ALN-AGT, in Development for the Treatment of Hypertension

RNAi ROUNDTABLE 2020

June 23, 2020

Alnylam® PHARMACEUTICALS

Agenda

Welcome
- Joshua Brodsky – Director, Investor Relations & Corporate Communications

Introduction
- John Maraganore, Ph.D. – Chief Executive Officer

Hypertension Background
- Akshay Desai, M.D., M.P.H – Director, Cardiomyopathy and Heart Failure Program, Cardiovascular Division, Brigham and Women's Hospital; Associate Professor of Medicine, Harvard Medical School

ALN-AGT Background and Development Program
- Jae Kim, M.D. – Vice President, Clinical Development

Commercial Outlook
- Lauren Melton – Senior Director, Program Leader, ALN-AGT

Q&A Session

Reminders

Event will run for approximately 60-75 minutes

Q&A session at end of presentation

- Questions may be submitted at any time via the ‘Ask a Question’ field on the webcast interface

Replay, slides and transcript available at www.alnylam.com/capella

Alnylam Forward Looking Statements

This presentation contains forward-looking statements, within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. There are a number of important factors that could cause actual results to differ materially from the results anticipated by these forward-looking statements. These important factors include: the direct or indirect impact of the COVID-19 global pandemic or a future pandemic, such as the scope and duration of the outbreak, government actions and restrictive measures implemented in response, material delays in diagnoses of rare diseases, initiation or continuation of treatment for diseases addressed by our products, or in patient enrollment in clinical trials, potential supply chain disruptions, and other potential impacts to our business, the effectiveness or timeliness of steps taken by us to mitigate the impact of the pandemic, and our ability to execute business continuity plans to address disruptions caused by the COVID-19 or a future pandemic; our ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of our product candidates, including ALN-AGT; pre-clinical and clinical results for our product candidates, including ALN-AGT; actions or advice of regulatory agencies; delays, interruptions or failures in the manufacture and supply of our product candidates, including ALN-AGT, and our marketed products; intellectual property matters including potential patent litigation relating to our platform, products or product candidates; our and our partner's ability to obtain regulatory approval for our product candidates, including lumasiran and inclisiran, and our ability to maintain regulatory approval and obtain pricing and reimbursement for products, including ONPATTRO® (patisiran) and GIVLAARI® (givosiran); our progress in continuing to establish a commercial and ex-United States infrastructure; our ability to successfully launch, market and sell our approved products globally, including ONPATTRO and GIVLAARI, and achieve net product revenues for ONPATTRO within our revised expected range during 2020; our ability to successfully expand the indication for ONPATTRO in the future; competition from others using similar technology and developing products for similar uses; our ability to manage our growth and operating expenses within the reduced ranges of guidance provided by us through implementation of further discipline in operations to moderate spend and our ability to achieve a self-sustainable financial profile in the future without the need for future equity financing; our ability to establish and maintain business alliances, including completing an agreement for funding by Blackstone of certain R&D activities for vutrisiran and ALN-AGT; our dependence on third parties, including Novartis, for the development, manufacture and commercialization of inclisiran, Regeneron, for development, manufacture and commercialization of certain products, including eye and CNS products, Ironwood, for assistance with the education about and promotion of GIVLAARI, and Vir for the development of ALN-COV and other potential RNAi therapeutics targeting SARS-CoV-2 and host factors for SARS-CoV-2; the outcome of litigation; and the risk of government investigations; as well as those risks and other factors more fully discussed in our most recent annual, quarterly and current reports filed with the SEC. If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements.

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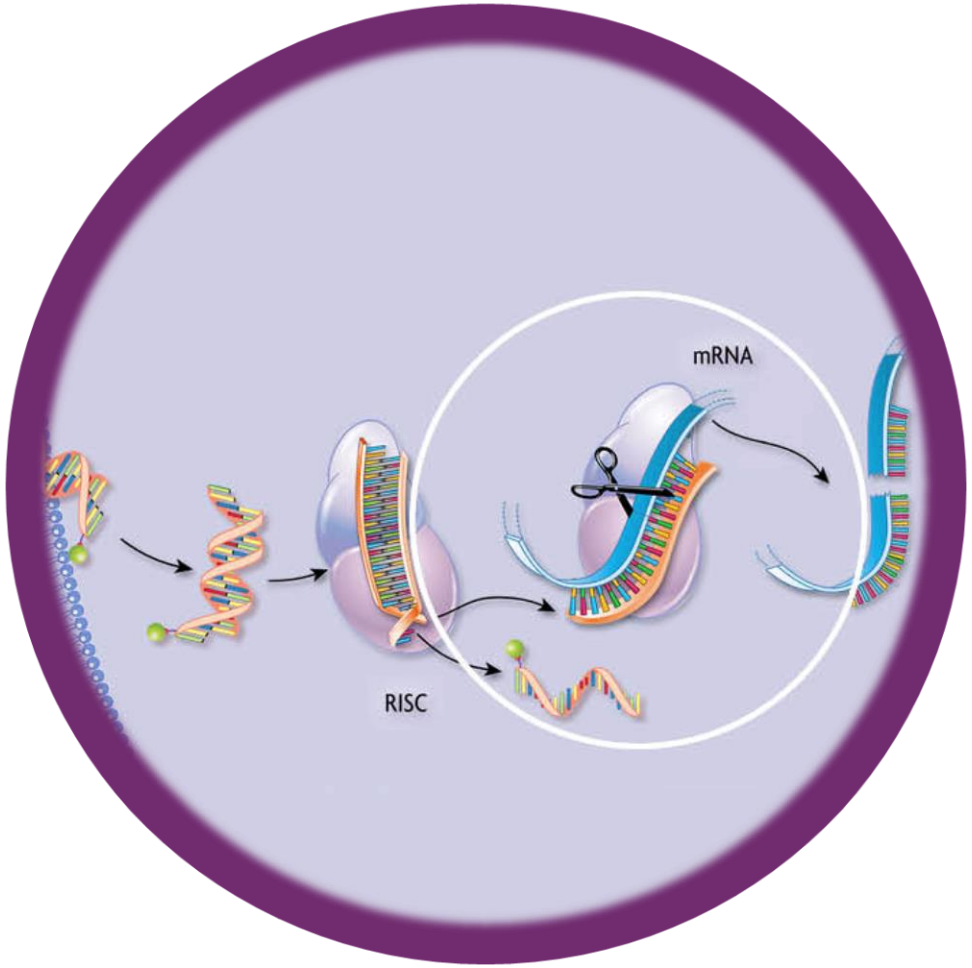
RNAi Therapeutics: New Class of Innovative Medicines

Clinically Proven Approach with Transformational Potential

- **Nobel Prize-winning science**
- **Silence any gene in genome**
- **Potent and durable mechanism of action**
- **Product engine for sustainable innovation**
- **Multiple products impacting patients globally**



Alnylam Commercial Products and Late Stage Clinical Development Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):

- Genetic Medicines
- Cardio-Metabolic Diseases
- Infectious Diseases
- CNS/Ocular Diseases

		BREAKTHROUGH DESIGNATION	LATE STAGE *(Phase 2-Phase 3)*	REGISTRATION	COMMERCIAL	COMMERCIAL RIGHTS
onpattro (patisiran) lipid complex injection 10 mg/5 mL	*hATTR Amyloidosis*[1]	●			●	Global
GIVLAARI® (givosiran) injection for subcutaneous use 189 mg/mL	*Acute Hepatic Porphyria*[2]	●			●	Global
Lumasiran	*Primary Hyperoxaluria Type 1*	●		●		Global
Inclisiran	*Hypercholesterolemia*			●		Milestones & up to 20% Royalties[3] **(Novartis)**
Patisiran	*ATTR Amyloidosis Label Expansion*		●			Global
Fitusiran	*Hemophilia and Rare Bleeding Disorders*		●			15-30% Royalties **(Sanofi)**
Vutrisiran	*ATTR Amyloidosis*		●			Global

[1] Approved in the U.S. and Canada for the polyneuropathy of hATTR amyloidosis in adults, in the EU, Switzerland and Brazil for the treatment of hATTR amyloidosis in adults with stage 1 or stage 2 polyneuropathy, and in Japan for the treatment of transthyretin (TTR) type familial amyloidosis with polyneuropathy

[2] Approved in the U.S. for the treatment of adults with acute hepatic porphyria (AHP), and in the EU for the treatment of AHP in adults and adolescents aged 12 years and older

[3] As part of Blackstone strategic financing collaboration, 50% of inclisiran royalty revenue will be payable to Blackstone

As of May 2020

Alnylam Early Stage Clinical Development and 2020 IND Pipeline

Focused in 4 Strategic Therapeutic Areas (STArs):

- Genetic Medicines
- Cardio-Metabolic Diseases
- Infectious Diseases
- CNS/Ocular Diseases

		HUMAN POC[1]	BREAKTHROUGH DESIGNATION	2020 IND CANDIDATES	EARLY STAGE *(Phase 1-Phase 2)*	COMMERCIAL RIGHTS
Cemdisiran	*Complement-Mediated Diseases*	✓			●	50-50 **(Regeneron)**
Cemdisiran/Pozelimab Combo[2]	*Complement-Mediated Diseases*				●	Milestone/Royalty **(Regeneron)**
ALN-AAT02 (DCR-A1AT)[3]	*Alpha-1 Liver Disease*	✓			●	Ex-U.S. option post-Phase 3 **(Dicerna)**
ALN-HBV02 (VIR-2218)	*Hepatitis B Virus Infection*	✓			●	50-50 option post-Phase 2 **(Vir)**
ALN-AGT	*Hypertension*	✓			●	Global
ALN-HSD	*NASH*			○		Milestone/Royalty **(Regeneron)**
ALN-COV (VIR-2703)	*COVID-19*			○		50-50 option post-Phase 2 **(Vir)**

2-4 *INDs per year planned from organic product engine*

[1] POC, proof of concept – defined as having demonstrated target gene knockdown and/or additional evidence of activity in clinical studies
[2] Cemdisiran is currently in Phase 2 development and pozelimab is currently in Phase 1 development; Alnylam and Regeneron are evaluating potential combinations of these two investigational therapeutics
[3] Dicerna is leading and funding development of ALN-AAT02 and DCR-A1AT and will select which candidate to advance in development

As of May 2020

ALN-AGT Opportunity

Uncontrolled & Difficult to Treat Hypertension

Disease Overview

Disease Definition

Uncontrolled hypertension defined as systolic/diastolic BP ≥130/80 mmHg, including variability, lack of night-time control, and poor adherence

Treatment resistant hypertension defined as uncontrolled BP while taking ≥3 classes of antihypertensive medications (or ≥4 regardless of BP level)[1]

Resistant Hypertension Patient Population[2]

~11 Million

in U.S.

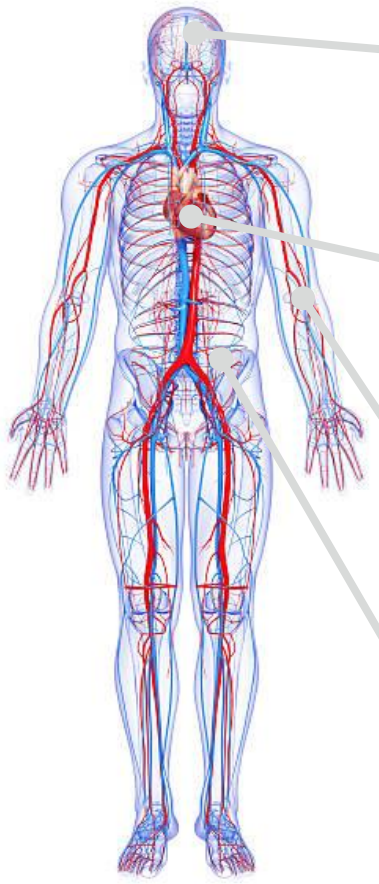
Uncontrolled BP in Patients with High-Risk for CV Events[3]

~10 Million

in U.S.

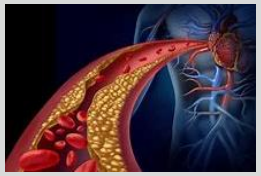
Patients with persistent hypertension despite multiple medications are at high risk for adverse cardiovascular events

Potential Complications of Hypertension



Stroke

Heart Attack



Arteriosclerosis

Kidney Failure

[1] https://www.ahajournals.org/doi/full/10.1161/HYP.0000000000000065
[2] Carey. Hypertension. 2018, : Judd. J Hum Hypertens. 2014 ; Sinnot. BMJ. 2017
[3] Estimated from multiple sources: Virani et al, Circulation. 2020;141:e139–e596. Mainous et al, Am J Prev Med 2018;55(3):384–388. Sonawane et al, J Clin Hypertens. 2019;21:766–773. Gu et al, Circulation. 2012;126:2105-2114. Gu et al, Clin Med Insights Cardiol. 2019;13:1–9. National Diabetes Statistics report 2020. 2018 USRDS Annual Data Report. US Census Bureau. TriNetX USA Network, accessed May 2020

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BRIGHAM HEALTH

BRIGHAM AND WOMEN'S HOSPITAL

Hypertension Overview

Akshay S. Desai MD, MPH
Director, Cardiomyopathy and Heart Failure Program
Cardiovascular Division
Brigham and Women's Hospital
Associate Professor of Medicine
Harvard Medical School
Boston, MA

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Objectives

BRIGHAM HEALTH
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- Outline basic epidemiology of hypertension and continuous association between blood pressure (BP) and cardiovascular (CV) risk
- Discuss changing definitions of hypertension and implications for treatment
- Highlight therapeutic gaps in hypertension
  - Undertreatment
  - Diurnal BP variation/Nocturnal Hypertension
  - Visit-to-Visit Variability
  - Adherence to Antihypertensive Therapy

Hypertension

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- **Leading risk factor for cardiovascular disease (CVD) and leading cause of disability-adjusted life years (DALY) worldwide**
- **Suboptimal BP control is the most common attributable risk factor for CVD and cerebrovascular disease (> 50%) and leading cause of chronic kidney disease (CKD) progression**

Global Disability-Adjusted Life Years by Systolic Blood Pressure Level and Cause

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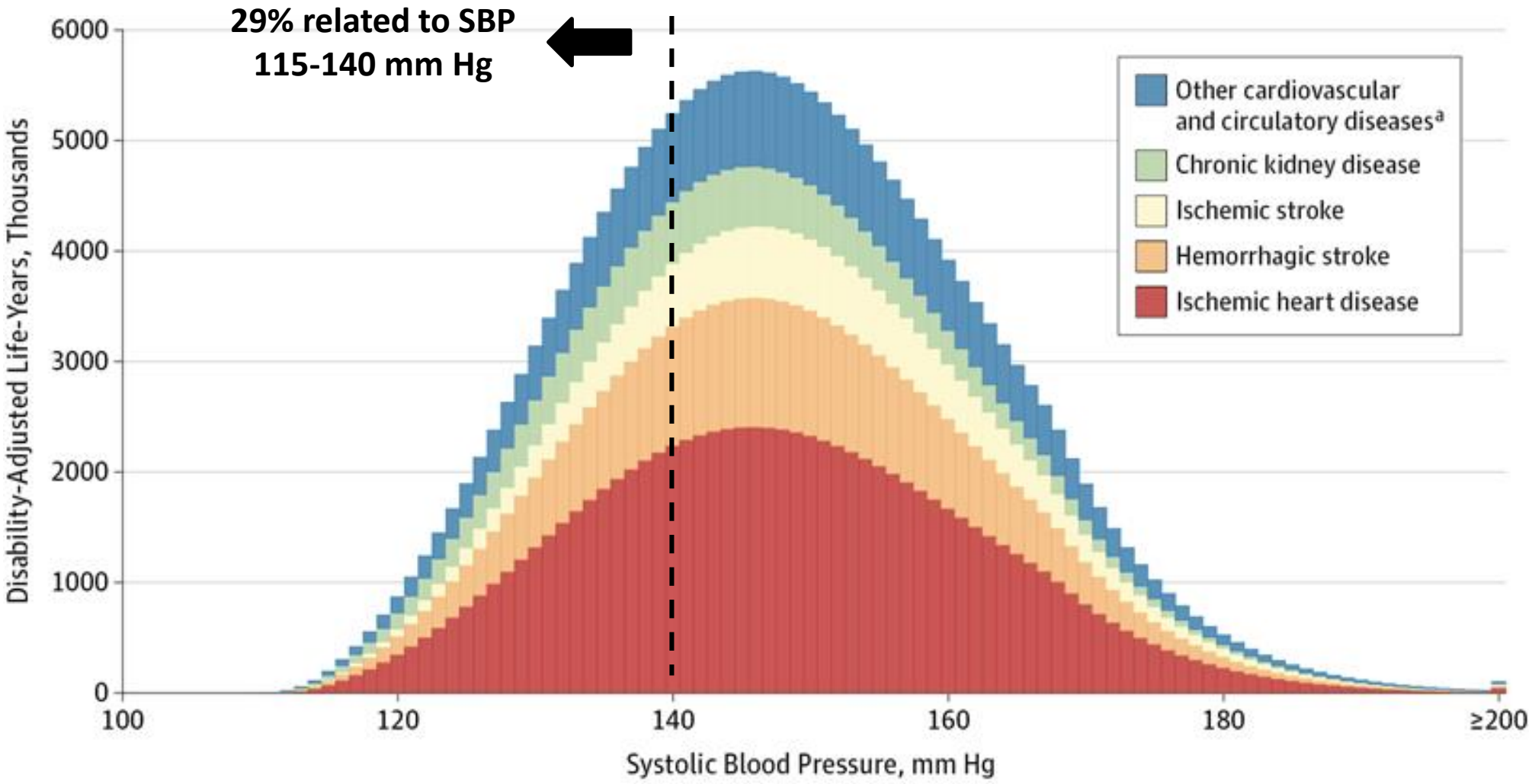

*1 DALY = 1 year of healthy life lost

Forouzanfar MH, et al. JAMA. 2017;317(2):165-182

Continuous Relationship between BP and CV risk

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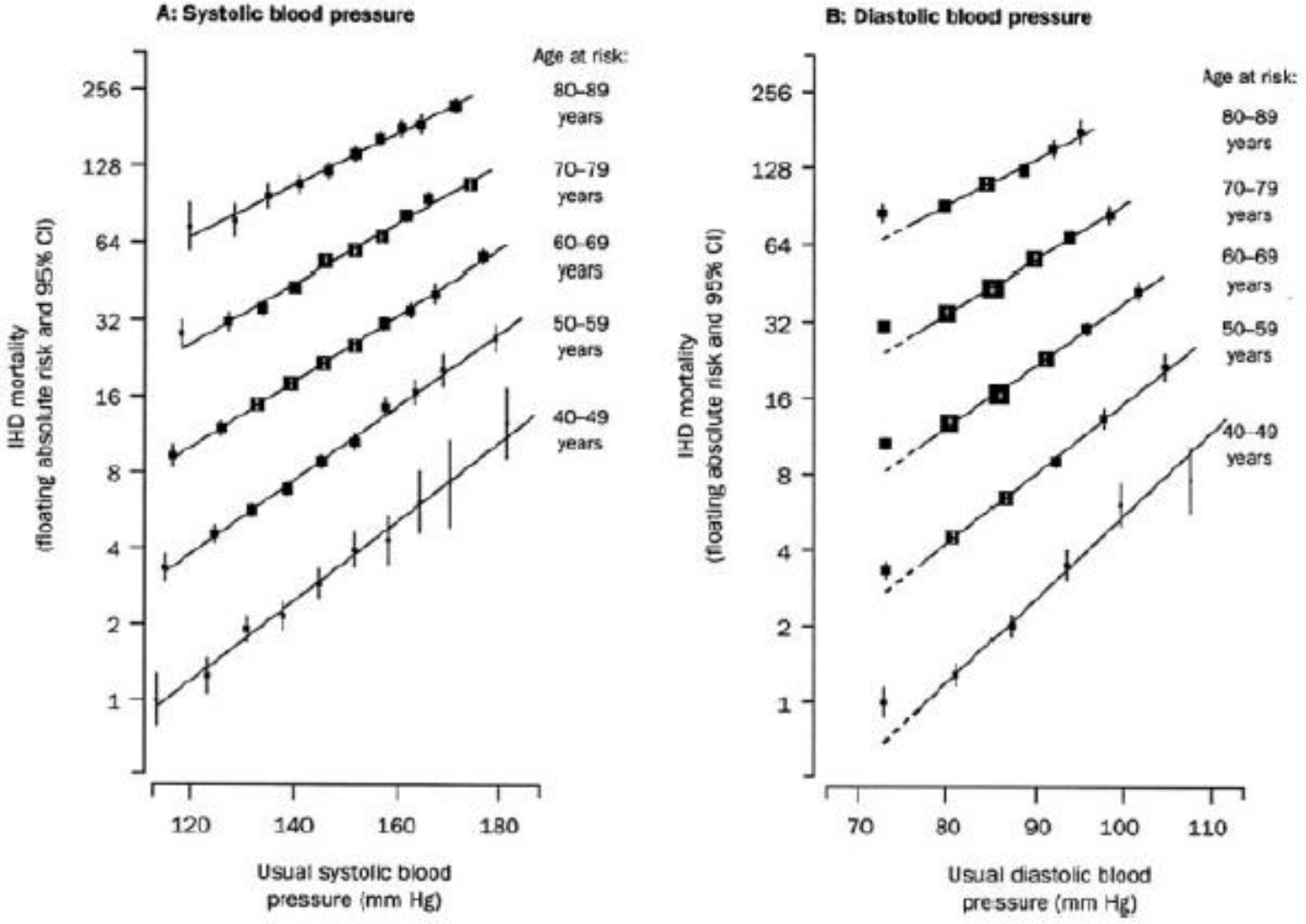

- At all ages and in both men and women, BP maintains a continuous, graded association with risk for fatal + nonfatal stroke, ischemic heart disease, heart failure
- No variation by ethnicity
- Risk persists down to a nadir of 115/75 mm Hg

Lewington S, et al. Lancet 2002;360:1903–1913
Chobanian A, et al. Hypertension. 2003;42:1206–1252

Doubling of Risk for each 20/10 mm Hg BP Increment

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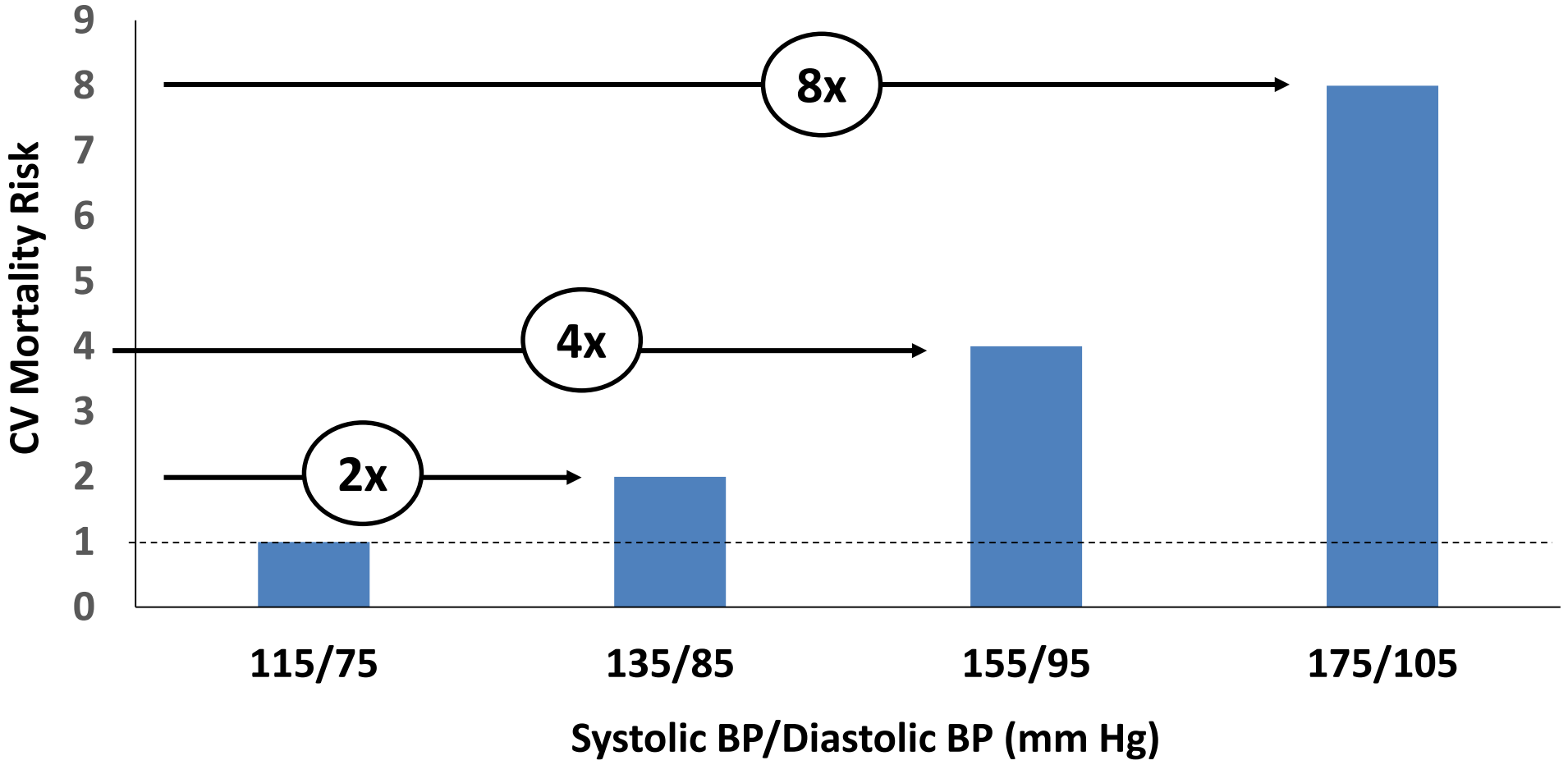

Lewington S, et al. Lancet 2002;360:1903–1913
Chobanian A, et al. Hypertension. 2003;42:1206–1252

Reduction in CV Risk with Antihypertensive Therapy

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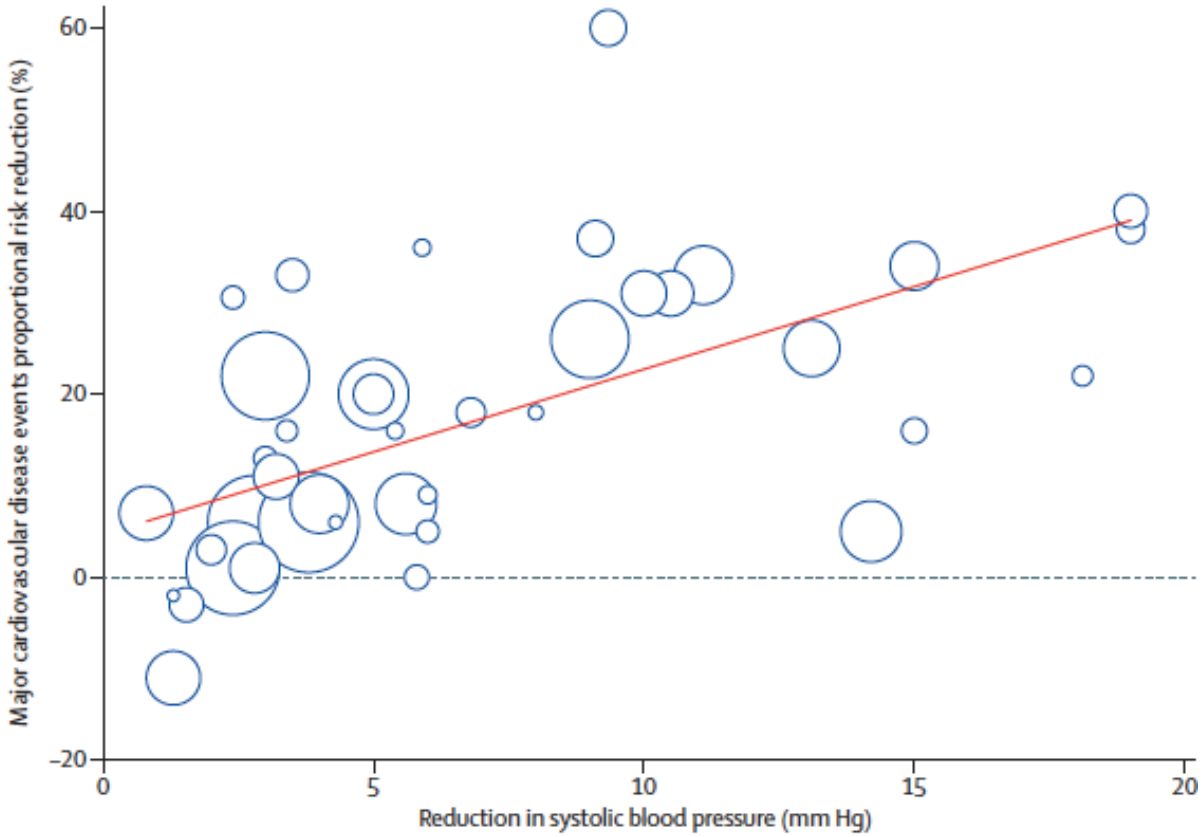

Meta-analysis of 123 studies, 613815 patients

	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%**

- No variation in benefit by comorbidity
- Consistent benefits in trials with lower initial BP (< 130 mm Hg)
- Effects largely consistent across drug classes (but beta-blockers slightly inferior)

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

Lifestyle Modification for BP Control

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Modification	Recommendation	Approximate SBP Reduction Range
Weight reduction	Maintain normal body weight (BMI=18.5-25)	5-20 mmHg/10 kg weight lost
DASH eating plan	Diet rich in fruits, vegetables, low fat dairy and reduced in fat	8-14 mmHg
Restrict sodium intake	<2.4 grams of sodium per day	2-8 mmHg
Physical activity	Regular aerobic exercise for at least 30 minutes at least 5 days of the week	4-10 mmHg
Moderate alcohol	≤2 drinks/day for men and ≤1 drink/day for women	2-4 mmHg

Chobanian AV et al. *JAMA* 2003;289:2560-2572

Pharmacologic Therapy of Hypertension

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ACE Inhibitors/ **A**ngiotensin Receptor Blockers

Beta Blockers

Less Effective
? Higher rates of stroke due to increase in visit-visit variability
Higher rates of Treatment Discontinuation
RESERVE FOR Established HFrEF/Prior MI

Calcium Channel Blockers

Diuretics

SPRINT: Intensive vs. Standard BP Control

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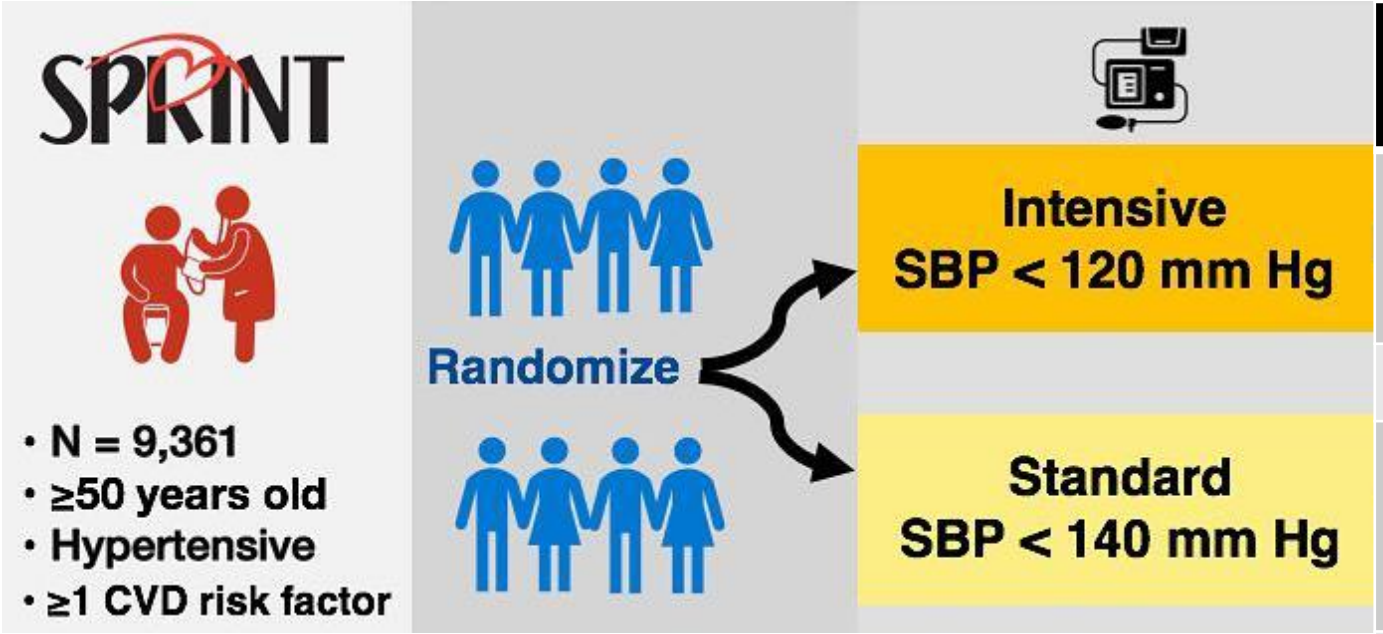

	EFFICACY		SAFETY	
	Primary Outcome**	Mortality	Hypotension	AKI
Intensive SBP < 120 mm Hg	5.2%	3.3%	3.4%	4.4%
Standard SBP < 140 mm Hg	6.8%	4.5%	2.0%	2.6%
	HR 0.75*	HR 0.73*	HR 1.7*	HR 1.7*

*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

SPRINT Results: Generalizability

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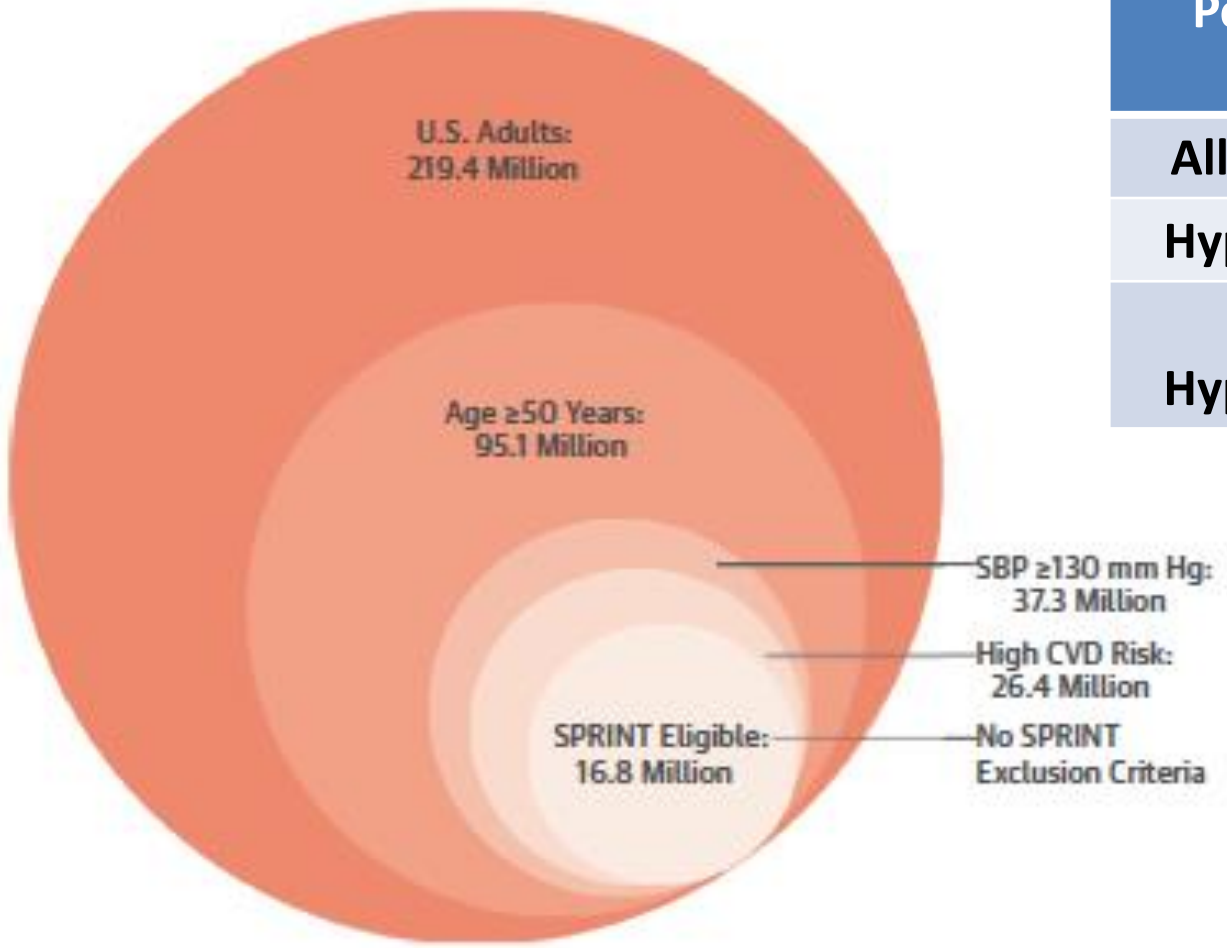

Population	Number in millions	% SPRINT Eligible
All US Adults	219.4	7.6%
Hypertension	68.5	20%
Treated Hypertension	49.5	16.7%

Bress, A.P. et al. J Am Coll Cardiol. 2016; 67(5):463–72.

Changing BP Targets

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SBP		DBP	2003 JNC 7	2017 ACC/AHA
<120	and	<80	Normal BP	Normal BP
120–129	and	<80	Prehypertension	Elevated BP
130–139	or	80–89	Prehypertension	Stage 1 hypertension
140–159	or	90-99	Stage 1 hypertension	Stage 2 hypertension
≥160	or	≥100	Stage 2 hypertension	Stage 2 hypertension

Whelton PK et al. J Am Coll Cardiol. 2017; doi: 10.1016/j.jacc.2017.11.006. [Epub ahead of print].

Hypertension Prevalence by New Definitions

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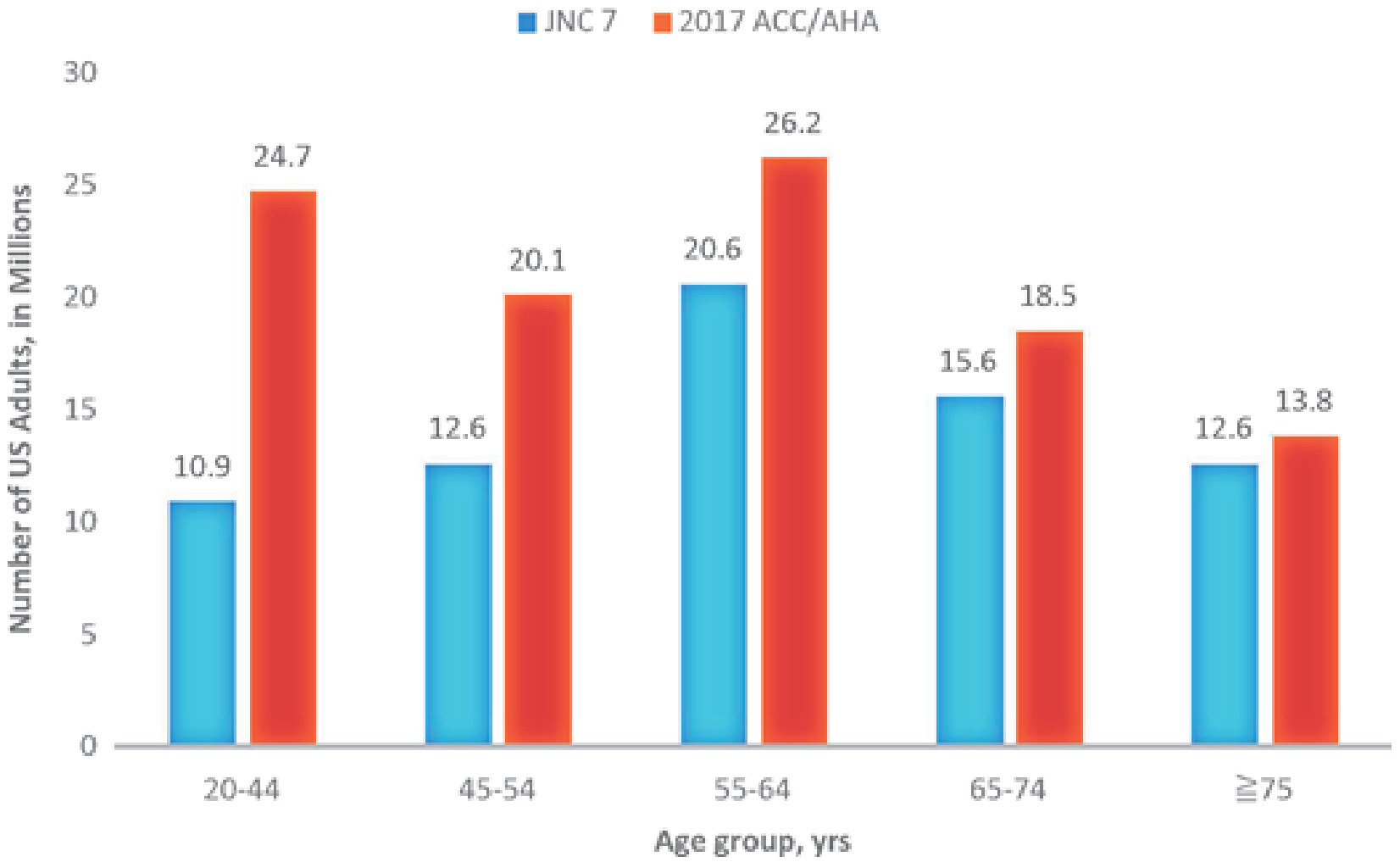

Tiwana J, Yang E. European Heart Journal, 2019; 40(26): 2106–2109

US Population Implications of New ACC/AHA BP Targets

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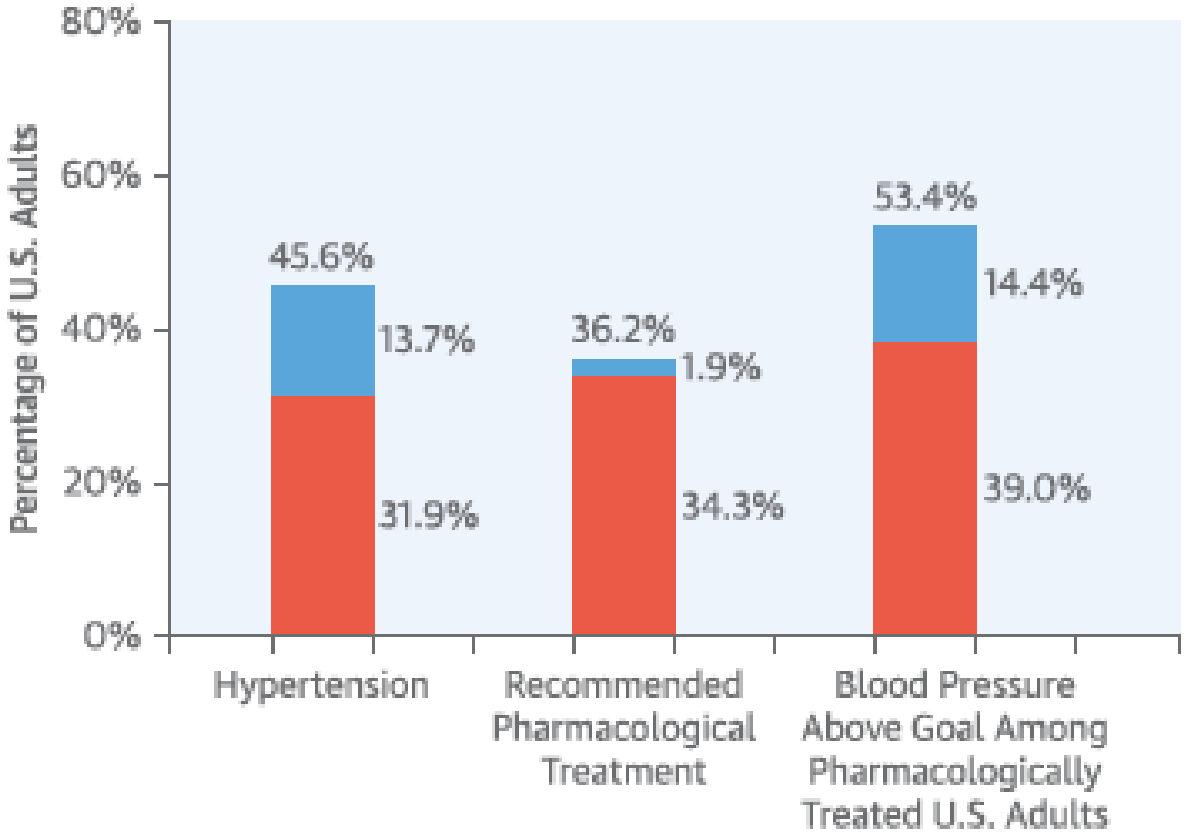

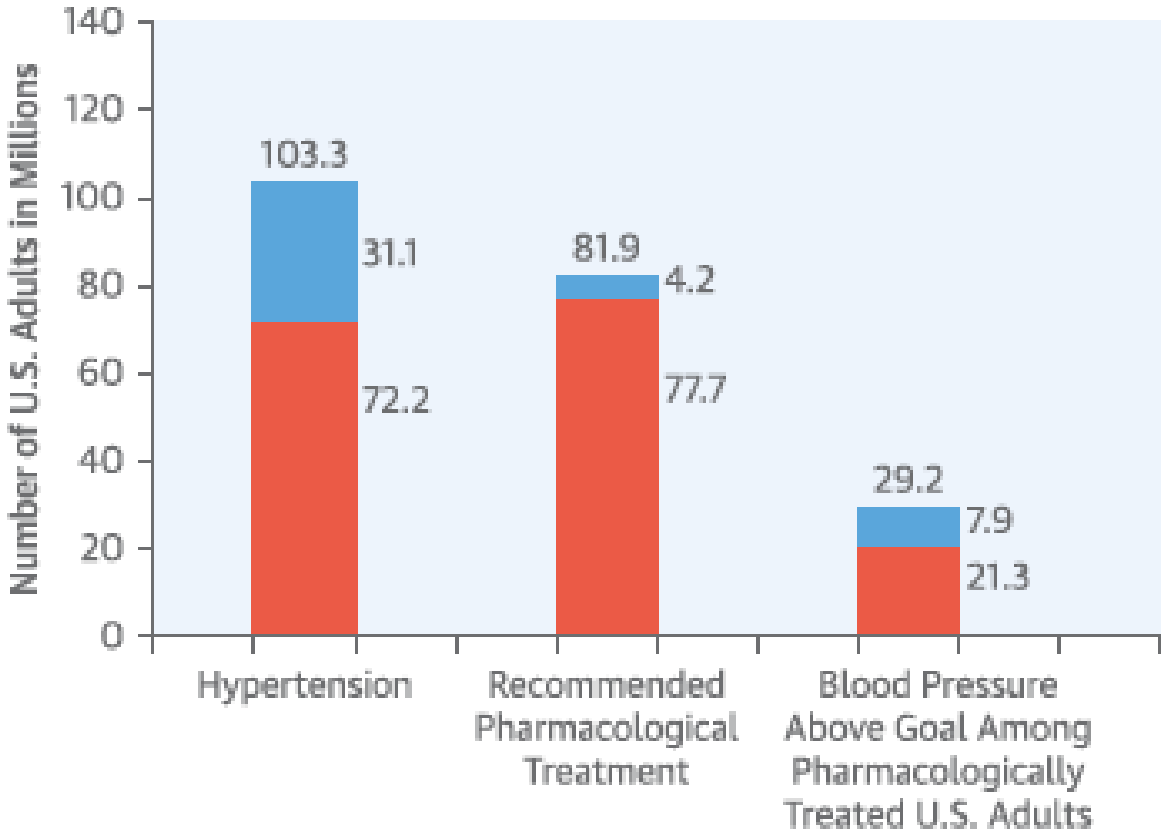

2017 ACC/AHA Guideline But Not JNC7
2017 ACC/AHA Guideline and JNC7

Muntner P, et al. Circulation. 2018;137:109–118.

Variability in BP

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

Circadian Variation in BP and CV Risk

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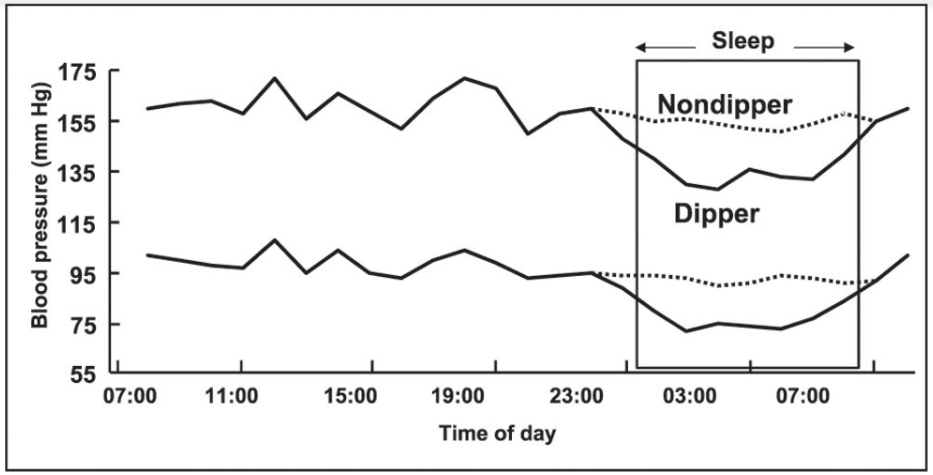
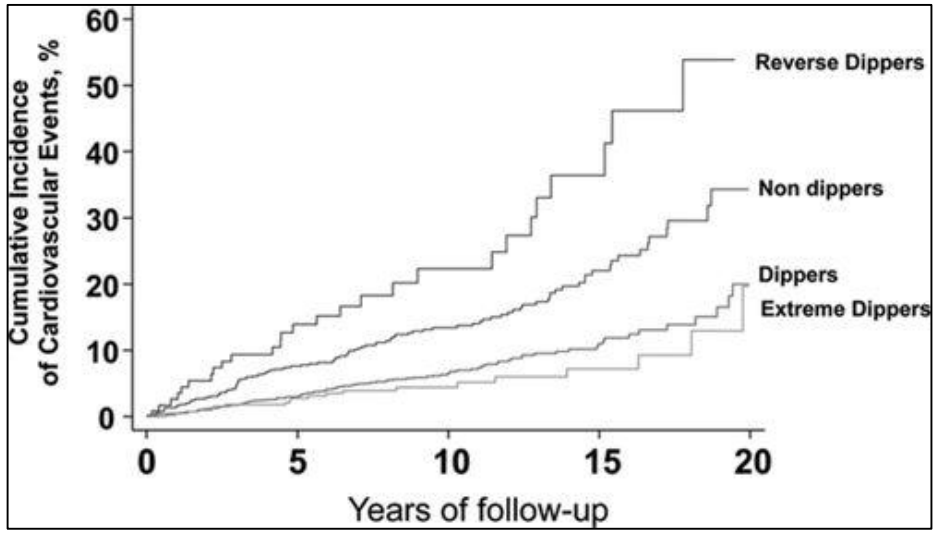
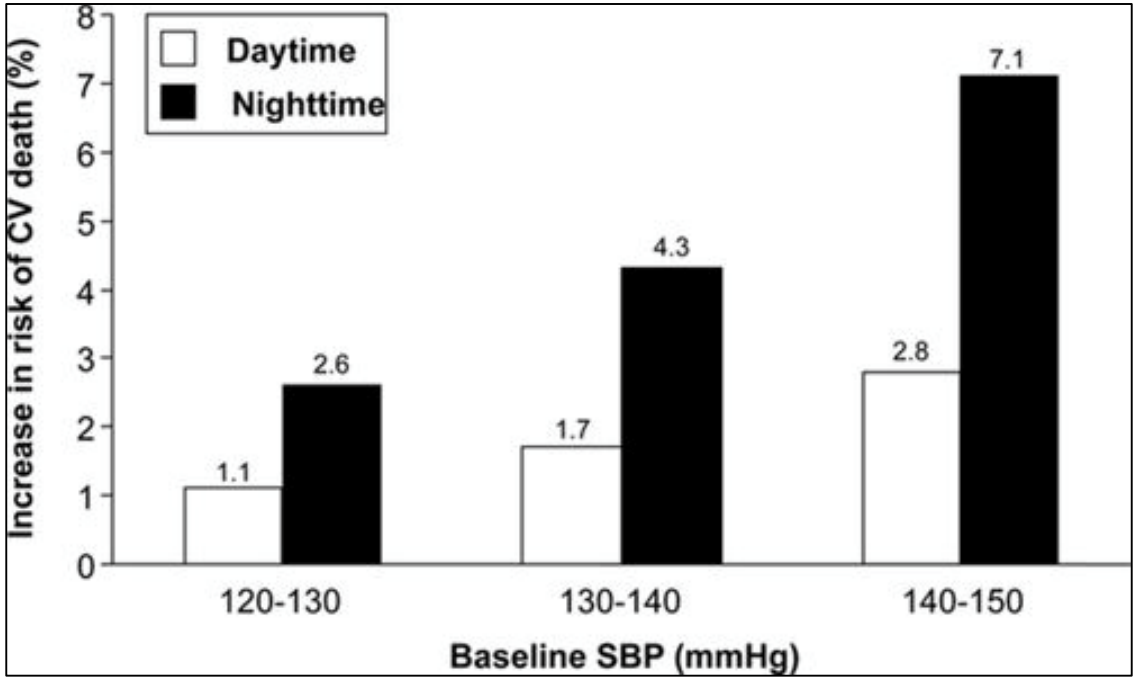




Nondipping associated with advanced age, obesity, diabetes



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.

Nocturnal Hypertension and CV risk

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Meta-analysis of 9 cohorts enrolling 13844 patients with hypertension

	All CV events	CAD	Stroke
Before Simultaneous Adjustment			
Nocturnal SBP	1.25 (1.22-1.29)	1.13 (1.05-1.22)	1.29 (1.19-1.39)
Daytime SBP	1.20 (1.15-1.26)	1.08 (0.99-1.18)	1.29 (1.20-1.38)
Clinic SBP	1.11 (1.06-1.16)	1.13 (0.95-1.34)	1.13 (1.06-1.21)
After simultaneous adjustment			
Nocturnal SBP	1.26 (1.20-1.31)	1.22 (1.13-1.31)	1.26 (1.09-1.46)
Daytime SBP	1.01 (0.94-1.08)	0.97 (0.88-1.07)	1.04 (0.92-1.17)
Clinic SBP	1.00 (0.95-1.05)	1.01 (0.93-1.09)	1.00 (0.97-1.03)

Greater dispersion in NSBP than DSBP or CSBP

Roush GC, et al. Journal of Hypertension 2014, 32:2332–2340

Visit-to-Visit Variability and Risk of Stroke in Hypertension

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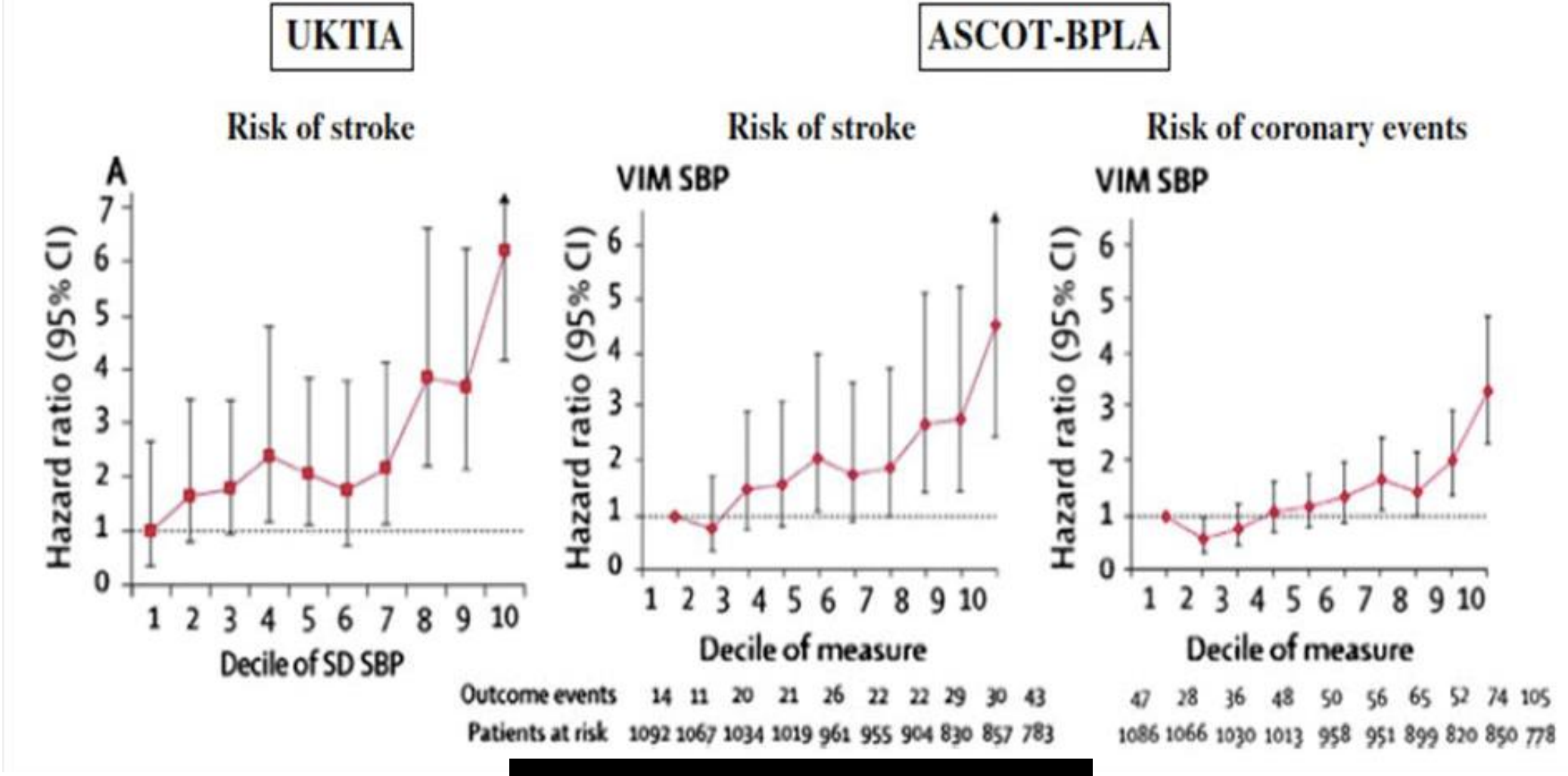

Effect independent of mean SBP

Rothwell PM, et al. Lancet 2010; 375: 895-905

Variability predicts CV events independent of baseline risk

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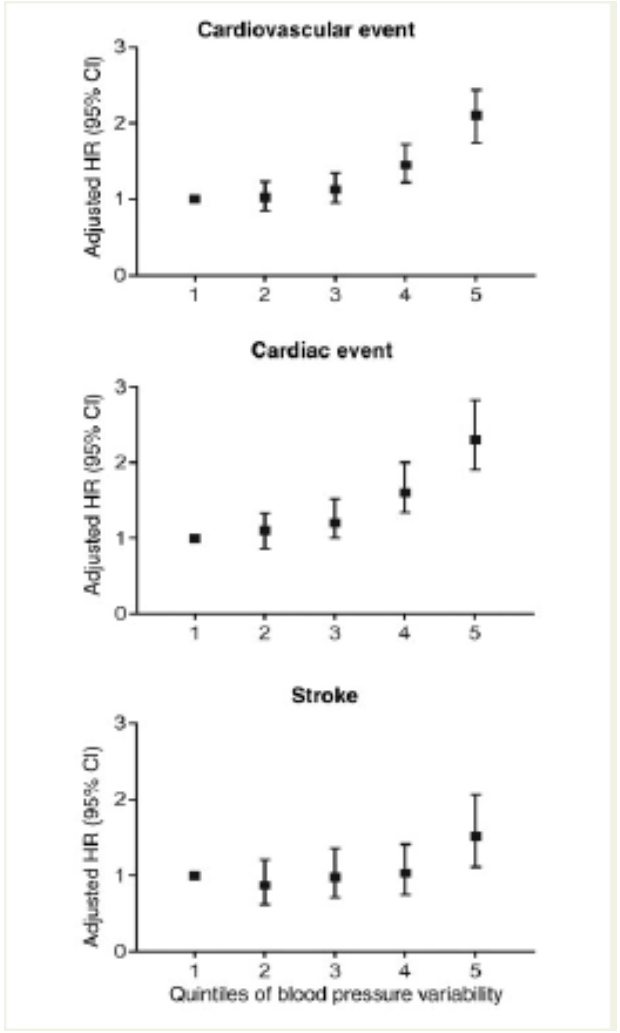
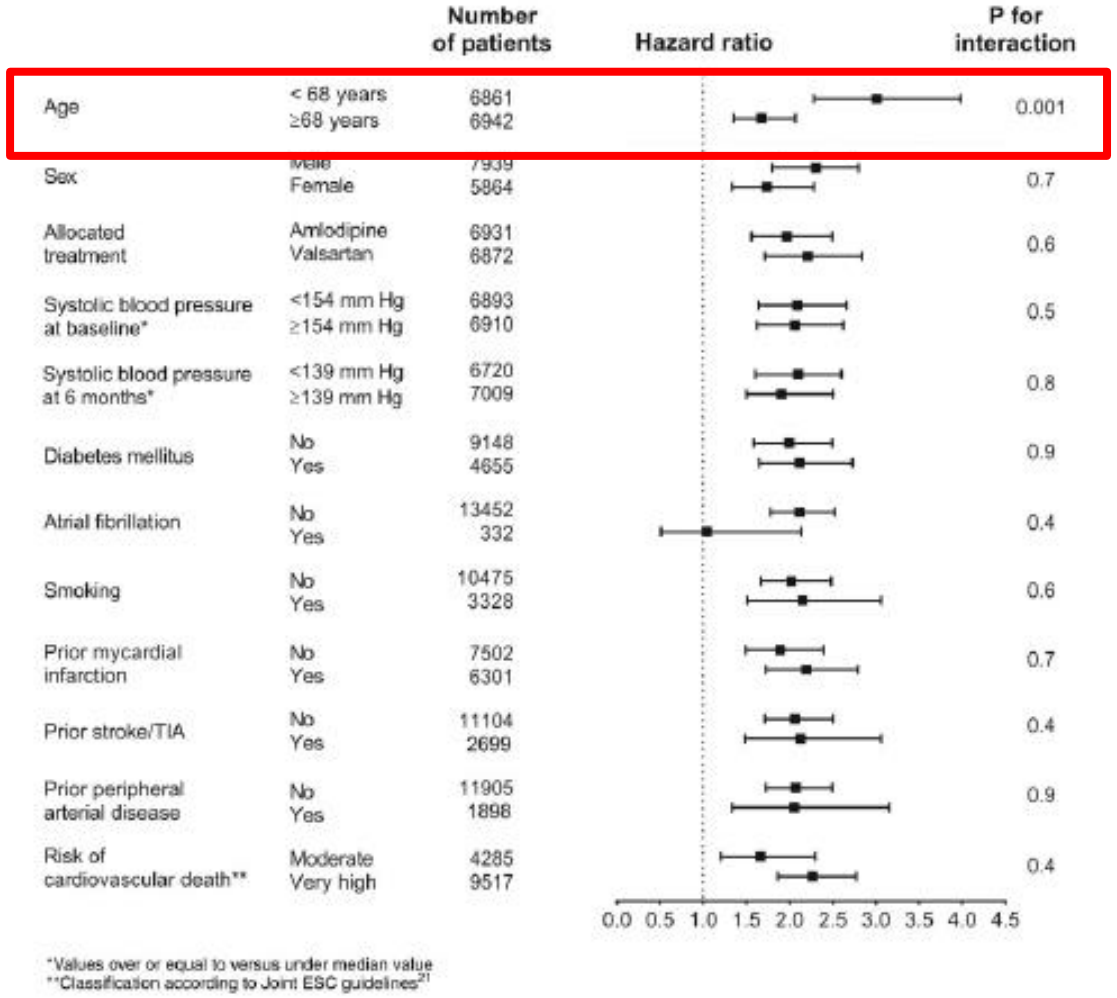


VALUE Trial (n=13803)



Mehlum MH, et al. Eur Heart J 2018;39: 2243–2251

Resistant Hypertension

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- **Uncontrolled despite ≥ 3 antihypertensive medications**
- **Variable Prevalence Depending on cohort examined**

Population Based	Time Period	n	Uncontrolled With ≥3 BP Medications, %	Controlled With ≥4 BP Medications, %	aTRH, %
NHANES[13]	1988–1994	2755	8.3	1.1	9.4
NHANES[13]	1999–2004	3031	8.8	2.9	11.7
NHANES[14]	2003–2008	3710	…	…	12.8
NHANES[13]	2005–2008	2586	9.7	4.8	14.5
REGARDS[15]	2003–2007	14731	9.1	5.0	14.1
REGARDS[16] (CKD)*	2003–2007	3134	…	…	28.1
Clinic based					
EURIKA[17] (diabetes mellitus)	2009–2010	5220	13.0†	3.1	16.1
Spanish ABPM[18]	2004–2009	68045	12.2	2.6	14.8
CRIC (CKD)[19]‡	2003–2008	3939	21.2	19.2	40.4
South Carolina[20]§	2007–2010	468877	9.5	8.4	17.9
Clinical trials					
ALLHAT[21]	1994–2002‖	14684	11.5	1.2	12.7
ASCOT[22]	1998–2005	19527	48.5	…	…
ACCOMPLISH[25]	2003–2006¶	10704	39	…	…
INVEST[26]	1997–2003#	17190	25.1	12.6	37.8

Carey RM, et al. Hypertension. 2018;72:e53-e90

Factors Associated with Inadequate BP Control

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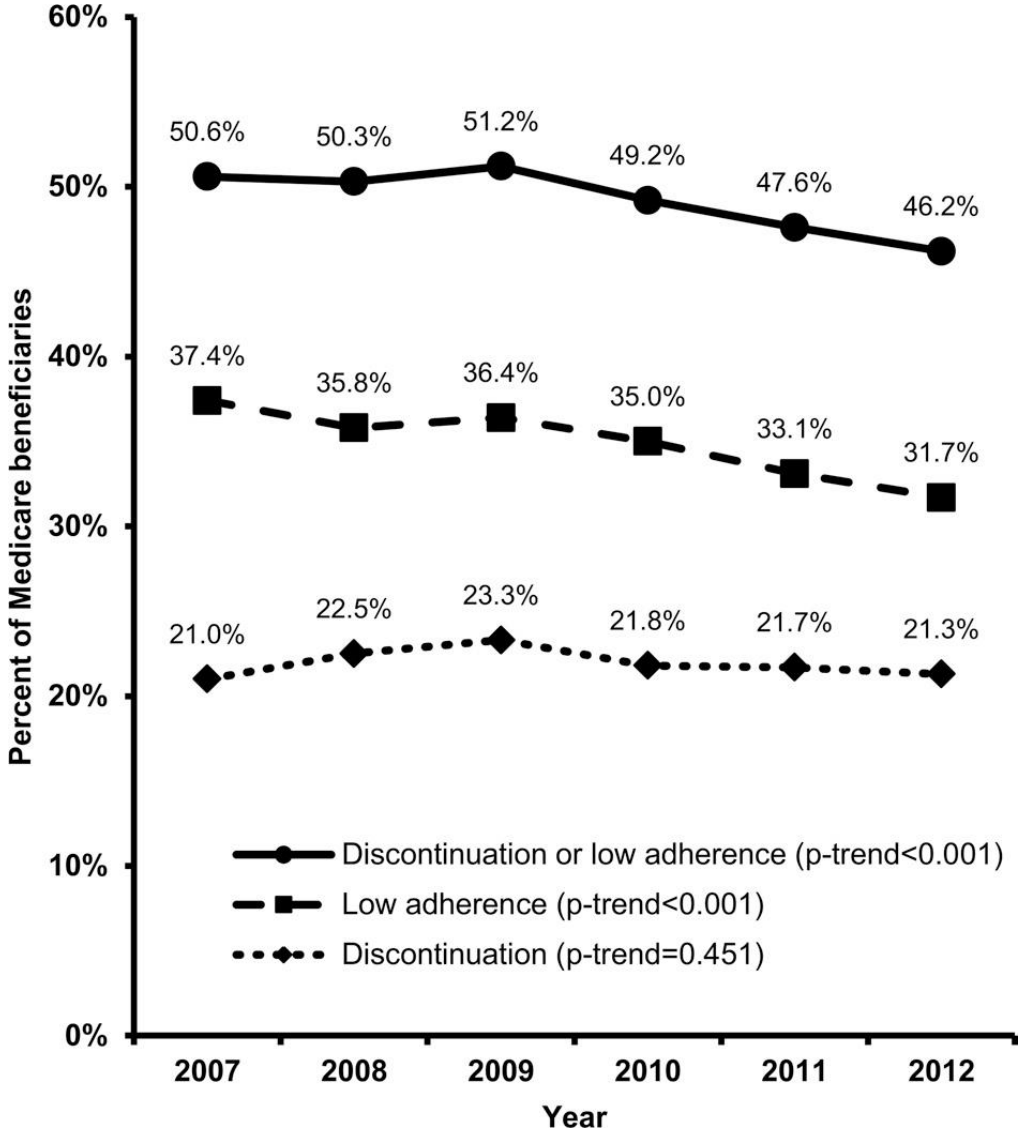
- Lack of health insurance or access to care
- Absence of a usual source of care
- Failure to diagnose HTN
- Therapeutic Inertia
- Inadequate patient education
- Inadequate guidance re: lifestyle modification
- Poor adherence to treatment
- Lack of tonic control

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

Adherence to Antihypertensive Therapy among Medicare Beneficiaries

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL



- 41135 Medicare Beneficiaries initiating antihypertensive therapy 2007-2012
- 21% of patients discontinued therapy prior to 1 year
- 31.7% of those not discontinuing therapy had low adherence to therapy (medication available for < 80% of days)

Tajeu GS, et al. Hypertension 2016;68(3):565-75

Adherence to Antihypertensive Therapy and Risk of CV Events

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL

N=18806 Newly Diagnosed Hypertensives in 400 Italian Primary Care Practices

Adherence	Hazard Ratio	P-value
Low (PDC<40%)	(ref)	(ref)
Intermediate (PDC 40-79%)	0.86 (0.71-1.03)	0.109
High (PDC≥80%)	0.62 (0.40-0.96)	0.032

PDC = proportion of days covered

High adherence associated with 38% lower risk of CV events than low adherence

Mazzaglia G, et al. Circulation. 2009;120:1598-1605

Factors Associated with Nonadherence

BRIGHAM HEALTH
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- Complex Medication Regimens (Multi-pill regimens)
- Convenience Factors (Dosing Frequency)
- Behavioral factors
- Adverse Effects of Medication
- Younger age
- Depression
- Poor access to care

Therapeutic Inertia

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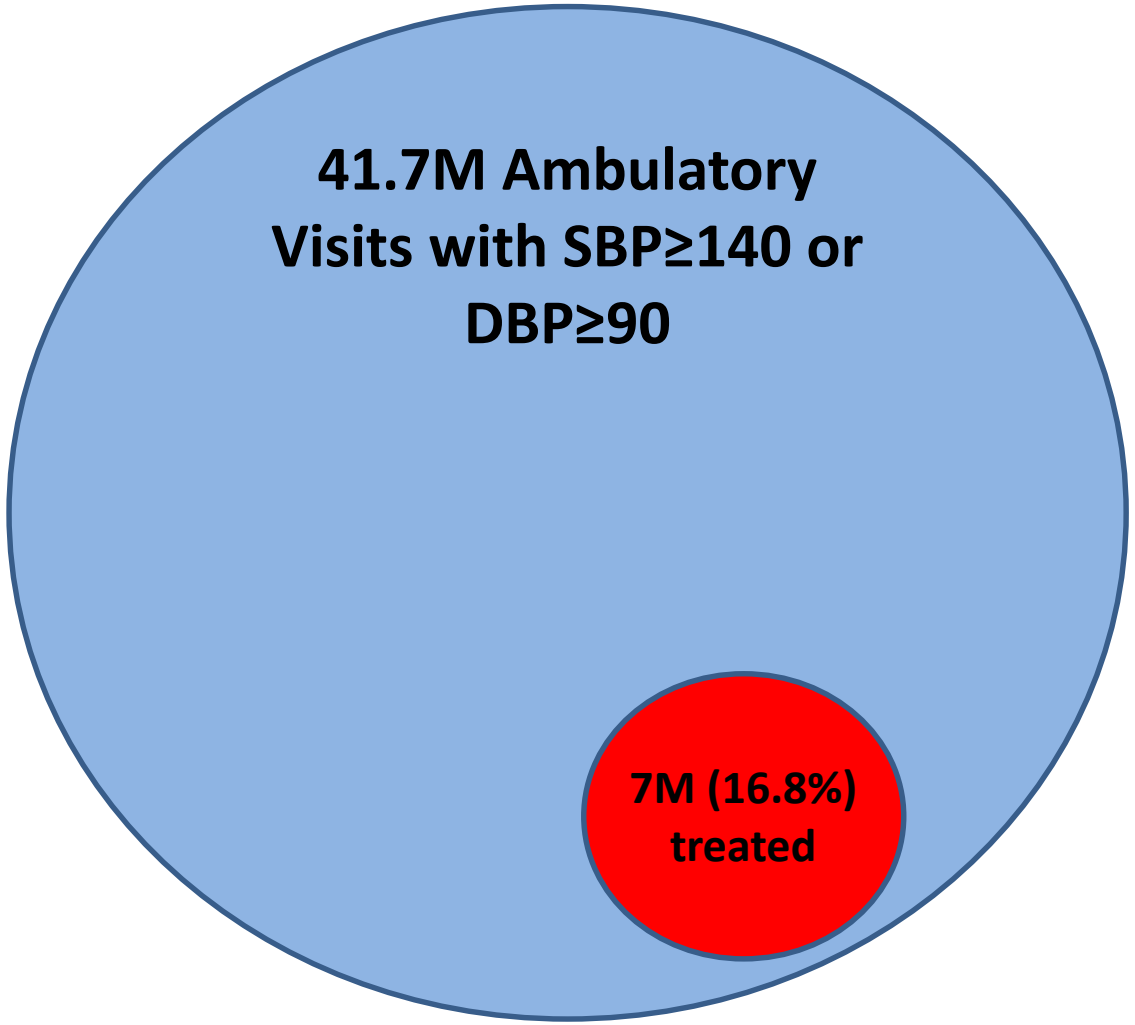

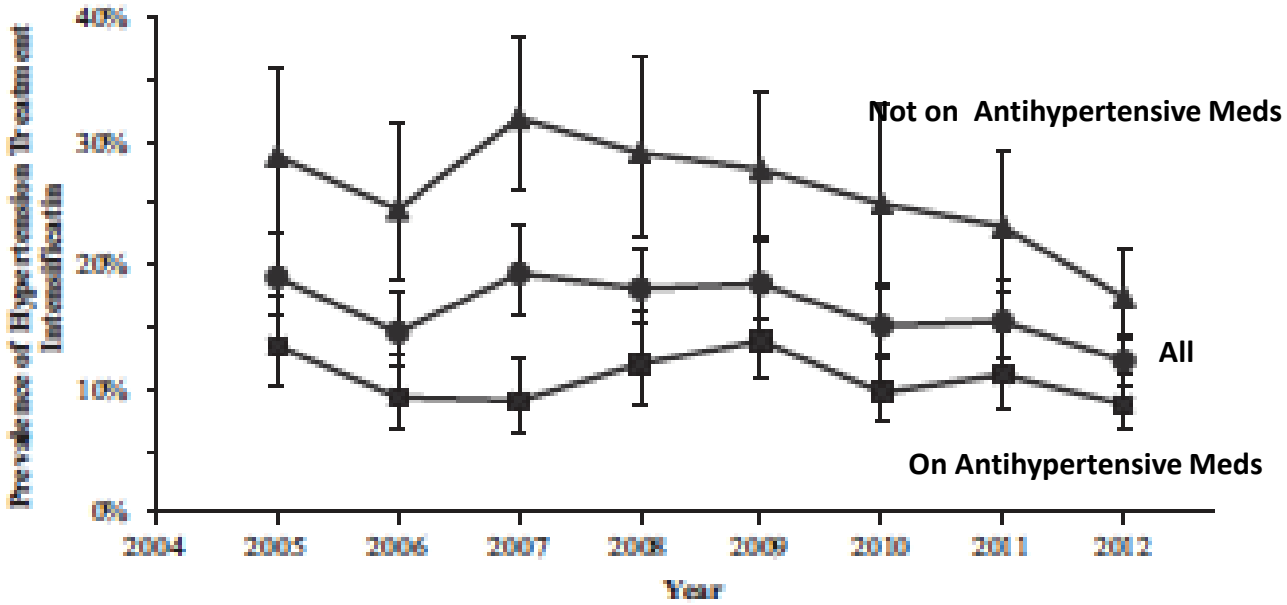

Possible Contributors

- Workflow Constraints/Time
- Lack of Awareness of Targets
- Concern about side effects
- Uncertainty about 'true' ambulatory BP

Mu L, Mukamal KJ. J Am Heart Assoc. 2016;5:e004188

Conclusions

BRIGHAM HEALTH
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- Continuous, graded association between SBP and risk of CV events
- Intensive BP control associated with reduction in CV events and mortality
- Large proportion of patients with hypertension are undertreated and 'resistant' hypertension is common
- Short and long-term variation in BP are associated with risk and can be modulated with pharmacologic therapy
- Nonadherence and therapeutic inertia contribute to inadequate BP control

BRIGHAM HEALTH

BRIGHAM AND WOMEN'S HOSPITAL

Thank You!

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Agenda

Welcome
- Joshua Brodsky – Director, Investor Relations & Corporate Communications

Introduction
- John Maraganore, Ph.D. – Chief Executive Officer

Hypertension Background
- Akshay Desai, M.D., M.P.H – Director, Cardiomyopathy and Heart Failure Program, Cardiovascular Division, Brigham and Women's Hospital; Associate Professor of Medicine, Harvard Medical School

ALN-AGT Background and Development Program
- Jae Kim, M.D. – Vice President, Clinical Development

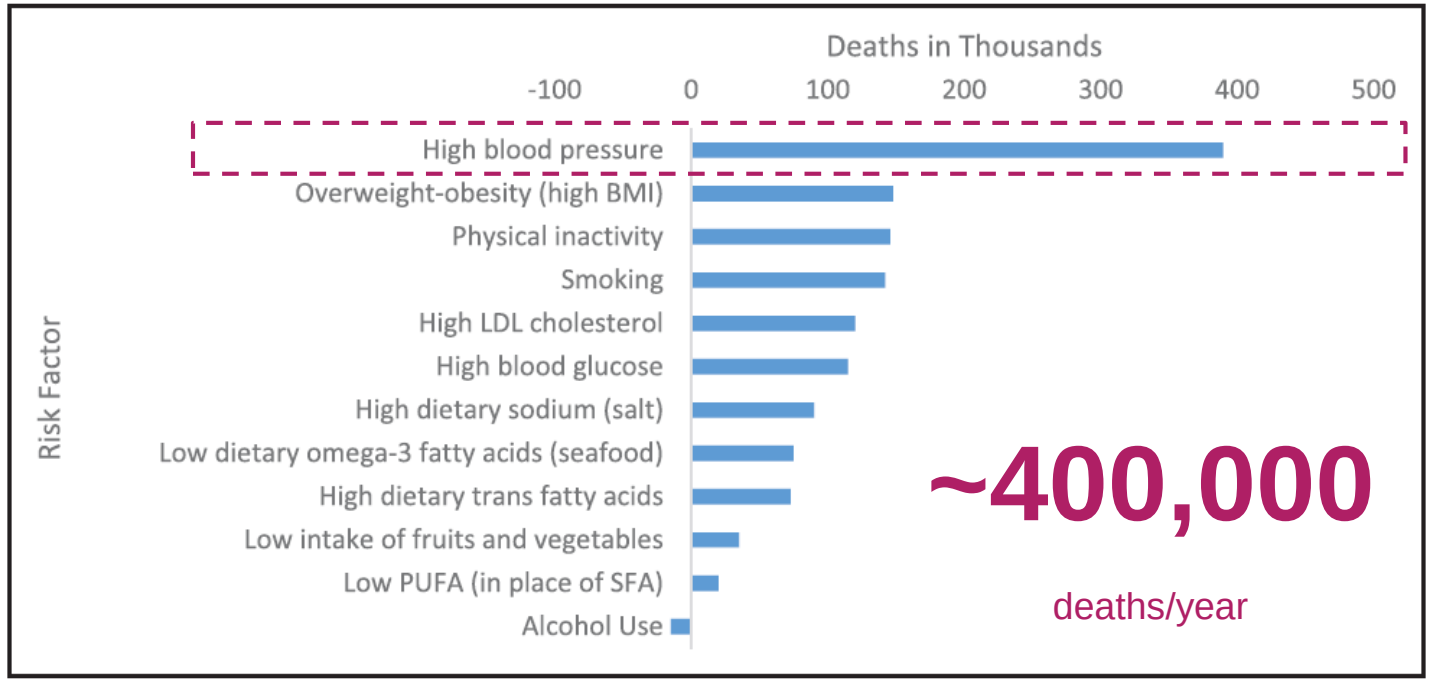
Commercial Outlook
- Lauren Melton – Senior Director, Program Leader, ALN-AGT

Q&A Session

Clinical Unmet Need in HTN: Urgent Call to Action

High Blood Pressure #1 Preventable CV Risk Factor for Premature Mortality in US

Preventable Causes of Death in the United States



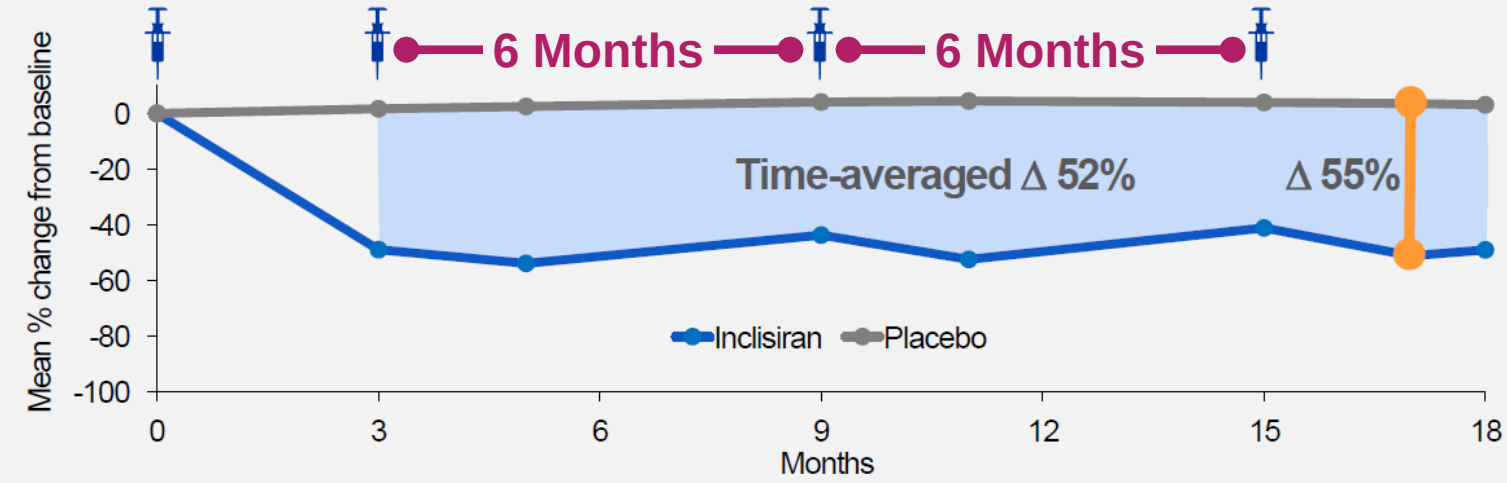
- HTN leads to strokes and heart attacks
  - In 2015, high BP leading cause of death and disability-adjusted life years worldwide
- 45.6% of U.S. adults have hypertension under 2017 ACC/AHA guidelines, with more than half of patients on medication remaining above BP target
- Despite availability of antihypertensives:
  - Poor adherence
  - BP variability
  - Inadequate night-time BP control
  - Resistant and refractory hypertension

McClellan et al., Circulation. 2019, Lim SS, Vos T, Flaxman AD et al. 2010. Lancet. 2012;380:2224-60. Danaei G, Ding EL, Mozaffarian D, et al. PLoS Med. 2009;6:e1000058. Willey JZ, Moon YP, Kahn E, et al. J Am Heart Assoc. 2014;3:e001106. Saran R, Li Y, Robinson B, et al. Am J Kidney Dis. 2015;66 Svii:S1-305 Wilson PW, Kannel WB, Silbershatz H, et al. Arch. Intern. Med. 1999; 159:1104-9. Vital signs: awareness and treatment of uncontrolled hypertension among adults-United States, 2003-2010 CDC 2012; AHA (www.heart.org). HTN: Muntner P et al, Circulation 2017 [Pubmed 29133599]. Forouzanfar MH et al, Lancet 2016 [Pubmed ID 27733284]

Lessons From Inclisiran: Investigational RNAi Therapeutic Targeting PCSK9

Highly Stable and Durable Efficacy with Safety Similar to Placebo Group

ORION Phase III Pooled Analysis (N = 3,660): Percent Change in LDL-C Over Time



P-value for placebo – inclisiran comparison at each time point <0.00001

All 95% confidence intervals are less than ±2% and therefore are not visible outside data points

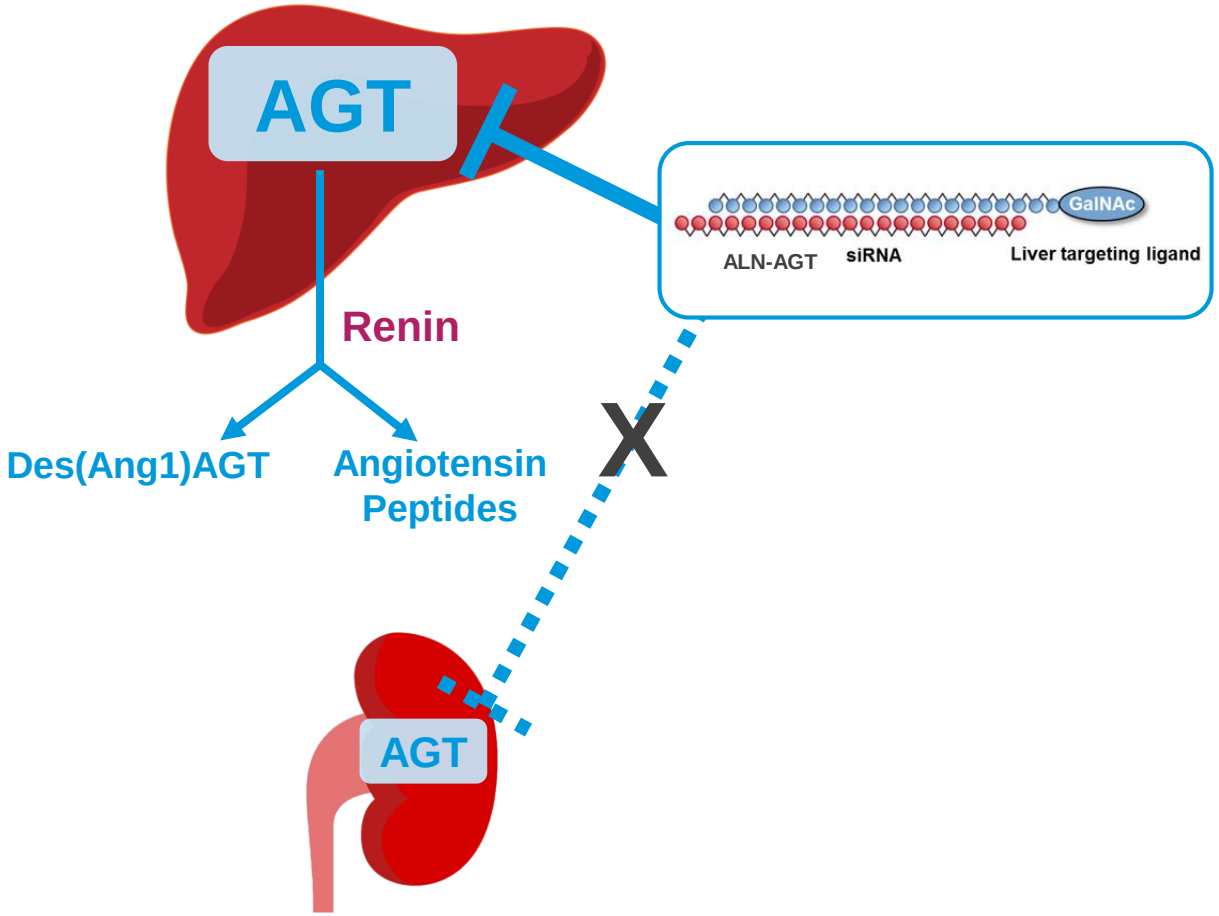
Safety observation of ~7,000 inclisiran injections and >2,700 years patient exposure

- Inclisiran safety profile similar to placebo
- No adverse changes in laboratory markers

Wright, et al. ACC 2020

ALN-AGT Therapeutic Hypothesis

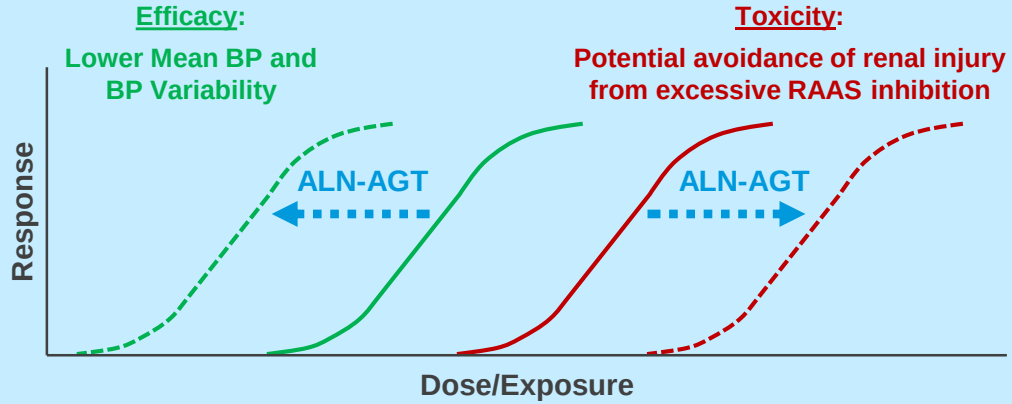
Liver-specific AGT knockdown



Potential Differentiated Profile to Improve Cardiovascular Health

Potential Mechanistic Advantages

- Liver-specific silencing → improved renal safety
- Enhanced efficacy through unique MOA
- Stable & durable silencing address night-time BP, BP variability, and adherence problems



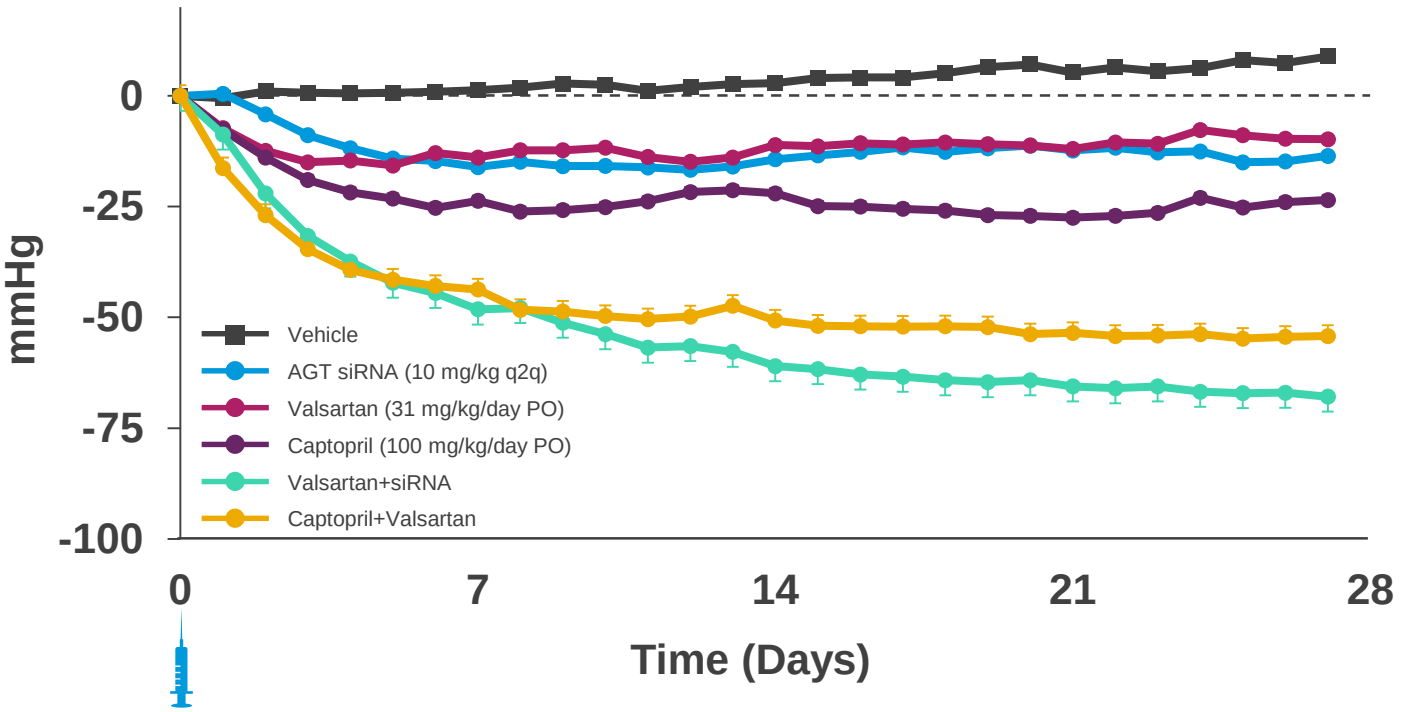
Potential Clinical Advantages

- Potent, durable, and stable reductions in BP
- Use with or without an ACEi/ARB
- Reductions in stroke, myocardial infarction, heart failure, kidney disease

ALN-AGT in Development for Hypertension

Angiotensinogen Silencing Results in BP Lowering in Rat Hypertension Model

Blood Pressure



- AGT siRNA reduced BP
- Combination of AGT siRNA + valsartan resulted in synergistic BP reduction, greater than captopril + valsartan
- Only AGT siRNA plus valsartan normalized cardiac hypertrophy

Preclinical Safety Parameters in AGT siRNA *with or without* Valsartan

- No reflexive change in heart rate
- No reduction in activity by radiotelemetry
- No decrease in urine output
- No change in directly-measured glomerular filtration rate (GFR)
- No acute kidney injury, measured by neutrophil gelatinase-associated lipocalin (NGAL), an early marker for kidney injury that precedes changes in kidney function

Uijl E, Mirabito Colafella KM, Sun Y, et al. Strong and Sustained Antihypertensive Effect of Small Interfering RNA Targeting Liver Angiotensinogen. Hypertension. 2019;73(6):1249–1257. doi:10.1161/HYPERTENSIONAHA.119.12703

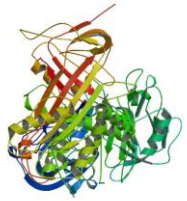
ALN-AGT for Hypertensive Diseases

Genetically Validated Target

Genetically validated, liver-expressed target gene

Biomarker for POC in Phase 1

Definable path to approval and patient access



Angiotensinogen (AGT):First Gene Linked to Primary Hypertension

Cell, Vol. 71, 169–180, October 2, 1992, Copyright © 1992 by Cell Press

Molecular Basis of Human Hypertension: Role of Angiotensinogen

Serum Biomarker
AGT levels

Clinical Biomarker
Blood Pressure

Blood Pressure

Validated Surrogate For:
Fatal and Nonfatal

Stroke

Myocardial Infarction

Jeunemaitre X et al. Cell, 1992; 2. Lifton RP , Science, 1996

Clinical Development Path

Drugs indicated to lower blood pressure: FDA recommendation to label indication, "Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions."[1]

Well-Established Endpoints:

- Systolic and diastolic BP by clinic blood pressure
- 24 Hour mean systolic and diastolic BP by ambulatory blood pressure monitoring (ABPM)

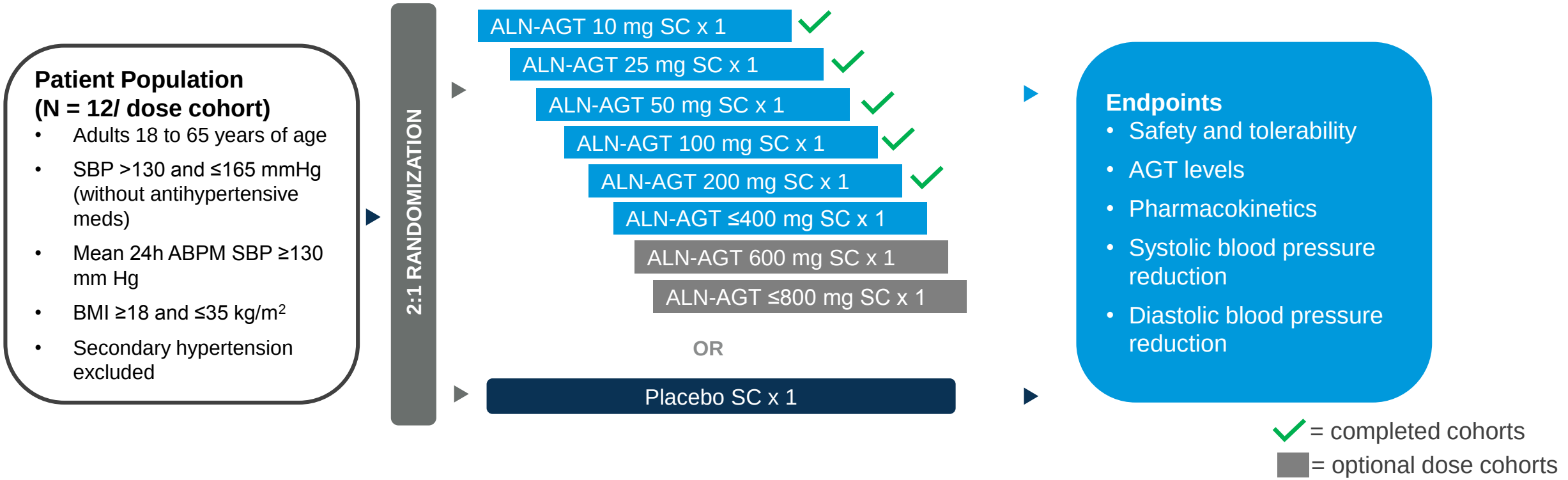
Opportunity for Novel Endpoints Subject to Alignment with Regulators:

- BP variability
- Night-time BP and night-time dip
- Improved adherence/ compliance (real-world pragmatic study)

[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/hypertension-indication-drug-labeling-cardiovascular-outcome-claims

ALN-AGT First-in-Human Single Ascending Dose Study

Initial Human Proof of Concept Achieved



Additional cohorts planned to evaluate the use of ALN-AGT

- Obese patients: PK/PD and effect of ALN-AGT on BP and body composition
- Salt control: tolerability in salt depletion, recovery of BP with high salt
- Addition of ARB in background of ALN-AGT: safety and tolerability

Initial Human Proof of Concept Achieved

Initial Phase 1 SAD Topline Results (N=48)[1]		Can Potentially Address Unmet Needs:
• >90% AGT knockdown	→	• "Clamped" pharmacology
• >10 mmHg reduction in mean 24-h systolic blood pressure relative to placebo	→	• Address uncontrolled BP with stable BP reductions: less variability & night-time BP lowering
• Durability supportive of once quarterly and possibly less frequent dosing	→	• Resolve adherence problems common with current daily oral medications
• Encouraging safety and tolerability profile with no drug-related SAEs	→	• Improved safety profile may be achievable with or without ACEi/ARB – data to inform[2]

Further results planned to be presented at scientific meeting in **late 2020**

[1] As of April 29, 2020 data transfer date; initial results reported on May 6, 2020

[2] ALN-AGT has not yet been studied in combination with ARB treatment; an additional planned cohort in Phase 1 SAD study to add an ARB in background of ALN-AGT

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ALN-AGT Commercial Opportunity: High Risk for Cardiovascular Events

Patients with Uncontrolled Blood Pressure at High Risk for Adverse CV Events

PREVALENCE

- ~5-16M patients in U.S. with high CV risk and HTN have uncontrolled BP on current regimen[1]
- High CV risk defined as previous history of myocardial infarction, angina, stroke, transient ischemic attack, heart failure, peripheral arterial disease, type 2 diabetes

CURRENT TREATMENT LANDSCAPE

- Guidelines specify treatment of HTN based on clinical severity and/or comorbidities
- Patients initiated on mono or combo therapy; increased doses or additional agents added if BP not controlled
- Uncontrolled HTN often due to non-adherence of prescribed therapy given daily pill burden[2]

DISEASE BURDEN

- Uncontrolled hypertension is the major risk factor for CV disease morbidity and mortality[3]
- ~1.5M people in U.S. have myocardial infarction or stroke annually, with ~50% of these major adverse cardiovascular events attributed to HTN[4,5]

COST BURDEN

- Annual direct and indirect cost of hypertensive disease and stroke in U.S.[6]: $55B and 45B*
- Suboptimal BP control cost $370B globally in 2001 (~10% of world's overall healthcare expenditure at that time[7])

Treatment of Uncontrolled Blood Pressure in Patients with High CV Risk

>$2B potential global market opportunity at peak

[1] Estimated based on historical rates of CV events: myocardial infarction, angina, stroke, transient ischemic attack, heart failure, peripheral arterial disease, type 2 diabetes. Sources: Virani et al, Circulation. 2020;141:e139–e596. Mainous et al, Am J Prev Med 2018;55(3):384–388. Sonawane et al, J Clin Hypertens. 2019;21:766–773. Gu et al, Circulation. 2012;126:2105-2114. Gu et al, Clin Med Insights Cardiol. 2019;13:1–9. National Diabetes Statistics report 2020. 2018 USRDS Annual Data Report. US Census Bureau. TriNetX USA Network, accessed May 2020.
[3] Zhou. Sci Rep. 2018; [4] Lawes. Lancet. 2001. [5] Korsnes. JMCP. 2015; [6] Benjamin. Circulation. 2019; [7] Gaziano. J Hypertens. 2009
* Not all stroke costs are associated with hypertension; additional cost related to heart disease and hypertension are observed

ALN-AGT Commercial Opportunity: Resistant Hypertension

Large Market, High Unmet Need in Patients with Difficult to Treat Hypertension

PREVALENCE

- U.S. and EU prevalence for resistant hypertension is ~20M (U.S. prevalence ~11M)
- ~20% of all drug treated hypertension classified as resistant hypertension[1]

CURRENT TREATMENT LANDSCAPE

- Treatment resistant hypertension defined as uncontrolled BP while taking ≥3 classes of antihypertensive medications (or ≥4 regardless of BP level)
- ~10% of treated patients on 4+ antihypertensive agents, often at maximally tolerated doses[2]

DISEASE BURDEN

- Patients with resistant hypertension at higher risk for poor outcomes, including death, myocardial infarction, heart failure, stroke, or CKD, compared to non-resistant patients[3]
- Estimated 30% of resistant hypertension due to non-adherence of prescribed therapy given daily pill burden[4]

COST BURDEN

- Annual direct and indirect cost of hypertensive disease and stroke in U.S.[6]: $55B and 45B*
- Suboptimal BP control cost $370B globally in 2001 (~10% of world's overall healthcare expenditure at that time[7])

Treatment of Resistant/Difficult to Treat Hypertension

>$2B potential global market opportunity at peak

[1] Carey. Hypertension. 2018.; [2] Estimated based on multiple literature sources and internal expert interviews;
[3] Carey. Hypertension. 2018; [4] Durand. J Hypertens. 2017., [5] Benjamin. Circulation. 2019; [6] Gaziano. J Hypertens. 2009
* Not all stroke costs are associated with hypertension; additional cost related to heart disease and hypertension are observed

Summary and Next Steps in Development of ALN-AGT

Significant unmet need for treatment of hypertension in patients with uncontrolled blood pressure

- Sustained blood pressure control with infrequent dosing could benefit patients with difficult to treat hypertension or patients at risk for CV events with uncontrolled blood pressure

Initial data from ongoing Phase 1 study in patients with mild to moderate hypertension encouraging

- Encouraging safety and tolerability profile
- >10 mmHg persistent reduction in mean 24-h systolic blood pressure relative to placebo
- Durability supportive of once quarterly and possibly less frequent dosing
- Additional clinical data expected to be presented late 2020

Initiation of Phase 2 Studies

- Studies planned for 2021; will explore use of ALN-AGT both alone and in combination with SOC antihypertensives

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Upcoming RNAi Roundtables

Early Stage RNAi Therapeutics Pipeline

- Friday, July 17, 9:30 am ET

Lumasiran, in Development for the Treatment of Primary Hyperoxaluria Type 1

- Date TBD

Patisiran and Vutrisiran, in Development for the Treatment of ATTR Amyloidosis

- Date TBD

Givosiran, for the Treatment of Acute Hepatic Porphyria

- Monday, September 14

Additional details for upcoming RNAi Roundtables, including speakers, dates and times, will be provided on the Capella section of the Company's website, www.alnylam.com/capella

Alnylam PHARMACEUTICALS