



Avoiding Cardiovascular Events through  
COMbination Therapy in Patients  
Living with Systolic Hypertension

**The First Outcomes Trial of  
Initial Therapy With  
Combination Antihypertensive Treatment**

# Disclosures

Jamerson KA et al. *Am J Hypertens*. 2003;16(part2)193A.



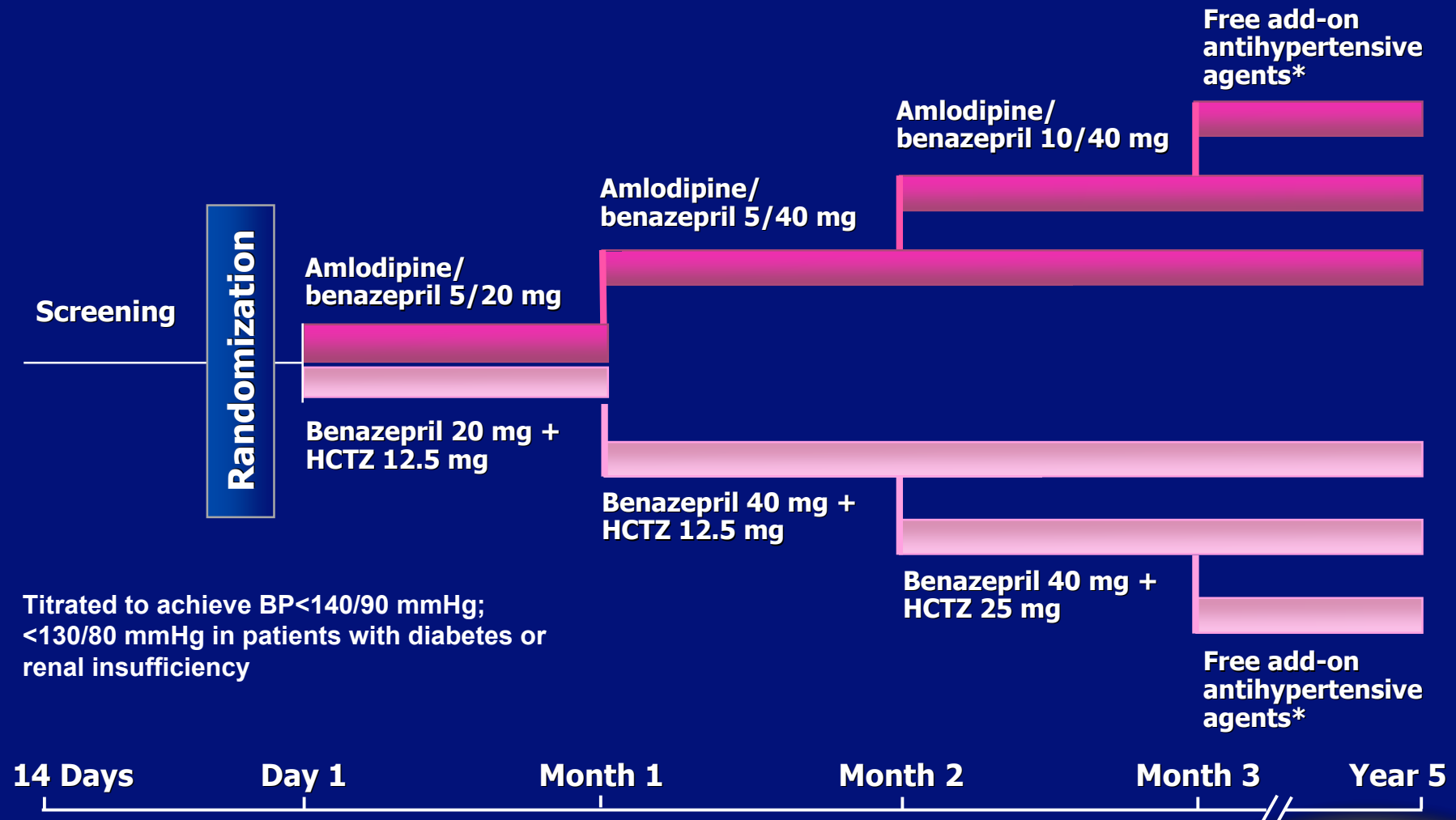
# Primary Study Objective

- To determine if amlodipine besylate / benazepril will confer a 15% reduction in cardiovascular morbidity and mortality in high-risk hypertensive subjects when compared with the combination of benazepril and HCTZ

# Study Overview

- Multinational, double-blind clinical trial
  - N = 11,508 subjects (550 centers)
- Designed to challenge current guidelines in defining the optimal therapeutic strategy for achieving blood pressure control and preventing CVD events in high-risk patients
  - First trial to randomize to initial antihypertensive combination therapy (amlodipine besylate / benazepril vs benazepril HCTZ)
- Event-driven trial of 5-year duration
- The DSMB recommended termination the trial in October 2007. LPLV January 24th 2008
- Interim analysis with 95.3% of end points adjudicated

# ACCOMPLISH: Design



Titrated to achieve BP <140/90 mmHg;  
<130/80 mmHg in patients with diabetes or  
renal insufficiency

\*Beta blockers; alpha blockers; clonidine; loop diuretics.

Jamerson KA et al. *Am J Hypertens*. 2004;17:793–801.



# Inclusion Criteria

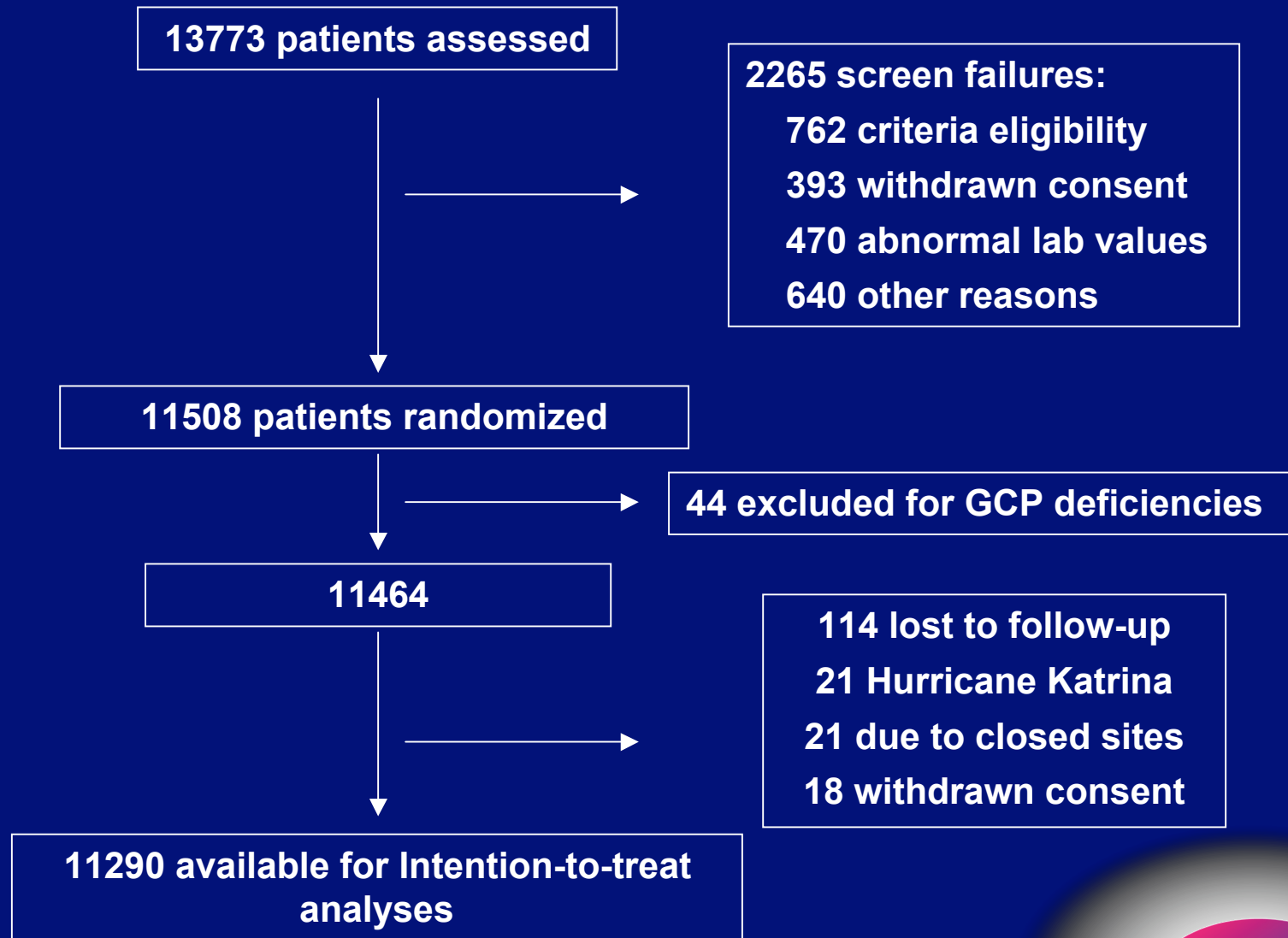
- High-risk men and women with hypertension
- Age  $\geq 60$  years with at least one or  $\geq 55$  years if two of the following criteria for “high-risk” are present:
  - History of diabetes
  - CHD (MI, coronary revascularization, or unstable angina)
  - Stroke
  - Peripheral arterial disease
  - LVH
  - Proteinuria
  - Chronic renal insufficiency (serum creatinine  $>1.6$  in men or  $>1.8$  mg/dL in women)

# Primary Endpoint

Cardiovascular Morbidity and Mortality,  
defined as:

- Cardiovascular death
- Fatal / Non-fatal myocardial infarction
- Fatal / Non-fatal stroke
- Hospitalization for unstable angina
- Coronary revascularization procedure (PCI or CABG)

# Trial Profile (Patient Profile)



Data as of 26-Feb-08



# Baseline Demographics

	<b>Treatment X</b> N=5741 (%)	<b>Treatment Y</b> N=5721 (%)
<b>Gender</b>		
Male	3506 (61.1)	3430 (60.0)
Female	2220 (38.7)	2277 (39.8)
<b>Race</b>		
Caucasian	4783 (83.3)	4801 (83.9)
Black	696 (12.1)	675 (11.8)
Asian	27 (0.5)	22 (0.4)
Other	220 (3.8)	209 (3.7)
<b>Age</b>		
Mean (years)	68.3	68.4
< 70	3400 (59.2)	3357 (58.7)
≥ 70	2326 (40.5)	2349 (41.1)
<b>Region</b>		
Nordic*	1676 (29.2)	1677 (29.1)
United States	4050 (70.5)	4030 (70.4)

\*Denmark, Finland, Norway or Sweden



# Baseline Risk Factors

	<b>Treatment X</b> N=5741 (%)	<b>Treatment Y</b> N=5721 (%)
<b>Prior MI</b>	1361 (23.7)	1329 (23.2)
<b>Diabetes mellitus</b>	3439 (59.9)	3455 (60.4)
<b>History of Stroke</b>	730 (12.7)	761 (13.3)
<b>Chronic Kidney Disease</b>		
<b>Systolic BP (mmHg <math>\pm</math> SD)</b>	145.5 $\pm$ 18.1	145.5 $\pm$ 18.5
<b>Diastolic BP (mmHg <math>\pm</math> SD)</b>	80.0 $\pm$ 10.7	80.1 $\pm$ 10.8



# ACCOMPLISH Participants Received Aggressive Medical Management Prior to Entry

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- 78% of patients on ACE/ARB
- 67% of patients on lipid lowering agents
- 63% of patients on anti-platelet therapy
- Mean LDL 101.6 mg/dl

# Baseline Traits of the ACCOMPLISH Cohort

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- Patient enrollment completed.
  - 50% of patients are obese
  - 60% of patients have Diabetes Mellitus
  - 97% of patients were treated previously for hypertension.
  - 74% of patients were treated with  $\geq 2$  Hypertensive Agents
- Only 37.5% of patients were controlled to  $<140/90$  mmHg



# Systolic Blood Pressure Over Time

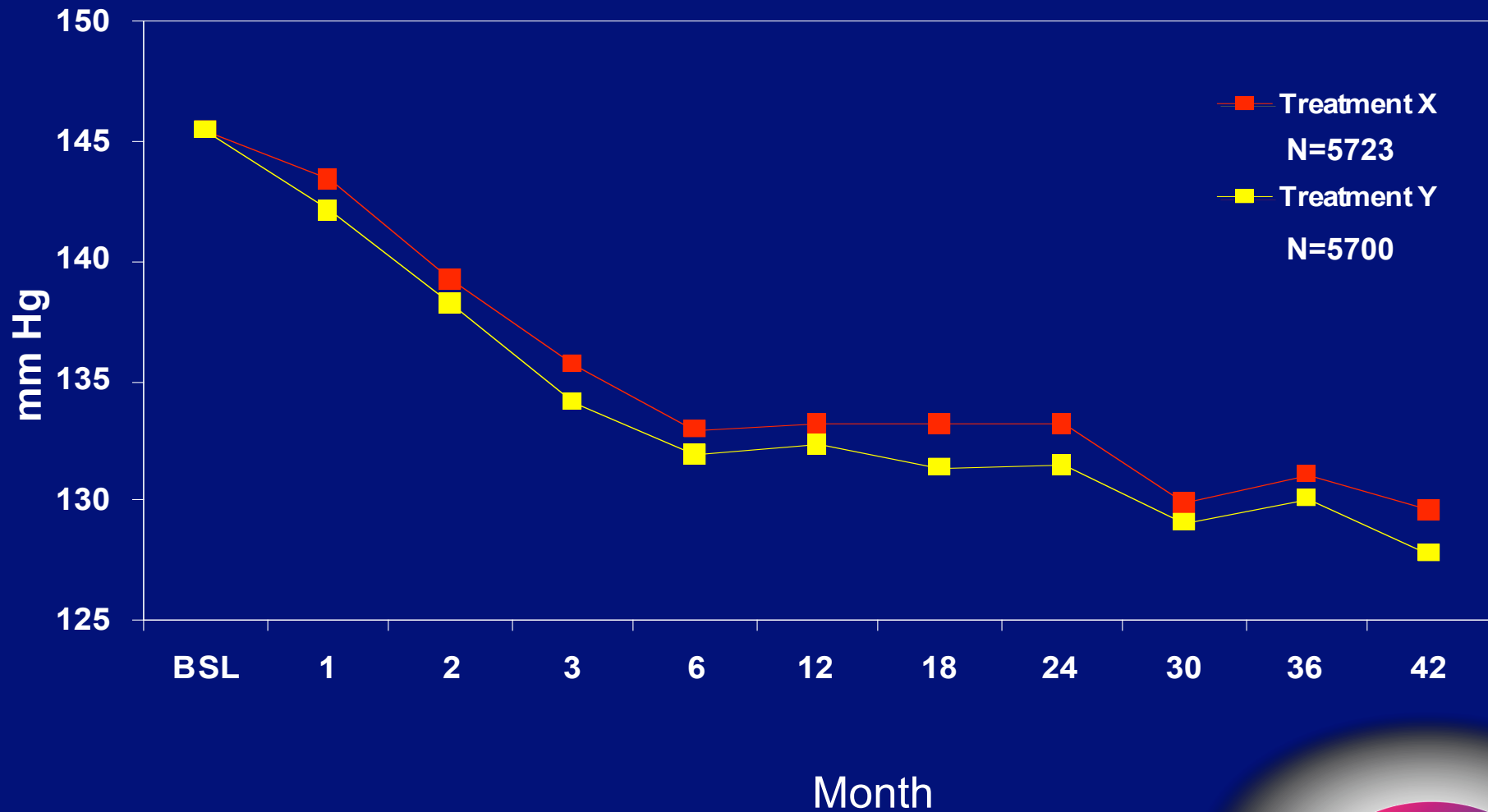
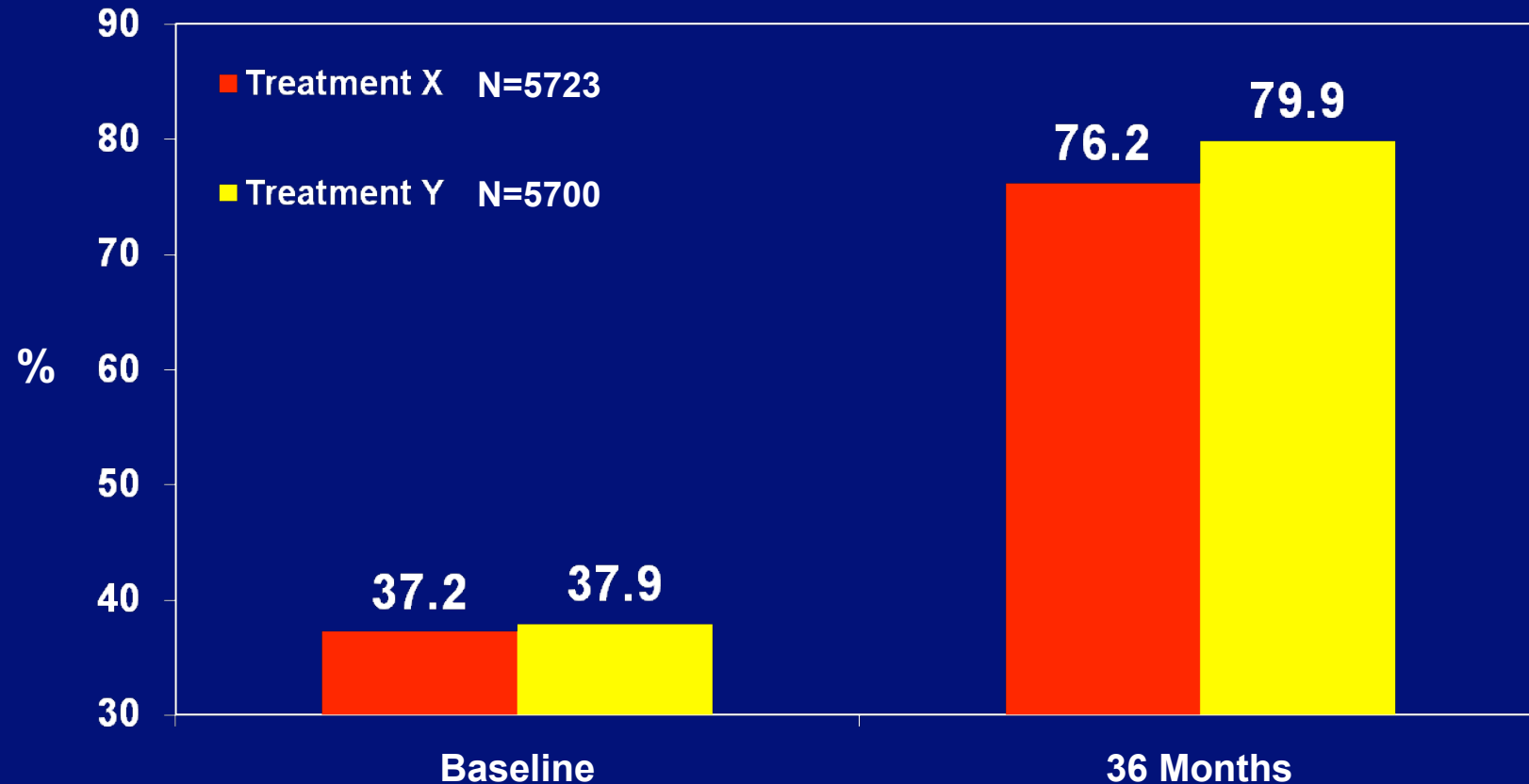


Table 5.1-1a Pages 1-2



# Fixed Dose Combinations Provided Exceptional BP Control

Between Treatment Comparison for Blood Pressure Control Rate\*  
(Safety population)

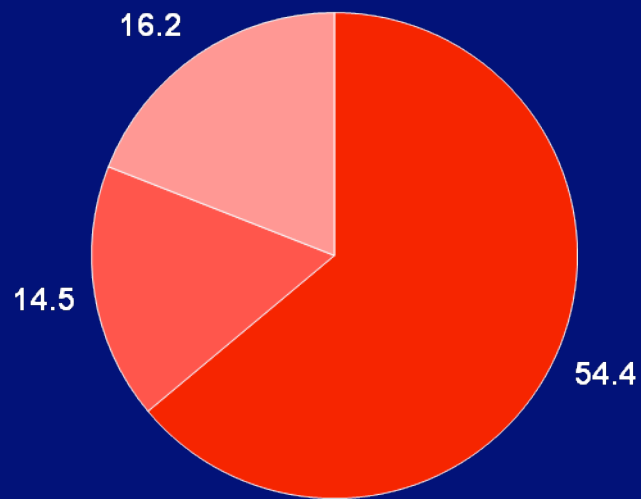


\* Blood pressure control rate is defined as the proportion of patients with SBP/DBP < 140/90 mmHg.

Table 5.3-1a

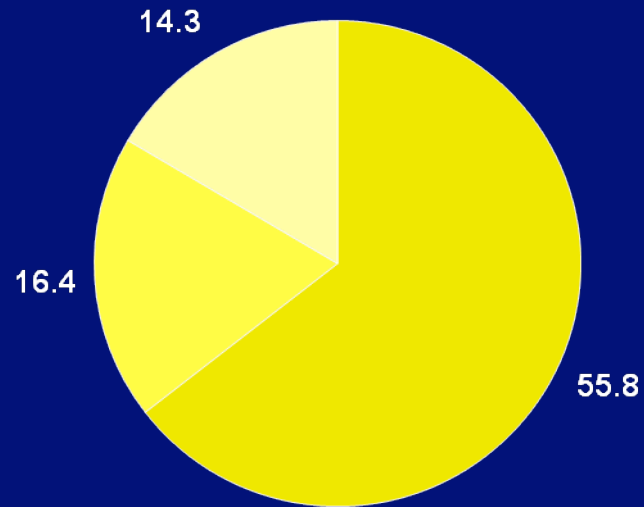


# Summary of Titration Status



Treatment X  
N=5723

- Study Medication Only
- Study + 1 Add-on
- Study +  $\geq 2$  Add-on



Treatment Y  
N=5700

- Study Medication Only
- Study + 1 Add-on
- Study +  $\geq 2$  Add-on

Includes patients receiving beta blockers, alpha blockers, clonidine, loopdiuretics. The number of patients with free add-on antihypertensive agents only include those patients who has reached dose level 3.

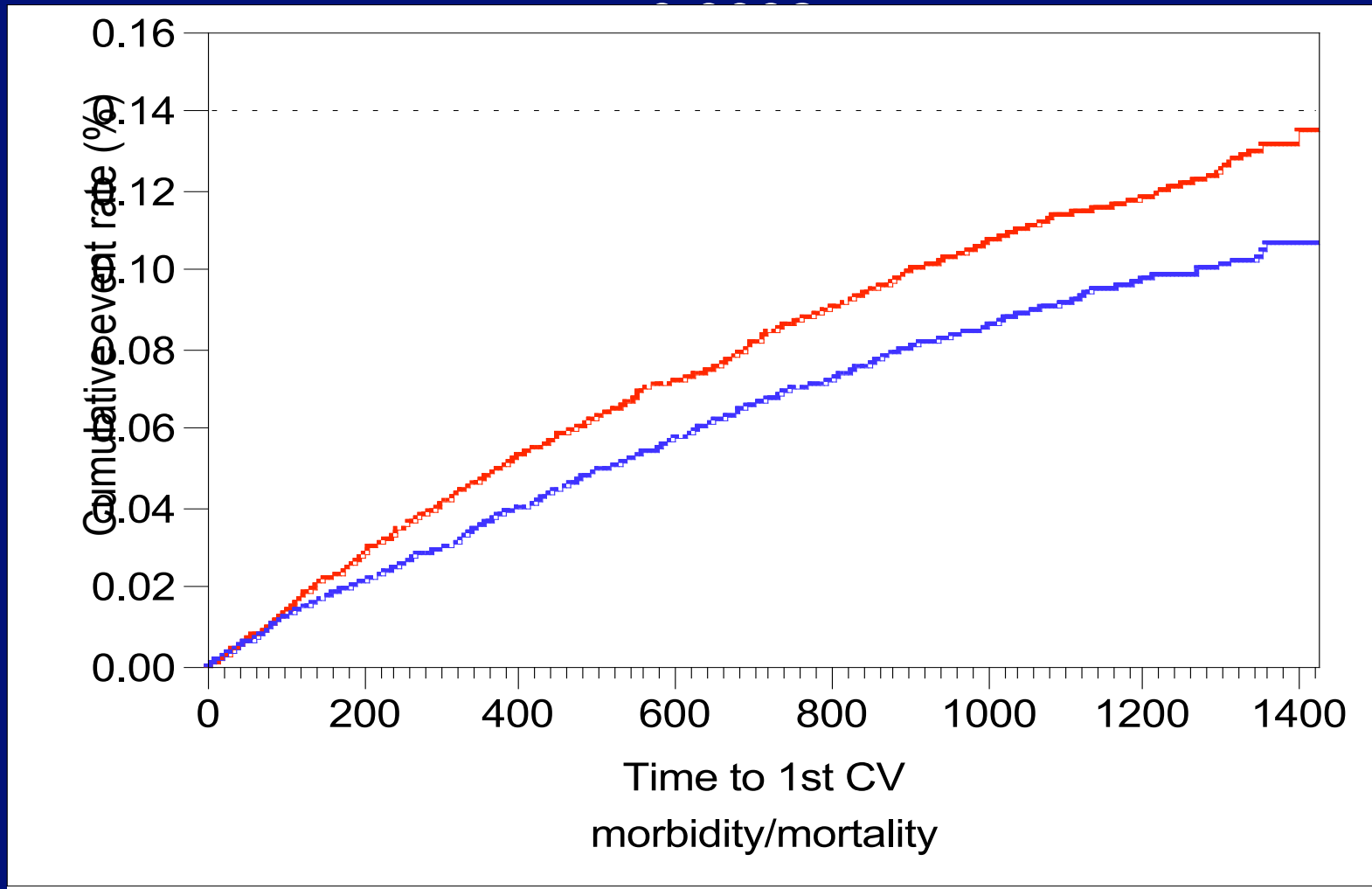
Table 6.1-1a (Page 7 of 10)





# Kaplan Meier for Primary Endpoint

HR (95% CI): 0.80 (0.71, 0.90);



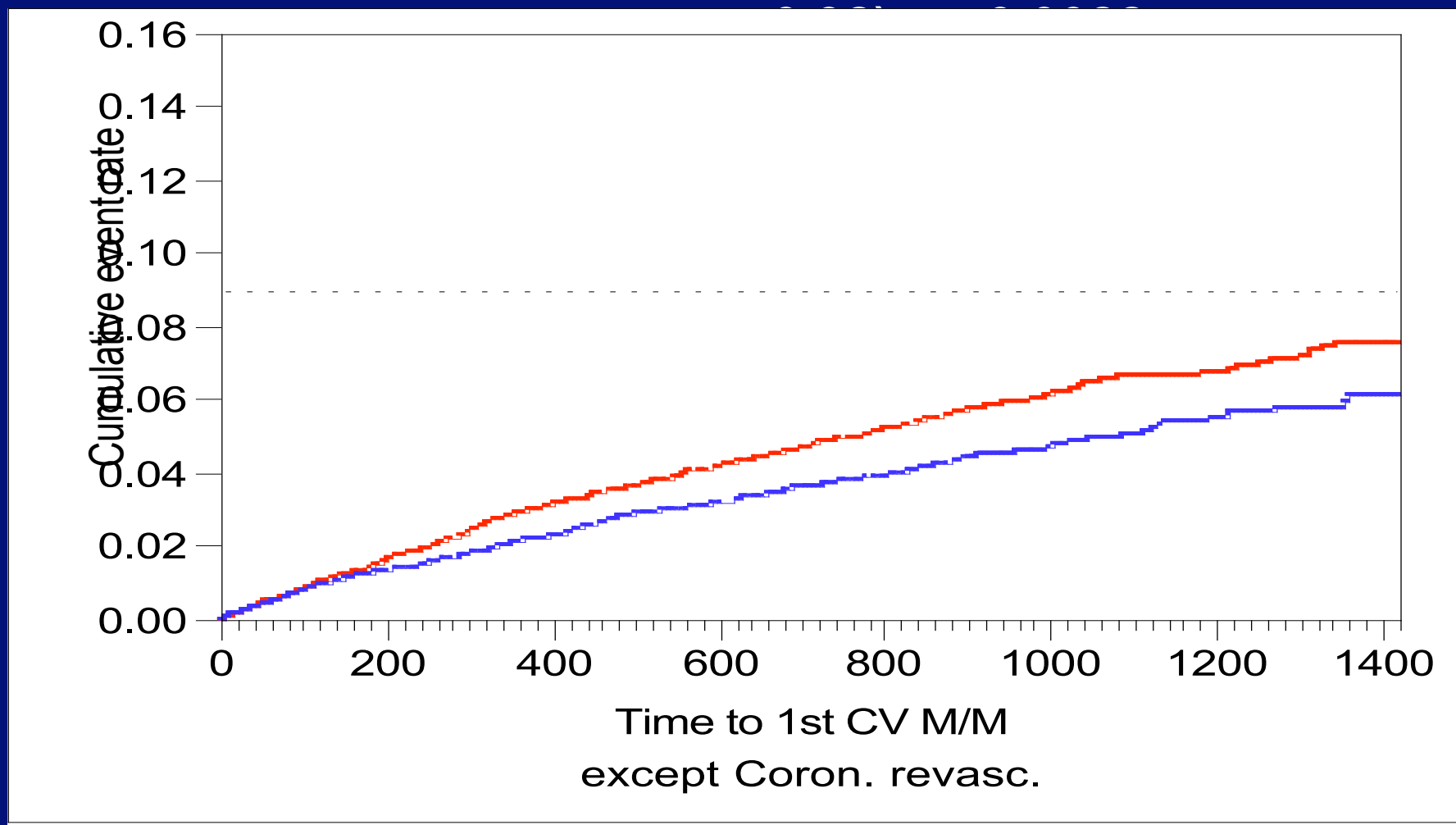
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# Kaplan Meier for Primary Endpoint Without Revasc

HR (95% CI): 0.79 (0.68,



Jamerson KA et al. *Am J Hypertens.* 2003;16(part2)193A.



# Primary Endpoint

Incidence of adjudicated primary endpoints, based upon cut-off analysis date 10/01/2007  
(Intent-to-treat population)

## Primary

Composite CV mortality/morbidity

Cardiovascular mortality

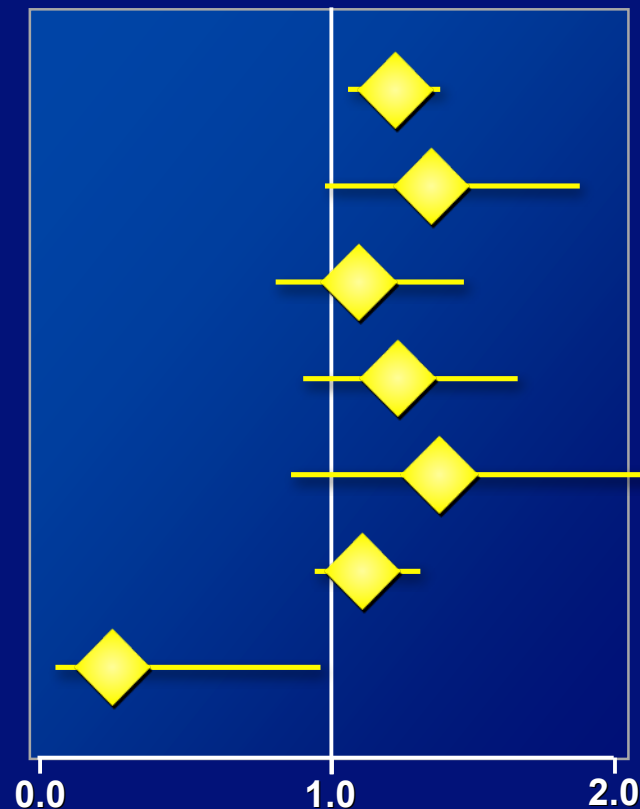
Non-fatal MI

Non-fatal Stroke

Hospitalization for unstable angina

Coronary revascularization procedure

Resuscitated sudden death



Risk Ratio  
(95%)

1.21 (1.06-1.37)

1.34 (0.98-1.84)

1.09 (0.82-1.45)

1.22 (0.91-1.63)

1.36 (0.87-2.13)

1.11 (0.95-1.30)

0.27 (0.08-0.97)

Data as of 3/20/08



# Primary and Other Endpoints

Incidence of adjudicated primary endpoints, based upon cut-off analysis date 10/01/2007  
(Intent-to-treat population)

## Primary

Composite CV mortality/morbidity

Risk Ratio  
(95%)

1.21 (1.06–1.37)

## Other

Fatal / Non-fatal MI

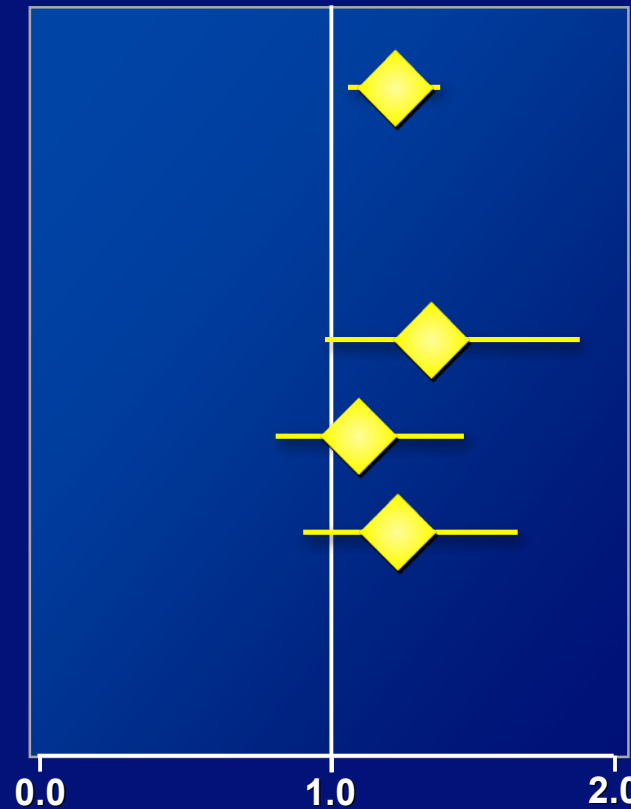
0.00 (0.00–0.00)

Fatal / Non-fatal Stroke

0.00 (0.00–0.00)

Composite Hard Endpoints

0.00 (0.00–0.00)



Data as of 3/20/08



# Summary

The combination of an ace inhibitor and calcium channel blocker was superior to the combination of the diuretic and ace inhibitor by reducing cardiovascular morbidity and mortality by 20%,  $p < 0.0001$

This is an interim analysis (the data base is not locked) based on adjudication of 95% of the end points

# Conclusions

The results of ACCOMPLISH provide compelling evidence for initial combination therapy with ace/ccb and challenges current diuretic based guidelines.