CVD risk - micro and macrovascular disease screening and management

Shafie Kamaruddin
Consultant Diabetes & Endocrinology
Disclosures

• Speaker Honoraria

  • Lilly, Boehringer Ingelheim, Sanofi, Novo Nordisk, Astra Zeneca, Takeda, Roche & Medtronic
Background

**Headline stats**

1. **4.7 million** people in the UK have diabetes.
2. Someone is diagnosed with diabetes every **two minutes**.
3. At least **10,350** people in the UK have end stage kidney failure because of their diabetes.
4. More than **1,700** people have their sight seriously affected by their diabetes every year in the UK.

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**Every week** diabetes leads to more than

- **169 amputations**
- **680 strokes**
- **530 heart attacks and almost 2,000 cases of heart failure.**

More than **500** people with diabetes die prematurely every week.
Microvascular

- Retinopathy
- Nephropathy
- Neuropathy
- Dermopathy
- Cheiroarthropathy
- Cardiomyopathy
- Cognitive impairment
UKPDS analysis: 1% (11mmols/mol) decrease in HbA1c is associated with a lower relative risk of complications

1% decrease in HbA$_{1c}$

- 43% Amputation or fatal peripheral blood vessel disease*
- 37% Microvascular complications e.g. kidney disease and blindness*
- 21% Deaths related to diabetes*
- 14% Heart attack*
- 12% Stroke†

*P<0.0001; †P=0.035.
UKPDS=UK Prospective Diabetes Study.
Retinopathy

Why bother screening?

• Leading cause of new onset blindness in the developed world
• Sight threatening microvascular complications
• >90% of vision loss resulting from proliferative retinopathy is preventable
• Majority are asymptomatic even at proliferative stage
Retinopathy

Type 1 Diabetes
• 25% will develop after 5 years
• 60-80% after 10-15 years

Type 2 Diabetes
• Proliferative Retinopathy (DPR) present in 25% after 15 years
Retinopathy

Risk factors:

• Long duration of diabetes
• Poor glycaemia
• Hypertension
• Pregnancy*
• Asian or Afro-Caribbean ethnic background
Retinopathy

Stages:

- **Background retinopathy (R1)**
  - bulge slightly (microaneurysms)
  - leak blood (retinal haemorrhages)
  - leak fluid (exudates)

- **Pre-proliferative (R2)**
  - R1 + hard exudates, cotton wool spots
  - IRMA

- **Proliferative (R3)**
  - Neovascularisation
  - Vitreous haemorrhage
  - Retinal detachment
  - S (stable), P (photocoagulation)

- **Maculopathy**
  - M0 – no macular involvement
  - M1
    - Above + leakage involving the fovea
Diabetic macular edema: Appearance on optical coherence tomography

(A) Optical coherence tomography (OCT) of diabetic macular edema. There are numerous large cysts visible within the macula (arrows), and the retinal thickness is increased.
(B) OCT of normal macula (for comparison) showing typical foveal contour.
**Retinopathy**

Management:

- Frequency of screening subject to staging and referral to ophthalmology
- Glycaemic control
- Drugs
  - Anti-VEGF & steroid injections
    - reduce macular oedema
    - reduce proliferation
  - ACE inhibitors
    - effect of lowering blood pressure
    - lower levels of vascular endothelial growth factor
  - Aspirin – no contraindication
Nephropathy

Definition:

• Presence of albuminuria with progressive decline in glomerular filtration rate

• Increased urinary albumin excretion is defined as ≥3.4 mg/mmol

Screening:

• Spot urine for albumin creatinine ratio – 2 samples
• Qualitative test – not useful for diagnosis or follow up
• Annual test
Nephropathy

• In Type 1 Diabetes, albuminuria is typically associated with retinopathy

• Rapid decline in eGFR is a greater prognostic importance as albuminuria can be variable and may regress

• However long duration of albuminuria (even after regression) can lead to up to four fold decline in eGFR when compared to patients with normoalbuminuria
Nephropathy

Management:

- Optimise glycaemia
- Optimise blood pressure
- ACE inhibitor /ARB renal protection
- SGLT2 inhibitor
  - CREDENCE Study
    - Type 2 DM + Chronic Kidney Disease (CKD)
    - eGFR 30–90
    - Urine albumin creatinine ratio (ACR) >30 mg/mmol

Image: Strict glycemic control prevents moderately increased albuminuria (formerly called microalbuminuria) in patients with type 1 diabetes mellitus.

Graph: Cumulative incidence of moderately increased albuminuria (formerly called microalbuminuria) in patients with type 1 diabetes treated with either conventional or intensive insulin therapy for up to nine years. There was an increasing benefit of intensive therapy over time (p<0.04).

CREDENCE: Canagliflozin and renal outcomes in type 2 diabetes and nephropathy

**Study design and participants**
- 4401 patients with T2DM & UACR >300 mg/g
- 62 years
- eGFR 57
- UACR 927 mg/g
  - 104.7 mg/mmol

**Intervention**
- Stable on maximum dose tolerated ACEi or ARB for 4 weeks

**Outcomes**

- **Primary outcome**
  - Doubling of serum creatinine, ESKD, death due to cardiovascular or kidney disease
  - HR 0.70
  - (95% CI 0.59-0.82)
  - NNT 21

- **End-stage kidney disease**
  - HR 0.68
  - (95% CI 0.54-0.86)
  - NNT 42

**Conclusion**
- In patients with type 2 diabetes and kidney disease, canagliflozin reduces the risk of kidney failure and cardiovascular events
  - No increased risk of:
    - Amputations
      - HR 1.10
      - (95% CI 0.79-1.56)
    - Fractures
      - HR 0.98
      - (95% CI 0.70-1.37)
Effects on eGFR in the CREDENCE study

LS Mean Change (±SE) in eGFR (mL/min/1.73 m²)

- Acute eGFR slope (3 weeks)
  Difference: −3.17 (95% CI −3.87, −2.47)

- Chronic eGFR slope
  Difference: 2.74/year (95% CI 2.37–3.11)

No. of Participants

Placebo: 2,178  2,084  1,985  1,882  1,720  1,536  1,006  583  210
Canagliflozin: 2,179  2,074  2,005  1,919  1,782  1,648  1,116  652  241

Neuropathy

• Peripheral & autonomic neuropathy is the commonest form in both type 1 and type 2 diabetes

• Prevalence varies with severity and duration of hyperglycaemia, superimposed upon cardiovascular risk factors

• Approximately 50% of patient with diabetes will develop neuropathy

• Substantial morbidity leading infection, ulcerations & amputations

• Diabetic foot ulcer associated with 2.5 increased risk of mortality
Neuropathy

Classification:

• Distal symmetric polyneuropathy

• Autonomic neuropathy

• Painful diabetic neuropathy

• Individual cranial and peripheral nerve involvement causing focal mononeuropathies, especially affecting the oculomotor nerve (cranial nerve III) and the median nerve

• Asymmetric involvement of multiple peripheral nerves, resulting in a mononeuropathy multiplex
Neuropathy

• Screening
  • 10 gauge monofilament testing
  • pulse / doppler
  • deformity
  • basic foot care
  • moderate to high risk – podiatry led*
  • Always consider other causes

• History
  • Distal symmetrical neuropathy
    • Pin prick & temperature (small fibres)
    • Sensory & vibration (large fibres)
  • Autonomic neuropathy (small fibres)
    • Hypoglycaemia unawareness
    • Orthostatic hypotension
    • Recurrent UTI’s, Sexual dysfunction & ED
    • Resting tachycardia
    • Abnormal sweating
    • Gastroparaesis
Neuropathy

• Management

  • Glycaemia control
    • Slow down progression, no reversal of neuronal loss

  • Risk assessment & frequency of review

  • Basic foot care

  • Appropriate foot wear

  • Pain management
    • Simple analgesia for mild to moderate then Duloxetine, Amitryptiline, Pregabalin
    • Tapentadol
Neuropathy

• Management of autonomic dysfunction
  • Gastroparaesis
    • Medication review that can affect gut motility – Anticholinergics, GLP-1 RA
    • Prokinetics – Metoclopramide (short term)
      • Domperidone & Erythromycin - tachyphylaxis
    • Insulin Pump Therapy (Type 1 DM)
    • Gastric pacemaker
  
• Orthostatic hypotension
  • Medication review
  • Adequate salt & fluid intake
  • Exercise to avoid deconditioning
  • Drugs - Midodrine
Macrovascular Complications

- Myocardial Infarction
- Stroke
- Heart Failure
- Erectile Dysfunction
- Peripheral Arterial Disease
<table>
<thead>
<tr>
<th>INTERVENTION</th>
<th>NNT OVER 5 YEARS TO PREVENT 1 CV EVENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowering HbA1C by 11mmol/mol (1%)</td>
<td>119</td>
</tr>
<tr>
<td>Lowering cholesterol by 1mmol/l</td>
<td>44</td>
</tr>
<tr>
<td>Lowering BP by 10/5mmHg</td>
<td>34</td>
</tr>
</tbody>
</table>
Type 2 Diabetes & CVD

• CVD remains the leading cause of death in T2D
  • Overall, CVD risk is around double in those with T2D (Emerging Risk Factors Collaboration, Lancet 2010)
  • Despite optimal treatment of risk factors, there is still significant residual CV risk in those with diabetes
    • TNT trial (NEJM 2005), STENO-2 study 21-year follow-up (Diabetologia 2016)
# Diabetes and the risk of vascular disease

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of cases</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coronary heart disease</strong></td>
<td>24 898</td>
<td>1.89 (1.81–1.98)</td>
</tr>
<tr>
<td>Coronary death</td>
<td>11 164</td>
<td>2.16 (2.01–2.31)</td>
</tr>
<tr>
<td>Non-fatal myocardial infarct</td>
<td>13 671</td>
<td>1.74 (1.64–1.84)</td>
</tr>
<tr>
<td><strong>Cerebrovascular disease</strong></td>
<td>11 036</td>
<td>1.76 (1.65–1.86)</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>3 659</td>
<td>2.19 (1.95–2.65)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>1 183</td>
<td>1.14 (0.90–1.43)</td>
</tr>
<tr>
<td>Unclassified stroke</td>
<td>4 973</td>
<td>1.68 (1.54–1.83)</td>
</tr>
<tr>
<td><strong>Other vascular deaths</strong></td>
<td>3 826</td>
<td>1.50 (1.34–1.68)</td>
</tr>
</tbody>
</table>

Data from 528,877 participants – adjusted for age, sex, cohort, SBP, smoking, BMI.
BMI, body mass index; CI, confidence interval; HR, hazard ratio; I², evolution of heterogeneity; SBP, systolic blood pressure
Prevalence of Established Cardiovascular Disease in Patients with Type 2 Diabetes Mellitus in the UK

Dominik Lautsch · Tongtong Wang · Lingfeng Yang · Swapnil N. Rajpathak

Atherothrombotic diseases
n=52,601 (35.4%)

Heart Failure
n=8,650 (5.8%)

Established cardiovascular disease
n=54,874 (36.9%)

No established cardiovascular disease
n=93,929 (63.1%)
How do we modify CV risk in T2D?

- Lifestyle modification
- Glycaemic control
- Blood pressure control
- Platelet inhibition
- Management of dyslipidaemia

CV, cardiovascular
Effects of modifying CV risk factors in diabetes: Lifestyle modification

**Improvements in CV risk factors, and glucose-lowering medications**

**Weight**
- Intervention: Main effect, −4 kg
- Control
- 95% CI: −5; −3
- p<0.001

**HbA1c**
- Intervention: Main effect: −0.22% 95% CI: −0.28; −0.16
- Control
- p<0.001

Effects of modifying CV risk factors in diabetes:
Blood pressure control

A 10 mmHg reduction in systolic blood pressure was associated with a significant reduction in macrovascular outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of studies</th>
<th>Events</th>
<th>Participants</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>20</td>
<td>2 334</td>
<td>27 693</td>
<td>0.87 (0.78; 0.96)</td>
</tr>
<tr>
<td>CV disease</td>
<td>17</td>
<td>3 230</td>
<td>25 756</td>
<td>0.89 (0.83; 0.95)</td>
</tr>
<tr>
<td>CHD</td>
<td>17</td>
<td>1 390</td>
<td>26 150</td>
<td>0.88 (0.80; 0.98)</td>
</tr>
<tr>
<td>Stroke</td>
<td>19</td>
<td>1 350</td>
<td>27 614</td>
<td>0.73 (0.64; 0.83)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>13</td>
<td>1 235</td>
<td>21 684</td>
<td>0.86 (0.74; 1.00)</td>
</tr>
</tbody>
</table>

Emdin et al. JAMA 2015: Meta-analysis

Blood pressure

Age < 80
- Clinic BP < 140/90
- ABPM or HBPM < 135/85
- Type 1 DM < 135/85

Age ≥ 80
- Clinic BP < 150/90
- ABPM or HBPM < 145/85

Postural Hypotension
- Base target on standing BP

CKD, albuminuria > 70mg/mmol
- <130/80 (systolic 120 - 129 mmHg)
Effects of modifying CV risk factors in diabetes:
Management of dyslipidaemia

37% reduction in acute coronary events, coronary revascularisation or stroke

Cumulative hazard (%)

<table>
<thead>
<tr>
<th>Time from randomisation (years)</th>
<th>Placebo</th>
<th>Atorvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**RR: -37%**
**(95% CI: -52; -17)**

*p* = 0.001

Colhoun *et al.* Lancet 2004

Adapted from Colhoun *et al.* Lancet 2004;364:685–96
Dyslipidaemia

Primary prevention

• Type 1 Diabetes
  • > 40 years
  • diabetes > 10 years
  • established nephropathy
  • CVD risk factors

• Type 2 Diabetes
  • 10% or greater 10-year risk of developing CVD (QRISK2)

Lipid modification

• Baseline lipid profile
  • non fasting

• Primary prevention
  • Atorvastatin 20 mg

• Secondary prevention
  • Atorvastatin 80 mg

• Target > 40% reduction in non-HDL
Effects of modifying CV risk factors in diabetes:
Platelet inhibition


**25% reduction in CV death, non-fatal MI and non-fatal stroke**

<table>
<thead>
<tr>
<th>BENEFIT per 1 000 patients (SD):</th>
<th>2P:</th>
<th>36 (3)</th>
<th>&lt;0.00001</th>
<th>38 (12)</th>
<th>&lt;0.002</th>
</tr>
</thead>
</table>

Antiplatelet therapy: 25% reduction
Control: 20% reduction

Diabetes

Antiplatelet Trialists’ Collaboration, 1994
# Effects of modifying CV risk factors in diabetes: Glycaemic control

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Events</th>
<th>Weight of study size</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>3071/1 549</td>
<td>426/259</td>
<td></td>
<td>0.75 (0.54; 1.04)</td>
</tr>
<tr>
<td>PROactive</td>
<td>2605/2 633</td>
<td>164/202</td>
<td></td>
<td>0.81 (0.65; 1.00)</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>5571/5 569</td>
<td>310/202</td>
<td></td>
<td>0.92 (0.78; 1.07)</td>
</tr>
<tr>
<td>VADT</td>
<td>892/899</td>
<td>77/90</td>
<td></td>
<td>0.85 (0.62; 1.17)</td>
</tr>
<tr>
<td>ACCORD</td>
<td>5128/5123</td>
<td>205/248</td>
<td></td>
<td>0.82 (0.68; 0.99)</td>
</tr>
<tr>
<td>Overall</td>
<td>17267/15773</td>
<td>1182/1 36</td>
<td>100.0</td>
<td>0.85 (0.77; 0.93)</td>
</tr>
</tbody>
</table>

**Multifactorial approach**

Favours intensive treatment

Favours standard treatment

The 2018 EASD/ADA consensus report has incorporated Cardiovascular Outcome Trial Data.

The EASD/ADA report is a consensus statement and should not be used as guidance.
ADA = American Diabetes Association; CVOT = cardiovascular outcome trial; EASD = European Association for the Study of Diabetes.
Pharmacologic Therapy for T2DM: ADA/EASD 2018 Recommendations

Among patients with T2DM who have established ASCVD, SGLT2 inhibitors or GLP-1 receptor agonists with proven cardiovascular benefit are recommended as part of glycemic management.
Conclusion

• Early intensive optimisation of glycaemia is essential in reducing microvascular complications

• Cardiovascular disease remains the leading cause of death in Diabetes

• Optimal management of CV risk factors is essential in reducing macrovascular complications

• SGLT2 inhibitors & GLP-1 receptor agonist have a significant impact on residual CV risk reduction