Engaging People with Type 2 Diabetes to Achieve Better Outcomes

Tools & Strategies for Managing Cardiovascular Disease

Jane Diggle, Practice Nurse
Church View Health Centre, South Kirkby

Amy Rylance, Head of Healthcare Engagement and Development
Diabetes UK
Declarations

Jane Diggle, Practice Nurse
Church View Health Centre, South Kirkby
Vice Chair of Primary Care Diabetes Society (PCDS) Committee
Associate Editor-in-Chief for Diabetes and Primary Care

I have received funding from the following companies for providing educational sessions and documents, and for attending advisory boards:
Abbott, BD, Boehringer Ingelheim, BMS/Astra Zeneca, Eli Lilly, Janssen, MSD, Nap, Takeda, Novo Nordisk and Sanofi.

Amy Rylance, Head of Healthcare Engagement and Development
Diabetes UK
Content

• Outlining the CVD and diabetes challenge

• Strategies for tackling cardiovascular disease in people with Type 2 Diabetes.

• Practical tools and tips to improve cardiovascular outcomes.

• How the results of recent cardiovascular outcome trials influence treatment.

Focus on practical management of:
  – Lifestyle changes
  – Hypertension
  – Lipids
  – Glycaemia & the use of glucose-lowering drugs with specific effects on CV risk

(Illustrated by a clinical case)
Background

- 7 million people in the UK are affected by cardiovascular disease.
- 26% of all deaths are caused by cardiovascular disease.
- 1 in 4 premature deaths are caused by cardiovascular disease.
- Cardiovascular disease costs the NHS £8.96 billion a year.
Compared to people without diabetes, people with **Type 2 diabetes** are

- Nearly 2.5 times more likely to have a heart attack.
- More than 2.5 times as likely to experience heart failure.
- 2 times as likely to have a stroke.

Compared to people without diabetes, people with **Type 1 diabetes** are

- More than 4 times as likely to have a heart attack
- 4.5 times more likely to experience heart failure
- 3.5 times more likely to have a stroke.
One quarter of people who end up in hospital because of a stroke, heart attack or heart failure have diabetes.

Every week diabetes causes more than 530 heart attacks and almost 2,000 cases of heart failure. 680 strokes.
Complications not inevitable but PREVENTABLE


Where are we now for blood pressure, cholesterol and HbA1c?

1. People are not controlling these factors
   - Type 1 diabetes only 19% met all three targets
   - Type 2 diabetes only 41% meet all three targets

2. Poor control has devastating consequences
   - “heart failure emerges as both the most common and the most deadly cardiovascular complication of diabetes... High blood pressure is an important risk factor for heart failure”

3. We can do something about them
   - Lifestyle changes and routine drugs e.g. statins

Non-adherence in chronic diseases averages 50% by one year. 

The self-care challenge:

Association Between Adherence to Pharmacotherapy and Outcomes in Type 2 Diabetes: A Meta-analysis

• The mean rate of poor adherence was 37.8%
• Compared to those with poor adherence, individuals with good adherence had:
  • 10% lower rate of hospitalisation events
  • 28% lower rate of all cause mortality
The self-care challenge:

- As little as 14% of medical information was remembered correctly when people received spoken medical instructions.\(^9\)

- When relevant written information with pictographs was supplied recall rose to over 80%\(^9\)

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Diabetes and high HbA1c
Information Prescription

Your last two HbA1c results are  ..../.../.... ..../.../....

Good glucose control is important to reduce your risk of devastating complications. Reducing HbA1c has been proven to have health benefits. Discuss and agree with your doctor or nurse a realistic personal target for HbA1c.

What is HbA1c?
It tells you your average blood glucose for the last two to three months. We all need glucose for energy, but if you have diabetes your body loses its ability to use glucose. HbA1c measures how much glucose is stuck in your red blood cells. A finger-prick test shows you a "snapshot" of your glucose at a moment in time, HbA1c acts like a film recording how your life have changed.

When is high HbA1c a problem?
of blood glucose over a long period damage the blood vessels. This puts you at great risk of heart attack, stroke, or experiencing eye health problems.

How can I lower my HbA1c?
It is important to understand that your HbA1c will change for many reasons including: how long you've had diabetes, sickness, depression, change in lifestyle or because of other medicine such as steroids. The actions you take to reduce your HbA1c will depend on whether you have Type 1 or Type 2 diabetes and your overall health. The next column has three main areas for you to consider.

1 Medication: It may be time to increase your dose or introduce new medication – ask for advice.

2 Education: Your healthcare team are there to provide support, but you manage your diabetes. Education can help you understand what affects your blood glucose. Ask what’s on offer in your area.

3 Lifestyle: Discuss what changes can lower HbA1c:

Keep to a healthy weight
- Reduce the size of your portions and cut down on fatty and sugary foods.

Eat a healthy balanced diet
- Eat less fatty food, processed meats, full-fat dairy, pastries and cakes.
- Carbohydrates change your blood glucose – you may need to eat less carbohydrates and choose wholegrains.
- If you drink, cut down on alcohol.
- Eat plenty of vegetables and fruit – aim for at least five portions a day.
- Aim for at least two portions of oily fish a week.

Get more active
- Aim for 30 minutes five times a week to raise your heart beat. Activities like walking fast and cycling all count. Twice a week add activities like gardening or yoga to strengthen your muscles.

Stop smoking
- For help giving up ask for your local stop smoking service.

Agreed action plan

My personal goal is:

To be achieved when:

The two steps that I will take to achieve this are:
- (Discuss and agree with your doctor or nurse. Think about what, where, when and how?)

For information or support, call Diabetes UK Helpline: 0345 123 2399* Monday to Friday, 8am – 6 pm, or go to www.diabetes.org.uk/info-p*

*Calls may be recorded for quality and training purposes.
Meet Jill

60 years old, lives with husband and runs her own cleaning business. Type 2 Diabetes was diagnosed 3 years ago. This prompted her to give up her smoking habit of 10 cigarettes a day. She has a sedentary life and failed to attend for her diabetes reviews at surgery for over 18 months. She attends after being discharged from hospital following a myocardial infarction (Non-STEMI).

<table>
<thead>
<tr>
<th>HbA1c</th>
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<tbody>
<tr>
<td>BP</td>
<td>155/84mmHg</td>
</tr>
<tr>
<td>Lipids</td>
<td>TC 5.6mmol/L</td>
</tr>
<tr>
<td></td>
<td>Non-HDL 4.7mmol/L</td>
</tr>
<tr>
<td>BMI &amp; Weight</td>
<td>28.3 kg/m² 68kgs</td>
</tr>
<tr>
<td>eGFR &amp; ACR</td>
<td>&gt;90 mL/min/1.73m² (G1)</td>
</tr>
<tr>
<td></td>
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<td>Current Medication</td>
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<td></td>
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<td></td>
<td>Metformin 1g bd</td>
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</table>

How should we manage Jill?

- Address lifestyle
- Multifactorial Approach
- Optimise BP & Lipids
- Optimise HbA1c
Meet Jill

60 years old, lives with husband and runs her own cleaning business. Type 2 Diabetes was diagnosed 3 years ago. This prompted her to give up her smoking habit of 10 cigarettes a day. She has a sedentary life and failed to attend for her diabetes reviews at surgery for over 18 months. She attends after being discharged from hospital following a myocardial infarction (Non-STEMI).

What are appropriate targets for Jill?

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• In a person with diabetes the preferred target is ≤ 140/80mmHg
  • CKD/proteinuria/retinopathy/neuropathy target is ≤ 130/80mmHg
  • Each 2mmHg rise in SBP associated with increased mortality – 7% from heart disease; 10% from stroke

Guidelines vary….

• Total cholesterol <4mmol/L
• 40% reduction in Non-HDL or Non-HDL <2.5mmol/L
• HbA1c level of 48-58 mmol/mol
BP

155/84mmHg
(persists >155/84mmHg on 2 additional readings)

↑ Atorvastatin 20mg to 80mg
Started Aspirin 75mg &
Clopidogrel 75mg
Ramipril 5mg
Metformin 1g bd

≤ 140/80mmHg

Current Medication

NICE CG 127 (August 2011; updated 2016).


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How to diagnose and treat hypertension in diabetes

Measure the blood pressure

- Check pulse rate and rhythm.
- Do not use electronic BP monitor in the presence of an irregular pulse.
- Measure BP at least annually in a person without previously diagnosed hypertension or renal disease.
- Ensure the appropriate cuff size is used. The bladder should fit around at least 80% of the arm, but no more than 100%. Measure around the upper arm at the midpoint between the shoulder and elbow.
- Measure BP in both arms.

<table>
<thead>
<tr>
<th>Upper arm measurement</th>
<th>Cuff size</th>
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<tbody>
<tr>
<td>17-22 cm</td>
<td>Small</td>
</tr>
<tr>
<td>22-32 cm</td>
<td>Medium</td>
</tr>
<tr>
<td>32-42 cm</td>
<td>Large</td>
</tr>
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</table>

About this series

The aim of the "How to..." series is to provide readers with a guide to clinical procedures and aspects of diabetes care that are covered in the clinic setting.

What and why

Hypertension is twice as common in people with diabetes and co-existence of these conditions significantly increases the risk for coronary heart disease, left ventricular hypertrophy, congestive heart failure and stroke (Grossman and Grossman, 2017).

In a person with diabetes, the preferred BP target is <140/90 mmHg or <130/80 mmHg if there is kidney, eye or cerebrovascular damage.

Regardless of age, first-line antihypertensive drug treatment in people with diabetes should be a once-daily, generic angiotensin-converting enzyme (ACE) inhibitor for exceptions see Box B.

In those whose BP is consistently high, it may be appropriate to consider antihypertensive therapy (Araujo-Pacheco et al., 2002).

References


NICE (2016) Cardiovascular lifetime risk assessment and reduction, including blood pressure.


Box A. Lifestyle interventions

- Physical activity (and weight management).
- Alcohol consumption.
- Diet (e.g. DASH eating plan).
- Carbohydrate and salt intake.
- Smoking cessation advice.
- Initiatives to promote support and promote lifestyle change referral to health trainer, if appropriate.

Treatment targets

- In a person with diabetes, the preferred target is <140/90 mmHg (130/80 mmHg).

- If elevated, then the target is <130/80 mmHg (125/75 mmHg).

* Ambulatory BP measurements have not been defined (Head et al., 2010), but are likely to be slightly lower. Suggested guidelines appear bracketed in tables.

Consider appropriate BP target level in special circumstances, e.g. those at risk of falls, those with postural hypotension, frailty, reduced life expectancy or polypharmacy.

Be mindful of BP and consider reduction of treatment if a person's systolic BP ≥110 mmHg.

If lifestyle measures do not reduce BP to <140/90 mmHg (<130/80 mmHg if there is kidney, eye or cerebrovascular damage) offer antihypertensive drug treatment to all those with diabetes and Stage 1 hypertension or above, regardless of QUADE value refer to Box B.

Box B. NICE drug treatment recommendations

1. ACE inhibitor or ARB

- Once daily, generic ACE inhibitor irrespective of age. Exceptions: people of African-Caribbean descent (an ACE inhibitor plus either a diuretic or a generic CCB) or women for whom, after informed discussion, there is a possibility of becoming pregnant (a CCB should be the first-line blood-pressure-lowering therapy).

- For a person with confirmed intolerance to an ACE inhibitor (other than renal deterioration or hyperkalaemia), substitute with an angiotensin II receptor antagonist (ARB).

- Do not use an ACE inhibitor and ARB in combination.

- 14 daily. Monitor potassium levels and renal function according to Box C.

2. Third-line therapy: ACE inhibitor or ARB plus CCB or Diuretic

- ACE inhibitor or ARB plus CCB or Diuretic

- Consider amlopidine 5 mg initially, increasing dosage as required.

- Consider a thiazide-like diuretic (e.g. indapamide).

- If BP is not reduced to the individually agreed target with triple therapy, consider adding: Alpha blocker or beta blocker or Spironolactone.

Consider referral for specialist advice if BP is still not well controlled with optimal doses of four antihypertensive agents.

Box C. Dural and potassium monitoring

Do not initiate an ACE inhibitor or ARB if pre-treatment serum potassium is ≥5.0 mmol/L.

Step ACE inhibitor or ARB if serum potassium is ≥5.0 mmol/L, and other drugs known to promote hyperkalaemia have been discontinued.

Following the introduction or dose increase of ACE inhibitor or ARB, do not modify the dose unless:

- eGFR decrease from pre-treatment baseline is >32.5%

- serum creatinine increase from baseline is >200%

Ongoing monitoring

Monitor the BP of a person who has attained and is maintaining his or her BP target every 4–6 months and check for possible adverse effects of antihypertensive therapy, including the risks from unnecessarily low BP.

Useful resources

- DASH (Dietary Approaches to Stop Hypertension)


- Creatinine: https://en.wikipedia.org/wiki/Creatinine

- CV: https://en.wikipedia.org/wiki/Creatinine


- GFR: https://en.wikipedia.org/wiki/Glomerular filtration rate

- DASH: https://en.wikipedia.org/wiki/Dietary_Angles_of_Step_Hypertension_Protection

- ACE: https://en.wikipedia.org/wiki/Angiotensin-converting_enzyme

- Angiotensin: https://en.wikipedia.org/wiki/Angiotensin

- Beta blocker: https://en.wikipedia.org/wiki/Beta_blocker

- Spironolactone: https://en.wikipedia.org/wiki/Spironolactone

- Thiazide: https://en.wikipedia.org/wiki/Thiazide
diabetic (CV: cardiovascular; ACE: angiotensin-converting enzyme; ACEInhibitor: antioxidant; renin; and, as a provocation of the RAS).
Diabetes and high blood pressure
Information Prescription

Your last blood pressure reading is ___/___

People with diabetes and high blood pressure are at increased risk of having a heart attack or stroke. By lowering your blood pressure, you can dramatically reduce your risk.

Recommended target for blood pressure is lower than 130/80

What does blood pressure mean?
The force your heart needs to push blood around your body. The two numbers show the biggest force your heart uses to push your blood and the lowest pressure when your heart has relaxed.

Blood vessel

Normal
High

When is high blood pressure a problem?
High blood pressure (sometimes called hypertension) is when the force used to push blood around your body is normally higher than recommended. High blood pressure puts more strain on your heart and blood vessels. If you have high blood pressure, you may feel healthy, but it is causing damage to blood vessels.

How can I lower my blood pressure?
Lifestyle changes are proven to reduce blood pressure and make you feel healthier. Other people with diabetes will need medication as well. Some people require more than one type of medicine.

Agreed action plan

My personal goal is:

To be achieved when:

The two steps that I will take to achieve this are:

Discuss and agree with your doctor or nurse.

Think about what, how, when, and how?

1

2

Keep to a healthy weight

Reduce the size of your portions and cut down on fatty and sugary foods.

Eat a healthy balanced diet

Reduce salt: eat less fast food, choose low-salt options, and do not add salt.

If you drink cut down on alcohol

Eat plenty of vegetables and fruit – aim for at least five portions a day.

Eat less fatty foods, processed meats, full-fat dairy, pastries and cakes.

Get more active

Aim for 30 minutes five times a week to raise your heart beat. Activities like walking fast and cycling all count. Add some activity that strengthens your muscles like gardening or yoga twice a week.

Stop smoking

For help giving up ask for your local stop smoking service.

For information or support, call Diabetes UK Helpline 0345 123 2309 Monday to Friday 9am—6pm, or go to www.diabetes.org.uk/info-p
Lipids

| Lipids | TC 5.6mmol/L | Non-HDL 4.7mmol/L |

- Total cholesterol <4mmol/L
- 40% reduction in Non-HDL or Non-HDL <2.5mmol/L

Secondary Prevention

Aim for maximum tolerated dose of statin (Atorvastatin 80mg).

Check LFTs pre-statin, at 3 months and at 12 months (not again unless clinically indicated). No need to stop providing LFT<3xULN)

Statin intolerance
- Consider “statin holiday”
- Reduce dose in same intensity group or change to lower intensity statin.
- Seek advice/consider ezetimibe if high risk and not meeting non-HDL target
- Do not initiate fibrates, or recommend stanols or sterols

NICE Clinical Guideline 181: Lipid Modification 2014
Diagnosing dyslipidaemia

Obtain an initial NON-FASTED venous blood sample (TC, HDL C, TG and non-HDL C).

- TC >7.5 mmol/L: Refer for specialist advice.
- TG >2.0 mmol/L: Refer for specialist advice.
- Non-HDL C >4.5 - 9.9 mmol/L: Repeat with fasting lipid profile (TC, HDL C and TGL) 3-14 days later.

Consider using QUAleD® to calculate risk.

Using the following formula:

\[ \text{QUAleD Score} = 0.5 \times (\text{TC} - \text{HDL C}) + \text{TG} \]

- TC >6.5 mmol/L: Refer for specialist advice.
- TG >1.12 mmol/L: Refer for specialist advice.

Assumed high CV risk based on risk factors (see above)

Lifestyle modifications

- Avoid alcohol consumption
- Healthy eating
- Weight management
- Smoking cessation
- Physical activity

Consider offering statins for primary prevention

- Offer atorvastatin 20 mg to people with type 2 diabetes with a 20% 10-year risk of developing CVD estimated using the QUAleD® assessment tool.

Monitoring dyslipidaemia

Before initiating a statin, check TC, HDL C, non-HDL C and LFTs with a NON-FASTED venous blood sample.

3 months after initiating statin treatment, recheck TC, HDL C, non-HDL C and LFTs with a NON-FASTED venous blood sample.

This applies for both primary and secondary prevention (NICE, 2014).

For a >40% reduction in non-HDL C

NOTE: Alternatively, the JBS3 consensus recommends aiming for a non-HDL C <2.5 mmol/L.

Ongoing monitoring

- CVD risk calculator or QUAleD® to motivate lifestyle change and concordance by demonstrating heart age and life years lost and gained by the various interventions, such as stopping smoking, statin and blood pressure medication.

Statin prescribing tips

- Do NOT routinely exclude from statin therapy people who have liver transaminase levels that are raised but are <3 times the upper limit of normal.
- Measure liver transaminase enzymes (alanine aminotransferase or aspartate aminotransferase) within 3 months of starting treatment and at 12 months, but not again unless clinically indicated.
- Do NOT measure CK levels in asymptomatic people who are being treated with a statin. If muscle pain is present prior to statin use, check CK prior to starting statin. If >5 times upper limit of normal, repeat 7 days. Do not start statin if >5 times normal. If elevated but <5 times normal start lower dose statin.
- Aim to treat with the maximum tolerated dose. If person reports adverse effects when taking statins discuss:
  - Stopping the statin and by when symptoms have resolved to check if symptoms are related to the statin.
  - Reduce the dose within the same intensity group.
  - Change the statin to a lower intensity group.

Advice for people with child-bearing potential: no potential teratogenic risk of statins. Stop them 3 months prior to conception and do not recommence until breastfeeding complete. Discuss this advice with the patient.
Diabetes and bad cholesterol
Information Prescription

Your last cholesterol reading is: Total [ ] HDL [ ]

People with diabetes and high levels of bad cholesterol are at higher risk of having a heart attack or stroke. By lowering your bad cholesterol, you can dramatically reduce your risk.

What is cholesterol?
Cholesterol is a type of fat in the blood. Sometimes it is called lipids. There is good cholesterol and bad cholesterol. HDL (high-density lipoprotein) is good cholesterol which helps protect you from heart disease. Both triglycerides and LDL (low-density lipoprotein) are bad for you.

Blood vessels
Normal [ ] Furred up with cholesterol [ ]

When is cholesterol a problem?
Too much bad cholesterol in the blood causes fatty material to build up in the blood vessels supplying the brain and heart, making them narrower. This can lead to a blockage in blood vessels, which can cause a heart attack or stroke.

How can I lower my bad cholesterol?
You can make changes that lower your risk of having a heart attack or stroke. The next column explains how.

Keep to a healthy weight

- Reduce the size of your portions and cut down on fatty and sugary foods.

Eat a healthy balanced diet

- Eat less fatty foods, processed meats, full-fat dairy, pastries and cereals.
- Include wholegrains and pulses.
- Aim for at least two portions of oily fish a week.
- Eat plenty of vegetables and fruit – aim for at least five portions a day.
- Replace butter, hard and ghee with vegetable oils and spreads.

Get more active

- Aim for 30 minutes five times a week to raise your heart beat. Activities like walking fast and cycling all count. Add some activity that strengthens your muscles, like gardening or yoga, twice a week.

Stop smoking

- For help giving up ask for your local stop smoking service.

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For information or support, call Diabetes UK Helpline: 0345 123 2309* Monday to Friday, 9am–9pm, or go to www.diabetes.org.uk/info-p

*Calls may be recorded for quality and training purposes.
• STOP smoking  
• Total Fat intake ≤ 30% of energy intake. 
• Sat fat ≤ 7% (for high risk), dietary cholesterol <300mg/day. Replace saturated fats with unsaturated fats and limit intakes of trans fatty acids. 
• Eat less red and processed meat, refined carbohydrates and sugar sweetened beverages 
• Decrease salt intake (<6g/day) - DASH-style diets 
• Eat more wholegrains, reduce refined sugars, eat 5 portions of fruit & veg per day, 2 portions of fish per week (including 1 portion oily fish), 4-5 portions of unsalted nuts, seeds and legumes per week. 
• Limit alcohol intake to <14 units a week [although red wine may have health benefits – in moderation!!!] 

If overweight aim for 5% weight loss.

Aim for at least 150 mins per week of moderate to vigorous physical activity, over at least 3 days.
Controversies over the link between saturated fat intake and heart disease persist......
Top food sources of saturated fat in the American diet

1. Cheese
2. Pizza
3. Grain-based desserts
4. Dairy-based desserts
5. Chicken dishes
6. Processed meats
7. Burgers
8. Mexican dishes
9. Beef dishes
10. Low-fat milk

Most of these are high carb foods. If we cut the carbs we’ll naturally cut the saturated fat from this junk food

For every 11mmol/mol (1%) increase in HbA1c the risk of stroke, coronary heart disease and death is increased 10% to 30%

What would be an appropriate HbA1c target for Jill to aim for?

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If HbA1c rises to 48 mmol/mol (6.5%) on lifestyle interventions:
- Offer standard-release metformin
- Support the person to aim for an HbA1c level of 48 mmol/mol (6.5%)

FIRST INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):
- Consider dual therapy with:
  - metformin and a DPP-4i
  - metformin and pioglitazone
  - metformin and an SU
  - metformin and an SGLT-2i
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

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Cardiovascular outcome studies for new antidiabetic agents

2008 FDA guidelines substantially raised the threshold for approval of antidiabetes drugs from proof of glucose lowering to robust assessment of cardiovascular safety

- CV outcomes trials are designed to demonstrate no increased CV risk vs placebo when used as part of usual care\textsuperscript{1–3}

- These trials are designed to evaluate CV safety\textsuperscript{3–5}

\textit{HbA\textsubscript{1c} is intended to be similar between the two groups through adjustment of antihyperglycaemic medications according to local treatment guidelines so that CV safety can be evaluated independently of HbA\textsubscript{1c}}

\textsc{Guidance for Industry}

\textit{Diabetes mellitus – evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes}

\begin{itemize}
\item \textsc{White WB et al. Am Heart J. 2011;162:620–626.e7.}
\item \textsc{Scirica BM et al. Am Heart J. 2011;162:818–825.e6.}
\item \textsc{Green JB et al. Am Heart J. 2013;166:983–989.e7.}
\item \textsc{White WB et al. N Engl J Med. 2013;369:1337–1346.}
\end{itemize}


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Should we give preferential consideration to the use of blood glucose lowering agents with proven cardiovascular benefit?
## DPP-4 inhibitors

<table>
<thead>
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<th>Key Inclusion Criteria</th>
<th>Median duration of follow up</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>TECOS</td>
<td>Sitagliptin</td>
<td>14,671</td>
<td>Pre-existing CVD</td>
<td>3 years</td>
<td>Non-inferior to placebo, Non-inferior</td>
</tr>
<tr>
<td>SAVOR-TIMI 53</td>
<td>Saxagliptin</td>
<td>16,492</td>
<td>High risk for CV events</td>
<td>2.1 years</td>
<td>Non-inferior to placebo, HR 1.27, (1.07-1.52), statistically significant ↑ in HFH</td>
</tr>
<tr>
<td>EXAMINE</td>
<td>Alogliptin</td>
<td>5,380</td>
<td>History of ACS 15-90 days</td>
<td>1.5 years</td>
<td>Non-inferior to placebo, Possible trend towards ↑HFH</td>
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**In summary:** all demonstrate non-inferiority for CV events in high risk populations (upper limit HR<1.3) when compared with placebo. Trend to increased hospitalisation for heart failure saxagliptin and alogliptin – FDA warnings
## SGLT-2 inhibitors

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<tr>
<td>EMPA-REG Outcome Zinman et al. NEJM 2015; 373: 2117-2128</td>
<td>Empagliflozin</td>
<td>7,020</td>
<td>Pre-existing CVD BMI&lt;=45 and eGFR &gt;/=30 (99% CVD)</td>
<td>3.1 years</td>
<td>14% RRR Superior Driven by 38% RRR in CV mortality Trend towards ↑ in stroke 32% RRR all cause mortality 35% RRR in HFH</td>
</tr>
<tr>
<td>CANVAS &amp; CANVASS R Neal et al. NEJM 2017; 377:644-657</td>
<td>Canagliflozin</td>
<td>10,142</td>
<td>Pre-existing CVD or high CV risk (66% CVD)</td>
<td>2.4 years</td>
<td>14% RRR Trend towards ↓ in All-Cause Mortality but not statistically significant 33% RRR in HFH 🔴 Doubling of risk for lower limb amputations (6.3 vs 3.4 cases per 1000 patient years and more fractures (15.4 vs 11.9 per 1000 patient years).</td>
</tr>
</tbody>
</table>

In summary: Significant ↓ in CV and all-cause mortality with empagliflozin. Significant ↓ in MACE (but not CV or all-cause mortality) with canagliflozin.

DECLARE-TIMI trial for dapagliflozin expected to complete in 2019
## GLP-1 Receptor Agonists

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>Numbers</th>
<th>Key Inclusion Criteria</th>
<th>Median duration of follow up</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEADER</td>
<td>Liraglutide</td>
<td>9,340</td>
<td>Pre-existing CVD/CKD/heart failure &gt;50; or ≥ one CV risk factor ≥ 60 (81% previous CVD)</td>
<td>3.8 years</td>
<td>13% RRR Superior (but only in those with established CVD); driven by 22% ↓ in CV death; 15% RRR all cause mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Non-significant reduction in HFH</td>
</tr>
<tr>
<td>ELIXA</td>
<td>Lixisenatide</td>
<td>6,068</td>
<td>ACS within 90 days (100% previous CVD)</td>
<td>2.1 years</td>
<td>Non-inferior</td>
</tr>
<tr>
<td>EXSCEL</td>
<td>Exenatide QW</td>
<td>14,752</td>
<td>73% previous CVD</td>
<td>3.2 years</td>
<td>Non inferior</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14% RRR in All-Cause Mortality</td>
</tr>
<tr>
<td>SUSTAIN 6</td>
<td>Semaglutide</td>
<td>3,297</td>
<td>Pre-existing CVD/CKD/heart failure &gt;50; or ≥ one CV risk factor ≥ 60 (60% previous CVD)</td>
<td>2.1 years</td>
<td>26% reduction Superior and driven by ↓ 39% RRR in non-fatal stroke</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Non inferior</td>
</tr>
</tbody>
</table>

**In summary:** Significant ↓ in CV and all cause mortality with liraglutide. Significant ↓ in non-fatal stroke with semaglutide.
5 Take Home Messages

1. A holistic approach that tackles lifestyle, blood pressure, lipids and glycaemia is the best way to reduce CV risk in people with Type 2 diabetes.

2. Regardless of age, the first-line antihypertensive drug treatment in those with diabetes is a once-daily, generic angiotensin-converting enzyme (ACE) inhibitor with the exceptions of those from African or Caribbean family origin, or women for whom there is a possibility of becoming pregnant with a treatment target of below 140/80mmHg (or below 130/80mmHg if there is kidney, eye or cerebrovascular damage).

3. Adherence to statin treatment in those treated to target (aiming for a 40% reduction from baseline in Non-HDL-Cholesterol) is likely to be better than in those treated on a “fire-and-forget” basis.

4. Managing diabetes in those who are elderly and frail with co-morbidities may require less stringent targets for HbA1c, blood pressure and cholesterol.

5. Latest guidelines are recommending preferential consideration for blood glucose drugs with proven CV benefit in those with established CVD.
8,757