Blood pressure: "The lower, the better"?

In this section, a panel of multidisciplinary team members give their opinions on a recently published paper. In this issue, we focus on the effect of systolic and diastolic blood pressure control on all-cause mortality in newly diagnosed T2D.

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Tight BP control does not influence all-cause mortality in T2D

1 Clinical guidelines recommend, in high-risk individuals (e.g. those with diabetes, coronary heart disease), lowering blood pressure (BP) to below 130/80 mmHg for further cardiovascular (CV) benefit.

2 The study authors examined the relationship between BP control and all-cause mortality in adults with newly diagnosed T2D with and without CV disease (CVD; myocardial infarction or stroke) in the first year of treatment.

3 A total of 126 092 adults with T2D (diagnosed between 1990 and 2005) were recruited; 9.8% of the cohort (n=12 379) had known CVD prior to T2D diagnosis. Individuals were followed up for a median of 3.5 years (until death or the end of the study).

4 During the study, BP was measured at least once and people were categorised into three groups: "tight control" (130/80 mmHg); "usual control" (130–9/80 to <85 mmHg); and "uncontrolled" (≥140 mmHg/≥85 mmHg).

5 Cox proportional regression models were used to estimate hazard ratios (HRs), and were adjusted for baseline characteristics.

6 During follow-up, 25 495 deaths were recorded (20.2%; an event rate of 42.3 deaths per 1000-patient years). In people with and without CVD, overall mortality was 28.6% (n=3535) and 19.3% (n=21 960), respectively.

7 In individuals with CVD, tight control of BP did not improve survival, compared with "usual" and "uncontrolled" groups (P<0.001 for all comparisons).

8 In people with CVD, the HR for systolic BP <110 mmHg was 2.79 (95% confidence interval [CI], 1.74–4.48; P<0.001), for diastolic BP 70–74 mmHg was 1.32 (95% CI, 1.02–1.78; P=0.04) and for diastolic BP <70 mmHg was 1.89 (95% CI, 1.40–2.56; P<0.001).

9 In people without CVD, similar associations were found. Findings were confirmed in subgroup analyses in people who were receiving hypertension medication or had hypertension at baseline.

10 The authors concluded that BP <130/80 mmHg did not reduce the risk of all-cause mortality in people with newly diagnosed T2D, with and without CVD. Low BP (particularly <110/75 mmHg) was associated with an increased risk for poor outcomes.

Association of systolic and diastolic blood pressure on all cause mortality in people with newly diagnosed type 2 diabetes: restrospective cohort study

Vamos EP, Harris M, Millett C et al (2012) *BMJ* **345**: e5567

Vinod Patel, Associate Professor, Warwick Medical School, University of Warwick and Honorary Consultant in Diabetes and Endocrinology, George Eliot Hospital NHS Trust, Nuneaton

This is a report on a retrospective cohort study from the UK General Practice Research Database. The population studied were 126 092 adult participants with newly diagnosed T2D – the median follow-up was 3.5 years. Vamos et al found that low blood pressure (BP) of 110/75 mmHg was associated with a 179% increase in the risk of all-cause mortality compared with a systolic BP of 130–139 mmHg – this is the main finding of this research.

My reading of the paper led me to conclude that the all-cause mortality, in participants with and without cardiovascular disease (CVD), is similar in all 10 mmHg bands of systolic BP above 110 mmHg, including up to a band of ≥160 mmHg. This I find difficult to believe, and is not explored in the discussion. A high level of academic argument is developed for the main finding; this appears sound based on, for me, incomprehensible – but I suspect sound – statistical analysis. My assertion, that this paper also concludes that systolic BP between 130 mmHg and 160 mmHg is CVD-event neutral may be the more interesting finding and requires further verification or discounting.

This paper will resound through the annals of cardiovascular (CV) epidemiology and will raise far more questions than it answers. Care will need to be exercised in designing CVD trials, and hypotheses examined in research will need to be carefully worded; they can no longer be along the lines of, "Is a lower BP better?", but instead, "Is lowering BP towards x/y with agent z beneficial or not?"

How will this study influence clinical practice and service delivery? We have learnt from the ACCORD (Action to Control Cardiovascular Risk in Diabetes) and the VADT (Veterans Affairs Diabetes Trial) that the idea of "the lower the HbA_{1c}, the better" has to be abandoned in light of clear evidence that aggressive improvement in glycaemic control in certain groups of people is hazardous in its contribution to increased mortality (The Action to Control Cardiovascular Risk in Diabetes Study Group, 2008; Duckworth et al, 2009). The study by Vamos et al may help develop the same hypothesis for BP lowering in people with T2D.

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What we do know is the intensively controlled cohort in the UKPDS (UK Prospective Diabetes Study) did rather better than the control group in terms of CVD. A BP of 144/82 mmHg versus 154/87 mmHg led to fewer CVD events (myocardial infarction [MI] incidence fell by 34%, heart failure by 35%, and strokes by 37%). Microvascular complications were also reduced by intensive BP control (UK Prospective Diabetes Study Group, 1998). In the Steno-2 study (conducted over 7.8 years in people with T2D and microalbuminuria) a BP of 131/73 mmHg versus 148/78 mmHg was associated with a 70% reduction in MIs, an 85% reduction in strokes, and a 50% reduction in amputation (Gaede et al, 2008). The ACCORD trial showed no evidence of benefit in reducing systolic BP to <120 mmHg versus standard therapy (121–139 mmHg; The Action to Control Cardiovascular Risk in Diabetes Study Group, 2008).

In practice, we can abandon the idea, for now, of "the lower the better" when it comes to BP control; this will also result in fewer falls and other effects of BP-lowering medications such as lethargy. Can we aim for 130/85 mmHg? In reality this is the NICE BP target from the diabetes guidelines.

Duckworth W, Abraira C, Moritz T et al (2009) Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* **360**: 129–39

Gaede P, Lund-Andersen H, Parving HH et al (2008) Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med* **358**: 580–91

The Action to Control Cardiovascular Risk in Diabetes Study Group (2008) Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* **358**: 2545–59

UK Prospective Diabetes Study Group (1998) Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* **317**: 703–13

"In essence, these data suggest that, in much the same way that we currently adopt an individualised approach to glucose control, a similar individualised treatment-target approach for blood pressure control may also be required in people with T2D."

Marc Evans, Consultant Physician, Llandough Hospital, Cardiff

Current guidelines recommend lowering blood pressure (BP) to a treatment goal of below 130/80 mmHg in high-risk individuals. With a view to provide further cardiovascular (CV) benefit, antihypertensive therapy is indicated in these people, even if their BP is in the normal range. Such BP targets are derived from RCTs in which intensive BP control resulted in CV outcome benefit, such as the UKPDS (UK Prospective Diabetes Study) and the HOT (Hypertension Optimal Treatment) trial (UK Prospective Diabetes Study Group, 1998; Zanchetti et al, 2003), and epidemiological evidence suggesting that above a BP level of 115/75 mmHg, CV risk may begin to increase (Lewington et al, 2002).

However, data from the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study failed to demonstrate further reduction in CV disease (CVD) risk with a BP below 130/80 mmHg (Cushman et al, 2010); as a result, aggressive treatment of BP in T2D is being questioned. Furthermore, there is a growing consensus, on the basis of clinical trial evidence, that lowering BP too intensively may actually do harm (Bakris et al, 2004).

There are currently limited data on the outcome effects of BP treatment in people with incident T2D. The results from the retrospective study by Vamos et al showed that in people with newly diagnosed T2D and CVD, systolic BP below 110 mmHg and diastolic BP below 75 mmHg were associated with a significantly increased risk of death. In people with T2D without established CVD, systolic BP below 120 mmHg and diastolic BP below 75 mmHg were associated with a significant increased risk of mortality.

The results of this study seem to support previous findings of a J-shaped association between BP reduction and outcome (Bangalore et al, 2010; Cooper-DeHoff et al, 2010). The results of this analysis specifically indicate that lower levels of BP maintained during the first year after diagnosis of T2D identify a subset of patients with a significantly increased risk of death.

While there appeared to be a potential detrimental effect of BP reduction, particularly below 115/75 mmHg, it is also noteworthy that BP below 130/80 mmHg was not associated with reduced risk of all-cause mortality in people with newly diagnosed diabetes, with or without known CVD. The results suggest that "the lower the better" approach might not apply to BP control beyond a critical level in high-risk individuals. The results of this analysis also support the concept that there is currently no robust evidence available for lowering the BP below 130/80 mmHg in people with diabetes.

Thus, as far as BP targets are concerned, in the management of people with T2D, these data indicate that it might be advisable to maintain BP between 130–139/80–85 mmHg (supported by other therapeutic and lifestyle interventions) in order to deliver optimal CV endpoints in people with T2D. In essence, these data suggest that, in much the same way that we currently adopt an individualised approach to glucose control, a similar individualised treatment-target approach for BP control may also be required in people with T2D.

Bangalore S, Messerli FH, Wun CC et al (2010) J-curve revisited: an analysis of blood pressure and cardiovascular events in the treating to new targets (TNT) trial. *Eur Heart J* **31**: 2897–908

Cooper-DeHoff RM, Gong Y, Handberg EM et al (2010) Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. *JAMA* **304**: 61–8

Cushman WC, Evans GW, Byington RP et al (2010) Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* **62**: 1575–85

Lewington S, Clarke R, Qizilbash N et al (2002) Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* **360**: 1903–13

UK Prospective Diabetes Study Group (1998) Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* **317**: 703–13

Zanchetti A, Hansson L, Clement D et al (2003) Benefits and risks of more intensive blood pressure lowering in hypertensive patients of the HOT study with different risk profiles: does a J-shaped curve exist in smokers? *J Hypertens* **21**: 797–804