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Review article

The diastolic blood pressure J-curve revisited: An update

Edward J. Filippone [a,*], Andrew J. Foy [b], Gerald V. Naccarelli [b]

[a] Division of Nephrology, Department of Medicine, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA, USA
[b] Department of Medicine, Penn State University Heart and Vascular Institute, Penn State M.S Hershey Medical Center and College of Medicine, Hershey, PA, USA

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ABSTRACT

Hypertension remains a leading cause of morbidity and mortality. Recent treatment guidelines stress more strict systolic blood pressure (SBP) targets without regard for abnormally low achieved diastolic blood pressures (DBP). However, as DBP falls below a critical level, adverse events increase, the so-called J-shaped curve. Proponents argue that the low DBP is causative due to reduced coronary perfusion during diastole with obstructive coronary artery disease (CAD), whereas others postulate the J-curve represents reverse causality from underlying comorbidity. Most data are observational, derived from population-based cohorts or post-hoc analyses of randomized controlled trials (RCT) conducted for other reasons. The purpose of this review is to analyze the observational studies performed over the last decade addressing the J-curve, with consideration of earlier data. Overall, a J-curve exists, but it remains uncertain whether low DBP is causative or instead reflects reverse causation from either diseased vasculature (widened pulse pressure) or severe underlying comorbidity. The most convincing data for causation come from studies restricted to patients with documented CAD, with evidence suggesting revascularization may mitigate risk. RCTs are needed to determine if a low DBP should preclude intensification of therapy, especially with documented CAD. Firm recommendations cannot be made with contemporary data.

1. Introduction

Systemic hypertension, specifically elevated systolic blood pressure (SBP), is the leading cause of death and disability-adjusted life-years according to the Global Burden of Disease Collaborators [1]. SBP increases steadily throughout adult life, whereas diastolic blood pressure (DBP) plateaus in the 6th decade of life and then subsequently declines [2]. SBP more correctly identifies a patient's hypertension status than DBP when each is considered alone (over 90% of cases correctly identified by SBP alone as opposed to less than 50% by DBP) [3].

The most recent guidelines for the treatment of hypertension recommend a goal BP of <130/80 mm/Hg for all patients [4,5]. SBP is notoriously harder to control to these targets than DBP. There is no specific recommendation in the Guidelines regarding altering SBP targets with low baseline DBP, although the European Guidelines target an optimal DBP of 70–79 mm/Hg. Furthermore, recent BP lowering trials attempting to determine the appropriate BP goal for various groups of patients target only SBP, with no concern for DBP [6–8].

Against this backdrop of a focus on SBP control, concern has been raised over a higher cardiovascular event (CVE) rate, especially myocardial infarction (MI), with excessive lowering of DBP below a certain threshold, the J-shaped curve phenomenon, first publicized over 40 years ago (see Fig. 1 showing more contemporary data). Hence the practicing clinician, when treating an individual patient, is faced with the dilemma of ignoring a potentially dangerously low DBP while attempting to attain target SBP. The purpose of this review is to summarize the available data regarding the J-curve phenomenon and to provide guidance based on the best available evidence.

2. J-shaped curve: the history

Anderson re-examined Framingham data in 1978 and noted no benefit with lower diastolic pressures (<90 mm/Hg) with the suggestion of increased events as DBP dropped further [9]. Using the IVth Korotkoff sound as the measure of DBP, Stewart followed 169 patients over a mean period of 6.25 years and in 1979 reported a relative risk of over 5 times

Abbreviations: BP, blood pressure; CHD, coronary heart disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CVE, cardiovascular events; DBP, diastolic blood pressure; HR, hazard ratio; ISH, isolated systolic hypertension; MI, myocardial infarction; PP, pulse pressure; RCT, randomized controlled trial; SBP, systolic blood pressure.

* Corresponding author at: 2228 South Broad St., Philadelphia, PA 19145, USA.
E-mail address: edward.filippone@jefferson.edu (E.J. Filippone).

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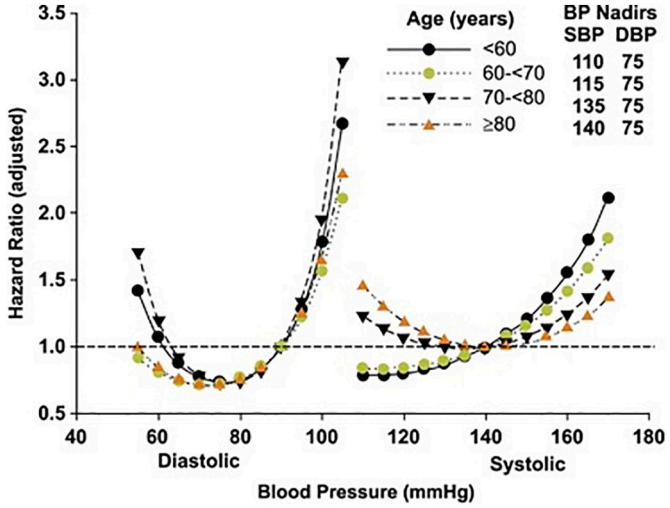

Fig. 1. The J-curve for diastolic blood pressure. From DeNardo et al. *AmJMed*, 2010;123: 719–726 with permission from Elsevier.

for developing an MI in those with final DBP < 90 mm/Hg compared to those with 100–109 mm/Hg ($p < 0.01$) [10]. Nearly a decade later, Cruickshank et al. found a J-shaped relationship between DBP (Vth Korotkoff sound) and death from MI with a nadir of 85–90 mm/Hg after following 902 patients for a mean of 6 years [11]. Importantly, this J-shaped relationship was only found in the 342 patients with evidence if ischemic heart disease ($p < 0.05$); no such relationship existed in those without ischemic heart disease.

In 1991, Farnett et al. reported results of a systematic review of studies published between 1966 and 1989 that included hypertensive subjects; treated for at least 1 year; with outcomes including MI, stroke, total mortality, and CV mortality from either MI or stroke; and, stratified by at least 3 BPs, including one DBP < 90 mm/Hg [12]. They identified 13 studies with over 48,000 subjects (including the studies of Stewart and Cruickshank noted above) with about half being cohort studies and half randomized controlled trials (RCT). Overall, there was consistent J-shaped relationship between DBP and cardiac events, but not for stroke. The threshold was approximately 85 mm/Hg. In 2009, Messerli and Panjrath updated the list to 27 observational analyses, including 23 showing a positive relationship between low DBP and adverse events and 4 reporting no clear association [13].

Only 3 RCTs published in the 1990s targeted different levels of DBP as their primary variable. In the Hypertension Optimal treatment (HOT) trial, 18,790 patients were randomized to three target DBPs: ≤ 90 versus ≤85 versus ≤80 mm/Hg, although achieved DBPs differed by only 2 mm/Hg between each group [14]. No significant differences were found between any of the groups with respect to CVEs or mortality. The nadir for CVEs was 82.6 mm/Hg and for mortality was 86.5 mm/Hg, with no evidence of a J-curve below these levels. However, when the 3080 patients with ischemic heart disease were considered separately, a J-curve for all MIs and silent MIs was found [15]. The Appropriate Blood Pressure Control in Diabetes (ABCD) trials randomized 950 diabetic patients with either normotension (470 patients) [16] or hypertension (480 patients) [17] to intensive versus moderate DBP control. Achieving a difference of 8–9 mm/Hg over 5 years produced no significant renal benefit (the primary endpoint), although the lower target produced less strokes in the hypertensive group and reduced death in the normotensive group. There was no evidence of a J-curve. No subsequent RCTs specifically targeted different levels of DBP.

Over the past decade, numerous observational studies have been published investigating the relationship between DBP and CVEs and/or mortality. Some studies involved analyses of observational cohort studies while others consisted of post hoc analyses of RCTs performed for other reasons. We will evaluate these newer data in detail and in the context of key prior older studies. The reader is referred to our prior narrative review [18] as well as the reviews of Farnett [12] and Messerli and Panjrath [13] for discussions of the earlier trials.

3. Observational studies of the general population (Table 1)

Using the CArdiovascular research using LInked Bespoke studies and Electronic health Records (CALIBER) programme, Rapsomaniki et al. followed a cohort of 1.25 million patients free of CV disease, a fifth of whom received anti-hypertensive therapy, for a median of 5.2 years and assessed the relationship between SBP and DBP at baseline with 12 acute and chronic CV diseases [19]. The lowest risk for CV disease occurred at SBP of 90–114 mm/Hg and DBP of 60–74 mm/Hg, with no evidence of a J-shaped curve for any specific event or for all events together. These results mirror those of the previously published Prospective Studies Collaboration meta-analysis of 61 observational studies totaling 1 million persons that found a log-linear relationship between both SBP and DBP and death from stroke, ischemic heart disease, and other vascular diseases starting with SBP of 115 mm/Hg and DBP of 75 mm/Hg without evidence of a J-curve [20].

In contrast, Sim et al. performed a retrospective cohort study of 398,419 hypertensive adults within the Kaiser Permanente Southern California health system and found a multivariable-adjusted significant J-shaped relationship between both SBP and DBP and the outcomes of mortality and end-stage kidney disease (ESKD) compared with the reference range of 130–139/60–79 mm/Hg [21]. A DBP <50 was associated with a 3-fold risk of both mortality/ESKD and mortality alone, and a 2.5-fold risk of ESKD alone. The nadir BP was 137/71 overall, 131/69 for those with diabetes, and 140/70 for those ≥70 years old.

Franklin et al. followed 791 individuals from the Framingham Offspring Study that survived a CV event and had isolated systolic hypertension (ISH, DBP < 90 mm/Hg) for a mean of 8.6 years [22]. Patients were divided into those with baseline DBP < 70 mm/Hg ($n = 225$) versus 70–89 mm/Hg ($n = 566$). The risk of recurrent CV events (CHD, heart failure, stroke) was significantly increased by multivariable analysis in those with DBP < 70 mm/Hg, with hazard ratios of 5.1 (95% CI 3.8–6.9, $p < 0.0001$) and 11.7 (95% CI 6.5–21.2, $p < 0.0001$) in patients treated or not treated for their ISH (treatment interaction $p = 0.71$). Individually, all 3 components were significantly associated with DBP < 70 mm/Hg, and when evaluated in groups above or below the median pulse pressure (PP, 68 mm/Hg), only the group with both low DBP and high PP had a significantly higher risk of recurrent events. These findings support wide pulse pressure in combination with low DBP as important risk factors, largely independent of antihypertensive treatment status. Hence, reverse causality may mediate the deleterious effect of low DBP (vide infra), as there was no interaction with treatment and the significance was restricted to those with higher PP.

McEvoy et al. studied 11,565 adults from the Atherosclerosis Risk in Communities (ARIC) cohort free of heart failure or known CV disease and analyzed DBP and high sensitivity cardiac-T (hs-cTnT) and their relationship to outcomes [23]. Compared to those with baseline DBP of 80–89 mm/Hg, those with baseline DBP < 60 and 60–69 mm/Hg had adjusted odds ratios of 2.2 and 1.5 for having a baseline elevated hs-cTnT (≥14 ng/l), and they also had a greater annual change of hs-cTnT over 6 years. A baseline DBP < 60 mm/Hg was associated with incident CHD (especially in those with elevated baseline hs-cTnT) and mortality, but not stroke over time. Evaluating DBP as a time-varying exposure produced similar results for DBP < 60 mm/Hg.

Rahman et al. evaluated 6811 participants without known cardiovascular disease from the Multi-Ethnic Study of Atherosclerosis (MESA) that were followed for a median of 12 years [24]. DBP < 60 mm/Hg at baseline was associated with a significantly increased risk of subsequent CHD events (HR 1.69, 95% CI 1.02–2.79) and all-cause mortality (HR 1.48, 95% CI 1.10–2.00) but not with stroke. Despite the lack of a significant interaction with coronary artery calcification (CAC), these

Table 1
Studies in the general population.

Study/year	Number	Population	Exposure[a]	Primary endpoint	Key secondary endpoints	Significance of J-curve	Nadir BP[a]	Comments
CALIBER 2014	1.25 million	General population aged ≥30 years, from 225 general practices	20/10 mm/Hg changes in SBP/DBP	Any one of 12 CVEs	NA	Negative	NA	Heterogeneous associations existed between SBP, DBP, and PP with various outcomes
KPSC 2014	398,419	Treated hypertensives	SBP and DBP	ESKD/ mortality	ESKD, mortality	Significant for both SBP versus 130–139 and DBP versus 60–79.	SBP 137, DBP 71	Diabetes similar (nadir 131/69) and age ≥ 70 (nadir 140/70)
Framingham Offspring Study 2015	791	Prior CVE	DBP < 70 versus 70–89	Recurrent CVE	CHD, CHF stroke	Significant for both primary and secondary events	NA	Independent of antihypertensive treatment and only in group with both low DBP and high PP
ARIC 2016	11,565	General population	DBP < 70 versus 80–89	Baseline hs-cTnT	CHD, stroke, mortality (combined and independently) and change in hs-cTnT over time	DBP < 70 significantly associated with all primary and secondary endpoints except stroke	NA	Associations with CHD and hs-cTnT highest if basline SBP ≥ 120 (higher PP)
MESA 2017	6811	General population	DBP < 60 versus 80–89	CHD, stroke, mortality	Interaction with CAC > 0	Significant for CHD and mortality, not stroke	NA	No significant statistical interaction with baseline CAC, but significance restricted to those woth CAC > O
Glasgow BP Clinic 2019	10,355	Referred hypertensive patients	Mean DBP over 5 years	CV admissions or mortality	MI, CHD, CHF, stroke	Positive for CVE and mortality	92 for composite CVE and 86 for all-cause mortality	Associated with increased non-cardiovascular mortality; U-shaped association for stroke.
KPNC 2019	1.3 million	General population	Mean SBP/ DBP	MI, stroke (ischemic or hemoorhagic)	NA	Positive only in unadjusted analyses	NA	HR for lowest quartile was 1.44 (p < 0.0001) but decreased to 0.9 (p < 0.001) with adjustment

ARIC: Atherosclerosis Risk in Community study; BP: blood pressure; CALIBER: CArdiovascular research using LInked Bespoke studies and Electronic health Records program; CHD: coronary heart disease; CHF: congestive heart failure; CV: cardiovascular; CVE: cardiovascular event; DBP: diastolic blood pressure; ESKD: end-stage kidney disease; KPNC: Kaiser Permanente Northern California; KPSC: Kaiser Permanente Southern California; MESA: Multi-Ethic Study of Atherosclerosis; MI: myocardial infarction; NA: not available; PP: pulse pressure; SBP: systoloic blood pressure;
[a] All blood pressure numbers in mm/Hg.

associations were only significant for the group with CAC > 0 and not for the group with CAC = 0, suggesting that the J-curve exists even for those with subclinical CAD.

Lip et al. analyzed 10,355 hypertensive patients referred to the Glasgow Blood Pressure Clinic using 30-year follow-up data comparing BP during the first 5 years of treatment and a composite outcome of CV admissions (MI, CHD, stroke, heart failure, peripheral arterial disease) and mortality (all-cause, CV, and non-CV) [25]. A significant U-shaped relationship between DBP and the primary CV outcome (nadir 92 mm/Hg) and a reverse J-shaped relationship with all-cause mortality (nadir 86 mm/Hg) and non-CV mortality (nadir 92 mm/Hg) was found. Reverse J-shaped relationships between DBP and MI, CHD, and heart failure admissions were also evident as was a U-shaped relationship for stroke (restricted to those under 60 years old).

Flint et al. followed 1.3 million adults from the Kaiser Permanente Northern California (KPNC) health system and found that both SBP and DBP independently predicted the composite outcome (MI, ischemic stroke, or hemorrhagic stroke) over 8 years of follow-up [26]. A J-curve with DBP and the primary outcome was found in unadjusted analysis (HR 1.44 for lowest quartile of DBP, 95% CI 1.41–1.48) that disappeared with adjustment (HR 0.90, 95% CI 0.88–0.92, $p < 0.001$).

Overall, these analyses of population-based cohorts indicate some evidence of a DBP J-curve that may be confounded by pulse pressure (as in the Framingham Offspring cohort) or other covariates (as in KPNC). The risk appears greatest for CHD events. These data should not dissuade attempts to optimize SBP control for fear of lowering DBP in the general hypertensive patient without evident CV disease in our opinion, as supported by the large CALIBER, Prospective Studies Collaboration, and KPNC databases.

4. Post hoc analyses of RCTs (Table 2)

The ONgoing Telmesartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) randomized 25,620 ACE-tolerant patients with vascular disease or diabetes to ramipril, telmisartan, or the combination and followed them for a mean of 56 months with a primary endpoint of CV death, MI, stroke, or heart failure hospitalization [27]. The Telmesartan Randomized AssessmeNt Study in ACE iNtolerant Study (TRANSCEND) randomized 5810 patients with CV disease to telmisartan or placebo with a similar follow-up and primary endpoint [28]. Bohm et al. analyzed the combined ONTARGET and TRANSCEND populations (31,546 patients) for the relation between baseline and mean on-treatment BPs and adverse events [29]. A baseline DBP <70 mm/Hg as well as a mean on-treatment DBP < 70 mm/Hg were both significantly associated with significant increases in the primary endpoint, MI, hospitalized heart failure, and all-cause mortality, although not stroke or CV mortality compared to those with DBP >70 mm/Hg. When restricting the analysis to the 16,099 patients with controlled SBP (mean on-treatment 120 - <140 mm/Hg), the results were similar: a mean DBP < 70 mm/Hg was associated with the primary

Table 2
Post hoc analyses of randomized controlled trials.

Trial Year of publication	Number	Comparisons	Exposure[a]	Primary endpoint	Secondary endpoint(s)	J-curve significance	Nadir DBP	Comments
ONTARGET/ TRANCEND [29] 2017	30,937	Ramipril vs telmisartan vs combination; Telmisartan versus placebo	Baseline DBP < 70 Achieved DBP < 70	Composite (MI, stroke, HF hospitalization, CV death)	Components of the composite	Baseline associated with all outcomes; on treatment associated with composite, MI, HF hospitalization, death	About 75	Association with all-cause mortality but not CV mortality suggests reverse causation
ONTARGET/ TRANCEND [30] Controlled SBP 2018	16,099 (SBP 120- < 140)	Ramipril vs telmisartan vs combination; Telmisartan vs placebo	Achieved DBP <70	Composite (MI, stroke, CHF hospitalization, CV death)	Components of the composite	Positive for composite, MI, hospitalization for HF, all-cause death	NA	Similar for SBP 120–129 or 130–139
SAVOR-TIMI 53 [31] 2018	12,175	Saxagliptin vs placebo	Baseline DBP starta	Composite (MI, ischemic stroke, CV death)	Components of the composite	Positive for composite and components	70–80	Relationships remained with time varying models
SPRINT 2017	8301	SBP < 120 vs <140	Baseline DBP 61 (lowest) vs 78 (mean of entire cohort)	Composite (MI, ACS, stroke, HF, CV death)	All-cause death ESKD or ≥50% decline in eGFR	Significant only for Composite	NA	Effect of intensive therapy not hindered by low DBP
SPRINT 2018	9361	SBP < 120 vs <140	DBP < 60 at 1 year	Composite (MI, ACS, stroke, HF, CV death)	NA	Positive	NA	Indirect effect became non-significant in mediation analysis
SPRINT 2018	9347	SBP < 120 vs <140	Quintiles of achieved DBP	Composite (MI, ACS, stroke, CHF, CV death)	Components of composite, all-cause death, ESKD or ≥50% decline in eGFR	DBP < 60: Positive for Composite, CHF, MI	NA	Increased risk not present in those free of CVD or CKD
SPRINT 2018	9361	SBP < 120 vs <140	Achieved DBP < 55	Composite (MI, ACS, stroke, CHF, CV death)	Components of composite, all-cause death,	Positive	NA	J-shaped relationship present in those with and without baseline CVD when considered separately
SPRINT 2018	8046	SBP < 120 vs <140	Achieved DBP ≤ 55	Composite (MI, ACS, stroke, HF, CV death) and all—cause death	NA	Positive	NA	Analysis restricted to the 8046 with baseline DBP ≥ 65
ACCORD 2010	4733	SBP < 120 vs <140	Baseline DBP and glycemic control	Composite (non-fatal MI, non-fatal stroke, CV death)	All-cause mortality	Positive only for all-cause mortality in intensive glycemia arm with intensive BP reduction	NA	Suggests intensive BP reduction safe with low DBP but only if standard glucose control
SPRINT/ ACCORD 2017	13,946	SBP < 120 vs <140	On treatment SBP	Composite (angina, MI, stroke, CHF, CV death)	All-cause mortality	Positive	Target	J-curve near target, independent of attained BP
SPRINT/ ACCORD 2021	7515	SBP < 120 vs <140	Treated DBP	Composite (all-cause death, MI, stroke)	Composite (CV death, nonfatal MI, stroke)	Positive for primary and secondary	70–80	Analysis restricted to the 7515 with controlled SBP (<130)
SPRINT/ ACCORD 2021	14,094	SBP < 120 vs <140	Baseline DBP	All-cause mortality	Composite (CV death, nonfatal MI, stroke)	Positive	NA	Intensive therapy associated with nonsignificant increase in death at low DBP

[a] All numbers in mm/Hg. ACS: acute coronary syndrome; CHF: congestive heart failure; CKD: chronic kidney disease; ESKD: end-stage kidney disease; CV: cardiovascular; CVD: cardiovascular disease; DBP: diastolic blood pressure; MI: myocardial infarction; NA: not available; SBP: systolic blood pressure;

endpoint (HR 1.29, $p < 0.0001$), MI (HR 1.54, $p < 0.0001$), heart failure hospitalization (HR 1.47, p, 0.0001), and all-cause mortality (HR 1.19, $p < 0.0001$), although not CV mortality or stroke [30]. These effects persisted in sensitivity analyses excluding patients with CVEs prior to the outcome of interest, baseline low SBP (<120 mm/Hg, to reduce possible reverse causation), and excluding those not taking any anti-hypertensive medications.

In the Satagliptin Assessment of Vascular Outcomes Recorded in patients with diabetes mellitus – Thrombolysis in Myocardial Infarction 53 trial (SAVOR-TIMI 53), 12,175 patients from the biomarker subgroup had baseline BP correlated with subsequent CVEs (CV death, MI, ischemic stroke) [31]. Relative to DBP of 80 - <90 mm/Hg, the adjusted HR for DBP < 60 mm/Hg for the composite endpoint was 1.58 (95% CI 1.15–2.17) and for MI was 2.30 (95% CI 1.50–3.53).

The Systolic Blood Pressure Intervention Trial (SPRINT) randomized 9361 high cardiovascular risk patients free of diabetes mellitus and stroke to more intensive SBP control (<120 mm/Hg) versus standard control (<140 mm/ hg) and found a significant reduction in the primary endpoint (MI, acute coronary syndrome, CHF, or CV death). The methodology of SPRINT was different from all other trials in that BP was usually measured unattended by staff to remove the white coat effect. By leaving patients unattended, SBP would be expected to be 10–15 mm/Hg lower than if attended [32] which alters the interpretation of the actual target BP [33].

The SPRINT database has been analyzed multiple times to determine if a J-curve for DBP exists and if the benefit to more intensive therapy is affected by an interaction with the treatment arm. Beddhu et al. evaluated baseline DBP divided into quintiles and found a significant U-shaped association with the primary endpoint, all-cause death, and CKD regardless of randomized treatment [34]. Within each quintile of baseline DBP, more intense therapy significantly reduced the occurrence of the primary endpoint and all-cause death, but a higher incidence of chronic kidney disease (CKD) development. Others evaluated achieved DBP as opposed to baseline DBP [35–38].

Stensrud and Strohmaier performed a mediation analysis to determine if the benefit to intensive therapy would be mediated through a potentially harmful indirect effect of low DBP at the one-year visit (<60 mm/Hg) [35]. Whereas low DBP per se was associated with significantly increased risk for the subsequent development of primary endpoint after adjusting for treatment, the indirect effect of intensive therapy causing low DBP was not significant when fully adjusted, suggesting that unaccounted for confounders explain the association and not the low DBP per se. These data suggest reverse causation explains the J-curve phenomenon and not the achieved DBP.

Del Pinto et al. analyzed the database divided into groups based on the presence of baseline cardiovascular disease (CVD, $n = 1230$), CKD ($n = 2002$), both ($n = 644$), and neither ($n = 5471$) [36]. In the whole SPRINT population, a higher risk of the primary endpoint was found for mean on-treatment DBP < 60 mm/Hg versus the reference range 70–79 mm/Hg (HR 1.46, $p < 0.001$). When considering patients with neither CVD nor CKD, no such increased risk was found, and no J-curve was present. Patients given intensive therapy had a significantly reduced primary endpoint with mean DBP between 60 and 80 mm/Hg, but not above or below these levels. In patients with CKD, a significantly increased risk of the primary endpoint, heart failure, and kidney disease progression was noted with DBP < 70 mm/Hg. In those with CVD, a trend for increased MI with low DBP was noted.

In contrast, Khan et al. similarly divided the SPRINT population into those with ($n = 1519$) or without ($n = 7574$) baseline CVD and found a significant J-shaped relationship between mean on-treatment DBP and the primary outcome regardless of the presence of baseline CVD (p values for non-linearity <0.0001 and <0.002 for those without or with CVD, respectively) or treatment arm (p values for interaction with treatment arm 0.47 and 0.75 in those without or with CVD, respectively) [37].

Lee et al. restricted their analysis to the 8046 SPRINT patients with baseline DBP ≥ 65 mm/Hg and found a significantly increased risk with on-treatment DBP ≤ 55 mm/Hg for the primary endpoint (HR 1.67, 95% CI 1.24–2.26) [38]. Again, this increased risk was independent of treatment arm (HRs 1.53, 95% CI 1.04–2.26, and 2.23, 95% CI 1.40–3.54 for intensive and standard therapy, respectively, $p = 0.09$ for interaction).

The Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial (ACCORD-BP) compared more intensive blood pressure control (<120 mm/Hg versus <140 mm/Hg) and more intensive glucose control with a 2 × 2 factorial design in 4731 patients with type 2 diabetes mellitus and high CV risk. Overall, more intensive BP control did not significantly reduce the primary endpoint (nonfatal MI, nonfatal stroke, or cardiovascular death), but did significantly reduce stroke. Ilkun et al. assessed the effect modification of baseline DBP in ACCORD-BP on the primary outcome and the interaction with randomized glycemic control [39]. Intensive BP control significantly reduced the primary endpoint in the standard glycemic control arm but not in those with more intensive glycemic control. Low baseline DBP did not modify these effects in either glycemic control arm by spline regression analysis. However, intensive BP therapy was associated with increased all-cause mortality with lower baseline DBP in the intensive glycemia therapy arm only.

Several studies combined data from ACCORD-BP and SPRINT to determine if a J-curve exists. Li et al. combined the ACCORD-BP and SPRINT databases and assessed the relationship between mean on-treatment DBP (<60, 60 to <70, 70 to <80, and ≥80 mm/Hg) and development of a primary outcome (all-cause death, non-fatal MI, non-fatal stroke) and a composite cardiovascular outcome (cardiovascular death, nonfatal MI, nonfatal stroke) in the 7515 patients with mean on-treatment systolic BP <130/80 mm/Hg [40]. In these patients with relatively well-controlled systolic BP, a mean DBP <60 mm/Hg was significantly associated with the primary outcome (HR 1.46, $p = 0.004$), the composite cardiovascular outcome (HR 1.74, $p = 0.001$), non-fatal MI (HR 1.73, $p = 0.008$), and non-fatal stroke (HR 2.67, $p = 0.01$). In a sensitivity analysis, they assessed the interaction between low baseline DBP (<60 mm/Hg) and intensity of treatment for both trials assessed separately and found no significant interaction for the primary outcome, all-cause death, and cardiovascular death, although data from both trials were not combined for this analysis.

We also combined patients from ACCORD-BP and SPRINT and included 14,094 patients [41]. There were statistically significant non-linear relationships with baseline DBP for all-cause death and the composite cardiovascular outcome (cardiovascular death, non-fatal MI, non-fatal stroke) observed among all participants. We noted a non-statistically significant interaction between baseline DBP and treatment group assignment for all-cause death ($p = 0.13$) that occurred around 60 mmHg. For intensive vs standard therapy, a baseline DBP of 50 mmHg was associated with an increase in death (HR 1.80, 95% CI, 0.95–3.39), but for a baseline DBP of 80 mmHg it was associated with a reduction (HR 0.77, 95% CI, 0.59–1.01). There was no interaction found between baseline DBP and treatment group assignment for the composite cardiovascular outcome ($p = 0.88$), and over the range of baseline DBP values there were consistent reductions in the composite cardiovascular outcome for patients assigned to intensive vs standard therapy.

Overall, these post hoc analyses of RCTs with higher risk individuals than the general hypertensive population support the existence of a J-curve, although implementation of this principal to the individual patient is not clarified from such population-based studies with patients having varying baseline comorbidities.

5. Trials in patients with CAD (Table 3)

The J-curve was investigated in one observational study and 4 RCTs with all patients specifically having CAD. The CLARIFY investigators analyzed the data of 22,672 adults with stable CAD in this prospective, international, observational registry [42]. After a median follow-up of 5 years, 2101 patients (9.3%) met the primary outcome (cardiovascular death, MI, or stroke). After multiple adjustments a steep, J-shaped curve existed for both average SBP and DBP. With DBP of 70–79 mm/Hg as the reference, DBP of 60–69 mm/Hg had an adjusted HR of 1.41 (95% CI 1.24–1.61) and DBP < 60 mm/Hg an adjusted HR of 2.01 (95% CI 1.50–2.70). Similar steep J-shaped curves were found for cardiovascular death, all-cause death, MI, and hospitalization for heart failure, but not for stroke. In a separate analysis, the J-shaped relationship persisted when the analysis was restricted to participants with the lowest pulse pressure (45–64 mm/Hg) with an adjusted HR of 1.53 (95% CI 1.27–1.83) for those with DBP < 70 mm/Hg compared to 70–79 mm/Hg [43].

In the International Verapamil-Trandolapril Study (INVEST), 22,576 patients with hypertension and CAD were randomized to a calcium antagonist strategy (verapamil based) or a non-calcium antagonist strategy (atenolol based) and followed for 24 months [44]. In a post-hoc analysis, a significant J-shaped relationship was found between average on-treatment DBP and the primary outcome (all-cause death, non-fatal MI, and non-fatal stroke), all-cause death, total MI, and to a much less extent for stroke [45]. Interestingly, a significant interaction between DBP and the primary outcome with previous revascularization was found as DBP decreased, suggesting revascularization resulted in better tolerance of lower DBP. There was no J-curve in the revascularized group, and the ratio of MI to stroke significantly increased with lower DBP.

In the Treating to New Targets (TNT) Trial, 10,001 patients with CAD and a low-density lipoprotein (LDL) cholesterol level < 130 mg/dl were randomized to atorvastatin 80 mg versus 10 mg and followed for a median of 4.9 years [46]. Using a non-linear, multivariate Cox proportional hazards model, the relationships between both average SBP and DBP with the primary endpoint (death from CHD, non-fatal MI, resuscitation after cardiac arrest, and non-fatal stroke) were significantly J-shaped with a nadir of 146.3/81.4 mm/Hg. A significant relationship between lower DBP was also found with non-fatal MI but not for death (all-cause or from CHD). The fact that a similar J-curve relationship was

Table 3
Trials with all patients having CAD.

Trial Year of publication	Number	Comparisons	Exposure	Primary endpoint	Secondary endpoint (s)	DBP-J-curve significance	Nadir	Comments
CLARIFY [42] 2016	22,672	Observational cohort of patients with CAD treated for hypertension	Mean DBP/ SBP[a]	CV death, MI, stroke	Components of primary endpoint, all-cause death, CHF hospitalization	Significant for primary endpoint, death (all-cause and CV), MI, and CHF hospitalization	About DBP 77 for primary endpoint (visual inspection)	SBP also had J-curve No J-curve for stroke vs either SBP or DBP
INVEST [45] 2006	22,576	Verapamil vs atenolol	Mean DBP/SBP	All-cause death, non-fatal MI, non-fatal stroke	All-cause death, total MI, total stroke	Significant for primary outcome and total MI	119/84	Interaction with revascularization
TNT [46] 2010	10,001	Atorvastatin 80 mg vs 10 mg	Mean DBP/SBP	CHD death, non-fatal MI, stroke, cardiac arrest	All-cause death, CV mortality, non-fatal MI, angina	Significant for primary and secondary outcomes	141.6/81.4	No J-curve for stroke
PROVE IT-TIMI 22 [63] 2010	4162	Pravastatin 40 mg vs atorvastatin 80 mg	Mean DBP/SBP	All-cause death, MI, UA, stroke, revascularization	Death from CHD, non-fatal MI, revascularization	Significant for primary, secondary, and individual outcomes	136/85	Curve relatively flat for DBP 70–90
EPHESUS [48] 2020	5929	Eplerenone vs placebo	Mean DBP	All-cause death CVE hospitalization	CV death	Significant for CV death or CV hospitalization	DBP about 70	Significant only in the group not revascularized

[a] All BP numbers in mm/Hg. CHF: congestive heart failure; CHD: coronary heart disease; CV: cardiovascular; CVE: cardiovascular events; DBP: diastolic blood pressure; MI: myocardial infarction; SBP: systolic blood pressure; UA: unstable angina.

found between the primary outcome and DBP after controlling for PP suggests that low DBP was indeed the culprit.

In the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) Trial, 4162 patients with acute coronary syndrome were randomized to pravastatin 40 mg or atorvastatin 80 mg and followed for an average of 24 months. Using a non-linear Cox proportional hazards model, a significant J-shaped relationship was independently found between both average SBP ($p < 0.0001$) and average DBP ($p < 0.0001$) and the primary endpoint (all-cause death, MI, unstable angina, coronary revascularization, or stroke) and the secondary outcome (CHD death, non-fatal MI, or revascularization) ($p < 0.0001$ for both SBP and DBP). Similar associations were found for tertiary outcomes, including all-cause mortality, cardiovascular mortality, and non-fatal MI. Importantly, these J-shaped relationships were not evident when using only baseline BPs, suggesting reverse causality is not the problem, rather low achieved on-treatment BP is. Similar to INVEST, the ratio of non-fatal MI to stroke was constant over a wide range of BPs, except for lower DBP, where the ratio was much higher.

In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), 6642 patients with MI and heart failure were randomized to eplerenone or placebo and followed up for a mean of 21 months [47]. In a post hoc analysis of 5929 EPHESUS patients, Bohm et al. used multivariate-adjusted Cox regression analyses to relate achieved blood pressures during the trial and the outcomes of CV death or hospitalization, CV death, or all-cause death [48]. Analyses were performed separately for the 45% that had coronary reperfusion and the 55% that did not. In those without revascularization, a mean DBP <70 mm/Hg was associated with significantly increased risk of CV death or hospitalization (HR 1.54, 95% CI 1.26–1.87, $p < 0.001$), CV death (HR 1.70, 1.3–3.22, $p < 0.001$), or all-cause death (HR 1.80, 1.41–2.30) compared to the reference DBP (76 - ≤ 80 mm/Hg). This significant relationship persisted in a sensitivity analysis restricted to patients with optimal SBP control (120–130 mm/Hg). No such relationship was found for those that were revascularized. Furthermore, a low SBP was also associated with increased risk, but the effect persisted regardless of revascularization status.

Overall, these data from trials of patients with documented CAD provide compelling evidence for a true J-curve in that particular population. This should prompt concern when treating the individual patient with known or suspected CAD. Whether revascularization mitigates this risk, as demonstrated in INVEST and EPHESUS, remains to be proven.

6. Discussion

Whereas the J-curve may be valid in population-based studies, the main issue is how this may affect treatment of the individual patient. The studies outlined above that find a significant DBP J-curve effect are notable for the variable nadirs. We suspect the variability is due to differing methodologies of analysis, underlying patient comorbidities, durations of follow-up, and other sources of heterogeneity. Unfortunately, this variability also precludes the ability to apply a specific threshold to an individual patient being treated in the clinic.

The diastolic J-curve phenomenon may be explained by 3 non-mutually exclusive factors: reduced myocardial oxygen supply relative to demand from CAD and/or LVH, widened pulse pressure indicating an abnormally stiff and already diseased vasculature, and reverse causality due to underlying comorbid diseases that cause both low DBP and increased morbidity/mortality.

Coronary blood flow occurs primarily in diastole, unlike the situation for the brain and kidneys which are perfused throughout the cardiac cycle. The brain appears to be much less susceptible to reduced DBP. The studies outlined above found no J-shaped curve regarding stroke, although one large observational cohort of 68,551 subjects did find an increased hazard ratio for stroke with DBP < 71 mm/Hg [49].

Coronary perfusion pressure (CPP) equals DBP minus left ventricular diastolic pressure [50], and autoregulation maintains coronary blood flow at a steady state over a range of CPPs. A normal coronary artery can dilate with coronary flow increasing up to 5-fold as CPP decreases [51]. With increasing coronary artery stenosis, however, the ability to increase flow in the face of reduced CPP will be severely blunted. Additionally, left ventricular hypertrophy (LVH) can shift the coronary flow-CPP curve to the right such that maximal flow can only increase perhaps 3-fold depending on the cause and degree of hypertrophy [51]. Oxygen demand is also increased with LVH. Furthermore, in hypertensive patients with LVH and unobstructed coronary arteries, coronary flow decreases as CPP decrease below 80–90 mm/Hg with acute treatment [52].

These experimental data provide an explanation for the repeated finding of the J-curve being detectable and most prominent in those with underlying heart disease, notably CAD and LVH. Rapid lowering of BP can induce ischemic (repolarization) electrocardiographic changes in patients with LVH [53], and in one study ejection fraction increased with abrupt drops in BP induced by trimethaphan in hypertensive

patients with either CAD or LVH, but not when both were present; in fact, ejection fraction fell [50]. Flattening of the J-curve only in revascularized patients in INVEST and EPHESUS supports obstructive CAD as a major factor in explaining this phenomenon.

A low DBP in the face of an elevated SBP necessitates that the PP is elevated. Such elevations with no other obvious cause (e.g., aortic valve insufficiency) indicate an abnormally stiff vasculature and are associated with subclinical atherosclerotic disease in various vascular beds [54,55]. A widened PP has been repeatedly associated with adverse CV outcomes, including MI [56–59]. Furthermore, Warren et al. followed 10,876 patients undergoing percutaneous coronary intervention and assessed the relationship between periprocedural PP and adverse outcomes [60]. They found that the group with high SBP (≥120 mm/Hg) and low DBP (≤70 mm/Hg) had a significantly greater incidence of MI and stroke at one year and significantly higher long-term mortality. It is certainly possible that at least some of the increased risk of low DBP results from coexisting underlying vascular disease indicated by a wide PP. Notably, however, the CLARIFY investigators noted a significant J-curve relationship between low DBP and adverse events even in the quintile with the lowest PP (≤45 mm/Hg; normal ~40 mm/Hg) [43].

In addition to the association with increased PP, a low DBP may also indicate poor health which may also explain a J-shaped relationship with adverse outcomes, i.e., reverse causality. Boutitie et al. interrogated the INdividual Data ANalysis of Antihypertensive intervention (INDIANA) database of 40,233 persons with hypertension from 7 RCTs of treatment (versus placebo or no intervention) that were alive at 1 year with a mean follow-up of 3.9 years [61]. A significant J-shaped relationship between in-trial DBP and mortality (total and CV mortality) was observed for both treated (nadirs 84 and 80 mm/Hg) and untreated control patients (nadirs 90 and 85 mm/Hg). For non-CV death, the nadir was 84 mm/Hg in the treated group, but the relationship in the control group was strictly negative. These relationships remained significant in patients with lower baseline DBP (<90 mm/Hg) and when stratified by PP. Since the J-curve was present in untreated patients, reverse causality is the likely explanation, with treatment merely shifting the curve to the left. Similarly, recurrent CVEs in Framingham Offspring patients were significantly increased with DBP < 70 mm/Hg versus 70–89 mm/Hg in both treated (for hypertension) and untreated patients [22]. In combined analysis of ACCORD-BP and SPRINT, the nadir SBP of the observed J-shaped curve mirrored the target BP for each group (intensive versus standard control) within that group suggesting the actual achieved BP was not the mediator, again supporting reverse causality [62].

7. Conclusion

There is little doubt that plotting DBP (baseline and/or achieved) with adverse CVEs/mortality often produces a J-shaped relationship, especially in certain populations such as patients with obstructive CAD. The major question, however, is whether the lower DBPs cause these adverse outcomes or merely serve as markers for either underlying atherosclerotic vascular disease (widened PP) and/or severe comorbidity which would be the actual mediators. Equipoise exists whether a low DBP should dissuade intensification of antihypertensive therapy in an individual patient to achieve a desired SBP target or should prompt deintensification if it remains too low on treatment. Currently available data cannot accurately answer these uncertainties. In our opinion, low DBP is possibly causative in those with obstructive CAD. When present (or suspected), each case should be approached individually considering how high the SBP is and what is the risk of other (than MI) CVEs, especially stroke. Clearly, RCTs are indicated to determine if intensification for therapy is indicated in those with baseline low DBP, if therapy should be de-intensified in those with very low on-treatment DBP, and if coronary revascularization is indicated in those with obstructive CAD to allow intensification of therapy. Firm global recommendations cannot be made at this time.

CRediT authorship contribution statement

EJF reviewed the literature and wrote the first draft.

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