The Global SYMPLICITY Registry: Safety and Effectiveness of Renal Artery Denervation In Real World Patients With Uncontrolled Hypertension

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on behalf of the GSR Investigators

March 30, 2014

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Conflicts of Interest – M. Böhm

- Deutsche Forschungsgemeinschaft
- Federal State of the Saarland (Ministry of Science and Economy
- BMBF
- European Union

1. Study Support:	**Astra Zeneca, Bayer AG, Boehringer Ingelheim, Medtronic, Novartis, Pfizer, Sanofi-Aventis, Servier, St. Jude**
2. Advisory Boards:	**Astra Zeneca, Bayer AG, Boehringer Ingelheim, Cordis, Daiichi-Sankyo, Medtronic, MSD, Novartis, Pfizer, Sanofi-Aventis, Servier,**
3. Speaker:	**Astra Zeneca, Bayer, Boehringer Ingelheim, Berlin-Chemie, Daiichi-Sankyo, Medtronic, MSD, Novartis, Pfizer, Sanofi-Aventis, Servier, St. Jude**

Global SYMPLICITY Registry

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(Non-voting members: Roxana Mehran, MD and Sorin Brener, MD)

Data Analysis

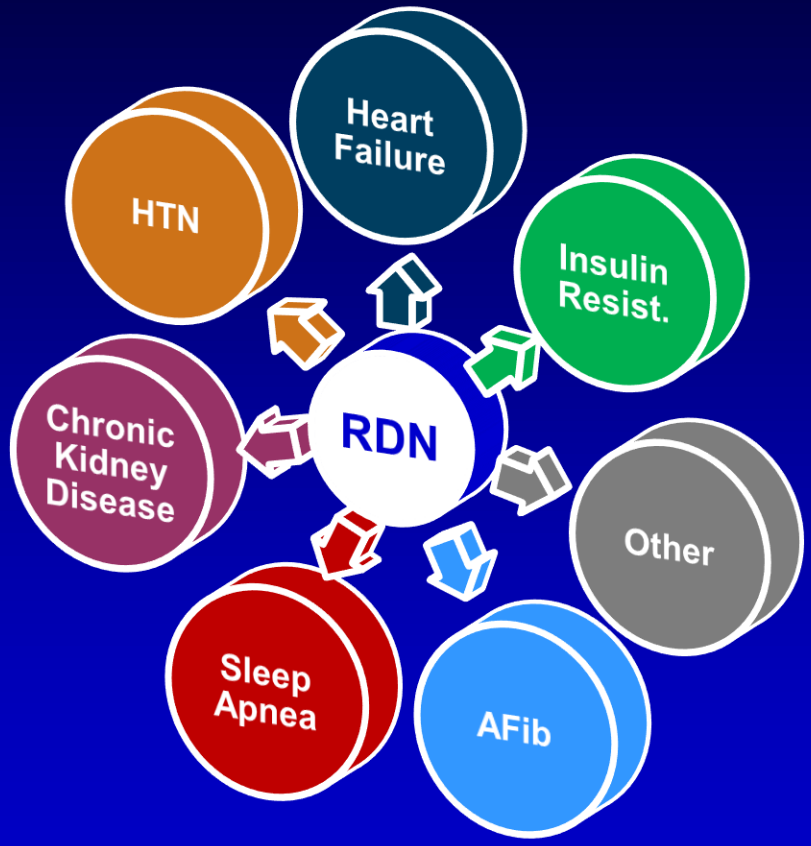
Institut für Herzinfarktforschung, IHF, Ludwigshafen, Germany

Sponsor

Medtronic, Inc.

Background

- Sympathetic nervous system overdrive is implicated in many diseases
- RDN has been studied extensively in subjects with uncontrolled hypertension
- Published reports describe the clinical benefit of renal denervation in several co-morbid conditions
- Safety and treatment effect in real life could differ



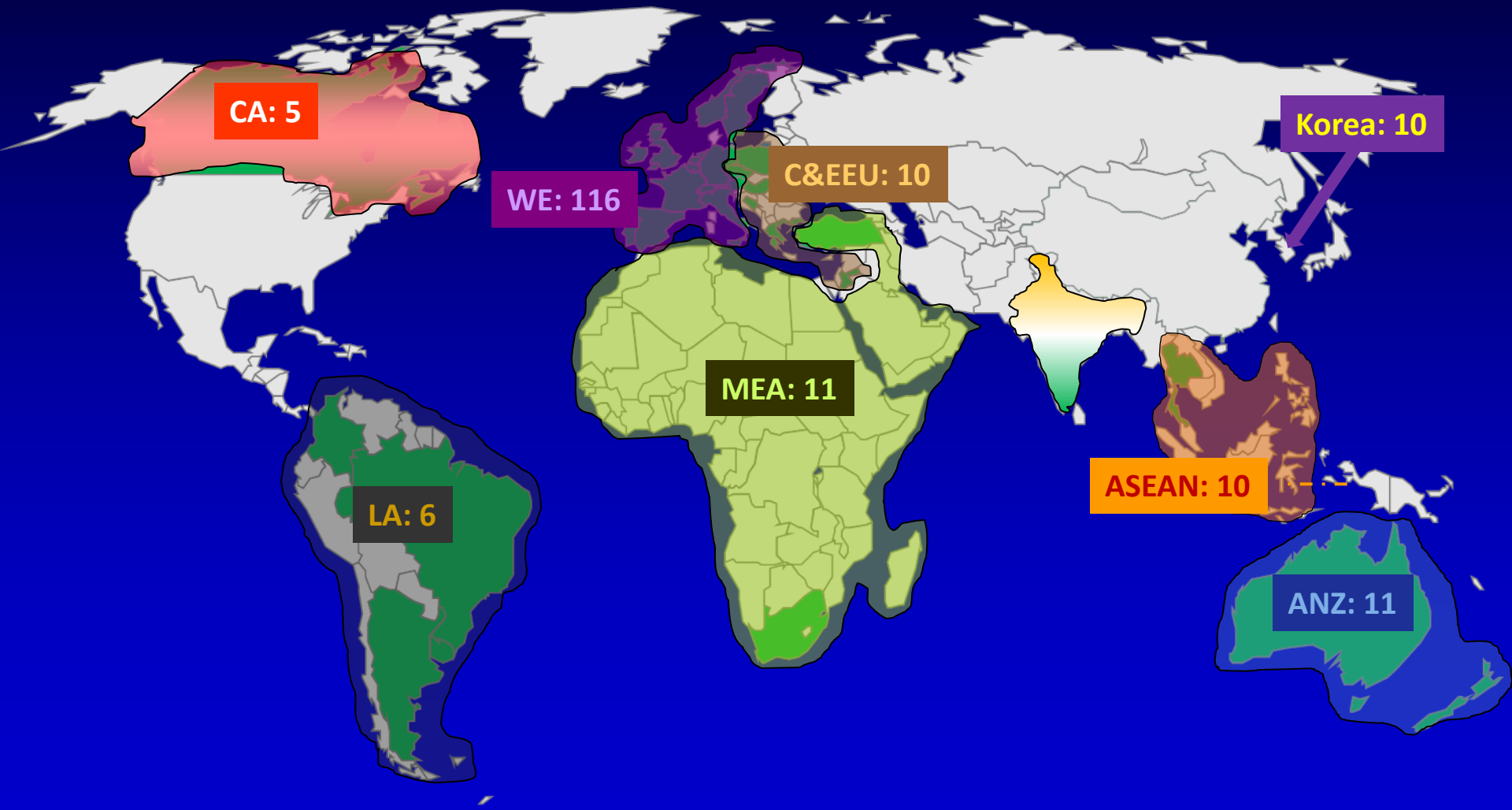
Objectives

- Primary: Safety
  - Peri-procedural safety
  - Long-term safety
    - Vascular
    - Renal
      - Hemodynamic
- Secondary
  - Patient characterization
  - Effect on blood pressure
  - Changes in baseline antihypertensive medication
- **New**
  - **Relationship of registry vs RCT (SYMPLICITY HTN-3)**

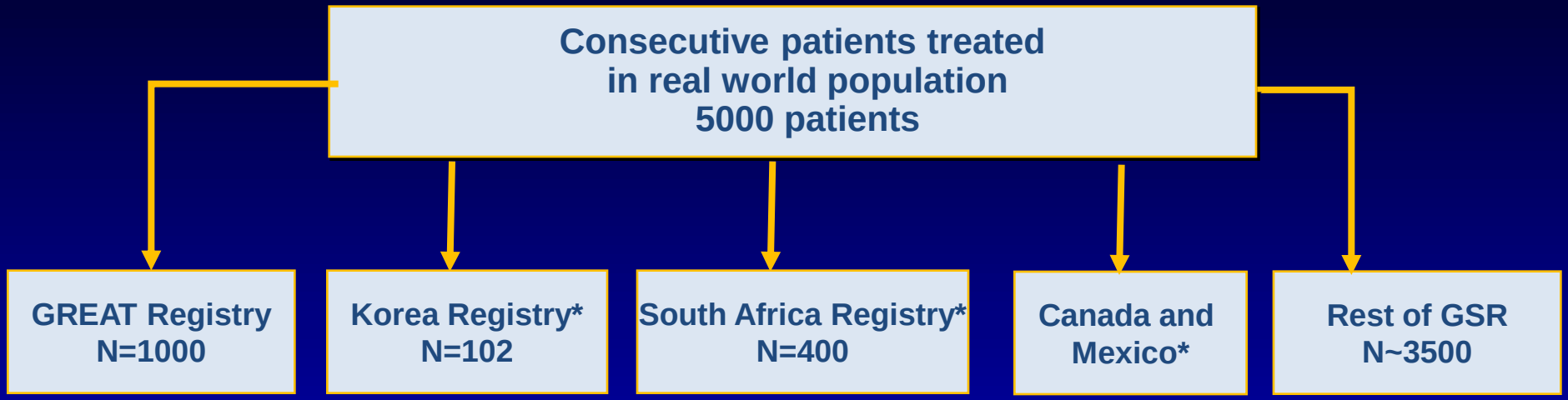
Design and Rationale

- Prospective, open label, multi-center, international registry
- Up to 5000 real world patients with uncontrolled hypertension and some with conditions associated with sympathetic nervous system activation
- Key Inclusion:
  - Older than 18 years
  - Candidates for renal denervation as defined by local regulations for use of the Symplicity™ catheter.
- NCT01534299

Global SYMPLICITY Registry – Current Activated Site Locations



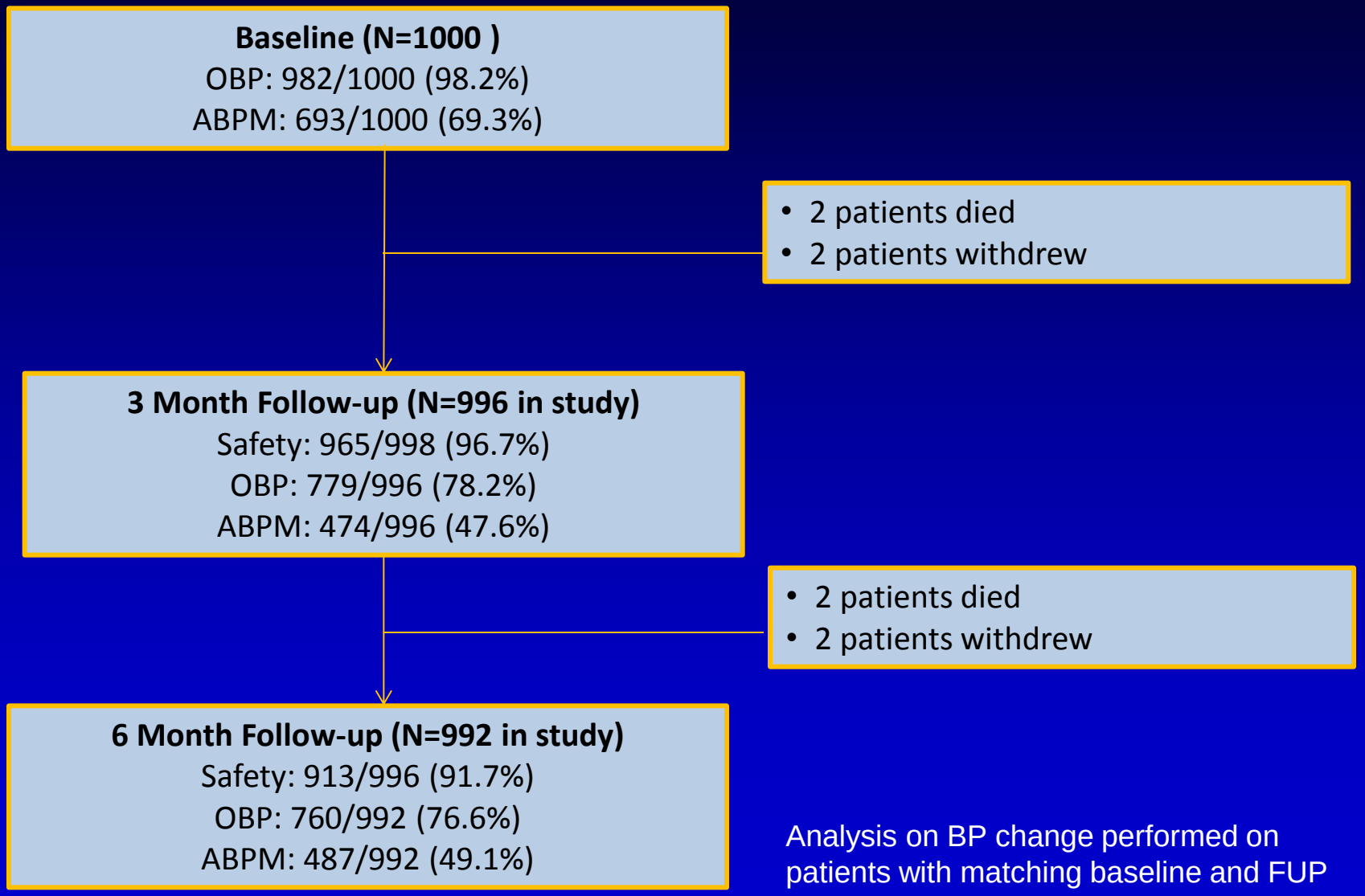
Global SYMPLICITY Registry



231 international sites in 37 countries
Min. 10% randomly assigned to 100% monitoring

* Limited to resistant hypertension only

Patient Disposition



Analysis on BP change performed on patients with matching baseline and FUP values

Baseline Patient Characteristics

	All Patients (N = 1000)	SBP ≥160 mm Hg & Ambulatory SBP ≥135* mm Hg (N = 327)
Gender, (% male)	61.2%	63.9%
Age (years)	60.7 ± 12.0	61.0 ± 10.9
BMI (kg/m^2)	30.5 ± 5.5	30.9 ± 5.5
Current smoking	10.0%	11.0%
History of cardiac disease	50.5%	52.9%
Renal impairment (eGFR <60 ml/min/1.73m^2)	23.4%	27.9%
Sleep apnea (AHI≥5)	4.2%	5.9%
Diabetes, Type 1	3.2%	2.5%
Diabetes, Type 2	38.5%	42.6%
1 co-morbidity	39.7%	36.7%
2 co-morbidities	35.5%	34.6%
3+ co-morbidities	24.6%	28.4%

* With ≥3 antihypertensive medication classes

Antihypertensive Medication Use

	All Patients (N = 1000)	SBP ≥160 mm Hg & Ambulatory SBP ≥135 mm Hg* (N = 327)
Antihypertensive medication classes	4.5 ± 1.3	4.7 ± 1.2
Beta-blockers	78.9%	81.0%
ACE inhibitors	33.8%	38.5%
Angiotensin-receptor blockers	67.3%	67.9%
Calcium channel blockers	76.3%	78.9%
Diuretics	78.2%	79.8%
Aldosterone antagonists	21.1%	19.3%
Spironolactone	18.6%	15.9%
Alpha adrenergic blockers	35.2%	40.1%
Direct-acting vasodilators	15.1%	19.0%
Centrally acting sympatholytics	33.2%	37.6%
Direct renin inhibitor	7.4%	7.7%

* With ≥3 antihypertensive medication classes

Procedural Detail

# renal arteries	2.2 ± 0.5
Length	41.5 ± 13.1 mm
Diameter left renal artery	5.6 ± 1.2 mm
Diameter right renal artery	5.7 ± 1.2 mm
Treatment time	50 min
# bilateral ablations	13.5 ± 4.1
# 120 sec bilateral ablations	11.3 ± 3.4
Contrast volume used	127.6 ± 81.1 cc

values are mean ± SD

Safety at 1 and 6 Months

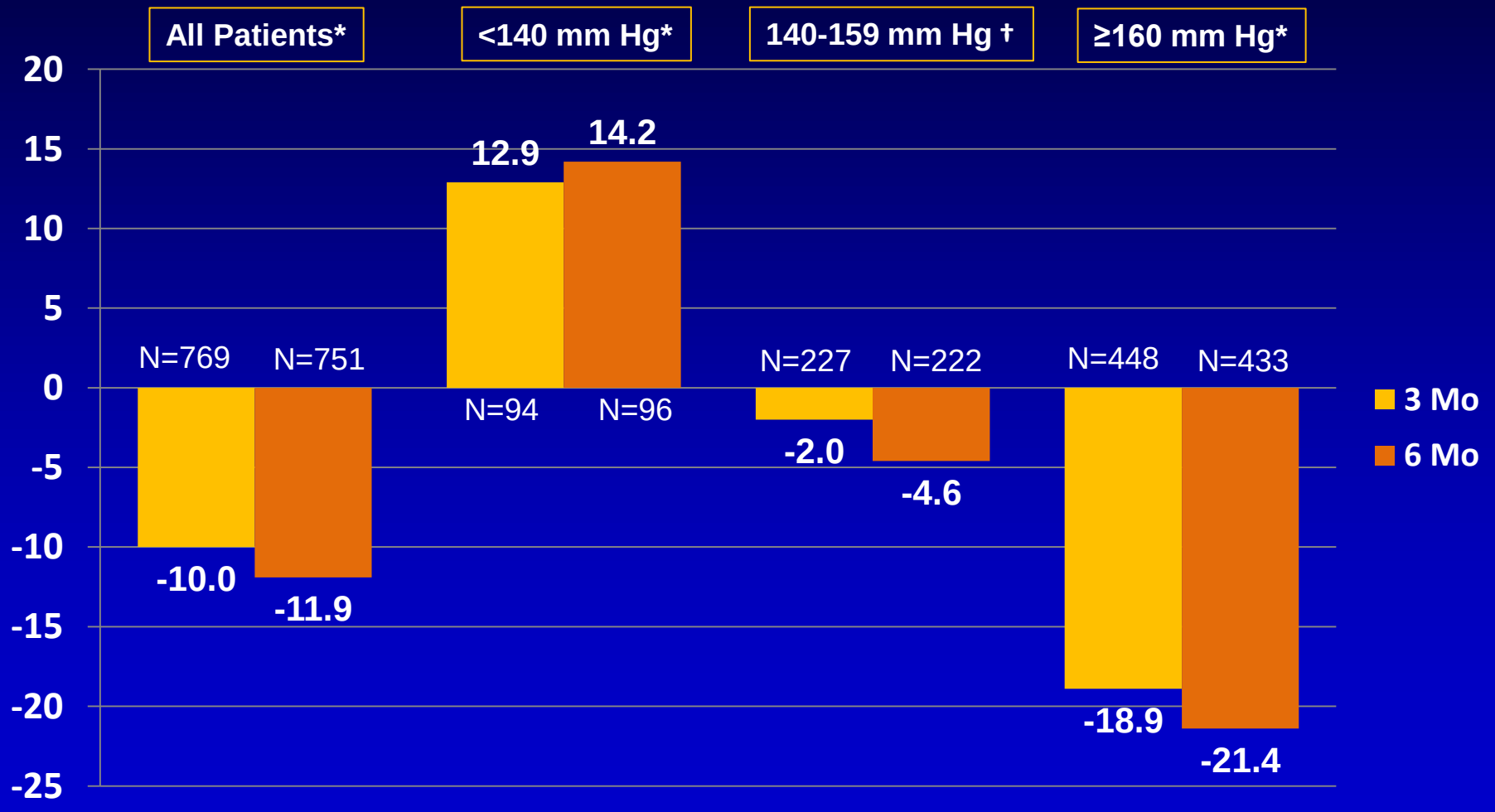
	1 Month n=967	6 Month n=913
Cardiovascular events		
Cardiovascular death	0.0% (0)	0.2% (2)
Stroke	0.2% (2)	0.9% (8)
Hospitalization for new onset heart failure	0.3% (3)	0.7% (6)
Hospitalization for atrial fibrillation	0.1% (1)	0.9% (8)
Hypertensive crisis/emergency	0.2% (2)	1.0% (9)
Myocardial infarction	0.0% (0)	0.6% (5)
Renal events		
New onset end stage renal disease	0.1% (1)	0.2% (2)
Serum creatinine elevation > 50%	0.1% (1)	0.2% (2)
New renal artery stenosis >70%	0.0% (0)	0.0% (0)
Post-procedural events		
Non-cardiovascular death	0.0% (0)	0.2% (2)
Renal artery re-intervention	0.1% (1)	0.2% (2)
Vascular complication	0.4% (4)	0.4% (4)

Safety in HTN-3 and GSR

	HTN-3 RDN arm (N=364)	GSR All Patients (N=1000)	GSR OSBP≥160 and ABPM≥135* (N=327)
MAE	1.4%	0.8%	1.3%
At 6 month			
Death	0.6%	0.4%	0.3%
New onset end stage renal disease	0.0%	0.2%	0.3%
Significant embolic event resulting in end-organ damage	0.3%	0.0%	0.0%
Renal artery re-intervention	0.0%	0.2%	0.0%
Vascular complication	0.3%	0.4%	0.7%
Hypertensive crisis/emergency	2.6%	1.0%	1.7%
New renal artery stenosis > 70%	0.3%	0.0%	0.0%

* With ≥3 antihypertensive medication classes

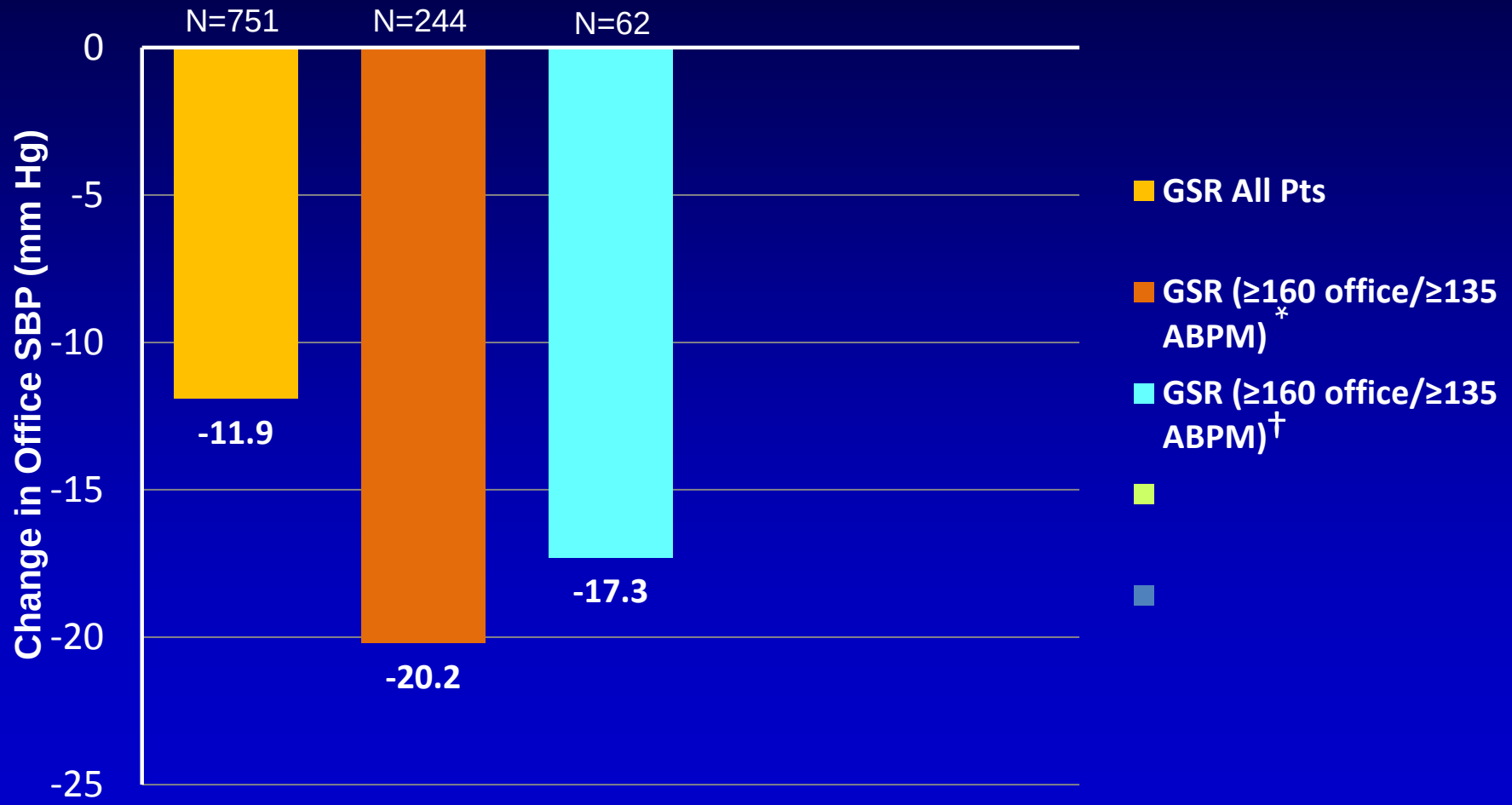
Change in Office Systolic BP for All Patients and Subgroups



*P<0.0001 for both 3 and 6 month change from baseline

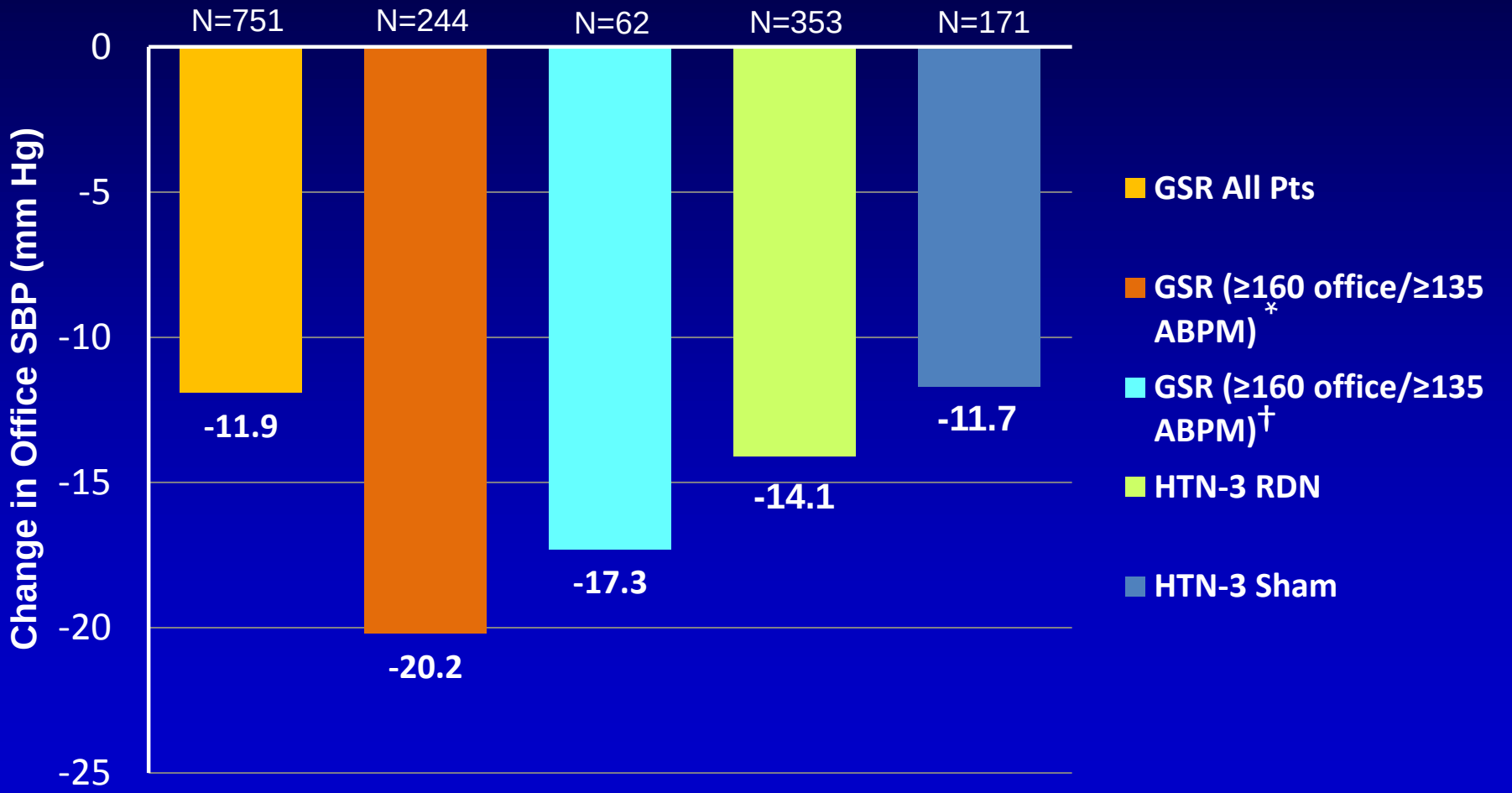
†P=0.14 at 3 months and P=0.0006 at 6 months

Change in Office SBP at 6 Months for GSR and SYMPLICITY HTN-3 Patients



*with ≥3 antihypertensive medication classes
† with ≥3 antihypertensive meds at maximum tolerated dose

Change in Office SBP at 6 Months for GSR and SYMPLICITY HTN-3 Patients



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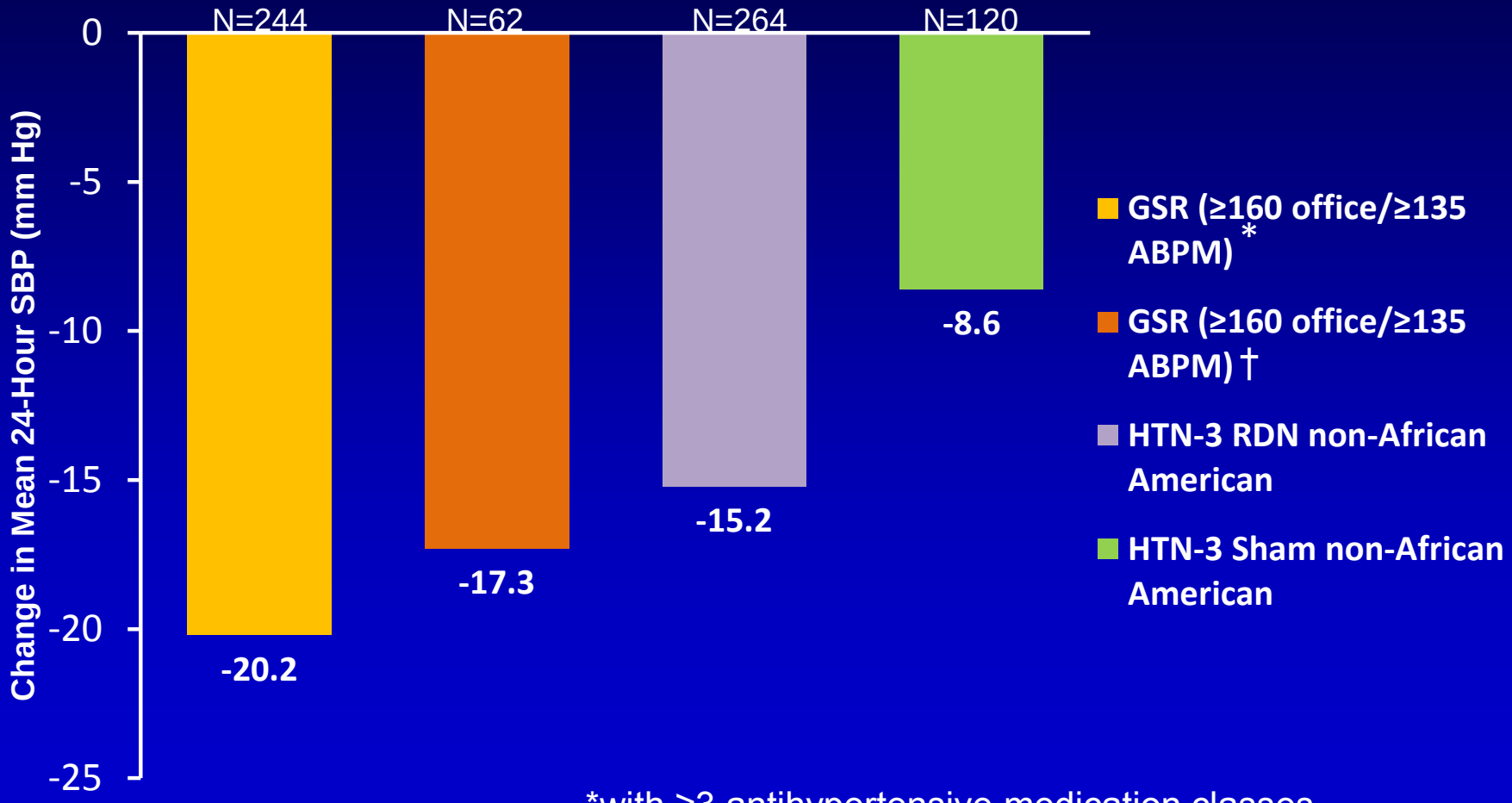
Change in Office SBP at 6 Months for GSR and Non-African American Patients in SYMPLICITY HTN-3



*with ≥3 antihypertensive medication classes
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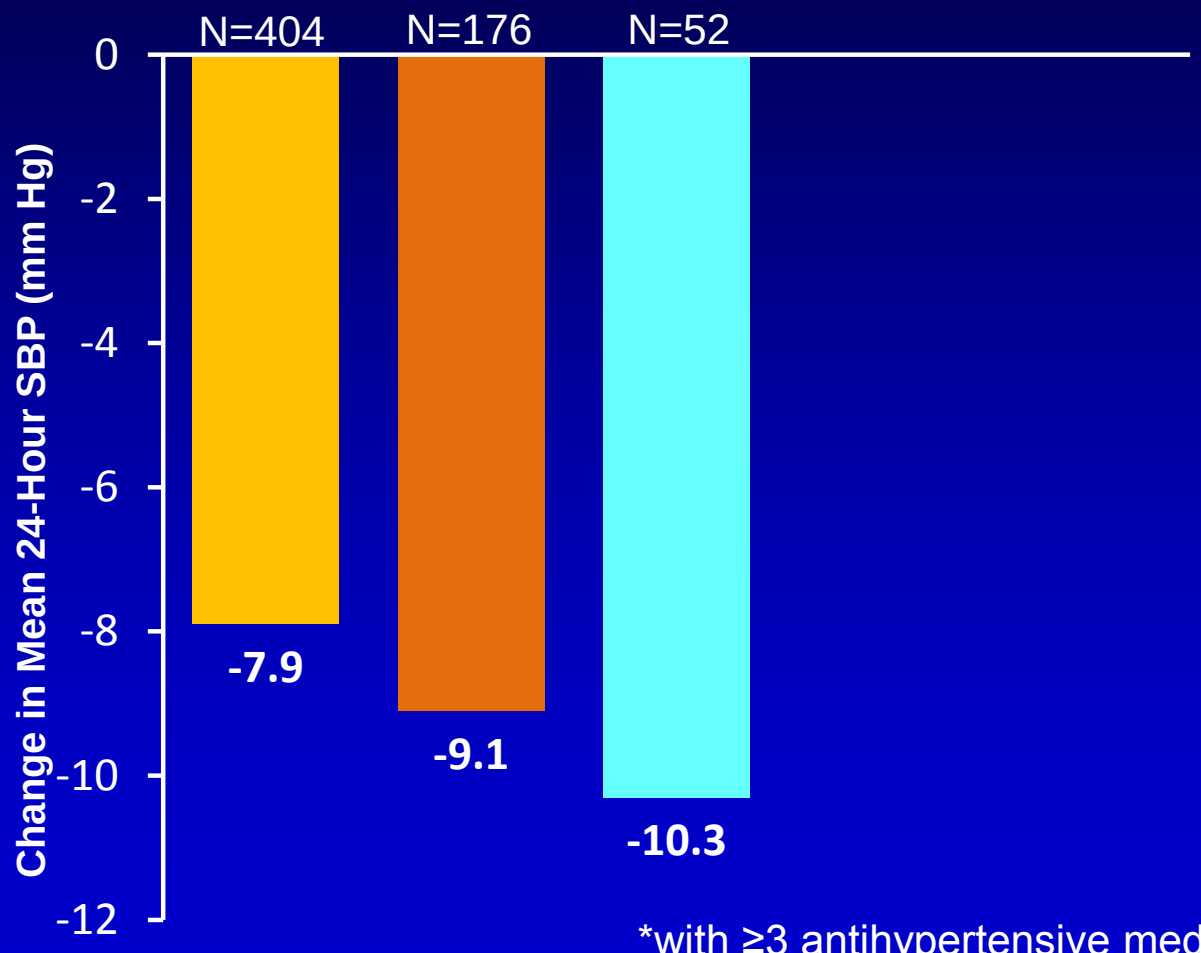
Change in Ambulatory SBP for GSR and SYMPLICITY HTN-3 Patients



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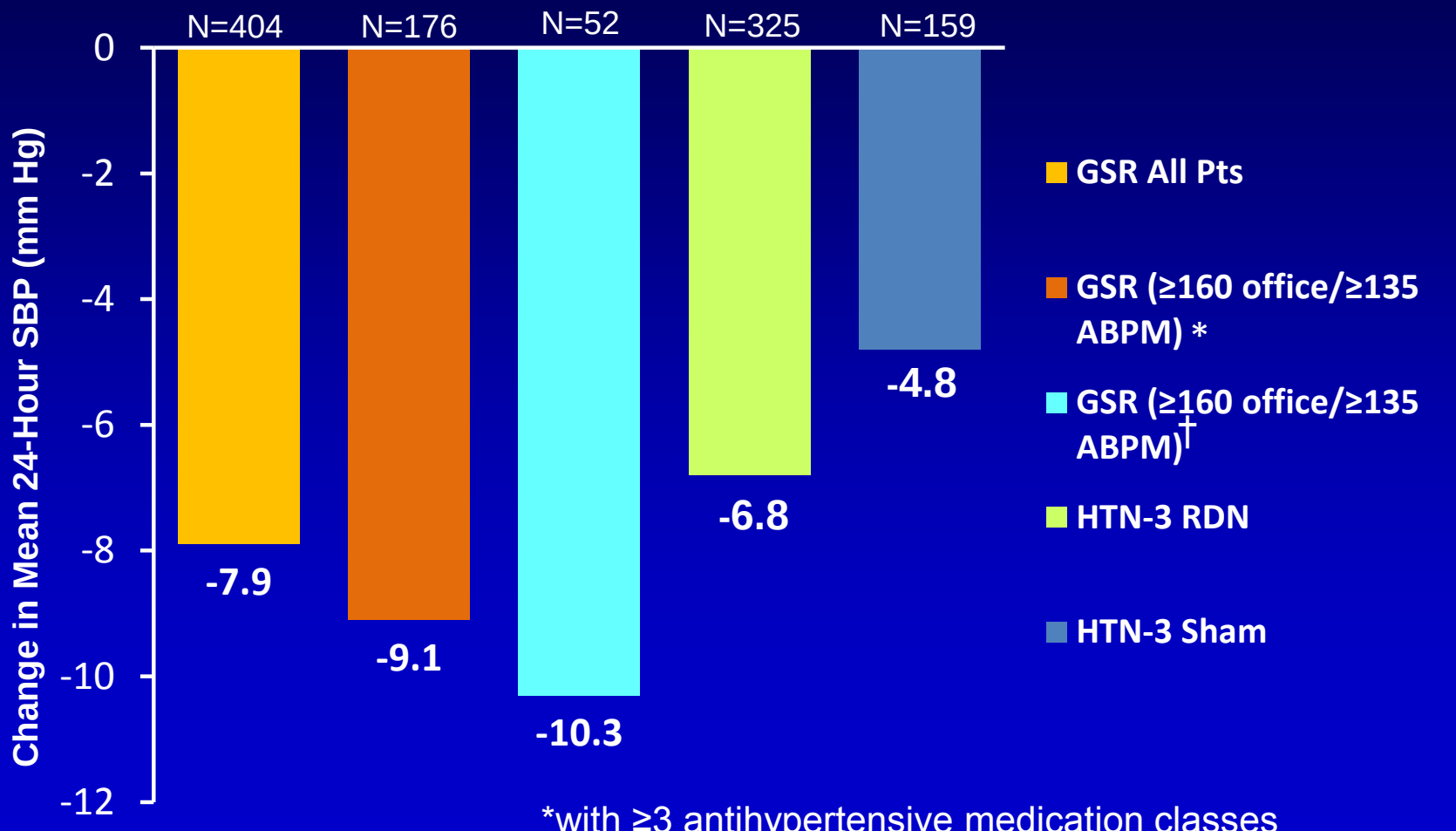
Change in Ambulatory SBP for GSR and SYMPLICITY HTN-3 Patients



*with ≥3 antihypertensive medication classes
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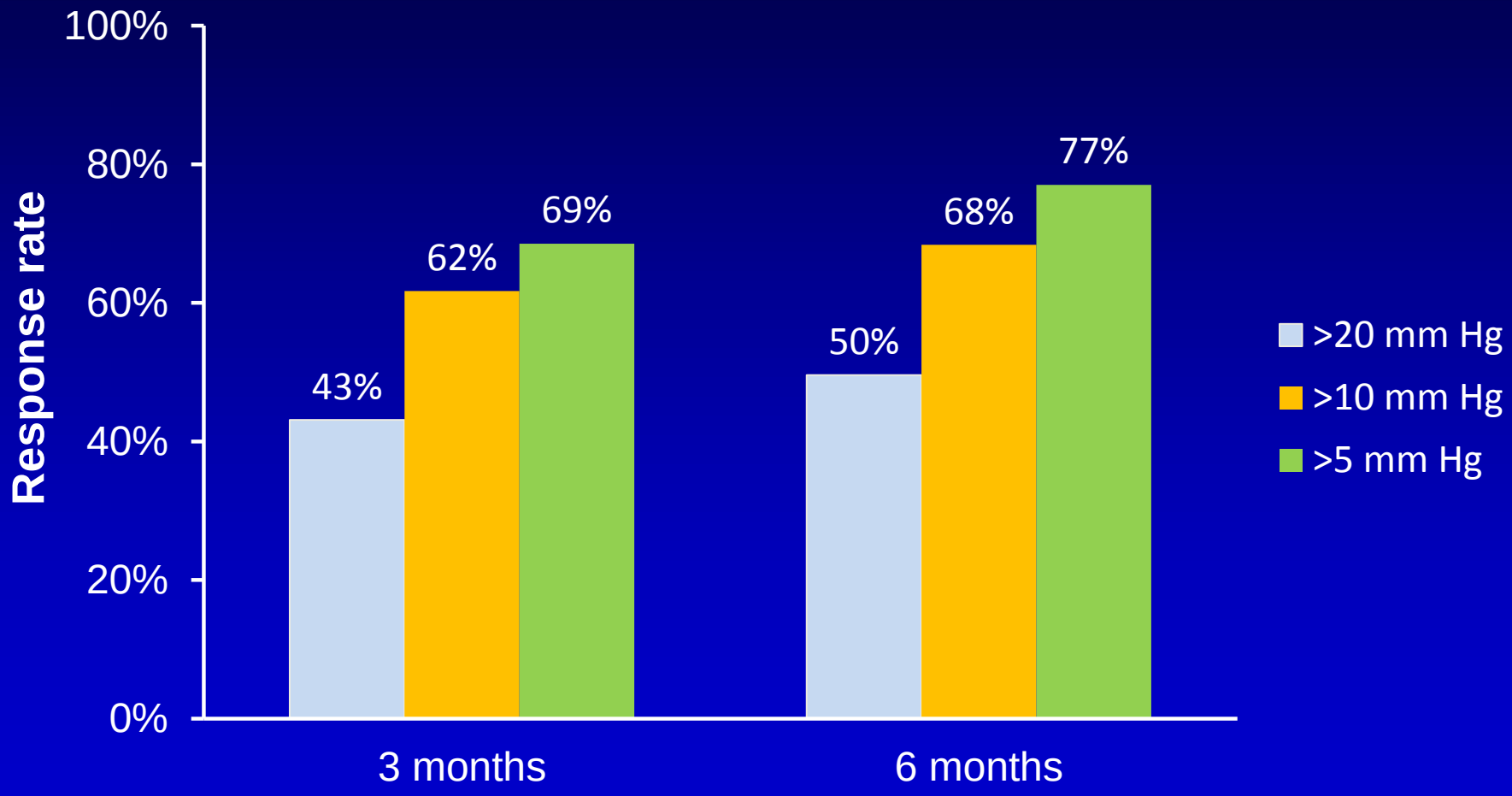
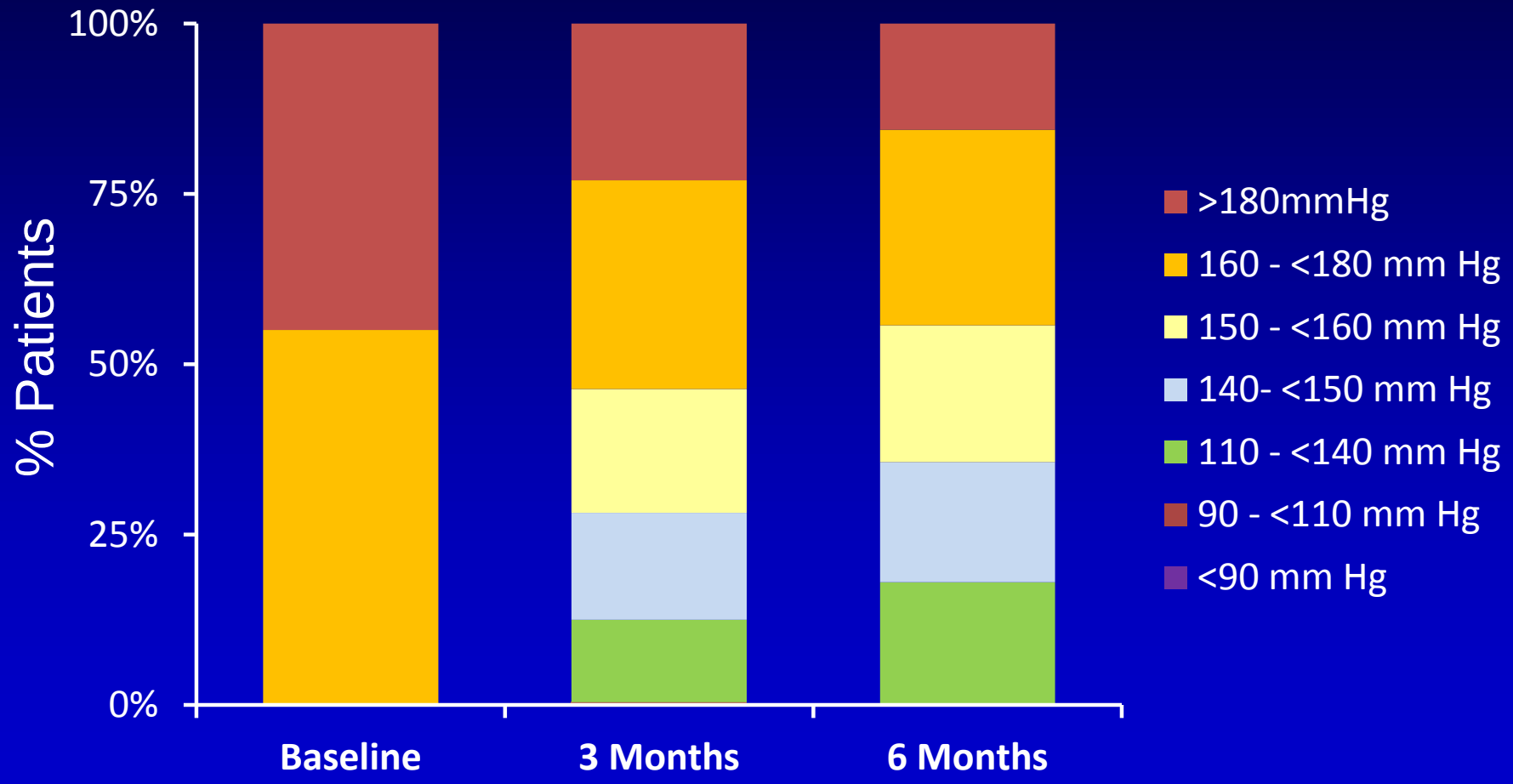
Response Rates* for Patients with Office SBP ≥160 mm Hg / Ambulatory SBP ≥135 mm Hg at Baseline†



*Reduction in mean office SBP of at least 5, 10, or 20 mm Hg
†with ≥3 antihypertensive medication classes

Distribution of SBP in Patients With Office SBP≥160 mm Hg and Ambulatory SBP ≥135 mm Hg* at Baseline



*with ≥3 antihypertensive medication classes

Conclusions

- Excellent procedural and clinical safety profile in the largest dataset of real world RDN patients to date
- Significant reductions in both office and ambulatory BP from baseline
  - Differences with SYMPLICITY HTN-3 include randomization, blinding, sham control, BP inclusion criteria, antihypertensive-drug treatment intensity, and African-American inclusion in HTN-3
  - Despite the limitations of comparing a registry with a randomized, blinded, controlled study, the reduction in blood pressure is numerically larger in the GSR at 6 months after treatment
  - Due to the registry nature of the GSR, it is difficult to account for the magnitude of a possible placebo effect.

Future Research

- Define appropriate treatment populations
  - Key subgroups
  - Optimal BP inclusion criteria
- Interaction with drug treatments
- Time course
- Technical issues
- Operator experience
  - Optimal training and proctoring

Thank you!

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