Hypertension Management in Patients with Type 2 Diabetes

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Part 1. Guidelines for Targeting Blood Pressure in Hypertensive Patients with Type 2 Diabetes Mellitus

Welcome, I'm Dr. Mark Molitch, Professor of Medicine, in the Division of Endocrinology, Metabolism, and Molecular Medicine at Northwestern University's Feinberg School of Medicine in Chicago. I'd like to welcome you to this Hypertension Management in Patients with Type 2 Diabetes Podcast, a course in the Type 2 Diabetes Mellitus curriculum programming, during which I will discuss hypertension management in patients with Type 2 diabetes.

I think one of the first things we have to think about is that hypertension is very, very common in people with both Type 1 and Type 2 diabetes, occurring in perhaps 60 to 70% of such patients. And obviously, this has to be put into context along with the cholesterol management and the glucose management in such patients.

The goals of treatment of hypertension may actually be different when we think about the cardiovascular outcomes of stroke and myocardial infarction versus the progression of diabetic nephropathy. Treatment of hypertension may also benefit progression of diabetic retinopathy as well, but that's probably a less important treatment outcome, as we'll talk about over the course of the next few minutes. We know from a number of studies that treatment of hypertension will reduce overall mortality and cardiovascular outcomes. This starts from the United Kingdom Prospective Diabetes Study where they had two different groups looking at blood pressure outcomes, finding that more intensive blood pressure management reduced mortality.

And in a retrospective analysis of their data, as you brought the systolic blood pressure down to less than 130 and even less than 120, there was continued benefit, in kind of a linear fashion. The Hypertension Optimal Treatment trial or HOT trial, really targeted diastolic blood pressure, and found that as you brought the diastolic blood pressure down from 90 to 85 and then down to less than 80, that there was, again, a considerable cardiovascular benefit.

At the same time that these vascular studies have been ongoing, there were also studies looking at the effects of blood pressure management on diabetic nephropathy. And so multiple studies show that lowering blood pressure was able to get a decrease in the rate of fall of glomerular filtration rate. However, some more recent studies have suggested that perhaps there were different effects of lowering blood pressure on the nephropathy outcome, compared to the cardiovascular outcome.
The first of such studies that showed a difference was called the Irbesartan Diabetic Nephropathy Trial. This was the trial that showed benefit of using the ARB irbesartan for the treatment of diabetic nephropathy. And in a retrospective analysis of that study, which clearly showed benefit of that ARB, if you lowered systolic blood pressures to lower and lower levels, to even less than 120, there was clear benefit in progression of diabetic nephropathy. However, when you looked at the cardiovascular outcomes, as you got to a systolic blood pressure less than 120, there was an increase in cardiovascular mortality. So we're starting to see a discrepancy here. The recent ACCORD study not only looked at blood sugar and lipid outcomes, it also looked at blood pressure. And there were two different targets for the ACCORD blood pressure arm. There was an intensive group that targeted systolic blood pressure of less than 120, and standard therapy targeted blood pressure less than 140. Although there was no difference in the primary outcome between these two groups, with the primary outcome being nonfatal MI, nonfatal stroke, and death from cardiovascular causes, when you looked at stroke as a separate outcome, there was continued benefit, even at the lowered blood pressure level. Again, a slight difference here for stroke compared to overall cardiovascular outcome.

Another new study, called the INVEST study, compared verapamil to trandolapril, an ACE inhibitor, and both groups were getting a diuretic, with a goal of achieving a blood pressure less than 130/85. In a retrospective, preplanned analysis, they looked at different levels of blood pressure control: a tight control group with a systolic of less than 130, a usual control group of 130 to 140, and an uncontrolled group of systolic greater than 140. And interestingly, in this...the usual group, actually, was substantially better, so that a systolic blood pressure achieved of 130 to 140, the people did overall much better than those who had a systolic of less than 130 or a systolic of greater than 140. So, this appears to be sort of the optimal blood pressure based upon that study.

And then, finally, the ONTARGET Study showed a similar type of an effect, where the optimal systolic blood pressure was about 130, and as you started to get systolic blood pressures much below that, the mortality rate started to increase. So, the overall ADA guidelines where we have a systolic blood pressure of less than 130 and a diastolic of less than 80 appears to be just about right. You really don't want to get to a systolic blood pressure much lower than that.

And when we're thinking about therapy for our patients, if they start off with a systolic of 130 to 139, and a diastolic of 80 to 89, we usually would start with lifestyle alone for a maximum of about three months. And if we don't achieve a goal of less than 130 at that point, then we go on to pharmacological agents. If the systolic is greater than 140 or the diastolic is greater than 90, then I think we go directly to pharmacological agents in the managing of the patients.
Part 2. Treatment Options for Management in Hypertensive Patients with Type 2 Diabetes Mellitus

There are a lot of data to guide us in the pharmacologic management of hypertension in patients with diabetes. The cornerstone of treatment are drugs that are active in the renin-angiotensin-aldosterone system. As you may recall, renin is released in response to a decrease in plasma volume. That stimulates a conversion of the angiotensinogen to angiotensin-I. Then angiotensin-converting enzymes stimulate the conversion of angiotensin-I to angiotensin-II. Angiotensin-II has direct vasoconstrictive properties, and it also stimulates the production of aldosterone, which then causes sodium reabsorption. We now have drugs that are active in three parts of this system. The original drugs were the ACE inhibitors that blocked the conversion of angiotensin-I to angiotensin-II. The angiotensin-II receptor blockers, or ARBs, block the stimulation of aldosterone by angiotensin-II. And the most recent drug, aliskiren, is a drug that blocks renin secretion to begin with.

We have studies that have looked at all aspects of this system and all of these kinds of medications. There are studies that show an effect directly on cardiovascular outcomes, and the MICRO-HOPE study is really the original one that looked primarily at cardiovascular outcomes. And in the study they showed that for both people with and without diabetes, that the use of an ACE inhibitor, ramipril, was able to significantly reduce the development of stroke, myocardial infarction, and cardiovascular death, as a composite primary outcome. Specifically looking at the diabetic subgroup, they also found that ramipril was able to reduce the development of diabetic nephropathy as manifested by albuminuria. Really, the first studies that looked at the effects of these drugs in patients with diabetes was the Captopril study that showed that ACE inhibitors were more renoprotective than conventional therapy for patients with Type 1 diabetes. And now we have data for Type 1 diabetes as well as for Type 2 diabetes with the MICRO-HOPE study.

There were several studies that looked at ARBs for the prevention of outcomes in patients with Type 2 diabetes. The first of these was the Losartan Treatment Study, or RENAAL Study, that showed losartan was able to decrease the endpoint of doubling of serum creatinine, end-stage renal disease, or death in patients who already had diabetic nephropathy.

The Irbesartan Diabetic Nephropathy Trial, or IDNT, showed similar type of data for irbesartan in the decreased development of the composite endpoint of end-stage renal disease or death. Interestingly, when you compare drugs that are ARBs versus ACEs, there really doesn't seem to be much difference in their activity. The DETAIL Study compared enalapril and telmisartan, and showed equivalence in the progression rate of diabetic nephropathy. And the BENEDICT study showed similar effects. So it's very clear then that either an ACE inhibitor or an ARB can be used in patients with Type 2 diabetes to decrease the rate of progression of diabetic nephropathy and also have benefit on cardiovascular outcomes.
Well, if we are going to use an ACE inhibitor or an ARB, and then blood pressure does not get under control, then we need to add second, and perhaps even third and fourth medications. There are a number of potential options. We could add a diuretic, we could add a calcium channel blocker, we could add a second drug active in the renin-angiotensin system, beta-blockers, alpha-blockers, vasodilators. All of these can be added to the initial ACE or an ARB that may be used as the first medication.

For most of us, we have tended to use a diuretic as the first add-on agent to an ACE inhibitor or an ARB, but the recent ACCOMPLISH Trial has called that into question. In this particular study, they had benazepril as their ACE inhibitor, and they then compared adding amlodipine, a calcium channel blocker, or hydrochlorothiazide. Looking at the renal endpoint of the doubling of serum creatinine or end-stage renal disease, and in fact, surprisingly, they found that amlodipine did better than did hydrochlorothiazide. This is a very significant improvement in that regard. Interestingly, there was also a decrease in the primary endpoint of cardiovascular death, nonfatal MI, stroke, or hospitalization. Both cardiovascular and renal endpoints were better with the added calcium channel blocker than with hydrochlorothiazide.

Another possibility is to have dual blockade of the renin-angiotensin system. You could add an ACE to an ARB or an ARB to an ACE, and this has been done in a number of studies, and they really tend to not show further improvement in many of these studies, except for perhaps some further reduction in proteinuria.

The ONTARGET Study compared giving telmisartan versus ramipril and then a combination of telmisartan plus ramipril, and there was really no difference between these. So for cardiovascular outcomes, the dual renin-angiotensin system blockade was no better than using either drug alone, and in fact, the renal outcome was actually worse. There was a worsening of GFR with the combination therapy. In addition, the combination caused more hyperkalemia and so this could be a problem when you're adding two different blockers in a renin-angiotensin system.

Aliskiren has been added to losartan. Aliskiren, as you recall, is the direct renin inhibitor. And so when this was added to losartan in the AVOID Study, there was a further reduction in urine albumin excretion, but there was no change in glomerular filtration rate. So this may prove to be of some benefit in the future, but at this point, its long-term outcomes have really not been shown.

Aldosterone blockers have also been added to ACE inhibitors or ARBs, and a systematic review has been done of this. There can be a further reduction in proteinuria. There can be a further reduction in blood pressure. But any further outcomes in GFR have really not been shown, as far as the benefit goes. And in addition, the patients are also at further risk of hyperkalemia.
So, we have a number of possibilities of adding second and third drugs. Some people may be concerned about the effects of hydrochlorothiazide or beta blockers on glucose metabolism. But these, in general, have been pretty minor effects and easily managed with some minimal adjustment of the antihyperglycemic medications that may be used.

When you look at many of the studies that have looked at blood pressure control, in fact, two, three, four and even five drugs are sometimes necessary to get blood pressure under control. So, when we come back to our ADA guidelines and think about what we're doing, I think that overall blood pressure goal of about 130/80 still seems to be a very reasonable goal, now based on lots and lots of data. This is important both for slowing of progression of cardiovascular disease, as well as the rate of fall of glomerular filtration rate.

The ACE inhibitors and the ARBs are clearly recognized as the cornerstone of therapy and should be part of almost all antihypertensive regimens. Combination therapy with ACEs and ARBs together has certainly been shown to have greater reduction in albuminuria, but no real added benefit on cardiovascular or chronic kidney disease outcomes. And they do raise issues about safety and tolerability, especially with regard to hyperkalemia. We don't have any long-term data on renal inhibition as well as an ACE or an ARB.

So, finally, I think it's very important to get blood pressure under control. It clearly has benefits. And it often takes two, three, four and five drugs to achieve our outcomes that were necessary. Thank you.