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

Kenneth Jamerson¹, George L. Bakris², Bjorn Dahlof³, Bertram Pitt¹, Eric J. Velazquez⁴, and Michael A. Weber⁵
for the ACCOMPLISH Investigators

University of Michigan Health System, Ann Arbor, MI¹; University of Chicago-Pritzker School of Medicine, Chicago, IL²; Sahlgrenska University Hospital, Gothenburg, Sweden³; Duke University School of Medicine, Durham, NC⁴; SUNY Downstate Medical College, Brooklyn, NY⁵
Avoiding Cardiovascular Events through COMbination Therapy in Patients Living with Systolic Hypertension

Disclosure Information...
The following relationships exist related to this presentation:

Kenneth Jamerson, George L. Bakris, Bjorn Dahlof, Bertram Pitt, Eric J. Velazquez, and Michael A. Weber for the ACCOMPLISH Investigators
Avoiding Cardiovascular Events through COMbination Therapy in Patients Living with Systolic Hypertension

Disclosure Information...
The following relationships exist related to this presentation:

Collectively, the authors have consulted for most pharmaceutical entities that manufacture cardiovascular products globally. Specifically, all authors have significant consultant, speaker, advisory, and research agreements with the trial sponsor, Novartis.
BACKGROUND
• Traditional approach to hypertension management:
  – Initiate monotherapy then sequentially add medications to achieve target BP

• ACCOMPLISH:
  – Initiate single tablet combination therapy in high-risk hypertension
  – Specific combinations may confer target organ protection in addition to their BP-lowering effects
ACCOMPLISH will test a new strategy for the treatment of hypertension – the first outcomes trial to compare initial therapy with two different combinations.

The combination of benazepril and amlodipine will reduce cardiovascular morbidity and mortality in patients with high-risk hypertension by 15% when compared to the combination of benazepril and HCTZ.
Primary Endpoint

Cardiovascular Mortality and Morbidity, defined as:

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

Jamerson KA et al. Am J Hypertens. 2003;16(part2)193A.
Targeted Population for Recruitment into the ACCOMPLISH Study

- Men or women age ≥ 55 years
- SBP ≥ 160 mmHg or currently on antihypertensive therapy
- Evidence of cardiovascular or renal disease or target organ damage
ACCOMPLISH Patients Were Receiving Significant Medical Management at Baseline

- 78% of patients on ACEI or 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

• 50% of patients were obese
• 60% of patients had Diabetes Mellitus
• 97% of patients were treated previously for hypertension
• 74% of patients were treated with $\geq 2$ antihypertensive agents
• Only 37.5% of patients were controlled to $<140/90$ mmHg
ACCOMPLISH: Design

Screening

- Amlodipine 5 mg + benazepril 20 mg
- Benazepril 20 mg + HCTZ 12.5 mg

Randomization

- Amlodipine 5 mg + benazepril 40 mg
- Benazepril 40 mg + HCTZ 12.5 mg
- Benazepril 40 mg + HCTZ 25 mg

14 Days

Day 1

Month 1

Month 2

Month 3

Free add-on antihypertensive agents*

Year 5

Titration 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. 2003;16(part2)193A
## Baseline Demographics

<table>
<thead>
<tr>
<th>Category</th>
<th>ACEI / HCTZ (N=5741) (%)</th>
<th>CCB / ACEI (N=5721) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3509 (61.1)</td>
<td>3436 (60.1)</td>
</tr>
<tr>
<td>Female</td>
<td>2226 (38.8)</td>
<td>2283 (39.9)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>4789 (83.4)</td>
<td>4814 (84.1)</td>
</tr>
<tr>
<td>Black</td>
<td>699 (12.2)</td>
<td>675 (11.8)</td>
</tr>
<tr>
<td>Asian</td>
<td>27 (0.5)</td>
<td>22 (0.4)</td>
</tr>
<tr>
<td>Other</td>
<td>220 (3.8)</td>
<td>208 (3.6)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (years)</td>
<td>68.3</td>
<td>68.4</td>
</tr>
<tr>
<td>&lt; 70</td>
<td>3407 (59.3)</td>
<td>3367 (58.9)</td>
</tr>
<tr>
<td>≥ 70</td>
<td>2328 (40.6)</td>
<td>2351 (41.1)</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nordic countries*</td>
<td>1676 (29.2)</td>
<td>1677 (29.3)</td>
</tr>
<tr>
<td>United States</td>
<td>4059 (70.7)</td>
<td>4042 (70.7)</td>
</tr>
</tbody>
</table>

*Denmark, Finland, Norway or Sweden
Systolic Blood Pressure Over Time

DBP: 71.1

DBP: 72.8

*Mean values are taken at 30 months F/U visit
ACCOMPLISH: Exceptional Control Rates with Initial Combination Therapy

Control rate (%)

Baseline Control Rates

P<0.001 at 30 months follow-up
Control defined as <140/90 mmHg
Includes patients receiving beta blockers, alpha blockers, clonidine, loop diuretics. The number of patients with free add-on antihypertensive agents only include those patients who has reached dose level 3.

At 30 month follow-up

ACEI / HCTZ
N=5733
- Study Medication Only: 19.8%
- Study + 1 Add-on: 49.6%
- Study + ≥ 2 Add-on: 16.2%
- Drug Interruption: 14.4%

CCB / ACEI
N=5713
- Study Medication Only: 17.5%
- Study + 1 Add-on: 61.0%
- Study + ≥ 2 Add-on: 16.5%
- Drug Interruption: 51.0%
Pre-specified efficacy boundary was crossed with 60% of the expected trial information

Executive Committee accepted the recommendation

Last patient last visit was Jan 24, 2008

Total of 1176 unique patients with events

95.3% of primary events are adjudicated
Kaplan Meier for Primary Endpoint

Cumulative event rate

- ACEI / HCTZ
- CCB / ACEI

20% Risk Reduction

Time to 1st CV morbidity/mortality (days)

p = 0.0002

HR (95% CI): 0.80 (0.72, 0.90)

INTERIM RESULTS Mar 08
Primary Endpoint and Components

Incidence of adjudicated primary endpoints, based upon cut-off analysis date 3/24/2008

(Intent-to-treat population)

- Composite CV mortality/morbidity
- Cardiovascular mortality
- Non-fatal MI
- Non-fatal stroke
- Hospitalization for unstable angina
- Coronary revascularization procedure
- Resuscitated sudden death

Risk Ratio

- Composite CV mortality/morbidity: Favors CCB / ACEI 0.80 (0.72–0.90)
- Cardiovascular mortality: Favors ACEI / HCTZ 0.81 (0.62–1.06)
- Non-fatal MI: Favors ACEI / HCTZ 0.81 (0.63–1.05)
- Non-fatal stroke: Favors ACEI / HCTZ 0.87 (0.67–1.13)
- Hospitalization for unstable angina: Favors ACEI / HCTZ 0.74 (0.49–1.11)
- Coronary revascularization procedure: Favors ACEI / HCTZ 0.85 (0.74–0.99)
- Resuscitated sudden death: Favors ACEI / HCTZ 1.75 (0.73–4.17)

INTERIM RESULTS Mar 08
Primary and Other Endpoints

Incidence of adjudicated primary endpoints, based upon cut-off analysis date 3/24/2008

(Intent-to-treat population)

- Composite CV mortality/morbidity
  - Risk Ratio: 0.80 (0.72–0.90)

- Primary w/o revascularization
  - Risk Ratio: 0.79 (0.68–0.92)

- Hard CV endpoint
  - (CV death, non-fatal MI, non-fatal stroke)
  - Risk Ratio: 0.80 (0.68–0.94)

- All cause mortality
  - Risk Ratio: 0.90 (0.75–1.08)

Favors

- CCB / ACEI
- ACEI / HCTZ

INTERIM RESULTS Mar 08
Summary

• Single tablet combination therapy was initiated in 11,462 high risk hypertensive patients

• After mean follow-up of 39 months,
  – The combination of ACEI / CCB was superior to ACEI / diuretic
  – CV morbidity / mortality was reduced by 20% (p=0.0002)
  – Hard CV Endpoint (CV death, stroke and MI) was reduced by 20% (p=0.007)
Summary (cont’d)

• Prior to study entry, 97% of patients were on antihypertensive medication, 74% receiving ≥ 2 therapies

• After mean follow up of 30 months,
  – Overall BP control rates increased from 37% to 80%
  – Mean SBP decreased from 145 to <130 mmHg
  – 50% of participants required only one tablet
ACCOMPLISH achieved exceptional BP control with combination therapy providing a new option for cardiovascular risk reduction to millions of patients with hypertension.

The results of ACCOMPLISH provide compelling evidence for initial combination therapy with ACEI / CCB and challenge current diuretic-based guidelines.