Emerging Evidence of Intensive Risk Factor Control to Prevent CVD in Diabetic Patients

Written by Maria Vinall

Blood Pressure-Lowering Strategies

Approximately 70% of diabetics aged >40 years have concomitant hypertension (HTN). Diabetes and HTN share several physiological traits, and both independently predict cardiovascular (CV) morbidity and mortality. However, until recently, the systolic blood pressure (SBP) targets that are currently recommended by major guidelines diabetics (<130 mm Hg) had little supporting evidence from large-scale randomized trials.

Rhonda M. Cooper-DeHoff, PharmD, MS, University of Florida, Gainesville, Florida, USA, discussed the current Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) guidelines for the treatment of HTN in patients with diabetes (JNC7). Describing the current guidelines approach as "one size fits all," Dr. Cooper-DeHoff noted the challenges with finding high-quality randomized prospective data to support the recommendations. She referred to several trials that were conducted between the publication of JNC4 and JNC7 (Table 1), noting that while each showed an association between a reduction in BP and a decrease in CV mortality, questions remained regarding optimal BP targets, especially in diabetics [Cooper-DeHoff R et al. *Nat Rev Cardiol* 2011].

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study randomized diabetic subjects to either an intensive (SBP <120 mm Hg) or standard (SBP <140 mm Hg) BP control regimen. The mean SBP achieved was 119.3 mm Hg in the intensive control group and 133.5 mm Hg in the standard group. There was no difference between the regimens in the primary composite outcome of nonfatal myocardial infarction (MI), nonfatal stroke, or death from CV causes (1.87% per year in the intensive therapy group vs 2.09% per year in the standard therapy group; HR, 0.88; 95% CI, 0.73 to 1.06; p=0.20) [Cushman WC et al. *N Engl J Med* 2010]. Indeed, a more aggressive BP-lowering strategy may be detrimental, as ACCORD patients with SBP <120 mm Hg had an incidence of serious adverse events that was almost 3 times higher than those with SBP >130 mm Hg. However, CV events were substantially less frequent than predicted in ACCORD, resulting in an underpowered trial. Despite the negative finding for the primary hypothesis in ACCORD, the intensive BP control group had a significantly lower risk of stroke (HR, 0.59; 95% CI, 0.39 to 0.89; p=0.01) but not MI (HR, 0.87; 95% CI, 0.68 to 1.10; p=0.25). This reduction in stroke with intensive BP control requires prospective confirmation, since it represents only one of many secondary endpoints that were assessed without correction for multiplicity of testing in a trial with a null primary finding.

Table 1. Evidence of Benefits.

	Study (Publication Year)	Patients with Diabetes (n)	Age at Baseline (%)	CVD at Baseline (%)	Baseline Mean BP (mm Hg)	End of Study Achieved Mean BP (mm Hg)		Outcome and Change in RR
						Active	Placebo	
Placebo Controlled Trials	SHEP (1996)	583	71	5% (hx MI)	170/76	146/68 (24/8)	155/72	CVD Events ↓34% CHD Events ↓56%
	SYSTEUR (1999)	492	70	35%	175/85	153/78 (22/7)	162/82	Stroke ↓ 69% CV Events ↓ 62%
	ADVANCE (2007)	11,140	66	32%	145/81	136/73 (9/8)	140/73	Mortality ↓ 14% CV Mortality ↓ 18%
						More Intense	Less Intense	
Intense vs Less Intense Trials	HOT (1998)	1501	62	6%	170/105	144/81 (26/24)	148/85	CVD Events ↓ 51% CV Mortality ↓ 70%
	UKPDS (1998)	1148	56	NA	160/94	144/82 (16/12)	154/87	Stroke ↓ 44% Diabetes Death ↓ 32%
	ABCD (1998)	470	58	53%	155/98	132/78 (23/20)	138/86	CVD Events ↔ All Cause Death ↓ 49%

Relatively small n's; Varying age, degree of CVD, baseline BP and delta BP.

Curb J et al. JAMA 1996; Tuomilehto J et al. *N EngU Med* 1999; Patel A et al. *Lancet* 2007; Hansson L et al. *Lancet* 1998; UKPDS. BMJ 1998; EstacioR et al. *N EngU Med* 1998.

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The International Verapamil SR-Trandolapril Study (INVEST) [Cooper-DeHoff RM et al. *JAMA* 2010] recruited 6400 subjects with diabetes and coronary artery disease (CAD) and followed them for a median of 4 years. Subjects were grouped into three SBP categories: tight control (<130 mm Hg), usual control (130 to 140 mm Hg), or uncontrolled (≥140 mm Hg). The usual and tight control groups showed little difference in the primary outcome of all-cause mortality, nonfatal MI, or nonfatal stroke (12.6% in the usual control group vs 12.7% in the tight control group; adjusted HR, 1.11; 95% CI, 0.93 to 1.32; p=0.24). However, extended follow-up revealed a significantly increased risk for all-cause mortality in the tight control versus the usual control group (22.8% in the tight control vs 21.8% in the usual control group; adjusted HR, 1.15; 95% CI, 1.01 to 1.32; p=0.04).

"How low should we really go in the diabetic patient?" asked Dr. Cooper-DeHoff. "Based on the current evidence [Furie KL et al. *Stroke* 2011], we should be looking at SBP <140 mm Hg for all diabetics, 120 to 130 mm Hg for those at high risk for stroke (eg, those with prior stroke

or transient ischemic attack), and <130 mm Hg, with caution, in those with CAD."

Although the ACCORD investigators concluded that there was no evidence supporting an intensive strategy, Roger S. Blumenthal, MD, Johns Hopkins Hospital, Baltimore, Maryland, USA, added that lifestyle changes that are focused on reducing SBP to 130 mm Hg was a reasonable goal in these patients.

Lipid-Lowering Strategies

Cholesterol management in patients with diabetes should primarily be focused on achieving an LDL-C level <100 mg/dL, with a lower goal of <70 mg/dL in patients with vascular disease. The non-HDL-C target should be no more than 30 mg/dL higher than the LDL-C goal. Nicotinic acid (niacin), has been shown to lower LDL-C, raise HDL-C, and improve triglyceride levels [Goldberg A et al. *Am J Cardiol* 2000]. Older clinical trials suggest CVD risk reduction with niacin therapy, although no trials of this drug that have specifically evaluated patients with diabetes have been performed. Furthermore, at higher doses, nicotinic acid can worsen hyperglycemia.

Fibrates are useful for lowering elevated triglyceride or non-HDL-C levels; however, clinical trials of these drugs have reported mixed results. The ACCORD lipid trial assessed whether adding fenofibrate to statin therapy reduced the rate of CV events compared with a statin alone in patients with diabetes. Although both triglycerides and total cholesterol levels decreased early in therapy in the fenofibrate/statin group, there was no difference between the combination treatment and statins alone in the primary endpoint of major fatal or nonfatal CV events (HR, 0.92; 95% CI, 0.79 to 1.08) [ACCORD Study Group. *N Engl J Med* 2010].

In summary, Dr. Blumenthal suggested that along with diet and exercise, statins are the mainstay of cholesterol control in diabetics and that more data are needed on fenofibrate and niacin (Figure 1).

Glycemic Control Strategies

In January 2010, the American Diabetes Association decided to add A1C ≥6.5% as a diagnostic criterion for diabetes. However, researchers from the Rancho Bernardo Study [Kramer CK et al. *Diabetes Care* 2010] found that A1C had limited sensitivity and specificity (44% and 79%, respectively; area under ROC 0.65) to diagnose diabetes and that the use of A1C criteria alone may result in a delayed diagnosis. Abhinav Goyal, MD, MHS, Emory University, Atlanta, Georgia, USA, noted that despite the controversy, A1C can underestimate average glucose in conditions of high red cell turnover: "…it is prudent to perform A1C testing in conjunction with another test (either fasting glucose or an oral glucose tolerance test) for diabetes screening."

Dr. Goyal next reviewed several randomized clinical trials that compared intensive glycemic control with less-intensive control and subsequent CVD in patients with diabetes (Figure 2). He suggested that these trials, particularly ACCORD, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE), and the Veterans Affairs Diabetes Trial (VADT), support a strategy of global CV risk reduction rather than glycemic control alone.

Figure 1. ABCDE Approach Summary.

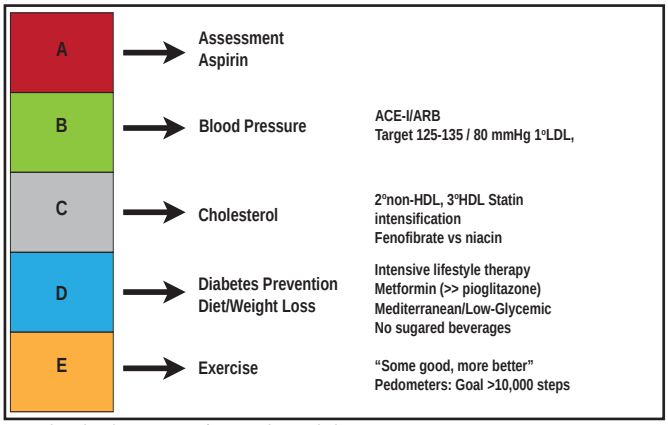

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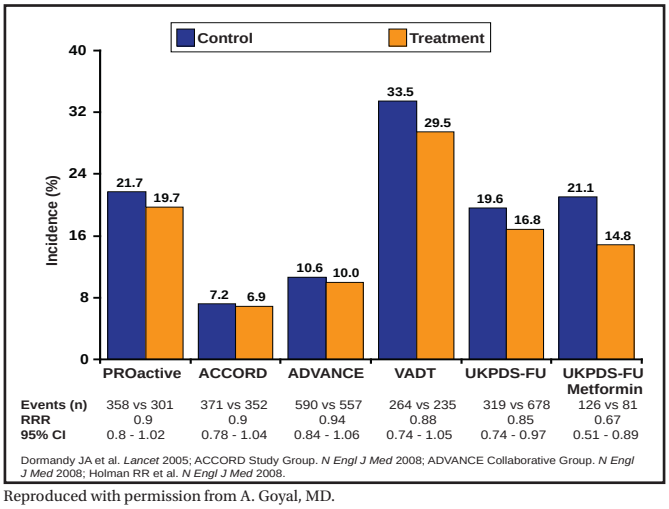
Figure 2. CV Effects of Glucose Control in Recent Large-Scale Trials.



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