Table 1. Search methodology

Ace inhibitors and Beta Blockers for congestive heart failure
Note: A question mark after a term indicates that the term was truncated. An exclamation point after a term indicates that the term was "exploded" – I.E. all narrower terms in the subject hierarchy were included. This feature is active in the MEDLINE, HealthSTAR, and EMBASE databases.

SEARCH #1A
DATABASES SEARCHED:
MEDLINE
HealthSTAR
EMBASE
Ageline
Social SciSearch
SciSearch
TIME PERIOD COVERED: 1985-2000
SEARCH STRATEGY:
angiotensin-converting enzyme inhibitors OR dipeptidyl carboxypeptidase inhibitor! OR captopril OR enalapril OR fosinopril OR lisinopril OR quinapril OR ramipril OR beta-adrenergic receptor blocking agent! OR adrenergic beta-antagonists OR carvedilol OR metoprolol OR bisoprolol OR bucindolol OR beta block? AND heart failure, congestive! OR congestive heart failure! OR heart failure AND black? OR negro? OR afr? american? OR aged! OR geriatric assessment OR aged/ti,de OR elderly care! OR geriatric? OR gerontolog? OR nursing homes! OR nursing home OR home(s) for the aged OR homes for the elderly OR institutionalized elderly OR Female? OR female! OR women! OR wom?n OR gender OR women's health OR women's health services OR kidney failure! OR kidney? fail? OR renal fail? OR kidney disease? OR renal disease? OR kidney dysfunction? OR renal dysfunction? OR diabetes mellitus! OR diabetes OR cognition disorders! OR disorders of higher cerebral function! OR thought disorder OR alzheimer disease OR alzheimer? OR senil? OR dementia! OR dementia OR (drug therapy, combination OR drug combinations OR drug? combin? OR pharmac? combin? OR polypharmac?) AND (econom? OR cost?) OR drug combination!-economic aspect! AND Document type=randomized controlled trial OR random? (COMBINED WITH ALL TOPICS EXCEPT NURSING HOMES AND DRUG COMBINATIONS)
TOTAL NUMBER OF TITLES RETRIEVED: 1391

SEARCH #1B:
NOTE – THIS SEARCH WAS PERFORMED TO CORRECT AN OMISSION OF THE TERM "ACE INHIBITOR(S)" FROM THE SOCIAL SCISEARCH AND SCISEARCH DATABASES IN SEARCH 1A.
DATABASES SEARCHED AND TIME PERIOD COVERED:
Social SciSearch 1972-2001
SciSearch (Archival) – 1974-1989
SciSearch (Current) – 1990-2001
SEARCH STRATEGY:
ace inhibitor? NOT (captopril OR enalapril OR fosinopril OR lisinopril OR quinapril OR ramipril OR trandolapril) AND heart failure AND black? OR negro? OR afr? american? OR aged/ti,de OR elderly OR geriatric? OR gerontolog? OR nursing home? OR home? for the aged OR home? for the elderly OR institutionali? aged OR institutionali? elderly OR Female? OR wom?n OR gender OR kidney? fail? OR renal fail? OR kidney disease? OR renal disease? OR kidney dysfunction? OR renal dysfunction? OR diabetes OR alzheimer? OR senil? OR dementia OR drug? combin? OR pharmac? combin? OR polypharmac?)
TOTAL NUMBER OF TITLES RETRIEVED: 256

Table 2. Outcome of requests for subgroup data from principal RCTs of ACE inhibitors and beta-blockers

ACE Inhibitor Trial Name	Outcome of Contact
AIRE	No response to letters.
CONSENSUS	Individual patient data obtained from Dr. Steve Snapinn at Merck.
SAVE	No response to letters.
SMILE	No response to letters.
SOLVD	Individual patient data obtained from Dr. Steve Snapinn at Merck.
TRACE	Individual patient data obtained from Dr. Christian Torp-Pederson.
Beta-blocker Trial Name	**Outcome of Contact**
BEST	Request refused.
CIBIS-II	No response to letters.
COPERNICUS	Study released while report was in progress. Individual patient data made available to us from the FDA when we went to access MERIT-HF.
MERIT-HF	Refused, "manuscript in process," subsequently published. Individual patient data obtained from FDA.
U.S. Carvedilol	Agreed in principle; however, individual patient data never obtained.

Table 3. Sources of data for meta-analysis from principal RCTs of ACE inhibitors and beta-blockers

ACE Inhibitor Trial Name	Source of Data
AIRE	Published data
CONSENSUS	Individual patient data
SAVE	Published data
SMILE	Published data
SOLVD	Individual patient data
TRACE	Individual patient data
Beta-blocker Trial Name	**Source of Data**
BEST	Published data
CIBIS-II	Published data
COPERNICUS	Individual patient data
MERIT-HF	Individual patient data
U.S. Carvedilol	Published data

Table 4. Cost-effectiveness model variables and values for assessing treatment analysis

Variable	Baseline Value (Plausible Range)	Discussion
Age at beginning of model	55	Mean age 59 in SOLVD trials
Probability of death during year[19] (general population)	(by age)	
Relative risk of death compared to general population for: Asymptomatic untreated patients[3,25] Asymptomatic patients treated with ACE inhibitors[3,25] Symptomatic patients treated with ACE inhibitors[24,25]	 3.3 (1.0-4.0) 2.9 (1.0-4.0) 6.5 (2.0-8.0)	
Probability of transition during year from asymptomatic to symptomatic for: Untreated patients[3] Treated patients[3]	 9.8% (5.0%-15.0%) 6.5% (5.0%-10.0%)	Weighted average
Probability of hospitalization per year if symptomatic[26]	11% (5%-30%)	Weighted average
Probability of hospitalization during first episode of heart failure[3]	33% (10%-50%)	
QALY weights for: Asymptomatic patients[13,27] Symptomatic patients[13,27]	 0.865 (0.68-1.0) 0.710 (0-1.0)	Time-trade-off method, collected from general population, and visual analog scale from SOLVD study.
Cost of ACE inhibitor[16,16]	$551 ($200-$1,000)	From average wholesale price of various manufacturers
Cost of hospitalization[17]	$9,425 ($7,000-$13,000)	Baseline value for DRG 127 (Heart Failure and Shock) from MGH analysis; range includes mean of hospital charges to Medicare
Cost of outpatient CHF management[28]	$470 ($200-$800)	Costs applied to AHA utilization survey findings
Cost of general health expenditures[14]	(by age)	
Deflation rate	(by year)	Consumer Price Index, Medical Care
Annual discount rate for costs and utilities[18]	3% (0%-6%)	

Table 5. Cost-effectiveness model variables and values for assessing screening analysis

Variable	Baseline Value (Range)	Comment
Cost of BNP	$29 (10-100)	Biosite price of 25 tests for $725
Cost of ECG	$31 (10-100)	Medicare reimbursement 2001
Cost of two-dimensional echocardiography	$213 (100-1000)	Medicare reimbursement 2001
Lifetime cost of care: Normal EF Low EF on ACE inhibitor Low EF, not on ACE inhibitor until CHF	 $51,898 ($25,000-100,000) $40,701 ($20,000-80,000) $36,983 ($20,000-80,000)	From Model of ACEi treatment for low ejection fraction (see appendix)
Survival: Normal EF Low EF on ACE inhibitor Low EF, not on ACE inhibitor until CHF	 14.96 (10-20) 8.76 (5-15) 8.12 (5-15)	From Model of ACEi treatment for low ejection fraction (see appendix)
Quality-adjusted survival: Normal EF Low EF on ACE inhibitor Low EF, not on ACE inhibitor until CHF	 12.94 (10-20) 7.22 (5-15) 6.56 (3-15)	From Model of ACEi treatment for low ejection fraction (see appendix)
Sensitivity BNP [20] Specificity BNP[20]	0.89 (0.5-1.0) 0.71 (0.5-1.0)	Threshold of 17.9 ng/ml (European assay)
Sensitivity ECG[21] Specificity ECG[21]	0.60 (0.5-1.0) 0.82 (0.5-1.0)	
Sensitivity echocardiography[22] Specificity echocardiography[22]	0.87 (0.8-1.0) 0.76 (0.8-1.0)	Assumes nuclear angiography is the gold standard
Prevalence of low ejection fraction	2.7%	Among patients >55 years of age, assumes 50% of low EF are asymptomatic
Deflation rate	(by year)	Consumer Price Index, Medical Care
Annual discount rate for costs and utilities[18]	3% (0%-6%)	

Table 6. Effect of ACE inhibitors on mortality from heart failure in male and female patients (relative risk analysis)

Study Name	Total N	N Male	N Female	Relative Risk, Male (95% CI)	Relative Risk, Female (95% CI)	Ratio of Relative Risks (95% CI)
CONSENSUS	253	179	74	0.61 (0.44, 0.85)	1.14 (0.68, 1.90)	1.86 (1.01, 3.42)
SAVE	2231	1841	390	0.80 (0.68, 0.95)	0.99 (0.67, 1.47)	1.24 (0.80, 1.90)
SMILE	1556	1128	428	0.61 (0.39, 0.96)	0.74 (0.47, 1.18)	1.22 (0.64, 2.32
SOLVD-prevention	4228	3752	476	0.90 (0.77, 1.05)	1.15 (0.74, 1.78)	1.27 (0.80, 2.02)
SOLVD-treatment	2569	2065	504	0.89 (0.80, 0.99)	0.86 (0.67, 1.09)	0.97 (0.74, 1.26)
TRACE	1749	1248	501	0.79 (0.68, 0.91)	0.90 (0.74, 1.11)	1.15 (0.90, 1.48)
Random-effects pooled estimate		10,213	2373	0.82 (0.74, 0.90)	0.92 (0.81, 1.04)	1.15 (0.99, 1.33)

Table 7. Effect of ACE inhibitors on mortality from heart failure in male and female patients (hazard ratio analysis)

Study Name	Total N	N Male	N Female	Hazard Ratio, Male (95% CI)	Hazard Ratio, Female (95% CI)	Ratio of Hazard Ratios (95% CI)
AIRE	1986	1461	525	0.76 (0.60, 0.97)	0.69 (0.49, 0.97)	0.91 (0.60, 1.38)
CONSENSUS	253	179	74	0.44 (0.28, 0.68)	1.08 (0.54, 2.15)	2.45 (1.08, 5.59)
SMILE	1556	1128	428	0.59 (0.36, 0.96	0.70 (0.40, 1.22)	1.19 (0.57, 2.48)
SOLVD-prevention	4228	3752	476	0.88 (0.75, 1.04)	1.15 (0.71, 1.85)	1.31 (0.79, 2.16)
SOLVD-treatment	2569	2065	504	0.84 (0.73, 0.97)	0.84 (0.62, 1.13)	1.00 (0.72, 1.39)
TRACE	1749	1248	501	0.75 (0.62, 0.90	0.86 (0.66, 1.13)	1.15 (0.83, 1.60)
Random-effects pooled estimate		9833	2508	0.76 (0.66, 0.87)	0.84 (0.72, 0.98)	1.11 (0.92, 1.32)

Table 8. Effect of ACE inhibitors on mortality from heart failure in male and female patients (relative risk analysis), random-effects pooled estimate (separately for prevention studies and treatment studies)

Analysis	Relative Risk, Male (95% CI)	Relative Risk, Female (95% CI)	Ratio of Relative Risks (95% CI)
Prevention studies	0.83 (0.72, 0.96)	0.96 (0.75, 1.22)	1.25 (0.94, 1.65)
Treatment studies	0.80 (0.68, 0.93)	0.90 (0.78, 1.05)	1.15 (0.88, 1.51)

Table 9. Number Needed to Treat (NNT) as a function of risk ratio and population mortality risk

Population Mortality Risk	Risk Ratio				
	0.5	**0.6**	**0.7**	**0.8**	**0.9**
0.1	20	25	34	50	100
0.2	10	13	17	25	50
0.3	7	9	12	17	34
0.4	5	7	9	13	25
0.5	4	5	7	10	20

Table 10. Effect of ACE inhibitors on mortality from heart failure in diabetic and nondiabetic patients (relative risk analysis)

Study Name	Total N	N Non-diabetic	N Diabetic	Relative Risk, Non-diabetic (95% CI)	Relative Risk, Diabetic (95% CI)	Ratio of Relative Risks (95% CI)
CONSENSUS	253	197	56	0.64 (0.46, 0.88)	1.06 (0.65, 1.74)	1.67 (0.93, 3.01)
SAVE	2231	1739	492	0.82 (0.68, 0.99)	0.89 (0.68, 1.16)	1.09 (0.79, 1.50)
SMILE	1556	1253	303	0.79 (0.54, 1.15)	0.44 (0.22, 0.87)	0.56 (0.25, 1.22)
SOLVD-prevention	4228	3581	647	0.97 (0.83, 1.15)	0.75 (0.55, 1.02)	0.77 (0.54, 1.09)
SOLVD-treatment	2569	1906	663	0.84 (0.74, 0.95)	1.01 (0.85, 1.21)	1.21 (0.97, 1.50)
TRACE	1749	1512	237	0.85 (0.74, 0.97)	0.73 (0.57, 0.94)	0.87 (0.65, 1.15)
Random-effects pooled estimate		10,188	2398	0.85 (0.78, 0.92)	0.84 (0.70, 1.00)	1.00 (0.80, 1.25)

Table 11. Effect of ACE inhibitors on mortality from heart failure in diabetic and nondiabetic patients (hazard ratio analysis)

Study Name	Total N	N Non-diabetic	N Diabetic	Hazard Ratio, Non-diabetic (95% CI)	Hazard Ratio, Diabetic (95% CI)	Ratio of Hazard Ratios (95% CI)
CONSENSUS	253	197	56	0.50 (0.33, 0.77)	0.68 (0.33, 1.42)	1.35 (0.58, 3.15)
SMILE	1556	1253	303	0.77 (0.50, 1.18)	0.39 (0.18, 0.884)	0.51 (0.21, 1.22)
SOLVD-prevention	4228	3581	647	0.96 (0.81, 1.14)	0.73 (0.52, 1.03)	0.76 (0.52, 1.12)
SOLVD-treatment	2569	1906	663	0.79 (0.68, 0.92)	0.98 (0.78, 1.24)	1.24 (0.94, 1.64)
TRACE	1749	1512	237	0.82 (0.69, 0.97)	0.64 (0.45, 0.91)	0.78 (0.53, 1.16)
Random-effects pooled estimate		8449	1906	0.80 (0.69, 0.93)	0.73 (0.56, 0.95)	0.91 (0.67, 1.23)

Table 12. Effect of ACE inhibitors on mortality from heart failure in black and white patients (relative risks analysis)

Study Name	Total N	N White	N Nonwhite	N Black	N Nonblack	Relative Risk, White (95% CI)	Relative Risk, Black (95% CI)	Ratio of Relative Risks (95% CI)
SAVE	2231	1993	238			0.78 (0.50, 1.21)	0.84 (0.71, 0.99)	1.08 (0.67, 1.73)
SOLVD-prevention	4228	3657	571	404	3824	0.95 (0.81, 1.12)	0.87 (0.60, 1.25)	0.91 (0.61, 1.36)
SOLVD-treatment	2569	2061	508	396	2173	0.89 (0.79, 1.00)	0.93 (0.74, 1.17)	1.04 (0.81, 1.35)
Random-effects pooled estimate		7711	1317	800	5997	0.89 (0.82, 0.97)	0.89 (0.74, 1.06)	1.01 (0.83, 1.24)

Table 13. Effect of ACE inhibitors on mortality from heart failure in black and white patients (hazard ratios analysis)

Study Name	Total N	N White	N Nonwhite	N Black	N Nonblack	Hazard Ratio, White (95% CI)	Hazard Ratio, Black (95% CI)	Ratio of Hazard Ratios (95% CI)
SOLVD-prevention	4228	3657	571	404	3824	0.94 (0.79, 1.111)	0.82 (0.54, 1.25)	0.87 (0.55, 1.37)
SOLVD-treatment	2569	2061	508	396	2173	0.85 (0.74, 0.98)	0.88 (0.65, 1.20)	1.04 (0.74, 1.45)
Random-effects pooled estimate		5718	1079	800	5997	NC	NC	NC

Table 14. Effect of beta-blockers on mortality from heart failure in male and female patients (relative risk analysis)

Study Name	Total N	N Male	N Female	Relative Risk, Male (95% CI)	Relative Risk, Female (95% CI)	Ratio of Relative Risks (95% CI)
CIBIS II	2647	2132	515	0.71 (0.58, 0.87)	0.52 (0.30, 0.89)	0.73 (0.41, 1.30)
COPERNICUS	2287	1822	465	0.68 (0.54, 0.86)	0.63 (0.39, 1.04)	0.93 (0.54, 1.59)
MERIT-HF	3991	3093	898	0.63 (0.50, 0.78)	0.93 (0.58, 1.49)	1.49 (0.88, 2.51)
US Carvedilol HF	1094	838	256	0.44 (0.24, 0.82)	0.32 (0.11, 0.93)	0.73 (0.21, 2.51)
Random-effects pooled estimate		7885	2134	0.66 (0.59, 0.75)	0.63 (0.44, 0.91)	0.99 (0.70, 1.41)

Table 15. Effect of beta-blockers on mortality from heart failure in male and female patients (hazard ratio analysis)

Study Name	Total N	N Male	N Female	Hazard Ratio, Male (95% CI)	Hazard Ratio, Female (95% CI)	Ratio of Hazard Ratios (95% CI)
COPERNICUS	2287	1822	465	0.65 (0.51, 0.83)	0.65 (0.38, 1.10)	1.00 (0.56, 1.78)
MERIT-HF	3991	3093	898	0.62 (0.49, 0.78)	0.94 (0.58, 1.53)	1.52 (0.88, 2.60)
US Carvedilol HF	1094	838	256	0.41 (0.22, 0.78)	0.23 (0.07, 0.72)	0.56 (0.15, 2.09)
Random-effects pooled estimate		5753	1619	0.62 (0.52, 0.73)	0.62 (0.34, 1.14)	1.15 (0.75, 1.76)
BEST	2708	2115	593	0.91 (0.79, 1.04)	0.91 (0.67, 1.24)	1.00 (0.71, 1.41)

Table 16. Effect of beta-blockers on mortality from heart failure in diabetic and nondiabetic patients (relative risk analysis)

Study Name	Total N	N Non-diabetic	N Diabetic	Relative Risk, Non-diabetic (95% CI)	Relative Risk, Diabetic (95% CI)	Ratio of Relative Risks (95% CI)
CIBIS II	2647	2335	312	0.66 (0.54, 0.81)	0.81 (0.52, 1.27)	1.23 (0.75, 2.02)
COPERNICUS	2287	1701	586	0.67 (0.52, 0.85)	0.68 (0.47, 1.00)	1.02 (0.65, 1.61)
MERIT-HF	3991	3006	985	0.62 (0.48, 0.79)	0.81 (0.57, 1.15)	1.32 (0.86, 2.02)
Random-effects pooled estimate		7042	1883	0.65 (0.57, 0.74)	0.77 (0.61, 0.96)	1.19 (0.91, 1.55)

Table 17. Effect of beta-blockers on mortality from heart failure in diabetic and nondiabetic patients (hazard ratio analysis)

Study Name	Total N	N Non-diabetic	N Diabetic	Hazard Ratio, Non-diabetic (95% CI)	Hazard Ratio, Diabetic (95% CI)	Ratio of Hazard Ratios (95% CI)
COPERNICUS	2287	1701	586	0.65 (0.50, 0.85)	0.66 (0.43, 1.00)	1.01 (0.62, 1.65)
MERIT-HF	3991	3006	985	0.61 (0.48, 0.78)	0.80 (0.55, 1.16)	1.31 (0.84, 2.05)
Random-effects pooled estimate		4707	1571	NC	NC	NC

Table 18. Effect of beta-blockers on mortality from heart failure in black and white patients (relative risk analysis)

Study Name	Total N	N White	N Nonwhite	N Black	N Nonblack	Relative Risk, White (95% CI)	Relative Risk, Black (95% CI)	Ratio of Relative Risks (95% CI)
COPERNICUS	2287	2069	218	121	2166	0.66 (0.53, 0.82)	0.62 (0.19, 2.01)	0.94 (0.28, 3.11)
MERIT-HF	3991	3755	236	207	3784	0.67 (0.54, 0.82)	0.79 (0.36, 1.76)	1.19 (0.52, 2.70)
US Carvedilol HF	1094			217	877	0.38 (0.20, 0.70)	0.53 (0.19, 1.48)	1.41 (0.43, 4.68)
Random-effects pooled estimate		5824	454	545	6827	0.63 (0.52, 0.77)	0.67 (0.39, 1.16)	1.17 (0.65, 2.11)
BEST	2708			627	2081	0.85 (0.74, 0.96)	1.17 (0.94, 1.47)	1.39 (1.07, 1.79)

Table 19. Effect of beta-blockers on mortality from heart failure in black and white patients (hazard ratio analysis)

Study Name	Total N	N White	N Nonwhite	N Black	N Nonblack	Hazard Ratio, White (95% CI)	Hazard Ratio, Black (95% CI)	Ratio of Hazard Ratios (95% CI)
COPERNICUS	2287	2069	218	121	2166	0.63 (0.50, 0.80)	0.60 (0.17, 20.5)	0.95 (0.27, 3.32)
MERIT-HF	3991	3755	236	207	3784	0.66 (0.53, 0.83)	0.85 (0.36, 1.99)	1.29 (0.53, 3.12)
US Carvedilol HF	1094			217	877	0.32 (0.17, 0.62)	0.44 (0.15, 1.28)	1.38 (0.39, 4.81)
Random-effects pooled estimate		5824	454	545	6827	0.59 (0.45, 0.76)	0.64 (0.36, 1.16)	1.21 (0.65, 2.27)
BEST	2708			627	2081	0.82 (0.70, 0.96)	1.17 (0.89, 1.53)	1.43 (1.04, 1.95)

Table 20. Cost-effectiveness base-case results for assessing treatment analysis

Strategy	Total Cost	Life Expectancy	Cost per Life Year	Quality-Adjusted Life Expectancy	Cost per QALY
No ACE inhibitor	$36,983	8.12		6.56	
ACE inhibitor	$40,701	8.76	$5,802	7.22	$5,644

Table 21. Cost-Effectiveness base-case results for assessing screening analysis

Strategy	Cost	Marginal Cost	Life Years	Marginal Life-years	QALYs	Marginal QALYs	Marginal Cost-Effectiveness $/QALY
No screening	$43,474		14.7753		12.7677		
ECG then Echo	$43,655	$181	14.7848	0.0094	12.7775	0.0098	Dominated (Extended)
BNP then Echo	$43,740	$266	14.7893	0.0140	12.7822	0.0145	$18,300
Echo alone	$44,089	$349	14.7906	0.0013	12.7836	0.0014	$268,500
ECG alone	$45,007	$918	14.7831	-0.0076	12.7762	-0.0074	Dominated
BNP alone	$45,918	$1,829	14.7865	-0.0042	12.7799	-0.0037	Dominated

NOTE: Marginal costs and quality-adjusted life years (QALYs) are ordered by cost and compared to the prior nondominated strategy. The ECG then Echo strategy is eliminated by extended dominance (greater benefit and lower cost can be obtained through a combination of No screening and BNP, then echo strategies). The cost-effectiveness ratio of BNP then Echo versus ECG then Echo is $18,700 per QALY gained.

Table 22. Cost-effectiveness literature review of prevalence of reduced ejection fraction

Population	Definition of EF Method	Prevalence (%)	Asymptomatic (%)
Primary care patients = 45 years[45]	< 40% echocardiography	1.8	50
Community age 25-N75[18]	= 30% echocardiography	3.2	51
Community age = 55[18]	= 30% echocardiography	5.4	Not stated
Community age = 55 with ischemic heart disease[18]	= 30% echocardiography	12.1	Not stated
Patients with CVA, TIA, or peripheral vascular disease[46]	< 40% echocardiography	28	54

NOTE: CVA = cardiovascular accident; EF = ejection fraction; TIA = transient ischemic attack.