George L. Bakris
MD, Hon. DSc, F.A.S.H, F.A.S.N., F.A.H.A.

Professor of Medicine
Director, ASH Comprehensive Hypertension Center
The University of Chicago Medicine, Chicago, IL

Dr. Bakris received his medical degree from the Rosalind Franklin School of Medicine and completed residency in *Internal Medicine* at the Mayo Graduate School of Medicine where he also completed a research fellowship in *Physiology and Biophysics*. He then completed fellowships in *Nephrology* and *Clinical Pharmacology* at the University of Chicago. From 1988 to 1991, he served as Director of Renal Research at the Ochsner Clinic and had faculty appointments in the Departments of Medicine and Physiology at Tulane University School of Medicine. He later was Professor and Vice Chairman of *Preventive Medicine and Director of the Rush University Hypertension Center* in Chicago from 1993 until 2006. **Currently**, he is a *Professor of Medicine* and *Director of the ASH Comprehensive Hypertension Center* in the Department of Medicine at the University of Chicago Medicine.

Dr. Bakris has published over 700 peer-reviewed articles and book chapters in the areas of diabetic kidney disease, hypertension and progression of nephropathy. He is the Editor or Co-Editor of 20 books, in the areas of Kidney Disease Progression and Diabetes as well as the new edition of **Hypertension: A Companion to Braunwald's The Heart**. Additionally, he is an Associate Editor of the **International Textbook of Cardiology**. He was a member of the NIH National High Blood Pressure Education Program Working Group on Hypertension and Renal Disease (1994). He also serves as a special government expert to the Cardio-renal Advisory Board of the FDA and to CMS. He was a co-principal investigator on the NIH Clinical Research training grant for clinical research (K30) (1999-2004). He chaired the *first* National Kidney Foundation Consensus report on blood pressure and impact on renal disease progression (2000). He has also served on many national guideline committees including: The Joint National Committee Writing Groups VI & 7 (1997, 2003), the JNC 7 executive committee (2003), the American Diabetes Association Clinical Practice Guideline Committee (2002-2004), the National Kidney Foundation (K-DOQI) Blood Pressure Guideline committee (2002-2004 & 2013) and (K-DOQI) Diabetes Guideline committee (2003-2005 & 2014). Dr. Bakris is the past-president of the ***American College of Clinical Pharmacology*** (2000-2002) and the ***American Society of Hypertension (ASH)***. He is the current Editor-in-Chief, ***Am J Nephrology,*** Editor-in-Chief- ***Up-to-Date, Nephrology section,*** Hypertension Section Editor ***Up-to-Date*** and Assoc. Ed of ***Diabetes Care***. He serves on more than 18 editorial boards including Nephrology, Dialysis & Transplant, Hypertension, J Hypertension and J American Soc. Hypertension.

Επίκαιρο Άρθρο

How to Treat Hypertension in Diabetes in 2017

George L. Bakris, MD, F.A.S.N., F.A.H.A.

ABSTRACT

Over the past 30 years many guidelines about blood pressure control in patients with diabetes have appeared. These guideline goals have been based on weak levels of evidence as there are only two prospective studies that test whether a lower blood pressure actually reduces cardiovascular events. Moreover, there are NO studies that evaluate level of blood pressure on progression of diabetic kidney disease. Hence, the preponderance of the evidence comes from moderate to long term follow-up of observational studies. The most recent consensus report on blood pressure by the American Diabetes Association has evaluated all the recent data from trials and meta-analyses most of which are included in this paper. The conclusion is the strongest evidence provides for a blood pressure goal of <140/90 mmHg that is sustained at these levels. Additionally, based on recent analyses if the patient agrees and can tolerate blood pressure reductions to levels between 125-130 mmHg systolic, every effort should be made to achieve this level as those who do achieve it have fewer cardiovascular events and reduced mortality. Additionally, there is new wording regarding diastolic blood pressure, i.e. levels should be kept above 60 mmHg regardless of the systolic pressure. Note that the last two recommendations have moderate evidence and not as strong as the <140/90 mmHg, nevertheless should be heeded. Lastly, ACE inhibitors and angiotensin receptor blockers are only mandated for those with kidney disease (eGFR<60 ml/min/1.73m^2) with >300 mg/day of albuminuria. They are not preferred in normotensive people with normal kidney function with or without microalbuminuria or hypertensive patients without albuminuria. The key is achieving blood pressure reduction and not the drug class.

The current blood pressure guideline goal by the American Diabetes Association and most international guidelines is <140/90 mmHg[1,2]. Lower goals of <130/80 mmHg were previously proposed but with no prospective data to support this level. In fact, all of the data that supported this level was derived from observational studies and post hoc analyses of negative clinical trials[3,4].

The only two prospective studies to evaluate different blood pressure goals on cardiovascular outcomes were the United Kingdom Prospective Diabetes Study (UKPDS) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Only the ACCORD had one group achieve a blood pressure level well below 130/80 mmHg. The UKPDS had an average systolic blood pressure of 147 mmHg in the intensive group. While both these trials showed a trend for reduced cardiovascular events in the lower blood pressure group, the ACCORD when the trial ended with less than a four-year follow-up, failed to reach its primary cardiovascular endpoint but did show a benefit on stroke reduction. The only other prospective trial to evaluate blood pressure level on cardiovascular outcome was the Hypertension Optimal Treatment (HOT) trial[5]. The primary outcome of HOT was negative but the post hoc subgroup analysis of the diabetes group, was positive, favoring a diastolic pressure of 80 mmHg, but this analysis was only hypothesis generating.

Professor of Medicine, Director, ASH Comprehensive Hypertension Center, University of Chicago Medicine Chicago, IL USA

✉ **Correspondence: George L. Bakris,** *Chicago, IL USA 60637* • Phone: 773-702-7936 • Email: gbakris@gmail.com

Since, these trials there have been long term follow-up data extending almost a decade and beyond in some studies demonstrating different outcomes, Table 1. For example, a long term follow-up (8.9 years) of ACCORD demonstrated an interaction between the aggressive glucose control group and intensive blood pressure group such that after correction there was a benefit trend for cardiovascular events[6]. Further data presented at the November, 2015 American Heart Association demonstrated that protection against stroke reduction seen in ACCORD was lost when systolic blood pressure was only 4 mmHg lower in the intensive group compared to the usual car group. Hence, there is no legacy effect of blood pressure on cardiovascular events, an effect also seen in UKPDS[4].

Within the past two years there have been three large meta-analyses of data involving cardiovascular outcomes from trials of patients with type 2 diabetes. The smallest of these meta-analyses reviewed over 44,000 subjects. All these meta-analyses demonstrate fewer CV events at BP levels well below 140/90 mmHg and some extending below 130/80 mmHg[7-9].

One meta-analysis evaluated 40 trials judged to be of low risk of bias (100,354 participants) among people with diabetes[7] and demonstrated findings similar to the UKPDS. The authors of the meta-analysis found that for each 10–mm Hg lower systolic BP there was a significantly lower risk of mortality with an absolute risk reduction in events per 1.000 patient-years (3.16; 95%CI, 0.90-5.22). A second meta-analysis involving 19 trials including 44,989 participants demonstrated a reduction in major CV events that was consistent across patient groups, with additional BP lowering having a clear benefit even in patients with systolic BP lower than 140 mm Hg[8]. These investigators also found that absolute CV benefits were greatest in trials that enrolled patients with vascular disease, chronic kidney disease, or diabetes. Lastly, the third and largest meta-analysis of 123 studies with 613, 815 participants further supported the concept that for every 10 mm Hg reduction in systolic BP there was a sig-

Table 1. Key Randomized Trials of Blood Pressure Control in Type 2 Diabetes Mellitus

Trial	Follow-up (years)	# of Subjects	BP Goal (mmHg)	BP Achieved (mmHg)	Main Results
UKPDS (1998)	8.4	1148 ·758 "tight" –390 control	<150/85 (tight) vs. <180/105 (control)	144/82 (tight) & 154/87 (control)	Tight control resulted in risk reduction in diabetes related end-points and strokes.
ACCORD (2010)	1	4.733 –2.362 "intensive" ·2371 control	<120 sys (intensive) vs. <140 sys (control)	119 sys (intensive) & 134 sys (control)	No reduction in fatal and non-fatal cardiovascular events.
ADVANCE (2007)	4.3	11,140 ·5.569 "intervention" –5571 placebo	none	135/74 (intervention) & 140/76 (control)	Reduced risk of major vascular events, including death.
SANDS (2008)	3	499	<115 sys (aggressive) vs.	117 sys (aggressive) &	No difference in clinical cardiovascular events.
HOT (1998)	3.8	18,790 6,262 80 mmHg 6,264 85 mmHg 6,264 90 mmHg	80 mmHg 85 mmHg 90 mmHg	81 mmHg & 83 mmHg & 85 mmHg	No advantage in CV events at lower BP (1o endpoint-Post hoc analysis of diabetes subgroup reduced events in lowest BP group
Normotensive ABCD (2002)	5.3	480 –237 "intensive" ·243 placebo	10 mmHg below baseline dia (intensive) vs. 80-89 dia (moderate)	128/75 (intensive) & 137/81 (moderate)	No significant improvement in composite cardiovascular events

nificant reduction in major CV disease events and a 13% reduction in all-cause mortality[9]. This effect persisted at systolic BP levels below 130 mmHg.

In addition to these meta-analyses a large study from Sweden further supports a lower level of blood pressure for those with diabetes[10]. The data come from nationwide clinical registries collected from 2006 to 2012. The study included 187,106 patients from 861 Swedish primary care clinics and hospital outpatient clinics, who had a mean follow-up of 5 years. The study compared the risk associated with systolic BP below 140mmHg with levels as low as 110mmHg. Individuals were followed from the index date till their first event, death or end of follow-up period. Study end points included nonfatal or total, acute myocardial infarction, stroke, coronary artery disease, heart failure events, as well as total mortality. Outcomes were evaluated within six deciles of BP ranges from 110-119mmHg, to ≥160mmHg. The analysis documented that the lowest systolic BP decile (110-119mmHg) had the lowest risk for CV events compared with the reference group (130-139mmHg).

One should not mix data from non-randomized trials with randomized trials and try to evolve meaningful conclusions. The totality of the data from randomized trials of patients with Type 2 diabetes and high CV risk with long term follow-up support the concept of having a systolic BP goal that approaches a range of 125-130 mmHg in those who can tolerate this level, as it is associated with lower CV events. The data are also overwhelming that for all people at high CV risk, at the very least, BP should be well below 140/90 mmHg.

Blood pressure level in low CV risk subjects with diabetes is unclear as there is no adequately powered trial to address this issue in Type 2 diabetes. The data from the registry suggests those at low risk who are able to stay in the normotensive range may have lower cardiovascular events.

Taken together, the upcoming guidelines from the American Diabetes Association will state that the evidence clearly supports achieving a blood pressure of <140/90 mmHg. The consensus report, upon which the guidelines are based, further supports a systolic blood pressure goal between 125-130 mmHg for those who can tolerate this level and understand why it is lower than the minimum. This blood pressure range was selected based on difference between clinical trial measured blood pressure like ACCORD and Systolic Blood Pressure Intervention Trial (SPRINT) and that done in most offices[11]. This later lower blood pressure recommendation comes from the results of all the meta-analyses as well as a focused meta-analysis comparing the outcomes from ACCORD and the recent SPRINT trial in nondiabetic subjects[12] at high CV risk.

Finally, the data on use of ACE inhibitors and angiotensin receptor blockers is clarified in the guidelines. There must be used in people with kidney disease and >300 mg/day of albumin. They should not be used in those with normotension with or without microalbuminuria regardless of diabetes status[13,14]. They certainly can be used to manage hypertension but have not been shown to have effects on outcomes independent of blood pressure lowering effects in any group except those with diabetic nephropathy.

REFERENCE

1. Standards of Medical Care in Diabetes-2016: Summary of Revisions. *Diabetes Care* 2016; 39 Suppl 1:S4-S5.
2. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31(7): 1281-357.
3. Bakris GL, Sowers JR. ASH position paper: treatment of hypertension in patients with diabetes-an update. *J Clin Hypertens (Greenwich)* 2008; 10(9): 707-13.
4. Adler AI, Stratton IM, Neil HA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ* 2000; 321(7258): 412-9.
5. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. HOT Study Group. *Lancet* 1998; 351(9118): 1755-62.
6. Margolis KL, O'Connor PJ, Morgan TM, et al. Outcomes of combined cardiovascular risk factor management strategies in type 2 diabetes: the ACCORD randomized trial. *Diabetes Care* 2014; 37(6): 1721-8.
7. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2015; 313(6): 603-15.
8. Xie X, Atkins E, Lv J, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. *Lancet* 2016; 387(10017): 435-43.
9. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 2016; 387(10022): 957-67.

10. Adamsson ES, Gudbjornsdottir S, Manhem K, et al. Blood pressure and complications in individuals with type 2 diabetes and no previous cardiovascular disease: national population based cohort study. *BMJ* 2016; 354: i4070.
11. Bakris GL. The Implications of Blood Pressure Measurement Methods on Treatment Targets for Blood Pressure. *Circulation* 2016 August 30.
12. Perkovic V, Rodgers A. Redefining Blood-Pressure Targets—SPRINT Starts the Marathon. *N Engl J Med* 2015; 373(22): 2175-8.
13. Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. *N Engl J Med* 2009; 361(1): 40-51.
14. Weil EJ, Fufaa G, Jones LI, et al. Effect of losartan on prevention and progression of early diabetic nephropathy in American Indians with type 2 diabetes. *Diabetes* 2013; 62(9): 3224-31.