Nutrition, Metabolism & Cardiovascular Diseases (2014) **24**, 577–584

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

VIEWPOINT

The ideal blood pressure target to prevent cardiovascular disease in type 2 diabetes: A neutral viewpoint

S. Frontoni [a,*], A. Solini [b], P. Fioretto [c], A. Natali [b], A. Zuccalà [d], F. Cosentino [e], G. Penno [f] on behalf of the Italian Society of Diabetology (SID) – Study Group on Diabetes, Hypertension and the Kidney

[a] *Department of Systems Medicine, University of Rome Tor Vergata – AFAR, Fatebenefratelli Hospital, Rome, Italy*
[b] *Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy*
[c] *Department of Medicine, University of Padova, Padova, Italy*
[d] *Nephrology Dialysis Unit, Civil Hospital Imola, Imola, Italy*
[e] *Cardiology, Department of Clinical and Molecular Medicine, University of Rome Sapienza, Rome, Italy*
[f] *Department of Clinical and Experimental Medicine, Section of Diabetes and Metabolic Disease, University of Pisa, Pisa, Italy*

Received 29 August 2013; received in revised form 27 December 2013; accepted 6 January 2014
Available online 22 January 2014

KEYWORDS
Anti-hypertensive treatment;
Blood pressure target;
J-shaped curve;
Type 2 diabetes;
Elderly

Abstract Type 2 diabetes mellitus (T2DM) and essential hypertension are often associated, and retrospective data analyses suggest an association between lower blood pressure (BP) values and lower cardiovascular (CV) risk in patients with T2DM. However, the most recent intervention trials fail to demonstrate a further CV risk reduction, for BP levels <130/80 mm Hg, when compared to levels <140/90 mm Hg. Moreover, a J-shaped, rather than a linear, relationship of BP reduction with incident CV events has been strongly suggested. We here debate the main available evidences for and against the concept of 'the lower the better', in the light of the main intervention trials and meta-analyses, with a particular emphasis on the targets to be pursued in elderly patients. Finally, the most recent guidelines of the scientific societies are critically discussed.

Type 2 diabetes mellitus (T2DM) and essential hypertension, two major risk factors for cardiovascular (CV) morbidity and mortality, often co-exist. European surveys report the presence of hypertension in over two-thirds of T2DM patients [1] with the diagnosis of the former often overlapping the development of hyperglycaemia [2]. Prospective longitudinal studies, such as the Framingham Heart Study and the Multiple Risk Factor Intervention Trial (MRFIT) [3,4], documented that T2DM patients have a greater risk of CV disease for a given blood pressure (BP) level, being a relevant percent of the excess CV risk in T2DM patients attributable to the presence of hypertension itself, even after controlling for other CV risk factors [5]. While diabetes magnifies CV risk, the relationship between BP and overall CV risk had a similar pattern in diabetic and non-diabetic subjects over the whole range of baseline and on-treatment BP values.

Retrospective data analyses suggest an association between lower BP values and lower CV risk in patients with T2DM. Such observation, however, is hampered by the consideration that most of the intervention trials failed to achieve mean systolic BP values <130 mm Hg. Moreover, appropriately powered prospective outcome trials show a lack of further CV risk reduction for BP levels <130/80 mm Hg when compared to levels <140/90 mm Hg. On the other hand, accumulating evidences strongly support the

* Corresponding author. Endocrinology, Diabetes and Metabolism, Fatebenefratelli "Isola Tiberina" Hospital, Department of Systems Medicine, University of Rome "Tor Vergata", Via Montpellier 1, 00133 Rome, Italy. Tel.: +39 06 6837884; fax: +39 06 6837406.
E-mail address: frontoni@uniroma2.it (S. Frontoni).

0939-4753/$ - see front matter © 2014 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.numecd.2014.01.004

possibility of a J-shaped, rather than linear, relationship of BP reduction with incident CV events, that is, a new increase of the rate of CV events when a more pronounced reduction of BP is induced [6]. The present viewpoint summarises the most significant points of a consensus statement on BP targets in diabetes, recently endorsed by the Italian Society of Diabetology (SID), Italian Society of Nephrology (SIN) and Italian Society of Arterial Hypertension (SIIA), trying to discuss the main available evidences for and against the concept of 'the lower the better', in the light of a neutral evaluation of the main intervention trials and meta-analyses, also summarising the suggestions of the major guidelines with regard to BP targets to be pursued in T2DM patients to reduce their CV risk.

Pros: the concept of 'the lower the better'

It is a matter of fact that a careful BP control is beneficial in improving the CV prognosis in hypertensive T2DM patients, and this has been proven in several large studies. In the HOT (Hypertension Optimal Treatment) study [7], a reduction of diastolic BP $\leq$ 80 mm Hg reduces major CV events by 51% and 24% with respect to less stringent targets ($\leq$90 mm Hg and $\leq$85 mm Hg, respectively). To our knowledge, the HOT study is the only one that compares the effects of different achieved BP values in three randomised groups suggesting no evidence of a J-shaped relationship between diastolic BP and incidence of major CV events in the diabetic subgroup (as well as in the entire low-CV-risk population). These results are consistent with those of the United Kingdom Prospective Diabetes Study (UKPDS) [8], where a tight BP control is associated with a 32% reduction in deaths and 44% reduction in stroke. However, in the UKPDS trial, the BP values achieved in the 'aggressively' treated group (144/82 mm Hg) were well above the levels that are more likely to be associated to an increased CV risk by an impairment of organ perfusion, so portraying a J-shaped curve. This observation might be extended to almost all intervention trials that included subgroups of T2DM subjects. Nevertheless, the positive relationship between BP and the incidence of major CV events described in observational studies has strengthened the conviction of the need for an aggressive reduction of BP in T2DM patients over the years. An epidemiological analysis of the UKPDS has shown a 12% reduction in the risk of any complication related to diabetes, 15% for deaths related to diabetes and 11% for myocardial infarction for every 10-mm Hg decrease of systolic BP, in the absence of a threshold effect [9]. The ADVANCE (Action in Diabetes and Vascular disease, PreterAx and DiamicroN MR Controlled Evaluation) study [10], performed in >11,000 T2DM patients, has shown that the addition of a fixed combination of perindopril and indapamide to standard anti-hypertensive therapy decreases the risk of macro- or microvascular events by 8% and 9%, respectively and the risk of CV death by 18%. However, it should be stressed that in such trial, a difference of 5.6 mm Hg for systolic and of 2.2 mm Hg for diastolic BP between perindopril–indapamide and placebo arm was observed during the follow-up.

The ABCD (Appropriate Blood Pressure Control in Diabetes) study, where lower systolic BP goals were achieved, documented a lack of effect of the intensive BP control on the primary end point, but an improvement in secondary outcomes. In particular, a systolic BP of 132 mm Hg reduced the total mortality in the hypertensive ABCD study [11], and a systolic BP of 128 mm Hg reduced the incidence of stroke in the normotensive ABCD study [12]. Furthermore, the normotensive ABCD study also demonstrated an association between intensive BP control and a significant slowing of incipient and overt nephropathy progression. The Syst-Eur (Systolic Hypertension in Europe) study, showing a greater reduction in all CV events, overall mortality and mortality from CV disease for the same differences in BP in T2DM as compared to non-diabetics, has strengthened the importance of a tight BP in these individuals [13].

The relatively small SANDS (Stop Atherosclerosis in Native Diabetics Study) study, comparing the efficacy, tolerability and safety of achieving tighter BP and LDL cholesterol targets with respect to standard targets, reported a greater reduction in carotid intima-media thickness and a decrease in the left ventricular mass in the aggressively treated group, even though no difference emerged in the rate of CV events [14].

It should be emphasised that the recommendation of a more stringent BP goal in T2DM proteinuric patients seems to be supported by the strong benefits in terms of CV and renal prognosis [15]; however, the complex issue of treating hypertension in a patient with chronic kidney disease (CKD) is beyond the scope of this viewpoint.

According to the results of the above-reported trials, in 2003, the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7 report) [16], recommended a BP < 130/80 mm Hg in patients with T2DM and hypertension and a BP < 125/75 mm Hg in those with proteinuria. The American Diabetes Association (ADA), in the 'Standards of Medical Care in Diabetes' published yearly up to 2012 [17] and other scientific associations [18,19], acknowledged this recommendation.

Contra: the concept of 'the lower the better'

In the past 5 years [20], a critical reappraisal of the stringent target BP values to be achieved in hypertensive T2DM, clearly stated by the international scientific societies, has been made mainly in the light of the fact that a target systolic BP < 130 mm Hg was truly reached only in the normotensive ABCD study [12] in association with an uncertain reduction in CV events. Evidence supporting the clinical indication for an anti-hypertensive treatment in T2DM patients with high-normal BP values is even scantier [21]. Recent evidence from large intervention trials show that, in T2DM, the lowest BP values are associated with an increased rate of CV events and mortality, and this is particularly true in the elderly [22–25].