EVIDENCE BASED MEDICINE IN CORONARY HEART DISEASE WITH CONGESTIVE HEART FAILURE

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CHRONIC DIGITALIS THERAPY

- Captopril-Digoxin Multicenter Research Group trial---Digoxin-treated patients showed a significant increase in EF but less improvement in exercise capacity than in captopril group.
- PROVED trial---NYHA II~III, randomized, double-blind. Withdrawal of digoxin induced worsening heart failure.
- RADIANCE trial---Randomized, double-blind. Withdrawal of digoxin induced deterioration of cardiac function.
- DIG study---Prospective, randomized, placebo-controlled, double-blind survival trial. Digoxin had no effect on overall mortality but reduced hospitalizations for heart failure.

DOCUMENTED VALUE OF DIGOXIN

Proven indication:

- **Symptomatic LV systolic failure and sinus rhythm: Symptomatic improvement, improved exercise capacity and decreased hospitalization for heart failure.**
- **CHFwith atrial fibrillation: Heart rate control.**

Acceptable indication:

- **Symptomatic heart failure due to diastolic dysfunction.**

Not proven: potentially harmful (contraindicated)

- **Bradycardia and AV block.**
- **Significant ventricular arrhythmias.**
- **Renal dysfunction.**
- **Electrolyte disturbances, hypokalemia in particular.**

DIURECTICS

- **Most long term studies have involved a small number of patients and utilized a variety of drugs and doses.**
- **No study has been performed examining the effect of diuretics on long term survival.**
- **The RALES trial showed the need for potassium supplement might be diminished by using potassium sparing diuretics.**
- **Studies show positive survival effects in heart failure- using ACE inhibitors, beta-blockers, or vasodilators- have all used diuretics as background treatment.**

DOCUMENTED VALUE OF DIURETICS

Proven indication:

- **Symptomatic improvement in case of congestion. Improvement of exercise capacity.**

Acceptable indication:

- **Long-term treatment in conjunction with other drugs for heart failure, such as ACE inhibitors, vasodilators and beta-blockers.**

Not proven:

- **Heart failure without congestion or edema.**
- **Severe decompensated hypokalemia or hyperuricemia.**

VASODILATORS

- **V-HeFT I---Randomized, placebo-controlled. The survival in the hydralazine-isosorvide treated group was better than the placebo group (P<0.028). The mortality rate in the prazosin group was not different from the placebo group.**
- **V-HeFT II---The all-cause mortality was lower in the enalapril group as compared with the hydralazine-isosorbide group (18% v.s. 25%, P=0.016).**
- **V-HeFT III---LVEF≤45%, randomized. Neither mortality (13.8% versus 12.8%) nor hospitalization (43% versus 42%) rates were improved by felodipine on top of enapapril/diuretics.**
- **PRAISE trial---NYHA III~IV, randomized, placebo controlled. The mortality was lower in the non-ischemic group by amlodipine (22%~35%, P<0.001) but was unchanged in the subgroup with ischemic heart failure.**
- **PROFILE trial---Flosequinan, a vasodilator with positive inotropic and choronotropic effects, increased mortality.**

DOCUMENTED VALUE OF VASODILATORS

Proven indication:

- **Short-term reduction of afterload in acute heart failure.**
- **Hydralazine-isosorbide dinitrate can be used for long term treatment in patients not tolerate ACE inhibitors.**

Acceptable indication:

- **Third generation calcium-blockers may be used for symptomatic treatment in non-ischemic etiology.**

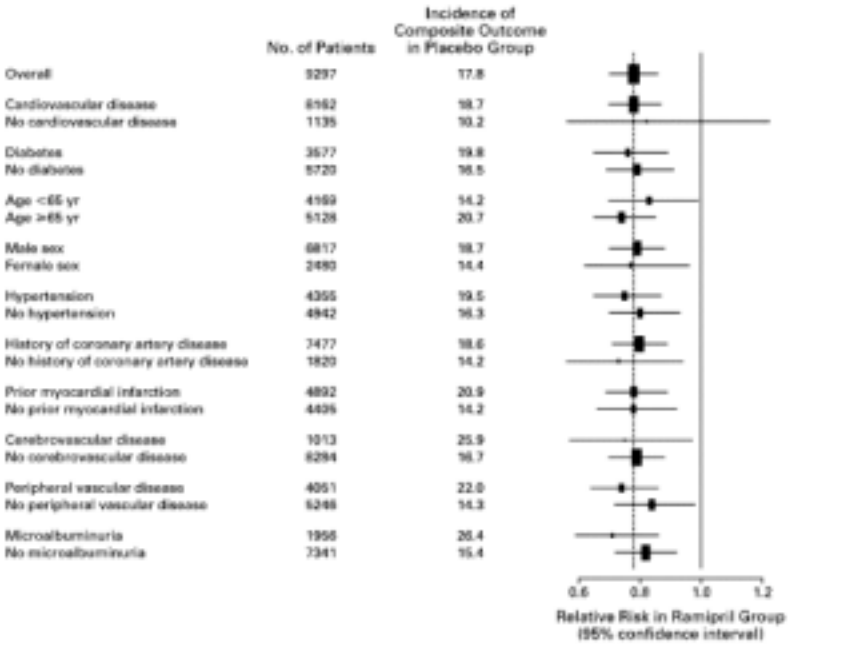
Not proven:

- **Other vasodilators than hydralazine-isosorbide dinitrate and amlodipine in ischemic etiology.**
- **Occurrence of significant valvular stenosis.**

ANGIOTENSIN CONVERTING ENZYME INHIBITOR

- CONSENSUS I---NYHA IV, randomized, placebo controlled. The ovreall mortality reduced by 27% in enalapril treated group (*P*=0.003). The duration of hospital stay was reduced and the NYHA classification improved.
- SOLVD---NYHA II~III, randomized, placebo controlled. Mortality reduced from 40% to 35% (*P*=0.0036). Hospitalizations for heart failure were also reduced.
- SAVE---Asymptomatic, LVEF≤40%, randomized, placebo-contraolled. Overall mortality was reduced in captopril group (20% v.s. 25%, RR 19%; *P*=0.019).
- TRACE---3~7 d post MI with LV dysfunction, randomized, placebo-controlled. Overall mortality was reduced in trandolapril group (34.7% v.s. 42.3%, RR 22%, *P*=0.00065).
- AIRE---3~10 d post MI with s/s of LV dysfunction, randomized, placebo-controlled. Overall mortality was reduced in ramipril group (17% v.s. 23%, RR 27%; *P*= 0.002).

THE BENEFICIAL EFFECT OF TREATMENT WITH RAMIPRIL



HOPE study investigators. *NEJM* 2000; 342:145-53

DOCUMENTED VALUE OF ACE INHIBITORS

Proven indication:

- **Symptomatic chronic heart failure and documented systolic myocardial dysfunction. Improved survival and reduced morbidity. Symptoms will be attenuated and exercise capacity improved.**
- **Following acute MI with heart failure or significant systolic dysfunction (LVEF<40%). Improved survival and reduced morbidity.**

Acceptable indication:

- **Heart failure due to diastolic dysfunction.**

Not proven:

- **Significant aortic or mitral stenosis.**
- **Hypotension (SBP <80mmHg)**
- **Pronounced renal dysfunction.**

ANGIOTENSIN II RECEPTOR (AT1) ANTAGONISTS

- **ELITE I---≥65 y/o with heart failure; randomized to losartan or captopril. Serum creatinine did not differ between the two groups. There was a 46% reduction of mortality among losartan group (4.8% v.s. 8.7%, *P*=0.035).**
- **ELITE II---NYHA II-IV, double-blind, randomized, controlled, LVEF ≤ 40%. There were no significant differences in all-cause mortality between the two treatment groups**
- **RESOLVD---Combined therapy with candesantan plus enalapril markedly reduced ventricular volumes and improved LVEF compared to either candesantan or enalapril alone.**
- **Val-HeFT---NYHA II-IV, valsartan in combination with ACE inhibitors and all other prescribed therapies.**

DOCUMENTED VALUE OF AT1-RECEPTOR ANTAGONISTS

Proven indication:

- **Symptomatic treatment of patients with heart failure who do not tolerate ACE inhibitors.**

NON-DIGITALIS INOTROPIC DRUGS

- PRIME-II---NYHA III-IV, randomized, placebo-controlled; Trial was prematurely terminated due to an increase in mortality in the β-agonist, ibopamine, treated patients (25% v.s. 20%, *P*=0.017%).
- PDE-inhibitors---Amrione, milrinone, enoimone, etc. All demonstrated a substantial increase in mortality on long term using.
- VEST---Placebo-controlled; prematurely terminated due to an 26% increase in mortality in the vensnarinone, a calcium-sensitizing agent, treated patients.

DOCUMENTED VALUE OF INOTROPIC DRUGS

Proven indication:

- Short term improvement of symptoms in patients with severe heart failure.
- Bridging towards more definitive surgical treatment, such as cardiac transplantation.

Acceptable indication:

- Intermittent short term treatment in chronic hear failure.

Not proven: potentially harmful (contraindicated)

- Long term treatment in chronic heart failure. May increase mortality risk.

BETA-ADRENERGIC BLOCKADE (I)

- MDC---DCM, randomized, placebo-controlled; a 34% reduction in the combined endpoint deaths and need for heart transplantation in metoprolol treated patients (*P*=0.058).
- CIBIS---Placebo-controlled. Patients without a previous MI had a more pronounced reduction in mortality in bisoprolol treated patients (12% v.s. 22.5%, *P*=0.01).
- RESOLVD---LVEF≤ 0.35, double-blind, placebo-controlled. Overall mortality was reduced in carvedilol group (3.2% v.s. 7.8%, RR 65%, 95% CI 0.39 ~ 0.80; *P*<0.001).
- CIBIS II---NYHA III~IV, LVEF≤ 35%, randomized to bisoprolol or placebo on top of diuretics and ACE-I, , F-U 1.3 yr. Overall mortality was reduced in bisoprolol group (11.8% v.s. 17.3%, hazard ratio 0.66, 95% CI 0.54 ~ 0.81; *P*<0.0001).

BETA-ADRENERGIC BLOCKADE (II)

- BEST--- NYHA III~IV, double-blind, randomized, placebo-Controlled. Bucindolol did not reduce death from heart failure.
- MERIT---NYHA II~IV, LVEF≤0.40, double-blinded, randomized to Metoprolol CR/XL or placebo, F-U 1 yr. All-cause mortality was lower in the metoprolol group (7.2% v.s. 11.0%, OR=0.66, 95% CI 0.53-0.81, *P*=0.00009)
- COMET---Carvedilol v.s. metoprolol, whether non-selectivity, vasodilation and other ancillary properties of carvedilol are critical to its benefit in CHF patients.

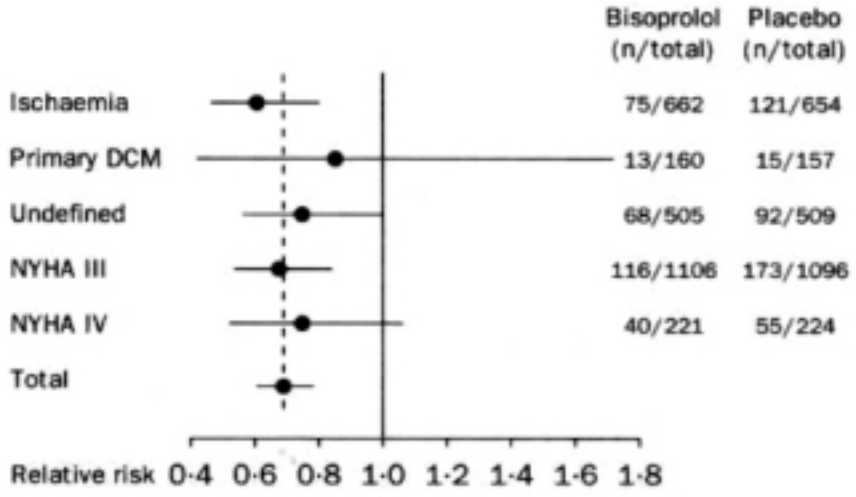
PRIMARY AND SECONDARY ENDPOINTS AND EXPLORATORY ANALYSES

	Placebo (n=1320)	Bisoprolol (n=1327)	Hazard ratio (95% CI)	p
Primary endpoint				
All-cause mortality	228 (17%)	156 (12%)	0.66 (0.54-0.81)	<0.0001
Secondary endpoints				
All-cause hospital admission	513 (39%)	440 (33%)	0.80 (0.71-0.91)	0.0006
All cardiovascular deaths	161 (12%)	119 (9%)	0.71 (0.56-0.90)	0.0049
Combined endpoint	463 (35%)	388 (29%)	0.79 (0.69-0.90)	0.0004
Permanent treatment withdrawals	192 (15%)	194 (15%)	1.00 (0.82-1.22)	0.98
Exploratory analyses				
Sudden death	83 (6%)	48 (4%)	0.56 (0.39-0.80)	0.0011
Pump failure	47 (4%)	36 (3%)	0.74 (0.48-1.14)	0.17
Myocardial infarction	8 (1%)	7 (1%)	0.85 (0.31-2.34)	0.75
Other cardiovascular	23 (2%)	28 (2%)	1.17 (0.67-2.03)	0.58
Non-cardiovascular deaths	18 (1%)	14 (1%)	0.75 (0.37-1.50)	0.41
Unknown cause of death	49 (4%)	23 (2%)	0.45 (0.27-0.74)	0.0012
Hospital admission for worsening heart failure	232 (18%)	159 (12%)	0.64 (0.53-0.79)	0.0001

Numbers refer to patients who presented at least once with given event. For hospital admissions, numbers refer to patients admitted at least once with any cause.

CIBIS-II investigators and committees. *The Lancet* 1999, 353:9-13

THE EFFECT OF BISOPROLOL ON MORTALITY BY ETIOLOGY AND FUNCTIONAL CLASS AT BASELINE



CIBIS-II. *The Lancet* 1999, 353:9-13

DOCUMENTED VALUE OF BETA-BLOCKERS

Proven indication:

- **To improve cardiac function and symptoms in patients with symptomatic chronic HF, already on conventional treatment with ACE inhibitors, diuretics or digitalis.**
- **Patients with acute MI and mild to moderate symptoms of CHF.**

Acceptable indication:

- **Symptomatic heart failure due to diastolic dysfunction.**
- **To improve long term survival in patients with heart failure.**

Not proven:

- **Acute decompensated heart failure.**
- **CHF with pronounced hypotension and/ or bradycardia.**

ANTIARRHYTHMIC DRUGS

- **CAST---Post-MI LV dysfunction with complex ventricular arrhthmias. The mortality was increased in patients treated with encainide, flecainide, or moricizine.**
- **GESICA---CHF on convention treatment, randomized, open-labeled. Both sudden death and death due to CHF were reduced in amiodarone treated group (P=0.02).**
- **CAMIAT---Complex arrhythmia. The arrhythmic deaths but not overall mortality were reduced in amiodarone group.**
- **SWORD---Post-MI, LVEF$\leq$ 0.40. Prematurely discontinued for increased mortality in oral sotalol group (RR = 1.65; P=0.006).**

DOCUMENTED VALUE OF ANTIARRHYTHMIC THERAPY IN HEART FAILURE

Proven indication:

- **Nil**

Acceptable indication:

- **The use of amiodarone in patients with ventricular arrhythmias after MI.**
- **Beta-adrenergic blockade in patients with ischemic heart failure.**
- **Class I antiarrhythmic drugs in patients with symptomatic ventricular arrhythmias.**

Not proven:

- **Class I antiarrhythmic drugs in patients with asymptomatic ventricular arrhythmias.**
- **Class III antiarrhythmic drugs, besides amiodarone.**

PREVENTION OF CARDIOVASCULAR EVENTS AND DEATH WITH PRAVASTATIN---THE LIPID STUDY

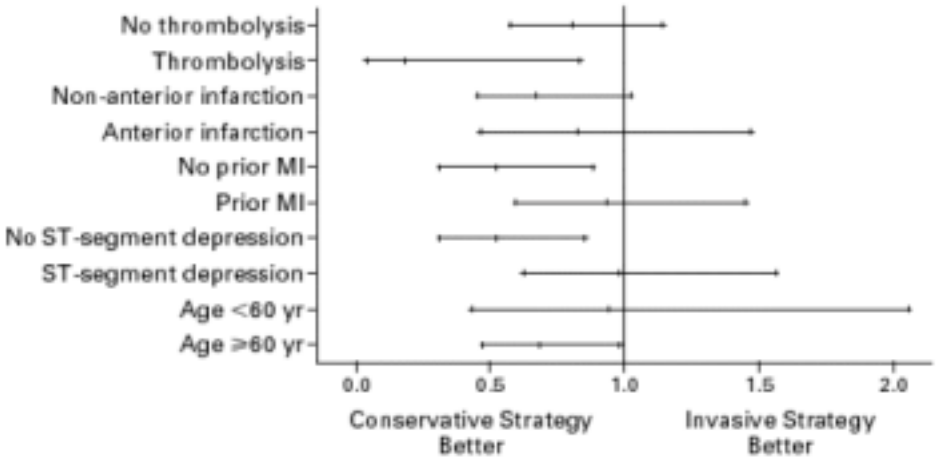
- **The effects of statin on cardiovascular mortality in CHD patients with cholesterol level 155~271 mg/dl.**
- **MI or unstable angina; randomized to pravastatin 40 mg QD v.s. placebo; F-U 6.1 yr.**
- **CHD death 6.4% v.s. 8.3% (RR 24%, 95% CI 12 ~35%, *P*<0.001).**
- **Overall mortality 11.0% v.s. 14.1% (RR 22%, 95% CI 13 ~31%, *P*<0.001).**
- **The incidence of all cardiovascular events was lower in pravastain group.**

EFFECTS OF PRAVASTATIN TREATMENT ONO DEATH DUE TO CORONOARY HEART DISEASE AND NONFATAL MYOCARDIAL INFARCTION

VARIABLE	TOTAL PATIENTS		PATIENTS WITH EVENT		REDUCTION IN RISK (95% CI)
	PLACEBO	PRAVASTATIN	PLACEBO	PRAVASTATIN	
	no.		no. (%)		%
Sex					
Female	760	756	104 (14)	86 (12)	11 (-18 to 33)
Male	3762	3750	611 (16)	487 (12)	26 (17 to 35)
Qualifying event					
Myocardial infarction	2875	2879	499 (17)	398 (14)	22 (11 to 32)
Hospitalization for unstable angina	1627	1633	216 (13)	159 (10)	29 (12 to 42)
Age					
<55 yr	1021	1065	132 (13)	96 (9)	32 (12 to 48)
55-64 yr	1708	1706	234 (14)	191 (11)	20 (3 to 34)
65-69 yr	1067	1031	203 (19)	151 (14)	29 (11 to 41)
≥70 yr	666	664	146 (21)	119 (18)	15 (-0 to 30)
Hypertension					
Yes	1691	1667	314 (17)	266 (14)	15 (0 to 29)
No	2809	2844	400 (15)	291 (11)	30 (19 to 40)
Diabetes					
Yes	386	396	88 (23)	76 (19)	19 (-10 to 41)
No	4116	4116	627 (15)	481 (12)	25 (15 to 33)
Smoking					
Current smoker	848	825	92 (21)	66 (16)	27 (0 to 47)
Former smoker	2814	2823	456 (16)	352 (12)	28 (17 to 37)
Non-smoker	1244	1164	167 (13)	139 (12)	11 (-12 to 29)
Total cholesterol					
<213 mg/dl	1094	1030	271 (14)	223 (12)	19 (4 to 32)
213-250 mg/dl	2069	2010	346 (17)	259 (13)	27 (15 to 38)
≥251 mg/dl	665	694	99 (15)	75 (12)	27 (1 to 46)
LDL cholesterol					
<135 mg/dl	1305	1232	185 (14)	163 (12)	16 (-4 to 32)
135-173 mg/dl	2338	2336	376 (16)	282 (12)	26 (14 to 37)
≥174 mg/dl	859	844	154 (18)	112 (13)	30 (10 to 45)
HDL cholesterol					
<39 mg/dl	2831	2880	467 (17)	368 (13)	24 (13 to 34)
≥39 mg/dl	1671	1622	228 (14)	169 (10)	25 (8 to 39)
Triglycerides					
<133 mg/dl	2022	1951	322 (16)	238 (12)	25 (12 to 37)
133-230 mg/dl	1661	1750	269 (15)	202 (12)	24 (9 to 37)
≥231 mg/dl	679	811	124 (18)	117 (14)	24 (2 to 41)

(LIPID) study *NEJM* 1998; 339:1349-57

HAZARD RATIOS FOR DEATH IN THE TWO STRATEGY GROUPS WITH STRATIFICATION ACCORDING TO FIVE PRESPECIFIED VARIABLES



William E. Boden, M.D. *NEJM* 1998;338:1785-92.

KEY RECOMMENDATIONS

Aim of treatment	Class of drug	Level of evidence
Symptomatic improvement of congestion, improvement of exercise capacity	Diuretics	Grade A
Improvement of symptoms, exercise capacity, and decreased hospitalization	Digitalis	Grade A
Improvement of survival, symptoms and exercise capacity, and reduced morbidity, in patients with asymptomatic and symptomatic left ventricular systolic dysfunction	Angiotensin converting enzyme inhibitors	Grade A
Symptomatic treatment of patients with heart failure who do not tolerate ACE inhibitors	Angiotensin II receptor antagonists	Grade A
Short-term improvement of symptoms in patients with severe congestive heart failure. Bridging towards more definitive surgical treatments, such as cardiac transplantation	Non-digitalis inotropic drugs	Grade A
Improvement of cardiac function and symptoms in patients with symptomatic chronic heart failure, already on conventional treatment	Beta-adrenergic blockers	Grade A
Improvement of survival	Beta-adrenergic blockers	Grade A
Prevention of arrhythmic deaths in patients with symptomatic ventricular arrhythmias	Amiodarone	Grade A