TREATING THE DIABETIC HYPERTENSIVE: CONSENSUS AND DIFFERENCES

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ABSTRACT

Hypertension and diabetes commonly coexist. Both are major modifiable risk factors for cardiovascular diseases. There has been a substantial shift in the recommendations of several expert committees on the management of hypertension in diabetics. It was once unanimously agreed by almost all major guidelines that the threshold for initiating diabetic patients with antihypertensive therapy is when blood pressure is >130/80 mmHg. The blood pressure target for treatment was also unanimously agreed to be <130/80 mmHg. These recommendations were, however, based on expert opinions and not on findings from major randomised controlled trials.

Since then, there have been several randomised controlled trials looking at blood pressure-lowering in the diabetic population. These include the ADVANCE and ACCORD, and a subanalysis of the INVEST trials. Together with the earlier UKPDS and HOT trials, one would expect there to be more agreement in the most recent recommendations, but in fact the opposite is the case. There are now two different systolic targets (<130 mmHg and <140 mmHg) and three different diastolic targets (<90 mmHg, 85 mmHg, and <80 mmHg). The reason for this involves the choice of trials included in the recommendation, and the interpretation of results from these trials by various guideline committees.

The recommendation for diabetic hypertensives will be more consistent if future trials begin by asking a relevant research question that has not yet been answered: does treating diabetics with different thresholds of blood pressure levels impact on clinical outcomes? The trial must not only determine a primary research question, but it must also be adequately powered to answer it. Only when this question is answered should the next questions be asked. Does it matter how blood pressure is lowered? And are some drugs better than others? In the meantime, guideline committees should try to narrow the gap in recommendations, particularly if the guidelines originate from the same country or region.

Keywords: Diabetes, hypertension, treatment, blood pressure (BP).

INTRODUCTION

Hypertension and diabetes are major contributors to cardiovascular (CV) events and total mortality. The World Health Organization (WHO) has identified both as top causes of total mortality worldwide for more than a decade.[1] These two major risk factors also commonly coexist. In recent mega trials on diabetes, up to 80% of the patients were hypertensive at baseline.[2,3] Diabetes is now regarded as a vascular disease with accompanying dyslipidaemia. Vascular diseases, particularly macrovascular disease, predate the onset of dysglycaemia.[4,5] The importance of blood pressure (BP) control in diabetics was highlighted by the UKPDS analysis which showed that while tighter control of BP improves macrovascular outcome, the same was not seen with tight diabetes control.[6] Surveys have shown that BP control in diabetic hypertensives is required.[7,8] It has been estimated that better control of BP, as in clinical trials in diabetes, could prevent up to 1.5 million deaths worldwide over a 4-year period.[9]

TARGET BLOOD PRESSURE: EVOLUTION OF EVIDENCE

The first insight into what level BP should be lowered to by treatment was provided by the HOT study.[10] Analysis of the diabetic subpopulation in this study showed that, unlike in the main study population, patients who were treated to a diastolic of <80 mmHg had significantly fewer CV events than those treated to a diastolic <90 mmHg. The study's diabetic population (n=1,915), however, constituted only 8% of the total study population. In the same year, the UKPDS 38 showed that, of newly diagnosed diabetics, patients whose BP was tightly controlled (achieved BP was 144/82 mmHg) had significantly fewer strokes than patients whose BP was less tightly controlled (achieved BP was 154/87 mmHg).[6] No significant difference was seen with myocardial infarction or all-cause mortality. It should be noted that the number of patients studied in the UKPDS BP-lowering arm was small (758 in the 'tight group' versus 390 in the 'less tight group'). In other words, both the HOT and UKPDS substudies were, strictly speaking, 'hypothesis-generating' and not definitive. The first study that looked at the effect of different levels of BP was the ABCD 2 trial.[11] In that study, 480 diabetic hypertensives with a mean baseline BP of 136/84 mmHg were randomised to placebo or active treatment (with nisoldipine or enalapril). The achieved BP in the treated group was 128/75 mmHg compared with 137/81 mmHg in the placebo-treated group. There were significantly fewer strokes, development of macroalbuminuria, and progression of retinopathy in the treatment group. Glomerular filtration rate estimated by a 24-hour creatinine clearance performed every 6 months over the 5-year study period, rather surprisingly, did not differ between the active treatment group compared with the placebo-group. These three studies (HOT, UKPDS, and ABCD 2) were the only available evidence at that time and, unsurprisingly, almost all major guidelines (for both hypertension and diabetes) at the turn of the century recommended that BP should be reduced to <130/80 mmHg in diabetic hypertensives. This is despite the fact that all three studies were either subanalyses with small sample sizes or small trials, which made them underpowered and not definitive evidence.

The first mega trial which looked at BP-lowering intervention in a diabetic population was the ADVANCE trial.[12] In this diabetes dedicated study, half of the 11,140 patients with baseline BP of 145/81 mmHg were randomised to either a single pill combination of perindopril 4 mg plus indapamide 1.5 mg (Coversyl Plus®) or placebo. One of the research questions asked in this trial was whether in the diabetic population, lowering systolic BP to <145 mmHg will provide additional benefits. The level of 145 mmHg was chosen because at the time that the study was being designed, the only available evidence for systolic level was from UKPDS 38, which managed to lower BP in the intensive arm to 144/82 mmHg. The ADVANCE trial showed that, in the treated group (achieved BP 135/75 mmHg), there was a significant reduction in CV death and all-cause mortality compared with the placebo group (achieved BP 140/77 mmHg). The ADVANCE trial was a 2-by-2 factorial design which also had a glucose-lowering arm with either standard diabetic care or intensive care, with the addition of gliclazide modified release (Diamicron® MR). In the glucose arm HbA1C dropped from a baseline of 7.1% to 6.5% in the intensive group and to 7.2% in the standard care group. The results from the glucose-lowering arm (10% reduction in combined macro and microvascular events with no impact on mortality) was not as exciting as the BP-lowering arm. A combined analysis of the BP and glucose-lowering intervention showed that the best outcomes were seen in the group that received both intensive BP and glucose lowering, with a significant 18% reduction of total mortality.[13]

The first trial which specifically looked at the effects of different achieved levels of BP on active treatment was the ACCORD trial.[14] In this open-label trial, more than 4,733 diabetics with a baseline BP of 139/75 mmHg were randomised to an intensive arm (systolic BP <120 mmHg) or a standard therapy (systolic BP <140 mmHg). In the intensive arm, the achieved BP was 119/64 mmHg while the BP achieved on the standard arm was 134/71 mmHg. Except for stroke, there were no differences in clinical outcomes between the intensive and standard therapy. There was, however, significantly more serious adverse events with the intensive group. The lack of benefit from intensive BP control was corroborated by a subanalysis of a mega trial, INVEST,[15] which looked at 22,576 hypertensives with underlying ischaemic heart disease. Patients were randomised to receive either atenolol with a thiazide as the second drug, compared with trandolapril with verapamil as a second drug. In a separately published subanalysis of INVEST,[16] 6,321 diabetics were categorised into

those with achieved systolic BP of <130 mmHg (tight BP control), 130–139 mmHg (usual BP control), and >140 mmHg (uncontrolled BP). As expected, the uncontrolled group showed significantly higher events (death, myocardial infarction, and stroke). There was no difference between the control group and the tight group.

One of the largest CV trials to enrol diabetics is the ONTARGET trial.[17] In this study, 25,620 patients were randomised to ramipril, telmisartan, or a combination of both. Of these participants, 9,612 patients (37.5%) were diabetic. In the overall population, there was no difference in primary outcome between those randomised to the two different monotherapies, while those randomised to the combination had worse renal outcomes and more adverse events. In a *post hoc* analysis of the diabetic population, CV events were significantly higher than the non-diabetic population at each level of baseline or achieved on-treatment BP.[18] This *post hoc* analysis did not suggest a BP threshold, which may be potentially harmful to the diabetic population.

SHIFTING PARADIGM: CONSENSUS AND DIFFERENCES

The latest round of hypertension guidelines was published in 2011 by the National Institute of Health Care and Excellence (NICE) UK.[19] No specific recommendation was made for target BP in diabetics. However, reference was made to the NICE Diabetes Guideline which recommended a BP target of <140/80 mmHg.[20] The next published guideline was the European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines in 2013.[21] The recommendation made by the ESH/ESC guidelines was a BP of <140/85 mmHg. This was followed by the Canadian Hypertension Education Programme (CHEP)[22] guidelines, the Japanese Society of Hypertension (JSH) guidelines,[23] and the Taiwan Society of Hypertension and Taiwan Society of Cardiology (TSOC) guidelines,[24] all of which recommended a target level of <130/80 mmHg. Three American-based guidelines including the American Heart Association/American College of Cardiology (AHA/ACC),[25] the Eighth Joint National Committee (JNC 8),[26] and the American Society of Hypertension/International Society of Hypertension (ASH/ISH)[27] all recommended a BP target of <140/90 mmHg. On the diabetic guideline front, until very recently, the American Diabetes Association (ADA) guidelines[28] concurred with British Diabetes NICE guidelines by recommending a BP target of <140/80 mmHg. The most recent ADA guideline of 2016, however, has revised the recommended BP for diabetics to a target of <140/90 mmHg.[29] There are therefore four different target BPs recommended to doctors by the different guidelines, as opposed to only one not so long ago (130/80 mmHg). These differing recommendations may leave practitioners confused; what makes it more perplexing is that the same evidence was quoted to justify the new recommendations.

WHY DIFFERENT RECOMMENDATIONS?

There are several reasons why this happened, the first of which was the particular selection of trials to provide the evidence-base. In some guidelines, studies were quoted only if it was primarily designed to test the hypothesis that separation of BP to pre-specified levels produces different outcomes. This was why JNC 8 did not accept the ADVANCE trial as evidence, even though the achieved diastolic BP in both the active and placebo treated groups in ADVANCE was <80 mmHg. JNC 8 argued that ADVANCE was not a hypertension study in the diabetic population because both hypertensives and normotensives were recruited. However, it is worth emphasising that the baseline BP in ADVANCE was 145/81 mmHg, which at that time was considered high for diabetics. Both ESH/ESC and JNC 8 quoted the ADVANCE trial but did not use it to justify their diastolic BP target recommendation (<85 mmHg in ESH/ESC and <90 mmHg in JNC 8). JNC 8's recommendation of BP <140/90 mmHg is based on expert opinion because none of the available studies were considered to be high level evidence, according to their strict criteria for grading of evidence. The AHA/ACC guidelines, meanwhile, do not quote primary data or studies in making its recommendation, but has made the decision to update its recommendation by reviewing all available evidence working together with the National Heart Lung Blood Institute (NHLBI). The update is due to be released in 2016.[30] The CHEP guidelines classified their recommendation for a systolic BP of <130 mmHg as Grade C while that for diastolic BP of <80 mmHg as Grade A evidence, but no reference was quoted. The HOT trial was quoted in the CHEP recommendation but was not used to justify this recommendation and the ACCORD, UKPDS, and

ADVANCE trials were not quoted. CHEP has not revised this recommendation in their subsequent yearly update.[31] The Canadian Diabetes Association (CDA) guidelines[32] meanwhile give the same recommendation for BP targets by quoting UKPDS, ABCD2, and HOT trials. Table 1 summarises the various recommendations thus far.

Another reason for the divergence of recommendations was the interpretation of the trial results. The ESH/ESC guidelines justified the diastolic BP target of <85 mmHg by quoting the UKDPS and HOT trials. These two trials, however, studied a small number of diabetic hypertensives and, strictly speaking, the recommendation was based on a subanalysis and is thus hypothesis-generating. The ASH/ISH meanwhile justified their recommendation by arguing that the previously recommended BP of <130/80 mmHg in diabetics lacks evidence and thus the goal of <140/90 mmHg should generally be used. The JNC 8 as mentioned above did not think any of the available evidence was good enough to be quoted and chose expert opinion for their recommendation.

The Japanese guidelines justified the decision to maintain the recommended BP target of <130/80 mmHg by quoting HOT, UKPDS, and the older recommendations from the ADA 2003, JNC 7, and the ESH/ESC 2007 guidelines. Meanwhile the Taiwanese Guideline justified their recommended target of <130/80 mmHg by highlighting the reality of the status of diabetes control in Taiwan, and quoted the Japanese guidelines target BP recommendation and the latest International Diabetes Federation (IDF) guidelines recommendation as supporting evidences.[33]

It is worth asking some basic questions of the interpretation of existing data from randomised control trials. While there is general agreement that available randomised control trials that specifically address the issue in question are lacking, there is obviously a lack of congruence in the interpretation, as discussed elsewhere by the author.[34] In the ADVANCE trial meanwhile, the achieved diastolic BP in the actively treated group was 75 mmHg compared with the control group which was 77 mmHg.

Table 1: Guidelines for blood pressure targets in diabetic hypertensives.

Guidelines	Year published	BP targets (mmHg)	Studies quoted
CHEP	2013, 2014, 2015	<130/80	Not specified
CDA	2013	<130/80	UKPDS, HOT, ABCD2
Japanese	2014	<130/80	UKPDS, HOT
Taiwan	2014	<130/80	UKPDS, HOT
Malaysian Diabetes	2015	<135/75	ADVANCE, ACCORD
NICE Diabetes and NICE Hypertension	2015 2011	<140/80	UKPDS, HOT
Malaysian Hypertension	2014	<140/80	ADVANCE
ADA	2015	<140/80	HOT
ESH/ESC	2013	<140/85	HOT, UKPDS
AHA/ACC	2014	<140/90	Not specified
ASH/ISH	2014	<140/90	Not specified
JNC 8	2014	<140/90	Expert opinion
ADA	2016	<140/90	HOT

CHEP: Canadian Hypertension Education Program; CDA: Canadian Diabetes Association; NICE: National Institute of Health Care and Excellence; ADA: American Diabetes Association; ESH: European Society of Hypertension; ESC: European Society of Cardiology; AHA: American Heart Association; ACC: American College of Cardiology; ASH: American Society of Hypertension; ISH: International Society of Hypertension; JNC 8: Eighth Joint National Committee; UKPDS: UK Prospective Diabetes Study; HOT: Hypertension Optimal Treatment; ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; ACCORD: Action to Control Cardiovascular Risk in Diabetes.

However, despite the fact that the ADVANCE trial was the largest diabetic dedicated trial to look at the effects of antihypertensive therapy on clinical outcomes, it was not accepted by many guidelines as a trial to be quoted for targeting BP-lowering in diabetics. This was mainly because as a placebo controlled trial it did not compare active treatment regimens. Although in the HOT trial, the diabetic subpopulation on treatment diastolic BP of <85 mmHg did not have different clinical outcomes compared with those with targeted diastolic BP of <90 mmHg, there was a significant difference between those who were targeted to achieve diastolic BP of <80 compared with <90 mmHg. Why then was the diastolic BP target of <80 mmHg not recommended by the ESH/ESC, which quoted the HOT diabetic subanalysis as their justification for their recommendation? A possible explanation was that even in the HOT trial the actual mean achieved diastolic BP in the intensive treated group was slightly more than 80 mmHg, i.e. 81 mmHg. Meanwhile, the ADA has revised their 2015 guideline, recommending the target diastolic BP of <90 mmHg[29] as opposed to <80 mmHg the previous year. Justification given for this shift was that the earlier recommendation was based on *post hoc* analysis of the HOT trial and for this latest recommendation is consistent with that of JNC 8.

CONCLUSION AND FUTURE RECOMMENDATIONS

Recently recommended BP targets for diabetic hypertensives show significant variation and lead to confusion among readers and practitioners. Many of the recommendations made were based on subanalyses of big studies involving small sample sizes, and are therefore by definition not definitive evidence. With the recent publication of the SPRINT trial[35] and the reopening of the debate on optimum BP to be achieved in hypertensive patients, the time is right for an adequately powered and *a priori* hypothesis-testing study dedicated to the diabetic hypertensive population to be designed and executed. This is especially so because the SPRINT trial excluded patients with diabetes. This also means that the findings from this large study (which showed that clinical outcomes are significantly better with a target systolic BP of <120 compared with <140 mmHg) cannot be extrapolated to the diabetic population. The question as to the best target BP to aim for in the diabetic patient with hypertension will remain unanswered until a SPRINT-type study is carried out in the diabetic population. The SPRINT trial has triggered interesting debates among experts in hypertension with more questions being asked.[36-38] However, on a reassuring note, a recent subanalysis of the SPRINT trials on patients >75 years old reaffirms that lowering systolic BP to <120 mmHg leads to a significant reduction in fatal and non-fatal CV events, also significantly lowering all-cause mortality.[39] While waiting for further studies to provide a definitive answer to the question of target BP for the diabetic hypertensives population, it is important that guideline committees narrow the differing recommendations so as not to create more confusion among practitioners, patients, and policy makers alike. It is also very important that specific countries' hypertension and diabetes associations produce guidelines which concur with each other on their recommendations, as has happened in Canada and more recently in the USA.

In Malaysia the guidelines also differ; the hypertension clinical practice guidelines differ in their recommendations from the Malaysian Diabetes Association guidelines, with the former recommending the target of <140/80 mmHg[40] and the latter <135/85 mmHg.[41] In this author's view, what can be deduced from all the studies done so far is that attaining a BP on treatment as low as 135/75 mmHg (as achieved in the ADVANCE trial) is beneficial for major clinical important outcomes including CV outcomes and even all-cause mortality. Of equal importance, it is safe to lower BP to that level in patients with diabetes. The ADVANCE trial is also the most important and largest study so far looking at diabetic population and BP-lowering treatment. We hope that a critical study to address this issue will one day be conducted and there will be uniformity in future recommendations. In the meantime, it should be noted that BP control rates in diabetics remain poor even based on the latest surveys and systematic reviews. A recent Dutch study showed that rates of hypertension control among Dutch of African-Surinamese origin was only 28.7%, of Ghanaian Origin was 41.7%, and of ethnic Dutch origin was 54.1%.[42] A systematic review involving 25,629 diabetic hypertensives from 19 countries all conducted between 2009 and 2014 revealed a control rate of only 35.7%. The review noted that hypertension control rates were the worst compared with glycaemic control (44.5%) and

cholesterol control (51.4%).[43] There is obviously a lot more work to be done. It will help if future recommendations correspond with one another rather than remaining contradictory.

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