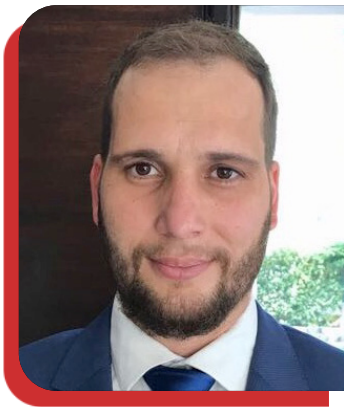
Highlights in Hypertension from the American College of Cardiology's Annual Scientific Session



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New Insight in Renal Denervation: TARGET BP I

The TARGET BP I trial, which employed a novel approach utilizing dehydrated alcohol to deactivate specific nerves surrounding the arteries of the kidneys and manage high blood pressure, was presented. In a pivotal phase 3 trial showcased at the American College of Cardiology's (ACC's) Annual Scientific Session in April 2024, the system successfully achieved its primary endpoint of reducing blood pressure at three months, as measured by a 24-hour ambulatory systolic blood pressure monitor.

This trial marked the largest randomized controlled study to date assessing alcohol-based technology for renal denervation, an innovative approach targeting connections between the kidneys and the nervous system implicated in blood pressure regulation. While the trial yielded positive overall results, it encountered complexities that needed careful navigation.

Researchers randomly assigned 301 participants to receive either renal denervation or a sham procedure. At three months post-procedure, renal denervation led to a notable reduction in 24-hour ambulatory systolic blood pressure compared to the sham group.

Despite observing a statistically significant reduction in the primary endpoint, no significant differences were noted in other measures of blood pressure, including office systolic or diastolic blood pressure. Notably, the sham control group exhibited unexpectedly large reductions in blood pressure, posing a challenge for interpretation (**Figure 1**).

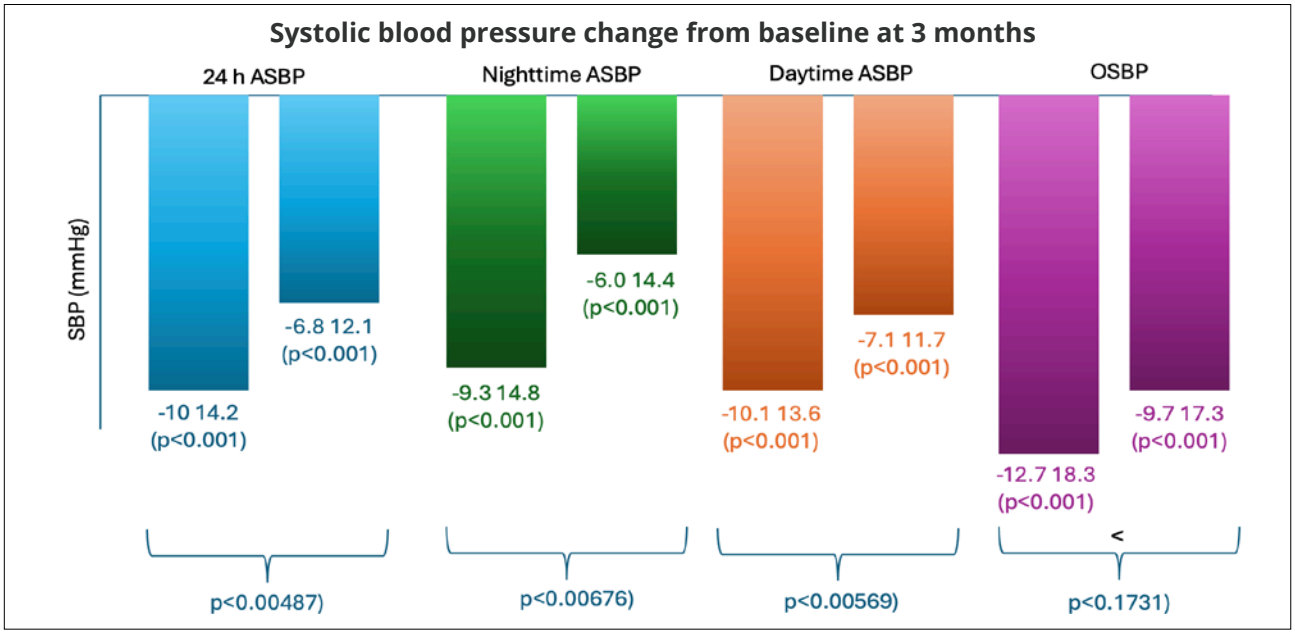


Figure 1: ASBP: Ambulatory Systolic Blood Pressure, OSBP: Office Systolic Blood Pressure
Adapted from Kandzari DE et al, Circulation 2024

The Importance of a Good Rest: Sleep Duration and Hypertension Incidence: Systematic Review and Meta-Analysis

Sleeping fewer than seven hours is associated with a higher risk of developing high blood pressure over time, as reported at the ACC's Annual Scientific Session. While the link between sleep duration and hypertension has been explored, findings have been inconsistent. This analysis consolidated data from 16 studies involving 1,044,035 individuals across six countries, all without prior hypertension history, over a median follow-up of five years. Short sleep duration correlated significantly with increased hypertension risk, even after adjusting for various demographic and cardiovascular factors. The risk was notably higher for those sleeping less than five hours.

Dr. Kaveh Hosseini, from the Tehran Heart Center, emphasized the significance of sleep duration, noting that sleeping fewer than seven hours raised the risk by 7%, spiking to 11% for those with less than five hours of sleep. Interestingly, age did not significantly alter this association, although females showed a higher risk with inadequate sleep. Despite these findings, the study didn't delve into the reasons behind this link, though disrupted sleep patterns due to lifestyle habits or comorbid conditions like sleep apnea could be contributing factors (**Figure 2**).

While the study had limitations, including reliance on self-reported sleep duration and variations in defining short sleep duration, Hosseini suggested future research should employ more accurate methods like polysomnography. Standardizing sleep research definitions could enhance comparability across studies.

The KARDIA-2: The angiotensinogen Silencer Reduces SBP With Just One Injection

The KARDIA-2, phase 2 study revealed promising outcomes regarding the efficacy and safety of zilebesiran, an investigational RNAi therapeutic, as an adjunctive treatment for hypertension. This study evaluated the impact of a single subcutaneous dose of zilebesiran when added to standard antihypertensive medications, including a thiazide-like diuretic (indapamide), calcium channel blocker (amlodipine), or angiotensin receptor blocker (olmesartan), on systolic blood pressure (SBP) reduction.

In a randomized, double-blind, placebo-controlled design, 1500 patients with mild-to-moderate hypertension were enrolled. The average age of

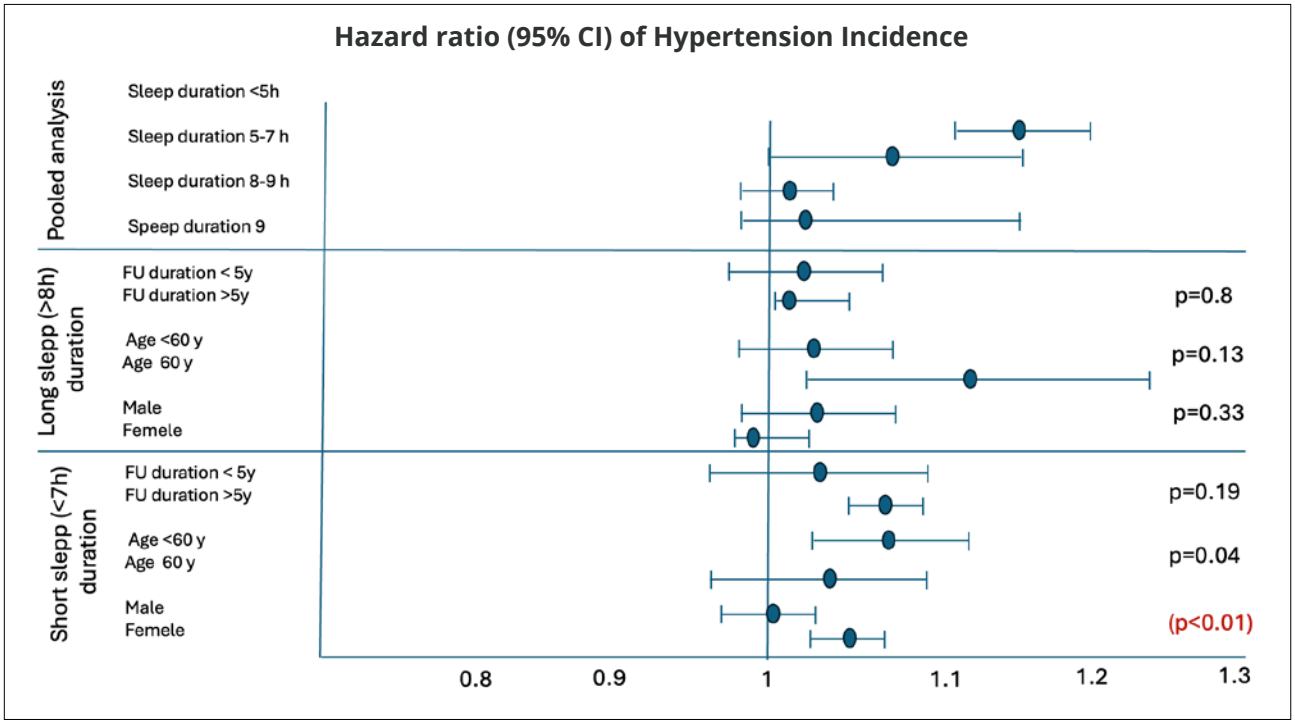


Figure 2: Adapted from Sood A et al. J Am Coll Cardiol. 2024 Apr, 83

Table 1: Adapted from Desai A, American College of Cardiology Annual Scientific Session

Key Endpoint	Indapamide (2.5 mg)	Amlodipine (5 mg)	Olmesartan 40 mg
Primary Endpoint:			
Change from Baseline to Month 3 in 24-Hour Mean SBP, Assessed by ABPM	- 12.1 mmHg (p<0.001)	- 9.7 mmHg (p<0.001)	- 4.0 mmHg (p=0.036)
Key Secondary Endpoints:			
Change from Baseline to Month 3 in Office SBP	- 18.5 mmHg (p<0.001)	- 10.2 mmHg (p<0.001)	- 7.0 mmHg (p<0.001)
Time Adjusted Change from Baseline Through Month 6 in 24-Hour Mean SBP, Assessed by ABPM	- 11.0 mmHg (p<0.001)	- 7.9 mmHg (p<0.001)	- 1.6 mmHg (p=0.26)
Time Adjusted Change from Baseline Through Month 6 in Office SBP	- 13.6 mmHg (p<0.001)	- 8.6 mmHg (p<0.001)	- 4.6 mmHg (p<0.001)

the participants was 59 years, with 43% being women and 28% identifying as Black. Most patients were initially taking one or two antihypertensive medications. The study commenced with a run-in period where patients received open-label therapy with one of the specified background antihypertensive medications for at least four weeks. Following this period, patients with elevated SBP levels, despite adherence to their medication regimen, were randomized to receive either zilebesiran 600 mg or placebo in addition to their standard antihypertensive medication for six months.

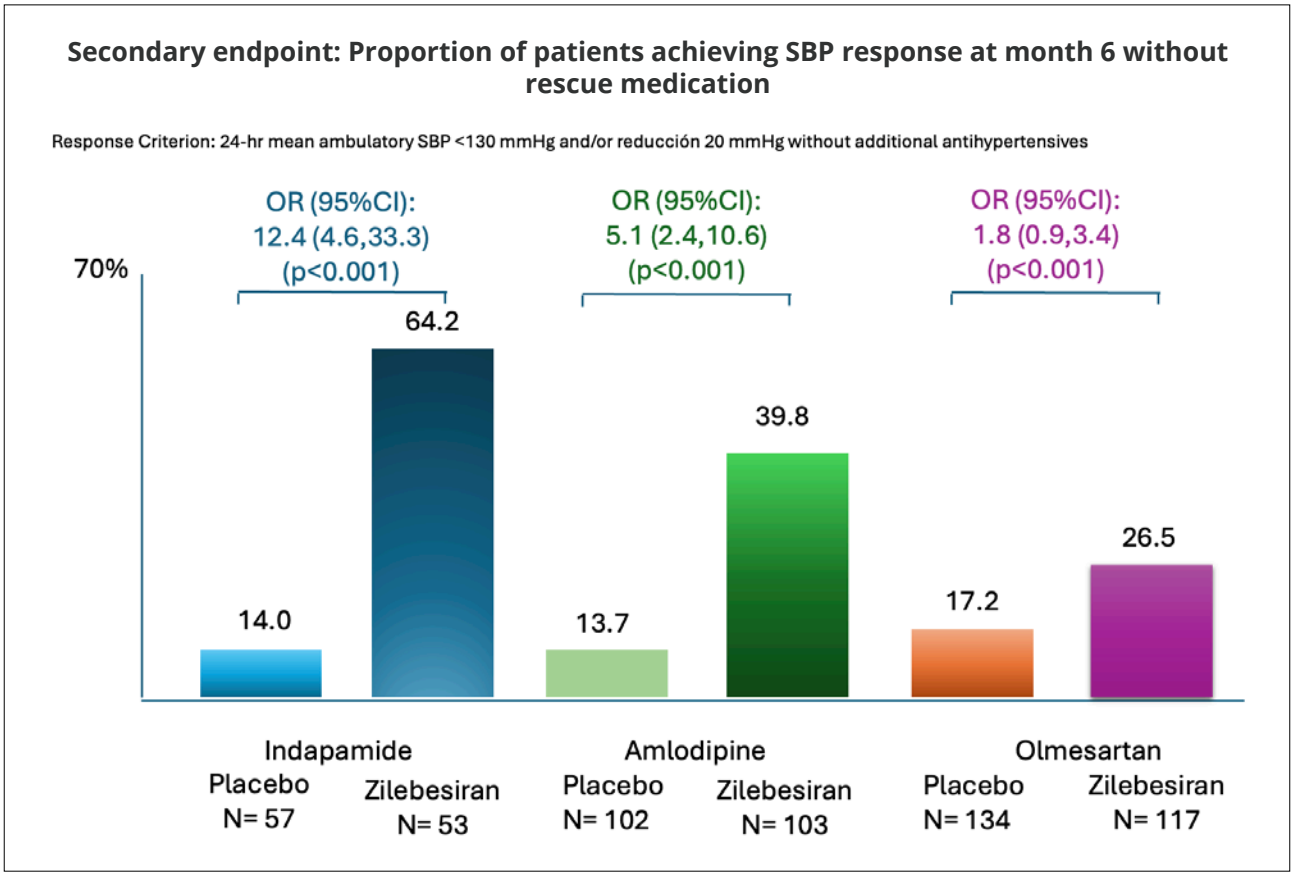
At three months, zilebesiran demonstrated statistically significant and clinically relevant reductions in 24-hour mean SBP when added to all three classes of background antihypertensive medications. The average placebo-adjusted reductions in 24-hour mean SBP were up to 12.1 mmHg with indapamide, 9.7 mmHg with amlodipine, and 4 mmHg with olmesartan, as measured by ambulatory blood pressure monitoring (ABPM). Moreover, zilebesiran consistently lowered office SBP across all cohorts, with reductions of 18.5 mmHg, 10.2 mmHg, and 7.0 mmHg for indapamide, amlodipine, and olmesartan, respectively (**see Table 1**).

The positive effects of zilebesiran on SBP persisted through the six-month duration of the study, indicating sustained efficacy. Even after the addition of rescue antihypertensive medications at three months, zilebesiran maintained its ability to reduce SBP, which suggests its potency in achieving blood pressure control. Importantly, zilebesiran exhibited an acceptable safety and tolerability profile, with no significant safety concerns observed. Most laboratory abnormalities were mild and reversible, and no adverse events led to study discontinuation during the six-month double-blind period (**Figure 3**).

Dr. Akshay Desai, Director of the Cardiomyopathy and Heart Failure Program at Brigham and Women's Hospital, emphasized the potential of zilebesiran in addressing the unmet needs in hypertension management. He highlighted the importance of reducing the pill burden and improving adherence, especially in patients with inadequate blood pressure control. The findings from the KARDIA-2 study underscore the potential of zilebesiran as a transformative approach to hypertension treatment, offering the possibility of consistent and durable blood pressure reduction with infrequent dosing.

The results from the KARDIA-2 study are encouraging and provide valuable insights into the efficacy and safety of zilebesiran as an adjunctive therapy for hypertension. Further research, including ongoing studies like KARDIA-3, will be essential to confirm the long-term efficacy and safety of zilebesiran, particularly in high-risk

Figure 3: Adapted of Desai A, American College of Cardiology Annual Scientific Session



patient populations. If proven effective in larger populations, zilebesiran could revolutionize the management of hypertension and improve cardiovascular outcomes for patients worldwide.

References

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