project to a positive cost avoidance for these events in an MCO population…”

# Overview of Described Effects of SGLT2 Inhibitors

## Favorable effects
- Reduction of pre-load (diuretic effects)
- Reduction of afterload (blood pressure, arterial stiffness)
- Improvement of mitochondrial efficiency
- Delay of decline in eGFR
- Delay of micro- and macroalbuminuria
- Weight loss
- Reduction in epicardial adipose tissue
- Improvement in glycemia
- Reduction in uric acid

## Unfavorable effects
- Amputations (in particular toe, metatarsal)
- Volume depletion/Hypotension
- Diabetic ketoacidosis
- Fractures
- Urinary and genital infections

Barriers to Best CVD Care in T2DM Patients

• Cardiologists
  ➢ General medicine poor
  ➢ Uncomfortable with Hypos
  ➢ Don’t like injectables!

• Diabetologists
  ➢ Disenfranchised by cardiologists
  ➢ Lack of effective CVD treatments until now
  ➢ Complex glucose centric guidelines
Cardiologists need to update themselves on good diabetes care

Checking the “diabetes” checks have been done is quick

Little additional work

Get to know your local diabetologist and what GPs can offer

Remember to screen for diabetes (HbA1c ≥ 6.5% or FPG ≥ 7 mmol/l)

“Take home” messages

It is NOT that complicated...

Surprise your patient: ask them about their diabetes!
Glucose Centric Guidelines Too Complicated…. 

<table>
<thead>
<tr>
<th>Healthy eating, weight control, increased physical activity</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy (+ HbA1c)</td>
<td>high</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>low risk</td>
</tr>
<tr>
<td>Weight</td>
<td>neutral/loss</td>
</tr>
<tr>
<td>Side effects</td>
<td>GI / lactic acidosis</td>
</tr>
<tr>
<td>Costs</td>
<td>low</td>
</tr>
</tbody>
</table>

If needed to reach individualized HbA1c target after ~3 months, proceed to two-drug combination (order not meant to denote any specific preference):

<table>
<thead>
<tr>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
</tr>
</thead>
</table>
| Sulfonlurea
| high |
| moderate risk |
| Hypoglycemia | low |
| gain |
| hypoglycemia | low |
| Thiazolidinediones
| high |
| low risk |
| gain |
| edema, HF, Frx |
| DPP-4 Inhibitor
| intermediate |
| low risk |
| neutral |
| GLP-1 receptor agonist
| high |
| low risk |
| loss |
| variable |

If needed to reach individualized HbA1c target after ~3 months, proceed to three-drug combination (order not meant to denote any specific preference):

<table>
<thead>
<tr>
<th>Metformin</th>
<th>Metformin</th>
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<th>Metformin</th>
</tr>
</thead>
</table>
| Sulfonlurea
| high |
| moderate risk |
| Hypoglycemia | low |
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| hypoglycemia | low |
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| high |
| low risk |
| gain |
| edema, HF, Frx |
| DPP-4 Inhibitor
| intermediate |
| low risk |
| neutral |
| GLP-1 receptor agonist
| high |
| low risk |
| loss |
| variable |

If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with one or two non-insulin agents:

- More complex insulin strategies
- insulin (multiple daily doses)

http://care.diabetesjournals.org/content/35/6/1364.full-text.pdf
Diabetes is a growing epidemic

World diabetes cases expected to jump 55 percent by 2035

Current and projected cases of diabetes by region

- South and Central America: 59.8%
- Africa: 109.6%
- North America/Caribbean: 37.3%
- Middle East/North Africa: 96.2%
- Europe: 22.4%
- Southeast Asia: 70.6%
- Western Pacific: 46.0%

Projected cases in 2035:

- 600 million people

Top 10 countries by number of people with diabetes in 2013, ages 20 to 79

1. China: 98.4 million
2. India: 65.1 million
4. Brazil: 11.9 million
5. Russia: 10.9 million
6. Mexico: 8.7 million
7. Indonesia: 8.5 million
8. Germany: 7.6 million
9. Egypt: 7.5 million
10. Japan: 7.2 million

≈1:10 people in the world will have diabetes by 2035....
Prevention is KEY!

“The commonest Instruments of suicide are a knife and fork”

Martin Fischer
Healthy Lifestyle and CVD in T2DM

CVD Incidence

- Number of Low-risk Lifestyle Factors
- HR (95% CI) of CVD Incidence
  - 0: 1
  - 1: 0.62
  - 2: 0.55
  - ≥3: 0.48

CVD Mortality

- Number of Low-risk Lifestyle Factors
- HR (95% CI) of CVD Mortality
  - 0: 1
  - 1: 0.63
  - 2: 0.46
  - ≥3: 0.32

Source: Lui, G et al, JACC 2018;71(25):2867-76
Heart Protection Study: Impact of Diabetes on CV outcome

SELECT: Trial Design, Population and Endpoint

N=17,500 patients
Male or female
≥45 years of age
BMI ≥ 27

Randomisation (1:1)

Semaglutide s.c. 2.4 mg once-weekly

Placebo s.c. once-weekly

Event driven
1225 first MACEs

Primary endpoint:
Time from randomisation to first occurrence of a composite endpoint consisting of either:
- CV death
- Non-fatal myocardial infarction
- Non-fatal stroke
Emerging Role of SGLT-2i For Treatment of Obesity.

Bodyweight Outcomes With Semaglutide 1mg and SGLT2i : (SUSTAIN 9)

Who else may benefit?

➢ Obese subjects with and without CVD?
➢ Patient with multiple CV RFs?
➢ Patients with Diabetes and no clinical CVD?
➢ Patients with Heart failure (HFPEF and HFREF) without Diabetes?
### Ongoing CV Outcome and HF Trials

<table>
<thead>
<tr>
<th>HF (Without Diabetes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ EMPEROR-Preserved (Empagliflozin – 4,126 pts)</td>
</tr>
<tr>
<td>➢ EMPEROR-Reduced (Empagliflozin – 2,850 pts)</td>
</tr>
<tr>
<td>➢ DEFINE-HF (Dapagliflozin : 4,500 pts)</td>
</tr>
<tr>
<td>➢ SOLOIST-WHF (Sotagliflozin : 4,000 pts)</td>
</tr>
</tbody>
</table>
Exciting New Era for CVD Management in DM

Diabetologists

Cardiologists

Primary Care

Nephrology