ADA/EASD guidelines for managing Type Diabetes.
Individualising care – cardiovascular and renal disease

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Clinical Director Diabetes NHS Lothian
Setting the scene

- Routine practice at that time focused on HbA1c and prevention of microvascular complications.
- Scepticism about improving CV outcomes in diabetes (poorer outcomes than non-diabetic subjects, patients with diabetes were older and more overweight).
- To increase awareness of macrovascular disease, MF suggested that diabetes should be redefined as “a state of premature cardiovascular death, that may also be associated with blindness and renal failure”.
- Recent CVOTs give us new options for CV risk reduction.
Outline of talk

• SIGN 154: key points
• ADA/EASD 2018 consensus document on glucose-lowering in T2DM
• CV risk
  • GLP-1 analogues
  • SGLT2 inhibitors
• CKD
## SIGN 154

### 1st LINE
In ADDITION to lifestyle measures

<table>
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<tr>
<th>METFORMIN*</th>
<th>EFICACY</th>
<th>CV BENEFIT</th>
<th>HYPOGLYCAEMIA RISK</th>
<th>WEIGHT</th>
<th>MAIN ADVERSE EVENTS</th>
<th>IN CKD STAGE 3A</th>
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<th>CV BENEFIT</th>
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In ADDITION to lifestyle measures

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<td>NO</td>
<td>HIGHEST</td>
<td>GAIN</td>
<td>HYPOGLYCAEMIA</td>
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</table>

Algorithm summarises evidence from the guideline in the context of the clinical experience of the Guideline Development Group. It does not apply in severe renal or hepatic insufficiency.

Prescribers should refer to the British National Formulary (www.medicinescomplete.com), the Scottish Medicines Consortium (www.scottishmedicines.org.uk) and Medicines and Healthcare products Regulatory Agency (MHRA) warnings for updated guidance on licensed indications, full contraindications and monitoring requirements.

*Continue medication at each stage if EITHER individualised target achieved OR HbA1c falls more than 0.5% (5.5 mmol/mol) in 3–6 months. **Discontinue if evidence that ineffective.**

**NOTES:**
1. Consider dose reduction. 2. Do not delay if first line options not tolerated / inappropriate. 3. See guideline pages 23 & 26-27. 4. See BNF: specific agents can be continued at reduced dose. 5. See BNF: no dose reduction required for insulin. 6. Poglitazone is contraindicated in people with (or with a history of) heart failure or bladder cancer. 7. Do not combine dapagliflozin with pioglitazone. 8. Caution with exenatide when eGFR <50 ml/min/1.73 m². 9. Adjust according to response. 10. Driving, occupational hazards, risk of falls, previous history.

**ABBREVIATIONS:**
CKD 3A = chronic kidney disease stage 3A (estimated glomerular filtration rate 45–59 ml/min/1.73 m²) CV = cardiovascular.
• What is a consensus report?
  – Comprehensive analysis of a medical issue by panel of experts. Expert opinion rather than guideline

• Last update: 2018
  – 5 EU and 5 US experts selected by ADA and EASD
  – Presented at EASD 5/10/18 in Berlin
  – Published simultaneously in *Diabetes Care* and *Diabetologia*
  – Informed by evidence generated in last 2 years

• Greater focus on:
  – Lifestyle, weight loss, obesity management (including surgery)
  – Patient-related issues and self management (impact on success of medications)
  – CVOT data and consideration of major clinical need
ADA/EASD: Decision cycle for patient centred care

Goals of care:
- Prevent complications
- Optimise quality of life

1. **Agree Management Plan**
2. **Implement Management Plan**
3. **Ongoing Monitoring and Support**
4. **Review & Agree Management Plan**
5. **Assess Key Patient Characteristics**
6. **Consider Specific Factors Which Impact on Choice of Treatment**
7. **Shared Decision Making to Create a Management Plan**
EASD/ADA guidelines
Overview

Goals of care
- Prevent complications
- Optimise quality of life

REVIEW & AGREE MANAGEMENT PLAN
- Review management plan
- Mutual agreement on changes
- Ensure agreed modification of therapy is implemented in a timeline fashion to avoid clinical inertia
- Decision cycle undertaken regularly (at least once/twice a year)

ONGOING MONITORING AND SUPPORT INCLUDING:
- Emotional well-being
- Check tolerability of medication
- Monitor glycaemic status
- Biofeedback including SMBG, weight, step count, HbA1c, BP, lipids

IMPLEMENT MANAGEMENT PLAN
- Patients not meeting goals generally should be seen at least every 3 months as long as progress is being made; more frequent contact initially is often desirable for DSMES

AGREE MANAGEMENT PLAN
Specify SMART goals:
- Specific
- Measurable
- Achievable
- Realistic
- Time limited

ASSESS KEY PATIENT CHARACTERISTICS
- Current lifestyle
- Comorbidities, i.e. ASCVD, CKD, HF
- Clinical characteristics, i.e. age, HbA1c, weight
- Issues such as motivation and depression
- Cultural and socio-economic context

CONSIDER SPECIFIC FACTORS THAT IMPACT ON CHOICE OF TREATMENT
- Individualised HbA1c target
- Impact on weight and hypoglycaemia
- Side-effect profile of medication
- Complexity of regimen i.e. frequency, mode of administration
- Choose regimen to optimise adherence and persistence
- Access, cost and availability of medication

SHARED DECISION MAKING TO CREATE A MANAGEMENT PLAN
- Involves an educated and informed patient (and their family/caregiver)
- Seeks patient preferences
- Effective consultation includes motivational interviewing, goal setting and shared decision-making
- Empowers the patient
- Ensure access to DSMES
Glucose lowering in T2DM – overall approach

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

EITHER/ OR

ASCVD PREDOMINATES

HF OR CKD PREDOMINATES

PFERABLY

SGLT2i with evidence of reducing HIF and/or CKD progression in CV/CKD if eGFR adequate

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate add GLP-1 RA with proven CV benefit

PREVENTABLE

SGLT2i with evidence of reducing HIF and/or CKD progression in CV/CKD if eGFR adequate

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate add GLP-1 RA with proven CV benefit

- Avoid T2D in the setting of HIF
  - Choose agents demonstrating CV safety:
    - Consider adding the other class with proven CV benefit
    - DPP-4i if not on GLP-1 RA
    - Basal insulin
    - T2D
    - SU

If further intensification is required or patient is new to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:

- Provod CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA, strong evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
- Be aware that SGLT2i vary by regime and individual agent with regard to indicated level of eGFR for initiation and continued use.
- Both empagliflozin and canagliflozin have shown reduction in HIF and reduction in CKD progression in CV/CKD.
- DPP-4i or GLP-1I have demonstrated CV safety
- Lower dose may be better tolerated though less well studied for CV effects
- Choose later generation SGL with lower risk of hypoglycaemia
- Consider basal insulin with lower risk of hypoglycaemia
Glucose lowering in established ASCVD or CKD

Use metformin unless contraindicated or not tolerated
If not at HbA<sub>1c</sub> target:
- Continue metformin unless contraindicated (remember to adjust dose/stop metformin with declining eGFR)
- Add SGLT2i or GLP-1 RA with proven cardiovascular benefit<br>  (See below)

If at HbA<sub>1c</sub> target:
- If already on dual therapy, or multiple glucose-lowering therapies and not on an SGLT2i or GLP-1 RA, consider switching to one of these agents with proven-cardiovascular benefit<br>  (See below)
- OR reconsider/review individualised target and introduce SGLT2i or GLP-1 RA
- OR reassess HbA<sub>1c</sub> at 3 month intervals and add SGLT2i or GLP-1 RA if HbA<sub>1c</sub> goes above target

---

ASCVD predominates

GLP-1 RA with proven CVD benefit<sup>1</sup>

EITHER/ OR

SGLT2i with proven CVD benefit<sup>2</sup>, if eGFR adequate<sup>2</sup>

If HbA<sub>1c</sub> above target

If further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CV benefit<sup>1</sup>
- DPP-4i if not on GLP-1 RA
- Basal insulin<sup>5</sup>
- TZD<sup>5</sup>
- SU<sup>7</sup>

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HF or CKD predominates

PREFERABLY
SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate<br>
- OR
- If SGLT2i not tolerated or contraindicated or if eGFR less than adequate<sup>4</sup> add GLP-1 RA with proven CVD benefit<sup>1</sup>

If HbA<sub>1c</sub> above target

- Avoid TZD in the setting of HF
- Choose agents demonstrating CV safety:
  - Consider adding the other class with proven CVD benefit<sup>1</sup>
  - DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
  - Basal insulin<sup>5</sup>
  - SU<sup>7</sup>

---

1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide = semaglutide = exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin = canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs
4. Cautions with GLP-1 RA in ESRD
5. Degludec or U100 glargine have demonstrated CVD safety
6. Low dose may be better tolerated though less well studied for CVD effects
7. Choose later generation SU to lower risk of hypoglycaemia
EASD/ADA guidelines

CVD predominates

Proven CVD benefit means it has label indication of reducing CVD.

For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release.

For SGLT2 inhibitors, evidence modestly stronger for empagliflozin > canagliflozin (but later data for dapagliflozin and data in autumn for ertugliflozin)
Semaglutide

Ozempic and SUSTAIN studies

- SMC approval 14/1/19
- GLP-1 RA with 94% homology to human GLP-1
- Weekly subcut injection. 0.25/0.5/1mg doses
- SUSTAIN 2 (Sita), 3 (Bydureon), 4 (lantus) and 7 (Trulicity): active comparator as add-on Rx to one or more OADs (ie as dual or triple therapy) All had similar design (30-56 weeks duration)
- SUSTAIN 5: semaglutide vs placebo as add-on to insulin
- SUSTAIN 6: CV outcomes trial of semaglutide vs placebo in T2DM with high risk of CV events
Double blind RCT

- 3297 pts >50 y/o with T2DM and HbA1c >53 mmol/mol and established CVD, CHF or CKD OR >60 y/o and ≥ 1 CV risk factor
- Mean age 64.6, duration DM 13.9 years, man weight 92.1 kg, HbA1c 72 mmol/mol and presence hypertension 92.8% - similar in both groups
SUSTAIN 6
CV outcomes

- Excluded pts with 2+ glc-lowering agents or insulin
- Baseline
  - 93.5% on antihypertensives
  - 76.5% on lipid-lowering drugs
  - 38.2% on diuretics
• Primary outcome: CV death, non-fatal MI or non-fatal CVA
  • HR 0.74 95% CI (0.58-0.95) p<0.001
SUSTAIN 6
CV outcomes

• Secondary outcome:

**B Nonfatal Myocardial Infarction**

Hazard ratio, 0.74 (95% CI, 0.51–1.08)

\[ P = 0.12 \]

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No. at Risk

Placebo 1649 1624 1598 1587 1562 1542 1516
Semaglutide 1648 1623 1609 1595 1582 1560 1543
SUSTAIN 6
CV outcomes

- Secondary outcome

![Graph showing nonfatal stroke outcomes]

**Nonfatal Stroke**

- Hazard ratio: 0.61 (95% CI, 0.38–0.99)
- \( P = 0.04 \)

**Patients with Event (%)**

**Weeks since Randomization**

**No. at Risk**

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SUSTAIN 6
CV outcomes

- Secondary outcome

**Death from Cardiovascular Causes**

- Hazard ratio, 0.98 (95% CI, 0.65–1.48)
  - P=0.92

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<tr>
<th>Weeks since Randomization</th>
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SUSTAIN 7
Dulaglutide vs semaglutide

- 40/52 open label RCT 4 armed trial
- 1119 adults with T2DM not controlled on MF randomised to:
  - 0.5mg semaglutide
  - 1mg semaglutide
  - 0.75mg dulaglutide
  - 1.5mg dulaglutide
- Primary endpoint change in HbA1c at week 40
- Secondary endpoint
  - Change in body weight at week 40
  - Proportion achieving HbA1c <53 mmol/mol
Semaglutide
SUSTAIN 7 (vs Trulicity)
Semaglutide Safety

- **SUSTAIN 6 (CV safety study vs placebo): increased risk of developing diabetic retinopathy complications vs placebo**
  - 3% (50) Ozempic vs 1.8% (29) placebo (HR 1.76; 95% CI 1.11-2.78; p=0.02).
  - Need for laser: 38 (2.8%) Ozempic vs 20 (1.2%) placebo
  - Vitreal bleed 16 (1%) vs 7 (0.4%); blindness 5 (0.3%) vs 1 (0.1%)
  - SMC calculate NNH for serious retinopathy = 77

- **Post hoc analysis**
  - **NO** increase in retinopathy in pts with no PHx of retinopathy
  - 969 pts (29.4%) had retinopathy at baseline: mean duration DM 17.08;
    baseline HbA1c 77 mmol/mol, 76% on insulin
  - Cannot exclude other mechanisms, but ?link to rapid HbA1c improvement
Semaglutide
Efficacy and safety summary

- Plus metformin: better HbA1c lowering and wt loss vs Trulicity
- Plus 1-2 OADs: better HbA1c lowering and weight loss than Bydureon and much better than sitagliptin
- Plus 2-3 OADs: better HbA1c lowering and weight loss vs glargine
- Caution needed around patients with pre-existing retinopathy
- No evidence for semaglutide as part of 4 medicine therapy or in combination with SGLT2 inhibitors
- Limited evidence in combination with pioglitazone
- Limited experience in >75 y/o or severe renal impairment
- Reduction in 3 point MACE driven by non-fatal CVA
Weekly GLP-1’s
Dulaglutide/Trulicity

- Modified human GLP-1 analogue (>90% homology)
- t½ 4.7 days: weekly use
- Ready-to-use, single-use pens
- 0.75mg and 1.5mg dose available
- 1.5mg dose for most
- (0.75mg dose for monotherapy or elderly)
- No reconstitution needed
- No waiting involved
- Hidden 29G needle included
Trulicity® (dulaglutide): Cardiovascular Outcomes

SUMMARY

- A meta-analysis of four phase 2 and five phase 3 studies evaluating once-weekly dulaglutide treatment for up to 104 weeks in 6010 patients with T2DM determined there was no increase in a composite endpoint of MACE-4 with dulaglutide treatment compared with control therapies (HR: 0.57; adjusted 98.02% CI: 0.30, 1.10). ¹

- The Reducing Cardiovascular Events with a Weekly INcretin in Diabetes, REWIND, study was an event-driven, randomized, double-blind, phase 3 study evaluating once-weekly dulaglutide 1.5 mg treatment compared with placebo when added to standard of care for a composite endpoint of MACE-3 in adults with T2DM and CV disease and/or risk factors. ²

- Top-line results showed dulaglutide 1.5 mg significantly reduced MACE-3 when compared to placebo. These results demonstrate the CV efficacy of dulaglutide in a population that included majority of participants who did not have established CV disease. Full REWIND data evaluations are ongoing. Detailed results will be released at scientific sessions of American Diabetes Association in June 2019. ³
SGLT2 inhibitors

- SGLT2 inhibitors
  - Empagliflozin
  - Canagliflozin (CREDENCE: renal)
  - Dapagliflozin (DECLARE-TIMI: CVOT; DEPICT: renal)
  - Ertugliflozin
Dapagliflozin selectively inhibits SGLT2 in the renal proximal tubule

1. FORXIGA Summary of Product Characteristics
• Similar HbA1c lowering to SUs

• 300Kcal/day lost in glycosuria:
  • 3-4kg weight loss

• Not linked to hypos

• Main side effect is thrush and UTIs (mode of action)
AIM: Examine long-term effects of empagliflozin on CV outcomes in patients with T2DM at high risk of CV events

- Study medication was given in addition to standard of care
  - Glucose-lowering therapy was to remain unchanged for first 12 weeks
- Treatment assignment double masked
- The trial was to continue until at least 691 patients experienced an adjudicated primary outcome event
CV death

HR 0.62
(95% CI 0.49, 0.77)
p < 0.0001
Hospitalisation for heart failure

HR 0.65
(95% CI 0.50, 0.85)
p = 0.0017
SGLT2 inhibitors

- Highly selective insulin-independent SGLT2 inhibition in PCT:
  - Reduces HbA1c
  - Secondary benefit of weight loss (net loss ~300Kcal/day)
  - Once a day, any time, with or without food, no titration
  - Does not directly cause hypoglycaemia
  - Main side effects relate to UTIs/thrush
  - Can be used with other oral agents or with insulin
  - Not currently licensed for type 1 diabetes

- Empagliflozin on formulary (based on CV secondary prevention data)
- Dapagliflozin: DECLARE-TIMI 58 CVOT
• 17,160 pts with T2DM randomized to dapagliflozin or placebo
  – 6,974 had ASCVD (3,584 had PHx MI, median time from event 5.4 years).
  –Pts with PHx MI were at ~2x higher risk for both MACE and HHF/CV death.
• Dapagliflozin reduced MACE by 16% (HR 0.84, 95% CI 0.72-0.99, p=0.039) in those with PHx MI
• Benefits driven by significant reductions in recurrent MI
• Did not reduce MACE in those with established ASCVD but no prior MI (HR 0.98, 0.81-1.19; p=0.85;)
• Trend towards fewer CHD deaths (HR 0.84), all-cause mortality (HR 0.83), and the composite of CHD death, nonfatal recurrent MI or sudden death (HR 0.81). Not significant
• MACE benefits greater in those with MI < 2 years ago.
• Benefit on hospitalisation for HF in all subgroups (greatest in patients with prior MI).
SGLT2 inhibitors: DECLARE-TIMI 58

### Primary Outcome – CV death, MI or ischemic stroke

**Patients with prior MI**

HR (95% CI) = HR 0.84 (0.72 to 0.99)

**Patients without prior MI**

HR (95% CI) = HR 1.00 (0.88 to 1.13)

**Absolute risk reduction**

2.6% (prior MI) vs. 0% (no prior MI)

---

**Number at risk:**

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SGLT2 inhibitors: DECLARE (Dapagliflozin)

Panel A. Effects of Dapagliflozin 10 mg vs. placebo

- Prior MI <2 years ago
  - MACE: NNT_{4yrs} = 38
  - CVD/HHF: NNT_{4yrs} = 53

- Prior MI

- CVD but no prior MI

- Primary Prevention

Type 2 Diabetes Population in DECLARE
EASD/ADA guidelines

HF/CKD predominates

1. Empa- , Canagliflozin (and dapagliflozin) have shown reduction in HF and CVD progression in CVOTs

Caution with GLP-1 RA in ESRD

Tresiba (Degludec) or Lantus have demonstrated CVD safety
SGLT2 in renal disease: CREDENCE NEJM April

• CREDENCE: 1st SGLT2 renal outcomes trial in CKD plus T2D
• Double-blind, placebo-controlled, multicenter RCT: evaluates efficacy and safety of canagliflozin versus placebo in preventing clinically important renal and CV outcomes in T2D and CKD
• Randomised 4,401 patients with T2D, eGFR 30-90 mL/min/1.73 m², and ACR >300-5,000 mg/g). All patients on maximum dose of ACE-I or ARB for < 4/52 prior to randomization. Median FU 2.62 years
• 1º composite endpoint was any of: ESKD, doubling of serum creatinine, and renal or CV death.
• 2º endpoints incl composite of CV death and HF hospitalisation.
• Trial stopped early at planned interim analysis – endpoints met
RR of 1° outcome 30% lower in canagliflozin than placebo (Event rate 43.2 & 61.2/1000 pt-years, respectively).

RR of the renal-specific composite of ESKD, doubling of creat, or death from renal causes was 34% lower.

RR of ESKD was 32% lower.

RR of CV death 22% lower.

RR of hospitalization for HF 39% lower (HR 0.61 95% CI 0.47-0.8 p<0.001).

No differences in rates of
Double blind multi-centre RCT

Enrolled patients with T2DM, ACR 30-3500mg/g, eGFR 25-75, HbA1c 53-97mmol/l, on stable dose ACE/ARB and OHAs for last 12/52.

Randomised: dapa 10mg or dapa 10mg+saxaglitpin 2.5mg or placebo

116 centres. 24/52 duration

Primary endpoint were change in baseline from ACR and HbA1c
SGLT2 in renal disease: DELIGHT Lancet April

1187 patients screened
- 623 excluded
  - 610 failed screening
  - 12 withdrawn by patient or legal representative
  - 1 lost to follow-up

564 patients entered run-in period
- 103 excluded
  - 95 failed screening
  - 8 withdrawn by patient or legal representative

461 participants randomly allocated to treatment
- 157 allocated to dapagliflozin-saxagliptin group
  - 2 excluded at single site
  - 155 included in intention-to-treat analysis
    - 5 did not complete follow-up
      - 2 withdrew from study
      - 2 did not meet inclusion criteria
      - 1 death
    - 150 (97%) patients completed study
- 151 allocated to dapagliflozin group
  - 6 excluded at single site
  - 145 included in intention-to-treat analysis
    - 8 did not complete follow-up
      - 3 withdrew from study
      - 2 lost to follow-up
      - 1 doctor's decision due to extreme non-compliance
      - 1 other reason
      - 1 death
    - 137 (94%) patients completed study
- 153 allocated to placebo group
  - 5 excluded at single site
  - 148 included in intention-to-treat analysis
    - 5 did not complete follow-up
      - 4 withdrew from study
      - 1 lost to follow-up
    - 143 (57%) patients completed study
SGLT2 in renal disease: DELIGHT Lancet April

A. Difference versus placebo at week 24

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Adjusted mean change in HbA1c (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=148)</td>
<td>-0.6% (-1.4% to 0.2%)</td>
</tr>
<tr>
<td>Dapagliflozin (n=144)</td>
<td>-0.2% (-1.0% to 0.6%)</td>
</tr>
<tr>
<td>Dapagliflozin-saxagliptin (n=152)</td>
<td>-0.4% (-1.2% to 0.4%)</td>
</tr>
</tbody>
</table>

B. Difference versus placebo at week 24

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Adjusted mean change in HbA1c (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=148)</td>
<td>0.0% (-0.6% to 0.6%)</td>
</tr>
<tr>
<td>Dapagliflozin (n=144)</td>
<td>0.3% (-0.4% to 1.0%)</td>
</tr>
<tr>
<td>Dapagliflozin-saxagliptin (n=152)</td>
<td>0.5% (-0.2% to 1.2%)</td>
</tr>
</tbody>
</table>

C. Difference versus placebo at week 24

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Adjusted mean change in bodyweight (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=148)</td>
<td>0.0% (-0.2% to 0.2%)</td>
</tr>
<tr>
<td>Dapagliflozin (n=144)</td>
<td>0.3% (-0.1% to 0.7%)</td>
</tr>
<tr>
<td>Dapagliflozin-saxagliptin (n=152)</td>
<td>0.4% (-0.0% to 0.8%)</td>
</tr>
</tbody>
</table>

D. Difference versus placebo at week 24

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Adjusted mean change in eGFR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=148)</td>
<td>0.0% (-0.3% to 0.3%)</td>
</tr>
<tr>
<td>Dapagliflozin (n=144)</td>
<td>0.2% (-0.1% to 0.5%)</td>
</tr>
<tr>
<td>Dapagliflozin-saxagliptin (n=152)</td>
<td>0.3% (-0.0% to 0.6%)</td>
</tr>
</tbody>
</table>

Patients per timepoint:
- Dapagliflozin: 144, 143, 137, 137, 136, 136, 133, 133
- Dapagliflozin-saxagliptin: 152, 151, 149, 144, 144, 143, 143, 143
• Dapa and dapa-saxa reduced ACR vs placebo
• At week 24, difference versus placebo in mean UACR change from baseline was -21% for dapagliflozin and -38% for dapa-saxa combo
• No difference in adverse events between groups
• No new drug-related safety signals

• Much smaller study than CREDENCE (461 vs 4401 randomised)
• Different endpoints:
  – DELIGHT looked at ACR and HbA1c
  – CREDENCE looked at 1° composite endpoint: ESKD, doubling of serum creatinine, and renal or CV death. 2° endpoints incl composite of CV death and HF hospitalisation (30-34% reductions)
### Key prescribing points

#### Diabetes and CKD

<table>
<thead>
<tr>
<th>Drug/eGFR</th>
<th>&lt;30 ml/min/1.73m²</th>
<th>30-44 ml/min/1.73m²</th>
<th>45-59 ml/min/1.73m²</th>
<th>&gt;60 ml/min/1.73m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>STOP</td>
<td>Dose reduction</td>
<td>OK</td>
<td>OK</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>STOP</td>
<td>Dose reduction</td>
<td>Dose reduction</td>
<td>OK</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>OK</td>
<td>OK</td>
<td>OK</td>
<td>OK</td>
</tr>
</tbody>
</table>

#### DPP-4 inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>&lt;30 ml/min/1.73m²</th>
<th>30-44 ml/min/1.73m²</th>
<th>45-59 ml/min/1.73m²</th>
<th>&gt;60 ml/min/1.73m²</th>
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</thead>
<tbody>
<tr>
<td>Alogliptin</td>
<td>Dose reduction</td>
<td>Dose reduction</td>
<td>Dose reduction</td>
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</tr>
<tr>
<td>Linagliptin</td>
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<td>OK</td>
<td>OK</td>
<td>OK</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>Dose reduction</td>
<td>Dose reduction</td>
<td>OK</td>
<td>OK</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>STOP</td>
<td>Dose reduction</td>
<td>Dose reduction</td>
<td>OK</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>Caution</td>
<td>Dose reduction</td>
<td>Dose reduction</td>
<td>OK</td>
</tr>
</tbody>
</table>

#### GLP-1 agonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>&lt;30 ml/min/1.73m²</th>
<th>30-44 ml/min/1.73m²</th>
<th>45-59 ml/min/1.73m²</th>
<th>&gt;60 ml/min/1.73m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dulaglutide</td>
<td>STOP</td>
<td>OK</td>
<td>OK</td>
<td>OK</td>
</tr>
<tr>
<td>Exenatide SR</td>
<td>STOP</td>
<td>Dose reduction</td>
<td>Dose reduction</td>
<td>OK</td>
</tr>
<tr>
<td>Exenatide MR</td>
<td>STOP</td>
<td>STOP</td>
<td>STOP</td>
<td>OK</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>STOP</td>
<td>OK</td>
<td>OK</td>
<td>OK</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>STOP</td>
<td>Caution</td>
<td>OK</td>
<td>OK</td>
</tr>
</tbody>
</table>

#### SGLT-2 inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>&lt;30 ml/min/1.73m²</th>
<th>30-44 ml/min/1.73m²</th>
<th>45-59 ml/min/1.73m²</th>
<th>&gt;60 ml/min/1.73m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>STOP</td>
<td>STOP</td>
<td>Dose reduction</td>
<td>OK</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>STOP</td>
<td>STOP</td>
<td>STOP</td>
<td>OK</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>STOP</td>
<td>STOP</td>
<td>Dose reduction</td>
<td>OK</td>
</tr>
</tbody>
</table>

Diabetes handbook being updated. Includes prescribing aide memoire with relevant hyperlinks, eg to this table.
Prescribing aide memoire

- Decide main priorities jointly with patient (CVD/hypo/weight etc)
- Discuss risks and benefits of new meds (BRAN). Realistic Medicine
- Review medication on a regular basis. If don’t achieve HbA1c drop of 5.5mmol/mol after 3-6 months check adherence and consider discontinuation.
- Hypoglycaemia. Consider the risk of developing hypos with SUs
- Ramadan/fasting: may need to reduce/stop Gliclazide. SBMG may help
- For frail and elderly patients, it is appropriate to relax HbA1c targets.
- Women of child-bearing age: discuss family planning. Statins, ACE-I’s, oral agents other than metformin and GLP-1 analogues contraindicated.
- Be mindful of dose adjustment or need to stop meds for CKD
- Sick Day Rules – NHS cards. During illness, may need to stop ACE inhibitors, ARBs, NSAIDs, diuretics, metformin and SGLT2 inhibitors
- CVD risk – currently, drugs with cardiovascular benefit include empagliflozin, canagliflozin, liraglutide and semaglutide
Summary EASD/ADA 2018 consensus

- Decision cycle for patient-centred care

- Glucose lowering in T2DM
  - 1st line metformin and lifestyle
  - Prioritise established ASCVD or CKD
  - If not, consider compelling need to:
    - Minimise hypo
    - Minimise weight gain or promote weight loss
    - Prioritise cost

- LJF reflects CV data
Move on to Prof Strachan’s talk and have panel discussion at the end
Number needed to treat (NNT) to prevent one death across landmark trials in patients with high CV risk

- **Simvastatin**: 30 NNT for 5.4 years
  - Pre-statin era: 1994
  - High CV risk: 5% diabetes, 26% hypertension

- **Ramipril**: 56 NNT for 5 years
  - Pre-ACEi/ARB era: 2000
  - High CV risk: 38% diabetes, 46% hypertension

- **Empagliflozin**: 39 NNT for 3 years
  - >80% ACEi/ARB
  - >75% statin
  - >80% ACEi/ARB
  - T2DM with high CV risk: 92% hypertension

1. 4S investigator. Lancet 1994; 344: 1383-89, [http://www.trialresultscenter.org/study2590-4S.htm](http://www.trialresultscenter.org/study2590-4S.htm)
SGLT2 inhibitors: DECLARE (Dapagliflozin)