J-curve Revisited
An Analysis of Blood Pressure and Cardiovascular Events in the Treating to New Targets (TNT) Trial

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Disclosure Information

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- **Sripal Bangalore**: Advisory board - Daiichi Sankyo

- **Franz H. Messerli**: Consulting: Abbott, Novartis, Pfizer, Bayer, Forest, Daiichi-Sankyo, Sanofi, Medtronics and received research/grants from Servier, Forest, and Novartis

- **Chuan-Chuan Wun**: Pfizer employee

- **Andrea L. Zuckerman**: Pfizer employee

- **David A DeMicco**: Pfizer employee

- **John B. Kostis**: None

- **John C. LaRosa**: None
Introduction

- 17.6 million Americans with SIHD
- 70-90% of patients with SIHD have hypertension (12.3-15.8 million)
- There is no robust clinical trial evidence for a BP target
- For more than 3 decades, major national and international guidelines have promoted “lower BP goals” for systolic pressure, based primarily on expert consensus
# Major Guideline Recommended BP Targets

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<td>Joint National Committee-7</td>
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<td>ACC/AHA</td>
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<td>British Hypertension Society</td>
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<td>World Health Organization/International Society of Hypertension</td>
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*BP targets for patients at high risk or those with established CV disease

The JNC 7 report. *JAMA* 2003;289:2560–2572  
Williams et al. *BMJ* 2004;328:634–40  
Trends in BP Target Recommendation: JNC I - 7

Lower the better approach!

Stroke & CHD Mortality Rate in Each Decade of Age vs. Usual BP at the Start of that Decade

Prospective Studies in Perspective

- Patients *without* known vascular disease
- Baseline BP used
- It is *not* treated BP
- It is OBSERVATIONAL/epidemiological
- It tests associations and not causation
Objectives

- To evaluate the relationship between achieved blood pressure as a predictor of long-term cardiovascular events in patients with CAD enrolled in the Treating to New Targets (TNT) trial
**Primary Endpoint:** Major cardiovascular event defined as death from coronary disease, nonfatal MI, resuscitated cardiac arrest, and fatal or nonfatal stroke at a median follow-up of 4.9 years
Methods: Follow-up

- Patients were followed up at Week 12 and at Months 6, 9, and 12 during the first year and then every 6 months thereafter.
- At each visit, vital signs, clinical end points, adverse events, and concurrent medication information were collected.
- BP management was at the discretion of the treating physician.
- For this analysis, the average follow-up BP were calculated for each patient by using all follow-up values, up to the last visit prior to the date of primary outcome or end of follow-up in those without events.
Statistical Analyses

- BP values were categorized as 10-mm Hg increments for association with clinical outcomes

- Three models were tested:
  - **Model 1**: Multivariable non-linear Cox proportional hazard analysis was performed including HR category as the major factor adjusting for baseline variables and treatment effect
  - **Model 2**: Multivariable non-linear Cox proportional hazard analysis using HR as a time dependent variable
  - **Model 3**: Multivariable Cox regression with restricted cubic splines including heart rate as a time-dependent covariate with three knots at 35, 55, and 75 bpm

- **Nadir HR** was calculated based on Delta method, which is equal to the coefficient of linear term divided by \(-2 \times \) coefficient of quadratic term
Primary outcome: Death from coronary heart disease (CHD), non-fatal, non-procedure-related MI, resuscitation after cardiac arrest, or fatal or non-fatal stroke

Bangalore et al. Eur Heart J, 2010: 31, 2897-2908
Primary outcome: Death from coronary heart disease (CHD), non-fatal, non-procedure-related MI, resuscitation after cardiac arrest, or fatal or non-fatal stroke

Nadir = 146 mm Hg
Primary outcome: Death from coronary heart disease (CHD), non-fatal, non-procedure-related MI, resuscitation after cardiac arrest, or fatal or non-fatal stroke
BP & CHD Mortality
SBP & Stroke
BP & Angina

Graph A: Hazard ratio vs. Systolic blood pressure (mmHg)

Graph B: Hazard ratio vs. Diastolic blood pressure (mmHg)
Limitations

- Post-hoc analysis that evaluated the relationship between BP and cardiovascular events in a CAD population with tight control of cholesterol levels and hence the results cannot be extrapolated to other populations.

- We did not adjust our analyses for dosage of medications received.
Conclusions

- In patients with CAD, a J-curve relationship or a non-linear relationship persists between BP and cardiovascular events such that a low BP (<110–120/<60–70 mmHg) portends an increased risk of future cardiovascular events.

- Our findings negate the dictum that with BP, lower is always better (except perhaps for SBP and stroke).
What Is the Optimal Blood Pressure in Patients After Acute Coronary Syndromes?: Relationship of Blood Pressure and Cardiovascular Events in the Pravastatin or Atorvastatin Evaluation and Infection Therapy Thrombolysis in Myocardial Infarction (PROVE IT-TIMI) 22 Trial
Sripal Bangalore, Jie Qin, Sarah Sloan, Sabina A. Murphy, Christopher P. Cannon and for the PROVE IT-TIMI 22 Trial Investigators
SBP and Primary Outcome

Primary outcome: Death, MI, unstable angina requiring hospitalization, revascularization performed after 30 days following randomization, and stroke

Adjusted Hazard Ratio
Nadir = 136.1 mm Hg

Patients post acute coronary syndrome

Bangalore et al. Circulation, 2010;122:2142-2151
Pathophysiological mechanisms for J-curve phenomenon

An increase in coronary morbidity and mortality with low pressure could be due to:

- Reverse causation
  - Debilitating chronic illness
- Epiphenomenon of impaired cardiac function
- Epiphenomenon of increased arterial stiffness
- Impaired coronary blood flow thereby giving rise to myocardial ischemia

Bangalore et al. Circulation, 2010;122:2142-2151
J-Curve Skeptics

- Rightfully so, results from non-randomized studies
- Impossible to control for all confounders
- The results show association but *not causation*
- Debate ongoing for 3 decades
Clinical Equipoise Post ACCORD

European Society of Hypertension poll on BP Targets (May 2011) (1869 responders)
ISCHEMIA-BP Trial (PROPOSED): Intensive vs. Standard Blood Pressure Control in ISCHEMIA Trial Patients

Pl: Sripal Bangalore
ISCHEMIA Overview

*International Study of Comparative Health Effectiveness with Medical and Invasive Approaches*

- **Patients**: at least moderate ischemia, EF $\geq 35\%$

- **Hypothesis**: an initial invasive strategy of cath and optimal revascularization (PCI or CABG) + OMT is superior to a conservative strategy of OMT alone with cath reserved for OMT failure

- **Sample Size**: 8,000

- **Follow-up**: average $\sim 4$ years

Chair- Judith Hochman, PI - David Maron
Co-PI’s William Boden, Bruce Ferguson, Robert Harrington, Gregg Stone, David Williams
Randomization & Follow-up (Proposed Study)

Standard BP Strategy (SBP goal <140)

Intensive BP Strategy (SBP goal <120)

SBP≥130 mm Hg (N=4000)

* As needed if BP is not at goal
Primary Prevention

Diabetes

Diabetes: powered for stroke

CAD

BP Strategy Trials
(Proposed or in progress)

SPRINT

Action to Control Cardiovascular Risk in Diabetes (ACCORD)

THRESHOLD (ECLA group)

ISCHEMIA-BP

NYU School of Medicine