ZILEBESIRAN

An Investigational RNAi Therapeutic for Patients with Hypertension and High Cardiovascular Risk

September 17, 2026

Alnylam Forward-Looking Statements

This presentation contains forward-looking statements. Forward looking statements include statements regarding Alnylam's expectations, beliefs, goals, plans or prospects including, without limitation, statements regarding: the efficacy or safety of zilebesiran for treatment of hypertension or any other indication; the potential product profile of zilebesiran, including its potential to support nighttime dipping, time in target blood pressure range, and reductions in biomarkers of CV and renal risk; the potential for zilebesiran to achieve continuous control of blood pressure with infrequent dosing and to improve outcomes in patients with hypertension; the number of patients who will be enrolled in the ZENITH Phase 3 clinical trial; the potential for the ZENITH Phase 3 clinical trial to read out successfully and to support a commercial launch of zilebesiran and adoption by providers, patients and payers; the rates of hypertension, CV disease burden and CV mortality, and the associated economic burden of hypertension, at any point in the future; the potential attributes of RNAi medicines and Alnylam's ability to build a portfolio of RNAi therapeutics with transformational patient impact; and the timing of the initiation of, or data readout from, any of Alnylam's clinical trials, and the potential for, and timing of, any product launches.

Actual results and future plans may differ materially from those indicated by these forward-looking statements as a result of various important risks, uncertainties and other factors, including, without limitation, risks and uncertainties relating to: Alnylam's ability to successfully execute on its *Alnylam 2030* strategy; Alnylam's ability to successfully launch, market and sell Alnylam's approved products globally; Alnylam's ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of its product candidates; the pre-clinical and clinical results for Alnylam's product candidates; actions or advice of regulatory agencies and Alnylam's ability to obtain and maintain regulatory approval for its product candidates, as well as favorable pricing and reimbursement; delays, interruptions or failures in the manufacture and supply of Alnylam's marketed products or its product candidates; obtaining, maintaining and protecting intellectual property; Alnylam's ability to manage its growth and operating expenses through disciplined investment in operations; Alnylam's ability to maintain strategic business collaborations; Alnylam's dependence on third parties for the development and commercialization of certain products; the outcome of litigation and government investigations; the risk of future litigation and government investigations; and unexpected expenditures; as well as those risks and uncertainties more fully discussed in the "Risk Factors" filed with Alnylam's most recent periodic report (Quarterly Report on Form10-Q or Annual Report on Form 10-K) filed with the SEC and in its other SEC filings. Alnylam explicitly disclaims any obligation, except to the extent required by law, to update any forward-looking statements.

RNAi 2026 ROUNDTABLES

Agenda

01	Introduction	**Pushkal Garg, M.D.** *Chief Research & Development Officer*
02	Hypertension: The Threat Beyond the Office	**Akshay S Desai, M.D., MPH** *Harvard Medical School* *Mass General Brigham*
03	The Potential for Continuous Control with Zilebesiran	**Ishir Bhan, M.D., MPH** *Executive Director, ZENITH Clinical Lead*
04	Realizing the Opportunity	**Simon Fox, Ph.D.** *Vice President, Zilebesiran Program Lead*
05	Q&A Session	

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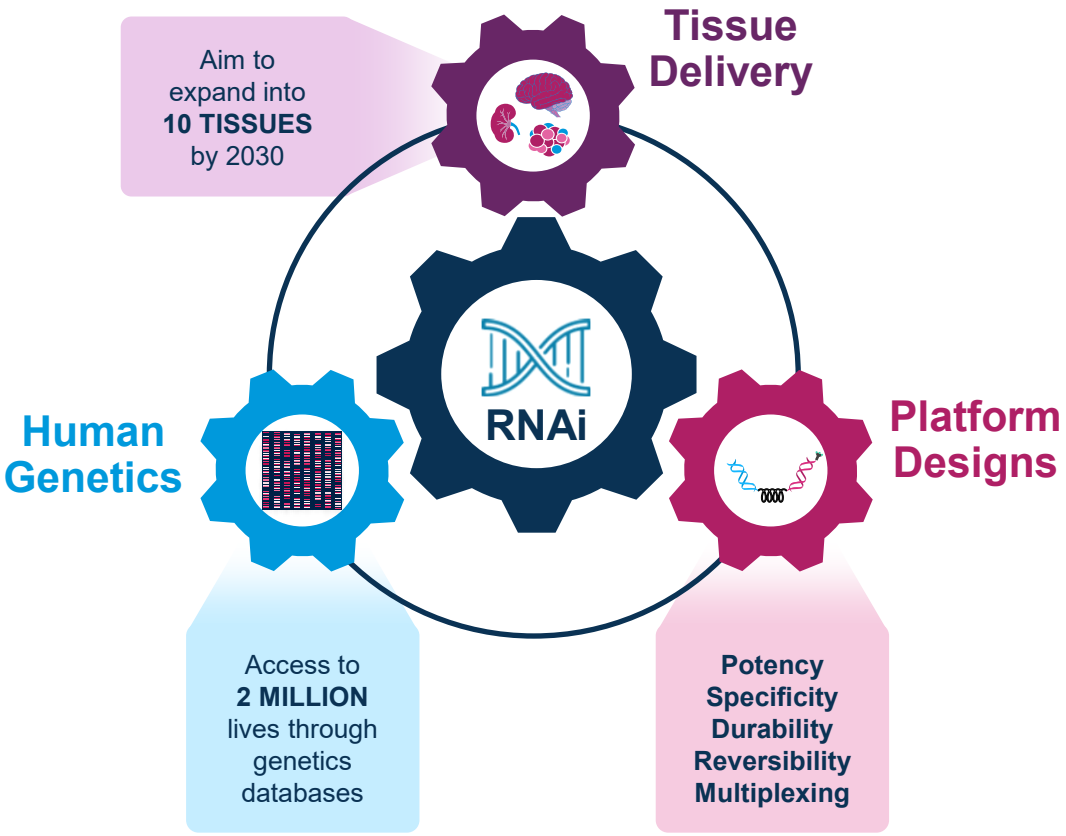
Pioneering a Generational Class of RNAi Medicines

- Silence *any* gene in genome
- Upstream of today's medicines
- Catalytic mechanism
- Highly potent
- Highly specific and reversible
- Infrequent administration

Building a Portfolio of RNAi Therapeutics with Transformational Patient Impact

Disciplined R&D Maximizes the Transformative Potential of RNAi

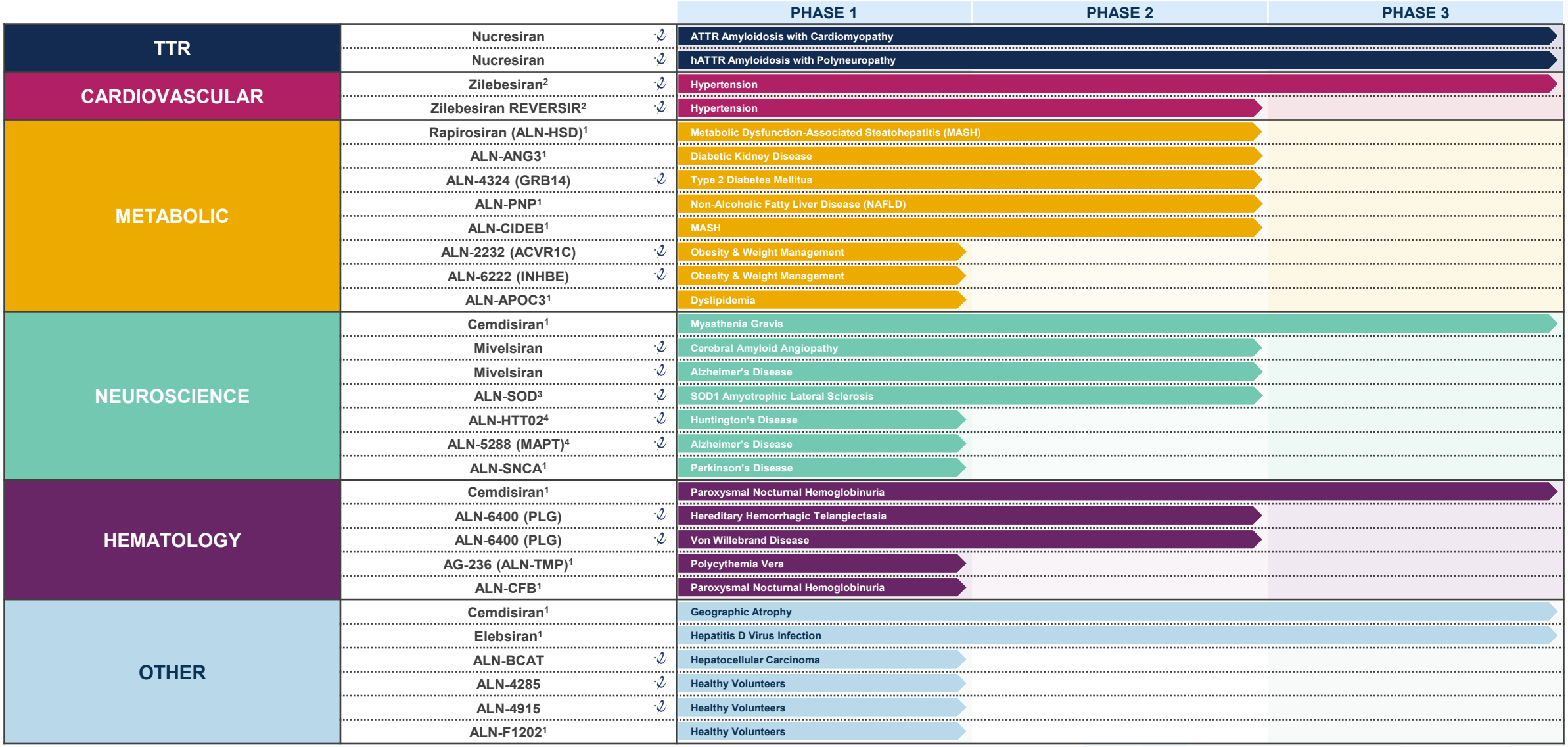
SUSTAINABLE INNOVATION ENGINE



STRATEGIC PRINCIPLES

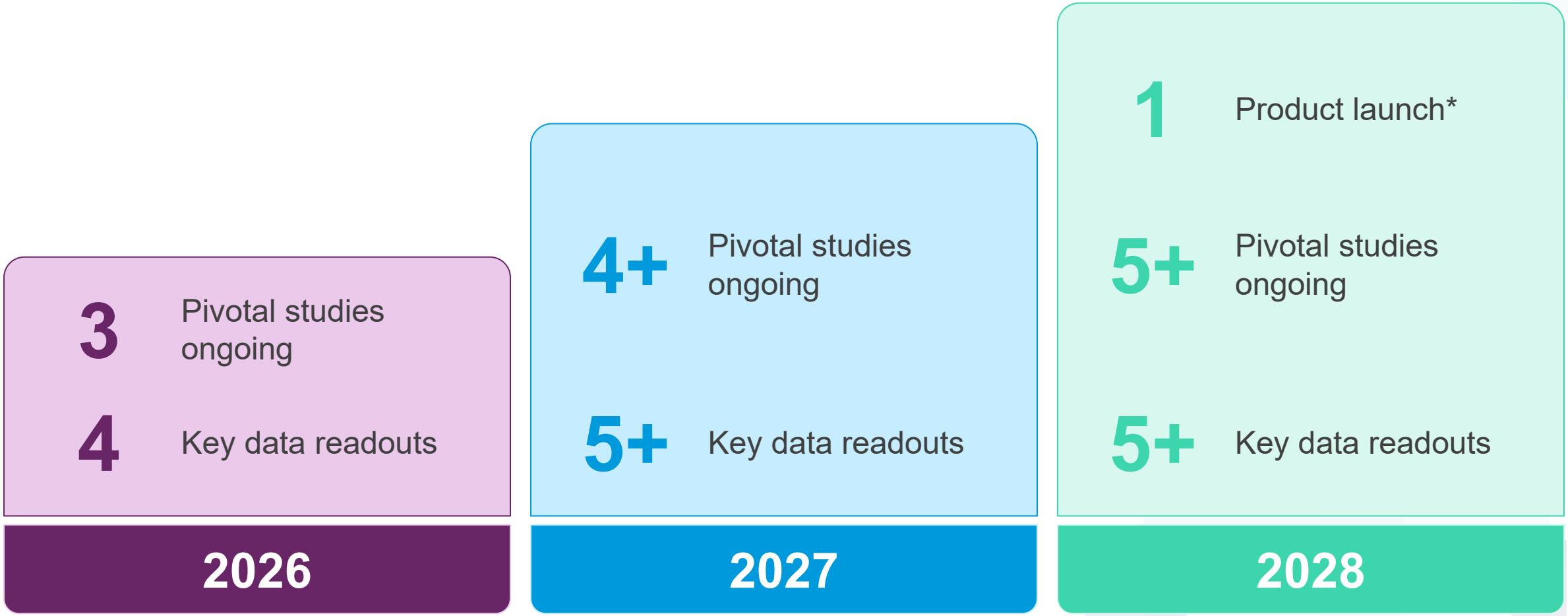
- **Address diseases with high morbidity & mortality**
- **Pursue high conviction targets**
  Strong biologic rationale, informed by human genetics
- **Potential to halt or reverse disease, & be best-in-class**
- **Drive to clear clinical proof-of-concept**
- **Encouraging market opportunity & access dynamics**

Industry Leading Pipeline of RNAi Therapeutics



[1] Out-licensed with milestones and/or royalties; [2] Partnered, Alnylam-led development with U.S. profit split and milestones/royalties ex-U.S.; [3] Partner-led with profit split; [4] Partnered, Alnylam-led with profit split; Alnylam-owned, -led, or –co-developed

Expect Significant Clinical Milestones Over the Next Two Years



** Assuming positive phase 3 data and regulatory approval*

Extending Our RNAi Leadership Across Major Drivers of Cardiovascular Disease

Addressing Major Determinants of Cardiovascular Morbidity and Mortality

Cardiovascular | Metabolic | TTR

Early Development	Late-Stage Development	Commercial
Obesity & Weight Management ALN-2232 • ALN-6222	**Hypertension** zilebesiran	amvuttra (vutrisiran) **ATTR Cardiomyopathy**
Type 2 Diabetes ALN-4324	**ATTR Cardiomyopathy** nucresiran	LEQVIO (inclisiran) **Hypercholesterolemia**

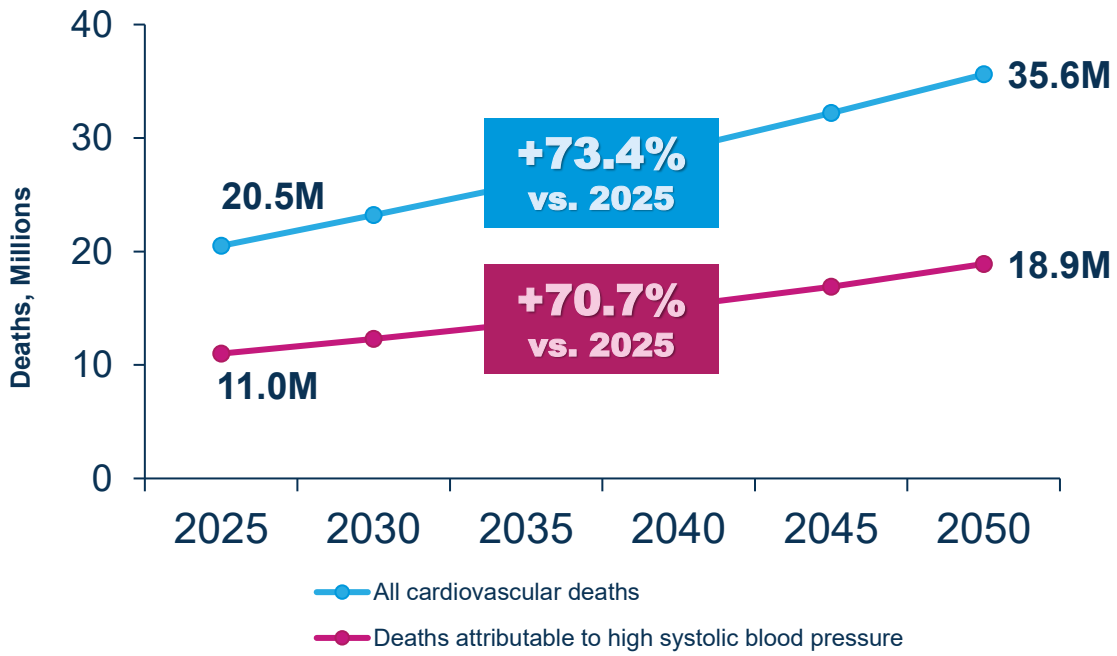
Redefining cardiovascular care

Targeting underlying drivers of disease to improve outcomes and reduce CV burden

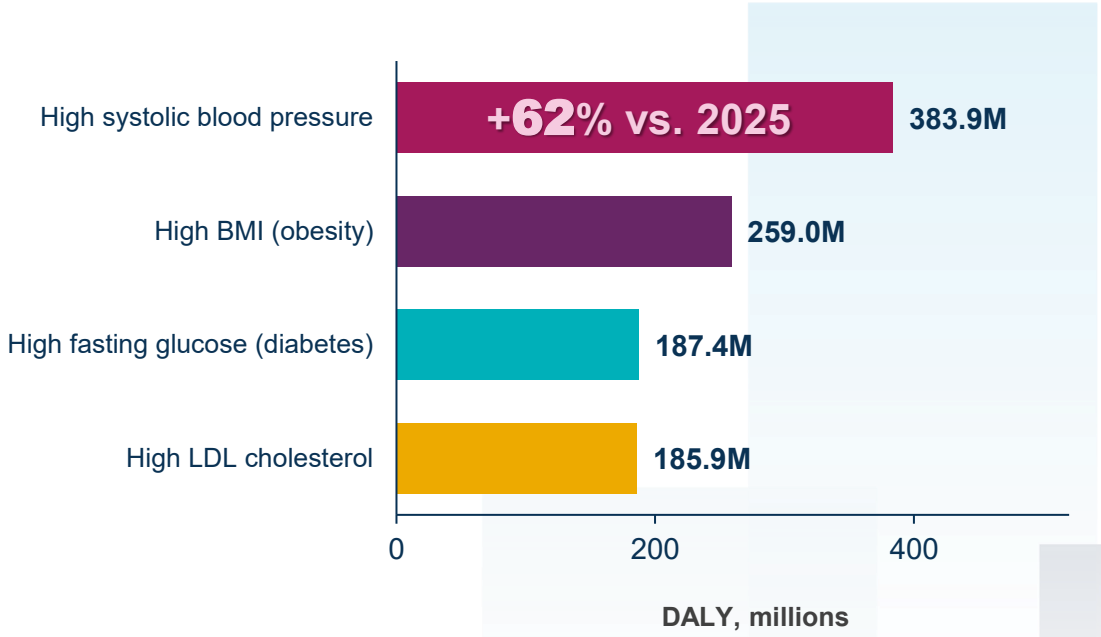
Cardiovascular Deaths Will Rise Through 2050 – Hypertension Remains the Leading Risk Factor

Cardiovascular Disease Burden Attributable to High Systolic Blood Pressure is Projected to Exceed that of Obesity, Diabetes, and High LDL Cholesterol by 2050

CV MORTALITY[1]



CVD BURDEN BY RISK FACTOR in 2050[2]



Disability-adjusted life year: one year of healthy life lost, combining years of life lost to premature death with years lived with disability.

1: Chong et al. European Journal of Preventive Cardiology (2025) 32, 1001-1015 (GBD 2019 based)

2: Supplementary Table 5 and Supplementary Table 19. Intermediate years interpolated between the published 2025 and 2050 estimates // Right: Supplementary Table 19 and Supplementary Table 20

CV, cardiovascular; CVD, cardiovascular disease; BMI, body mass index; LDL, low-density lipoprotein

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Hypertension: The Threat Beyond the Office

Akshay S. Desai MD, MPH

Director, HF Population Health

Mass General Brigham

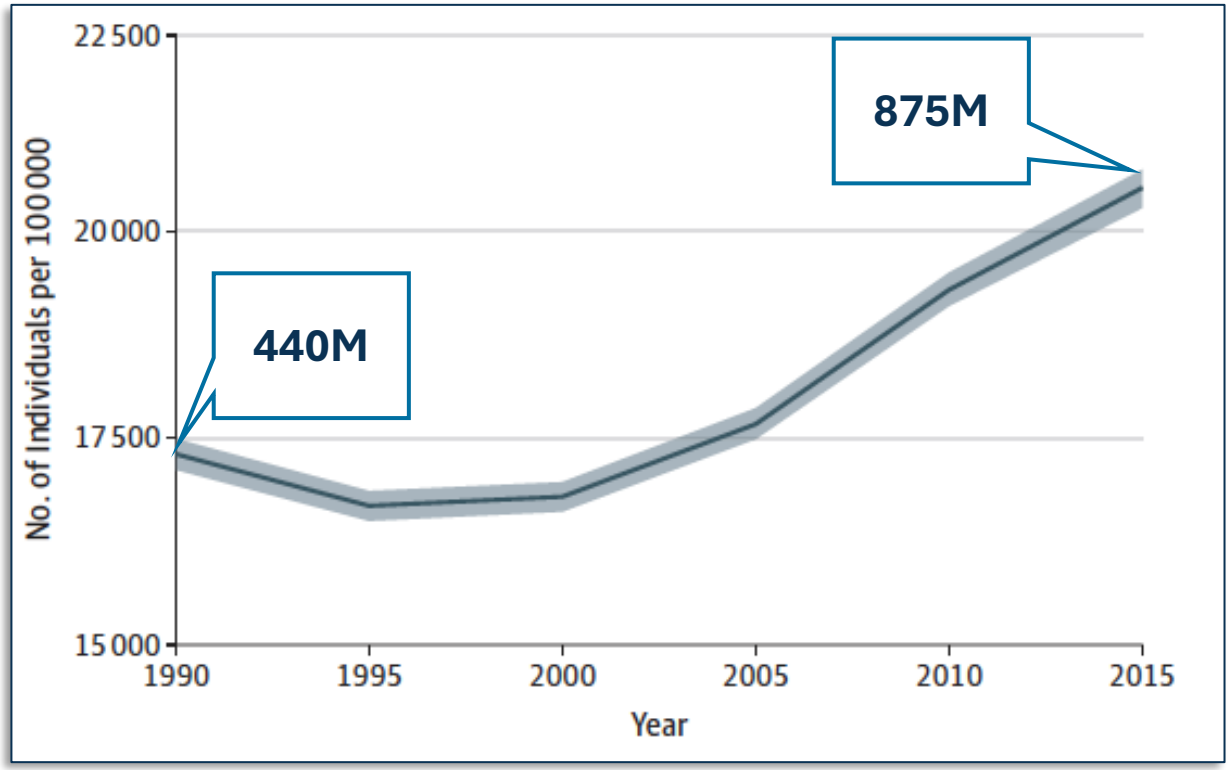
Professor of Medicine

Harvard Medical School

Boston, MA

Hypertension Remains a Global Health Priority

Global burden of Hypertension, 1990-2015

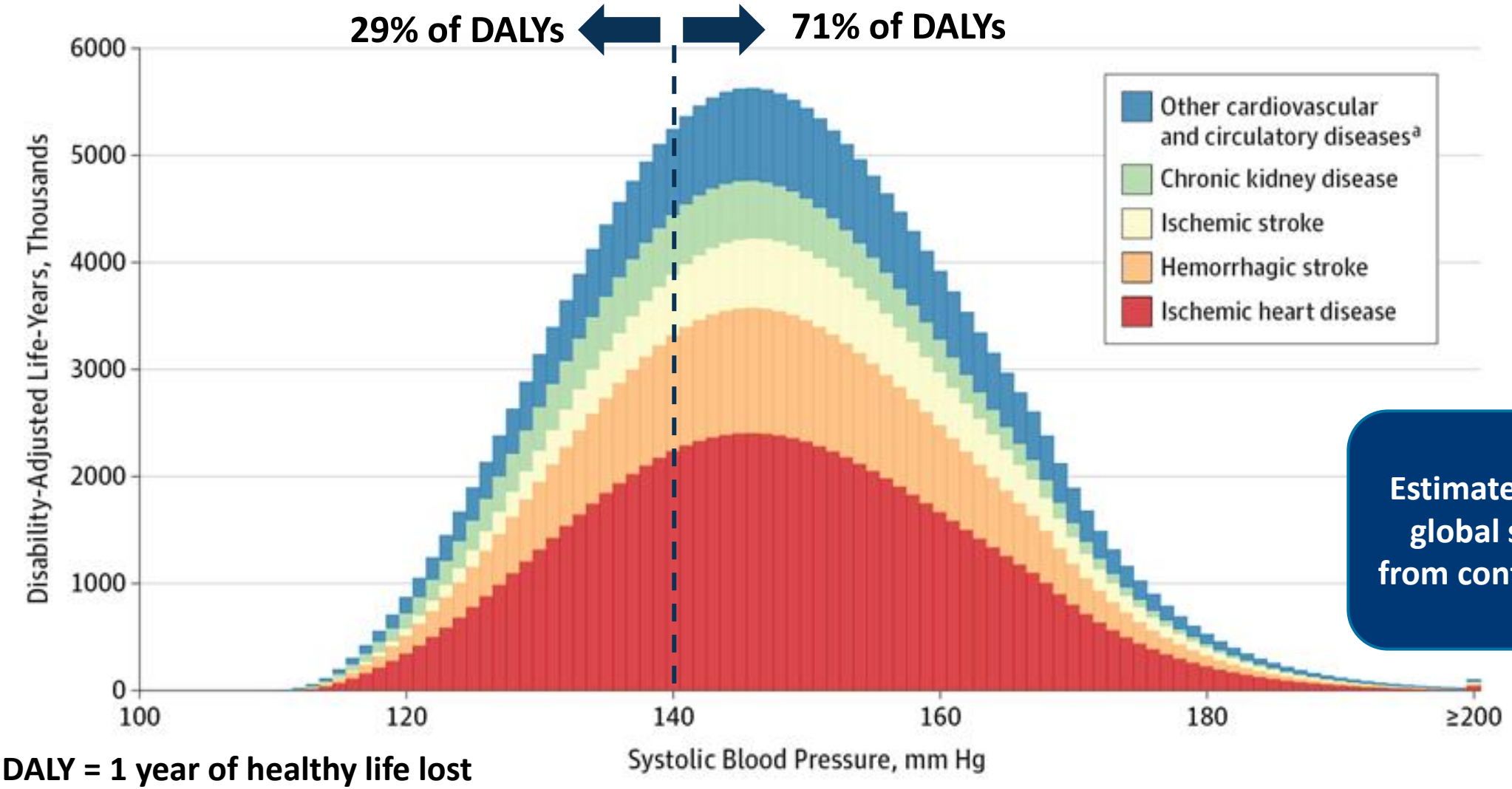


- **> 1 billion with SBP>140 mm Hg**
- **Prevalence rising with aging, obesity**
- **Leading risk factor for CVD and DALY worldwide**
- **10% of global health care expenditure**

Fourouzanfar MD, et al. JAMA. 2017;317(2):165-182

Gaziano T, et al J Hypertens 2009; 27(7):1472-7.

Disability-Adjusted Life Years by SBP and Cause

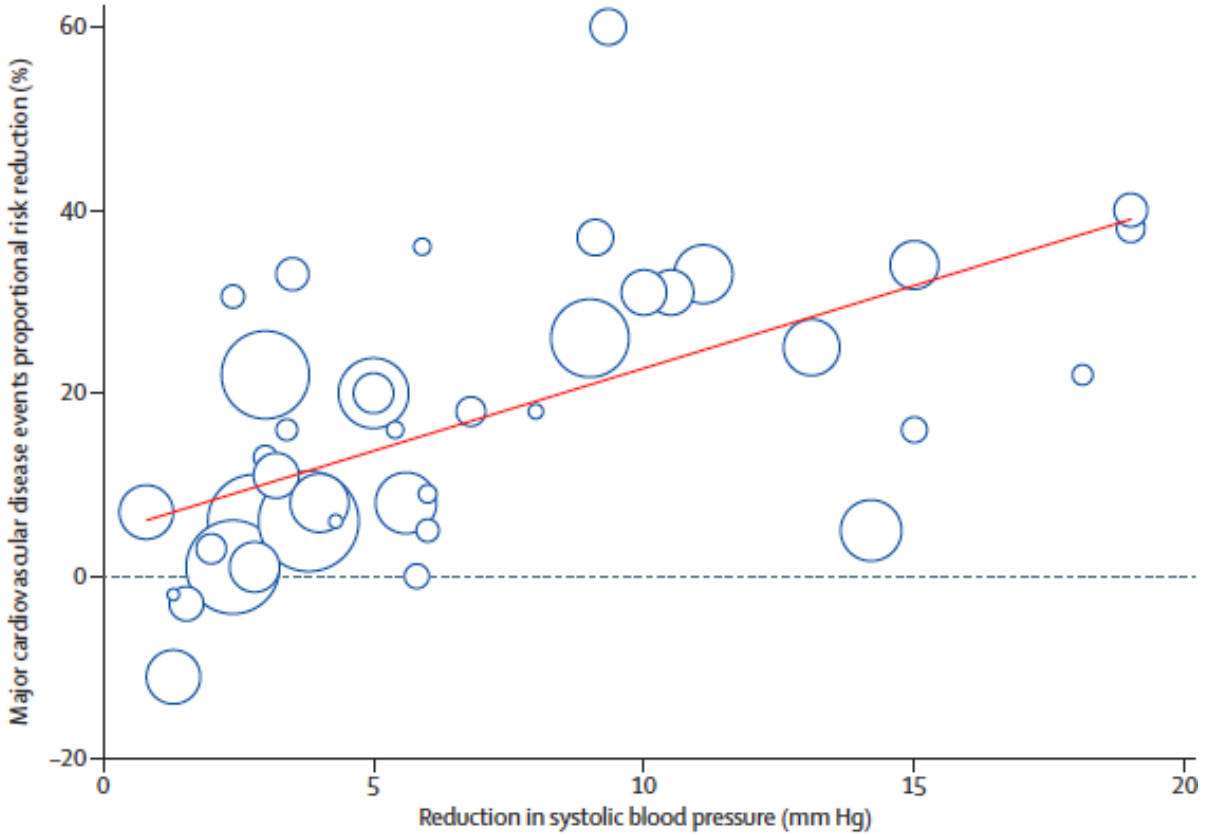


Estimated $100B global savings from control of BP

*1 DALY = 1 year of healthy life lost

Fourouzanfar MD, et al. JAMA. 2017;317(2):165-182

CV Risk is Lower With Effective BP Reduction



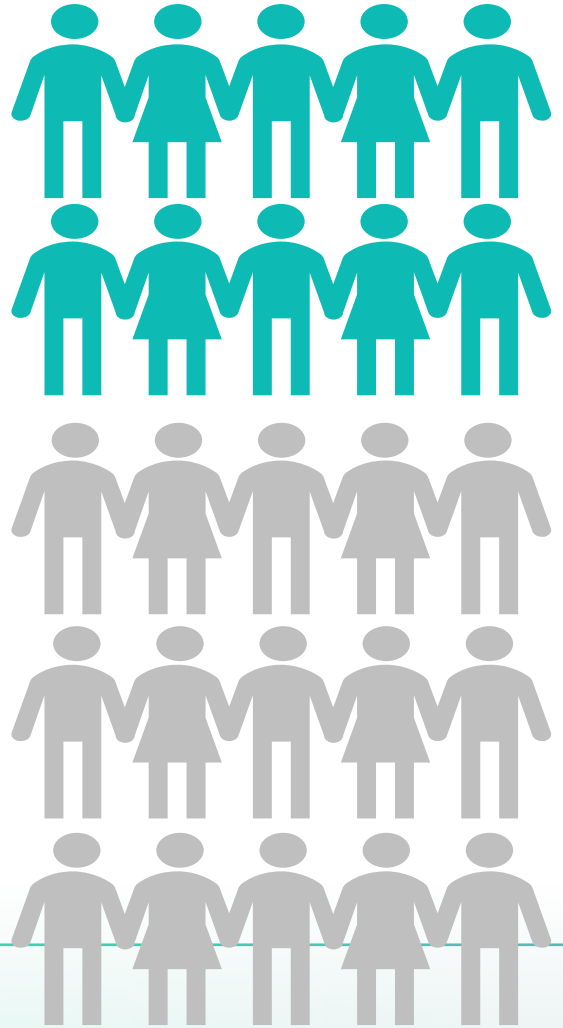
Meta-analysis of 123 studies, 613815 patients

	Risk reduction per 10 mm Hg decrease in SBP
Major CV Events	20%
CHD	17%
Stroke	27%
HF	28%
Renal Failure	5%
All cause mortality	13%

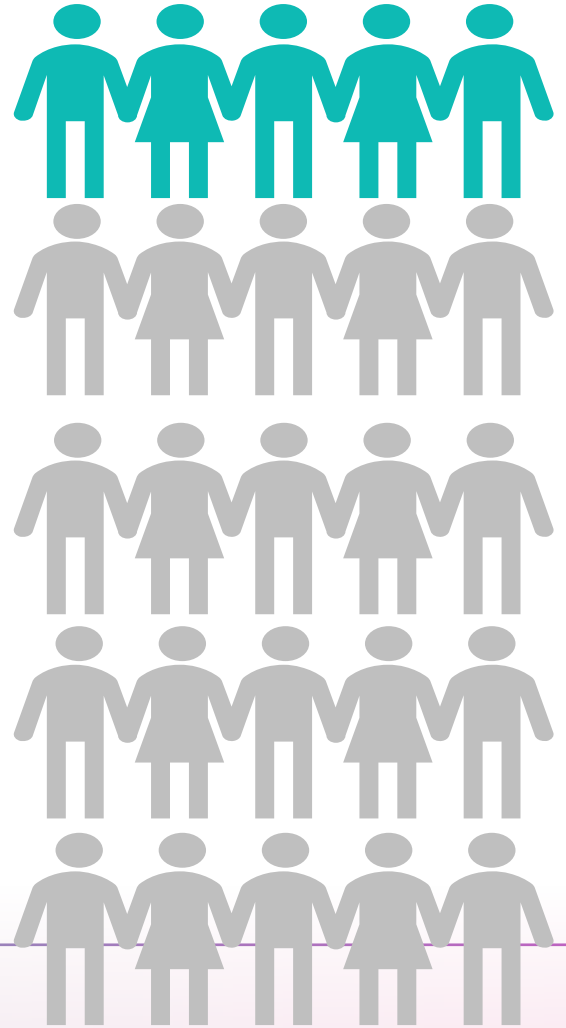
Ettehad D, et al. Lancet 2016; 387: 957–67

A Large Implementation Gap

BP Treatment (~40%)

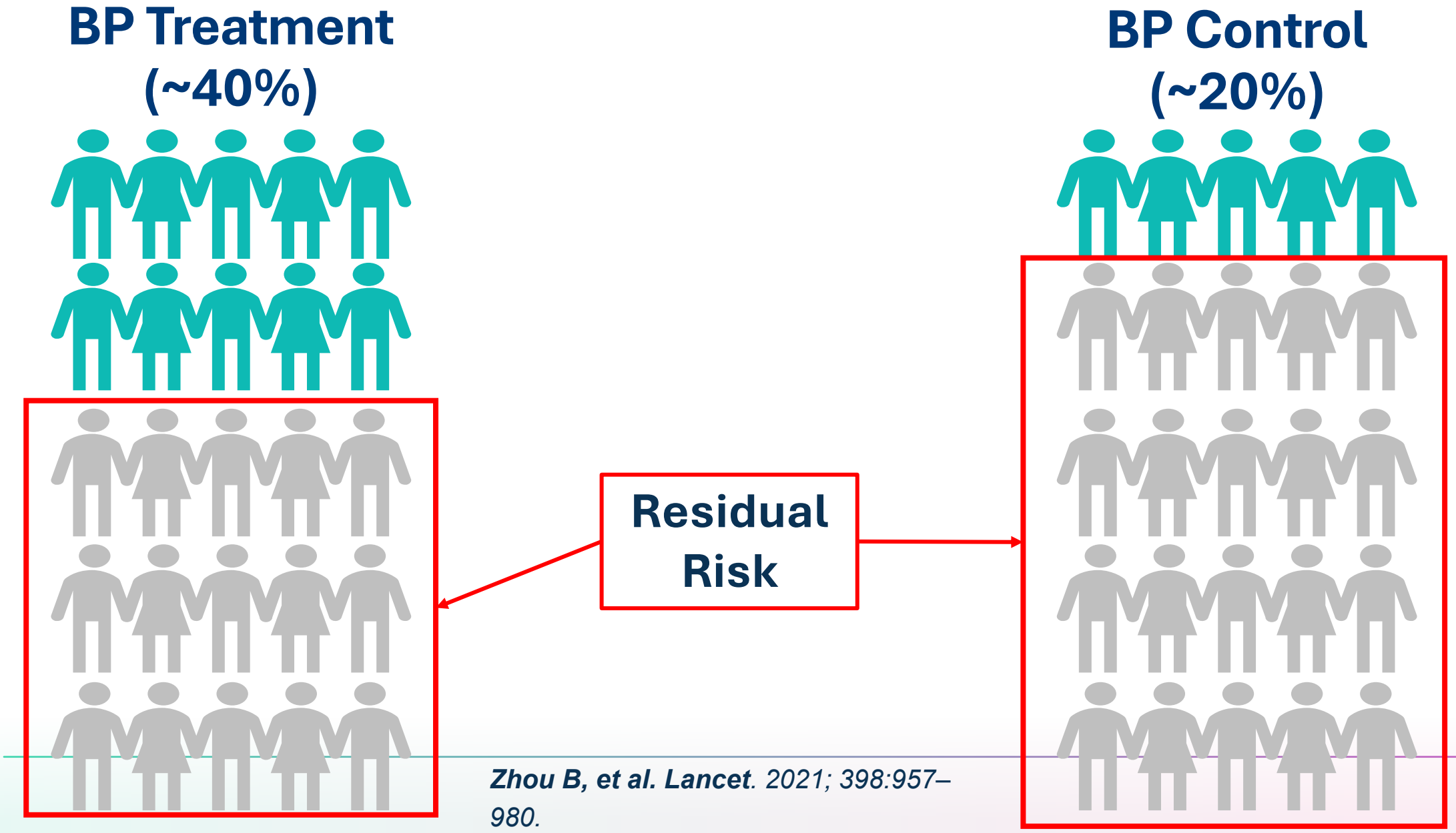


BP Control (~20%)



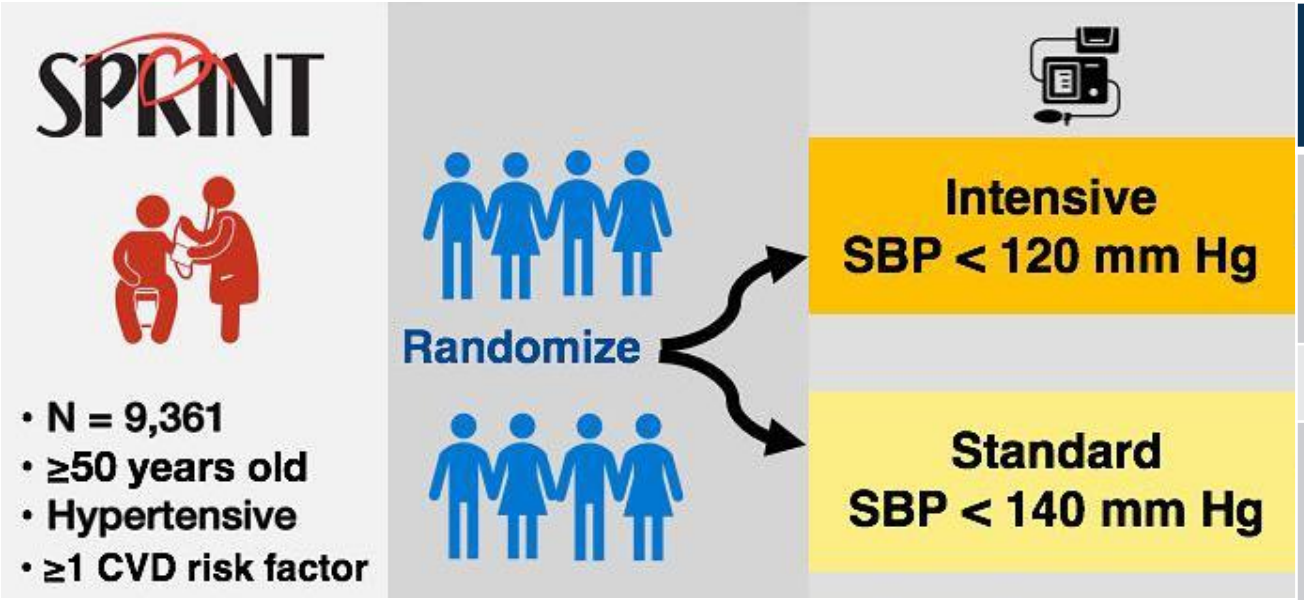
Zhou B, et al. Lancet. 2021; 398:957–980.

A Large Implementation Gap



Zhou B, et al. Lancet. 2021; 398:957–980.

SPRINT: Intensive vs. Standard BP Control



	EFFICACY		SAFETY	
	Primary Outcome**	Mortality	Hypotension	AKI
Intensive SBP < 120 mm Hg	5.2%	3.3%	3.4%	4.4%
Standard SBP < 140 mm Hg	6.8%	4.5%	2.0%	2.6%
	HR 0.75*	HR 0.73*	HR 1.7*	HR 1.7*

*p<0.001
**MI, ACS, Stroke, HF, or CV Death

- **Terminated early for overwhelming benefit at median follow up of 3.26 yrs**
- **Mean SBP 122 mm Hg vs. 135 mm Hg**
- **Mean 2.8 vs. 1.8 antihypertensives**

SPRINT Research Group. N Engl J Med 2015; 373:2103-2116

2025 Hypertension Guideline Set Even Lower Targets for BP

Blood Pressure Category	SBP		DBP
Normal	< 120 mmHg	and	< 80 mmHg
Elevated	120 to 129 mmHg	and	< 80 mmHg
Stage 1 Hypertension	130 to 139 mmHg	or	80 to 89 mmHg
Stage 2 Hypertension	≥ 140 mmHg	or	≥ 90 mmHg

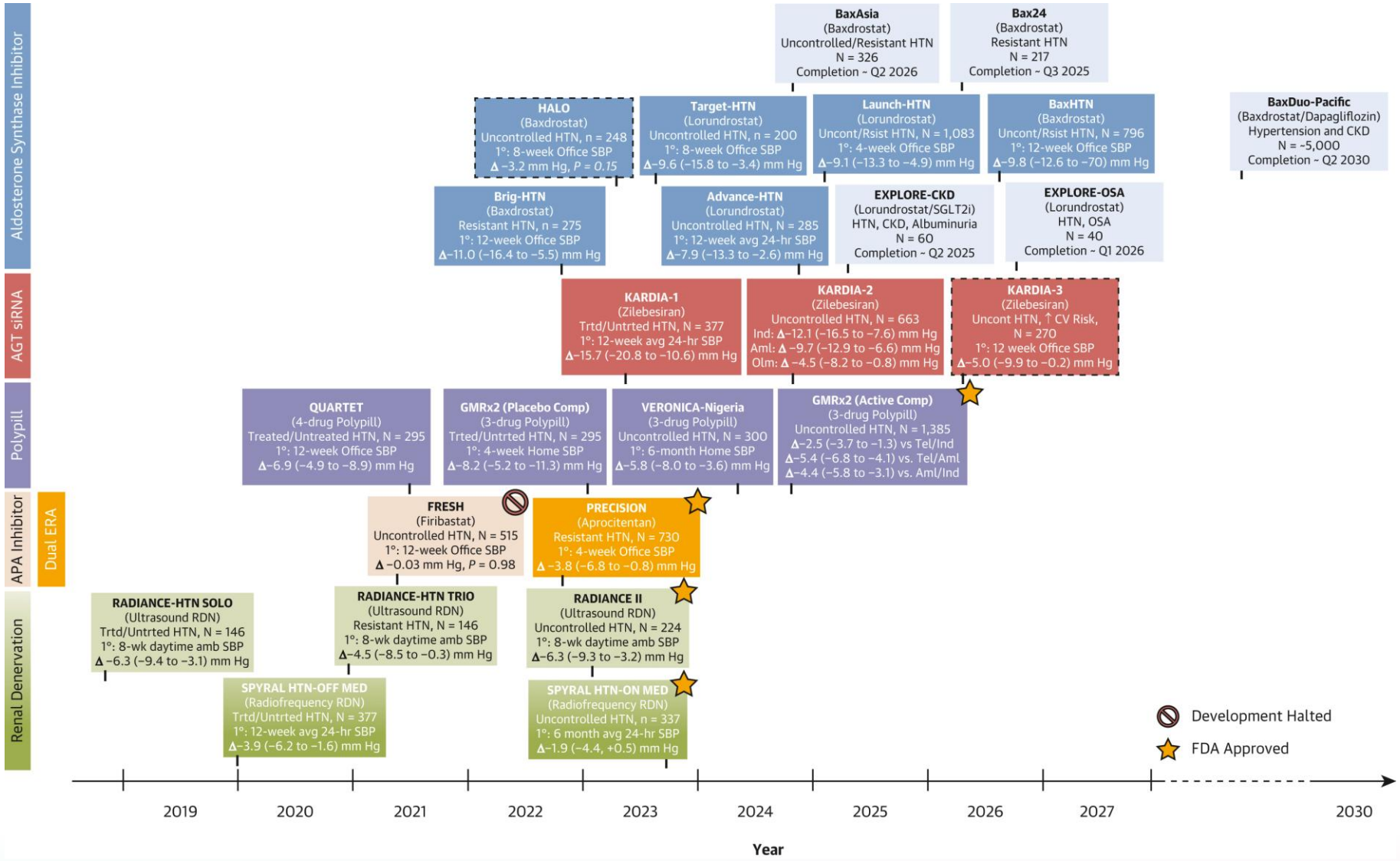
American Heart Association.

AMERICAN COLLEGE of CARDIOLOGY®

Overarching blood pressure treatment goal is <130/80 mm Hg for all adults

Jones D, et al. Circulation. Published online August 14, 2025. doi: 10.1161/CIR.0000000000001356

Therapeutic Options for Hypertension are Expanding



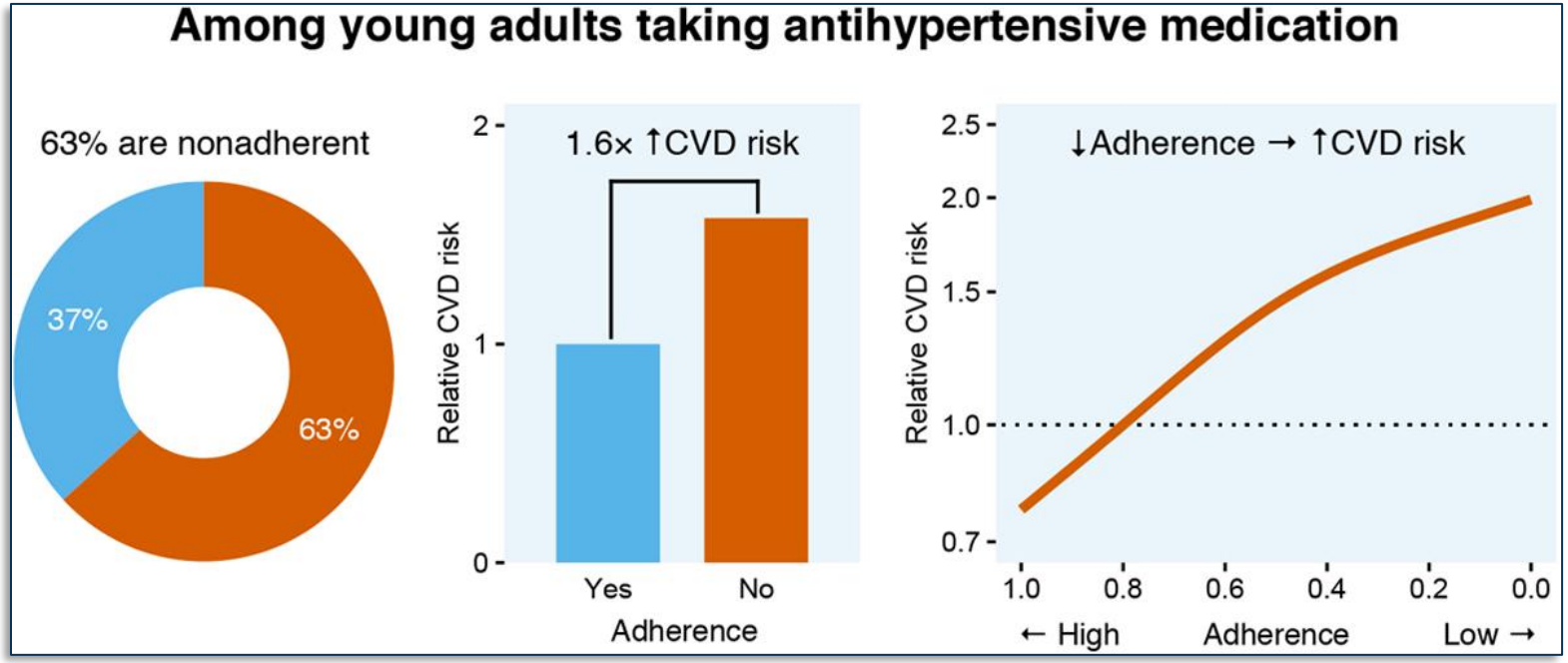
Desai AS. J Am Coll Cardiol 2025 Nov, 86 (18) 1514–1516.

Residual Barriers to Effective BP Control

- Poor access to care
- Inadequate education/awareness
- Failure to diagnose hypertension
- Therapeutic Inertia (providers)
- Poor adherence to daily oral regimens (patients)
- Resistance to antihypertensive treatment (~10%)

Carey RM, et al. J Am Coll Cardiol 2018;72:1278–93

Poor Adherence to Antihypertensives Enhances CV Risk



~50% of patients discontinue prescribed medications within 1 year

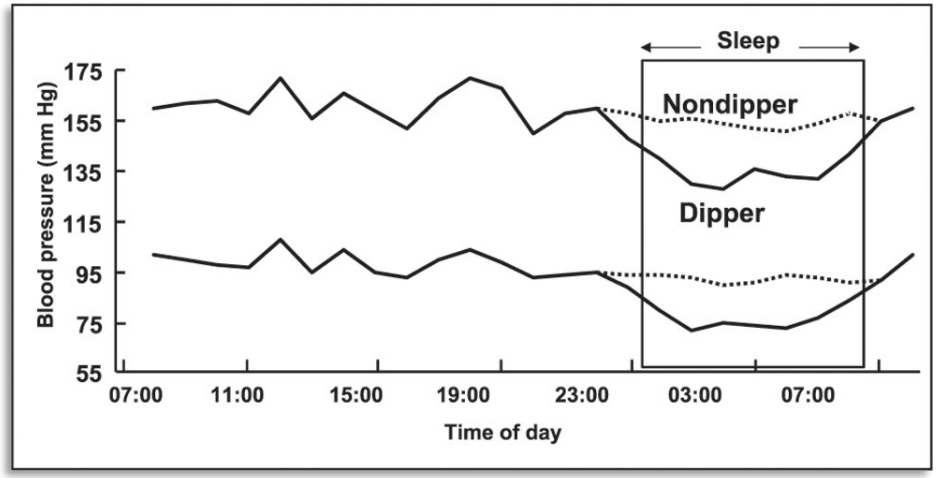
~10% of daily medication doses are omitted

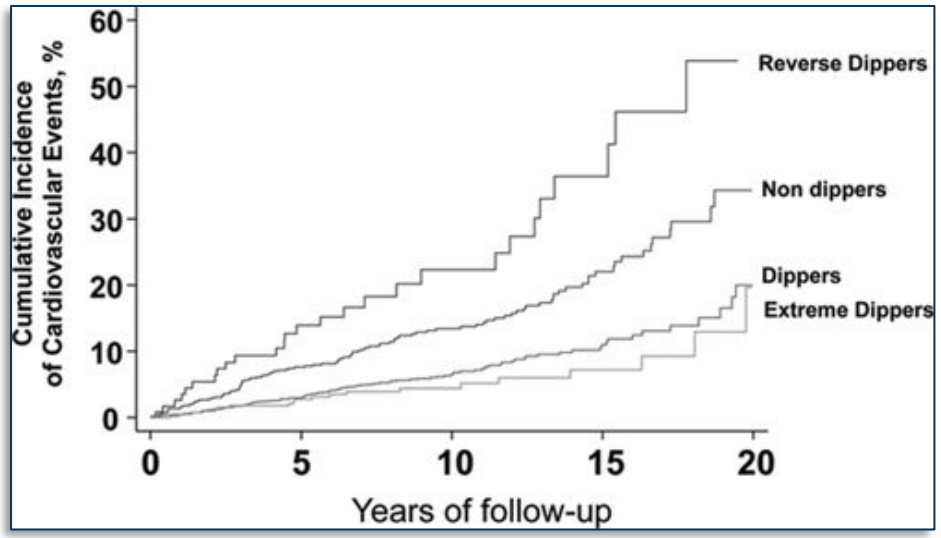
Lee H, et al. Hypertension 2021; 77(4): 1341-49; Vrijens B, et al. 2008;336(7653):1114-7

Need for Continuous Control of Blood Pressure

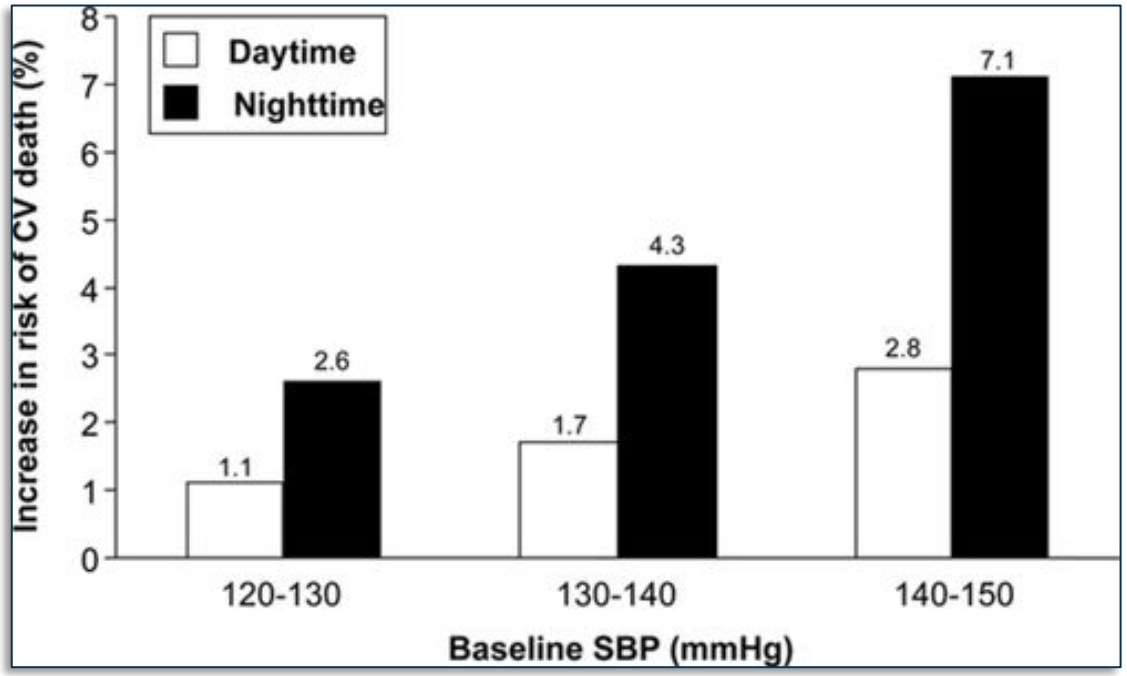
- Mean of office BP readings over several visits is typically utilized to direct therapy
- However, BP fluctuates over both short and long-term
- Episodic high values often disregarded
- Emerging evidence suggests that diurnal variation and visit-to-visit variability in BP are not merely ‘noise’, but carry prognostic importance

24-Hour Ambulatory Blood Pressure and Cardiovascular Risk





Nocturnal HTN is the most Potent Predictor of CV Risk

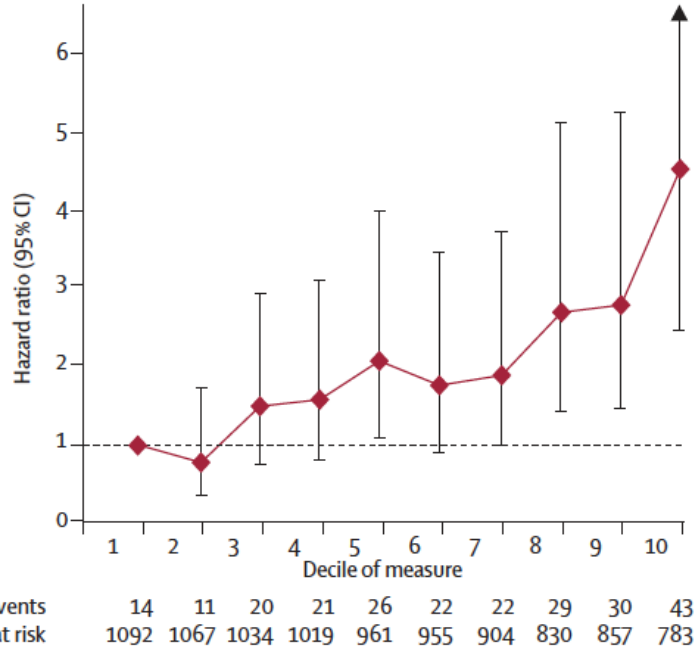


LaRochelle P. J Clin Hypertens. 2002; 4: 3-8; Verdecchia P, et al. Hypertension. 2012; *60*:34–42 Sega R, et al.Circulation. 2005; *111*:1777–1783; Roush GC, et al. Journal of Hypertension 2014, 32:2332–2340

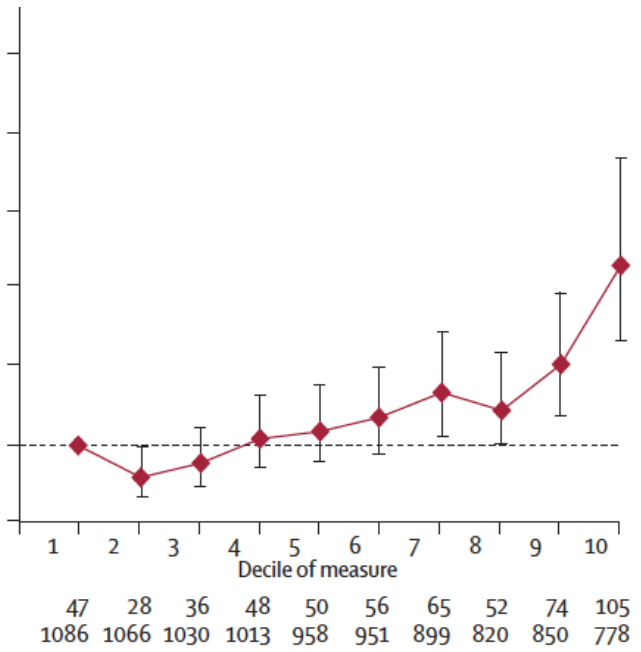
Excessive BP variability Increases Cardiovascular Risk

Visit-to-Visit Variability (independent of mean)

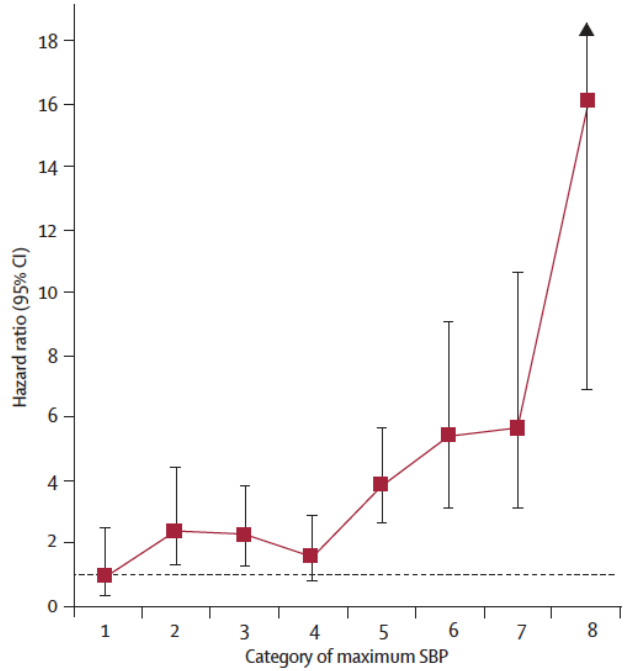
Risk of Stroke



Risk of Coronary Events



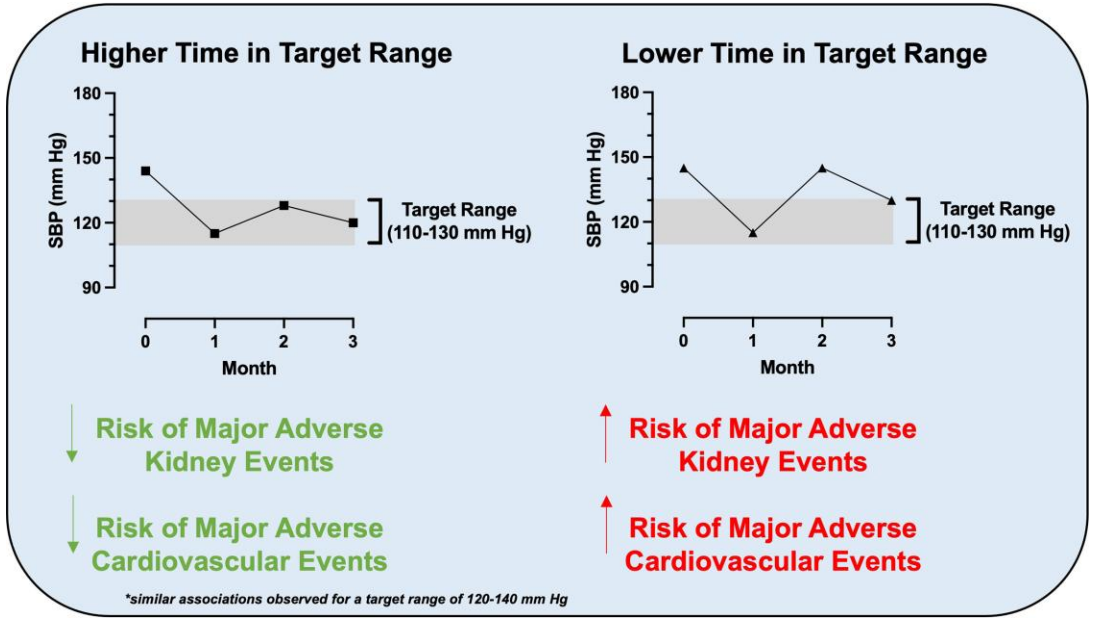
Maximum BP and Stroke Risk

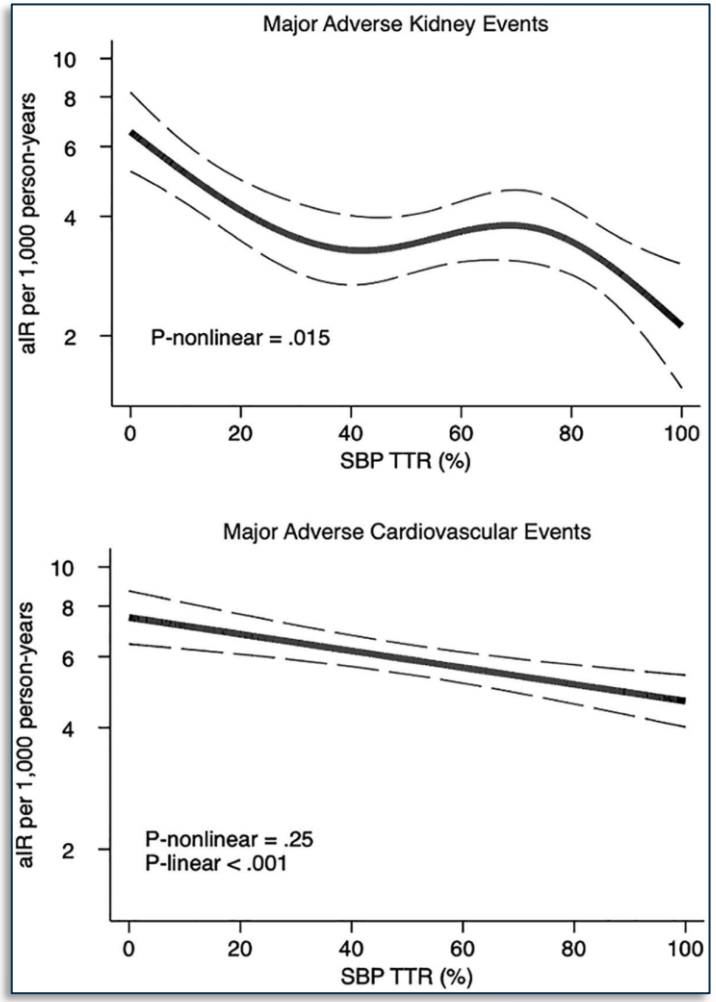


18% ↑ CV death, 15% ↑ stroke per 1 SD increase in SBP variability

ASCOT-BPLA Trial, Rothwell PM, et al. Lancet 2010; 375: 895-905; Stevens et al., BMJ 2016;354:i4098

Higher Time in Target Range (TTR) Lowers Risk of CV and Renal Events





Buckley L, et al. Hypertension. 2023;80(2):305–313

Hypertension Needs a New Therapeutic Approach

- Despite effective therapy, many patients with hypertension remain poorly controlled
- Physicians commonly fail to adapt therapy even when blood pressure is high, contributing to poor time in the therapeutic range
- Adherence to daily oral antihypertensive regimens is poor in clinical practice and undermines BP control
- Even when office BP appears controlled, residual visit-to-visit BP variability and nocturnal hypertension contribute to ongoing CV risk
- Effective reduction in CV risk requires a strategy to address therapeutic inertia, treatment non-adherence, and BP variability over the short- and long-term
- Novel oral antihypertensives are unlikely to effectively meet this challenge

Thank you

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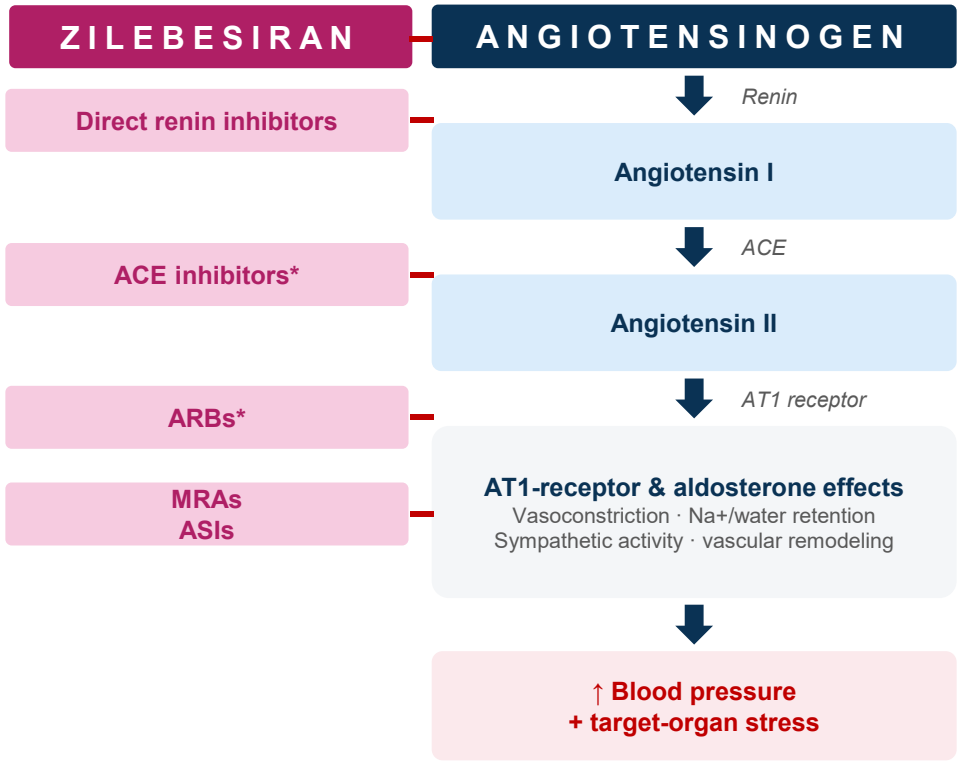
Targeting AGT to Achieve Continuous Control of Blood Pressure with the Potential to Improve CV Outcomes

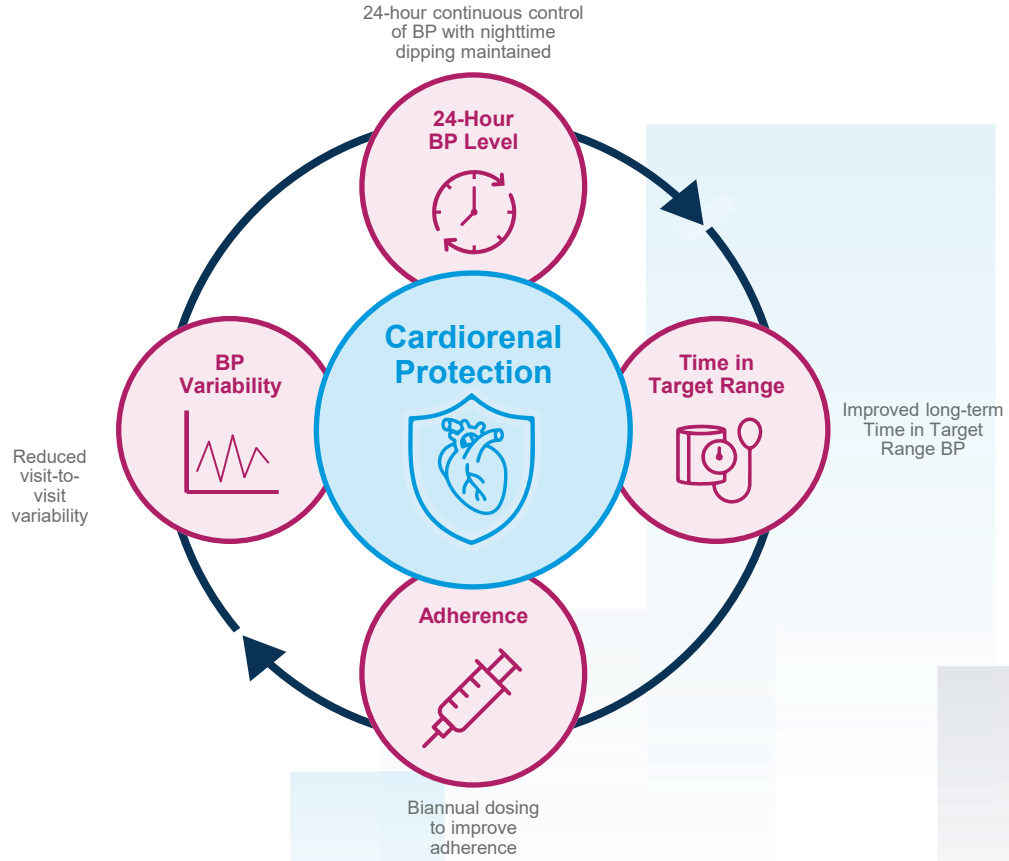
Zilebesiran Targets Angiotensinogen

The most upstream precursor to the RAAS, the main BP-regulating pathway



Zilebesiran Therapeutic Hypothesis

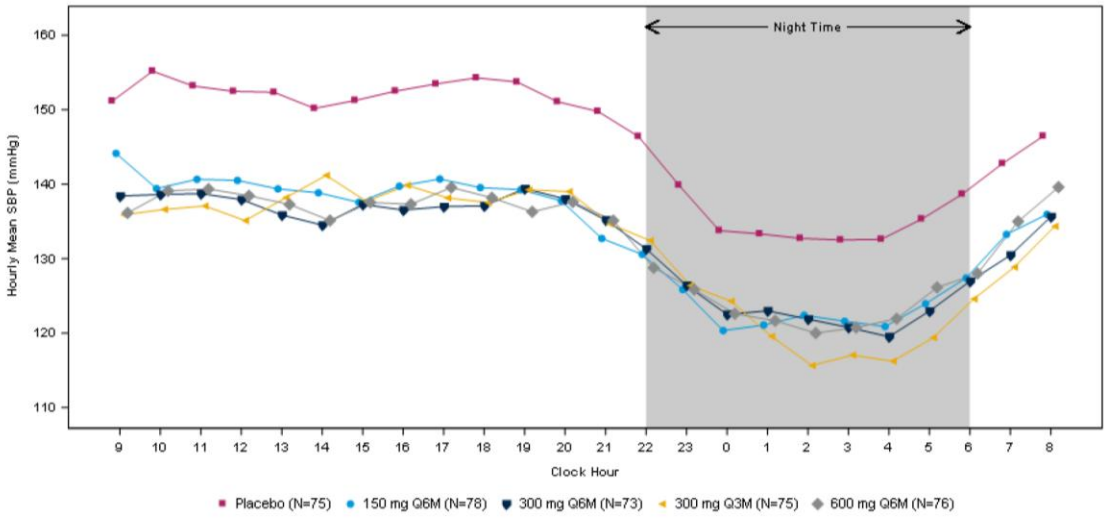
Continuous Control of BP to Improve CV Outcomes



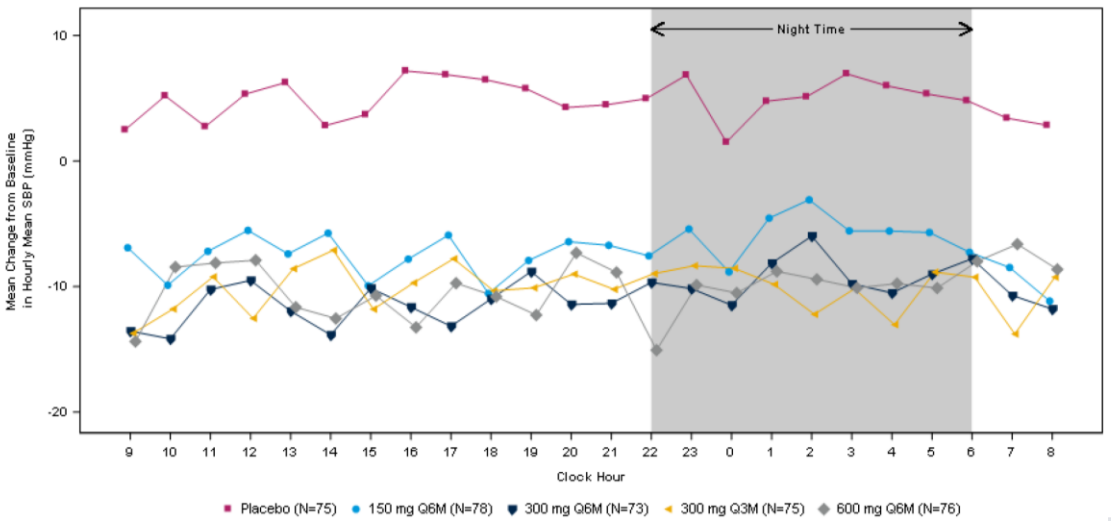
Illustrative mechanism. RAAS, renin–angiotensin–aldosterone system;
AGT, angiotensinogen; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; ASI – aldosterone synthetiase inhibitor; MRA, mineralocorticoid-receptor antagonist; RNAi, RNA interference; BP, blood pressure

Single Dose of Zilebesiran Achieved Continuous Control of Blood Pressure Throughout the 24-Hour Period

Hourly Mean SBP Assessed by ABPM at Month 3

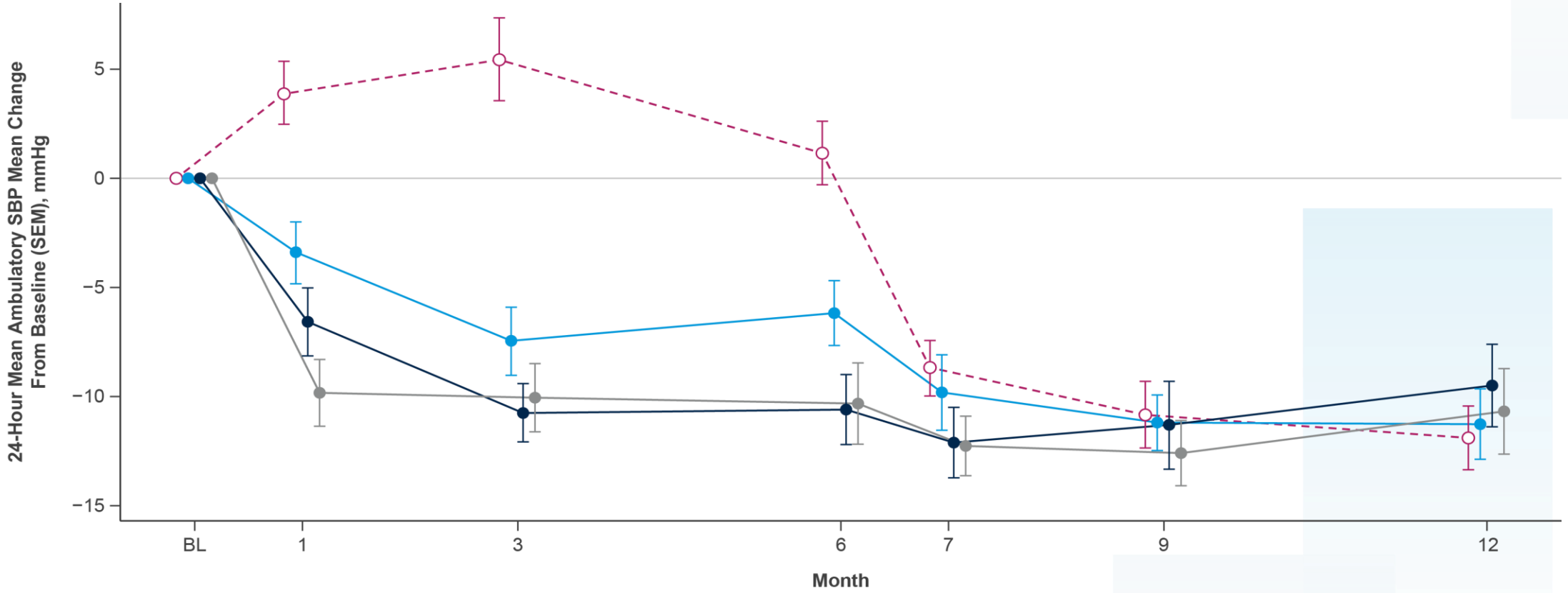


Change from Baseline in Hourly Mean SBP Assessed by ABPM at Month 3



Both panels show sustained 24-hour separation from placebo, including through the night-time interval.
Hourly mean systolic BP across the full 24-hour interval, shown as absolute values and as change from baseline (full analysis set)
SBP, systolic blood pressure; ABPM, ambulatory blood pressure monitoring
Ph 2 in patients with mild to moderate hypertension
Pagidipati et al. Presented at European Society of Cardiology Congress 2025, Madrid, Spain; Data on file

Continuous Control of Blood Pressure Observed Through Month 12 with Twice-Yearly Dosing



No. of Patients							
Placebo/150, 300, 600mg Q6M pooled	66	61	62	62	61	59	57
150mg Q6M/150mg Q6M	78	73	72	66	68	63	63
300mg Q6M/300mg Q6M	73	67	72	69	64	62	59
600mg Q6M/600mg Q6M	76	70	70	68	61	62	60

SBP, systolic blood pressure
Data on file

Encouraging Safety Observed Across Phase 2

KARDIA Program Evaluated Zilebesiran Across Monotherapy and Add-On Settings, Including Patients with Both Low and High Cardiovascular Risk

889 patients exposed to zilebesiran across Phase 2 studies

Safety Measure	KARDIA$_1$ zilebesiran monotherapy vs. placebo	KARDIA$_2$ zilebesiran + diuretic, CCB, or ARB vs. placebo	KARDIA$_3$ zilebesiran + 2-4 aHTNs vs. placebo
Hypotension AEs	4.3% vs. 1.3%	3.3% vs. 2.1%	2.7% vs. 2.6%
Hyperkalemia*	0.7% vs. 0%	1.5% vs. 0%	2.7% vs. 0.9%
AEs leading to study-drug discontinuation	2.6% vs. 2.7%	1.5% vs. 1.8%	Not reported†

Most events were mild or moderate, transient and resolved without intervention;
SAEs were rare, supporting continued investigation of zilebesiran 300 mg Q6M in ZENITH.

**Confirmed K^+ >5.5 mmol/L,*
CCB, calcium channel blocker; ARB, angiotensin-receptor blocker; aHTNs, antihypertensives, AE, adverse event; SAE, serious adverse event
Data on file

KARDIA-3 Insights Informed Target Phase 3 Patient Population

KARDIA-3

A Phase 2 Trial in Patients With Uncontrolled Hypertension on 2–4 Antihypertensives and High CV Risk or Established CVD

COHORT A FULL POPULATION (N=270)
eGFR ≥45 mL/min/1.73 m²

COHORT A (1:1:1)

- Zilebesiran 300 mg SC (N=91)
- Zilebesiran 600 mg SC (N=91)
- Placebo SC (N=88)

PRESPECIFIED ANALYSIS (N=174)

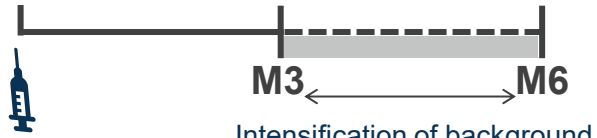
Patients receiving a diuretic at baseline

POST HOC ANALYSIS (N=108)

Patients receiving a diuretic at baseline, with baseline office systolic blood pressure ≥140 mmHg

COHORT B

eGFR 30–44 mL/min/1.73 m²



Intensification of background antihypertensives permitted

OBJECTIVE

To assess the blood pressure-lowering effects of zilebesiran in patients with uncontrolled hypertension receiving a diuretic at baseline

CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate

KARDIA-3 Population Largely Reflects ZENITH-Like Population

Demographic/Characteristic	Cohort A Full Population (eGFR ≥45 mL/min/1.73 m2)	
	Placebo (N=88)	Zilebesiran 300 + 600 mg Pooled (N=182)
Age, years, mean (SD)	66.3 (9.0)	66.4 (8.4)
Female, %	37.5	48.4
Black, %	22.7	23.1
Hispanic or Latino, %	55.7	55.5
Previous CV event or CVD history, %	21.6	23.1
Type 2 diabetes, %	53.4	50.5
BMI, kg/m^2, median (IQR)	29.6 (5.4)	31.1 (7.0)
Office systolic BP, mmHg, median (IQR)	144.0 (15.0)	142.0 (16.0)
24-hour ambulatory systolic BP, mmHg, median (IQR)	142.0 (12.5)	141.5 (12.5)
Receiving ACEi or ARB, %	88.6	91.8

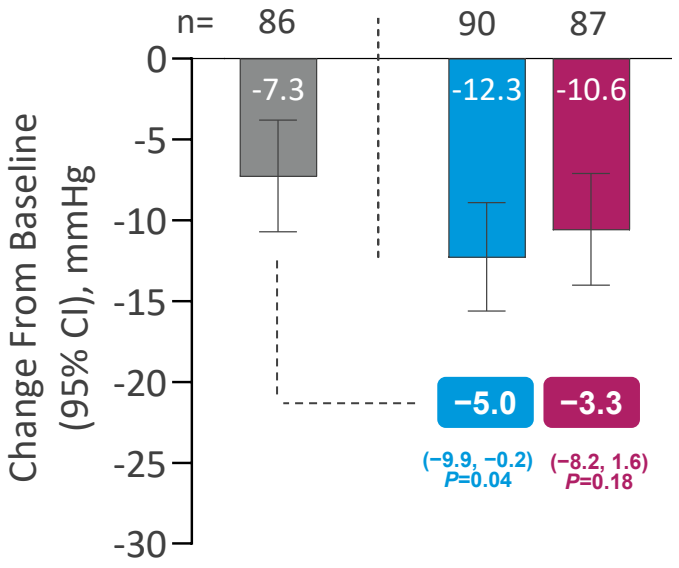
SD, standard deviation; IQR, interquartile range; cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio; BMI, body mass index; BP, blood pressure; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker

Data on file

Enhanced Blood Pressure Lowering in ZENITH-Like Patients[1]

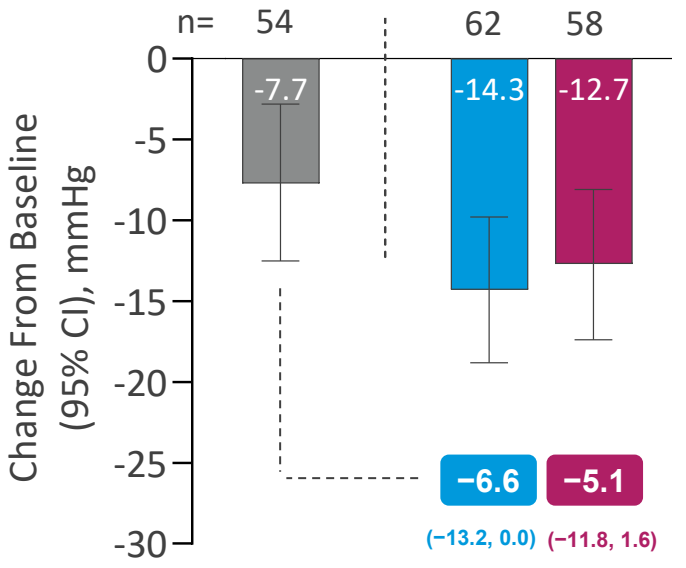
Placebo Zilebesiran 300 mg Zilebesiran 600 mg

Cohort A
Full Population



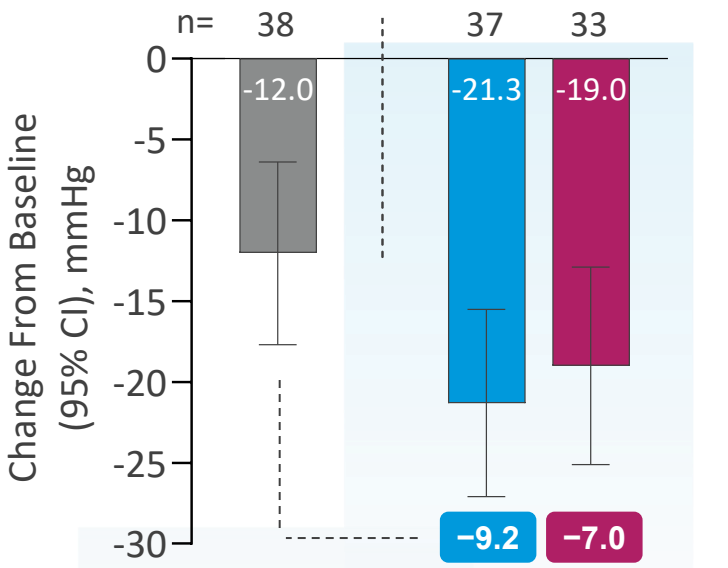
Baseline Diuretic
(Prespecified)

66% of Full Population



Baseline Diuretic and Baseline Systolic BP ≥140 mmHg (*Post Hoc*)

41% of Full Population

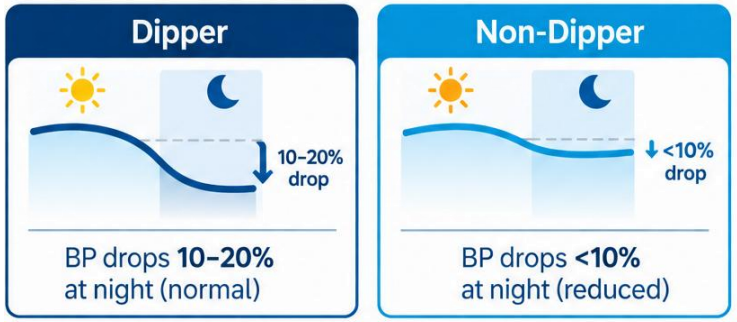


Changes sustained to Month 6:
−8.3 (−16.4, −0.2) mmHg
−6.2 (−14.4, 2.0) mmHg

[1]*Findings from post hoc analysis evaluating zilebesiran in patients with an office systolic BP (SBP) ≥140 mmHg and receiving a diuretic at baseline compared to the overall KARDIA-3 population*
BP, blood pressure
Pagidipati et al. Presented at European Society of Cardiology Congress 2026, Munich, Germany

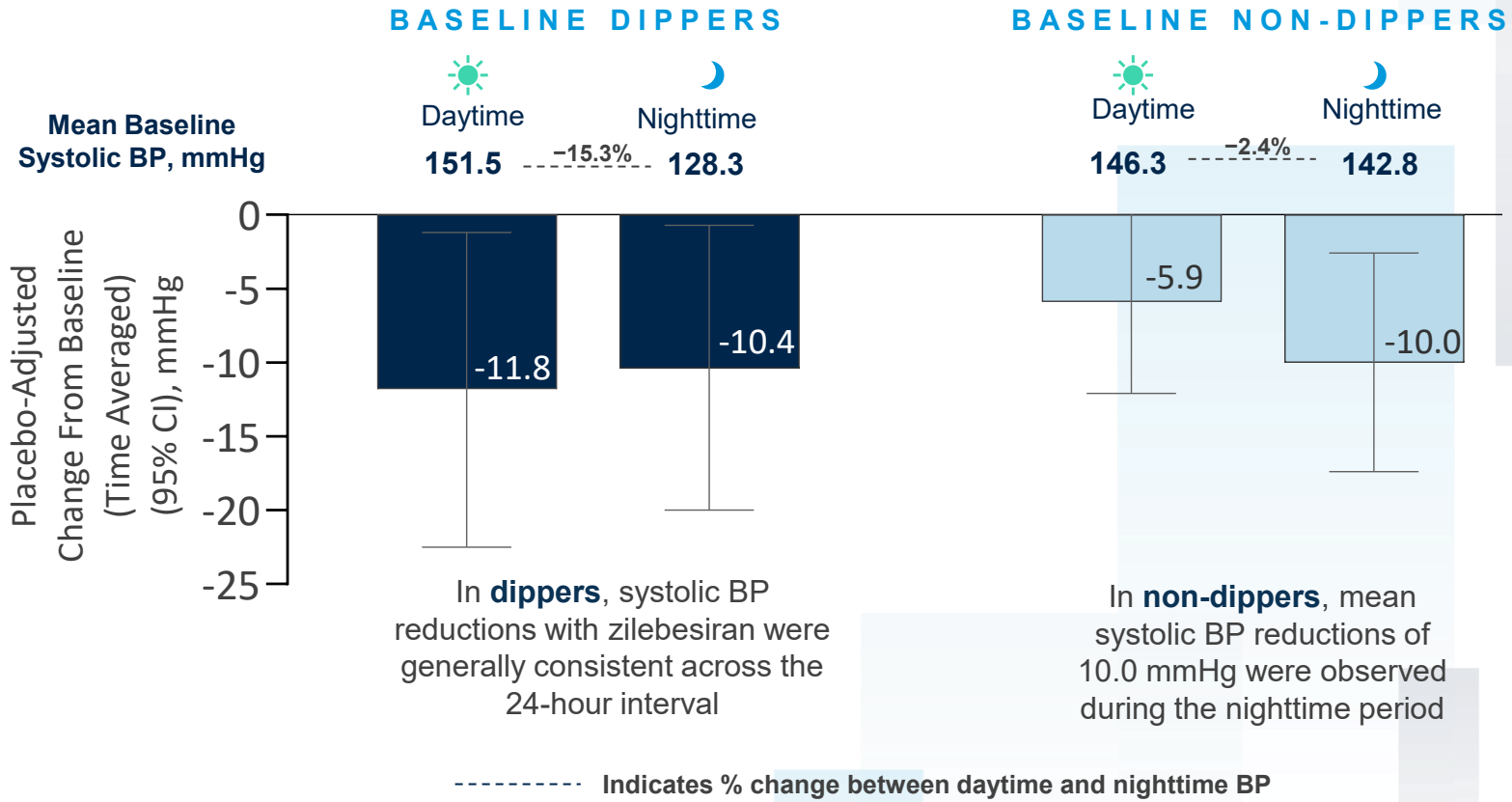
A Single Dose of Zilebesiran Improved Nighttime Blood Pressure Control, Independent of Dipping Status

Non-dipping is associated with cardiovascular risk[1]



The majority of patients in KARDIA-3 were **non-dippers**

Zilebesiran (300 + 600 mg pooled)

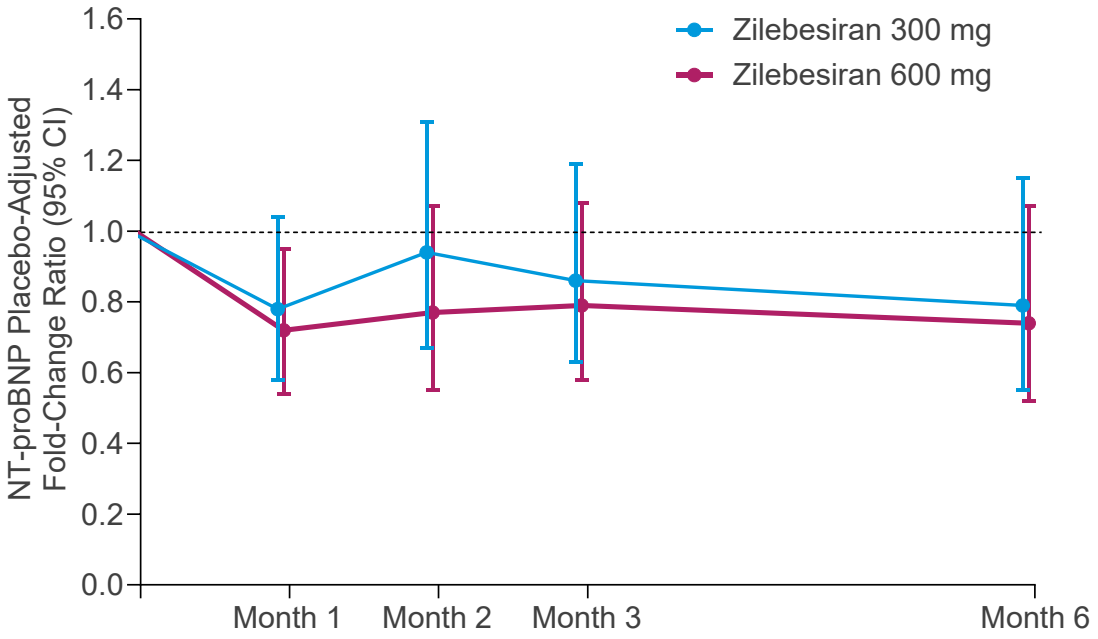


[1]Kario, et al. Circulation. 2020;142:1810–1820
Post hoc: baseline diuretic and baseline Office Systolic BP ≥140 mmHg
BP, blood pressure
Non-dipper was defined as <10% reduction in mean nighttime versus mean daytime systolic BP at baseline
Pagidipati et al. Presented at European Society of Cardiology Congress 2026, Munich, Germany

Rapid, Sustained Reductions in Biomarkers of CV and Renal Risk

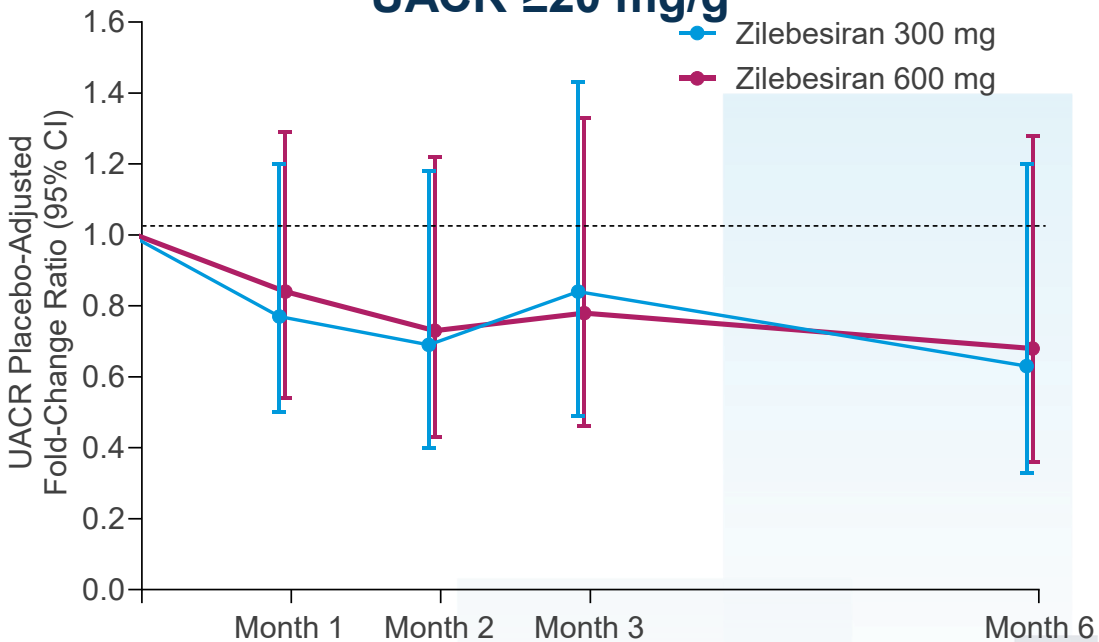
Exploratory Outcome

Patients with Baseline NT-proBNP ≥12 pmol/L



NT-proBNP	Zilebesiran 300 mg (n=34)	Zilebesiran 600 mg (n=39)
Placebo-adjusted geometric mean reduction at Month 6	–21%	–26%

Patients with Baseline Proteinuria UACR ≥20 mg/g



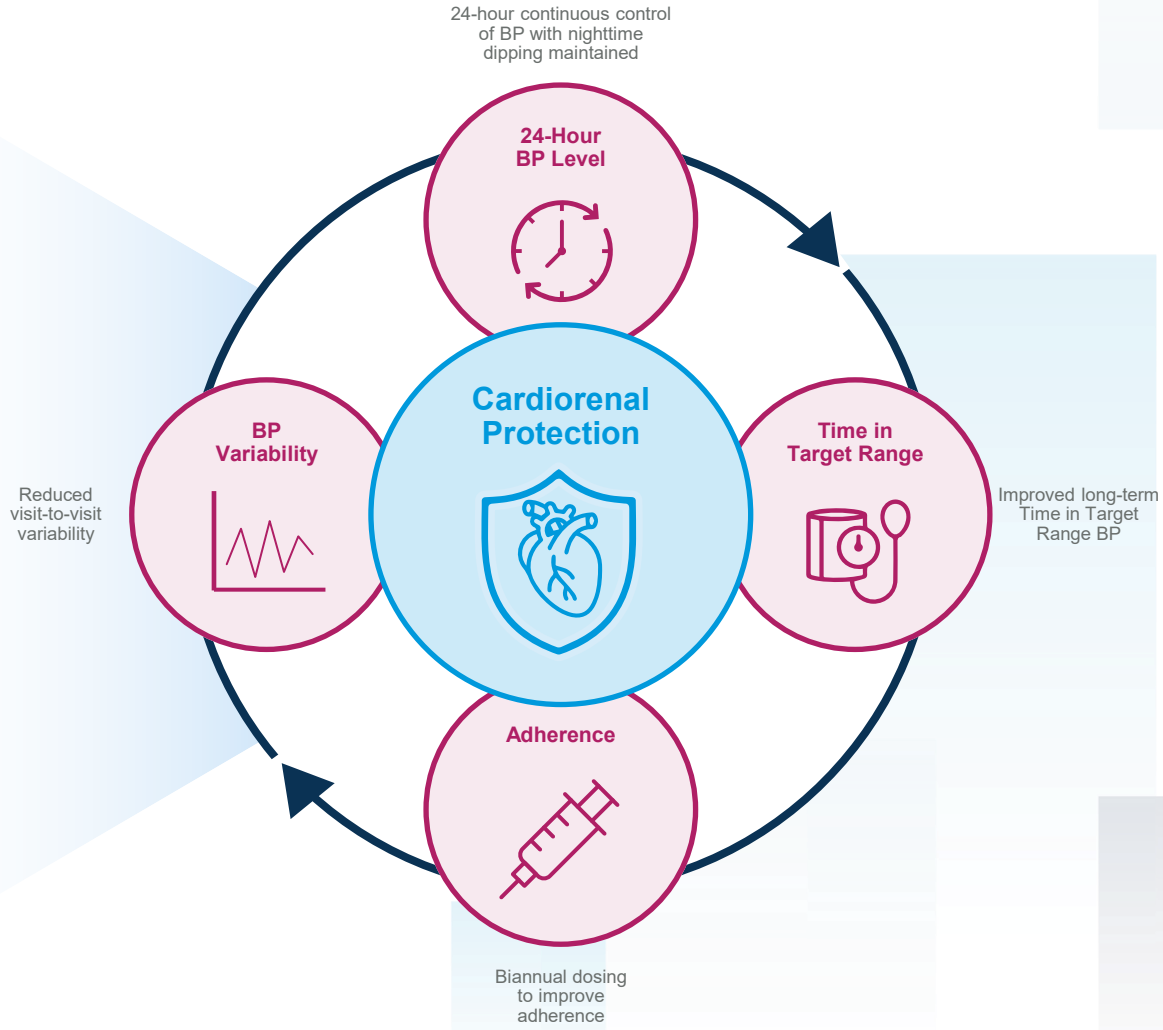
UACR	Zilebesiran 300 mg (n=25)	Zilebesiran 600 mg (n=26)
Placebo-adjusted geometric mean reduction at Month 6	–37%	–32%

UACR, urine albumin-to-creatinine ratio
Data on file

Addressing Persistent Cardiovascular Risk Requires a New Approach to Blood Pressure Management

KARDIA-3 data in ZENITH-like patients support zilebesiran's potential to deliver continuous control and continued evaluation in the ongoing Phase 3 CVOT

- In Phase 2 patients on zilebesiran experienced **continuous control of blood pressure** with encouraging safety
- **Enhanced blood pressure lowering** in the Phase 3 target population*
- Findings support the potential of zilebesiran to **modify key drivers of cardiovascular risk**
- **Results shaped the design of ZENITH**, the ongoing Phase 3 CVOT



*Patients receiving a background diuretic and with baseline SBP ≥140 mmHg

CVOT, cardiovascular outcomes trial; BP, blood pressure

RNAi 2026 ROUNDTABLES

Agenda

01	Introduction	**Pushkal Garg, M.D.** *Chief Research & Development Officer*
02	Hypertension: The Threat Beyond the Office	**Akshay S Desai, M.D., MPH** *Harvard Medical School* *Mass General Brigham*
03	The Potential for Continuous Control with Zilebesiran	**Ishir Bhan, M.D., MPH** *Executive Director, ZENITH Clinical Lead*
04	Realizing the Opportunity	**Simon Fox, Ph.D.** *Vice President, Zilebesiran Program Lead*
05	Q&A Session	

Phase 3 Cardiovascular Outcomes Trial

Randomized, Double-Blind, Event-Driven Study in High CV Risk Patients with Uncontrolled Hypertension

Study Population

- Adult patients with uncontrolled hypertension and established CV disease or at high risk
- Office systolic BP ≥140 mmHg on stable treatment (≥2 antihypertensive medications, one of which is a diuretic)
- Excluded: eGFR <30 mL/min/1.73m^2, potassium >4.8 mEq/L

Randomize 1:1 (n≈11,000)

Zilebesiran SC 300 mg Q6M + standard of care	Placebo SC Q6M + standard of care

Event-driven with a minimum follow-up of 2 years

Primary Outcome: CV death, nonfatal myocardial infarction (heart attack), nonfatal stroke, or HF event

FAST TRACK DESIGNATION

BREAKTHROUGH THERAPY DESIGNATION

CV, cardiovascular; CVD, cardiovascular disease; BP, blood pressure; eGFR, estimated glomerular filtration rate; SC, subcutaneous; HF, heart failure

zenith: Global Footprint & Strong Execution

GLOBAL SCALE

>1,000 sites

35 countries

Actively screening and enrolling in all countries

EXECUTION UPDATE

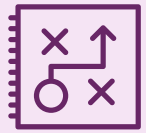
Global activation and enrollment remain on track

Executing a Comprehensive Strategy to Realize Zilebesiran's Full Potential

WHAT WE ARE DOING TODAY TO DELIVER TOMORROW

01 PHASE 3 EXECUTION

02 REAL WORLD EVIDENCE



03 MEDICAL AFFAIRS & EDUCATION

04 LINE EXTENSIONS

05 siRELIS™ ENZYMATIC LIGATION

06 COMMERCIAL READINESS

TO UNLOCK ZILEBESIRAN'S BROAD CLINICAL AND COMMERCIAL POTENTIAL

Hypertension is a Global Health Crisis

Uncontrolled Hypertension is Highly Prevalent and Carries Substantial Risk of Morbidity and Mortality

~219M

patients with hypertension[2]
in the 7 major markets[3]

DESPITE MULTIPLE TREATMENT OPTIONS…

Multiple oral antihypertensive classes **still leave most patients uncontrolled**

Daily-oral adherence limits **durable, long-term control**

of patients remain uncontrolled[4]

Prolonged, uncontrolled hypertension is a systemic disease that drives end-organ damage and poor outcomes.

**US, UK, DE, FR, ESP, IT,JP*

BP, blood pressure; CV, cardiovascular; MM, million; mmHg, millimeters of mercury

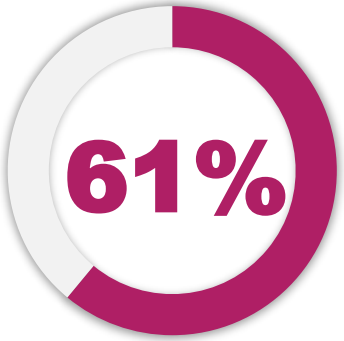
1. Extrapolated for 7 major markets (7MM) based on proportion of US hypertension population with prior history of CVD or Framingham Risk Score of >10%, excluding patients with history of stroke and women of child-bearing potential; 2. Estimated from multiple sources and internal estimates: Dorans et al. J Am Heart Assoc 2018;7:e008888; Al Kibria et al. Hypertens Res. 2019;42:1631–43; CDC Hypertension Cascade. 2019; High CV risk: ASCVD risk score ≥20% and/or history of CVD; 3. Excluding stroke and WOCBP; 4. NCHS Data Brief No. 511, October 2024

The Economic Burden of Hypertension

A Large and Growing Financial Toll on the U.S. and Global Health Systems

$292B

estimated annual U.S. medical cost of hypertension[1]



of total cost comes from

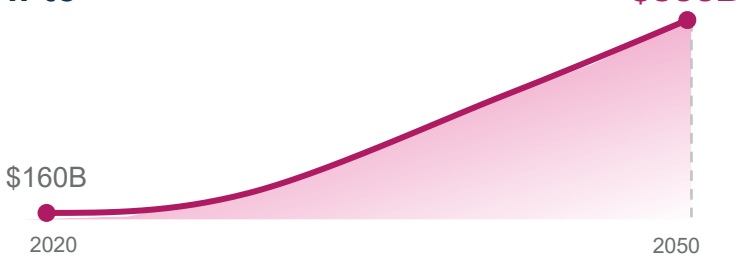
UNCONTROLLED HYPERTENSION

Global burden projected to grow to

>$500B

by 2050[2]

as prevalence rises



1. ATI Advisory, "Quantifying the Annual Macroeconomic Impact of Hypertension," May 2026 (2025 US$): $292B total = $266B medical + $26B labor; uncontrolled population = $177B (61%); working-age (18–64) burden $132B, employers 53%; ~$33B addressable via guideline-based treatment of uncontrolled HTN. 2. Kazi DS et al., "Forecasting the Economic Burden of Cardiovascular Disease and Stroke… Through 2050," AHA Presidential Advisory, Circulation. 2024;150:e89–e101 (2022 US$): HTN health-care cost $160B (2020) → $513B (2050), +220%; all CV risk factors $400B → $1,344B. Note: estimates use different methods/base years and are not directly additive.

Real World Evidence: Most High-Risk Patients Spend a Very Low Proportion of Time in Target Range Blood Pressure

~80%

spend a low proportion time in target range

PATIENTS WITH HYPERTENSION AND HIGH CV RISK ON MULTIPLE BACKGROUND THERAPIES

DISTRIBUTION OF TIME IN TARGET RANGE BP[1]

(<130/80 mmHg[2]) Over 12 Months

Cohort of patients with hypertension and high CV risk[1]

Most patients are not achieving guideline-recommended targets.[1]

Low time in target range is an independent predictor of MACE.[3]

1. Data on file, Alnylam internal real-world data analysis of patients with hypertension and high CV risk; time in target range (TTR) over 12 months. 2. Target range per 2025 AHA/ACC guideline. Illustrative; internal analysis.
3. Laffin et al Current Cardiology Reports (2024) 26:1145–1151
BP, blood pressure; CV, cardiovascular; MACE, major adverse cardiovascular event

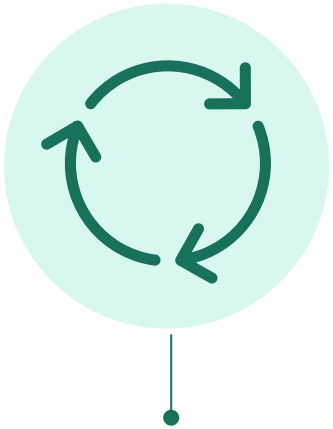
Zilebesiran: A Potential Category Creator

Generating Cardiovascular Outcomes to Maximize Value

VALUE PROPOSITION

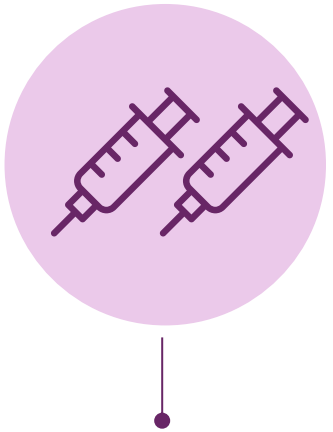
Cardiovascular Outcomes

Clinically significant MACE reduction



Continuous Control

Durable control beyond office BP snapshot



Infrequent Dosing

Twice-yearly dosing to optimize adherence

Favorable Safety

Generally well tolerated with the ability to combine with other antihypertensives

Zilebesiran is an investigational therapeutic in development for hypertension and improving cardiovascular outcomes. The safety and efficacy of zilebesiran have not been established or approved by the FDA, EMA or any other health authority. The safety and efficacy of zilebesiran are currently being evaluated by these regulatory authorities. This information is intended to provide an overview of the potential clinical profile of zilebesiran for the treatment of hypertension, assuming positive results in ongoing and planned clinical trials.

MACE, major adverse cardiovascular event; BP, blood pressure; HCPs, healthcare professionals

Early Insights Signal Strong Adoption Intent

Demand is Validated Across Prescribers, Patients and Payers

PROVIDERS

3 in 4

intend to prescribe

Viewed as a cardiovascular protective agent, not just another antihypertensive

PATIENTS

EAGER

for a new option

Drawn to twice-yearly dosing

PAYERS

OUTCOMES 1st

CV risk reduction is the #1 decision driver

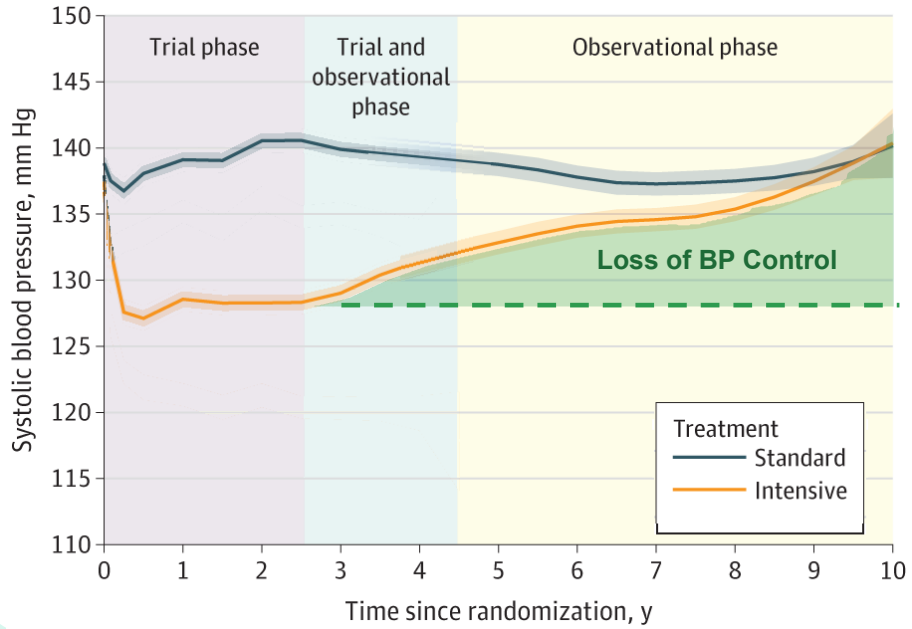
Meaningful CV outcomes support favorable guideline positioning

> ***I'm literally so excited… yes, I would definitely approach my physician and explore this!***
>
> - Deborah, 50-59, MI / stroke patient

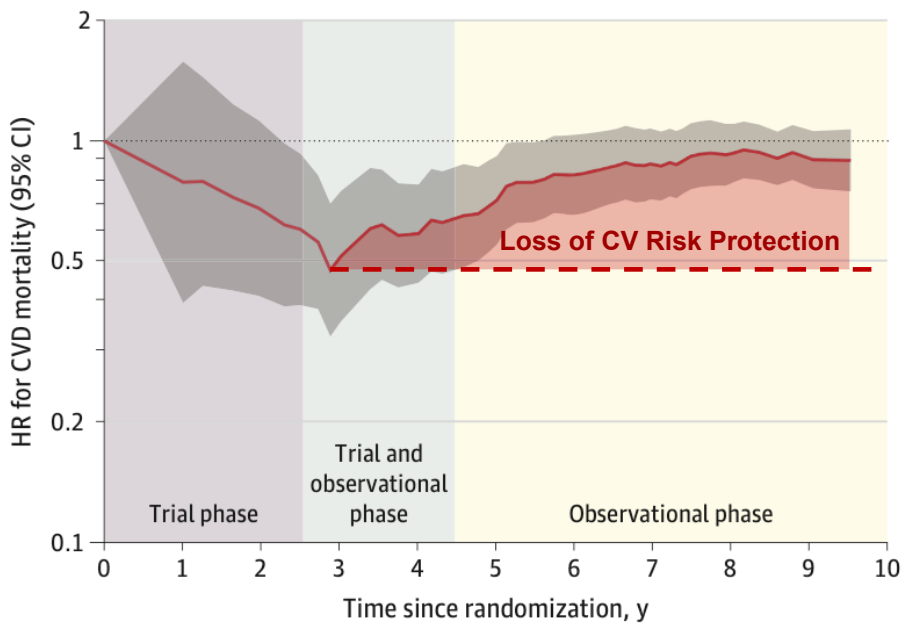
Source: Zilebesiran HCP TPP Testing, Ipsos 2026 (quant n=211; qual n=58) • Zilebesiran uHTN Patient Journey research (Now What, 2024). Blinded profiles; intent-to-prescribe and share are hypothetical, market-research measures. • Economic burden: ATI Advisory, "Quantifying the Annual Macroeconomic Impact of Hypertension," May 2026 (2025 US$).

The Reality Highlights the Importance and Need for Long-Term Continuous Control of Blood Pressure

Mean Systolic Blood Pressure Intensive vs. Standard Treatment



Time-Dependent HR for CV Death Intensive vs. Standard Treatment



Zilebesiran offers the Potential to:

Reduce cardiovascular risk through continuous control of blood pressure with twice yearly dosing – aiming to go from achieving a number to ***maintaining a state.***

1. Jaeger et al. Longer-Term All-Cause and Cardiovascular Mortality With Intensive Blood Pressure Control JAMA Cardiology; 2022 7; (11):1138-1146

HR, hazard ratio; CV, cardiovascular; CVD, cardiovascular disease JAMA Cardiology, 2022 | HR, hazard ratio; CV, cardiovascular; CVD, cardiovascular disease

Bringing the Need for Better Control Into Focus

Bob, Living with Hypertension

Bringing the Need for Better Control Into Focus

"For years, I felt fine and convinced myself that I had a handle on my high blood pressure. Looking back, that decision nearly cost me my life …

Bob, Living with Hypertension

Bringing the Need for Better Control Into Focus

"… At 45, I suffered a heart attack that left permanent damage to my heart. Hypertension is often called the 'silent killer' for a reason …

Bob, Living with Hypertension

Bringing the Need for Better Control Into Focus

"... My experience taught me that even when you feel healthy, uncontrolled blood pressure can have life-threatening consequences."

Bob, Living with Hypertension

Q&A

Up next…

RNAi 2026 ROUNDTABLES

Oct. 26

NEUROSCIENCE

ALN-HTT02

Unique targeting strategy aiming to reduce progression of Huntington's disease