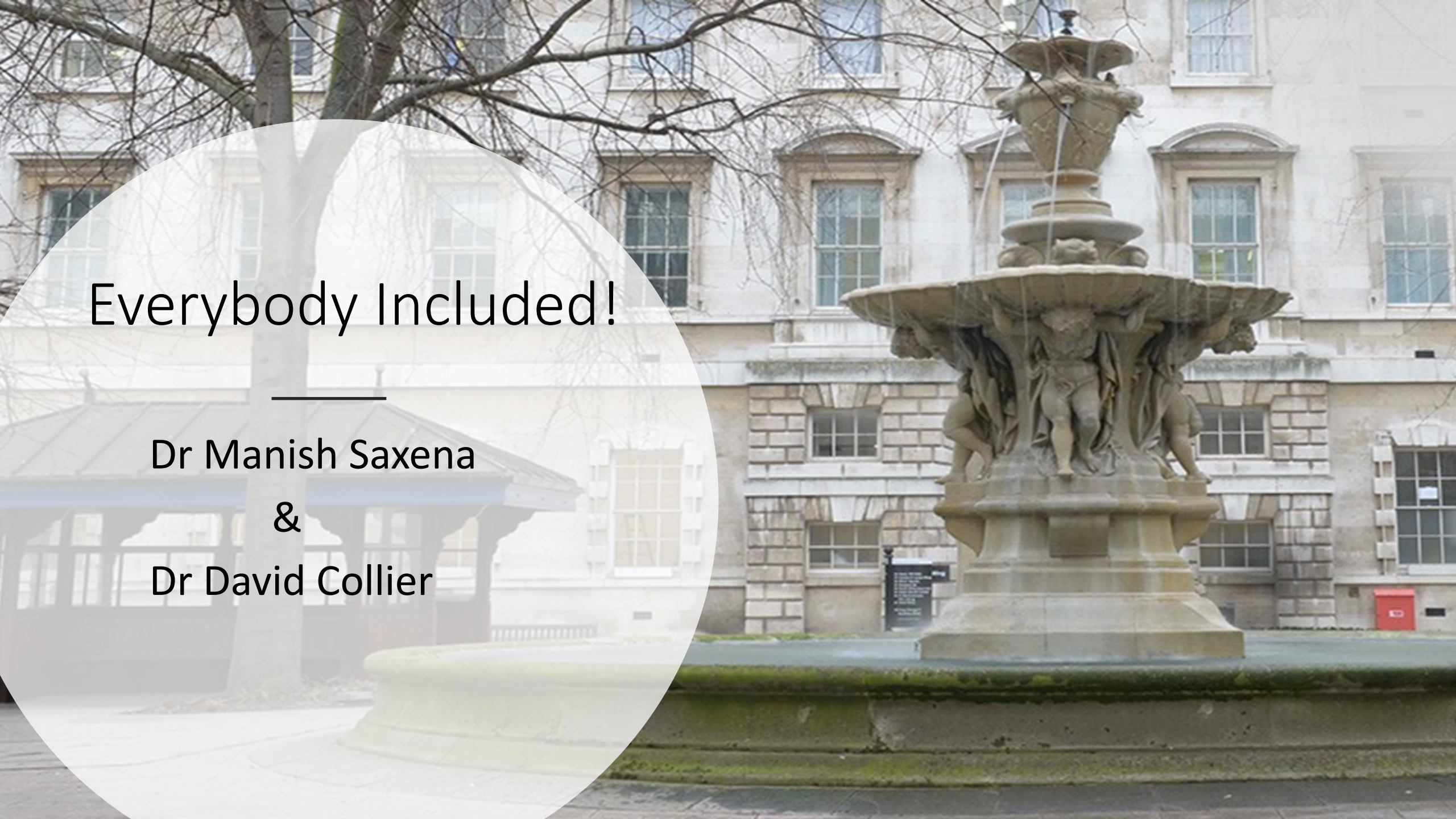

Everybody Included!

Dr Manish Saxena

&

Dr David Collier

Cardiovascular Disease Burden

- CVD Leading cause of global CV morbidity and mortality
- 7.4 million people living with CVD in the UK
- CVD causes 27% of all deaths in the UK and costs £19 billion each year to UK economy
- HTN and Type II Diabetes are important risk factors

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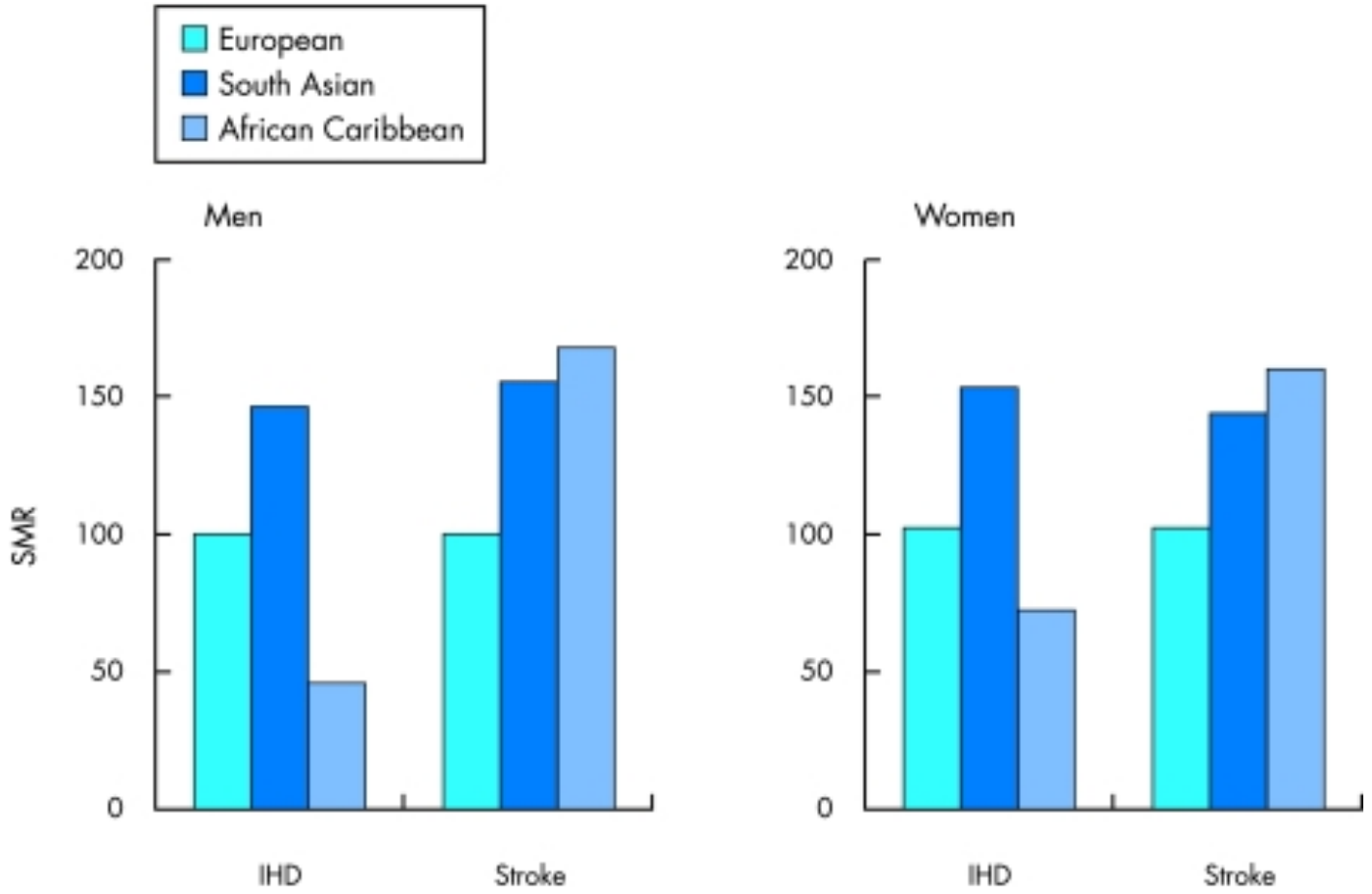
CV mortality based on Ethnicity



Standardised mortality ratios (SMR) for heart disease and stroke in South Asians and African Caribbeans compared to Europeans (Wild, BMJ 1997)

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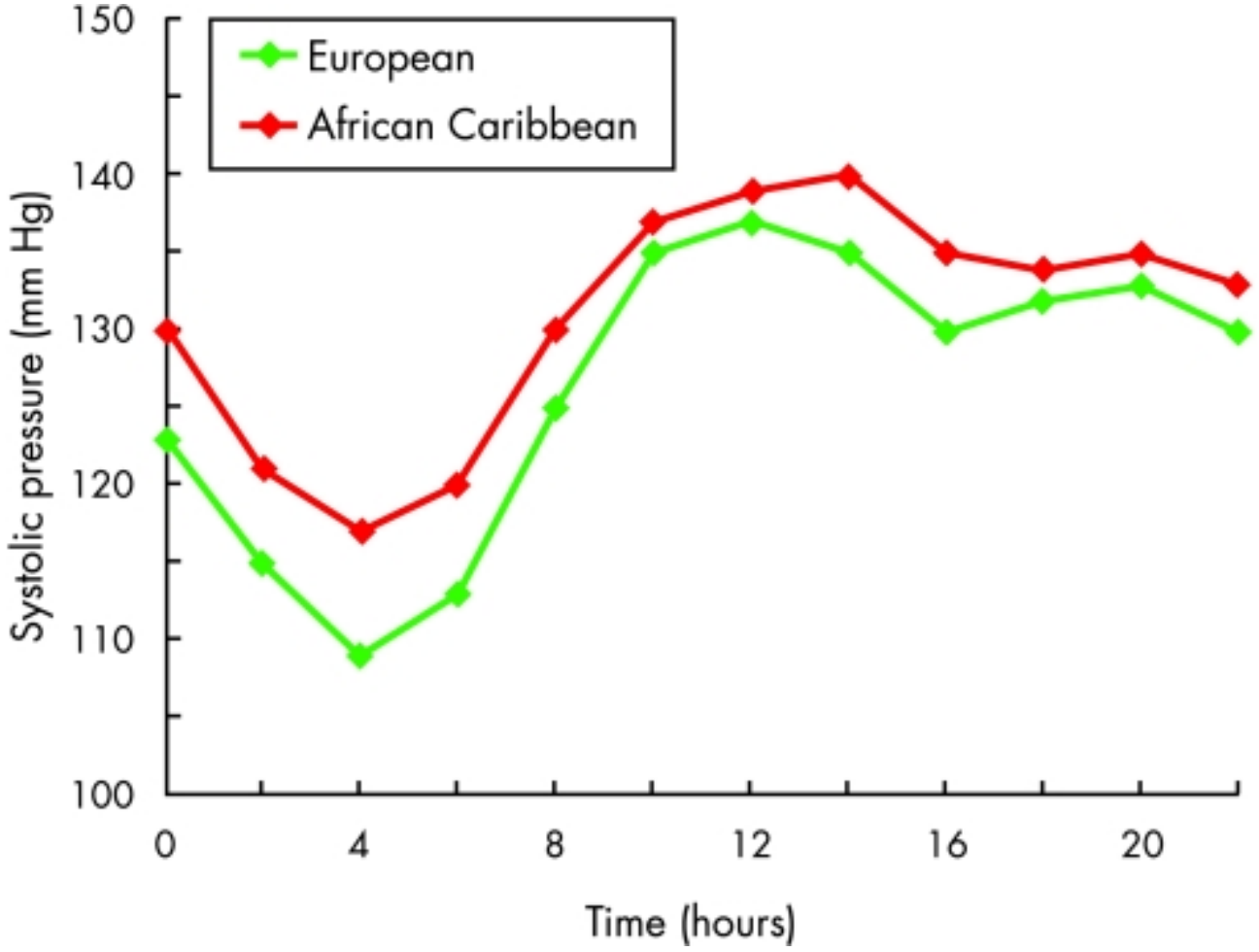
BP Difference based on Ethnicity



ASBP in African Caribbeans/ Europeans (Chaturvedi, Hypertension 1993)

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BP and CVD risk reduction

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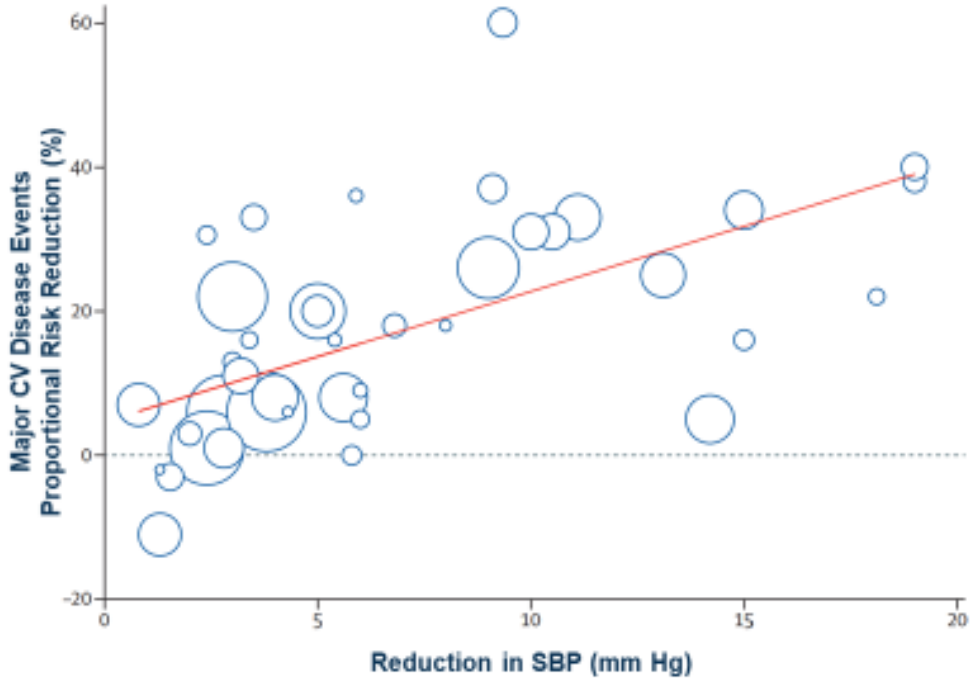
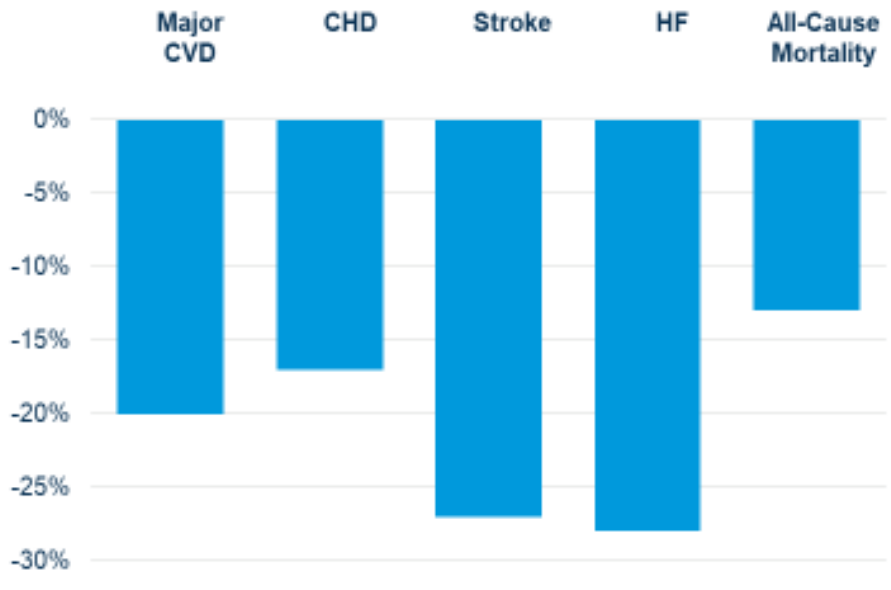
Blood Pressure Reduction Correlates to Reduced Risk

Risk Reduction Observed Across All Major Adverse Cardiac Events

Percent Risk Reduction by Achieved SBP
(Meta-regression n=613,815 across 123 studies)



Percent Risk Reduction per 10 mm Hg Reduction in SBP[a]
(Meta-regression n=613,815 across 123 studies)



[a]Irrespective of initial BP or comorbid conditions.
BP, Blood Pressure; CHD, Coronary Heart Disease; CVD, Cardiovascular Disease; HF, Heart Failure; SBP, Systolic Blood Pressure
Ettehad D. et al. *Lancet* 2016; 387:957-67

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Long Acting Si RNA targeting hepatic AGT for HTN

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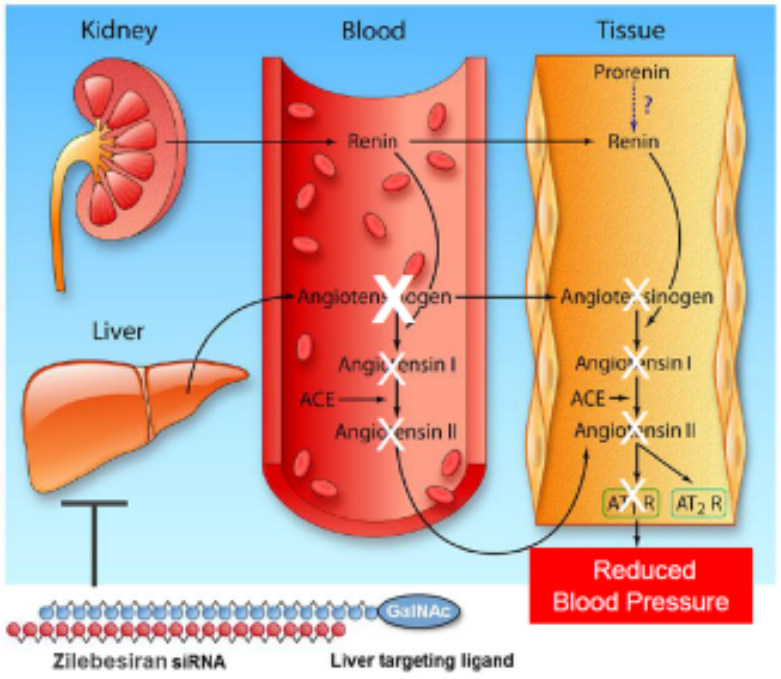
Zilebesiran Mechanism of Action



The renin-angiotensin-aldosterone system (RAAS) cascade has a demonstrated role in blood pressure regulation[1,2]

- Traditional RAAS-targeted antihypertensive pharmacotherapy targets include
  - Renin inhibition
  - Inhibition of Ang I cleavage
  - Inhibition of Ang II receptor binding

Angiotensinogen (AGT) is the most upstream precursor of the RAAS cascade, and is predominantly produced in the liver[2]

Zilebesiran is an investigational **liver-targeted** RNAi therapeutic that degrades AGT mRNA

- Preclinical data[3] demonstrated durable reductions in AGT protein and ultimately in downstream products, including the vasoconstrictor angiotensin Ang II

AGT, Angiotensinogen; GalNAc, N-Acetylgalactosamine; mRNA, Micro-Ribonucleic Acid; RNAi, Ribonucleic Acid Interference

1. te Riet, L et al. *Circ Res.* 2015. 116(6): 960-975; 2. Kumar, R. et al. *Heart Failure: A Companion to Braunwald's Heart Disease*, 2nd Edition, by Douglas Mann, Saunders Press 2011, pp. 134-151; 3. Uijl E. et al. *Hypertension*. 2019. 73:1249-1257.

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BP Reduction with Zilebesiran

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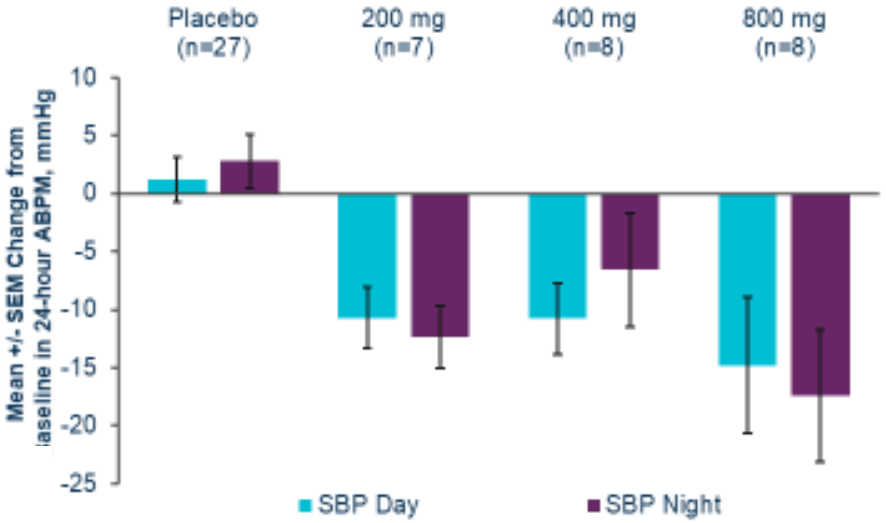
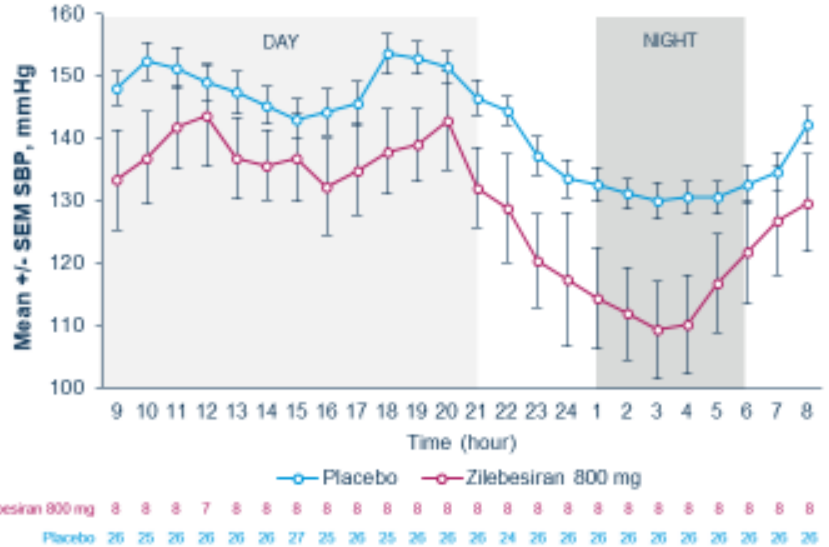
Post-Hoc Analysis: Change From Baseline in 24-hr ABPM and SBP

- Marked reductions in both daytime and nighttime SBP were observed with zilebesiran doses ≥200 mg at Week 8[a]
  - These reductions in daytime and nighttime SBP were sustained to later timepoints (Weeks 12 and 24; data not shown)
  - Similar improvements during daytime and nighttime were also seen for DBP (data not shown)

Change From Baseline in Daytime/Night-time ABPM at Week 8[b,c]



24-Hour SBP at Week 8



patients at Week 8 were receiving zilebesiran only (no rescue antihypertensives). [b]Hourly adjusted mean; daytime [9 am to 9 pm], nighttime [1 am to 6 am]. [c]Median baseline SBP/DBP: Placebo – 142/88 mmHg; 200 mg – 139/83 mmHg; mg – 138/90 mmHg; 800 mg – 142/88 mmHg

[a]M, Ambulatory Blood Pressure Monitoring; AGT, Angiotensinogen; BP, Blood Pressure; DBP, Diastolic Blood Pressure; SBP, Systolic Blood Pressure; SEM, Standard Error of the Mean.

ai et al. Poster presentation at American Heart Association 2021: Virtual.

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