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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Appendix A Therapeutic Equivalence of Dihydropyridine Calcium Antagonists[1]

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.

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[1] This appendix was written by Anne Holbrook, Lisa Dolovich, Margaret Woodruff, Centre for Evaluation of Medicines.

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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[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:
DISEASES: hypertension, stable angina, angina, angina pectoris
DRUGS: calcium channel blockers, calcium antagonists, calcium entry blockers, CCB, CEB, amlodipine, felodipine, nicardipine, nifedipine
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)
2. Angina pectoris (mh)
3. Angina,unstable (mh)
4. Angina pectoris, variant (mh)
5. Angina (tw)
6. Stable angina (tw)
7. Angina pectoris (tw)
8. hypertension(tw)
9. 1 or 2 or 3 or 8
10. randomized controlled trials (mh)
11. RCT (mh)
12. controlled clinical trials (mh)
13. Random allocation (mh)
14. Double blind method (mh)
15. Comparative study (mh)
16. Exp evaluation studies (mh)
17. ((doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti.ab.
18. Random$.ti.ab.
19. randomized controlled trials (tw)
20. RCT (tw)
21. controlled clinical trials (tw)
22. Random allocation (tw)
23. Double blind method (tw)
24. Comparative study (tw)
25. evaluation studies (tw)
26. randomized controlled trials (pt)
27. controlled clinical trials (pt)
28. 10 or 11 or 12 or .....or 27
29. office visits (mh)
30. hospitalizations (mh)
31. long-term care(mh)
32. death (mh)
33. death, sudden cardiac (mh)
34. compliance (mh)
35. quality of life (mh)
36. survival (mh)
37. patient readmission (mh)
38. morbidity (mh)
39. mortality (mh)
40. Hypotension (mh)
41. Tachycardia (mh)
42. Flushing (mh)
43. Edema(mh)
44. Pulmonary edema (mh?)
45. Arrythmia(mh)
46. physicians visits (tw)
47. office visits (tw)
48. hospitalizations(tw)
49. long-term care (tw)
50. long-term care admissions (tw)
51. cardiovascular death(tw)
52. Death (tw)
53. Death, sudden cardiac (tw)
54. compliance(tw)
55. quality of life(tw)
56. survival(tw)
57. patient readmission(tw)
58. morbidity(tw)
59. mortality(tw)

60. Hypotension (tw)
61. Tachycardia (tw)
62. Flushing (tw)
63. Edema(tw)
64. Pulmonary edema (tw)
65. Arrythmia(tw)
66. Dysrhythmia (tw)
67. 29 or 30 or 66
68. Calcium channel blockers (mh)
69. amlodipine (mh)
70. felodipine (mh)
71. nicardipine (mh)
72. nifedipine (mh)
73. Dihydropyridines (mh)
74. CCB (tw)
75. CEB (tw)
76. Calcium channel blockers (tw)
77. Calcium antagonists (tw)
78. Calcium entry blockers (tw)
79. Dihydropyridines (tw)
80. amlodipine (tw)
81. felodipine (tw)
82. nicardipine (tw)
83. nifedipine (tw)
84. 68 or 69 or....83
85. 9 and 28 and 67 and 84
86. Limit 83 to English
87. Limit 84 to Human
88. hypertension (mh)
89. Angina pectoris (mh)
90. Angina,unstable (mh)
91. Angina pectoris, variant (mh)
92. Angina (tw)
93. Stable angina (tw)
94. Angina pectoris (tw)
95. hypertension(tw)
96. 1 or 2 or 3 8
97. meta-analysis (pt)
98. Meta-anal: (tw)
99. Metaanal: (tw)
100. Quantitative: review: OR quantitative: overview: (tw)
101. Systematic: review: OR systematic: overview: (tw)
102. Methodologic: review: OR methodologic: overview (tw)
103. Review (pt) AND medline (tw)
104. 10 or 11 or 12 or ..16
105. office visits (mh)
106. hospitalizations (mh)
107. long-term care(mh)
108. death (mh)
109. death, sudden cardiac (mh)
110. compliance (mh)
111. quality of life (mh)
112. survival (mh)
113. patient readmission (mh)
114. morbidity (mh)
115. mortality (mh)
116. Hypotension (mh)
117. Tachycardia (mh)
118. Flushing (mh)
119. Edema(mh)
120. Pulmonary edema (mh?)
121. Arrythmia(mh)
122. physicians visits (tw)
123. office visits (tw)
124. hospitalizations(tw)
125. long-term care (tw)
126. long-term care admissions (tw)
127. cardiovascular death(tw)
128. Death (tw)
129. Death, sudden cardiac (tw)
130. compliance(tw)
131. quality of life(tw)
132. survival(tw)
133. patient readmission(tw)
134. morbidity(tw)
135. mortality(tw)
136. Hypotension (tw)
137. Tachycardia (tw)
138. Flushing (tw)
139. Edema(tw)
140. Pulmonary edema (tw)
141. Arrythmia(tw)
142. Dysrhythmia (tw)
143. 18 or 19 or 55
144. Calcium channel blockers (mh)
145. amlodipine (mh)
146. felodipine (mh)
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

CCB COMPARISON **OFFICE BP**; ND=no difference; 2=better; 1=not as good				
ARTICLE	nifedepine	amlodipine	felodipine	nicardipine
(1)	ND	ND		
(2)	ND		ND	
(3)	ND		ND	
(5)		2	1	
(6)	ND	ND		
(7)	ND	ND		
(8)	ND	ND		
(9)	ND		ND	
(10)	ND		ND	
(11)		ND	ND	
(12)	1		2	
(13)	ND		ND	
(14)	1		2	
(15)	1	2		
(16)	ND			ND
(17)	ND	ND		
(18)	ND			ND
(19)	1	2		
(20)	ND	ND		

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Table A3. Summary of Calcium Channel Blocker Comparisons in Angina

CCB COMPARISON **ANGINA**; ND=no difference; 2=better; 1=not as good				
ARTICLE	nifedipine	amlodipine	felodipine	nicardipine
(1)	ND		ND	
(2)	ND			ND
(3)	1			2 (less dizziness)
(4)	ND			ND
(5)	ND		ND	
(6)		ND	ND	
(7)	1		2 (more time to angina)	

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

ARTICLE	DRUGS COMPARED	SAMPLE SIZE	endpt of trial	NO SIG. DIFF	SIGNIFICANT DIFFERENCE - EXPLAIN	FURTHER COMMENTS
(Bremner et al., 1993)	amlodipine vs nifedipine retard	97	**BP** adverse effects (esp. HD, flushing)		A/E sign. greater with nifedipine retard than amlodipine	A-5 mg od N retard-20 mg bid
(Carroll et al., 1995)	nifedipine SR vs felodipine ER	41	**BP** 24 h AMBP; BP; adverse effects	~ [3]		N SR-20 mg bid F er 10 mg od
(Dees et al., 1997)	felodipine ER vs nifedipine retard	115	**BP** efficacy, tolerability	~		FER-2.5mg and 5mg od N retard-10 and 20 mg bid
(Hoegholm et al., 1995)	felodipine ER amlodipine	118	**BP** efficacy and safety, BP; ABPM	~ [4] except...	Ambulatory SBP sig. greater amlodipine and HD flushing less	FER-5,10, or20mg od A-5 or 10 mg od
(Minami et al., 1998)	amlodipine vs nifedipine retard	20	**BP** HR, BP, ABPM, autonomic nerve activity	~ except...	Sign diff nifedipine	A 2.5 mg od N retard 20mg bid
(Testa et al., 1998)	nifedipine GITS vs amlodipine	356	**BP** SBP,DBP,QofL	~ except...	Nifedipine sgn. better QofL	N GITS 30mg od A -5mg od
(Zidek et al., 1995)	nifedipine coat core vs	207	**BP** efficacy, safety; ABPM	~		N cc-30mg od

[3]No significant difference was found between the two agents

[4]No significant difference was found between the two agents except that noted in second last column

ARTICLE	DRUGS COMPARED	SAMPLE SIZE	endpt of trial	NO SIG. DIFF	SIGNIFICANT DIFFERENCE - EXPLAIN	FURTHER COMMENTS
	amlodipine		ABPM			A -5 mg od
(Hosie J and et al, 1992)	felodipine ER vs nifedipine retard	77	**BP** effect, tolerability, QoL	except ...	Felodipine better tolerated	F ER - 5 mg od N retard- 20mg bid
(Abelardo et al., 1989)	felodipineER vs nifedipine retard	23	**BP** SBP, DBP			F ER -10 mg od N retard - 20mg bid
(Koenig and et al, 1993)	felodipine vs amlodipine	118	**BP** efficacy, tolerability			F -5 to 10 mg od A - 5 to 10 mg od
(Littler, 1990)	felodipine ER vs nifedipine retard	100	**BP** 3 h and 12h/24h, DBP, SBP, HR, A/E	except ...	DBP lower in Felodipine gp at 24h post-dose	also on metoprolol F ER - 10 mfg od N retard -20 mg bid
(Aberg et al., 1985)	felodipine vs nifedipine	18	**BP poorly controlled** SBP, DBP, ECG, blood tests, HR, weight, ankle measure			F- 5-10 mg tid N - 10- 20 mg tid
(Goudie A.W. and et al, 1994)	felodipine ER vs nifedipine retard	134	**BP** efficacy (HR, BP), tolerability	HR	felodipine sig. greater decrease seated BP (fewer A/E - sig.?)	F ER -5 - 10 mg qam N retard -10-20 mg bid
(Ueda et al., 1993)	amlodipine vs Nifedipine GITS	9	**BP** pressor response to angiotensin II and NA	BP, HR	amlodipine- more smoothly sustained efficacy for 48 h post-dose	A - 5mg od N GITs -60 mg od
(Iliopoulou et al., 1983)	nicardipine vs nifedipine	6	**BP** BP,HR, STI(systolic time			3 oral treatments -Nic 40mg; Nif 20mg

ARTICLE	DRUGS COMPARED	SAMPLE SIZE	endpt of trial	NO SIG. DIFF	SIGNIFICANT DIFFERENCE - EXPLAIN	FURTHER COMMENTS
			intervals)			
(Lorimer et al., 1994)	amlodipine vs nifedipine retard	111	**BP** BP, HR, weight, A/E	~		A- 5 -10mg od N retard-20-40 mg bid
(Rumboldt et al., 1988)	nicardipine vs nifedipine SR	95	**BP** BP,HR, A/E, lab exam	~		Nic-40mg od Nif SR- 20mgod
(Bompadre S and et al, 1991)	amlodipine vs nifedipine AR	8	**BP** BP, HR, plasma concentration	~	amlodipine smoother SBP,DBP over 24 hrs	A- 10mg od N AR -20mg bid

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

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

[5]No significant difference found between the two agents

[6]No significant difference found between the 2 agents except that mentioned in second last column

ARTICLE	DRUGS COMPARED	SAMPLE SIZE	endpt of trial	NO SIG. DIFF	SIGNIFICANT DIFFERENCE - EXPLAIN	FURTHER COMMENTS
	vs nifedipine SR		testing; total time, time to onset	...	angina sig. longer for Felodipine	N SRB 20 mg bid
(Koenig and Hoher, 1997)	felodipine ER vs amlodipine	52	**Angina-**exercise induced; antiischemic, antianginal efficacy	~		F ER -5-10 mg od A- 5-10mg od

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

ARTICLE	DRUGS COMPARED	SAMPLE SIZE	endpt of trial	NO SIG. DIFF	SIGNIFICANT DIFFERENCE - EXPLAIN	FURTHER COMMENTS
(Ardissino et al., 1991)	felodipine vs nifedipine	30	**Prinzmetal=s variant angina**: ischemic episodes recorded by Holter monitoring; angina attacks reported on daily cards	~		F -10-20mg od B20 mg qid *compliance MAY be better with F
(Bremner et al., 1993)	amlodipine vs nifedipine retard	97	**BP** adverse effects (esp. HD, flushing)		A/E sign. greater with nifedipine retard than amlodipine	A-5 mg od N retard-20 mg bid
(Carroll et al., 1995)	nifedipine SR vs felodipine ER	41	**BP** 24 h AMBP; BP; adverse effects	~		N SR-20 mg bid F er 10 mg od
(Dees et al., 1997)	felodipine ER vs nifedipine retard	115	**BP** efficacy, tolerability	~		FER-2.5mg and 5mg od N retard-10 and 20 mg bid
(Ekelund et al., 1994)	felodipine vs nifedipine	24	**Angina** single dose-chronic stable effort angina	~		Patients also on beta blockers and NTG; F-5 and 10 mg N 10 and 20mg
(DeWood and Wolbach, 1990)	nicardipine vs nifedipine	250	**Angina** dizziness, flushing, HD, pedal edema, palpitations	~ exce pt...	Nifedipine more dizziness- sig diff	Nif-20mg tid Nic-30mg tid

ARTICLE	DRUGS COMPARED	SAMPLE SIZE	endpt of trial	NO SIG. DIFF	SIGNIFICANT DIFFERENCE - EXPLAIN	FURTHER COMMENTS
(Hoegholm et al., 1995)	felodipine ER amlodipine	118	**BP** efficacy and safety, BP; ABPM	exce pt...	Ambulatory SBP sig. greater amlodipine and HD flushing less	FER-5,10, or20mg od A-5 or 10 mg od
(Minami et al., 1998)	amlodipine vs nifedipine retard	20	**BP** HR, BP, ABPM, autonomic nerve activity	exce pt...	Sign diff nifedipine caused □HR; □SNS;□PNS	A 2.5 mg od N retard 20mg bid
(Testa et al., 1998)	nifedipine GITS vs amlodipine	356	**BP** SBP,DBP,QofL	exce pt...	Nifedipine sgn. better QofL	N GITS 30mg od A -5mg od
(Zidek et al., 1995)	nifedipine coat core vs amlodipine	207	**BP** efficacy, safety; ABPM			N cc-30mg od A -5 mg od
(Di Pasquale et al., 1984)	nicardipine vs nifedipine	12	**Angina** chronic effort			Nic -20mg qid Nif -10mg qid
(Hosie J and et al, 1992)	felodipine ER vs nifedipine retard	77	**BP** effect, tolerability, QoL	exce pt ...	Felodipine better tolerated	F ER - 5 mg od N retard- 20mg bid
(Abelardo et al., 1989)	felodipineER vs nifedipine retard	23	**BP** SBP, DBP			F ER -10 mg od N retard - 20mg bid
(Koenig and et al, 1993)	felodipine vs amlodipine	118	**BP** efficacy, tolerability			F -5 to 10 mg od A - 5 to 10 mg od
(Bowles et al., 1986)	nicardipine vs nifedipine	41	**Angina** efficacy, exercise testing			Nic - 30 mg tid Nif 10 mg tid

ARTICLE	DRUGS COMPARED	SAMPLE SIZE	endpt of trial	NO SIG. DIFF	SIGNIFICANT DIFFERENCE - EXPLAIN	FURTHER COMMENTS
(Schulte, 1995)	felodipine ER vs nifedipine SR	43	**Angina** exercise testing; total time, time to onset	~ exce pt ...	Time to onset of angina sig. longer for Felodipine	F ER- 10 mg qam N SRB 20 mg bid
(Littler, 1990)	felodipine ER vs nifedipine retard	100	**BP** 3 h and 12h/24h, DBP, SBP, HR, A/E	~ exce pt ...	DBP lower in Felodipine gp at 24h post-dose	also on metoprolol F ER - 10 mfg od N retard -20 mg bid
(Aberg et al., 1985)	felodipine vs nifedipine	18	**BP poorly controlled** SBP, DBP, ECG, blood tests, HR, weight, ankle measure	~		F- 5-10 mg tid N - 10- 20 mg tid
(Goudie A.W. and et al, 1994)	felodipine ER vs nifedipine retard	134	**BP** efficacy (HR, BP), tolerability	~ HR	felodipine sig. greater decrease seated BP (fewer A/E - sig.?)	F ER -5 - 10 mg qam N retard -10-20 mg bid
(Ueda et al., 1993)	amlodipine vs Nifedipine GITS	9	**BP** pressor response to angiotensin II and NA	~ BP, HR	amlodipine- more smoothly sustained efficacy for 48 h post-dose	A - 5mg od N GITs -60 mg od
(Koenig and Hoher, 1997)	felodipine ER vs amlodipine	52	**Angina-**exercise induced; antiischemic, antianginal efficacy	~		F ER -5-10 mg od A- 5-10mg od
(Iliopoulou et al., 1983)	nicardipine vs nifedipine	6	**BP** BP,HR, STI(systolic time intervals)	~		3 oral treatments -Nic 40mg; Nif 20mg
(Lorimer et al.,	amlodipine vs		**BP** BP, HR, weight,			A- 5 -10mg od

ARTICLE	DRUGS COMPARED	SAMPLE SIZE	endpt of trial	NO SIG. DIFF	SIGNIFICANT DIFFERENCE - EXPLAIN	FURTHER COMMENTS
1994)	nifedipine retard	111	A/E	~		N retard-20-40 mg bid
(Rumboldt et al., 1988)	nicardipine vs nifedipine SR	95	**BP** BP,HR, A/E, lab exam	~		Nic-40mg od Nif SR- 20mgod
(Bompadre S and et al, 1991)	amlodipine vs nifedipine AR	8	**BP** BP, HR, plasma concentration	~	amlodipine smoother SBP,DBP over 24 hrs	A- 10mg od N AR -20mg bid

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Appendix B Therapeutic Equivalence of ACE inhibitors[7]

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 studies[3-25] evaluated ACE in the treatment of hypertension and 15 studies[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[4,6] found no significant differences while 2 studies[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 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.[8] Trandolapril was also able to maintain the blood pressure lowering effect over the entire 24-hour dosing period beter than enalapril.[23] One study[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.[7] Captopril therapy for 4 weeks produced a better quality of life that enalapril (n=379)[14], and ramapril produced a better quality of life when compared to captopril after 8 weeks of therapy (n=60)[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.[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,[1,27,35] but there were no statistically significant differences found among perindopril, captopril, and enalapril in terms of ACE inhibition.[27] An additional recent study also found that perindopril produced less first-dose hypotension than enalapril[41] The results of this review are consistent with recent guidelines for the management of heart failure[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.[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 tranolapril.

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[8] 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:

[8]benazepril, 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. ((doubl$ or trebl$ or tripl$) adj25 (blind$ or 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)
120. lisinopril (mh)
121. ramipril (mh)
122. ACEI(tw)
123. angiotensin converting enzyme inhibitors(tw)
124. benazepril(tw)
125. captopril(tw)
126. cilazapril(tw)
127. enalapril(tw)
128. fosinopril(tw)
129. lisinopril(tw)
130. perindopril(tw)
131. quinapril(tw)
132. ramipril(tw)
133. trandolapril(tw)

134. 80 or 81 or...99

135. 13 and 32 and 79 and 100

136. Limit 101 to English
137. Limit 102 to Human
138. hypertension (mh)
139. heart failure, congestive (mh)
140. congestive heart failure (mh)
141. CHF (mh)
142. Myocardial infarction (mh)
143. MI (mh)
144. hypertension(tw)
145. congestive heart failure(tw)
146. CHF(tw)
147. heart failure(tw)
148. Myocardial infarction (tw)
149. MI(tw)

150. 13 and 21 and 68 and 89
151. Limit 90 to English
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. [1,2] 23 studies[3-25] evaluated ACE in the treatment of hypertension and 15 studies[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[4,6] found no significant differences while 2 studies[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 that enalapril 5-20mg, a result that is most likely explained by under dosing of enalapril.[8] Trandolapril was also able to maintain the blood pressure lowering effect over the entire 24-hour dosing period beter than enalapril.[23] One study[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.[7] Captopril therapy for 4 weeks produced a better quality of life that enalapril (n=379)[14], and ramapril produced a better quality of life when compared to captopril after 8 weeks of therapy (n=60)[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.

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,[1,27,35] but there were no statistically significant differences found among perindopril, captopril, and enalapril in terms of ACE inhibition.[27]

Table B1: Frequency of PAIRED Comparisons for ACE -BP and HF

Frequency of PAIRED Comparisons for ACE -BP and HF

	captopril	Enalapril
enalapril	8[11,12,14,15,26,33,39]	
lisinopril	10[13,18,22,24,24,28,29,31,34,36]	7[3,4,6,8,19,20,37]
benazepril	1[17]	1[9]
cilazepril	2[30,32]	
quinapril		1[21]
trandolapril		1[23]
ramipril	1[16]	1[25]
perindopril	2[5,7]	1[10]
fosinopril		1[38]

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

ARTICLE	captopril	enalapril	lisinopril	trandolapril	benazepril	quinapril	cilazapril	perindopril	ramipril
Gourlay et al, 1993[3]		1	2						
Enstrom et al, 1992[4]		ND	ND						
Lees et al, 1989[5]	1							2	
Dews et al, 1989[6]		ND	ND						
Grandi et al, 1991[7]	ND							ND	
Johnston et al, 1991[8]		1	2						
MacDonald et al, 1993[9]		ND			ND				
Alcocer et al, 1995[10]		ND						ND	
Chrysant et al, 1985[11]	ND	ND							
Rumboldt, et al 1988[12]	ND	ND							

ARTICLE	captopril	enalapril	lisinopril	trandolapril	benazepril	quinapril	cilazapril	perindopril	ramipril
Rumboldt et al, 1993[13]	1		2						
Thind et al, 1985[15]	1	2							
Yajnik et al, 1994[16]	ND								ND
Chen et al, 1995[17]	ND				ND				
Whelton, et al 1990[18]	ND		ND						
Whelton et al, 1992[19]		1	2						
Conway et al, 1990[21]		ND				ND			
Taylor et al, 1989[22]	1		2						
1993[24]	ND		ND						
Testa et al, 1993[14]	ND	ND							
Vaur et al, 1995[23]		1		2					

Note: Conway et al[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

ARTICLE	DRUGS COMPARED	SAMPLE SIZE	endpt of trial	NO SIG. DIFF.	SIGNIFICANT DIFFERENCE - EXPLAIN	FURTHER COMMENTS
(Gourlay et al., 1993)[3]	lisinopril vs enalapril	28	**BP** ABPM	1st 12 hrs SBP; DBP[9]	lisinopril decreased mean SBP sig more than enalapril- confined to 2nd 12 hrs of dosing interval	L - 10mg od E - 10mg od
(Enstrom et al., 1992)[4]	enalapril vs lisinopril	58	**BP** BP at rest, exercise, during 24 h	[10]		E 20mg od L 20 mg od
(Lees et al., 1989)[5]	captopril vs perindopril	165	**BP** efficacy, acceptability	A/E	perindopril more effective DBP	P-4-8mg od C- 25mg-50 bid
(Dews et al., 1989)[6]	lisinopril vs enalapril	16	**BP** single dose, BP up to 24 h post dose	except..	time to max. effect longer for lisinopril	L - 10mg E - 10mg
(Grandi et al., 1991)[7]	perindopril vs captopril	20	**BP** effects on LV, BP			P - 4-8 mg od C - 25-50mg bid
(Johnston et al., 1991)[8]	lisinopril vs enalapril	169	**BP** efficacy, safety - acute & 12 week	except...	Lisinopril 10mg vs enalapril 5mg sig greater hypertensive effects	L- 10-40mg E - 5-20mg

[9] No significant difference was shown except for endpoint mentioned, all other enpoints showed no significant difference

[10] No significant difference between two agents was found

ARTICLE	DRUGS COMPARED	SAMPLE SIZE	endpt of trial	NO SIG. DIFF.	SIGNIFICANT DIFFERENCE - EXPLAIN	FURTHER COMMENTS
(Macdonald et al., 1993)[9]	benazepril vs enalapril	18	**BP** old vs young- kinetics vs dynamics - single dose	□		B- 10 mg E - 10mg
(Alcocer et al., 1995)[10]	perindopril vs enalapril	161	**BP** efficacy, acceptability	□ except	Withdrawal sig higher for enalapril	P - 4 -8mg od E - 10-20 mg od
(Chrysant et al., 1985)[11]	captopril vs enalapril	20	**BP** BP, metabolic evaluation, A/E	□		E - 5-20mg bid C - 25-100mg tid
(Rumboldt et al., 1988)[12]	captopril vs enalapril	69	**BP** DBP, HR, Lab work, A/E	□		C - 25 -50mg bid E - 20-40 mg od
(Rumboldt et al., 1993)[13]	captopril vs lisinopril	91	**BP** DBP, efficacy, acceptability, BP normalization	□ except ..	Lisinopril sig reached dose normalization more	C - 12.5-50 mg bid L - 10 - 40 mg od
(Testa et al., 1993)[14]	Captopril vs enalapril	379	**BP** Q of L	□ except ..	captopril sig better QofL	C - 25-50 mg bid E - 5-20 mg od
(Thind et al., 1985)[15]	captopril vs enalapril	32	**BP** BP,HR,A/E		enalapril sig decreased BP more	C - 25-100 mg tid E - 5 - 20mg bid
(Yajnik et al., 1994)[16]	ramipril vs captopril	60	**BP** DBP, HR, hypotension, K+ levels, A/E, QofL	□ except ...	Ramipril better QofL (instrument not validated)	R - 5 mg od C - 50mg bid
(Chen et al., 1995)[17]	benazepril vs captopril	75	**BP** DBP, SBP, ABPM, HR, lab work, A/E	□		B - 10 mg od C - 25 mg tid
(Whelton et al., 1990)[18]	lisinopril vs captopril	70	**BP** BP office and ABPM, A/E, HR	□ except	lisinopril sig. lower BP with ABPM	L - 10-40 mg C - 25-1000mg bid

ARTICLE	DRUGS COMPARED	SAMPLE SIZE	endpt of trial	NO SIG. DIFF.	SIGNIFICANT DIFFERENCE - EXPLAIN	FURTHER COMMENTS
				...		
(Whelton et al., 1992)[19]	lisinopril vs enalapril	110	**BP** BP office, ABPM, ACE activity, aldosterone	except ...	Lisinopril sig diff than placebo in second half of dosing schedule enalapril not	L - 10 mg od E - 10 mg od
(Conway et al., 1990)[20]	lisinopril vs enalapril	19	**BP** ABPM, HR, A/E	except. ..	lisinopril sig. better in decreasing 24 hr SBP	L - 10 mg od E - 10 mg od
(Taylor, 1989)[21]	quinapril vs enalapril	258	**BP** DBP, SBP,A/E			Q - 10- 40 mg od E - 10 - 40 mg od
(Gosse et al., 1989)[22]	lisinopril vs captopril	304	**BP** BP, lab work, HR, body weight, A/E	except. ..	Lisinopril sig. better in decreasing SBP	L - 20 mg od C - 50 mg od
(1993)[23]	captopril vs lisinopril	25	**BP** BP, A/E, ABPM, lab work			C - 100mg od L - 40 mg od
(Vaur et al., 1995)[24]	trandolapril vs enalapril	88	**BP** ABPM-missed dose		trandolapril sig maintained BP while enalapril only did in daytime	T - 2 mg E - 20 mg

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

ARTICLE	captopril	enalapril	lisinopril	Fosinopril	cilazapril	perindopril
Lange et al, 1994[26]	1	2				
MacFadyen et al, 1991[27]	1	1				2
Giles et al, 1989[28]	1		2			
Giles et al, 1988[29]	1		2			
1995[30]	ND				ND	
Bach and Zardini, 1992[31]	ND		ND			
Bulpitt et al, 1998[32]	ND				ND	
Haffner et al, 1995[33]	2	1				
Morisco et al, 1997[34]	ND		ND			
Navookarasu et al, 1999[35]	1	1	1			2
Powers et al, 1987[36]	1		2			
Reid et al, 1993[1,2]	1	1				2
Zannad et al, 1992[37]		ND	ND			
Zannad et al, 1998[39]	2	1				
Packer at al, 1986[38]		1		2		

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

ARTICLE	DRUGS COMPARED	SAMPLE SIZE	endpt of trial	NO SIG. DIFF.	SIGNIFICANT DIFFERENCE - EXPLAIN	FURTHER COMMENTS
(Lange MR and et al, 1994)[26]	enalapril vs captopril	117	**HF** safety, tolerability-BP, serum activity, clinical status after first dose	[11] mag.BP& A/E	enalapril sig. I(Inhibit) ACE activity greater extent except at 1 hr	C- 6.25mg E- 2.5 mg
(MacFadyen et al., 1991)[27]	captopril vs enalapril vs perindopril	48	**HF** first dose-BP, HR, drug conc., plasma renin and ACE activity	except...	perindopril less hypotension	C-6.25mg E-2.5 mg P-2mg
(Giles et al., 1989)[28]	lisinopril vs captopril	189	**HF** lab, clinical, exercise, QofL	safety	Lisinopril sig. greater exercise duration, and it increased LVEF	L 5-20mg od C 12.5-50 mg tid
(Giles et al., 1988)[29]	lisinopril vs captopril	189 (65 subset-above)	**HF** lab, clinical, exercise	except...	Sig increase in LVEF in lisinopril not captopril	C 12.5 - 50 mg tid L 5-20 mg od
(1995)[30]	cilazapril vs captopril	443	**HF** exercise tolerance, clinical status, weight	[12]		Cil - 2.5 mg od Cap - 25-50 mg tid
(Bach and Zardini, [31]	lisinopril vs	287	**HF** exercise, ectopic			L - 5-20mg od

[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

ARTICLE	DRUGS COMPARED	SAMPLE SIZE	endpt of trial	NO SIG. DIFF.	SIGNIFICANT DIFFERENCE - EXPLAIN	FURTHER COMMENTS
1992)[31]	captopril		activity, A/E			C - 12.5-50mg bid
(Bulpitt et al., 1998)[32]	cilazapril vs captopril	367	**HF** QofL	□		Cil - 1 mg od Cap - 25 mg tid
(Haffner et al., 1995)[33]	captopril vs enalapril	80	**HF** first dose effect, GFR, effective renal plasma flow, exercise tolerance, symptoms	□ except ...	Captopril sig more improved in GFR, less GI symptoms, less symptomatic hypotension	C - 12.5 mg bid E - 2.5 mg bid
(Morisco et al., 1997)[34]	lisinopril vs captopril	271	**HF** efficacy, safety, tolerability; exercise, LVEF, SV, symptoms, A/E	□		L - 5-20 mg od C - 12.5 mg od - 25 mg bid
(Navookarasu et al., 1999)[35]	captopril vs enalapril vs perindopril vs lisinopril	80	**HF** first dose response	□ except ...	Perindopril did not produce first-dose hypotension (unlike res- although timing difft)	C - 6.25mg E - 2.5 mg P - 2 mg L - 2.5 mg
(Powers et al., 1987)[36]	lisinopril vs captopril	129	**HF** exercise, efficacy, A/E	□ except ...	Lisinopril improved exercise sig more but had more increase in BUN	L - 5 mg od C - 37.5 mg od (doses could be □)
(Reid et al., 1993)[1,2]	captopril vs enalapril vs perindopril	72	**HF** first dose	□ except ...	Perindopril did not produce first-dose hypotension (unlike rest-although timing diff)	C - 6.25 mg E - 2.5 mg P - 2 mg
(Zannad et al., 1992)[37]	lisinopril vs enalapril	278	**HF** exercise, ectopic activity, symptoms	□		L - 5-20 mg od E - 5 - 20 mg od
(Zannad et al.,	fosinopril vs	254	**HF** symptoms,		fosinopril sig better all	F - 5-20 mg od

ARTICLE	DRUGS COMPARED	SAMPLE SIZE	endpt of trial	NO SIG. DIFF.	SIGNIFICANT DIFFERENCE - EXPLAIN	FURTHER COMMENTS
1998)[38]	enalapril		survival,hypotension		measures	E - 5 - 20 mg od
(Packer et al., 1986)[39]	captopril vs enalapril	42	**HF** BP, hypotension, lab		enalapril sig. hypotension causing K+ retention and decline in creatinine clearance	E - 40 mg od C - 150 mg od

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