Effect of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on cardiovascular mortality in hypertension: a meta-analysis of randomized controlled trials

Disclosure of interests

JJM has received honoraria for punctual consultancy, conferences or both from almost all pharmaceutical companies developing antihypertensive agents in Europe.
Hypertension remains the first cause of death.

Attributable mortality (in percent) of 56 000 000 deaths in year 2000

- High blood pressure: 12.7%
- Smoking: 8.7%
- High cholesterol: 7.9%
- High BMI: 4.6%
- Physical inactivity: 3.4%
- Alcohol: 3.2%

Adapted from Ezzati et al. Lancet. 2002;360:1347-1360.
Hypertension Guidelines: an ultimate goal

Goals of treatment

“The primary goal of treatment of the hypertensive patient is to achieve the maximum reduction in the long-term total risk of cardiovascular morbidity and mortality.”

Therapeutic management of hypertension

“Antihypertensive treatment translates into significant reductions of cardiovascular morbidity and mortality while having a less significant effect on all cause mortality.”

RAAS inhibitors are a cornerstone of anti-hypertensive treatment.

Source: IMS. Medical Universe - MAT in prescriptions, 35 countries, 2009

Canada, United States, Austria, Belgium, Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Poland, Portugal, Slovakia, Spain, Switzerland, United Kingdom, Australia, Egypt, Indonesia, Japan (includes hospital data), New Zealand, Pakistan, Philippines, Saudi Arabia, South Africa, Thailand, Turkey, Argentina, Brazil, Colombia, Mexico, Venezuela.
Morbidity and mortality benefits of ACE inhibition in stable CAD patients

**2000**  
HOPE (HT 46%)¹

![Graph showing CV death, MI, stroke](image)

- Placebo
- Ramipril 10 mg  
  - RRR -22%  
  - \( P=0.001 \)

**2003**  
EUROPA (HT 27%)²

![Graph showing CV death, MI, cardiac arrest](image)

- Placebo  
- Perindopril 10 mg  
  - RRR -20%  
  - \( P=0.0003 \)

Less than half of the patients were hypertensive

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*Corresponds to perindopril tert-butylamine 8 mg*
Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin–angiotensin–aldosterone system inhibitors involving 158 998 patients

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1Department of Cardiology, Thoraxcenter, Erasmus MC, 3015 GE Rotterdam, The Netherlands; 2Lille Heart Institute, Lille, France; 3Royal Brompton and National Heart Hospital, London, UK; and 4Avicenne University Hospital, Bobigny and Paris 13 University, Paris, France
Meta-analysis

Context:
The impact of RAAS inhibitors (ACE inhibitors and ARBs) is:
- Well established for the reduction of cardiovascular morbidity across specific populations (other than hypertension \textit{per se}).
- Have not been convincingly demonstrated with regard to \textit{mortality} in hypertensive patients.

Primary hypothesis:
RAAS inhibitors as a class of drugs would produce:
- A significant \textit{further} mortality reduction:
  - In their main indication, hypertension.
  - In patients representative of those treated in the 21\textsuperscript{st} century.
Meta-analysis: Methodology

Inclusion criteria:

• Prospective, randomized, controlled morbidity-mortality trials that compared active treatment (ACE inhibitor or ARB) with control, published between Jan 2000 and Mar 2011.

• Trials including a large majority of hypertensive patients (>66% of studied population, according to the definition used in these trials).

• Different hypertensive populations for whom the benefits of RAAS inhibition would be expected to be mainly due to BP reduction.

• All-cause mortality: a prespecified end point or reported in the principal study publication
Meta-analysis: Methodology

Exclusion criteria:

• Trials in specific populations (heart failure, acute coronary syndrome, stroke, atrial fibrillation, post-cardiac surgery, hemodialysis trials)
• Post hoc and subgroup analyses
• Less than 66% of the studied population being hypertensive
• All-cause mortality not reported
• Trials with RAAS inhibitors simultaneously investigated in both arms (ONTARGET, ACCOMPLISH, INVEST, etc.)
(ADIS) ISI Web of Science
Drug class is antihypertensive
AND age is adult OR elderly
AND study design is randomized
AND phase is III OR III/IV OR IV
AND text contains "mortality" OR "morbidity“ OR "death“
AND comorbidity is hypertension =148

OVID MEDLINE
1. "Antihypertensive Agents"[Mesh]
   OR "Angiotensin-Conv.Enzyme Inhibitors"[Mesh]
   OR "Angiotensin II Type 1 Receptor Blockers"[Mesh]
   OR "Calcium Channel Blockers"[Mesh]
   OR “Indapamide”[Mesh] OR "Thiazides”[Mesh] =101314
2. 1 AND Limits: Humans, Random, Controlled Trial, English =8049
3. Mortality OR morbi OR death =27591
4. 2 AND 3 =1174
5. "2000/01/01"[Publication Date] =135661
6. 4 AND 5 =732
7. "Hypertension”[Mesh] OR hyperten =12327
8. 6 AND 7 =364

➢ Two authors independently extracted data from these reports and resolved differences by consensus
## Trial selection process

### Potentially relevant publications identified and screened for retrieval (n=512)

- Publications excluded on basis of title, abstract review (n=181)
  - Lacking a clinical outcome (n=64)
  - Not related to the topic of the meta-analysis (38)
  - Treatment did not include RAAS blockers (n=79)

### Publications retrieved for more detailed evaluation (n=331)

- Publications excluded after obtaining the full text (n=282)
  - Not a prospective morbidity-mortality RCT (n=212)
  - Duplicated publication (n=22)
  - Excluded because of HF or ACS, acute stroke and post-cardiac surgery, AF and hemodialysis (n=53)

### Potentially appropriate randomized controlled trials (RCT) for meta-analysis (n=44)

- RCT excluded (n=24)
  - <2/3 of patients with hypertension (n=8)
  - <10 events (n=6) or <100 patients (n=4) in one arm
  - All-cause mortality not reported (n=1)
  - RAAS inhibitors in both treatment arms (n=5)

### Randomized controlled trials included in the meta-analysis (n=20)
## Baseline characteristics of study population

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>N</th>
<th>Active treatment</th>
<th>Control</th>
<th>Mean FU, years</th>
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<th>Mean SBP, mm Hg</th>
<th>Mean age, years</th>
<th>IR, control</th>
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<td>55.4</td>
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<tr>
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<td>1650</td>
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<td>9306</td>
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<td><strong>OVERALL</strong></td>
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<td></td>
<td><strong>4.3</strong></td>
<td><strong>91%</strong></td>
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</tr>
</tbody>
</table>

ARB=angiotensin receptor blocker, FU=follow-up, IR=incidence rate/1000 patient-years, HCTZ=hydrochlorothiazide, SBP=systolic blood pressure.
All-cause mortality: effect of ACE inhibitors

- **ALLHAT** (lisinopril)
  - HR (95% CI): 1.03 (0.90-1.15)
- **ANBP-2** (enalapril)
  - HR (95% CI): 0.90 (0.75-1.09)
- Pilot HYVET (lisinopril)
  - HR (95% CI): 0.99 (0.62-1.58)
- JMIC-B (lisinopril, enalapril)
  - HR (95% CI): 1.32 (0.61-2.86)
- ASCOT-BPLA (perindopril)
  - HR (95% CI): 0.89 (0.81-0.99)
  - P: 0.03
- ADVANCE (perindopril)
  - HR (95% CI): 0.86 (0.75-0.98)
  - P: 0.03
- HYVET (perindopril)
  - HR (95% CI): 0.79 (0.65-0.95)
  - P: 0.02

Overall

- HR (95% CI): 0.90 (0.84-0.97)
  - P: 0.004

N= 76,615

van Vark LC et al. Eur Heart J. 2012; 33:2088–2097
All-cause mortality: effect of ARBs

Random effects model | HR (95% CI) | P

RENAAL (losartan) | 1.03 (0.83-1.29) |
IDNT (irbesartan) | 0.92 (0.69-1.23) |
LIFE (losartan) | 0.88 (0.77-1.01) |
SCOPE (candesartan) | 0.96 (0.81-1.14) |
VALUE (valsartan) | 1.04 (0.94-1.14) |
MOSES (eprosartan) | 1.07 (0.73-1.57) |
JIKEI HEART (valsartan) | 1.09 (0.64-1.85) |
PRoFESS (telmisartan) | 1.03 (0.93-1.14) |
TRANSCEND (telmisartan) | 1.05 (0.91-1.22) |
CASE-J (candesartan) | 0.85 (0.62-1.16) |
HIJ-CREATE (candesartan) | 1.18 (0.83-1.67) |
KYOTO HEART (valsartan) | 0.76 (0.40-1.30) |
NAVIGATOR (valsartan) | 0.90 (0.77-1.05) |

Overall | 0.99 (0.94-1.04) | 0.683

N=82 383

van Vark LC et al. Eur Heart J. 2012; 33:2088–2097
All-cause mortality: effect of ACE inhibitors

<table>
<thead>
<tr>
<th>Study</th>
<th>ACE Inhibitor</th>
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Overall

0.90 (0.84-0.97)  0.004

N= 76,615

van Vark LC et al. Eur Heart J. 2012; 33:2088–2097
We decided to study the impact of ACE inhibitors and ARBs on cardiovascular mortality in hypertension.
Baseline characteristics of study population

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ARB=angiotensin receptor blocker, FU=follow-up, IR=incidence rate/1000 patient-years, HCTZ=hydrochlorothiazide, SBP=systolic blood pressure.

van Vark LC et al. Eur Heart J. 2012; 33:2088–2097
16 trials: Cardiovascular mortality reduction

Random effects model | HR (95% CI)
---|---
LIFE | 0.87 (0.72 to 1.05)
ALLHAT | 1.02 (0.93 to 1.12)
ANBP-2 | 0.99 (0.72 to 1.35)
SCOPE | 0.94 (0.75 to 1.18)
Pilot HYVET | 1.00 (0.60 to 1.67)
JMIE-B | 1.04 (0.34 to 3.23)
VALUE | 1.01 (0.86 to 1.18)
ASCOT-BPLA | 0.76 (0.65 to 0.90)
JIKEI HEART | 1.03 (0.41 to 2.60)
ADVANCE | 0.82 (0.68 to 0.98)
HYVET | 0.77 (0.60 to 1.01)
PRoFESS | 0.94 (0.87 to 1.01)
TRANSCEEND | 1.03 (0.85 to 1.24)
HIJ-CREATE | 1.14 (0.66 to 1.95)
KYOTO HEART | 0.66 (0.30 to 1.60)
NAVIGATOR | 1.09 (0.85 to 1.40)
Overall | 0.93 (0.88 to 0.99)

Favors RAAS inhibitor | Favors Control
Cardiovascular mortality: effect of ACE inhibitors

- **ALLHAT** (lisinopril): HR = 1.02 (0.93-1.12)
- **ANBP-2** (enalapril): HR = 0.99 (0.72-1.35)
- **Pilot HYVET** (lisinopril): HR = 1.00 (0.60-1.67)
- **JMIC-B** (lisinopril, enalapril): HR = 1.04 (0.34-3.23)
- **ASCOT-BPLA** (perindopril): HR = 0.76 (0.65-0.90), P = 0.001
- **ADVANCE** (perindopril): HR = 0.82 (0.68-0.98), P = 0.03
- **HYVET** (perindopril): HR = 0.77 (0.60-1.01)

**Overall**: HR = 0.88 (0.77-1.0), P = 0.051

N = 76,615
Cardiovascular mortality: effect of ACE inhibitors

<table>
<thead>
<tr>
<th>Study</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLHAT (lisinopril)</td>
<td>1.02 (0.92-1.11)</td>
<td>0.747</td>
</tr>
<tr>
<td>ANBP-2 (enalapril)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pilot HYVET (lisinopril)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JMIC-B (lisinopril, enalapril)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N= 42 347</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCOT-BPLA, ADVANCE, HYVET (perindopril)</td>
<td>0.78 (0.70-0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N= 34 242</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>0.88 (0.77-1.0)</td>
<td>0.051</td>
</tr>
<tr>
<td>N= 76 615</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cardiovascular mortality: effect of ARBs

Random effects model

<table>
<thead>
<tr>
<th>Study</th>
<th>ARB</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIFE (losartan)</td>
<td>Control</td>
<td>0.87 (0.72-1.05)</td>
</tr>
<tr>
<td>SCOPE (candesartan)</td>
<td>ARB</td>
<td>0.94 (0.75-1.18)</td>
</tr>
<tr>
<td>VALUE (valsartan)</td>
<td>Control</td>
<td>1.01 (0.86-1.18)</td>
</tr>
<tr>
<td>JIKEI HEART (valsartan)</td>
<td>ARB</td>
<td>1.03 (0.41-2.60)</td>
</tr>
<tr>
<td>PRoFESS (telmisartan)</td>
<td>Control</td>
<td>0.94 (0.87-1.01)</td>
</tr>
<tr>
<td>TRANSCEND (telmisartan)</td>
<td>ARB</td>
<td>1.03 (0.85-1.24)</td>
</tr>
<tr>
<td>HIJ-CREATE (candesartan)</td>
<td>ARB</td>
<td>1.14 (0.66-1.95)</td>
</tr>
<tr>
<td>KYOTO HEART (valsartan)</td>
<td>Control</td>
<td>0.66 (0.30-1.60)</td>
</tr>
<tr>
<td>NAVIGATOR (valsartan)</td>
<td>ARB</td>
<td>1.09 (0.85-1.40)</td>
</tr>
</tbody>
</table>

Overall ARB better 0.96 (0.90-1.01) 0.143

N= 73 088
Systematic Review: Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors or Angiotensin II–Receptor Blockers for Ischemic Heart Disease

William L. Baker, PharmD; Craig L. Coleman, PharmD; Jeffrey Kluger, MD; Kurt M. Reinhardt, PharmD; Ripple Talati, PharmD; Robert Quercia, MS; Olivia J. Phang, PharmD; and C. Michael White, PharmD

Context
Do patients already receiving standard therapy for ischemic heart disease benefit from additional treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II–receptor blockers (ARBs)?

Contribution
Authors of this systematic review concluded that ACE inhibitors reduce risk for mortality, stroke, and myocardial infarction in patients with stable ischemic heart disease and preserved left ventricular function who already receive standard treatments, such as β-blockers, statins, and aspirin. Evidence about effects of ARBs was scant. Combining ACE inhibitors and ARBs increased risks for hypotension and syncope compared with ACE inhibitor therapy alone.

—The Editors

All-cause mortality: ARB vs active treatment

Bangalore S et al. BMJ; 2011; 342-d2234
Angiotensin receptor blockers and risk of myocardial infarction: meta-analyses and trial sequential analyses of 147,020 patients from randomised trials

Sipal Bangle, director of research,1 assistant professor of medicine;2 Sunil Kumar, fellow in cardiovascular medicine;3 Jarn Wetterleif, chief physician;4 Franz H Messerli, director, hypertension program; professor of clinical medicine5

WHAT IS ALREADY KNOWN ON THIS TOPIC
Angiotensin receptor blockers are important in the treatment of cardiovascular conditions
Previous studies have shown an increased risk of myocardial infarction with these drugs and have raised concern among physicians and patients

WHAT THIS STUDY ADDS
There is firm evidence to refute the hypothesis of angiotensin receptor blockers increasing the risk of myocardial infarction (ruling out even a 0.3% absolute increase)

Fig 2 | Angiotensin receptor blockers (ARBs) and myocardial infarction, stratified by comparison group (placebo vs active treatment)
Conclusion

- ACE inhibitors were associated with a 12% reduction in CV death (HR=0.88; 95% CI, 0.77–1.00; \( P<0.051 \)).

- No significant reduction in cardiovascular mortality could be demonstrated with ARBs\( y \) (HR=0.96; 95% CI, 0.90–1.01; \( P=0.128 \)) in 73,098 patients. No heterogeneity was observed for the effects of the different ARBs.

- We found evidence of heterogeneity with respect to CV mortality reduction with different ACE inhibitors (\( P \) for heterogeneity 0.031, \( I^2 57\% \)).

- Perindopril-based regimens were associated with a significant 22% reduction in CV mortality (HR=0.78; 95% CI, 0.70–0.87, \( P<0.001 \)), whereas the remaining ACE inhibitors were not.

- Because of the high prevalence of hypertension, the widespread use of ACE inhibitors may result in an important gain in lives saved.