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THE IMPACT OF REFERENCE PRICING OF
CARDIOVASCULAR DRUGS ON HEALTH CARE
COSTS AND HEALTH OUTCOMES: EVIDENCE FROM
BRITISH COLUMBIA – VOLUME III: ACE and CCB
LITERATURE REVIEW

Lisa R. Dolovich, Anne M. Holbrook, Margaret Woodruff

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Abstract

The Impact of Reference Pricing of Cardiovascular Drugs on Health Care Costs and Health Outcomes: Evidence from British Columbia -- Volume III: ACE and CBB Literature Review

P.V. Grootendorst, L.R. Dolovich, A.M. Holbrook, A.R. Levy, B.J. O'Brien

Objective: We estimate the effects of Reference Pricing, a drug cost control policy introduced by the BC Ministry of Health Pharmacare program in 1995, on its program expenditures for seniors, out of pocket costs paid by its senior beneficiaries, indicators of beneficiary health status and attendant Ministry of Health expenditures on physicians and hospitals services. Rationale: Reference pricing (RP) limits the reimbursement of a group of drugs with similar therapeutic effect but different active ingredients to a fixed "reference price". The setting of the reference price varies by jurisdiction but typically is based on an average of the lowest cost "reference standard" drugs within the group. Critics of RP contend that the partially subsidized and fully subsidized (reference standard) drugs are not therapeutically interchangeable, and therefore patient health will be compromised and use of other non-pharmacologic health services may increase as a result, thus partially or wholly offsetting any potential cost savings from the policy.

Findings: The application of RP to 3 groups of cardiac drugs produced annualized savings to Pharmacare of about $7.7 million, or 3.6% of the $213.7 million that Pharmacare spent on drugs for seniors (not including dispensing fees) in 1997. The additional costs for physician consultations were modest, around $500,000 in the subsample of seniors we studied, from the introduction of the RP plans to March 1998, although the costs could be greater, perhaps up to twice this amount, if we accounted for all seniors exposed to the RP over the same period. We found no effects of RP on mortality, or premature admission to a longterm care facility.

Seniors using the nitrate drugs for angina that were no longer fully subsidized when RP was introduced faced a higher probability in the short run of using medicines to deal with acute exacerbations of angina and in the longer run having bypass surgery or other revascularization procedures. No long run effects of morbidity were observed for the application of RP to two different types of anti-hypertensive medications, although there was a short run increase in the rate of revascularizations among those taking 1 type of anti-hypertensive: the ACE inhibitors. The results of these morbidity models should be seen as tentative, until these results can be replicated using alternative estimation strategies.

Conclusions: The introduction of RP can indeed reduce Ministry of Health drug expenditures. The effects of RP on patient morbidity remain to be fully investigated before definitive policy recommendations can be offered.
Health Transitions Fund Project NA222:

The impact of reference pricing of cardiovascular drugs on health care costs and health outcomes: evidence from British Columbia

Volume III: Review of the literature on the therapeutic equivalence of the ACE inhibitors and Dihydropyridine Calcium Channel Blockers

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Key words: reference pricing, reference based pricing, prescription drugs, utilization, ACE inhibitors, calcium channel blockers, nitrates, pharmaceutical cost control, seniors, copayments, charges, user fees, costs

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October 4, 2001
Appendix A Therapeutic Equivalence of Dihydropyridine Calcium Antagonists

The dihydropyridine calcium antagonists (DHP CAs) considered for this evaluation included nifedipine, nicardipine, felodipine and amlodipine. These were the calcium antagonists (CAs) affected by the reference pricing policy in British Columbia. The non-dihydropyridine CAs, diltiazem and verapamil, were exempted from the policy. Since nicardipine is rarely used in Canada, the comparisons of nifedipine, felodipine and amlodipine are the most relevant.

We conducted systematic searches of the literature for randomized controlled trials (see Table A1 for search strategy), meta-analyses followed by searches of authoritative clinical practice guideline sources. The search was directed towards studies comparing dihydropyridine CAs with each other in patients with hypertension or angina. Guidelines for stable angina or hypertension were reviewed for their classification of CAs and any comments on similarities, differences or interchangeability. Data were extracted by a single reviewer with a subsequent review and summary of results by a different reviewer.

Based on 19 studies on blood pressure effects (see Tables A2 and A4)\(^{(1-19)}\) and 7 \(^{(20-26)}\) on angina (see Tables A3 and A5), there is no evidence that the dihydropyridine CAs are not interchangeable once dose equivalence and half-life of effect are taken into account (Table A6). The inference of therapeutic equivalence is particularly strong when long-acting preparations are being compared. Limitations in this assessment include the small sample size of individual studies (10/19 hypertension studies and 6/7 angina studies with N<100). Meta-analysis might improve the precision of comparisons. Leading clinical guidelines and systematic reviews do not distinguish amongst DHP CAs in general, particularly the long-acting formulations.\(^{(27-34)}\) Since these drugs are listed as a group and recommended by family name rather than individually, it appears that the expert clinical community implicitly agrees with interchangeability.

In conclusion, no evidence was found that indicated that the dihydropyridine calcium antagonists are not interchangeable keeping dose equivalence and dose frequency in mind. Furthermore authoritative clinical guidelines and overviews in both hypertension and angina treat them as if they were interchangeable.

References:

BP references:


\(^{1}\) This appendix was written by Anne Holbrook, Lisa Dolovich, Margaret Woodruff, Centre for Evaluation of Medicines.


Angina references:

Clinical Guideline References:
Table A1. Search Strategy for Calcium Channel Blocker Comparisons

Steps in Search Strategy

1. Question and strategy developed (below)
2. Ovid search carried out to end of October 1999 (terms below)
3. 1184 abstracts found and reviewed
4. 32 articles identified and retrieved
5. retrieved articles reviewed for inclusion criteria and references checked
6. An additional 22 articles identified from references
7. the additional articles retrieved and reviewed for inclusion criteria and references
8. no further references were identified (actually 2 to discuss)
9. 25 articles meet inclusion criteria (see summary) - still waiting for 4 articles

CCB SEARCH STRATEGY

QUESTION:
Are individual dihydropyridine Calcium Channel Blockers (CCBs) available in Canada\textsuperscript{2} for oral use therapeutically equivalent (ie. equivalent with respect to morbidity, mortality and major adverse effects) in the treatment of hypertension and stable angina?

SEARCH STRATEGY/INCLUSION CRITERIA:
A thorough search of MEDLINE and EMBASE was conducted from 1980 to the present. The search included all English-language literature using the following search headings:

\textbf{DISEASES:} hypertension, stable angina, angina, angina pectoris
\textbf{DRUGS:} calcium channel blockers, calcium antagonists, calcium entry blockers, CCB, CEB, amlodipine, felodipine, nicardipine, nifedipine
\textbf{ADVERSE EFFECTS:} hypotension, tachycardia, flushing, edema, dysrhythmia

OUTCOMES:

quality of life, survival, readmission, morbidity, mortality, physicians visits, hospitalizations, long-term care admissions, cardiovascular deaths

The search was limited to human studies that were randomised controlled trials of 2 or more CCBs in the treatment of hypertension or stable angina. Any meta-analysis of head to head RCT of CCBs were also searched and included. References of each retrieved article and recent review articles (1998-) were manually searched.

POPULATION:
The search included all patients with hypertension (measured by office method or ambulatory blood pressure monitoring) or stable angina independent of the severity of the disorder.
OUTCOMES:
Morbidity end points included differences between CCBs in number of physicians visits, hospitalizations or long-term care admissions. Mortality end points are the differences in cardiovascular deaths between the agents. Differences between the agents in rates of hypotension, tachycardia, flushing, edema and dysrhythmia constitute the adverse effect end points.

EXCLUSION CRITERIA:
Articles pertaining to use of CCBs for headache, GI motility, myocardial infarction and congestive heart failure are not included, nor are articles pertaining to non-dihydropyridine CCBs. As mentioned above, only RCTs are included hence we excluded: reviews (except for the purpose of locating references as discussed above), placebo controlled randomised trials with a single CCB, other uses of CCBs for purposes not identified here, other research questions, editorials, and letters to the editor.

TERMS USED FOR OVID SEARCH RCT:

1. hypertension (mh) 30. hospitalizations (mh)
2. Angina pectoris (mh) 31. long-term care(mh)
3. Angina, unstable (mh) 32. death (mh)
4. Angina pectoris, variant (mh) 33. death, sudden cardiac (mh)
5. Angina (tw) 34. compliance (mh)
6. Stable angina (tw) 35. quality of life (mh)
7. Angina pectoris (tw) 36. survival (mh)
8. hypertension(tw) 37. patient readmission (mh)
9. 1 or 2 or 3 or .......8 38. morbidity (mh)
10. randomized controlled trials (mh) 39. mortality (mh)
11. RCT (mh) 40. Hypotension (mh)
12. controlled clinical trials (mh) 41. Tachycardia (mh)
13. Random allocation (mh) 42. Flushing (mh)
14. Double blind method (mh) 43. Edema(mh)
15. Comparative study (mh) 44. Pulmonary edema (mh?)
16. Exp evaluation studies (mh) 45. Arrhythmia(mh)
17. ((doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti.ab. 46. physicians visits (tw)
18. Random$.ti.ab. 47. office visits (tw)
19. randomized controlled trials (tw) 48. hospitalizations(tw)
20. RCT (tw) 49. long-term care (tw)
21. controlled clinical trials (tw) 50. long-term care admissions (tw)
22. Random allocation (tw) 51. cardiovascular death(tw)
23. Double blind method (tw) 52. Death (tw)
24. Comparative study (tw) 53. Death, sudden cardiac (tw)
25. evaluation studies (tw) 54. compliance(tw)
26. randomized controlled trials (pt) 55. quality of life(tw)
27. controlled clinical trials (pt) 56. survival(tw)
28. 10 or 11 or 12 or ......or 27 57. patient readmission(tw)
29. office visits (mh) 58. morbidity(tw)
29. mortality(tw)
60. Hypotension (tw) 105. office visits (mh)
61. Tachycardia (tw) 106. hospitalizations (mh)
62. Flushing (tw) 107. long-term care (mh)
63. Edema (tw) 108. death (mh)
64. Pulmonary edema (tw) 109. death, sudden cardiac (mh)
65. Arrhythmia (tw) 110. compliance (mh)
66. Dysrhythmia (tw) 111. quality of life (mh)
67. 29 or 30 or ... 66 112. survival (mh)
68. Calcium channel blockers (mh) 113. patient readmission (mh)
69. amlodipine (mh) 114. morbidity (mh)
70. felodipine (mh) 115. mortality (mh)
71. nicardipine (mh) 116. Hypotension (mh)
72. nifedipine (mh) 117. Tachycardia (mh)
73. Dihydropyridines (mh) 118. Flushing (mh)
74. CCB (tw) 119. Edema (mh)
75. CEB (tw) 120. Pulmonary edema (mh?)
76. Calcium channel blockers (tw) 121. Arrhythmia (mh)
77. Calcium antagonists (tw) 122. physicians visits (tw)
78. Calcium entry blockers (tw) 123. office visits (tw)
79. Dihydropyridines (tw) 124. hospitalizations (tw)
80. amlodipine (tw) 125. long-term care (tw)
81. felodipine (tw) 126. long-term care admissions (tw)
82. nicardipine (tw) 127. cardiovascular death (tw)
83. nifedipine (tw) 128. Death (tw)
84. 68 or 69 or ... 83 129. Death, sudden cardiac (tw)
85. 9 and 28 and 67 and 84 130. compliance (tw)
86. Limit 83 to English 131. quality of life (tw)
87. Limit 84 to Human 132. survival (tw)
88. hypertension (mh) 133. patient readmission (tw)
89. Angina pectoris (mh) 134. morbidity (tw)
90. Angina, unstable (mh) 135. mortality (tw)
91. Angina pectoris, variant (mh) 136. Hypotension (tw)
92. Angina (tw) 137. Tachycardia (tw)
93. Stable angina (tw) 138. Flushing (tw)
94. Angina pectoris (tw) 139. Edema (tw)
95. hypertension (tw) 140. Pulmonary edema (tw)
96. 1 or 2 or 3 .... 8 141. Arrhythmia (tw)
97. meta-analysis (pt) 142. Dysrhythmia (tw)
98. Meta-anal: (tw) 143. 18 or 19 or ..... 55
99. Metaanal: (tw) 144. Calcium channel blockers (mh)
100. Quantitative: review: OR quantitative: overview: (tw) 145. amlodipine (mh)
101. Systematic: review: OR systematic: overview: (tw) 146. felodipine (mh)
102. Methodologic: review: OR methodologic: overview: (tw) 147. nicardipine (mh)
148. nifedipine (mh)
149. Dihydropyridines (mh)
150. CCB (tw)
151. CEB (tw)
152. Calcium channel blockers (tw)
153. Calcium antagonists (tw)
154. Calcium entry blockers (tw)
155. Dihydropyridines (tw)
156. amlodipine (tw)
157. felodipine (tw)
158. nicardipine (tw)
159. nifedipine (tw)
160. 57 or 58 or ...72
161. 9 and 17 and 56 and 73
162. Limit 73 to English
163. Limit 74 to Human
Table A2. Summary of Dihydropyridine Calcium Channel Blocker Comparisons in Hypertension

<table>
<thead>
<tr>
<th>ARTICLE</th>
<th>nifedipine</th>
<th>amlodipine</th>
<th>felodipine</th>
<th>nicardipine</th>
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<td>(1)</td>
<td>ND</td>
<td>ND</td>
<td></td>
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<td>(2)</td>
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<tr>
<td>(18)</td>
<td>ND</td>
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<td></td>
<td>ND</td>
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<tr>
<td>(19)</td>
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<td>2</td>
<td></td>
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<td>(20)</td>
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Reference List


Table A3. Summary of Calcium Channel Blocker Comparisons in Angina

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<thead>
<tr>
<th>ARTICLE</th>
<th>nifedipine</th>
<th>amlodipine</th>
<th>felodipine</th>
<th>nicardipine</th>
</tr>
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<tbody>
<tr>
<td>(1)</td>
<td>ND</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(2)</td>
<td>ND</td>
<td></td>
<td></td>
<td>ND</td>
</tr>
<tr>
<td>(3)</td>
<td>1</td>
<td></td>
<td></td>
<td>2 (less dizziness)</td>
</tr>
<tr>
<td>(4)</td>
<td>ND</td>
<td></td>
<td></td>
<td>ND</td>
</tr>
<tr>
<td>(5)</td>
<td>ND</td>
<td></td>
<td></td>
<td>ND</td>
</tr>
<tr>
<td>(6)</td>
<td>ND</td>
<td></td>
<td></td>
<td>ND</td>
</tr>
<tr>
<td>(7)</td>
<td>1</td>
<td></td>
<td></td>
<td>2 (more time to angina)</td>
</tr>
</tbody>
</table>

References
### Table A4. CCB HEAD TO HEAD, RCT, BLINDED STUDIES- BLOOD PRESSURE

<table>
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<tr>
<th>ARTICLE</th>
<th>DRUGS COMPARED</th>
<th>SAMPLE SIZE</th>
<th>endpt of trial</th>
<th>NO SIG. DIFF</th>
<th>SIGNIFICANT DIFFERENCE - EXPLAIN</th>
<th>FURTHER COMMENTS</th>
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</thead>
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<tr>
<td>(Bremner et al., 1993)</td>
<td>amlodipine vs nifedipine retard</td>
<td>97</td>
<td>BP adverse effects (esp. HD, flushing)</td>
<td></td>
<td>A/E sign. greater with nifedipine retard than amlodipine</td>
<td>A-5 mg od N retard-20 mg bid</td>
</tr>
<tr>
<td>(Carroll et al., 1995)</td>
<td>nifedipine SR vs felodipine ER</td>
<td>41</td>
<td>BP 24 h AMBP; BP; adverse effects</td>
<td></td>
<td></td>
<td>N SR-20 mg bid F er 10 mg od</td>
</tr>
<tr>
<td>(Dees et al., 1997)</td>
<td>felodipine ER vs nifedipine retard</td>
<td>115</td>
<td>BP efficacy, tolerability</td>
<td></td>
<td></td>
<td>FER-2.5mg and 5mg od N retard-10 and 20 mg bid</td>
</tr>
<tr>
<td>(Hoegholm et al., 1995)</td>
<td>felodipine ER amlodipine</td>
<td>118</td>
<td>BP efficacy and safety, BP; ABPM</td>
<td></td>
<td>Ambulatory SBP sig. greater amlodipine and HD flushing less</td>
<td>FER-5,10, or20mg od A-5 or 10 mg od</td>
</tr>
<tr>
<td>(Minami et al., 1998)</td>
<td>amlodipine vs nifedipine retard</td>
<td>20</td>
<td>BP HR, BP, ABPM, autonomic nerve activity</td>
<td></td>
<td>Sign diff nifedipine</td>
<td>A 2.5 mg od N retard 20mg bid</td>
</tr>
<tr>
<td>(Testa et al., 1998)</td>
<td>nifedipine GITS vs amlodipine</td>
<td>356</td>
<td>BP SBP,DBP,QofL</td>
<td></td>
<td>Nifedipine sgn. better QofL</td>
<td>N GITS 30mg od A -5mg od</td>
</tr>
<tr>
<td>(Zidek et al., 1995)</td>
<td>nifedipine coat core vs</td>
<td>207</td>
<td>BP efficacy, safety; ABPM</td>
<td></td>
<td></td>
<td>N cc-30mg od</td>
</tr>
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3No significant difference was found between the two agents

4No significant difference was found between the two agents except that noted in second last column
<table>
<thead>
<tr>
<th>ARTICLE</th>
<th>DRUGS COMPARED</th>
<th>SAMPLE SIZE</th>
<th>endpt of trial</th>
<th>NO SIG. DIFF</th>
<th>SIGNIFICANT DIFFERENCE - EXPLAIN</th>
<th>FURTHER COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Hosie J and et al, 1992)</td>
<td>amlodipine</td>
<td>ABPM</td>
<td></td>
<td></td>
<td></td>
<td>A -5 mg od</td>
</tr>
<tr>
<td>(Abelardo et al., 1989)</td>
<td>felodipine ER vs nifedipine retard</td>
<td>77</td>
<td>BP effect, tolerability, QoL</td>
<td>- except</td>
<td>Felodipine better tolerated</td>
<td>F ER - 5 mg od</td>
</tr>
<tr>
<td>(Koenig and et al, 1993)</td>
<td>felodipine ER vs nifedipine retard</td>
<td>23</td>
<td>BP SBP, DBP</td>
<td>-</td>
<td></td>
<td>N retard- 20mg bid</td>
</tr>
<tr>
<td>(Littler, 1990)</td>
<td>felodipine vs nifedipine retard</td>
<td>118</td>
<td>BP efficacy, tolerability</td>
<td>-</td>
<td></td>
<td>F ER -10 mg od</td>
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<tr>
<td>(Aberg et al., 1985)</td>
<td>felodipine vs nifedipine</td>
<td>18</td>
<td>BP poorly controlled SBP, DBP, ECG, blood tests, HR, weight, ankle measure</td>
<td>-</td>
<td></td>
<td>N - 10- 20 mg tid</td>
</tr>
<tr>
<td>(Goudie A.W. and et al, 1994)</td>
<td>felodipine ER vs nifedipine retard</td>
<td>134</td>
<td>BP efficacy (HR, BP), tolerability</td>
<td>- HR</td>
<td>felodipine sig. greater decrease seated BP (fewer A/E - sig?</td>
<td>F ER -5 - 10 mg qam</td>
</tr>
<tr>
<td>(Ueda et al., 1993)</td>
<td>amlodipine vs Nifedipine GITS</td>
<td>9</td>
<td>BP pressor response to angiotensin II and NA</td>
<td>- BP, HR</td>
<td>amlodipine- more smoothly sustained efficacy for 48 h post-dose</td>
<td>A - 5mg od</td>
</tr>
<tr>
<td>(Iliopoulos et al., 1983)</td>
<td>nicardipine vs nifedipine</td>
<td>6</td>
<td>BP BP,HR, STI(systolic time)</td>
<td>-</td>
<td>3 oral treatments -Nic 40mg; Nif 20mg</td>
<td></td>
</tr>
<tr>
<td>ARTICLE</td>
<td>DRUGS COMPARED</td>
<td>SAMPLE SIZE</td>
<td>endpt of trial</td>
<td>NO SIG. DIFF</td>
<td>SIGNIFICANT DIFFERENCE - EXPLAIN</td>
<td>FURTHER COMMENTS</td>
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<td>--------------</td>
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<td>------------------</td>
</tr>
<tr>
<td>(Lorimer et al., 1994)</td>
<td>amlodipine vs nifedipine retard</td>
<td>111</td>
<td><strong>BP</strong> BP, HR, weight, A/E</td>
<td>-</td>
<td></td>
<td>A- 5 -10mg od N retard-20-40 mg bid</td>
</tr>
<tr>
<td>(Rumboldt et al., 1988)</td>
<td>nicardipine vs nifedipine SR</td>
<td>95</td>
<td><strong>BP</strong> BP, HR, A/E, lab exam</td>
<td>-</td>
<td></td>
<td>Nic-40mg od Nif SR- 20mgod</td>
</tr>
<tr>
<td>(Bompadre S and et al, 1991)</td>
<td>amlodipine vs nifedipine AR</td>
<td>8</td>
<td><strong>BP</strong> BP, HR, plasma concentration</td>
<td>-</td>
<td>amlodipine smoother SBP, DBP over 24 hrs</td>
<td>A- 10mg od N AR -20mg bid</td>
</tr>
</tbody>
</table>
References Cited


Table A5. CCB HEAD TO HEAD, RCT, BLINDED STUDIES- ANGINA

<table>
<thead>
<tr>
<th>ARTICLE</th>
<th>DRUGS COMPARED</th>
<th>SAMPLE SIZE</th>
<th>endpt of trial</th>
<th>NO SIG. DIFF</th>
<th>SIGNIFICANT DIFFERENCE - EXPLAIN</th>
<th>FURTHER COMMENTS</th>
</tr>
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<tr>
<td>(Ardissino et al., 1991)</td>
<td>felodipine vs nifedipine</td>
<td>30</td>
<td><strong>Prinzmetal</strong>=s variant <strong>angina</strong>: ischemic episodes recorded by Holter monitoring; angina attacks reported on daily cards</td>
<td>5</td>
<td></td>
<td>F -10-20mg od B20 mg qid *compliance MAY be better with F</td>
</tr>
<tr>
<td>(Ekelund et al., 1994)</td>
<td>felodipine vs nifedipine</td>
<td>24</td>
<td><strong>Angina</strong> single dose-chronic stable effort angina</td>
<td></td>
<td></td>
<td>Patients also on beta blockers and NTG; F-5 and 10 mg N 10 and 20mg</td>
</tr>
<tr>
<td>(DeWood and Wolbach, 1990)</td>
<td>nicardipine vs nifedipine</td>
<td>250</td>
<td><strong>Angina</strong> dizziness, flushing, HD, pedal edema, palpitations</td>
<td>6</td>
<td>Nifedipine more dizziness- sig diff</td>
<td>Nif-20mg tid Nic-30mg tid</td>
</tr>
<tr>
<td>(Di Pasquale et al., 1984)</td>
<td>nicardipine vs nifedipine</td>
<td>12</td>
<td><strong>Angina</strong> chronic effort</td>
<td></td>
<td></td>
<td>Nic -20mg qid Nif -10mg qid</td>
</tr>
<tr>
<td>(Bowles et al., 1986)</td>
<td>nicardipine vs nifedipine</td>
<td>41</td>
<td><strong>Angina</strong> efficacy, exercise testing</td>
<td></td>
<td></td>
<td>Nic - 30 mg tid Nif 10 mg tid</td>
</tr>
<tr>
<td>(Schulte, 1995)</td>
<td>felodipine ER</td>
<td>43</td>
<td><strong>Angina</strong> exercise</td>
<td></td>
<td>except</td>
<td>F ER- 10 mg qam</td>
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</table>

5No significant difference found between the two agents

6No significant difference found between the 2 agents except that mentioned in second last column
<table>
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<th>ARTICLE</th>
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<th>SAMPLE SIZE</th>
<th>endpt of trial</th>
<th>NO SIG. DIFF</th>
<th>SIGNIFICANT DIFFERENCE - EXPLAIN</th>
<th>FURTHER COMMENTS</th>
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<td>vs nifedipine SR</td>
<td>testing; total time, time to onset</td>
<td>...</td>
<td>angina sig. longer for Felodipine</td>
<td>N SRB 20 mg bid</td>
<td></td>
<td></td>
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<tr>
<td>(Koenig and Hoher, 1997)</td>
<td>felodipine ER vs amlodipine</td>
<td>52</td>
<td>Angina-exercise induced; antiischemic, antianginal efficacy</td>
<td>F ER -5-10 mg od A- 5-10mg od</td>
<td></td>
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References Cited


### Table A6. SUMMARY CCB HEAD TO HEAD STUDIES – ALL STUDIES

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<th>ARTICLE</th>
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<th>SAMPLE SIZE</th>
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<th>SIGNIFICANT DIFFERENCE - EXPLAIN</th>
<th>FURTHER COMMENTS</th>
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<tr>
<td>(Ardissino et al., 1991)</td>
<td>felodipine vs nifedipine</td>
<td>30</td>
<td><strong>Prinzmetal=s variant angina</strong>: ischemic episodes recorded by Holter monitoring; angina attacks reported on daily cards</td>
<td>-</td>
<td></td>
<td>F -10-20mg od B20 mg qid *compliance MAY be better with F</td>
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<tr>
<td>(Bremner et al., 1993)</td>
<td>amlodipine vs nifedipine retard</td>
<td>97</td>
<td>BP adverse effects (esp. HD, flushing)</td>
<td>A/E sign. greater with nifedipine retard than amlodipine</td>
<td>A-5 mg od N retard-20 mg bid</td>
<td></td>
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<tr>
<td>(Carroll et al., 1995)</td>
<td>nifedipine SR vs felodipine ER</td>
<td>41</td>
<td><strong>BP 24 h AMBP; BP; adverse effects</strong></td>
<td>-</td>
<td></td>
<td>N SR-20 mg bid F er 10 mg od</td>
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<td>(Dees et al., 1997)</td>
<td>felodipine ER vs nifedipine retard</td>
<td>115</td>
<td><strong>BP efficacy, tolerability</strong></td>
<td>-</td>
<td></td>
<td>FER-2.5mg and 5mg od N retard-10 and 20 mg bid</td>
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<tr>
<td>(Ekelund et al., 1994)</td>
<td>felodipine vs nifedipine</td>
<td>24</td>
<td><strong>Angina</strong> single dose-chronic stable effort angina</td>
<td>-</td>
<td></td>
<td>Patients also on beta blockers and NTG; F-5 and 10 mg N 10 and 20mg</td>
</tr>
<tr>
<td>(DeWood and Wolbach, 1990)</td>
<td>nicardipine vs nifedipine</td>
<td>250</td>
<td><strong>Angina</strong> dizziness, flushing, HD, pedal edema, palpitations</td>
<td>- except...</td>
<td>Nifedipine more dizziness- sig diff</td>
<td>Nif-20mg tid Nic-30mg tid</td>
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<td>FURTHER COMMENTS</td>
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<tr>
<td>(Hoegholm et al., 1995)</td>
<td>felodipine ER vs amlodipine</td>
<td>118</td>
<td>BP efficacy and safety, BP; ABPM</td>
<td>- except...</td>
<td>Ambulatory SBP sig. greater amlodipine and HD flushing less</td>
<td>FER-5,10, or20mg od A-5 or 10 mg od</td>
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<td>(Minami et al., 1998)</td>
<td>amlodipine vs nifedipine retard</td>
<td>20</td>
<td>BP HR, BP, ABPM, autonomic nerve activity</td>
<td>- except...</td>
<td>Sign diff nifedipine caused □HR; □SNS; □PNS</td>
<td>A 2.5 mg od N retard 20mg bid</td>
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<tr>
<td>(Testa et al., 1998)</td>
<td>nifedipine GITS vs amlodipine</td>
<td>356</td>
<td>BP SBP, DBP, QoL</td>
<td>- except...</td>
<td>Nifedipine sgn. better QoL</td>
<td>N GITS 30mg od A -5mg od</td>
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<td>(Zidek et al., 1995)</td>
<td>nifedipine coat core vs amlodipine</td>
<td>207</td>
<td>BP efficacy, safety; ABPM</td>
<td>-</td>
<td></td>
<td>N cc-30mg od A -5 mg od</td>
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<td>(Di Pasquale et al., 1984)</td>
<td>nicardipine vs nifedipine</td>
<td>12</td>
<td>Angina chronic effort</td>
<td>-</td>
<td></td>
<td>Nic -20mg qid Nif -10mg qid</td>
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<td>(Hosie J and et al., 1992)</td>
<td>felodipine ER vs nifedipine retard</td>
<td>77</td>
<td>BP effect, tolerability, QoL</td>
<td>- except ...</td>
<td>Felodipine better tolerated</td>
<td>F ER - 5 mg od N retard- 20mg bid</td>
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<tr>
<td>(Abelardo et al., 1989)</td>
<td>felodipineER vs nifedipine retard</td>
<td>23</td>
<td>BP SBP, DBP</td>
<td>-</td>
<td></td>
<td>F ER -10 mg od N retard - 20mg bid</td>
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<td>(Koenig and et al, 1993)</td>
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<td>118</td>
<td>BP efficacy, tolerability</td>
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<td></td>
<td>F -5 to 10 mg od A - 5 to 10 mg od</td>
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<td>(Bowles et al., 1986)</td>
<td>nicardipine vs nifedipine</td>
<td>41</td>
<td>Angina efficacy, exercise testing</td>
<td>-</td>
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<td>Nic - 30 mg tid Nif 10 mg tid</td>
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<td>SIGNIFICANT DIFFERENCE - EXPLAIN</td>
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<td>------------------</td>
</tr>
<tr>
<td>(Schulte, 1995)</td>
<td>felodipine ER vs nifedipine SR</td>
<td>43</td>
<td><strong>Angina</strong> exercise testing; total time, time to onset</td>
<td>- except ...</td>
<td>Time to onset of angina sig. longer for Felodipine</td>
<td>F ER- 10 mg qam N SRB 20 mg bid</td>
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<tr>
<td>(Littler, 1990)</td>
<td>felodipine ER vs nifedipine retard</td>
<td>100</td>
<td><strong>BP</strong> 3 h and 12h/24h, DBP, SBP, HR, A/E</td>
<td>- except ...</td>
<td>DBP lower in Felodipine gp at 24h post-dose</td>
<td>also on metoprolol F ER - 10 mfg od N retard -20 mg bid</td>
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<td>(Aberg et al., 1985)</td>
<td>felodipine vs nifedipine</td>
<td>18</td>
<td><strong>BP poorly controlled</strong> SBP, DBP, ECG, blood tests, HR, weight, ankle measure</td>
<td>-</td>
<td></td>
<td>F- 5-10 mg tid N - 10- 20 mg tid</td>
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<td>(Goudie A.W. and et al, 1994)</td>
<td>felodipine ER vs nifedipine retard</td>
<td>134</td>
<td><strong>BP efficacy (HR, BP), tolerability</strong></td>
<td>- HR</td>
<td>felodipine sig. greater decrease seated BP (fewer A/E - sig.?)</td>
<td>F ER -5 - 10 mg qam N retard -10-20 mg bid</td>
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<td>(Ueda et al., 1993)</td>
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<td>9</td>
<td><strong>BP</strong> pressor response to angiotensin II and NA</td>
<td>- BP, HR</td>
<td>amlodipine- more smoothly sustained efficacy for 48 h post-dose</td>
<td>A - 5mg od N GITs -60 mg od</td>
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<td>(Koenig and Hoher, 1997)</td>
<td>felodipine ER vs amlodipine</td>
<td>52</td>
<td><strong>Angina</strong>-exercise induced; antiischemic, antianginal efficacy</td>
<td>-</td>
<td></td>
<td>F ER -5-10 mg od A- 5-10mg od</td>
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<td>(Iliopoulou et al., 1983)</td>
<td>nicardipine vs nifedipine</td>
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<td><strong>BP</strong> BP,HR, STI(systolic time intervals)</td>
<td>-</td>
<td></td>
<td>3 oral treatments -Nic 40mg; Nif 20mg</td>
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<td>(Lorimer et al., 1984)</td>
<td>amlodipine vs</td>
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<td><strong>BP</strong> BP, HR, weight,</td>
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<td>A- 5 -10mg od</td>
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<td>1994)</td>
<td>nifedipine retard</td>
<td>111</td>
<td>A/E</td>
<td>-</td>
<td></td>
<td>N retard-20-40 mg bid</td>
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<td>(Rumboldt et al., 1988)</td>
<td>nicardipine vs nifedipine SR</td>
<td>95</td>
<td>BP BP, HR, A/E, lab exam</td>
<td>-</td>
<td></td>
<td>Nic-40mg od Nif SR- 20mgod</td>
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<tr>
<td>(Bompadre S and et al, 1991)</td>
<td>amlodipine vs nifedipine AR</td>
<td>8</td>
<td>BP BP, HR, plasma concentration</td>
<td>-</td>
<td>amlodipine smoother SBP,DBP over 24 hrs</td>
<td>A- 10mg od N AR -20mg bid</td>
</tr>
</tbody>
</table>
References Cited

Appendix B Therapeutic Equivalence of ACE inhibitors

SUMMARY OF REVIEW

QUESTION AND METHODS:

A systematic review was conducted to determine if individual Angiotensin Converting Enzyme Inhibitors (ACEs) available in Canada for oral use are therapeutically equivalent (i.e. equivalent with respect to morbidity, mortality and major adverse effects) in the treatment of hypertension and congestive heart failure. MEDLINE and EMBASE were searched from 1980 to October 1999 using a sensitive search strategy (described below). Any meta-analyses of head to head RCT of ACEs were also reviewed for additional information. References of each retrieved article and recent review articles (1998-) were also manually searched. An additional search was carried out between 1999 and March 2001 to identify if there were new studies available that could add information to this review. Included studies were all English language studies done in humans that were randomized controlled trials carried out in patients with hypertension (measured by office method or ambulatory blood pressure monitoring) or (congestive) heart failure independent of the severity of the disorder addressing the outcomes of interest. Articles pertaining to diabetic nephropathy or use of ACEs after myocardial infarction were not included. Reviews (except for the purpose of locating references as discussed above), placebo controlled randomized trials with a single ACE, other uses of ACEs for purposes not identified here, other research questions, editorials, and letters to the editor, and studies examining parenteral dosage forms of ACEs were not included. All citations reviewed by one person to determine if each met the inclusion criteria and to complete data extraction. The analysis of the literature was done qualitatively.

RESULTS:
1710 abstracts were found and reviewed from MEDLINE and EMBASE searches. 77 articles (56 from MEDLINE and EMBASE and 21 from other sources) were identified as potential meeting the inclusion criteria. 38 studies were included in the final analysis. One study was reported twice. 1,2 23 studies3-25 evaluated ACE in the treatment of hypertension and 15 studies1,26-39 evaluated ACE in the treatment of CHF. The majority of studies compared captopril or enalapril to other agents (Table B1)

HYPERTENSION:
The majority of studies did not find any differences among the ACE evaluated for lowering blood pressure (Table B2, Table B3). When lisinopril was compared to enalapril using the same per milligram dose, two studies4,6 found no significant differences while 2 studies3,19 found that while there were no differences between the agents during the first 12 hours of the 24-hour dosing period, lisinopril was more effective in maintaining a lower blood pressure during the later half of the 24-hour dosing period. Another comparison of lisinopril with enalapril showed that lisinopril 10-40mg was more effective that enalapril 5-20mg, a result that is most likely

7 This appendix was written by Lisa Dolovich, Anne Holbrook, and Margaret Woodruff. Centre for Evaluation of Medicines.
explained by under dosing of enalapril.\textsuperscript{8} Trandolapril was also able to maintain the blood pressure lowering effect over the entire 24-hour dosing period better than enalapril.\textsuperscript{53} One study\textsuperscript{5} found that perindopril was more effective than captopril at reducing diastolic blood pressure, however another study did not find any any significant differences between these two agents.\textsuperscript{7} Captopril therapy for 4 weeks produced a better quality of life that enalapril (n=379)\textsuperscript{14}, and ramapril produced a better quality of life when compared to captopril after 8 weeks of therapy (n=60)\textsuperscript{16}, however as these studies used different quality of life measures, one study is quite small, and neither study has been duplicated it cannot be concluded ramapril is more effective than the other agents in improving quality of life. The results of this review are consistent with well recognized guidelines for the treatment of hypertension which do not differentiate among ACE.\textsuperscript{40}

**HEART FAILURE:**
The majority of studies did not find any differences among the ACE evaluated for heart failure (Table B4, Table B5). Perindopril did not produce as much first dose hypotension when compared with captopril, enalapril, or lisinopril,\textsuperscript{1,27,35} but there were no statistically significant differences found among perindopril, captopril, and enalapril in terms of ACE inhibition.\textsuperscript{27} An additional recent study also found that perindopril produced less first-dose hypotension than enalapril\textsuperscript{41} The results of this review are consistent with recent guidelines for the management of heart failure\textsuperscript{42} and a recent systematic overview of long term ACE therapy in patients with heart failure that do not differentiate among ACE when evaluating their therapeutic effectiveness.\textsuperscript{43}

**CONCLUSIONS:**
There are no major differences among ACE in the treatment of hypertension or congestive heart failure. Enalapril dosed once a day may not maintain a lowered blood pressure during the later 12 hours of the dosing schedule compared to lisinopril or tranlalapril.

**Application to Reference Based Pricing Analysis:**
- Assume that all ACE are therapeutically interchangeable
- Determine how many patients were using enalapril once daily and potentially consider doing a subgroup analysis to compare outcomes in these patients compared to patients using other ACE.
QUESTION AND DETAILED METHODS

QUESTION:
Are individual Angiotensin Converting Enzyme Inhibitors (ACEs) available in Canada for oral use therapeutically equivalent (ie. equivalent with respect to morbidity, mortality and major adverse effects) in the treatment of hypertension and congestive heart failure?

DESIGN: SYSTEMATIC REVIEW

STUDY IDENTIFICATION:
A thorough search of MEDLINE and EMBASE was conducted from 1980 to the October 1999 using the following search headings:

DISEASES: hypertension, congestive heart failure, CHF, heart failure
DRUGS: ACE, angiotensin converting enzyme inhibitors, benazepril, captopril, cilazapril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, trandolapril, physicians visits, hospitalizations, long-term care admissions, cardiovascular death, compliance(these last 4 are outcomes)
OUTCOMES: quality of life, survival, readmission, morbidity, mortality, physicians visits, hospitalizations, long-term care admissions, cardiovascular deaths, angioedema, hyperkalemia, hematological abnormalities, taste disturbances, cough and renal dysfunction (serum creatinine, blood urea nitrogen), renal insufficiency

Any meta-analysis of head to head RCT of ACEs were also reviewed for additional information. References of each retrieved article and recent review articles (1998-) were also manually searched.

SEARCH STRATEGY:

8benazepril, captopril, cilazapril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril, trandolapril
35. hypertension (mh)
36. heart failure, congestive (mh)
37. congestive heart failure (mh)
38. CHF (mh)
39. Myocardial infarction (mh)
40. MI (mh)
41. hypertension(tw)
42. congestive heart failure(tw)
43. CHF(tw)
44. heart failure(tw)
45. Myocardial infarction (tw)
46. MI(tw)

47. 1 or 2 or 3 or ......12
48. randomized controlled trials (mh)
49. RCT (mh)
50. controlled clinical trials (mh)
51. Random allocation (mh)
52. Double blind method (mh)
53. Comparative study (mh)
54. Exp evaluation studies (mh)
55. ((doub$| trebl$| tripl$) adj25 (blind$| mask$))ti.ab.
56. Random$.ti.ab
57. randomized controlled trials (tw)
58. RCT (tw)
59. controlled clinical trials (tw)
60. Random allocation (tw)
61. Double blind methods (tw)
62. Comparative study (tw)
63. evaluation studies (tw)
64. randomized controlled trials (pt)
65. controlled clinical trials (pt)

66. 14 or 15 or 17 or ......or 31
67. office visits (mh)
68. hospitalizations (mh)
69. long-term care(mh)
70. death (mh)
71. death, sudden cardiac
72. compliance (mh)
73. quality of life (mh)
74. survival (mh)
75. patient readmission (mh)

76. morbidity (mh)
77. mortality (mh)
78. angioneurotic edema (mh)
79. hyperkalemia (mh)
80. Exp. hematological diseases(mh)
81. taste disturbances (mh)
82. cough (mh)
83. renal dysfunction (mh)
84. creatinine (mh)
85. blood urea nitrogen (mh)
86. Kidney failure(mh)
87. physicians visits(tw)
88. office visits (tw)
89. hospitalizations(tw)
90. long-term care (tw)
91. long-term care admissions(tw)
92. cardiovascular death(tw)
93. Death(tw)
94. Death, sudden cardiac(tw)
95. compliance(tw)
96. quality of life(tw)
97. survival(tw)
98. patient readmission(tw)
99. morbidity(tw)
100.mortality(tw)
101.angioedema(tw)
102. Angioneurotic edema(tw)
103. hyperkalemia(tw)
104. hematological abnormalities(tw)
105. hematological diseases(tw)
106. taste disturbances(tw)
107.cough(tw)
108.renal dysfunction(tw)
109.kidney failure(tw)
110.creatinine(tw)
111.blood urea nitrogen(tw)
112.renal insufficiency(tw)

113.33 or 34 or ......78
114.ACEI (mh)
115.angiotensin converting enzyme inhibitors (mh)
116.captopril (mh)
117.cilazapril (mh)
118.enalapril (mh)
119. fosinopril (mh) 136. Limit 101 to English
120. lisinopril (mh) 137. Limit 102 to Human
121. ramipril (mh) 138. hypertension (mh)
122. ACEI(tw) 139. heart failure, congestive (mh)
123. angiotensin converting enzyme inhibitors(tw) 140. congestive heart failure (mh)
124. benazepril(tw) 141. CHF (mh)
125. captopril(tw) 142. Myocardial infarction (mh)
126. cilazapril(tw) 143. MI (mh)
127. enalapril(tw) 144. hypertension(tw)
128. fosinopril(tw) 145. congestive heart failure(tw)
129. lisinopril(tw) 146. CHF(tw)
130. perindopril(tw) 147. heart failure(tw)
131. quinapril(tw) 148. Myocardial infarction (tw)
132. ramipril(tw) 149. MI(tw)
133. trandolapril(tw) 150. 13 and 21 and 68 and 89
134. 80 or 81 or...99 151. Limit 90 to English
135. 13 and 32 and 79 and 100 152. Limit 91 to Human

**STUDY SELECTION:**
Included studies were all English language studies done in humans that were randomized controlled trials carried out in patients with hypertension (measured by office method or ambulatory blood pressure monitoring) or (congestive) heart failure independent of the severity of the disorder addressing the outcomes of interest.

**OUTCOMES OF INTEREST:**
Morbidity end points: number of physicians visits, hospitalizations, or long-term care admissions.
Mortality end points: cardiovascular deaths
Adverse effects: rates of angioedema, hyperkalaemia, hematological abnormalities, cough, renal dysfunction (increases in serum creatinine and blood urea nitrogen) and taste disturbances

**EXCLUSION CRITERIA:**
Articles pertaining to diabetic nephropathy or use of ACEs after myocardial infarction were not included. Reviews (except for the purpose of locating references as discussed above), placebo controlled randomized trials with a single ACE, other uses of ACEs for purposes not identified here, other research questions, editorials, and letters to the editor, and studies examining parenteral dosage forms of ACEs were not be included.

**ANALYSIS:**
- Citations reviewed by one person for inclusion
- Data extraction done by one person
- Analysis done qualitatively

**RESULTS:**
1710 abstracts were found and reviewed from MEDLINE and EMBASE searches. 77 articles (56 from MEDLINE and EMBASE and 21 from other sources) were identified as potential meeting the inclusion criteria. 38 studies were included in the final analysis (XX can’t find the other 5 articles). One study was reported twice. \textsuperscript{1,2} 23 studies\textsuperscript{3-25} evaluated ACE in the treatment of hypertension and 15 studies\textsuperscript{1,26-39} evaluated ACE in the treatment of CHF. The majority of studies compared captopril or enalapril to other agents (Table B1)

**HYPERTENSION:**

The majority of studies did not find any differences among the ACE evaluated for lowering blood pressure (Table B2, Table B3). When lisinopril was compared to enalapril using the same per milligram dose, two studies\textsuperscript{4,6} found no significant differences while 2 studies\textsuperscript{3,19} found that while there were no differences between the agents during the first 12 hours of the 24-hour dosing period, lisinopril was more effective in maintaining a lower blood pressure during the later half of the 24-hour dosing period. Another comparison of lisinopril with enalapril showed that lisinopril 10-40mg was more effective than enalapril 5-20mg, a result that is most likely explained by under dosing of enalapril.\textsuperscript{8} Trandolapril was also able to maintain the blood pressure lowering effect over the entire 24-hour dosing period better than enalapril.\textsuperscript{23} One study\textsuperscript{5} found that perindopril was more effective than captopril at reducing diastolic blood pressure, however another study did not find any significant differences between these two agents.\textsuperscript{7} Captopril therapy for 4 weeks produced a better quality of life that enalapril (n=379)\textsuperscript{14}, and ramipril produced a better quality of life when compared to captopril after 8 weeks of therapy (n=60)\textsuperscript{16}, however as these studies used different quality of life measures, one study is quite small, and neither study has been duplicated it cannot be concluded ramipril is more effective than the other agents in improving quality of life.

**HEART FAILURE:**

The majority of studies did not find any differences among the ACE evaluated for heart failure (Table B4, Table B5). Perindopril did not produce as much first dose hypotension when compared with captopril, enalapril, or lisinopril\textsuperscript{1,27,35} but there were no statistically significant differences found among perindopril, captopril, and enalapril in terms of ACE inhibition.\textsuperscript{27}
Table B1: Frequency of PAIRED Comparisons for ACE -BP and HF

Frequency of PAIRED Comparisons for ACE -BP and HF

<table>
<thead>
<tr>
<th></th>
<th>Captopril</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril</td>
<td>$^{8,11,12,14,15,26,33,39}$</td>
<td></td>
</tr>
<tr>
<td>Lisinopril</td>
<td>$^{10,13,18,22,24,28,29,31,34,36}$</td>
<td>$^{7,3,4,6,8,19,20,37}$</td>
</tr>
<tr>
<td>Benazepril</td>
<td>$^{1,17}$</td>
<td>$^{1,9}$</td>
</tr>
<tr>
<td>Cilazepril</td>
<td>$^{2,30,32}$</td>
<td></td>
</tr>
<tr>
<td>Quinapril</td>
<td></td>
<td>$^{1,21}$</td>
</tr>
<tr>
<td>Trandolapril</td>
<td></td>
<td>$^{1,23}$</td>
</tr>
<tr>
<td>Ramipril</td>
<td>$^{1,16}$</td>
<td>$^{1,25}$</td>
</tr>
<tr>
<td>Perindopril</td>
<td>$^{2,5,7}$</td>
<td>$^{1,10}$</td>
</tr>
<tr>
<td>Fosinopril</td>
<td></td>
<td>$^{1,38}$</td>
</tr>
</tbody>
</table>

NOTE: 3 MULTIPLE COMPARISONS NOT INCLUDED ABOVE$^{1,27,35}$
### Table B2: Summary ACE head to head studies in the treatment of hypertension

**SUMMARY ACE HEAD TO HEAD STUDIES - OFFICE BP; ND=no difference; 2=better; 1=not as good**

<table>
<thead>
<tr>
<th>ARTICLE</th>
<th>captopril</th>
<th>enalapril</th>
<th>lisinopril</th>
<th>trandolapril</th>
<th>benazepril</th>
<th>quinapril</th>
<th>cilazapril</th>
<th>perindopril</th>
<th>ramipril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gourlay et al, 1993(^3)</td>
<td></td>
<td></td>
<td>1</td>
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<tr>
<td>Enstrom et al, 1992(^3)</td>
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<td>ND</td>
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<td>Lees et al, 1989(^5)</td>
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<tr>
<td>Dewes et al, 1989(^6)</td>
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<tr>
<td>Grandi et al, 1991(^7)</td>
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<tr>
<td>Johnston et al, 1991(^8)</td>
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<tr>
<td>MacDonald et al, 1993(^9)</td>
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<td>Alcocer et al, 1995(^10)</td>
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<td>Chrysant et al, 1985(^11)</td>
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<tr>
<td>Rumboldt et al 1988(^12)</td>
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<tr>
<td>ARTICLE</td>
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<td>enalapril</td>
<td>lisinopril</td>
<td>trandolapril</td>
<td>benazepril</td>
<td>quinapril</td>
<td>cilazapril</td>
<td>perindopril</td>
<td>ramipril</td>
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<td>Thind et al, 1985</td>
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<td>Conway et al, 1990</td>
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<td>Taylor et al, 1989</td>
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<td>ND</td>
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<td>ND</td>
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<tr>
<td>Testa et al, 1993</td>
<td>ND</td>
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<td></td>
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</tr>
<tr>
<td>Vaur et al, 1995</td>
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</tr>
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</table>

Note: Conway et al\textsuperscript{20} not included measures only ABPM not office
Table B3: Descriptive analysis of ACE head to head studies in the treatment of hypertension

**SUMMARY ACE HEAD TO HEAD, RCT, BLINDED STUDIES-BLOOD PRESSURE**

<table>
<thead>
<tr>
<th>ARTICLE</th>
<th>DRUGS COMPARED</th>
<th>SAMPLE SIZE</th>
<th>endpt of trial</th>
<th>NO SIG. DIFF.</th>
<th>SIGNIFICANT DIFFERENCE - EXPLAIN</th>
<th>FURTHER COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Gourlay et al., 1993)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>lisinopril vs enalapril</td>
<td>28</td>
<td>BP ABPM</td>
<td>□ 1st 12 hrs SBP, □ DBP</td>
<td>lisinopril decreased mean SBP sig more than enalapril- confined to 2&lt;sup&gt;nd&lt;/sup&gt; 12 hrs of dosing interval</td>
<td>L - 10mg od E - 10mg od</td>
</tr>
<tr>
<td>(Enstrom et al., 1992)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>enalapril vs lisinopril</td>
<td>58</td>
<td>BP BP at rest, exercise, during 24 h</td>
<td>□ -</td>
<td></td>
<td>E 20mg od L 20 mg od</td>
</tr>
<tr>
<td>(Lees et al., 1989)&lt;sup&gt;5&lt;/sup&gt;</td>
<td>captopril vs perindopril</td>
<td>165</td>
<td>BP efficacy, acceptability</td>
<td>□ A/E DBP</td>
<td>perindopril more effective</td>
<td>P-4-8mg od C- 25mg-50 bid</td>
</tr>
<tr>
<td>(Dews et al., 1989)&lt;sup&gt;6&lt;/sup&gt;</td>
<td>lisinopril vs enalapril</td>
<td>16</td>
<td>BP single dose, BP up to 24 h post dose</td>
<td>□ except..</td>
<td>time to max. effect longer for lisinopril</td>
<td>L - 10mg E - 10mg</td>
</tr>
<tr>
<td>(Grandi et al., 1991)&lt;sup&gt;7&lt;/sup&gt;</td>
<td>perindopril vs captopril</td>
<td>20</td>
<td>BP effects on LV, BP</td>
<td>□</td>
<td></td>
<td>P - 4-8 mg od C - 25-50mg bid</td>
</tr>
<tr>
<td>(Johnston et al., 1991)&lt;sup&gt;8&lt;/sup&gt;</td>
<td>lisinopril vs enalapril</td>
<td>169</td>
<td>BP efficacy, safety - acute &amp; 12 week</td>
<td>□ except ..</td>
<td>Lisinopril 10mg vs enalapril 5mg sig greater hypertensive effects</td>
<td>L- 10-40mg E - 5-20mg</td>
</tr>
</tbody>
</table>

---

<sup>3</sup> No significant difference was shown except for endpoint mentioned, all other endpoints showed no significant difference

<sup>4</sup> No significant difference between two agents was found
<table>
<thead>
<tr>
<th>ARTICLE</th>
<th>DRUGS COMPARED</th>
<th>SAMPLE SIZE</th>
<th>endpt of trial</th>
<th>NO SIG. DIFF.</th>
<th>SIGNIFICANT DIFFERENCE - EXPLAIN</th>
<th>FURTHER COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Macdonald et al., 1993)</td>
<td>benazepril vs enalapril</td>
<td>18</td>
<td>BP old vs young-kinetics vs dynamics - single dose</td>
<td></td>
<td></td>
<td>B- 10 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>E - 10mg</td>
</tr>
<tr>
<td>(Alcocer et al., 1995)</td>
<td>perindopril vs enalapril</td>
<td>161</td>
<td>BP efficacy, acceptability</td>
<td></td>
<td>Withdrawal sig higher for enalapril</td>
<td>P - 4 -8mg od</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>E - 10-20 mg od</td>
</tr>
<tr>
<td>(Chrysant et al., 1985)</td>
<td>captopril vs enalapril</td>
<td>20</td>
<td>BP BP, metabolic evaluation, A/E</td>
<td></td>
<td></td>
<td>E - 5-20mg bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C - 25-100mg tid</td>
</tr>
<tr>
<td>(Rumboldt et al., 1988)</td>
<td>captopril vs enalapril</td>
<td>69</td>
<td>BP DBP, HR, Lab work, A/E</td>
<td></td>
<td></td>
<td>C - 25 -50mg bid</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>E - 20-40 mg od</td>
</tr>
<tr>
<td>(Rumboldt et al., 1993)</td>
<td>captopril vs lisinopril</td>
<td>91</td>
<td>BP DBP, efficacy, acceptability, BP normalization</td>
<td></td>
<td>Lisinopril sig reached dose normalization more</td>
<td>C - 12.5-50 mg bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>L - 10 - 40 mg od</td>
</tr>
<tr>
<td>(Testa et al., 1993)</td>
<td>Captopril vs enalapril</td>
<td>379</td>
<td>BP Q of L</td>
<td></td>
<td>captropil sig better QoFL</td>
<td>C - 25-50 mg bid</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>E - 5-20 mg od</td>
</tr>
<tr>
<td>(Thind et al., 1985)</td>
<td>captopril vs enalapril</td>
<td>32</td>
<td>BP BP,HR,A/E</td>
<td></td>
<td>enalapril sig decreased BP more</td>
<td>C - 25-100 mg tid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>E - 5 - 20mg bid</td>
</tr>
<tr>
<td>(Yajnik et al., 1994)</td>
<td>ramipril vs captopril</td>
<td>60</td>
<td>BP DBP, HR, hypotension, K+ levels, A/E, QoL</td>
<td></td>
<td>Ramipril better QoL (instrument not validated)</td>
<td>R - 5 mg od</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>C - 50mg bid</td>
</tr>
<tr>
<td>(Chen et al., 1995)</td>
<td>benazepril vs captopril</td>
<td>75</td>
<td>BP DBP, SBP, ABPM, HR, lab work, A/E</td>
<td></td>
<td></td>
<td>B - 10 mg od</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C - 25 mg tid</td>
</tr>
<tr>
<td>(Whelton et al., 1990)</td>
<td>lisinopril vs captopril</td>
<td>70</td>
<td>BP BP office and ABPM, A/E, HR</td>
<td></td>
<td>lisinopril sig. lower BP with ABPM</td>
<td>L - 10-40 mg</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>C - 25-1000mg bid</td>
</tr>
<tr>
<td>ARTICLE</td>
<td>DRUGS COMPARED</td>
<td>SAMPLE SIZE</td>
<td>endpt of trial</td>
<td>NO SIG. DIFF.</td>
<td>SIGNIFICANT DIFFERENCE - EXPLAIN</td>
<td>FURTHER COMMENTS</td>
</tr>
<tr>
<td>---------------------------</td>
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<td>--------------------------------------------------------</td>
<td>---------------</td>
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<td>------------------------</td>
</tr>
<tr>
<td>(Whelton et al., 1992)²⁹</td>
<td>lisinopril vs enalapril</td>
<td>110</td>
<td>BP BP office, ABPM, ACE activity, aldosterone</td>
<td>☐ except ...</td>
<td>Lisinopril sig diff than placebo in second half of dosing schedule enalapril not</td>
<td>L - 10 mg od E - 10 mg od</td>
</tr>
<tr>
<td>(Conway et al., 1990)²⁰</td>
<td>lisinopril vs enalapril</td>
<td>19</td>
<td>BP ABPM, HR, A/E</td>
<td>☐ except. ..</td>
<td>lisinopril sig. better in decreasing 24 hr SBP</td>
<td>L - 10 mg od E - 10 mg od</td>
</tr>
<tr>
<td>(Taylor, 1989)²¹</td>
<td>quinapril vs enalapril</td>
<td>258</td>
<td>BP DBP, SBP, A/E</td>
<td>☐</td>
<td></td>
<td>Q - 10- 40 mg od E - 10 - 40 mg od</td>
</tr>
<tr>
<td>(Gosse et al., 1989)²²</td>
<td>lisinopril vs captopril</td>
<td>304</td>
<td>BP BP, lab work, HR, body weight, A/E</td>
<td>☐ except. ..</td>
<td>Lisinopril sig. better in decreasing SBP</td>
<td>L - 20 mg od C - 50 mg od</td>
</tr>
<tr>
<td>(1993)²³</td>
<td>captopril vs lisinopril</td>
<td>25</td>
<td>BP BP, A/E, ABPM, lab work</td>
<td>☐</td>
<td></td>
<td>C - 100mg od L - 40 mg od</td>
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<tr>
<td>(Vaur et al., 1995)²⁴</td>
<td>trandolapril vs enalapril</td>
<td>88</td>
<td>BP ABPM-missed dose</td>
<td></td>
<td>trandolapril sig maintained BP while enalapril only did in daytime</td>
<td>T - 2 mg E - 20 mg</td>
</tr>
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</table>
Table B4: Summary of ACE head to head studies- Heart Failure

Summary of ACE head to head studies- Heart Failure; ND = no difference; 2 = better 1= not as good

<table>
<thead>
<tr>
<th>ARTICLE</th>
<th>captopril</th>
<th>enalapril</th>
<th>lisinopril</th>
<th>Fosinopril</th>
<th>cilazapril</th>
<th>perindopril</th>
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<td>Lange et al, 1994&lt;sup&gt;26&lt;/sup&gt;</td>
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<td>Morisco et al, 1997&lt;sup&gt;34&lt;/sup&gt;</td>
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<td>Navookarasu et al, 1999&lt;sup&gt;35&lt;/sup&gt;</td>
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<td>Powers et al, 1987&lt;sup&gt;16&lt;/sup&gt;</td>
<td>1</td>
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<td>Reid et al, 1993&lt;sup&gt;12&lt;/sup&gt;</td>
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<td>Zannad et al, 1992&lt;sup&gt;37&lt;/sup&gt;</td>
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<tr>
<td>Zannad et al, 1998&lt;sup&gt;39&lt;/sup&gt;</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Packer et al, 1986&lt;sup&gt;38&lt;/sup&gt;</td>
<td>1</td>
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Table B5: Descriptive analysis of ACE head to head studies in the treatment of heart failure.

**SUMMARY ACE HEAD TO HEAD, RCT, DOUBLE BLINDED STUDIES - HEART FAILURE**

<table>
<thead>
<tr>
<th>ARTICLE</th>
<th>DRUGS COMPARED</th>
<th>SAMPL LE SIZE</th>
<th>endpt of trial</th>
<th>NO SIG. DIFF.</th>
<th>SIGNIFICANT DIFFERENCE - EXPLAIN</th>
<th>FURTHER COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Lange MR and et al, 1994)(^{26})</td>
<td>enalapril vs captopril</td>
<td>117</td>
<td>HF safety, tolerability-BP, serum activity, clinical status after first dose</td>
<td>□(^{11})</td>
<td>enalapril sig. I(Inhibit) ACE activity greater extent except at 1 hr</td>
<td>C- 6.25mg E- 2.5 mg</td>
</tr>
<tr>
<td>(MacFadyen et al., 1991)(^{27})</td>
<td>captopril vs enalapril vs perindopril</td>
<td>48</td>
<td>HF first dose-BP, HR, drug conc., plasma renin and ACE activity</td>
<td>□excep pt...</td>
<td>perindopril less hypopression</td>
<td>C-6.25mg E-2.5 mg P-2mg</td>
</tr>
<tr>
<td>(Giles et al., 1989)(^{28})</td>
<td>lisinopril vs captopril</td>
<td>189</td>
<td>HF lab, clinical, exercise, QoL</td>
<td>□safety</td>
<td>Lisinopril sig. greater exercise duration, and it increased LVEF</td>
<td>L 5-20mg od C 12.5-50 mg tid</td>
</tr>
<tr>
<td>(Giles et al., 1988)(^{29})</td>
<td>lisinopril vs captopril</td>
<td>189 (65 subset-above)</td>
<td>HF lab, clinical, exercise</td>
<td>□ except. ..</td>
<td>Sig increase in LVEF in lisinopril not captopril</td>
<td>C 12.5 - 50 mg tid L 5-20 mg od</td>
</tr>
<tr>
<td>(1995)(^{30})</td>
<td>cilazapril vs captopril</td>
<td>443</td>
<td>HF exercise tolerance, clinical status, weight</td>
<td>□(^{12})</td>
<td></td>
<td>Cil - 2.5 mg od Cap - 25-50 mg tid</td>
</tr>
<tr>
<td>(Bach and Zardini, 1991)</td>
<td>lisinopril vs captopril</td>
<td>287</td>
<td>HF exercise, ectopic</td>
<td>□</td>
<td></td>
<td>L - 5-20mg od</td>
</tr>
</tbody>
</table>

\(^{11}\)No significant difference was found between the two agents except what is mentioned in second last column

\(^{12}\)No significant difference was found between the two agents
<table>
<thead>
<tr>
<th>ARTICLE</th>
<th>DRUGS COMPARED</th>
<th>SAMPLE SIZE</th>
<th>endpt of trial</th>
<th>NO SIG. DIFF.</th>
<th>SIGNIFICANT DIFFERENCE - EXPLAIN</th>
<th>FURTHER COMMENTS</th>
</tr>
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<tbody>
<tr>
<td>1992)11</td>
<td>captopril</td>
<td></td>
<td>activity, A/E</td>
<td></td>
<td></td>
<td>C - 12.5-50mg bid</td>
</tr>
<tr>
<td>(Bulpitt et al., 1998)32</td>
<td>cilazapril vs captopril</td>
<td>367</td>
<td>HF QoL</td>
<td></td>
<td></td>
<td>Cil - 1 mg od Cap - 25 mg tid</td>
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<tr>
<td>(Haffner et al., 1995)33</td>
<td>captopril vs enalapril</td>
<td>80</td>
<td>HF first dose effect, GFR, effective renal plasma flow, exercise tolerance, symptoms</td>
<td>□ except ...</td>
<td>Captopril sig more improved in GFR, less GI symptoms, less symptomatic hypotension</td>
<td>C - 12.5 mg bid E - 2.5 mg bid</td>
</tr>
<tr>
<td>(Morisco et al., 1997)34</td>
<td>lisinopril vs captopril</td>
<td>271</td>
<td>HF efficacy, safety, tolerability; exercise, LVEF, SV, symptoms, A/E</td>
<td></td>
<td></td>
<td>L - 5-20 mg od C - 12.5 mg od - 25 mg bid</td>
</tr>
<tr>
<td>(Navookarasu et al., 1999)35</td>
<td>captopril vs enalapril vs perindopril vs lisinopril</td>
<td>80</td>
<td>HF first dose response</td>
<td>□ except ...</td>
<td>Perindopril did not produce first-dose hypotension ( unlike res- although timing diff)</td>
<td>C - 6.25mg E - 2.5 mg P - 2 mg L - 2.5 mg</td>
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<tr>
<td>(Powers et al., 1987)36</td>
<td>lisinopril vs captopril</td>
<td>129</td>
<td>HF exercise, efficacy, A/E</td>
<td>□ except ...</td>
<td>Lisinopril improved exercise sig more but had more increase in BUN</td>
<td>L - 5 mg od C - 37.5 mg od (doses could be □)</td>
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<tr>
<td>(Reid et al., 1993)1,2</td>
<td>captopril vs enalapril vs perindopril</td>
<td>72</td>
<td>HF first dose</td>
<td>□ except ...</td>
<td>Perindopril did not produce first-dose hypotension ( unlike rest-although timing diff)</td>
<td>C - 6.25 mg E - 2.5 mg P - 2 mg</td>
</tr>
<tr>
<td>(Zannad et al., 1992)37</td>
<td>lisinopril vs enalapril</td>
<td>278</td>
<td>HF exercise, ectopic activity, symptoms</td>
<td></td>
<td></td>
<td>L - 5-20 mg od E - 5 - 20 mg od</td>
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<tr>
<td>(Zannad et al., 36</td>
<td>fosinopril vs</td>
<td>254</td>
<td>HF symptoms,</td>
<td></td>
<td>fosinopril sig better all</td>
<td>F - 5-20 mg od</td>
</tr>
<tr>
<td>ARTICLE (Packer et al., 1986)\textsuperscript{59}</td>
<td>DRUGS COMPARED</td>
<td>SAMPLE SIZE</td>
<td>endpt of trial</td>
<td>NO SIG. DIFF.</td>
<td>SIGNIFICANT DIFFERENCE - EXPLAIN</td>
<td>FURTHER COMMENTS</td>
</tr>
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<tr>
<td>1998\textsuperscript{78}</td>
<td>enalapril</td>
<td>survival, hypotension</td>
<td>measures</td>
<td>enalapril sig. hypotension causing K+ retention and decline in creatinine clearance</td>
<td>E - 5 - 20 mg od</td>
<td></td>
</tr>
</tbody>
</table>
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S. Webb |
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C.H. Feaver  
B.G. Spencer |
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<td>J.B. Burbidge, L. Magee, A.L. Robb</td>
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<td>B.G. Spencer</td>
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<td>S. Davies, M. Denton</td>
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<tr>
<td>No. 368:</td>
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<td>W. Scarth, M. Souare</td>
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