What's Known and Not Known About Renal Denervation for Hypertension: Critical Appraisal of the Clinical Data

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Disclosures for Dr. Bhatt

Advisory Board: Medscape Cardiology; Board of Directors: Boston VA Research Institute, Society of Chest Pain Centers; Chair: American Heart Association Get With The Guidelines Science Subcommittee; Honoraria: American College of Cardiology (Editor, Clinical Trials, Cardiosource), Duke Clinical Research Institute (clinical trial steering committees), Slack Publications (Chief Medical Editor, Cardiology Today Intervention), WebMD (CME steering committees); Other: Senior Associate Editor, Journal of Invasive Cardiology; Research Grants: Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic, Sanofi Aventis, The Medicines Company; Unfunded Research: FlowCo, PLx Pharma, Takeda.

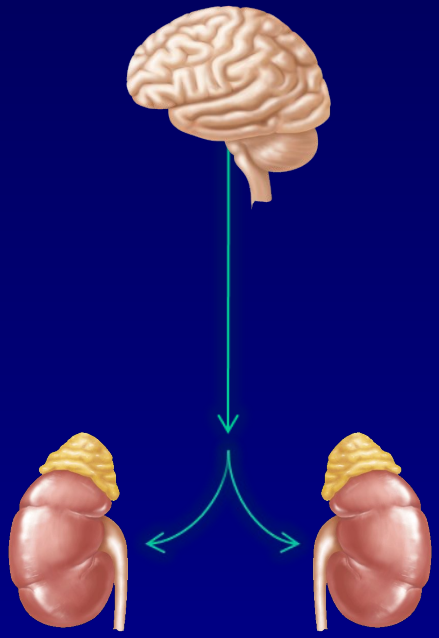
This presentation discusses off-label and/or investigational uses of various drugs and devices. The Symplicity catheter is investigational in the USA and not FDA approved. The EnligHTN and OneShot catheters are not FDA approved.

Drs. Bakris and Bhatt are co-PIs of SYMPLICITY-3.

MECHANISM OF ACTION

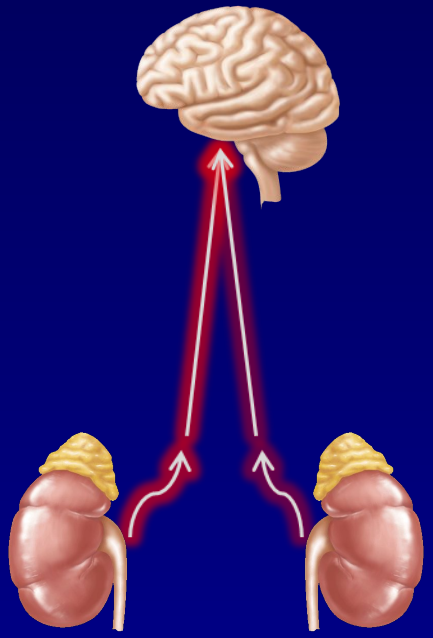
Renal Nerves and the SNS

Efferent Renal Nerves



Sympathetic drive from the CNS acts on the kidney to:
(1)Decrease renal blood flow
(2)Increase sodium retention
(3)Stimulate renin release

Afferent Renal Nerves

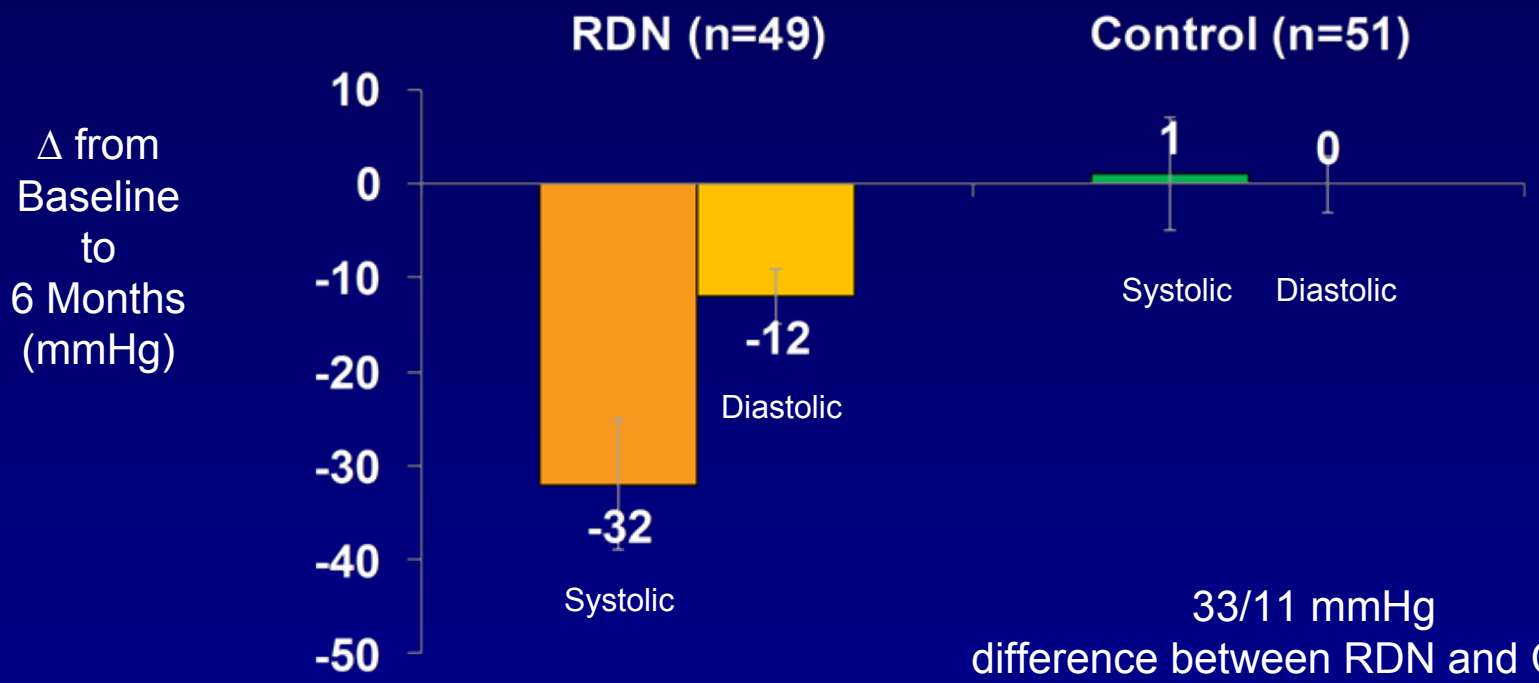


The kidney is a source of central sympathetic activity, sending signals to the CNS

Schlaich MP, et al. *Hypertension*. 2009;54:1195-1201.

EFFECT SIZE

Primary Endpoint: 6-Month Office BP

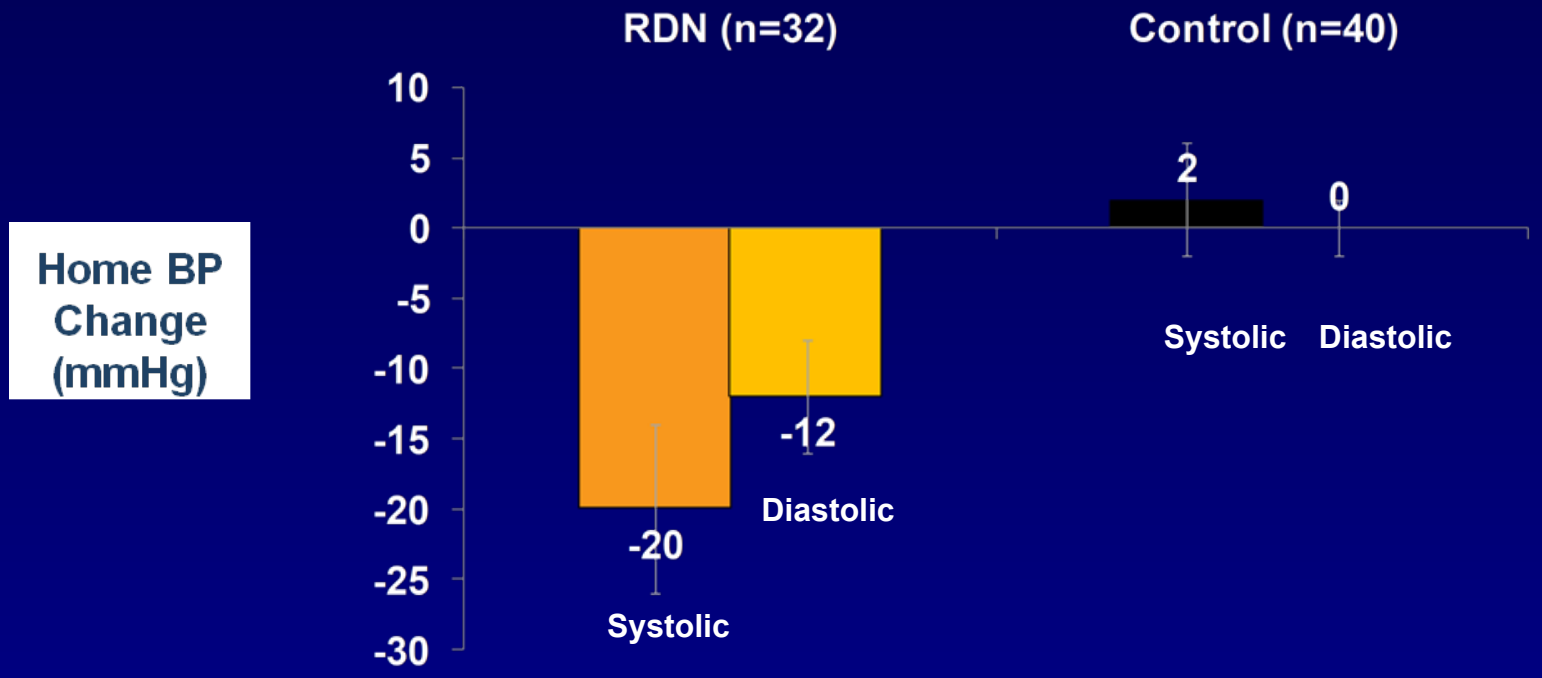


33/11 mmHg
difference between RDN and Control
($p<0.0001$)

- **84% of RDN patients had ≥ 10 mmHg reduction in SBP**
- **10% of RDN patients had no reduction in SBP**

Symplicity HTN-2 Investigators. *Lancet*. 2010;376:1903-1909.

Home and 24-Hour Ambulatory BP

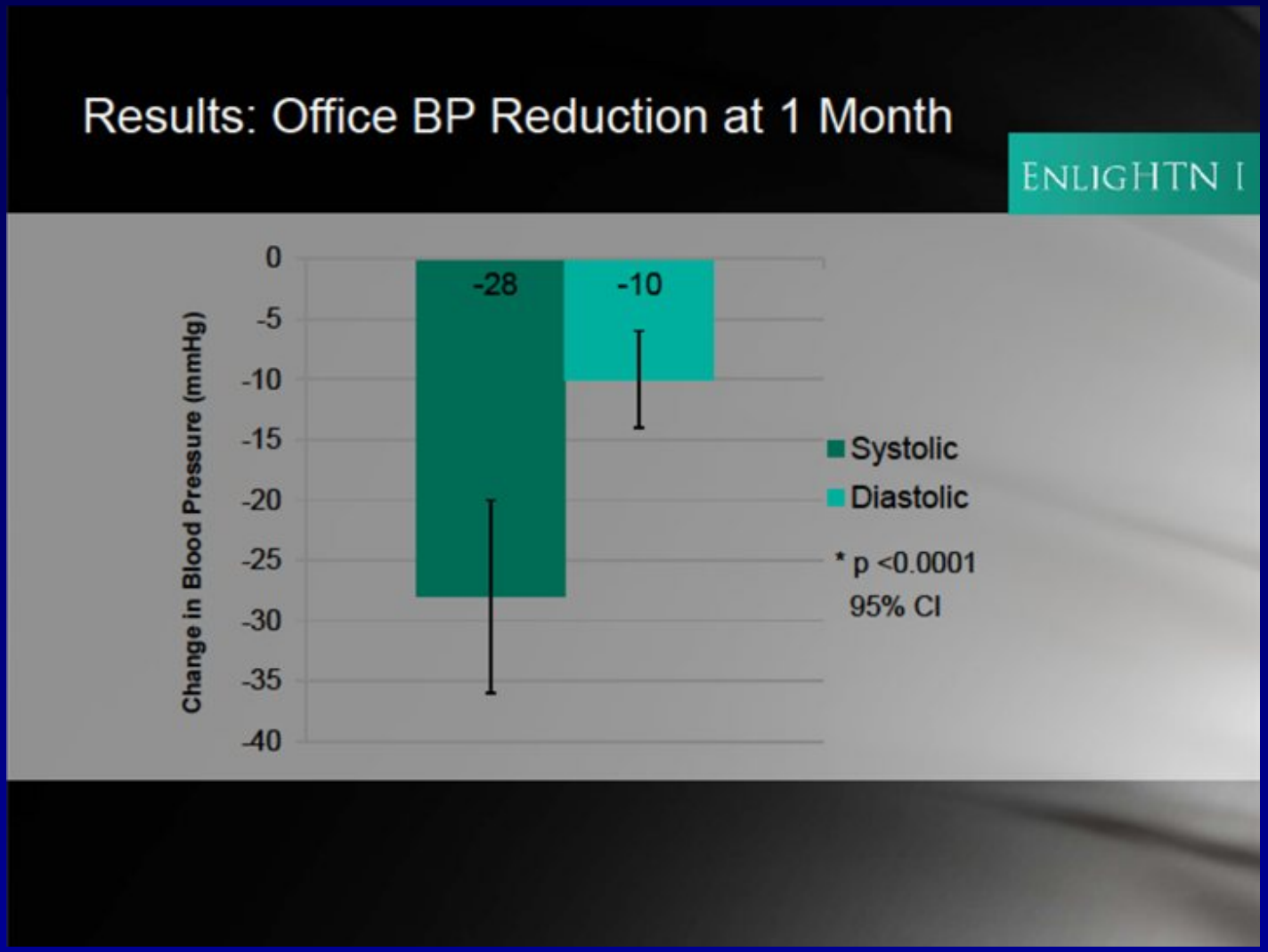


24-h ABPM:

- Analysis on technically sufficient (>70% of readings) paired baseline and 6-month
- RDN (n=20): -11/-7 mmHg (SD 15/11; p=0.006 SBP change, p=0.014 for DBP change)
- Control (n=25): -3/ -1 mmHg (SD 19/12; p=0.51 for systolic, p=0.75 for diastolic)

Symplicity HTN-2 Investigators. *Lancet*. 2010;376:1903-1909.

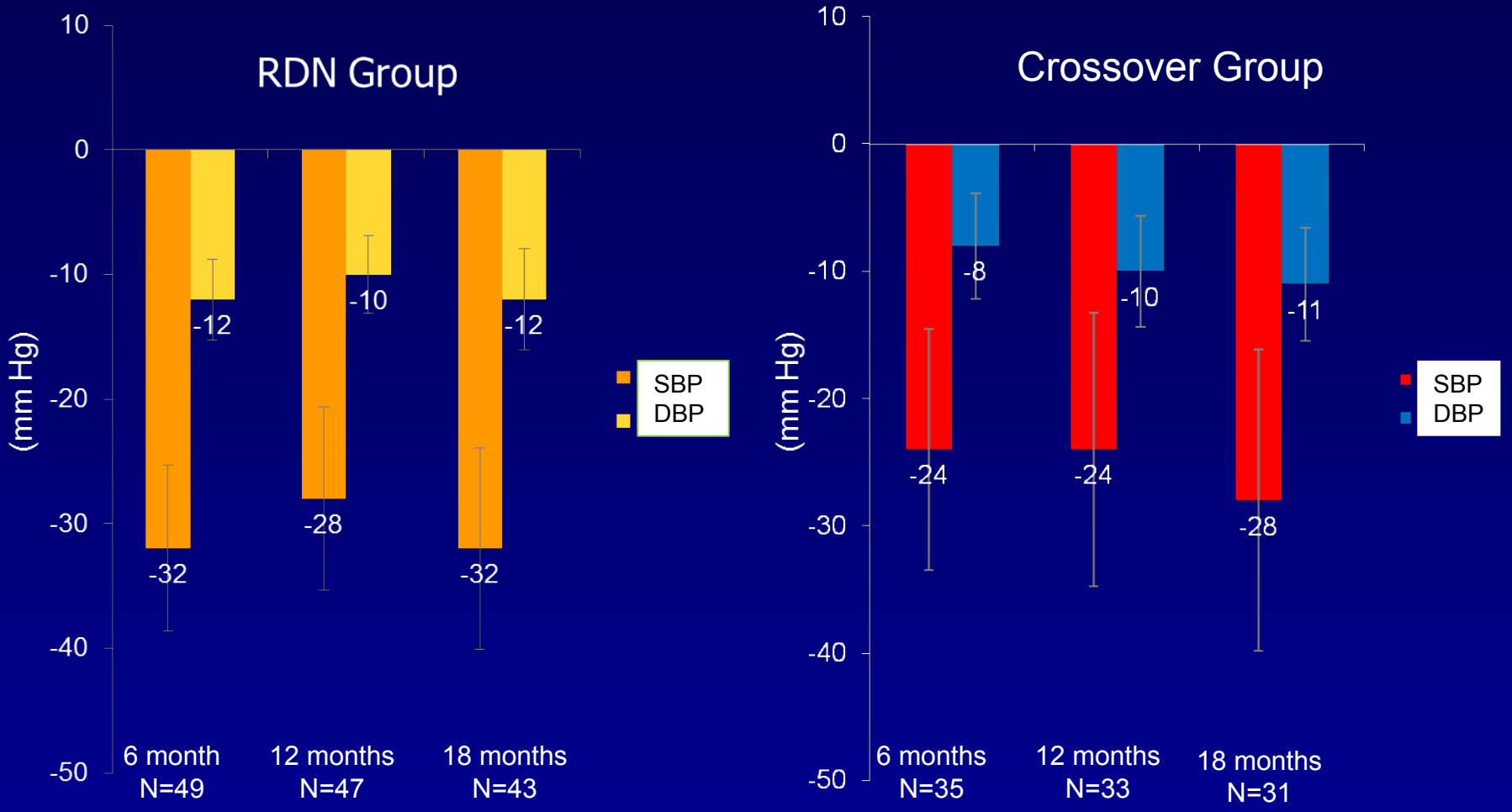
ARSENAL Results



Worthley P. EuroPCR 2012.

DURABILITY

Change in Office Blood Pressure Through 18 Months*



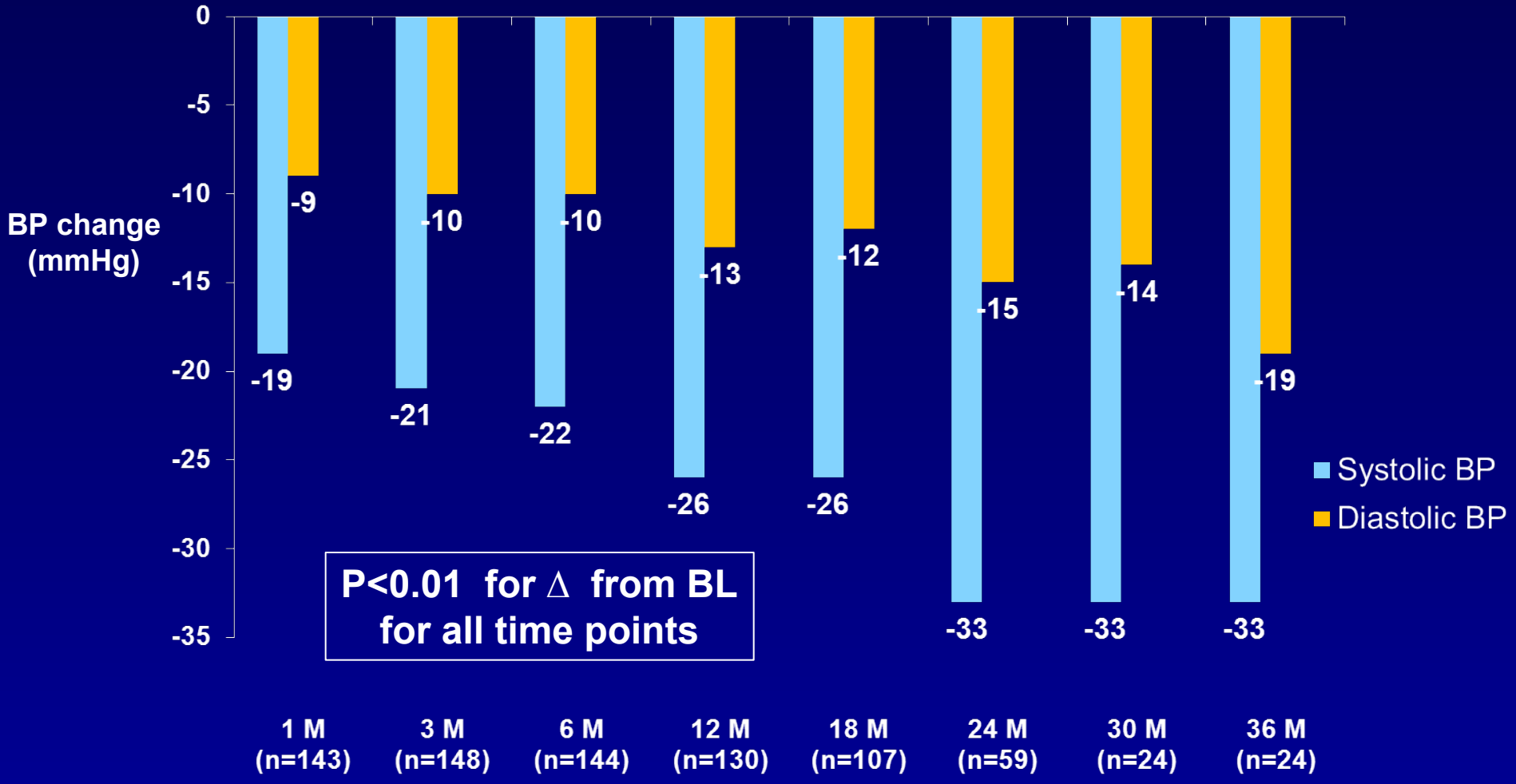
P-values < 0.01 at each time point
compared to pre-procedure values for each group

*Post-Procedure follow up

Esler M et al. Symplicity HTN-2. Longer term follow up. ESC 2012.

NON-RESPONDERS

Change in Office Blood Pressure Through 36 Months



Sobotka P et al. Symplicity HTN-1. Long term follow up. ACC 2012.

ARSENAL Results

- Responder rate at 1 month:
  - 78% of patients with > or = 10 mmHg SBP reduction
  - 41% of patients < 140 mmHg SBP

Worthley P. EuroPCR 2012.

Limitations

- Relatively small numbers of patients in trials
  - Small trials tend to overestimate treatment effects
  - Small trials tend to underestimate side effects
  - Rare side effects (?renal artery stenosis) missed?
  - No systematic imaging for renal artery stenosis
  - Generalizeable to broader patient populations?
  - Applicable to African Americans with HTN?
  - Generalizeable to other operators?
- Limited number of patients with long-term follow-up
  - Durability of effect

Limitations

- Methodological limitations
  - Lack of a blinded “sham” control arm; true, placebo effect unlikely, but not impossible (remember TMR)
  - Not all patients on a diuretic and at least 3 meds
  - Low utilization of aldosterone blockade
  - No ABPM to screen out “white coat hypertension”
  - No rigorous assurance of “compliance”

Symplicity HTN-3 Trial: Inclusion Criteria

- Average SBP ≥160mmHg (measured per guidelines)
- On stable medication regimen of full tolerated doses of 3 or more antihypertensive meds, with one being a diuretic
  - No changes for a minimum of 2 weeks prior to screening
  - No planned medication changes for 6 months
- Age 18-80
- eGFR ≥45mL/min

Kandzari, Bhatt, Sobotka, et al. *Clinical Cardiology*. 2012.

Randomization

- N = 530 randomized (enrolled at 90 US sites)
- Randomization
  - 2:1 ratio – Treatment or Control
  - Stratified by study center and by race (African American vs. non-African American)
- Single Blind
  - Specific staff & subject until 6 months

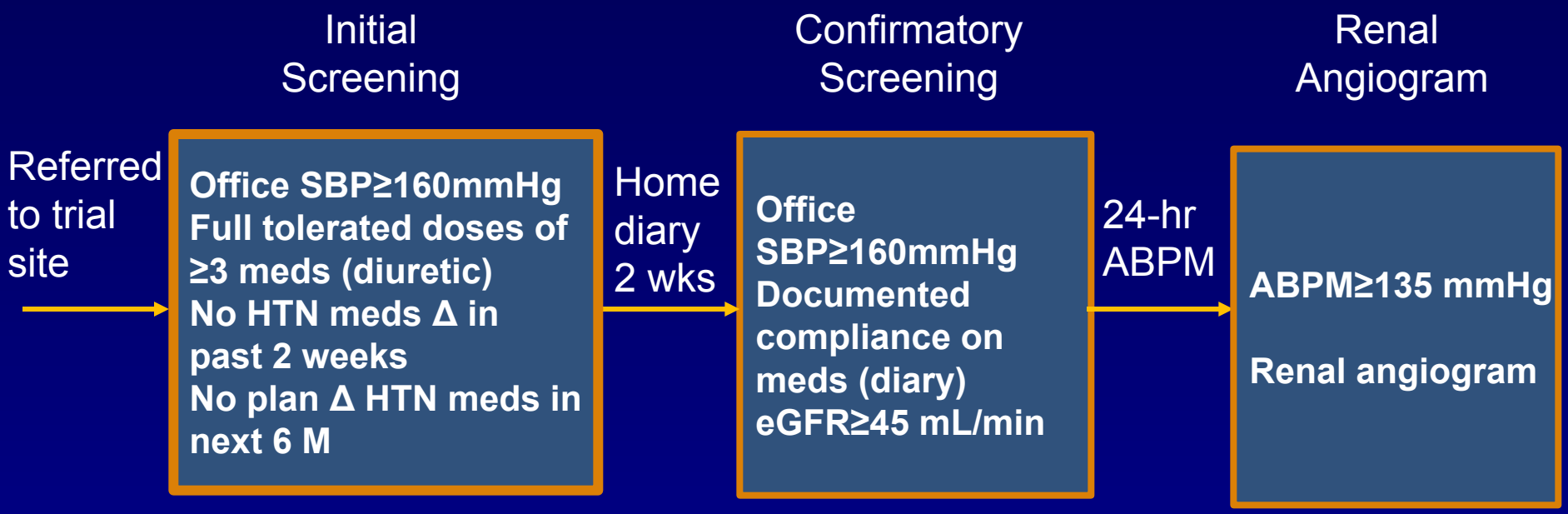
Kandzari, Bhatt, Sobotka, et al. *Clinical Cardiology*. 2012.

Endpoints

- Primary efficacy endpoint: Change in office SBP from baseline to 6 months
- Secondary efficacy endpoint: Change in 24hr ABPM SBP average from baseline to 6 months
- Primary safety endpoint: Mortality, ESRD, or procedural complications w/in 1 month or new RAS w/in 6 months

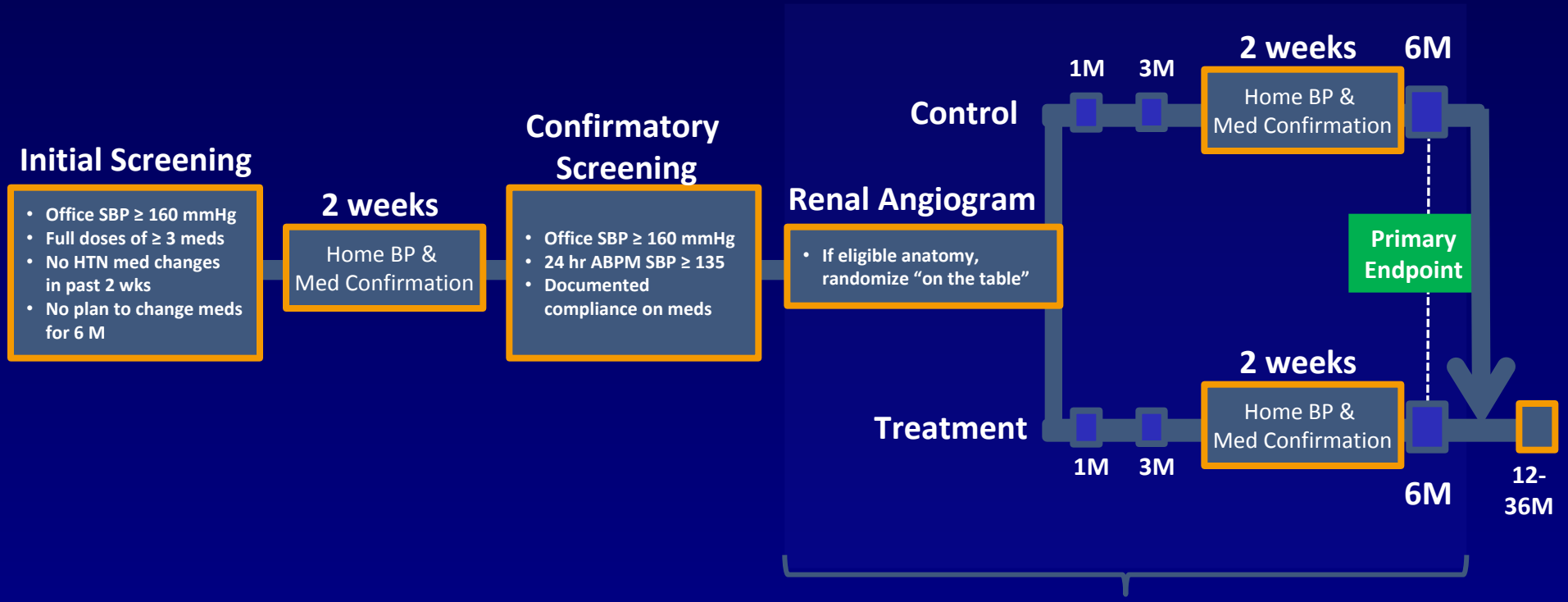
Kandzari, Bhatt, Sobotka, et al. *Clinical Cardiology*. 2012.

Symplicity HTN-3 Trial: Referral to Randomization Steps



Kandzari, Bhatt, Sobotka, et al. *Clinical Cardiology*. 2012.

Study Design Flow Chart



- Patient and research staff assessing BP and performing follow-up are blinded to treatment status
- No changes in medications for 6M

Kandzari, Bhatt, Sobotka, et al. *Clinical Cardiology*. 2012.

Summary

- Renal denervation data to date seem promising
- Longer term follow-up data accruing
- Symplicity-3 will be the pivotal US study for FDA approval – designed to overcome prior limitations
- Other devices being investigated with positive early data