type 2 diabetes: hypertension & cardiovascular disease
T2DM and cardiovascular disease

- Coronary heart disease and stroke increased 2-4 fold in T2DM
- CVD accounts for 60-75% of deaths in diabetics
- Life expectancy decreased by 5-10 years
- Confers cardiovascular risk equivalent to ageing 15 years
- Diabetes may account for 30% of all CVD
UK Prospective Diabetes Study

blood pressure control study
<table>
<thead>
<tr>
<th>Control Type</th>
<th>Mean Blood Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less Tight Control</td>
<td>154 / 87</td>
</tr>
<tr>
<td>Tight Control</td>
<td>144 / 82</td>
</tr>
<tr>
<td>Difference</td>
<td>10 / 5</td>
</tr>
</tbody>
</table>

Mean over 9 years
any diabetes-related endpoints

Less tight blood pressure control (390)

Tight blood pressure control (758)

risk reduction
24% p=0.0046
diabetes-related deaths

- Less tight blood pressure control (390)
- Tight blood pressure control (758)

Risk reduction 32% $p=0.019$
stroke

Less Tight Blood Pressure Control (390)
Tight Blood Pressure Control (758)

risk reduction 44% p=0.013
myocardial infarction

- Less Tight Blood Pressure Control (390)
- Tight Blood Pressure Control (758)

% of patients with event over Years from randomisation

Risk reduction 21% p=0.13
microvascular endpoints

- Less Tight Blood Pressure Control (390)
- Tight Blood Pressure Control (758)

% patients with event

Years from randomisation

risk reduction
37% p=0.0092
heart failure

- Less Tight Blood Pressure Control (390)
- Tight Blood Pressure Control (758)

risk reduction 56% p=0.0043
T2DM and hypertension

• important in diabetes because:
  – it accelerates **macrovascular disease**
  – it accelerates **microvascular disease**
  – it’s very **common** in diabetes

• long-term survivors of diabetes tend to have lower blood pressure
T2DM and hypertension

• the cause of the association between diabetes and hypertension is not well understood
  – there is evidence for both sodium retention and activation of the renin-angiotensin system (RAS)

• increased frequency of hypertension because of obesity and 'syndrome X'

• at age 45, 40% of type 2 patients have hypertension with the proportion increasing to 60% by age 75

• diabetes accelerates the rise of blood pressure with age

• systolic hypertension a particular problem

• loss of the nocturnal 'dip' – strong predictor of CV death
type 2 diabetes and hypertension

choice of therapy
hypertension in T2DM – ‘target culture’

- there is an association between low BP values and a lower incidence of CV events, but no clear BP threshold has been identified as a therapeutic target
- whatever target is chose, it will be difficult to achieve in many patients
- does it make sense to apply the same target to patients with different risk?
- is a blood pressure of 141/81 really that much worse than one of 139/79?
- any reduction in blood pressure is beneficial
- however, targets do give us something to aim for
hypertension in T2DM – treatment

- diabetics tend to have ‘salt-sensitive’ hypertension, so reducing salt intake tends to lower the BP significantly
- there is hot debate about the relative benefits of different classes of antihypertensive drug
- there are no significant differences between different BP lowering regimens in terms of stroke, CHD, heart failure, total major CV events, CV deaths, or total mortality in patients with diabetes
- the exception being CCBs, which were associated with a higher risk of heart failure when they were compared with diuretics or beta-blockers
- the important thing is blood pressure reduction - which drugs are used is of secondary importance
hypertension in T2DM – treatment

- the only considerations that distinguish antihypertensive agents in T2DM are effects on renal endpoints, metabolic worsening and cost
- the best evidence for prevention of renal disease and limitation of metabolic worsening relates to the renin angiotensin system-blockers (RAS-blockers) (ACEI and A2RB)
- thiazides and beta blockers are diabetogenic, especially in combination - thus less suitable for those at risk of diabetes and those with early T2DM – not a problem in patients on insulin
TYPE 2 DIABETES

National clinical guideline for management in primary and secondary care (update)

This is an update of the following NICE (inherited) clinical guidelines on Type 2 diabetes which were published in 2002:
E - retinopathy; F - renal disease; G - blood glucose; H - management of blood pressure and blood lipids

NICE type 2 diabetes guidelines (2008)
NICE type 2 diabetes guidelines (2008) - blood pressure recommendations

• “measure blood pressure at least annually in a person without previously diagnosed hypertension or renal disease

• offer and reinforce preventive lifestyle advice.

• for a person on antihypertensive therapy at diagnosis of diabetes, review control of blood pressure and medications used, and make changes only where there is poor control or where current medications are not appropriate because of microvascular complications or metabolic problems”
“offer lifestyle advice if blood pressure is confirmed as being consistently above 140/80 mmHg (or above 130/80 mmHg if there is kidney, eye or cerebrovascular damage).

add medications if lifestyle advice does not reduce blood pressure to below 140/80 mmHg (below 130/80 mmHg if there is kidney, eye or cerebrovascular damage)

monitor blood pressure 1-2 monthly, and intensify therapy if on medications, until blood pressure is consistently below 140/80 mmHg (below 130/80 mmHg if there is kidney, eye or cerebrovascular disease)”
NICE type 2 diabetes guidelines (2008) - blood pressure recommendations

- “first-line blood pressure-lowering therapy should be:
  - a once daily, generic **ACE inhibitor (ACEI)**

- the first-line blood pressure-lowering therapy for a person of African-Caribbean descent should be:
  - an **ACEI** plus either a **diuretic** or a generic **calcium channel blocker (CCB)**

- a **CCB** should be the first-line blood pressure-lowering therapy for a woman for whom, after an informed discussion, it is agreed there is a possibility of her becoming pregnant

- for a person with continuing intolerance to an ACEI (other than renal deterioration or hyperkalaemia), substitute an **angiotensin II-receptor antagonist (ARB)** for the ACEI”
NICE type 2 diabetes guidelines (2008) - blood pressure recommendations

• “if the person’s blood pressure is not reduced to the individually agreed target with first-line therapy, add a calcium channel blocker or a diuretic (usually bendroflumethiazide, 2.5 mg daily)

• add the other drug (that is, the calcium channel blocker or diuretic) if the target is not reached with dual therapy

• if the person’s blood pressure is not reduced to the individually agreed target with triple therapy, add an alpha-blocker, a beta-blocker or a potassium-sparing diuretic

• monitor the blood pressure of a person who has attained and consistently remained at his or her blood pressure target every 4-6 months, and check for possible adverse effects of antihypertensive therapy - including the risks from unnecessarily low blood pressure”
management of blood pressure in type 2 diabetes

1. Measure blood pressure annually.
2. If above target:
   - Start ACEI (and titrate dose).
     - For Afro-Caribbean patients, combine with a diuretic or CCB.
   3. If above target:
      - Add CCB or diuretic.
   4. If above target:
      - Add diuretic or CCB.
   5. If above target:
      - Add α-blocker, β-blocker, or K-sparing diuretic, or refer to specialist.

Targets:
- Patients with kidney, eye or cerebrovascular disease: <130/80
- Others: 140/80

Women where pregnancy a possibility:
- Avoid ACEI and A2RB drugs - begin with CCB.

In people with intolerance to ACEI (not renal deterioration or hyperkalaemia):
- Substitute A2RB.
choice of agents

- **ACEI**
  - PERINDOPRIL may be better choice than RAMIPRIL

- **diuretic**
  - controversy regarding best agent
  - evidence base for low-dose BENDROFLU(METHI)AZIDE is questionable

- **CCB**
  - AMLODIPINE
choice of agents

Aliskiren and the calcium channel blocker amlodipine combination as an initial treatment strategy for hypertension control (ACCELERATE): a randomised, parallel-group trial

- initiation with combination therapy achieved quicker blood pressure reduction with no more adverse effects
NICE guidelines for hypertension – August 2011
NICE guidelines for hypertension – controversies

- techniques for measuring blood pressure
- choice of diuretic therapy
NICE guidelines for hypertension – BP measurement

- clinic blood pressure measurement (CBPM) on repeated clinic visits has long been the standard method for the diagnosis of hypertension and subsequent monitoring blood pressure control on treatment in clinical practice

- the increased availability of automated blood pressure measuring devices has led to their increased use in clinical practice and clinical studies

- home blood pressure measurement (HBPM) or ambulatory blood pressure measurement (ABPM) both provide multiple measurements of blood pressure away from the clinic setting in a more usual environment

- which of these methods is ‘best’?
NICE guidelines for hypertension – BP measurement

- The predictive value for clinical outcomes of blood pressure measurement based on clinic blood pressure measurement (CBPM), home blood pressure measurement (HBPM) and ambulatory blood pressure measurement (ABPM) have been compared.

- The clinical outcomes of interest were mortality, stroke, MI, heart failure, diabetes, vascular procedures, hospitalisation for angina, and other major adverse cardiac and cerebrovascular events (MACCE).

- The results showed that when CBPM was compared to ABPM, in 8 out of 9 studies ABPM was superior to CBPM at predicting clinical events - there was no difference in one study.

- In some studies the daytime ABPM average was the most predictive of clinical outcomes, whereas in others the ABPM night-time average was the most predictive, but there was no conclusive evidence suggesting a preference for day versus night-time averages.
NICE guidelines for hypertension – BP measurement

- there were fewer data comparing CBPM with HBPM - only three studies:
  - HBPM was superior to CBPM at predicting clinical outcomes in two of these studies and no difference between the methods was noted in one small study

- all three blood pressure measurement methods were compared with each other in only two studies:
  - in one of which there was no difference in their predictive value and in the other, ABPM and HBPM were similar to each other but superior to CBPM at predicting clinical outcomes

- the guidelines conclude that multiple blood pressure measurements away from the clinic setting are the best predictor of blood pressure-related clinical outcomes and that to date, studies with ABPM provided the most robust evidence
NICE guidelines for hypertension – BP measurement

• ambulatory BP monitoring not practicable currently in diabetes clinics
• not necessary if clinic blood pressures consistently above threshold
• currently limited to young patients with type 1 diabetes and patients where there is a suspicion of ‘white coat’ effect
• evidence base for home BP monitoring is not strong enough to guide clinical decision-making
NICE & hypertension - choice of diuretic

- predominant thiazide-type diuretic used in the UK for the treatment of hypertension is low dose (2.5mg o.d.) BENDROFLUMETHIAZIDE (BFZ)

MRC trial of treatment of mild hypertension: principal results

MEDICAL RESEARCH COUNCIL WORKING PARTY

Abstract
The main aim of the trial was to determine whether drug treatment of mild hypertension (phase V diastolic pressure 90-109 mm Hg) reduced the rates of stroke, of death due to hypertension, and of coronary events in men and women aged 35–64 years. Subsidiary aims were: to compare the course of blood pressure in two groups, one taking bendrofluazide and one taking propranolol, and to compare the incidence of suspected adverse reactions to these two drugs. The study was single blind and based almost entirely in general practices; 17,354 patients were recruited, and 85,372 patient years of observation have accrued. Patients were randomly allocated at entry to take bendrofluazide or propranolol or placebo tablets.

- dose of bendrofluazide used in this trial was 10mg/day
NICE guidelines for hypertension – choice of diuretic

- the use of low-dose BFZ was based on a study of 257 patients randomised to four different doses– under-powered to detect differences in BP-lowering effect

- low-dose BFZ has never been tested in studies with clinical endpoints

- low-dose BFZ is rarely used elsewhere in the world

- the guidelines recommend that, if a diuretic is to be initiated or changed, a thiazide-like diuretic, such as CHLORTALIDONE (12.5 mg–25.0 mg once daily) or INDAPAMIDE (1.5mg slow release or 2.5 mg once daily) should be used in preference to a conventional thiazide diuretic such as bendroflumethiazide or hydrochlorothiazide
summary
hypertension in T2DM - summary

- Lowering blood pressure is highly effective in reducing microvascular and macrovascular complications.
- The important thing is to reduce blood pressure - the way you do it is less important.
- Drugs that act on the RAA axis are recommended for first-line use.
- ACE inhibitor should be considered first, but ARB should be substituted if ACE inhibitor not tolerated.
- Use a diuretic, and in a dosage, which has been shown effective in clinical endpoint trials.
- ABPM correlates more closely with CV outcomes than CBPM.
management of hypertension in type 2 diabetes

1. Measure blood pressure annually
   - Above target: start perindopril
     (If Afro-Caribbean, combine with diuretic or CCB)
       - Above target: add amlodipine or indapamide
         - Above target: add indapamide or amlodipine
           - Above target: add α-blocker, β-blocker, or K⁺-sparing diuretic, or refer to specialist

2. Targets:
   - Patients with kidney, eye or cerebrovascular disease: systolic <130/80
   - Others: systolic 140/80

3. Women where pregnancy is a possibility:
   - Avoid ACEI and ARB drugs - begin with CCB

4. In people with intolerance to ACEI (not renal deterioration or hyperkalaemia):
   - Substitute losartan
thanks for your attention!