

Management issues in hypertensive diabetics

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Abstract

This article discusses seven issues in the management of hypertension in diabetic patients, namely the importance of blood pressure control, optimal blood pressure control levels, the importance of blocking the renin-angiotensin system, the inevitability of combination anti-hypertensive therapy, drug choices, the diabetogenic effects of high dose thiazide diuretics and beta-blockers and the importance of treating other risk factors, like dyslipidaemia.

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INTRODUCTION

Diabetes mellitus and hypertension are common clinical conditions that often co-exist. This combination has been called "the deadly duet" to emphasise the increased cardiovascular risk that is associated with the combination of these two conditions.¹ Hypertension also occurs more commonly in diabetics than in non-diabetics.²

The prevalence of hypertension in diabetics is about two times higher than the prevalence of hypertension as observed in the general population.³ In type 2 diabetes mellitus (T₂DM), hypertension is often present as part of an underlying metabolic syndrome or insulin resistance syndrome. In type 1 diabetes mellitus (T₁DM), however, hypertension is often due to diabetic nephropathy.

Hypertensive patients are 2.5 times more likely to develop diabetes mellitus within 5 years after the onset of hypertension.⁴ This may be due to the presence of an underlying metabolic syndrome or may, additionally, be due to the type of antihypertensive drug used (e.g. high dose thiazides combined with high-dose beta-blockers especially atenolol).

The co-existence of hypertension and diabetes mellitus greatly increases the risk for macrovascular and microvascular complications. In patients with diabetes, the presence of hypertension causes a 7.2-fold increase in mortality and in diabetic nephropathy, the presence of hypertension causes a 37-fold increase in mortality.⁵

Most of the patients with diabetes and hypertension will die from a cardiovascular cause. Hypertension exacerbates all the vascular complications of diabetes including coronary artery disease, renal disease, stroke, peripheral artery disease, leg amputations and reti-

nopathy. Diabetes increases the risk of coronary artery disease - two-fold in men and four-fold in women. Women are, therefore, at particular risk.

MANAGEMENT PRINCIPLES:

I Blood pressure control is crucial

Data from clinical trials emphasise the need for tight blood pressure control in patients with diabetes and hypertension.

In the UK Prospective Diabetes Study (UKPDS) each 10mmHg decrease in mean systolic blood pressure was associated with a risk reduction of 12% for any complication related to diabetes, a risk reduction of 15% of deaths, a risk reduction of 11% for myocardial infarction and a risk reduction of 13% for microvascular complications.⁶ There was no threshold where risk was not observed.

II What is the Blood Pressure goal?

Both the UKPDS and HOT-trials (Hypertension Optimal Treatment) demonstrated improved outcomes in patients assigned to lower blood pressure targets. Epidemiological analyses show that blood pressure measurements $\geq 120/70$ mmHg are associated with increased cardiovascular event rates and mortality in patients with diabetes. A target blood pressure goal $\leq 130/80$ mmHg is both reasonable and safe to achieve. Achieving lower levels will decrease risk, but can be difficult to achieve and will increase the cost of treatment and the side-effect profile.⁵ Control of especially systolic blood pressure is important.

III The need for multiple-drug therapy

Evidence shows that to achieve the set goal of $\leq 130/80$ mmHg, requires the use of multiple-drug antihyperten-

sive therapy. Agents should be used that have been shown to reduce cardiovascular risk while not worsening concomitant conditions (e.g. new onset diabetes, abnormal lipids).

IV Blockade of the renin-angiotensin system (RAS)

Agents blocking RAS, such as angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB's), should be one of the partner drugs used in combination in hypertensive patients with diabetes or glucose intolerance.⁷ These drugs (ACE-I and ARB's) are also important to use if there are any microalbuminuria or proteinuria present as they reduce the progression to end-stage renal disease. The evidence is especially impressive with ARBs. Other drugs have also been shown to reduce proteinuria (e.g. indapamide and non-dehidropiridine calcium channel blockers, like verapamil).

V Which drug to use?

Clinical trials with diuretics, beta-blockers, ACE-inhibitors, angiotensin receptor blockers (ARB) and calcium channel antagonists have all demonstrated benefit in the treatment of hypertension in type 1 diabetes mellitus as well as type 2 diabetes mellitus.⁸ This is related to the degree of blood pressure lowering. The question of which drug is superior has not clearly been answered, but is probably not necessary to answer, because the hypertensive diabetic will require two or more drugs to reach the lower target blood pressure. It is also important to evaluate the patients for either known complications (e.g. coronary artery disease or other concomitant disease) to decide on the best combination of drugs.

The *Blood Pressure Lowering Treatment Trialist Collaboration* published a meta-analysis of 27 randomised trials with 158,709 patients to evaluate the effect of blood-pressure lowering on major cardiovascular events in patients with and without diabetes mellitus.⁹ The results from this meta-analysis demonstrated that major cardiovascular events were reduced to a comparable extent in individuals with and without diabetes by regimens based on angiotensin-converting enzyme inhibitors (ACE-I), calcium antagonists, angiotensin receptor blockers (ARB) and diuretic-beta blocker combinations. This effect was for short- to medium term duration. There is no data for long-term event reduction. The data also did not evaluate specific indications for specific drug groups.

The implications of this meta-analysis clearly demonstrate that there are no particular drug or drugs that are superior in diabetes and that the majority of patients will in any case require two or more drugs to achieve goal blood pressure.

VI New-onset diabetes and the use of antihypertensive drugs

People with elevated blood pressure levels are 2.5 times more likely to develop diabetes mellitus within 5 years than people with normal blood pressure levels. This phenomenon is made worse by the chronic administration of diuretics and beta-blockers, especially when administered in combinations with high doses.¹¹ The issue is currently hotly debated in the literature as to the exact mechanism and clinical implications. There is no question that the dys-metabolic effects of diuretics and beta-blockers are dose dependent. There is indirect trial evidence that diuretics (thiazide-type) in doses from 25mg to 50mg and higher are associated with increased incidence of new-onset diabetes mellitus, particularly when combined with high doses of beta-blockers (e.g. 100mg of atenolol).

A meta-analysis was recently presented of seven studies, in almost 60,000 patients, showing that compared to beta-blockers and diuretics, blockers of the renin-angiotensin system decreased the occurrence of new onset diabetes by 20% ($P < 0.001$) and calcium antagonists decrease onset of diabetes by 16% ($P < 0.001$).¹²

Another study reported a 16-year follow-up of almost 800 initially untreated hypertensive patients of whom 6.5% had diabetes at the onset and 5.8%

developed new onset diabetes on treatment. The risk for cardiovascular disease was similar in the group with pre-existing diabetes and the group who developed new-onset diabetes on treatment for hypertension.¹³ This suggests that the development of diabetes on antihypertensive treatment increases cardiovascular risk considerably. It could be that the combination of a low-dose diuretic with a blocker of the renin-angiotensin system or a calcium channel blocker may prevent the metabolic deleterious effect of a thiazide diuretic, as was shown with an ACE-inhibitor.¹⁴

SUMMARY OF TREATMENT:

1. The goal Blood Pressure is 138/80mmHg.
2. Multiple drugs are best to achieve target.
3. ACE-I (or ARB) should be part of the regimen.
4. In T₁DM with any degree of albuminuria an ACE-I is necessary.
5. In T₂DM with any degree of albuminuria an ARB is necessary, especially with renal insufficiency.¹⁰
6. Add a statin to reduce macrovascular risk.

IN CONCLUSION

Hypertension treatment as part of a global cardiovascular risk reduction

Cardiovascular risk factors tend to cluster and insulin resistance, type 2 diabetes mellitus, obesity and hypertension are commonly found in the same patient. Metformin, used to lower glucose, reduces cardiovascular risk in type 2 diabetes mellitus (T₂DM) and also reduces the risk of a cardiovascular event in established macrovascular disease.¹⁵

British Guidelines suggest a reduction of LDL-cholesterol levels to $< 2\text{mmol/L}$ in T₂DM patients¹⁶ using a statin. A meta-analysis of 12 randomised control clinical trials clearly demonstrated that in both primary and secondary prevention, diabetics had similar cardiovascular risk reductions than non-diabetics when using a statin.¹⁷ The vast majority, if not all, T₂DM patients should thus receive a statin. The aim of therapy is to reduce overall cardiovascular risk by targeting blood pressure reduction, blood sugar reduction and by routinely adding a statin in all diabetics. 🙋

See CPD Questionnaire, page 48

P This article has been peer reviewed

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