

Introduction:

“Clinical Trials: Assessing Safety and Efficacy for a Diverse Population”

FDA and JHU-CERSI

White Oak, Maryland

Wednesday, December 2, 2015

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Has disclosed the following affiliations.

Any real or apparent COIs related to the presentation have been resolved.

Speaker's Bureau-None

Grant/Research Support-Boehringer Ingelheim
Consultant

-Amgen, Sanofi.Boehringer Ingelheim, Eli Lilly

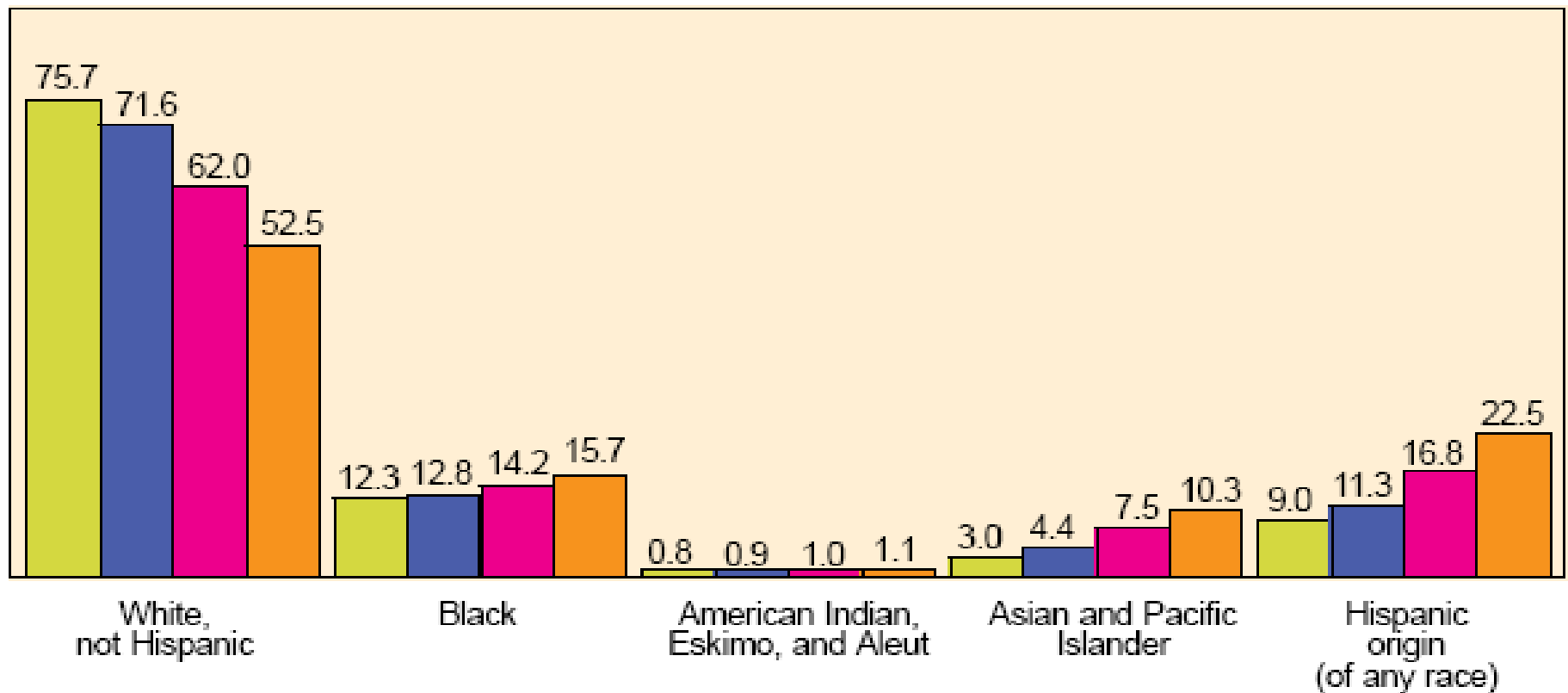
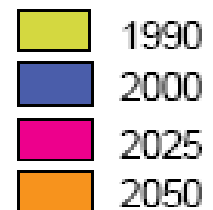
Stocks-None

Patents-None

Population Trends: Increasing Diversity

Percent of the Population, by Race and Hispanic Origin: 1990, 2000, 2025, and 2050

(Middle-series projections)



National Population Projections. Current Population Reports, U.S., by Age, Sex, Race, and Hispanic Origin: 1993 to 2050. http://cps.ipums.org/cps/cpr/2_ps.pdf

Guidance for Industry

Collection of Race and Ethnicity Data in Clinical Trials

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiologic Health (CDRH)
Office of the Commissioner (OC)

September 2005
Clinical Medical

Clinical Trials Shed Light on Minority Health

The Food and Drug Administration (FDA) is working to increase the participation of people in racial, ethnic and other minority groups in the clinical trials that test new medical products.

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Why is this important?

Ensuring meaningful representation of minorities in clinical trials for regulated medical products is fundamental to FDA's regulatory mission and public health, says Jonca Bull, M.D., director of the agency's Office of Minority Health (OMH). Racial and ethnic minorities include African American, American Indian, Alaska Native, Asian American, Hispanic American, Native Hawaiian and Pacific Islander communities.

OMH project manager Christine Merenda, M.P.H., R.N. explains that clinical trials are the proving ground for new drugs, vaccines and devices. They provide the data that will determine whether FDA approves a manufacturer's application for marketing approval.

"Potential racial, ethnic and other differences in response to drugs are important to FDA's efforts to help ensure that the safety and effectiveness of drugs are studied in all people



April is Minority Health Month

FDA's Office of Minority Health (OMH) helps identify agency actions that can help reduce disparities in health and health care. There will be several Consumer Updates this month highlighting the work of this office:

- The work being done to lessen health disparities
- The importance of including minorities in clinical trials
- Research and collaborations

To read these Consumer Updates, go to: <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm347896.htm>

And to learn more about OMH Director Jonca Bull's perspective on her office's top priorities, go to: <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm335589>

who will use the products once they are approved," she says.

Considering Genetic Differences

Bull explains that there are biological

differences in how people process drugs. For example, variations in genetic coding can make a cancer treatment more toxic in one ethnic group than it would be in another.

<http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM349488.pdf>
April 2013

Clinical Trials Shed Light on Minority Health

- African Americans represent 12% of the U.S. population but only 5% of clinical trial participants;
- Hispanics make up 16% of the population but only 1% of clinical trial participants; and
- “Men make up more than two-thirds of the participants in clinical tests of cardiovascular (heart and blood vessel) devices?”

whether FDA approves a manufacturer's application for marketing approval.

Potential racial, ethnic and other differences in response to drugs are important to FDA's efforts to help ensure that the safety and effectiveness of drugs are studied in all people

who will use the products once they are approved,” she says.

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<http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM349488.pdf>
April 2013

FDA Report

FDA ACTION PLAN TO ENHANCE THE COLLECTION AND AVAILABILITY OF DEMOGRAPHIC SUBGROUP DATA

Margaret A. Hamburg,
M.D., Commissioner of
Food and Drugs
<http://www.fda.gov/>
April 2014

August 2014



FDA ACTION PLAN TO ENHANCE THE COLLECTION AND AVAILABILITY OF DEMOGRAPHIC SUBGROUP DATA

One of the core tenets of rigorous biomedical research, as well as a guiding principle of the FDA's goal to meet the health needs of patients across the demographic spectrum, is the importance of encouraging diversity in clinical trials.

August 2014



Margaret A. Hamburg,
M.D., Commissioner of
Food and Drugs
<http://www.fda.gov/>
April 2014

Reporting and representation of ethnic minorities in cardiovascular trials: A systematic review

Tony Zhang, BHSc,^a Wendy Tsang, MD,^b Harindra C. Wijeyesundera, MD, PhD,^{a,c,d,e} and
Dennis T. Ko, MD, MSc^{a,c,d,e} Ontario, Canada; and Chicago, IL

American Heart Journal, 2013-07-01

Background Ethnic minority groups in the United States are at increased risk of developing cardiovascular diseases, experiencing adverse outcomes, and receiving suboptimal treatment. Such discrepancies may be related to a difference in race-specific outcomes in the management of cardiovascular diseases. However, little is known about the reporting and representation of ethnic minorities in major cardiovascular trials.

Methods A systematic review of major cardiovascular randomized controlled trials published in *The Journal of the American Medical Association*, *The Lancet*, and *The New England Journal of Medicine* between 1997 and 2010 was performed. We determined the reporting rate of the following ethnic minority groups in studies that enrolled American patients: whites, African Americans, Asians, and Hispanics.

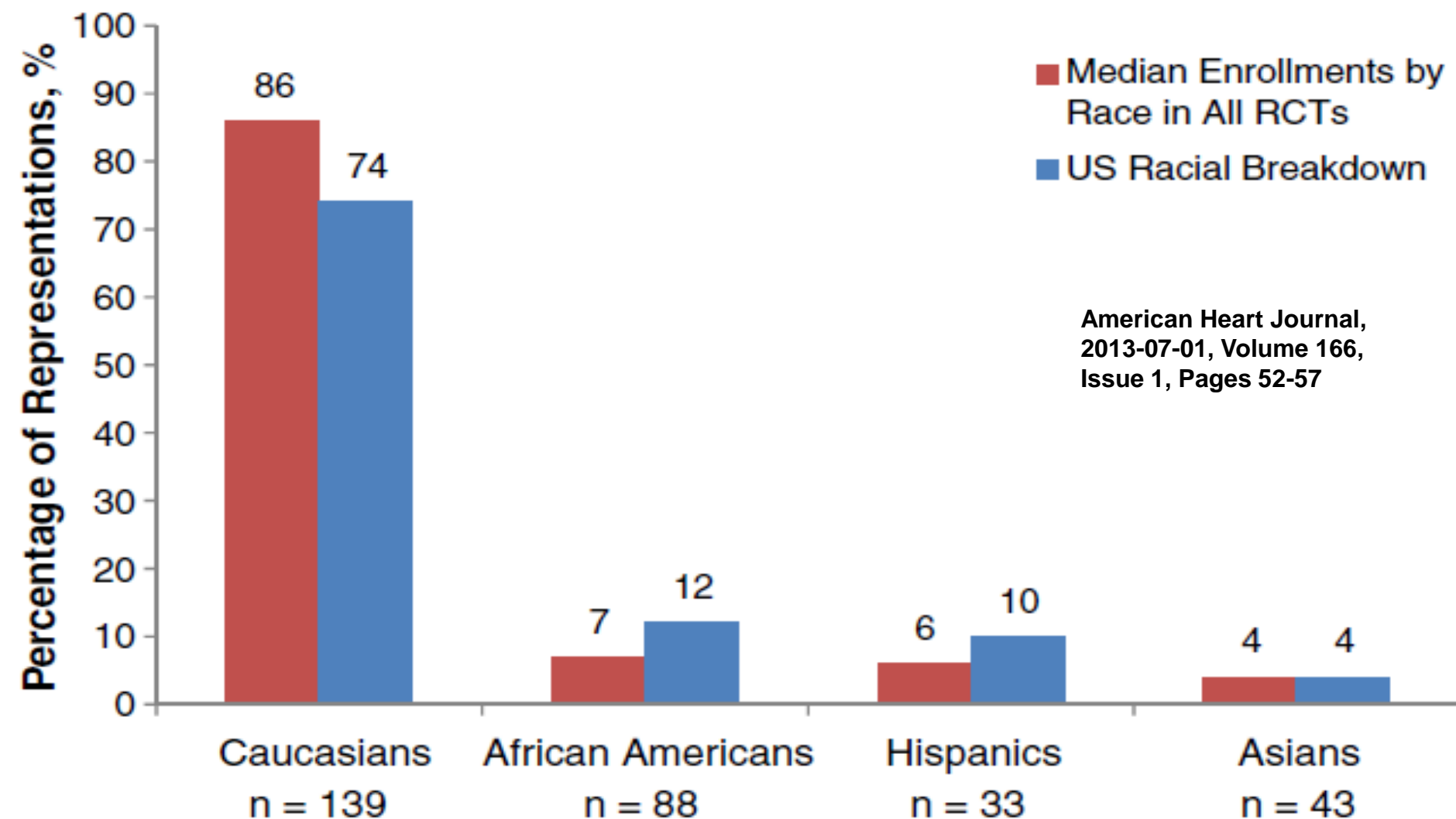
Results A total of 250 randomized controlled trials that enrolled 1,103,694 patients were included in the systematic review. Among them, 56% (n = 140) of the trials reported information on race. No significant temporal changes in racial reporting were observed during the study period ($P = .21$). The median enrollment rate in trials for whites, African Americans, Hispanics, and Asians was 86%, 7%, 6%, and 4%, respectively. When compared with the population prevalence of disease burden, we found that whites were overrepresented (88% vs 78%, $P < .001$), whereas African Americans were underrepresented (3% vs 11%, $P < .001$), in trials of coronary artery disease.

Conclusions Despite significant changes in the ethnic composition of the United States, we found that only about half of all major cardiovascular trials reported any racial information. Underrepresentation of ethnic minority groups in cardiovascular trials was observed. (Am Heart J 2013;166:52-7.)

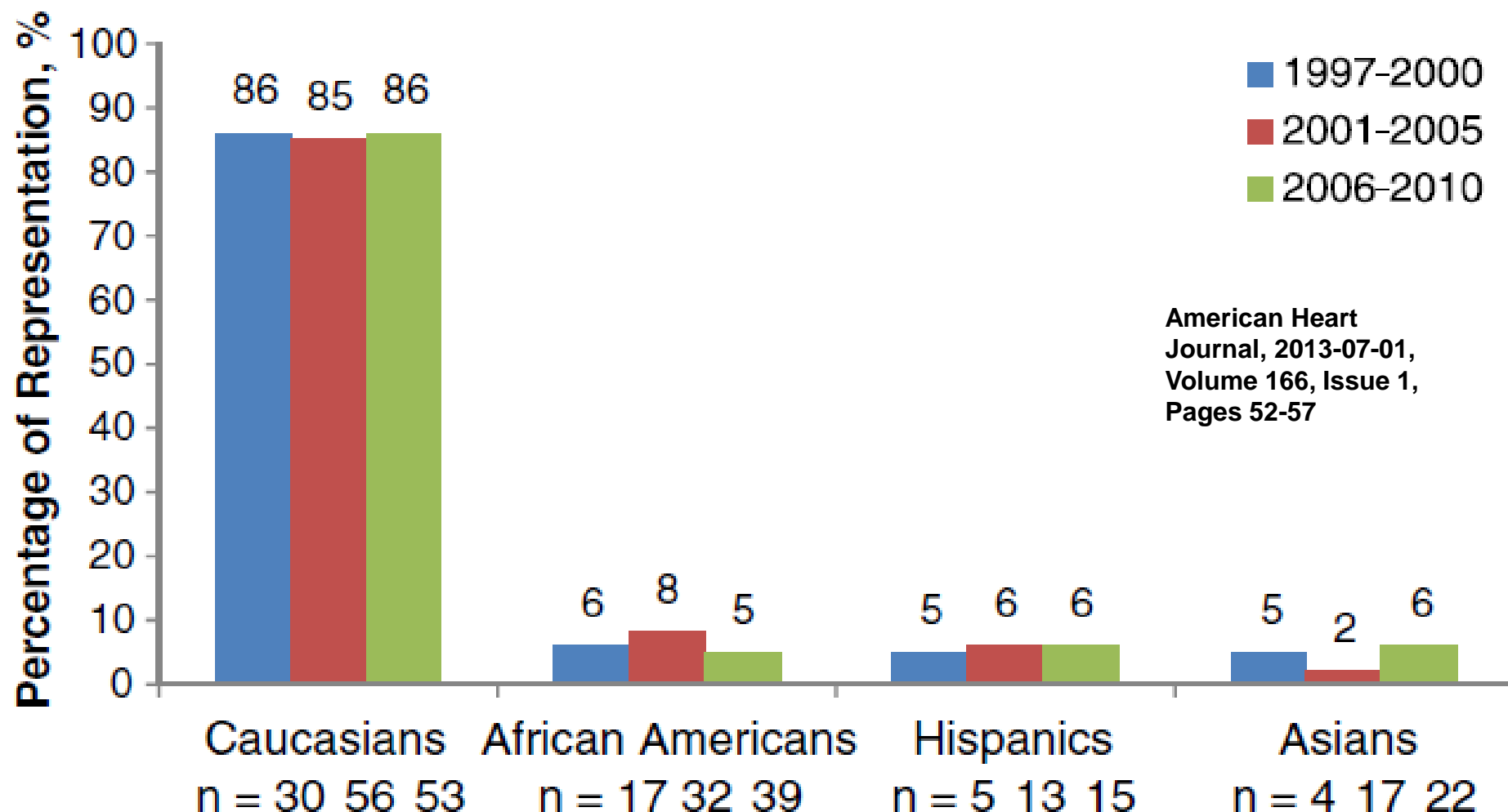
Reporting and representation of ethnic minorities in CV trials

- 250 major CV randomized clinical trials
- Systematic review 1997-2010 with recruitments of Americans.
- N=1,103,694.
- Mean age 63 years, and 35% female.

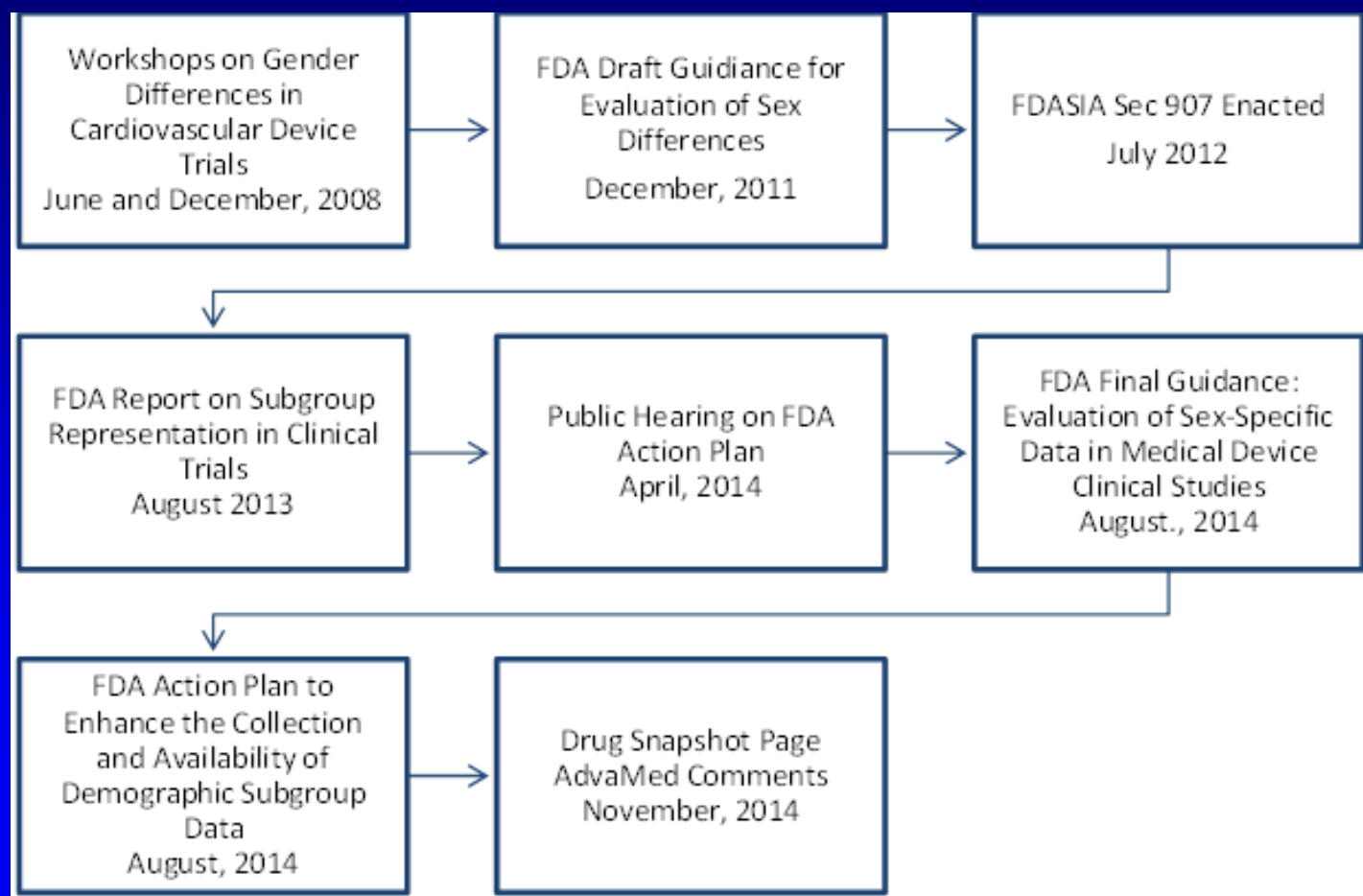
Comparison observed racial enrollments in all trials and US racial demographics.



Racial representation over time. Median % racial enrollments in race-reporting trials 1997-2010.



FDA timeline of significant events concerning underrepresented populations



Chapter 2

Effects of Sex Differences in the Pharmacokinetics of Drugs and Their Impact on the Safety of Medicines in Women

Emmanuel O. Fadiran and Lei Zhang

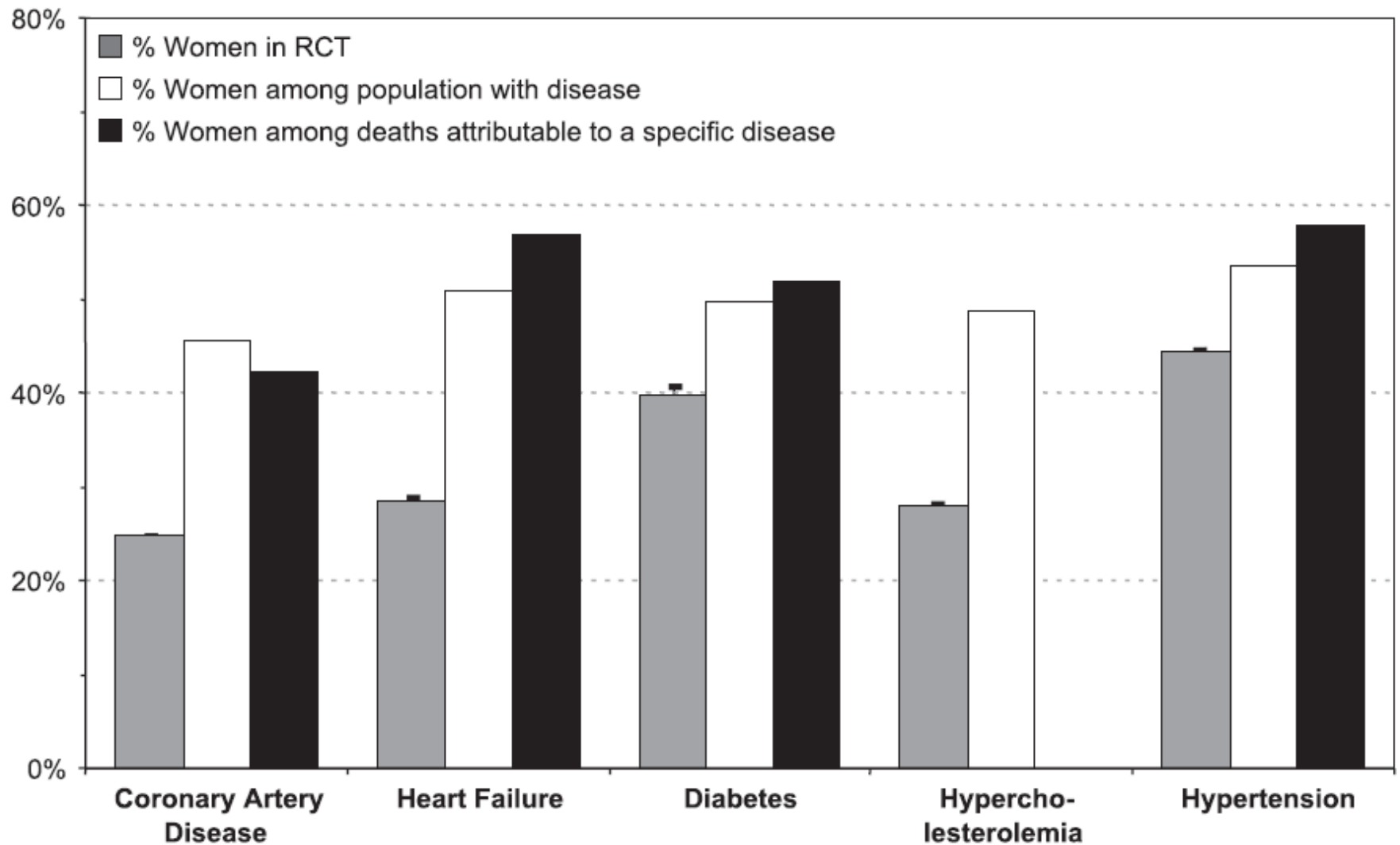
© Springer International Publishing Switzerland
2015 M. Harrison-Woolrych (ed.), *Medicines For
Women*, DOI 10.1007/978-3-319-12406-3_2

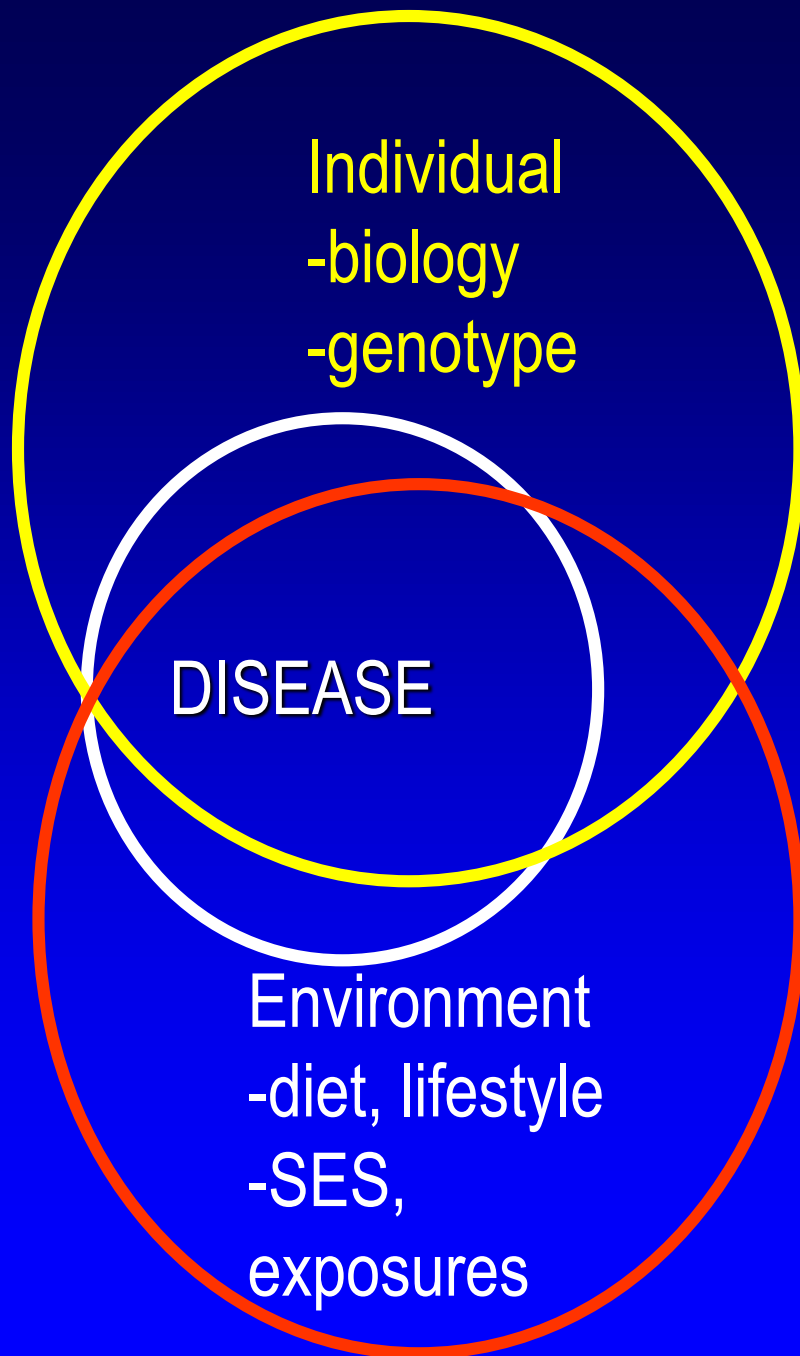
Introduction

Inclusion of women in clinical trials and analysis of clinical trial data for sex/gender effects have been an integral component of the US FDA's consideration for approval of pharmaceutical products since the mid-1980s ([FDA Guidance for Industry 1993](#)). The study of sex differences is now a routine component of drug development because of existing data in drug exposure and response differences between men and women and the need to understand such differences for proper dosing (Harris et al. [1995](#); Schwartz [2003](#); Institute of Medicine (US) [2001](#); Franconi et al. [2007](#); Parekh et al. [2011](#)). The resulting expanding knowledge of sex differences in the exposure and responses to drugs has led to a better understanding of the mechanisms contributing to these differences and improved pharmacotherapy for men and women.

Sex-based differences may be due to pharmacokinetics (differences in exposure in men and women following administration of the same dose of a drug) and/or pharmacodynamics (differences in the body's response to the same dose of a drug in men and women) and can manifest as differences in safety and/or efficacy of pharmacotherapy. For example, when compared to men, women are 1.5–1.7 times more likely to develop an adverse drug reaction (Rademaker [2001](#)), which

Women in Trials of CVD Prevention





“Race”
is a crude
proxy.

Initial Medications For The Management of Hypertension

Lifestyle Modification—Especially Diet and Exercise

β -blockers should be included in the regimen if there is a compelling indication for a β -blocker

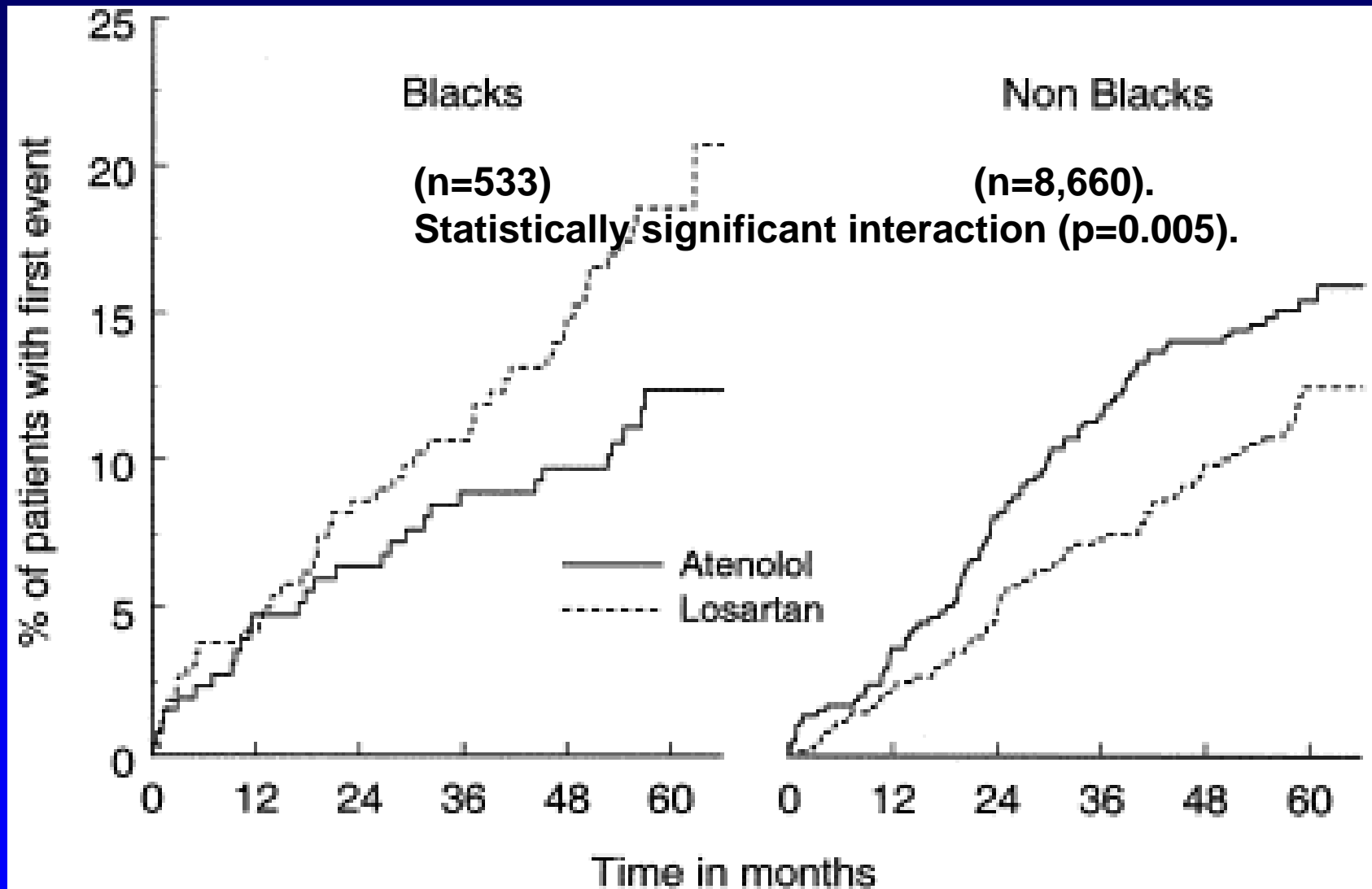
**ACE inhibitors
or
ARBs**

Diuretics

Black population

**Calcium
antagonists**

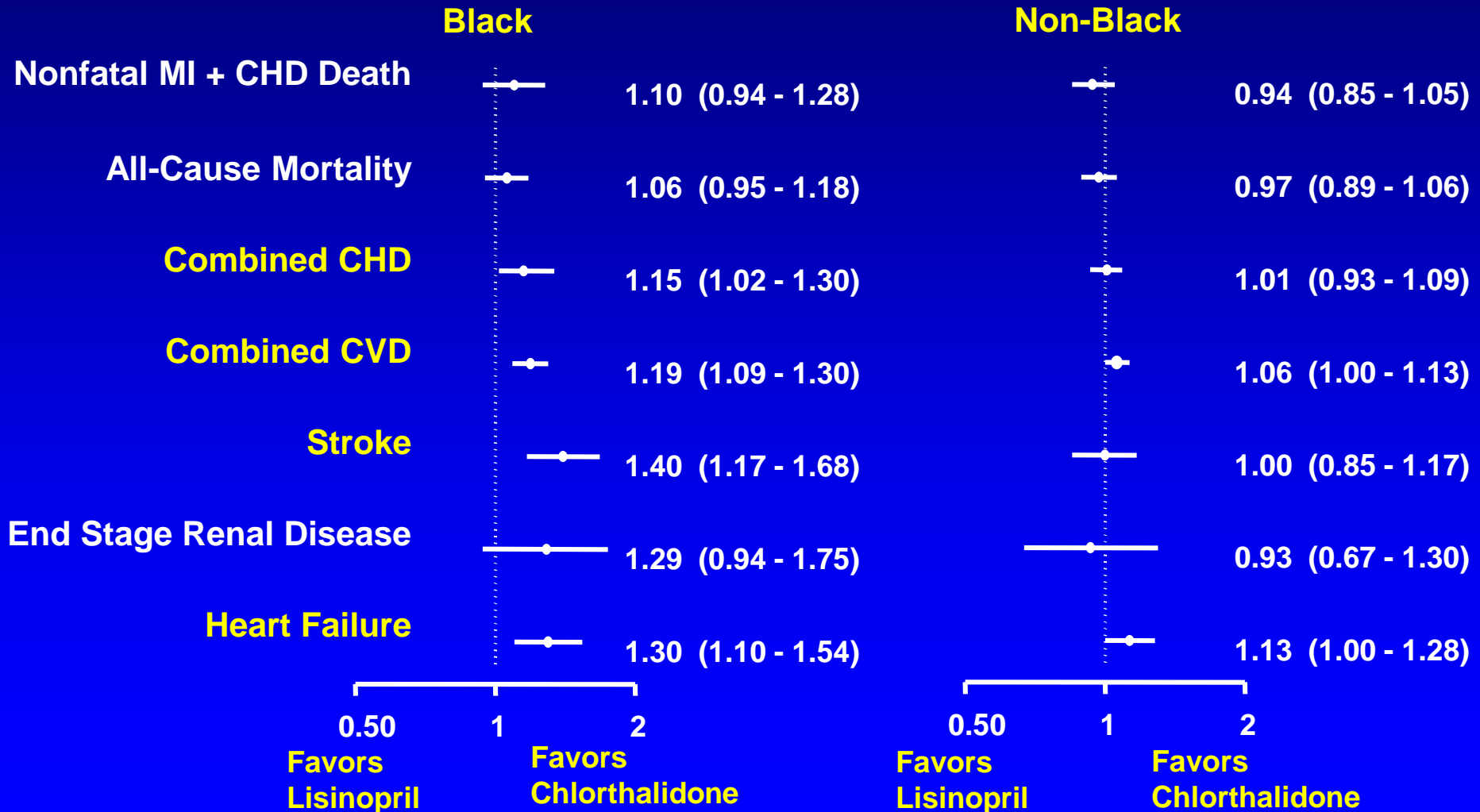
Blacks in LIFE: U.S. primary composite end point blacks versus non-blacks



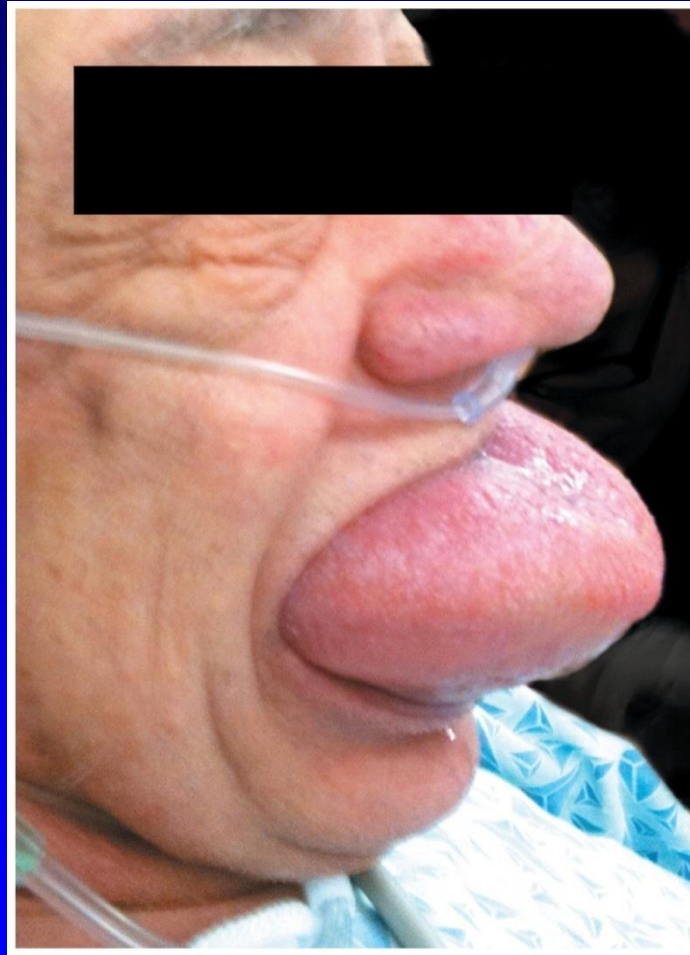


Black vs. Non-Black Lisinopril/Chlorthalidone RR and 95% CIs

Wright JT,
et al.
JAMA
2005;293:1
595-1608

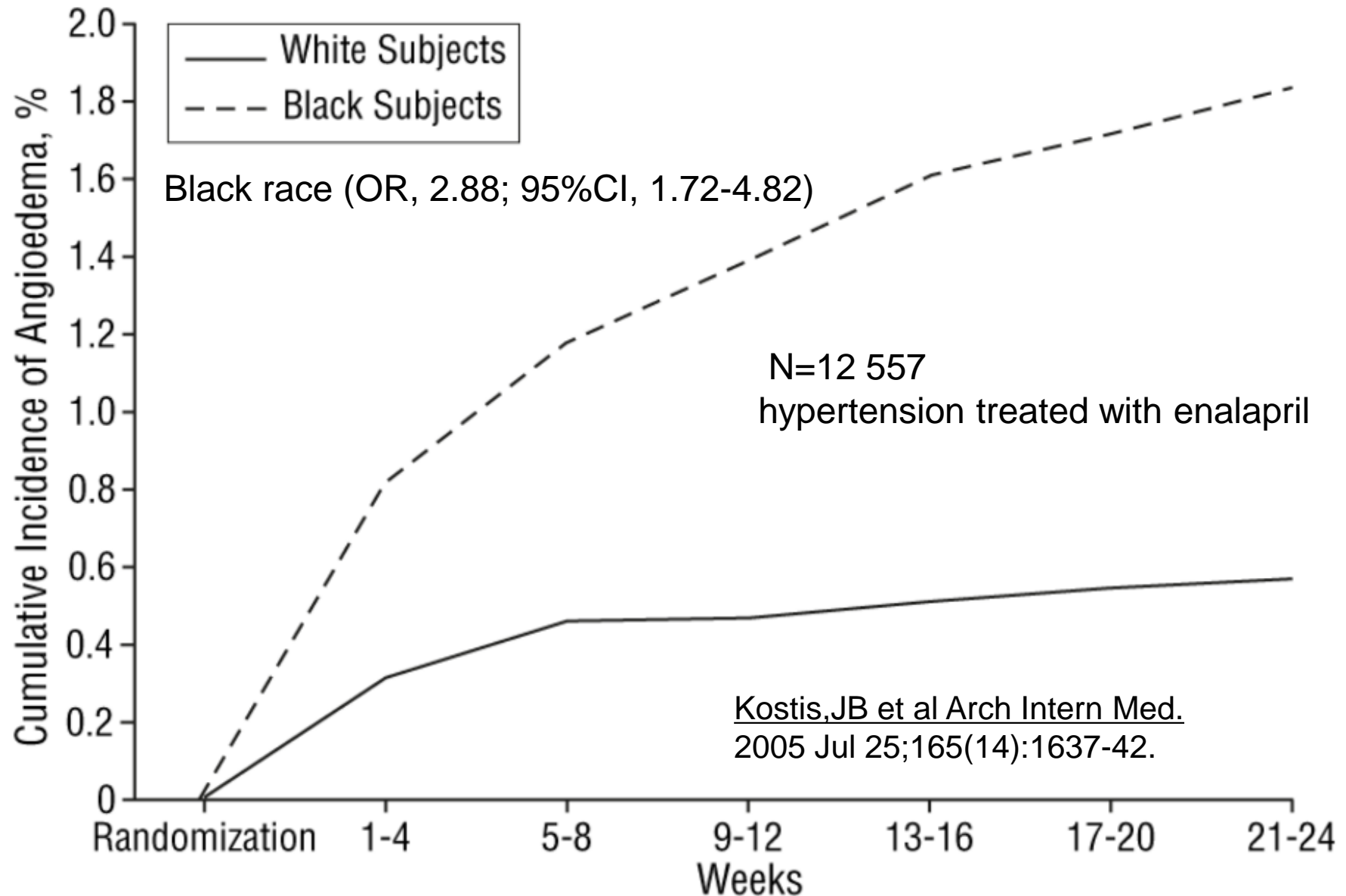


Angioedema



Bramante RM, Rand M. N Engl J Med 2011;365:e4.

Incidence Angioedema Associated With Enalapril



ANGIOEDEMA

	Total	Blacks	Non-blacks
Chlorthalidone	8 / 15,255 0.1%	2 / 5,369 <0.1%	6 / 9,886 0.1%
Lisinopril	41 / 9,054 0.5%	23 / 3,210 0.7%	18 / 5,844 0.3%
	p<.001	p<.001	p=.002



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Landmark NIH study shows intensive blood pressure management may save lives

Embargoed for Release: September 11, 2015, 10:30 AM EDT

Lower blood pressure target greatly reduces cardiovascular complications and deaths in older adults

More intensive management of high blood pressure, below a commonly recommended blood pressure target, significantly reduces rates of cardiovascular disease, and lowers risk of death in a group of adults 50 years and older with high blood pressure. This is according to the initial results of a landmark clinical trial sponsored by the National Institutes of Health called the Systolic Blood Pressure Intervention Trial (SPRINT). The intervention in this trial, which carefully adjusts the amount or type of blood pressure medication to achieve a target [systolic](#) pressure of 120 millimeters of mercury (mm Hg), reduced rates of cardiovascular events, such as heart attack and heart failure, as well as stroke, by almost a third and the risk of death by almost a quarter, as compared to the target systolic pressure of 140 mm Hg.

Systolic Blood Pressure Intervention Trial (SPRINT)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

November 9, 2015,
DOI:
10.1056/NEJMoa15
11939

ABSTRACT

BACKGROUND

The most appropriate targets for systolic blood pressure to reduce cardiovascular morbidity and mortality among persons without diabetes remain uncertain.

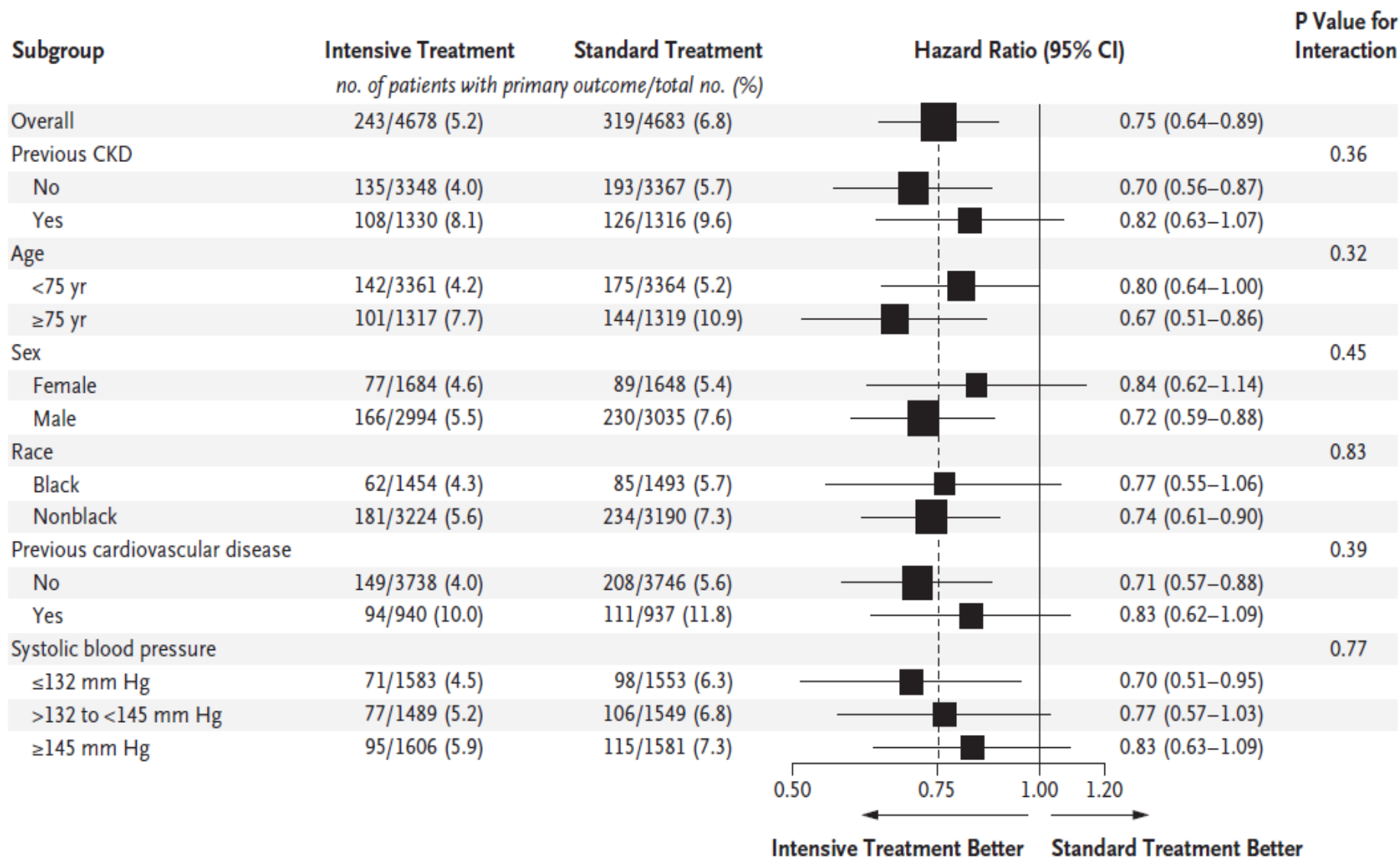
METHODS

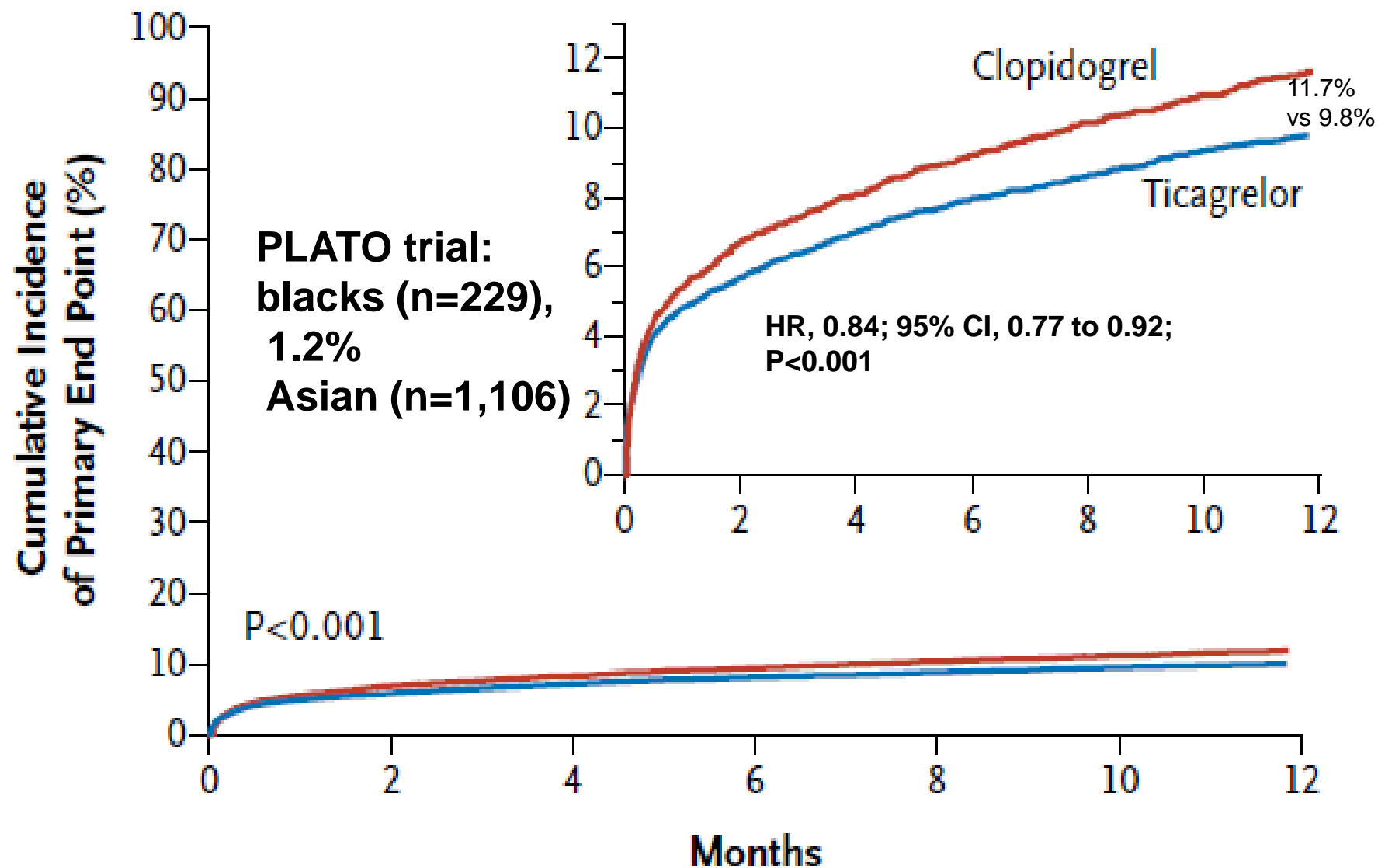
We randomly assigned 9361 persons with a systolic blood pressure of 130 mm Hg or higher and an increased cardiovascular risk, but without diabetes, to a systolic blood-pressure target of less than 120 mm Hg (intensive treatment) or a target of less than 140 mm Hg (standard treatment). The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes.

The members of the writing committee (Jackson T. Wright, Jr., M.D., Ph.D., Jeff D. Williamson, M.D., M.H.S., Paul K. Whelton, M.D., Joni K. Snyder, R.N., B.S.N., M.A., Kaycee M. Sink, M.D., M.A.S., Michael V. Rocco, M.D., M.S.C.E., David M. Reboussin, Ph.D., Mahboob Rahman, M.D., Suzanne Oparil, M.D., Cora E. Lewis, M.D., M.S.P.H., Paul L. Kimmel, M.D., Karen C. Johnson, M.D., M.P.H., David C. Goff, Jr., M.D., Ph.D., Lawrence J. Fine, M.D., Dr.P.H., Jeffrey A. Cutler, M.D., M.P.H., William C.ushman, M.D., Alfred K. Cheung, M.D., and

Table 1. Baseline Characteristics of the Study Participants.*

Characteristic		Intensive Treatment (N = 4678)	Standard Treatment (N = 4683)
Criterion for increased cardiovascular risk — no. (%)†			
Age ≥75 yr	⇒	1317 (28.2)	1319 (28.2)
Chronic kidney disease‡		1330 (28.4)	1316 (28.1)
Cardiovascular disease		940 (20.1)	937 (20.0)
Clinical		779 (16.7)	783 (16.7)
Subclinical		247 (5.3)	246 (5.3)
Framingham 10-yr cardiovascular disease risk score ≥15%		2870 (61.4)	2867 (61.2)
Female sex — no. (%)	⇒	1684 (36.0)	1648 (35.2)
Age — yr			
Overall		67.9±9.4	67.9±9.5
Among those ≥75 yr of age		79.8±3.9	79.9±4.1
Race or ethnic group — no. (%)§			
Non-Hispanic black		1379 (29.5)	1423 (30.4)
Hispanic		503 (10.8)	481 (10.3)
Non-Hispanic white		2698 (57.7)	2701 (57.7)
Other		98 (2.1)	78 (1.7)
Black race§¶	⇒	1454 (31.1)	1493 (31.9)
Baseline blood pressure — mm Hg			
Systolic		139.7±15.8	139.7±15.4
Diastolic		78.2±11.9	78.0±12.0





No. at Risk		N Engl J Med 2009;361:1045-57					Am Heart J. 2015 Jun;169(6):899-905.e1	
Ticagrelor	9333	8628	8460	8219	6743	5161	4147	
Clopidogrel	9291	8521	8362	8124	6650	5096	4047	

East Asians (EAs) Varying Responses to Antithrombotic Treatment by Race/Ethnicity

- EAs lower risk of thrombosis and ↑risk of bleeding during antithrombotic treatment for ACS than do whites
- Because EAs have higher prevalence of CYP450 2C19 loss-of-function allele than whites (≈65% vs ≈25%), the antiplatelet effect with clopidogrel loading is more limited among EAs
- Asians more susceptible to heparin, and their optimal dose ≈10 U/kg lower than for non-Asians

Jeong,Y-H et al, JAMA August 11, 2015 Volume 314, Number

Ticagrelor vs. Clopidogrel in Black Patients With Stable CAD

- Blacks higher prevalence of loss-of-function CYP2C19*2 allele
- Blacks higher on-treatment platelet reactivity (HPR) vs. whites
- Clinically significant because HPR is an independent RF for 12-month CV death and nonfatal MI
- Paucity of data in blacks, often under-represented in antiplatelet RTCs



Race, Common Genetic Variation, and Therapeutic Response Disparities in Heart Failure

Mathew R. Taylor, MD,* Albert Y. Sun, MD,† Gordon Davis, MS,‡ Mona Fiuzat, PHARM.D,† Stephen B. Liggett, MD,§ Michael R. Bristow, MD, PhD*‡

JACC:HEARTFAILURE VOL.2,NO.6,2014
DECEMBER 2014:561–72

ABSTRACT

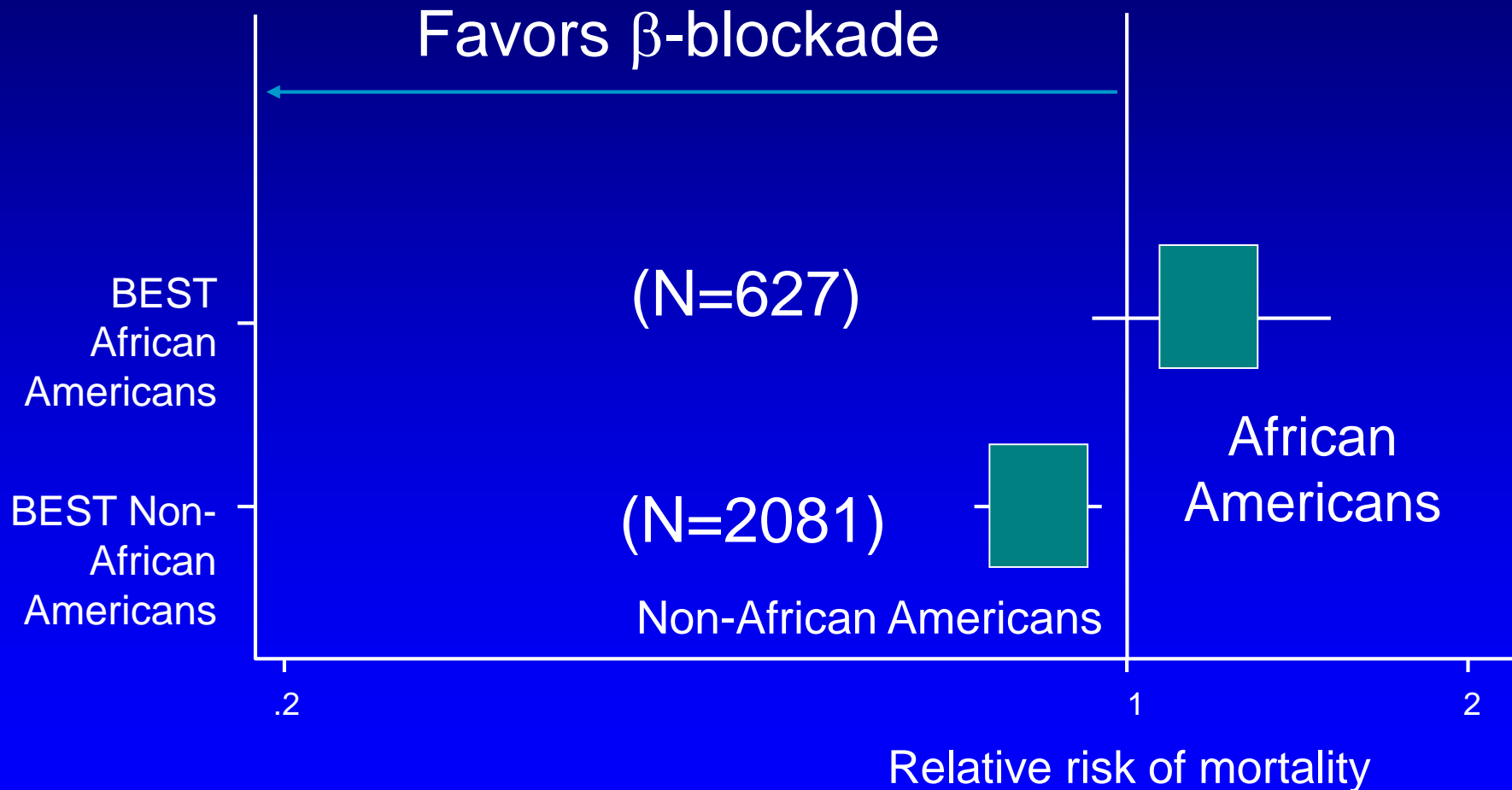
Because of its comparatively recent evolution, *Homo sapiens* exhibit relatively little within-species genomic diversity. However, because of genome size, a proportionately small amount of variation creates ample opportunities for both rare mutations that may cause disease as well as more common genetic variations that may be important in disease modification or pharmacogenetics. Primarily because of the East African origin of modern humans, individuals of African ancestry (AA) exhibit greater degrees of genetic diversity than more recently established populations, such as those of European ancestry (EA) or Asian ancestry. Those population effects extend to differences in frequency of common gene variants that may be important in heart failure natural history or therapy. For cell-signaling mechanisms important in heart failure, we review and present new data for genetic variation between AA and EA populations. Data indicate that: 1) neurohormonal signaling mechanisms frequently (16 of the 19 investigated polymorphisms) exhibit racial differences in the allele frequencies of variants comprising key constituents; 2) some of these differences in allele frequency may differentially affect the natural history of heart failure in AA compared with EA individuals; and 3) in many cases, these differences likely play a role in observed racial differences in drug or device response. (J Am Coll Cardiol HF 2014;2:561-72) © 2014 by the American College of Cardiology Foundation.

Heart Failure Trials

Trial	Rx	Total	Non-African Americans (%)	African Americans	African Americans (%)
V-HeFT I + II ¹	ISDN/HYD, Enalapril	1419	1024	395	28
SOLVD ²	Enalapril	2569	2175	394	15
US Carvedilol ³	Carvedilol	1094	877	217	20
COPERNICUS ⁴	Carvedilol	2289	2168	121	5
BEST ⁵	Bucindolol	2708	2081	627	23
MERIT-HF ⁶	Metoprolol	3991	3783	208	5
EPHESUS ⁷	Eplerenone	6632	6558	74	1
Val-HeFT ⁸	Valsartan	5010	4666	344	7
VALIANT ⁹	Valsartan, Valsartan/Captopril	14703	14296	407	3
CHARM ¹⁰	Candesartan	3023	2897	126	4
A-HeFT¹¹	ISDN/HYD	1050		1050	100
	TOTAL	44,488	40,525	3,963	7

1. Carson P et al. *J Card Fail.* 1999;5:178-187; 2. Hall WD. *Ethn Dis.* 1999;9:333-340; 3. Yancy CW et al. *N Engl J Med.* 2001;344:1358-1365; 4. Packer M et al. *N Engl J Med.* 2001;344:1651-1658; 5. BEST Investigators. *N Engl J Med.* 2001;344:1659-1667; 6. MERIT-HF study group. *Lancet.* 1999;353:2001-2007; 7. Pitt B et al. *N Engl J Med.* 2003;348:1309-1321; 8. Cohn JN. *N Engl J Med.* 2001;345:1667-1675; 9. Pfeffer MA et al. *N Engl J Med.* 2003;349:1893-1906; 10. Yusuf S et al. *Lancet.* 2003;362:777-781.

BEST : No Survival Advantage with β -blocker Bucindolol in African Americans with HF



Volume 14;Number 5; May 2008

A GRK5 polymorphism that inhibits β -adrenergic receptor signaling is protective in heart failure

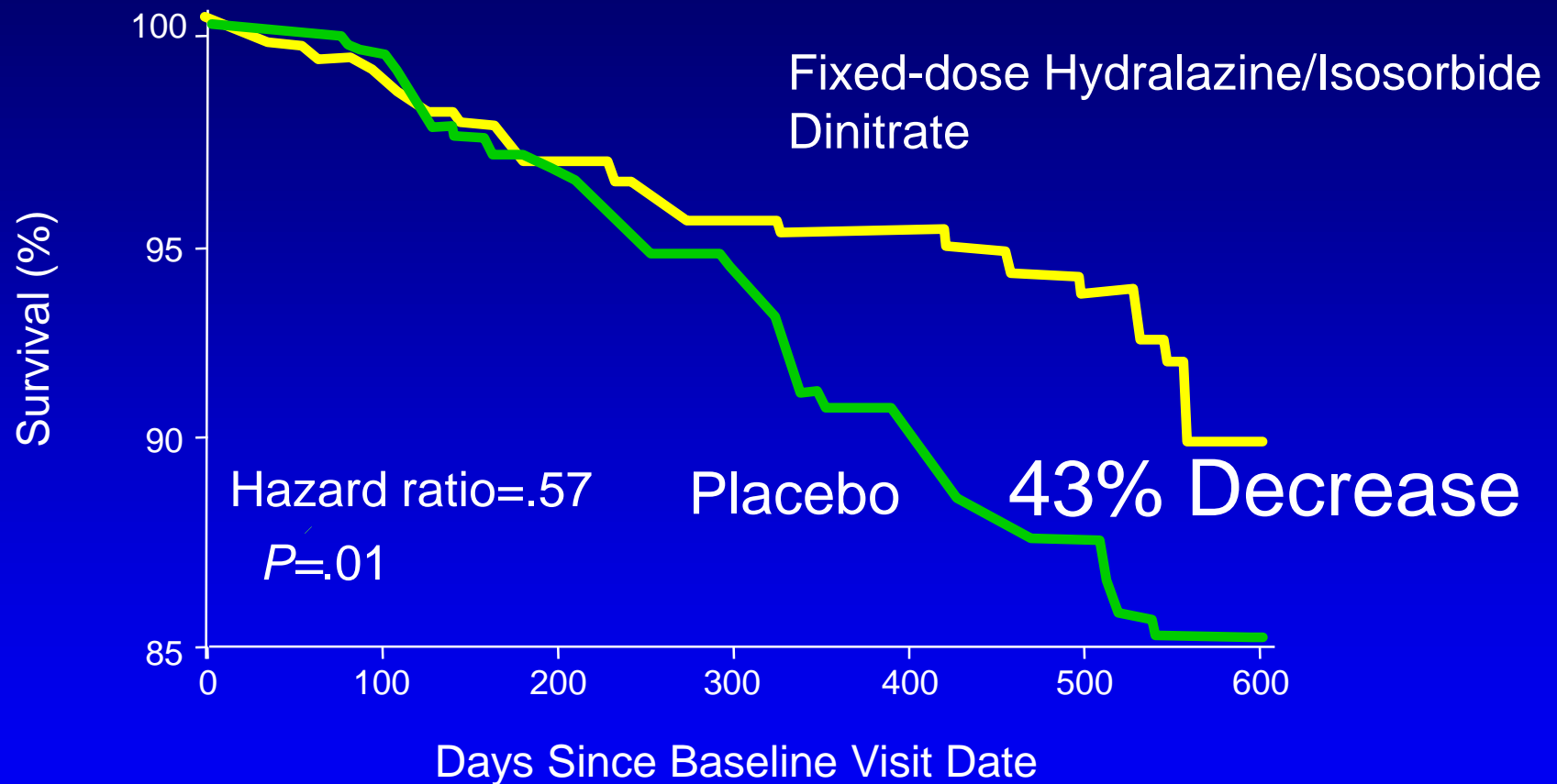
Stephen B Liggett^{1,6,7}, Sharon Cresci^{2,7}, Reagan J Kelly^{3,7}, Faisal M Syed¹, Scot J Matkovich², Harvey S Hahn¹, Abhinav Diwan¹, Jeffrey S Martini⁴, Li Sparks¹, Rohan R Parekh¹, John A Spertus⁵, Walter J Koch⁴, Sharon L R Kardia³ & Gerald W Dorn II^{1,2}

β -adrenergic receptor (β AR) blockade is a standard therapy for cardiac failure and ischemia. G protein-coupled receptor kinases (GRKs) desensitize β ARs, suggesting that genetic GRK variants might modify outcomes in these syndromes. Re-sequencing of GRK2 and GRK5 revealed a nonsynonymous polymorphism of GRK5, common in African Americans, in which leucine is substituted for glutamine at position 41. GRK5-Leu41 uncoupled isoproterenol-stimulated responses more effectively than did GRK5-Gln41 in transfected cells and transgenic mice, and, like pharmacological β AR blockade, GRK5-Leu41 protected against experimental catecholamine-induced cardiomyopathy. Human association studies showed a pharmacogenomic interaction between GRK5-Leu41 and β -blocker treatment, in which the presence of the GRK5-Leu41 polymorphism was associated with decreased mortality in African Americans with heart failure or cardiac ischemia. In 375 prospectively followed African-American subjects with heart failure, GRK5-Leu41 protected against death or cardiac transplantation. Enhanced β AR desensitization of excessive catecholamine signaling by GRK5-Leu41 provides a 'genetic β -blockade' that improves survival in African Americans with heart failure, suggesting a reason for conflicting results of β -blocker clinical trials in this population.

G protein-coupled receptor kinase 5 (GRK5)

- Regulates beta-adrenergic receptor (β AR) signaling
- Allele frequencies for GRK5-Leu41 are:
 - ~33% in African Americans
 - ~1-2% in European Americans
- GRK5-Leu41 enhances uncoupling of β AR response

A-HeFT: All-Cause Mortality



Fixed-dose I/H	518	463	407	359	313	251	13
Placebo	532	466	401	340	285	232	24

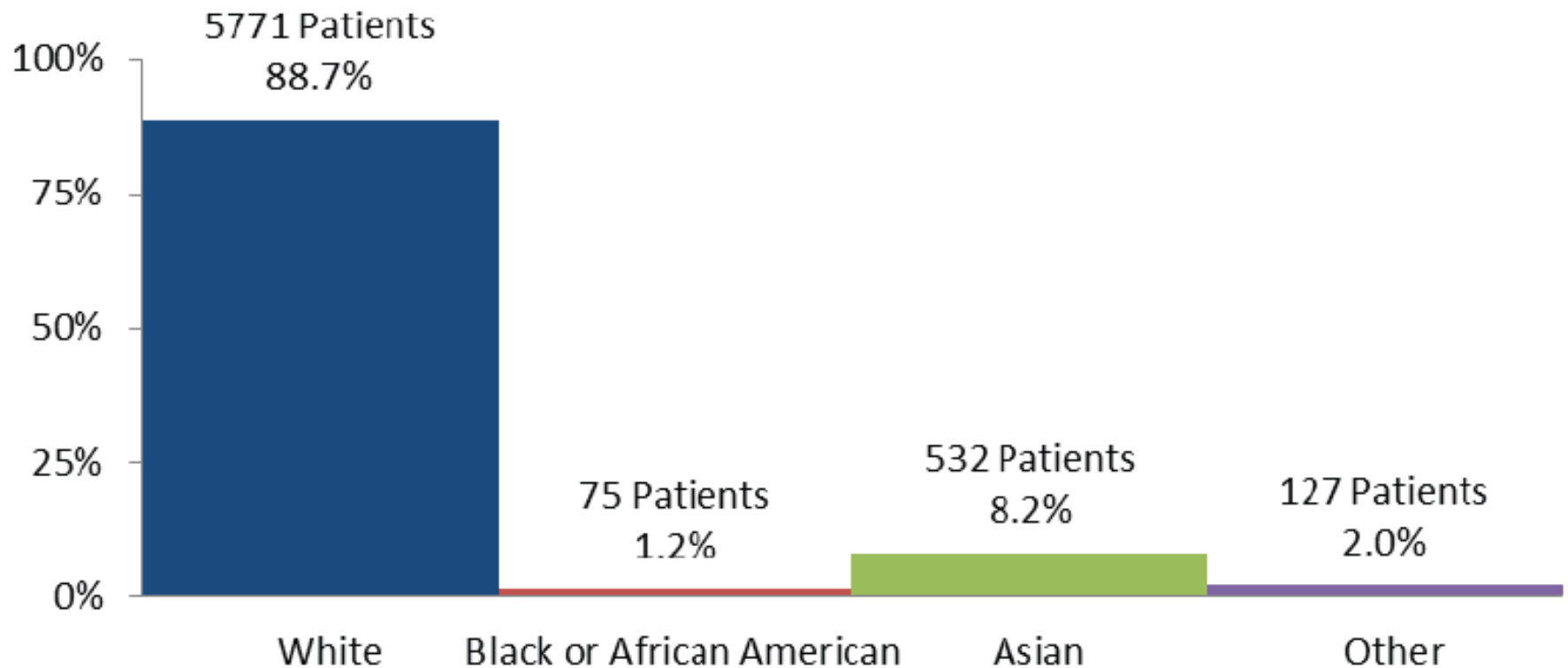
Apr. 15, 2015

FDA Approves Ivabradine

- Indicated to reduce the risk of hospitalization for worsening HF
- in patients with stable, symptomatic chronic HF with LV EF $\leq 35\%$,
- who are in sinus rhythm with resting HR ≥ 70 bpm and either are on maximally tolerated doses of beta blockers or have a contraindication to beta blocker use

FDA Snapshot: Ivabradine

Baseline Demographics (6505 Patients)



PRESCRIBING INFORMATION Ivabradine in Blacks

	% of Total Population	Corlanor n(%)	Placebo n(%)	HR (95% CI)
Age				
>=65 years	38.0%	386 (30.5%)	410 (33.9%)	0.89 (0.77-1.02)
>=75 years	11.1%	125 (33.9%)	133 (37.7%)	0.89 (0.70-1.14)
Age quartile				
19 to <= 53	26.6%	145 (17.4%)	227 (25.4%)	0.64 (0.52-0.79)
> 53 to <= 60	23.9%	175 (23.0%)	195 (24.7%)	0.90 (0.74-1.11)
> 60 to <= 69	26.5%	241 (27.7%)	261 (30.6%)	0.89 (0.74-1.05)
> 69	23.1%	232 (29.9%)	254 (35.1%)	0.84 (0.70-1.00)
Sex				
Male	76.4%	624 (25.3%)	725 (28.9%)	0.84 (0.76-0.94)
Female	23.6%	169 (21.7%)	212 (28.0%)	0.74 (0.60-0.91)
Race				
Caucasian	88.7%	722 (25.1%)	835 (28.9%)	0.84 (0.76-0.93)
Black	1.2%	9 (28.1%)	15 (34.9%)	0.62 (0.27-1.45)
Asian	8.2%	47 (17.5%)	68 (25.8%)	0.64 (0.44-0.93)
Other/unknown	2.0%	15 (24.2%)	19 (29.2%)	0.74 (0.37-1.47)
Cause of heart failure				
Non-ischaeic	32.1%	218 (21.2%)	296 (27.9%)	0.72 (0.60-0.85)
Ischaemic	67.9%	575 (26.0%)	641 (29.1%)	0.87 (0.78-0.97)
Weight quartile				
<= 69.4	25.0%	224 (27.8%)	290 (35.2%)	0.74 (0.62-0.89)
> 69.4 to <= 79.6	25.0%	196 (24.9%)	234 (28.0%)	0.88 (0.72-1.06)
> 79.6 to <= 91	25.7%	191 (22.6%)	203 (24.6%)	0.88 (0.72-1.07)
> 91	24.3%	182 (22.7%)	210 (27.0%)	0.81 (0.66-0.99)
Baseline heart rate quartile				
<= 73	30.1%	199 (20.1%)	211 (21.8%)	0.91 (0.75-1.11)
> 73 to <= 77	22.2%	169 (23.4%)	181 (25.0%)	0.92 (0.74-1.13)
> 77 to <= 84	23.1%	197 (25.9%)	202 (27.2%)	0.94 (0.77-1.14)
> 84	24.4%	228 (29.8%)	343 (41.6%)	0.64 (0.54-0.76)

FDA: Snapshot Ivabradine

- Ivabradine appeared to be similarly effective in whites and Asians. Because of the limited number of Black patients in the trial, differences in response for Blacks could not be determined.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

SEPTEMBER 11, 2014

VOL. 371 NO. 11

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

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ABSTRACT

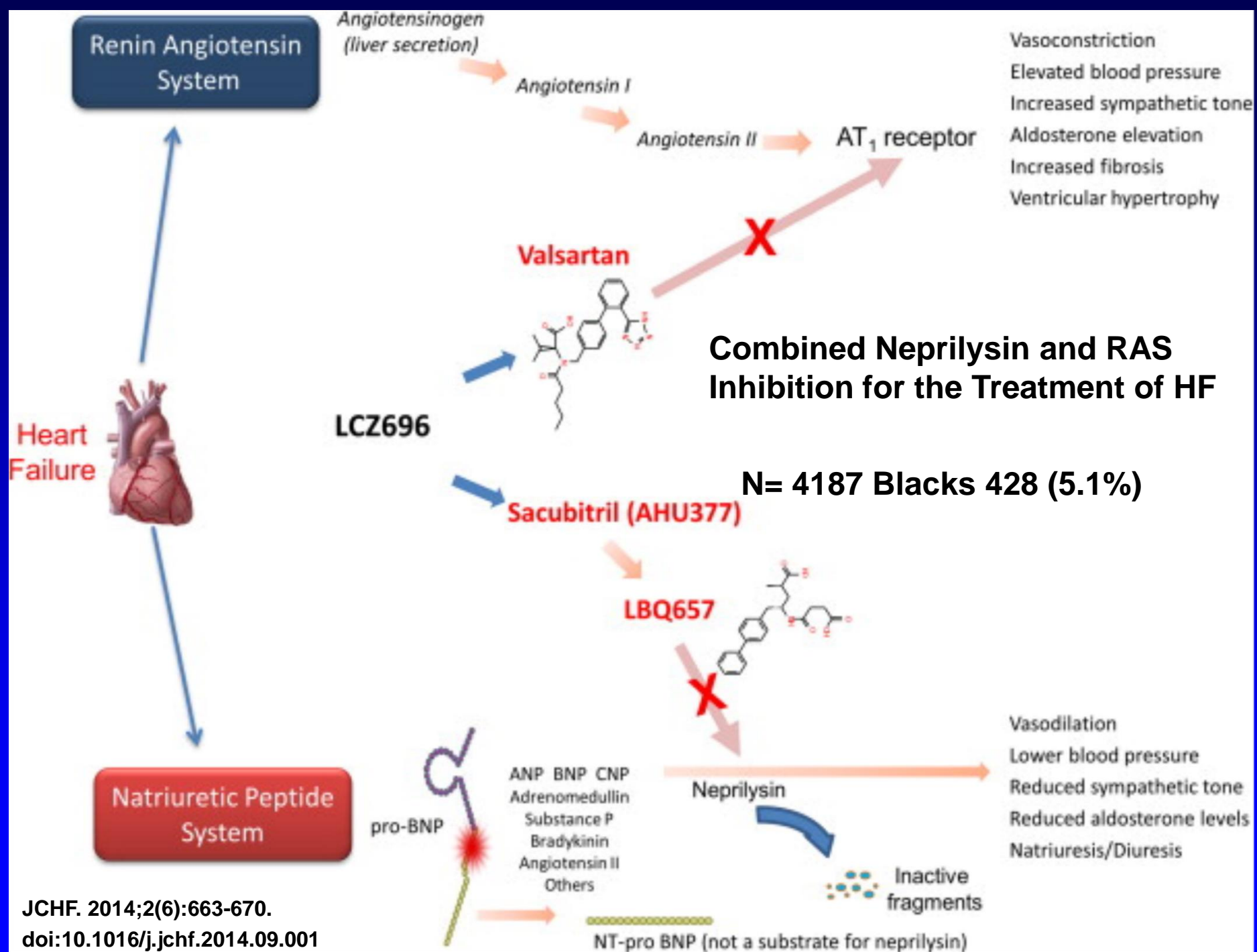
BACKGROUND

We compared the angiotensin receptor–neprilysin inhibitor LCZ696 with enalapril in patients who had heart failure with a reduced ejection fraction. In previous studies, enalapril improved survival in such patients.

METHODS

In this double-blind trial, we randomly assigned 8442 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either LCZ696 (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to recommended therapy. The primary outcome was a composite of death from

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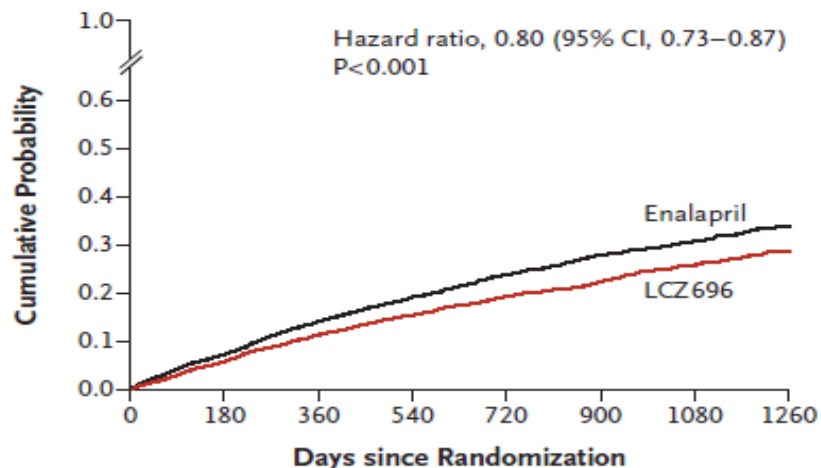
LCZ696 Angiotensin–Neprilysin Inhibition vs. Enalapril

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	LCZ696 (N = 4187)	Enalapril (N = 4212)
Age — yr	63.8±11.5	63.8±11.3
Female sex — no. (%)	879 (21.0)	953 (22.6)
Race or ethnic group — no. (%)†		
White	2763 (66.0)	2781 (66.0)
Black	213 (5.1)	215 (5.1)
Asian	759 (18.1)	750 (17.8)
Other	452 (10.8)	466 (11.1)
Region — no. (%)		
North America	310 (7.4)	292 (6.9)
Latin America	713 (17.0)	720 (17.1)
Western Europe and other‡	1026 (24.5)	1025 (24.3)
Central Europe	1393 (33.3)	1433 (34.0)
Asia–Pacific	745 (17.8)	742 (17.6)
Systolic blood pressure — mm Hg	122±15	121±15

LCZ696 Angiotensin–Neprilysin Inhibition vs. Enalapril

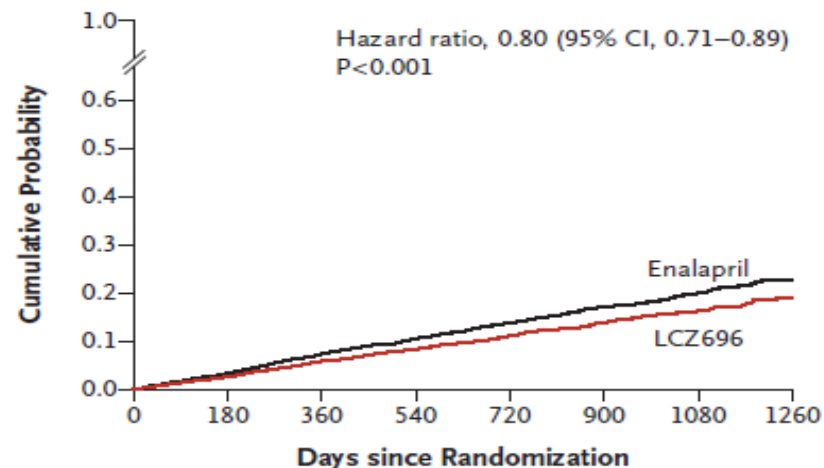
A Primary End Point



No. at Risk

LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

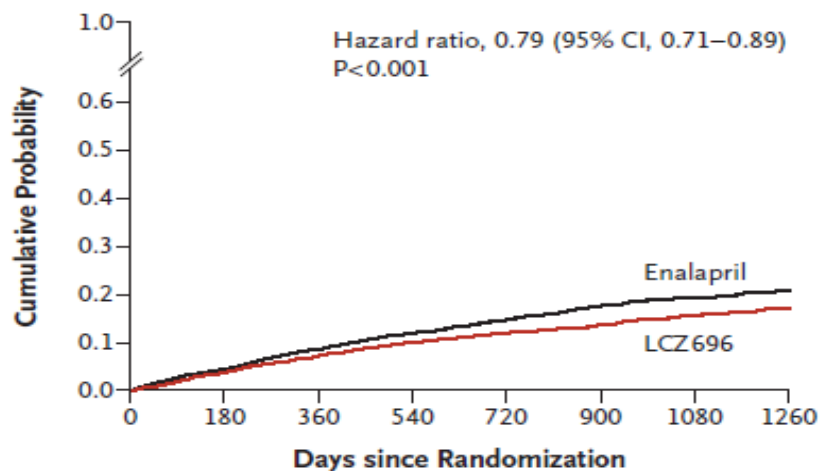
B Death from Cardiovascular Causes



No. at Risk

LCZ696	4187	4056	3891	3282	2478	1716	1005	280
Enalapril	4212	4051	3860	3231	2410	1726	994	279

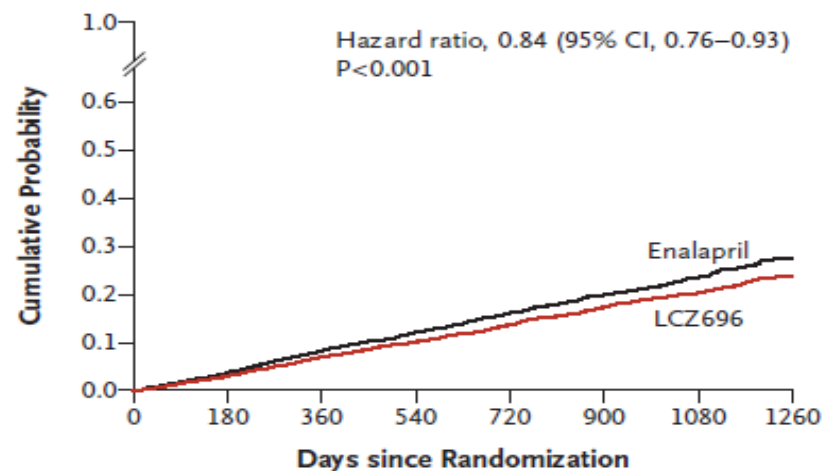
C Hospitalization for Heart Failure



No. at Risk

LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

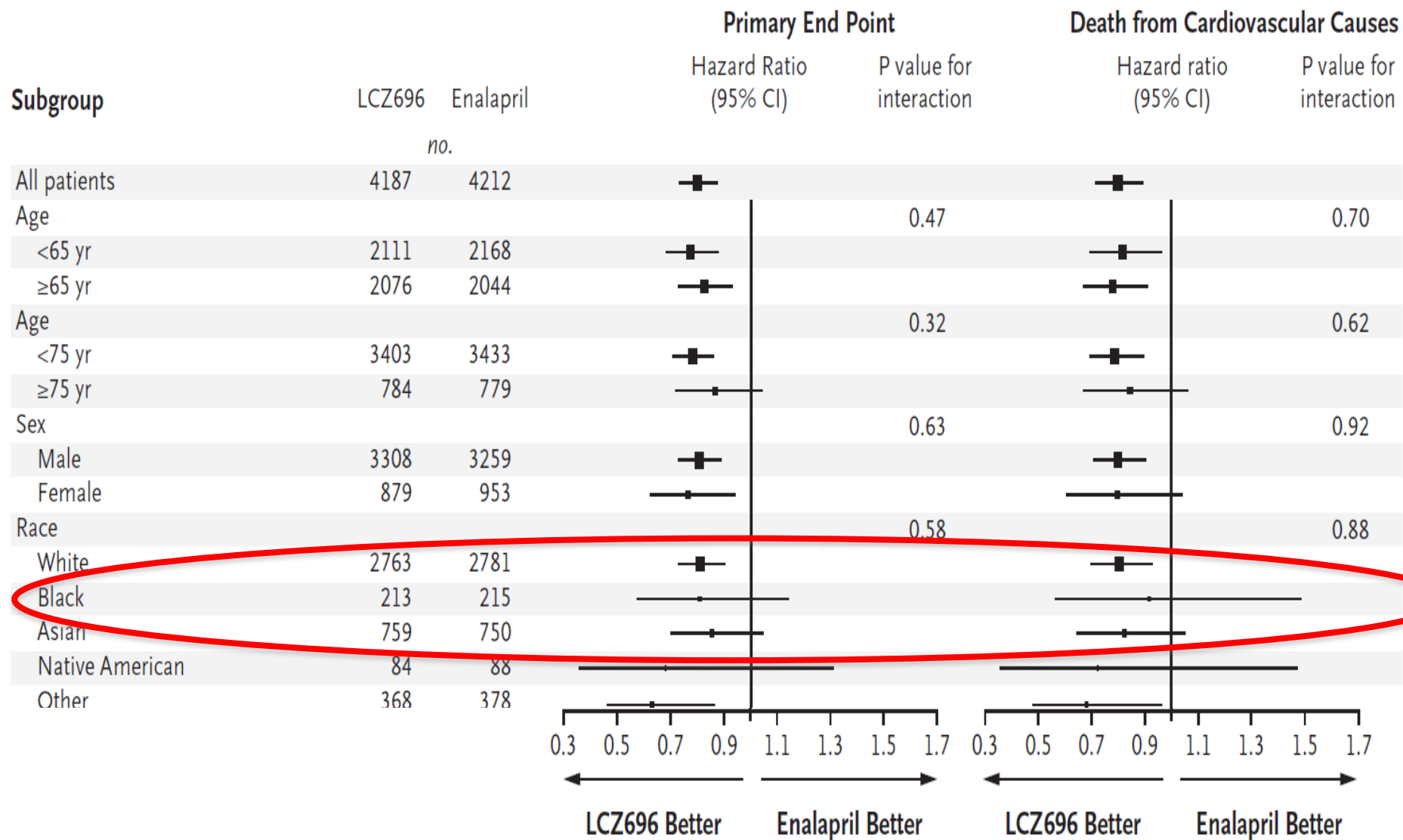
D Death from Any Cause



No. at Risk

LCZ696	4187	4056	3891	3282	2478	1716	1005	280
Enalapril	4212	4051	3860	3231	2410	1726	994	279

LCZ696 Prespecified Subgroup Analyses: primary end point



Confirmed blinded adjudication: blacks higher rate of LCZ696 angioedema

- Overall angioedema: 19 patients LCZ696 and 10 patients enalapril ($P=0.13$).
- Blacks: enalapril 1/214 (0.5%) vs. LCZ696 5/213 (2.4%)
- U.S. blacks: 0/57 enalapril vs. 3/54 LCZ696 (5.6%)

Conclusions

- FDA is committed to ensuring diversity in clinical trials
- However, research diversity remains suboptimal in contemporary CV studies
- Pharmacologic responses and side effects and perhaps device utility may differ among subpopulations
- Recently FDA approved HF drugs may be utilized based on limited data in blacks

Thank You!

