

Hypertension in patients with Type 2 Diabetes Mellitus – why are we failing to meet the targets?

Walter van der Merwe
Renal Physician,
North Shore Hospital

How can we reduce the risk of macro and microvascular complications in type 2 diabetes?

Smoking cessation - all

Aspirin – (no current evidence for primary prevention POPADAD + JPAD trials)/
yes for secondary prevention or macrovascular events

**Statins – all for primary and secondary prevention of
macrovascular events**

Tight glycaemic control?

Tight blood pressure control?

Take home message...

Every individual with diabetes should be on a statin irrespective of baseline LDL level

CARDS Study [Lancet 204;364:685-696](#)

Atorvastatin 10mg daily vs placebo in type 2 diabetics with no previous history of cardiovascular disease and without high concentrations of LDL

2838 pts randomised

Trial terminated early because of significant difference in CV events between the 2 arms

Atorvastatin 10mg reduced risk of:

- MI by 36%
- Coronary revascularisations by 31%
- Stroke by 48%
- Death rate by 27%

No increase in adverse events in the atorvastatin arm

How can we reduce the risk of macro and microvascular complications in type 2 diabetes?

Smoking cessation - all

Aspirin – (no current evidence for primary prevention POPADAD + JPAD trials)/
yes for secondary prevention or macrovascular events

Statins – all for primary and secondary prevention of macrovascular events

Tight glycaemic control?

Tight blood pressure control?

Glycaemic control and vascular complications in type 2 diabetes

Tight glycaemic control does reduce risk of microvascular complications (retinopathy, nephropathy) in most but not all large trials.

Yes

- UKPDS
- Kunamoto Trial
- Advance Trial

No

- Veterans Affairs Diabetes Trial

Although there is an epidemiological association between chronic hyperglycaemia and worse macrovascular complications, to date most randomised clinical trials have not demonstrated a beneficial effect of tight glycaemic control on macrovascular outcomes in type 2 diabetes.

UKPDS, VACS DM/ VADT and ADVANCE trials showed no benefit (but no disadvantage) of tight glycaemic control

ACCORD which compared standard care (HbA1C 7-7.9%) with intensive care (HbA1C < 6%) was stopped early because of unexpectedly higher no. of cardiovascular deaths in the intensive group (no clear explanation for this unexpected result)

What about tight blood pressure control for primary prevention of microvascular and macrovascular disease in type 2 diabetes?

Substantial clinical trial evidence that tight BP control (< 130/80) reduces the risk of microvascular and macrovascular complications in type 2 diabetes (UKPDS, HOT, HOPE and others)

There is some (but not conclusive currently) evidence that RAS blocking drugs (ACE-inhibitors and ARB's) are better than other antihypertensives in primary prevention of microvascular disease (compared with other antihypertensives) for same level of BP-lowering

Are there any benefits of tight glycaemic control in secondary prevention of patients with established type 2 diabetes and established nephropathy (proteinuria +/- reduced GFR)?

ie: can tight glycaemic control reverse or stabilise micro or macroalbuminuria and/or halt or slow progression of renal disease in type 2 diabetes

Short answer May be beneficial but no clinical trial evidence to date

What about the evidence for tight blood pressure control for secondary prevention in patients with type 2 diabetes and established nephropathy?

ie: Can tight BP control (< 130/80) reverse or stabilise micro or macroalbuminuria and/or halt or slow progression of renal disease in type 2 diabetes?

Absolutely

Evidence from large well conducted clinical trials – IRMA, RENAAL, STENO, UKPDS

(All except UKPDS showed preferential results with RAS-blockers – most trial evidence for ARB's, but ACE-inhibitors likely to be equivalent)

Important Considerations in diabetes and hypertension

- (1) More than 50% of individuals with 2 diabetes have elevated blood pressure (IN US NHANES database 58.9% of white type 2 diabetics have hypertension and 78.1% of blacks)
- (2) Individuals with high blood pressure are 2-3x more likely than those with normal blood pressure to have diabetes
- (3) Individuals with type 2 diabetes alone are at risk of premature macrovascular (heart attack, stroke, peripheral macrovascular disease) and microvascular complications (retinopathy, nephropathy, peripheral gangrene)
- (4) Individuals with high blood pressure alone are at risk of premature macrovascular (heart attack, stroke) and microvascular (nephrosclerosis) complications

(5) Patients with diabetes and hypertension and twice as likely to experience a cardiovascular event than those with diabetes only or hypertension only, and 5-6 times more likely to develop end stage renal disease

(6) An estimated 35-75% of cardiovascular and renal complications can be attributed to high blood pressure

Target Blood Pressure in individuals with diabetes is
< 130/80

(same for CKD and secondary prevention of cardiovascular disease + there is extensive overlap of these conditions with diabetes)

Achievement of this target is very uncommon

For example NHANES 3 survey showed that only 11% of people with diabetes treated for high BP achieved 130/80 target

What am I getting at?

- High blood pressure is very common in people with type 2 diabetes and almost universal in those with established diabetic nephropathy
- Evidence is unequivocal that tight BP control is effective at primary and secondary prevention of microvascular and macrovascular complications in type 2 diabetes is unequivocally more beneficial than tight glycaemic control
- Despite this, achievement of BP target is very uncommon in type 2 diabetics with raised blood pressure

Why are BP control rates poor in type 2 diabetes?

- (1) Diabetologists and diabetes nurse specialist focus more on glucose control than blood pressure targets (personal observation)
- (2) Diabetes nurses able to adjust diabetes medications autonomously, but not BP medications
- (3) Many doctors seem to feel that provided the patient is on a ACE-inhibitor their obligation to the patient's BP is discharged (when the focus should be principally on achieving target BP not just prescription of a particular class of drug)

- (4) Apparent reluctance of doctors to use multi-drug regimens to control BP
- (5) Because BP target is 10/10 lower the general BP target of 140/90 it is harder to achieve
- (6) Resistant hypertension is commoner in diabetics and particularly in those with established diabetic nephropathy
- (7) “Clinician Inertia” (possibly most important factor)

Pharmacological considerations in treating blood in patients with type 2 diabetes (including those with established nephropathy)

- (1) ACE-inhibitor or ARB should be part of the antihypertensive regimen but monotherapy with one of these drugs will seldom get the patient to target on its own
- (2) Because target is $< 130/80$, usually minimum of 1 extra drug required to get to target (cf target of $140/90$ in general hypertensive population - “10/5 rule” – each drug added unlikely to reduce BP by $> 10/5$)
- (3) Only 30% of patients with diabetes and elevated BP will achieve BP target on ≤ 2 drugs
- (4) When starting treatment, initiate with 2 drugs when BP $> 150/90$

- (5) Only a minority of patient with established diabetic nephropathy will achieve blood pressure target on ≤ 3 drugs
- (6) Drugs need to be given in full doses
- (7) All regimens containing > 2 drugs should include a diuretic
- (8) “All” patients with chronic kidney disease (reduced GFR) should have a diuretic included in their regimen
 - high blood pressure in CKD is “never” controllable without a diuretic
 - the lower the GFR, the more the diuretic dose required to control BP

When should we call hypertension “Resistant”?

Resistant hypertension in diabetes or CKD is defined as

BP > 130/80 on optimal doses of a minimum of three, complementary antihypertensive drugs one of which is a diuretic

What about
prediabetic states
and hypertension?

Impaired fasting glucose

Impaired glucose tolerance

Metabolic syndrome with IFG

Metabolic syndrome with IGT

...all associated with increased cardiovascular risk and high incidence of hypertension



Ethnic Specific Values for Waist Circumference[†]

Ethnic group	Waist circumference (as measure of central obesity)
Europeids*	
Men	≥94 cm
Women	≥80 cm
South Asians	
Men	≥90 cm
Women	≥80 cm
Chinese	
Men	≥90 cm
Women	≥80 cm
Japanese	
Men	≥85 cm
Women	≥90 cm
Ethnic South and Central Americans	Use South Asian recommendations until more specific data are available
Sub-Saharan Africans	Use European data until more specific data are available
Eastern Mediterranean and middle east (Arab) populations	Use European data until more specific data are available

Metabolic Syndrome Definitions

WHO

FPG > 6.1 or 2hr
GTT > 11.1

Plus at least 2 of:

- Abdo obesity (W/H ratio > 0.9, BMI > 30, or waist girth > 94cm)
- TG > 1.7 or HDL < 0.9
- BP > 140/90 or on antihypertensives

2001 NCEP

3 out of 5 of:

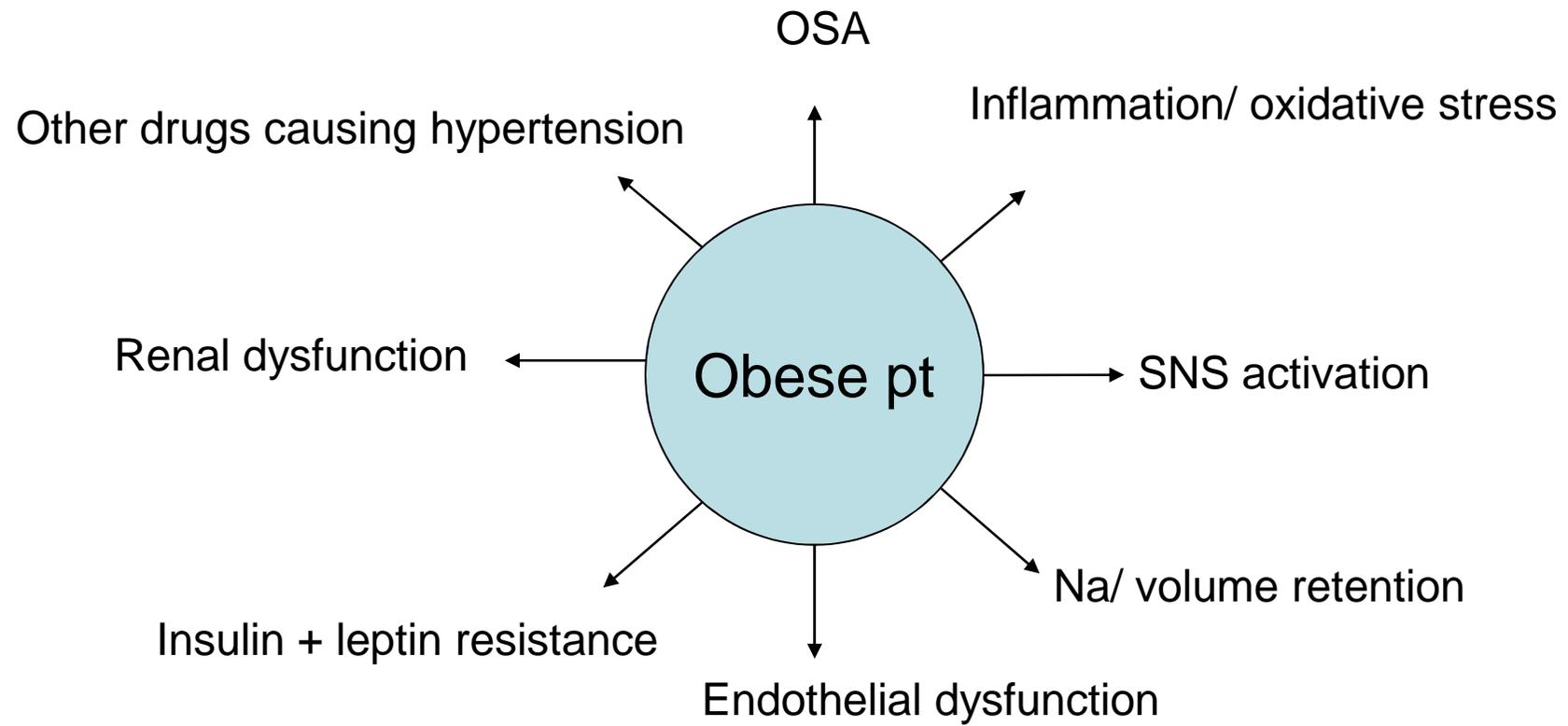
- Waist circ > 102cm (men) 88cm (women)
- TG > 1.7
- HDL < 1
- BP > 130/85
- FPG > 6.1

IDF

Increased waist circumference

Plus at least 2 of:

- TG > 1.7
- HDL < 1.03 (men) or 1.25 (women)
- BP > 130/85
- FPG > 5.6



Multiple causes of hypertension in the Metabolic Syndrome including activation of RAAS and SNS but also importantly



Hyperinsulinaemia (associated with insulin resistance) causes..



..increased proximal renal tubular sodium reabsorption, which results in ..



..important volume-dependent (salt-sensitive) hypertension, which..



..often requires more potent diuretic therapy to manage to target

Case Study

Mr JH, 55 year old European business man
15 year history of hypertension, 5 year history of type 2 diabetes Referred to
Diabetes Nurse Clinic for assessment/ education

Meds

Metformin 850mg BD
Glipizide 5mg BD
Aspirin 100mg daily
Felodipine 10mg daily
Inhibace Plus 1 daily
Metoprolol CR 95mg daily

O/E Ht 173 cm, wt 90 kg, waist girth 105 cm
HR 56 bpm reg, resting BP in both arms sitting and standing 160/95

Labs

Fasting glucose 5.8mmol./l, HbA1c 7.1%

Hb 144 wcc 5.8 platelets 200

Na 142 K 3.9 urea 11mmol/l creatinine 124umol/l

fasting cholesterol 5.2mmol/l HDL 0.9 LDL 3.8 TG 3.0

spot urine albumin/creatinine ratio 8mg/mmol

Why is his blood pressure poorly controlled?

How should his treatment be optimised?

BMI 30, waist girth 105cm, high BP, diabetes, microalbuminuria, low HDL, high triglyceride

Metabolic Syndrome

("needs more diuretic")

Male age 55, creatinine 124umol/l – eGFR 53 ml/min

Chronic Kidney Disease (CKD 3)

("needs more diuretic")

... what diuretic is he getting currently?

Metformin 850mg BD

Gliclazide 5mg BD

Aspirin 100mg daily

Felodipine 10mg daily

Metoprolol CR 95mg daily

Inhibace Plus 1 daily

(*cilazapril 5mg + hydrochlorothiazide 12.5mg*)

Take home message

“Inhibace Plus is the Work of the Devil”

Because...

It combines a full dose (usual maximum) of ACE-inhibitor with an (often) ineffective dose of thiazide diuretic which (at this dose) has not been shown to improve outcome in clinical trials

Take home message...

The best thiazide (or thiazide-like) diuretic is chlorthalidone (12.5 – 25mg daily)

- more potent
- long half-life
- proven in clinical trials
- works better at lower GFR's than other thiazides

Back to Mr JH...

Inhibace Plus stopped and replaced with cilazapril 5mg and chlorthalidone 12.5mg daily



BP down to 150/91



Chlorthalidone increased to 25mg daily



BP down to 142/86

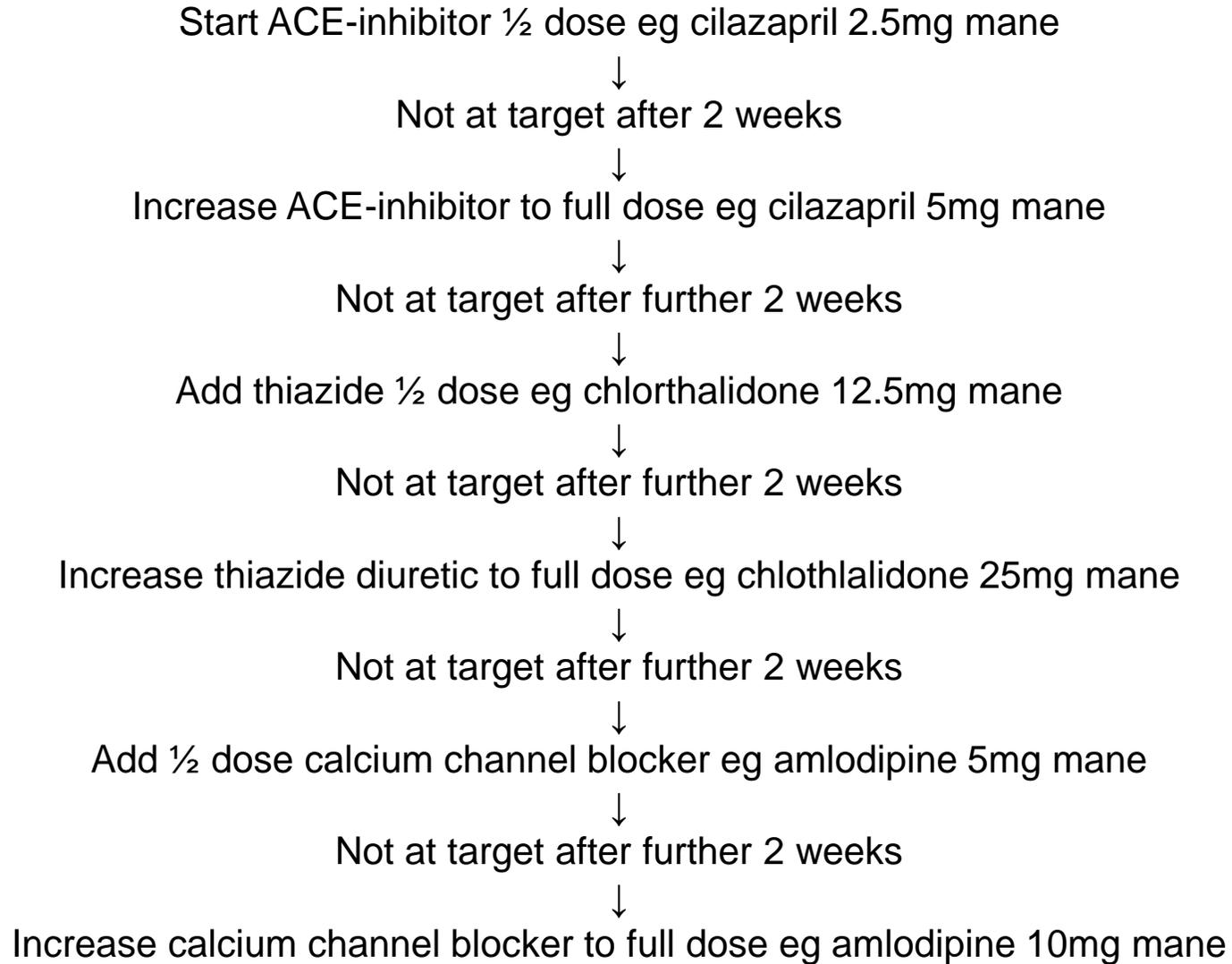


Spirolactone 12.5mg daily added



BP down to 128/78 (At target!)

How to use antihypertensive medication to achieve target blood pressure in a previously untreated patient with type 2 diabetes (if baseline BP < 150/90)



Take home message...

Apart from RAAS-blockers (ACE inhibitors and ARB's, which are interchangeable)

..the 2 most important other antihypertensive drug classes (in diabetics and non-diabetics)

Are Thiazide Diuretics and Calcium Channel Blockers

Other drug classes are often required, but should not be introduced until the potential of these 3 classes has been optimised (usually in combination)

Beta blockers are reserved in diabetics for those with compelling indications (post MI, CHF, arrhythmia) and as an add-on 4th or 5th drug in resistant hypertension

Summary

- Current evidence suggests that in the management of patients with type 2 diabetes mellitus achieving target BP $\leq 130/80$ may be the most important therapeutic goal
- Internationally, there is very poor compliance with BP targets in diabetics
 - partly due to genuine difficulty achieving the BP target
 - important contribution of “clinican inertia”
- The key to achieving BP target is effective antihypertensive combination therapy
- All diabetics should probably (and those with proteinuria should definitely) have an RAAS-blocker in their antihypertensive regimen, but...
- ...most diabetics with normal renal function will need ≥ 2 drugs to achieve target
- Most diabetics with impaired renal function will need ≥ 3 drugs to achieve target
- Individuals with metabolic syndrome and CKD and need more diuretic
- The commonest cause of resistant hypertension in diabetics with normal and impaired renal function is undertreatment with diuretic