Drug Therapy for Prevention of Recurrent Myocardial Infarction

Menno E van der Elst, Henk Buurma, Marcel L Bouvy, and Anthonius de Boer

OBJECTIVE: To provide an evidence-based overview of drug treatment for long-term secondary prevention of myocardial infarction (MI).

DATA SOURCES: We conducted searches of MEDLINE (1966–August 2002), the Cochrane Controlled Trial Register, and the reference list of each identified study.

STUDY SELECTION/DATA EXTRACTION: Trials and meta-analyses were included using the following criteria: (1) randomized trials, (2) description of identification procedure, inclusion criteria, outcome measures, and statistical methods, (3) confirmed MIs, (4) treatment continued for at least 1 month, and (5) all-cause mortality as primary outcome; other events as secondary outcomes. All authors interpreted the results from trials that met the inclusion criteria.

DATA SYNTHESIS: In randomized clinical trials, low-dose aspirin, high-intensity oral anticoagulants, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and statins decreased the risk of mortality and reinfarction after MI. Randomized clinical trials using calcium-channel blockers, antiarrhythmics, and hormone replacement therapy did not show benefits in patients with prior MI. Effects of the combined use of aspirin or oral anticoagulants with β-blockers or ACE inhibitors plus statins must be derived from subgroup analysis of trials, but seem to be beneficial.

CONCLUSIONS: The use of at least aspirin or an oral anticoagulant, a β-blocker or an ACE inhibitor, plus a statin should be incorporated in the treatment routine. Clopidogrel treatment might be an alternative to aspirin. Standard addition of a β-blocker to ACE inhibitor–treated patients without reduced left-ventricular ejection fraction seems to be untimely.

KEY WORDS: myocardial infarction, secondary prevention.

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Myocardial infarction (MI) is one of the most prevalent causes of death worldwide.[1-3] Therefore, strategies to reduce mortality and cardiovascular morbidity in patients with MI have been studied extensively. Investigation of the in-hospital management of acute MI[4-7] has led to the American College of Cardiology/American Heart Association[8] and European Society of Cardiology[9] guidelines for the management of acute MI. Despite the progress in acute management, survivors of MI are still at increased risk of cardiovascular mortality and morbidity. In the first year after MI, the mortality rate is 10% and remains 5% for each subsequent year. These death rates are 6 times that in people of the same age without coronary artery disease.[10,11] Guidelines for secondary prevention of MI remain inconclusive concerning combination therapy.[8,9,12]

Given the importance of long-term secondary prevention of MI, the lack of clear recommendations concerning combination therapy in guidelines, and the widespread practice of it, an overview of evidence-based medicine after MI is timely. The objective of this article is to present an overview of pharmacologic strategies for long-term secondary prevention of MI that have been shown to be effective in lowering mortality and morbidity. Full names of clinical trials are shown in Appendix I.

Author information provided at the end of the text.

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Data Sources

MEDLINE searches were conducted (1966–August 2002) with search terms myocardial infarction, secondary prevention, aspirin, antiplatelet, beta-blocker, ACE inhibitor, anticoagulant, statin, calcium-channel blocker, anti-arrhythmic, hormone replacement, and estrogen; the Cochrane Controlled Trial Register was also used. We reviewed the reference list of each identified study. All studies on pharmacologic long-term secondary prevention of MI were identified. Trials and meta-analyses were included using the following criteria: (1) randomized trials, (2) description of identification procedure, inclusion criteria, outcome measures, and statistical methods, (3) all patients had to have a confirmed MI or a subgroup analysis of data on these patients was performed, (4) the treatment continued for at least 1 month, and (5) primary outcome had to be all-cause mortality; reinfarction, death from cardiac causes, stroke, or combined endpoints could be secondary outcomes. Both placebo-controlled trials and comparative studies were included to assess the effects of monotherapy and combination therapy and to differentiate specific pharmacologic regimens. All authors interpreted the results from individual trials that met the inclusion criteria. Baseline characteristics and exclusion criteria of meta-analyses on secondary prevention of MI are shown in Tables 1 and 2.[13-18] Table 3[19-58] presents the results of the clinical trials.

Aspirin and Other Antiplatelet Agents

The beneficial effects of antiplatelet agents including aspirin after MI have been well established by the Antiplatelet Trialists' Collaboration.[13] Their overview comprised data from 12 randomized clinical trials containing 20 006 patients with a history of MI (Table 1). Overall, antiplatelet agents reduced the risk of all-cause mortality and nonfatal reinfarction compared with placebo (Table 2).[13] Antiplatelet treatment also reduced the risk of vascular death (OR 0.85; 95% CI 0.75 to 0.95), nonfatal stroke (OR 0.61; 95% CI 0.39 to 0.83), and all vascular events (OR 0.75; 95% CI 0.67 to 0.83). Vascular deaths comprised deaths from a cardiac, cerebrovascular, venous thromboembolic, hemorrhagic, and other vascular or unknown causes. Vascular events included nonfatal MI, nonfatal stroke, and vascular deaths. Low aspirin doses (75–150 mg/d) seemed to be as effective as aspirin doses of 160–325 and 500–1500 mg/d.[13,59-61] It is unclear whether doses <75 mg/d are as effective as higher doses.[13] Bleeding complications were the main adverse effects of aspirin, with intracerebral hemorrhage as the most serious manifestation, followed by gastrointestinal bleeding. Gastrointestinal adverse effects seldom result in withdrawal from treatment, and fatalities are rare. Two meta-analyses on the adverse effects of aspirin indicated that gastrointestinal adverse effects of aspirin were probably dose related.[62,63] A third meta-analysis did not confirm this tendency, probably due to different definitions of adverse events.[64]

Dipyridamole, sulfinpyrazone, or suloctidil showed no advantages to aspirin.[13] The CAPRIE trial assessed the efficacy of clopidogrel compared with aspirin in 19 185 patients with MI, stroke, or peripheral artery disease.[23] Clopidogrel treatment for an average of 1.9 years lowered the risk of the combined endpoint of ischemic stroke, MI, or vascular death in all patients (RR 0.93; 95% CI 0.83 to

Table 1. Characteristics and Main Exclusion Criteria of Meta-Analyses on Secondary Prevention of MI

Reference	Treatment	Years of Trials Reviewed	Trials (n)	Pts. (n)	PC	Time Between Event and Inclusion	Duration of Follow-Up (mo)	Age (y)	Men	Main Exclusion Criteria
APT (2002)[13]	antiplatelet agents	1974–1995	12	20 006	+	1–5 d	12–72	30–80	++[a]	aspirin intolerance, history of GI bleeding, former cardiac surgery, severe hypertension
Anand et al. (1999)[14]	OAC	1960–1998	31	10 056	+	<90 d	3–24	61	++[a]	increased risk for bleeding, need for po anticoagulant treatment
Yusuf et al. (1985)[15]	β-blockers	1972–1985	23	20 312	+	days to months	1.5–48	<70	++[a]	AV block, bradycardia, hypotension, severe heart failure, COPD, age >70 y
Freemantle et al. (1999)[16]	β-blockers	1967–1997	31	24 974	+	days to months	1.5–48	<70	++[a]	AV block, bradycardia, hypotension, severe heart failure, COPD, age >70 y
Teo et al. (1993)[17]	class I anti-arrhythmics	1961–1992	51	23 229	+/–	hours to days	NA	NA	NA	AV block, hypotension, heart failure, ventricular arrhythmia
Amiodarone Trials Meta-Analysis Investigators (1997)[18]	class III antiarrhythmics (amiodarone)	1987–1997	8	5101	+	<60 d	1.34	61	81%	AV block, severe heart failure or angina, severe hypotension, thyroid dysfunction, bradycardia

AV = atrioventricular block; COPD = chronic obstructive pulmonary disease; GI = gastrointestinal; MI = myocardial infarction; NA = data not available; OAC = oral anticoagulants; PC = placebo-controlled.
[a]The majority of patients.

0.99), but failed to lower total mortality (Table 3). In a subgroup of MI (33% of all patients), clopidogrel treatment tended to lower both fatal and nonfatal MI. Data on total mortality for the subgroup of MI patients were absent. Severe gastrointestinal bleeding was more frequent in the aspirin group (RR 1.49; 95% CI 1.17 to 1.89).

Anticoagulants

The effects of oral anticoagulants after MI have been studied since the 1960s. Anand and Yusuf[14] classified 31 randomized trials by the intensity of oral anticoagulant treatment and the type of control treatment. They did not perform 1 meta-analysis including all trials, but performed separate meta-analyses for trials using high-intensity (international normalized ratio [INR] 2.8–4.8) and moderate-intensity (INR 2–3) therapy. Baseline characteristics and exclusion criteria are shown in Table 1. High-intensity treatment in 10 056 patients reduced total mortality, fatal and nonfatal reinfarctions (Table 2), stroke (OR 0.56; 95% CI 0.43 to 0.72), and the combined outcome of death, reinfarction, and stroke (OR 0.59; 95% CI 0.54 to 0.66). Moderate-intensity treatment in 1562 patients reduced fatal and nonfatal reinfarction and stroke (OR 0.47; 95% CI 0.27 to 0.85), but failed to lower total mortality.

The Sixty Plus Reinfarction study showed that discontinuation of high-intensity oral anticoagulation in patients on treatment for up to 6 years after their first MI was harmful.[65] No significant differences in total mortality or MI between oral anticoagulant treatment of any intensity and aspirin were noted by Anand and Yusuf.[14]

The meta-analysis of Anand and Yusuf[14] also revealed that bleeding complications occurred more frequently in oral anticoagulant–treated patients than in placebo-treated patients (OR 4.7; 95% CI 4.0 to 5.6 for total bleeds; OR 6.0; 95% CI 4.4 to 8.2 for major bleeds). The increase in bleeding complications was related to the intensity of oral anticoagulant treatment. Compared with aspirin, the OR was 2.4 (95% CI 1.6 to 3.6) for high- or moderate-intensity oral anticoagulant treatment.

β-Blockers

Hjalmarson et al.,[66] the APSI trial,[67] the BHAT trial,[68,69] the Norwegian Multicentre Study Group,[70] and the CAPRICORN[25] study all found reduced risk of all-cause mortality in patients treated with a β-blocker compared with placebo.[25,66-70] One meta-analysis of β-blocker trials was published in 1985[15] and another in 1999.[16] Baseline characteristics and exclusion criteria are shown in Table 1. The Yusuf et al.[15] meta-analysis of 23 trials involving 20 312 patients showed a reduction in both total mortality and nonfatal reinfarction when β-blocker treatment was compared with placebo. In the Freemantle et al.[16] meta-analysis, data on 4662 patients from 8 long-term trials were added to the data from the Yusuf et al. analysis. Again, β-blocker treatment was associated with a significant reduction in mortality (Table 2) when compared with placebo. The CAPRICORN trial differed from the other β-blocker trials, as only patients with reduced left-ventricular ejection fraction (LVEF) were included. Carvedilol treatment provided additional benefits to angiotensin-converting enzyme (ACE) inhibitor treatment in lowering mortality or nonfatal MI (Table 3).[25] Although individual trials only established the benefits of acebutolol, metoprolol, propranolol, carvedilol, and timolol, both meta-analyses indicated that benefits of β-blocker treatment are a class effect. Nevertheless, β-blockers with intrinsic sympathomimetic activity appear to be

Table 2. Results from Meta-Analyses on Secondary Prevention of MI

Reference	Treatment	Control	Sample Size (n)	Total Mortality		Nonfatal Reinfarction		All Reinfarctions	
				OR	95% CI	OR	95% CI	OR	95% CI
APT (2002)[13]	antiplatelet agents	placebo	20 006	0.88	0.78 to 0.98[a]	0.70	0.58 to 0.82[a]	NA	
Anand et al. (1999)[14]	OAC (INR 2.8–4.8)	placebo	10 056	0.78	0.69 to 0.87[a]	NA		0.58	0.52 to 0.66[a]
	OAC (INR 2–3)	placebo	1562	0.82	0.63 to 1.06	NA		0.48	0.36 to 0.63[a]
	OAC (INR 2–4.8)	aspirin	3457	0.93	0.69 to 1.28	NA		0.88	0.63 to 1.24
	OAC (INR 2–4.8) + aspirin	aspirin	480	0.74	NS	NA		0.55	NS
Yusuf et al. (1985)[15]	β-blockers	placebo	20 312	0.77	0.70 to 0.85[a]	0.74	0.66 to 0.83[a]	NA	
Freemantle et al. (1999)[16]	β-blockers	placebo	24 974	0.77	0.69 to 0.85[a]	NA		NA	
Teo et al. (1993)[17]	class I antiarrhythmics	placebo	23 229	1.14	1.01 to 1.28	NA		NA	
Amiodarone Trials Meta–Analysis Investigators (1997)[18]	class III antiarrythmics (amiodarone)	placebo	5101	0.92	0.78 to 1.08	NA		NA	

INR = international normalized ratio; MI = myocardial infarction; NA = data not available; OAC = oral anticoagulants.
[a]Statistically significant.

Table 3. Results from Randomized Clinical Trials on Secondary Prevention of MI

Reference	Treatment	Control	Sample Size (n)	Total Mortality	95% CI	Nonfatal Reinfarction	95% CI	All Reinfarctions	95% CI
APRICOT-2 (2002)[19]	aspirin + coumarin median INR 2.6)	aspirin	308	∞		NA		RR 0.28	0.08 to 0.98[a,b]
ASPECT-2 (2002)[20]	aspirin + coumadin mean INR 2.4	aspirin	999	RR 0.60	0.26 to 1.36	NA		RR 0.70	0.31 to 1.58
WARIS II (2002)[21]	aspirin + warfarin mean INR 2.2	aspirin	2414	RR 1.03	0.78 to 1.36[b]	NA		RR 0.56	0.41 to 0.78[a]
CHAMP (2002)[22]	aspirin + warfarin median INR 1.8	aspirin	5059	RR 0.98	0.87 to 1.11	NA		RR 1.02	0.88 to 1.17[b]
CAPRIE (1996)[23]	clopidogrel	aspirin	19 185	RR 0.98	0.87 to 1.10	RR 0.84	0.70 to 1.00[b]	RR 0.82	0.70 to 0.97[a,b]
CURE (2001)[24]	clopidogrel + aspirin	aspirin	12 562	RR 0.93	0.80 to 1.07[b]	NA		RR 0.77	0.67 to 0.89[a]
CAPRICORN (2001)[25]	β-blocker carvedilol	placebo	1959	RR 0.77	0.60 to 0.98[a]	RR 0.59	0.39 to 0.90	NA	
Nabel et al. (1991)[26]	ACE inhibitors captopril	placebo	38	OR 0.29	0.01 to 7.44	NA		NA	
PRACTICAL (1994)[27]	enalapril	placebo	225	OR 0.46	0.20 to 1.06	NA		NA	
AIRE (1993)[28]	ramipril	placebo	1986	RR 0.70	0.56 to 0.87[a]	NA		OR 0.93	0.66 to 1.32[a]
ECCE (1997)[29]	captopril	placebo	208	OR 0.71	0.14 to 3.67	NA		NA	
TRACE (1995)[30]	trandolapril	placebo	1749	OR 0.73	0.60 to 0.88[a]	NA		OR 0.86	0.66 to 1.13
SAVE (1992)[31]	captopril	placebo	2231	OR 0.79	0.64 to 0.96[a]	NA		OR 0.75	0.60 to 0.95[a]
HOPE (2000)[32]	ramipril	placebo	9297	OR 0.84	0.75 to 0.95[a]	NA		OR 0.80	0.70 to 0.90[a]
Søgaard et al. (1993)[33]	captopril	placebo	58	OR 1.00	0.10 to 10.20	NA		NA	
CONSENSUS II (1992)[34]	enalapril	placebo	6090	RR 1.10	0.93 to 1.29	RR 1.01	0.85 to 1.21	NA	
CATS (1994)[35]	captopril	placebo	298	OR 1.31	0.57 to 3.05	NA		OR 2.48	0.83 to 7.43[a]
Sharpe et al. (1991)[36]	captopril	placebo	100	OR 1.43	0.27 to 7.61	RR 0.24	0.03 to 2.18	NA	
EDEN (1997)[37]	enalapril	placebo	356	OR 1.48	0.06 to 36.56	NA		NA	
DAVIT II (1990)[38]	calcium-channel blockers verapamil	placebo	1775	RR 0.80	0.61 to 1.05	NA		RR 0.77	0.58 to 1.03[a,b]
DAVIT I (1984)[39]	verapamil	placebo	1436	OR 0.91	0.67 to 1.24	NA		NA	
DAVIT III (1997)[40]	verapamil	placebo	100	OR 0.96	0.06 to 15.79	NA		OR 0.14	0.01 to 1.02[a,b]
CRIS (1996)[41]		placebo	1073	RR 1.06	0.64 to 1.77	NA		RR 0.81	0.53 to 1.24[a]
DEFIANT II (1997)[42]	calcium-channel blockers dihydropyridines	placebo	542	OR 0.14	0.02 to 1.15	NA		OR 0.78	0.35 to 1.76[b]
SPRINT I (1988 and 1994)[43,44]		placebo	2276	OR 1.02	0.71 to 1.45	NA		NA	
SPRINT II (1988 and 1994)[43,45]		placebo	1358	RR 1.33	0.98 to 1.80	NA		NA	
Ishikawa et al. (1997)[46]		placebo	936	OR 1.36	0.88 to 2.10	OR 1.75	0.25 to 12.48	OR 2.02	0.73 to 5.62
MDPIT (1988)[47]	calcium-channel blockers diltiazem	placebo	2466	RR 1.02	0.82 to 1.27	RR 0.84	0.64 to 1.12	NA	
INTERCEPT (2000)[48]	diltiazem	placebo	874	OR 1.03	0.36 to 2.97	RR 0.79	0.41 to 1.50	NA	
Ishikawa et al. (1997)[46]	diltiazem	placebo	774	OR 1.14	0.65 to 2.01	OR 1.67	0.15 to 18.48	OR 3.42	1.18 to 9.88
4S (1994)[49]	statins simvastatin	placebo	4444	RR 0.70	0.58 to 0.85[a]	RR 0.63	0.54 to 0.73[a]	NA	
LIPID (1998)[50]	pravastatin	placebo	9014	RR 0.78	0.69 to 0.87[a]	NA		RR 0.71	0.62 to 0.82[a]
HPS (2002)[51]	simvastatin	placebo	20 536	RR 0.80	0.81 to 0.94[a]	RR 0.62	0.54 to 0.70	NA	
CARE (1996)[52]	pravastatin	placebo	4159	NA		RR 0.77	0.61 to 0.96	RR 0.63	0.38 to 1.05
MIRACL (2001)[53]	atorvastatin	placebo	3086	RR 0.94	0.67 to 1.31	RR 0.90	0.69 to 1.16	NA	
HERS (1998)[54]	hormone replacement therapy	placebo	2763	RR 1.08	0.84 to 1.38	RR 0.91	0.71 to 1.17	NA	
HERS II (2002)[55,56]		placebo	2321	RR 1.14	0.89 to 1.46	RR 0.98	0.69 to 1.40	NA	
HERS + HERS II (2002)[55,56]		placebo	2321	RR 1.10	0.92 to 1.31	RR 0.94	0.77 to 1.15	NA	
ERA (2000)[57]		placebo	309	RR 0.94	0.36 to 2.47[b]	RR 0.88	0.36 to 2.17[b]	NA	
WAVE (2002)[58]		placebo	423	RR 1.8	0.75 to 4.3	RR 1.01	0.26 to 4.00[b]	NA	

ACE = angiotensin-converting enzyme; INR = international normalized ratio; MI = myocardial infarction; NA = data not available.
[a]Statistically significant.
[b]RR or OR and 95% CI calculated based upon trial data.

associated with reduced benefits.[16] It is unclear whether cardioselectivity is a predictor of benefit, as both meta-analyses showed contradictory associations between cardioselectivity and outcome measures. Doses of β-blockers studied varied between trials. The most frequent adverse effects in the treatment groups were bradycardia and hypotension. Dizziness, depression, cold extremities, and fatigue were less common.[10,16] Adverse effects were significantly more common in treatment groups than in control groups.[68,71]

ACE Inhibitors

The effects of ACE inhibitors after MI have been investigated in a number of randomized clinical trials, but no complete meta-analysis is available. Eleven trials including 13 339 patients met the criteria.[26-31,33-37] The design, baseline characteristics of randomized patients, and the use of non-study drugs are shown in Table 4.[26-39,41-48,72] The results of these trials are summarized in Table 3. In the PRACTICAL,[27] AIRE,[28] HOPE,[32] TRACE,[30] and SAVE[31] studies, the use of enalapril, ramipril, trandolapril, or captopril caused a significant reduction in total mortality. Risk of cardiac death was significantly reduced in the PRACTICAL, HOPE, SAVE, and TRACE studies. The HOPE and SAVE studies also showed a significant reduction in reinfarctions in the ACE inhibitor group. The HOPE study revealed consistent benefits of ramipril on recurrent MI in both patients using non-study aspirin, β-blockers, or statins and patients not using other drugs.[73] In other, mostly small studies, the use of ACE inhibitors did not cause a statistically significant effect on total mortality or cardiac death.[26,29,33-37] Hypotension was reported as the most frequent adverse effect. Other adverse drug reactions, such as cough, rash, dizziness, and loss of taste, were reported less frequently.

Statins

The benefits of hydroxymethylglutaryl coenzyme A inhibitors (statins) in subjects with elevated cholesterol levels have been clearly established in the 4S study.[49] Baseline characteristics of randomized patients and exclusion criteria of long-term trials evaluating statins are shown in Table 5.[49-53] In 4444 patients with angina pectoris or previous MI, simvastatin treatment reduced the risk of all-cause mortality and reinfarction (Table 3). The results from the 4S study have been confirmed by the LIPID study.[50] The recently published Heart Protection Study included 20 536 patients with coronary disease and a broad range of cholesterol levels (total cholesterol >135 mg/dL) who were randomly allocated to receive simvastatin 40 mg/d or placebo.[51] Baseline characteristics of randomized patients and exclusion criteria are shown in Table 5. Simvastatin treatment reduced all-cause mortality, nonfatal MI, stroke, and the need for revascularization (Table 3). There was no excess of death from noncardiovascular causes or cancer in the treatment group. Event rates were similarly and significantly reduced among both patients with and without prior MI, patients with and without elevated cholesterol levels, men and women, and patients of all ages. The benefits of simvastatin were in addition to those of aspirin, β-blockers, and ACE inhibitors.

The CARE trial enrolled 4159 patients with a normal cholesterol level and prior MI.[52] Baseline characteristics and exclusion criteria are shown in Table 5. Pravastatin treatment for a mean period of 5 years reduced the combined endpoint of death from coronary heart disease and nonfatal MI (RR 0.76; 95% CI 0.64 to 0.91). The death rate from coronary heart disease was not reduced significantly (RR 0.80; 95% CI 0.61 to 1.05). Data on total mortality were absent. The MIRACL trial evaluated the short-term (16 wk) effects of atorvastatin in 3086 patients who had recently experienced unstable angina or MI.[53] Baseline characteristics and exclusion criteria are shown in Table 5. Atorvastatin treatment reduced the combined endpoint of death, nonfatal acute MI, cardiac arrest with successful resuscitation, and a recurrent ischemic event requiring hospitalization (RR 0.84; 95% CI 0.70 to 1.00). Atorvastatin treatment did not reduce the risk of each endpoint component except for recurrent ischemic events requiring hospitalization.

Calcium-Channel Blockers

The effects of calcium-channel blockers after MI have been investigated in many randomized clinical trials, and none of them, except for the DAVIT III pilot study,[40] showed any statistically significant benefit concerning total mortality, cardiac mortality, or reinfarction. No meta-analysis that met our inclusion criteria was available. Ten randomized clinical trials evaluated long-term calcium-channel blocker treatment in patients with MI.[38,39,41,42,44-48,72] The design of the randomized clinical trials and the baseline characteristics of randomized patients are shown in Table 4. Results of these trials are summarized in Table 3.

Antiarrhythmics

The preventive effects of antiarrhythmics on mortality and morbidity after MI have been investigated, as a substantial proportion of deaths after MI is due to ventricular fibrillation. Antiarrhythmics can be subdivided into 4 major classes. The effects of class II (β-blockers) and class IV antiarrhythmics (diltiazem, verapamil) have been discussed separately. A meta-analysis of class I antiarrhythmics reviewed 51 trials that included 23 229 patients with a history of confirmed or suspected MI (Table 1).[17] The risk of mortality was significantly increased in patients assigned to class I agents compared with placebo (Table 3). No differences were found between early and late intervention trials.

Meta-analysis of the class III antiarrhythmic amiodarone comprised 8 trials including 5101 patients with a history of MI.[18] Baseline characteristics and exclusion criteria of these patients are shown in Table 1. Amiodarone treatment tended to lower the risk of total mortality (Table 3).

Table 4. Design of Long-Term Trials Evaluating ACE Inhibitor or Calcium-Channel Blocker Treatment for Secondary Prevention of MI

	Design				Baseline Characteristics								Nonstudy Drugs at Entry (%)						
								Mean BP (mm Hg)											
	R, DB	PC	Days Between Event and Inclusion	Mean Follow-Up (mo)	Pts. (n)	Mean Age (y)	Men (%)	SBP	DBP	HR (beats/min)	LVEF (%)	Q wave (%)	Throm-bolytic	Aspirin	Anticoag-ulants	β-Blockers	CCBs	ACE Inhibitors	Exclusion Criteria
Nabel et al. (1991)[26]	+	+	<1	3	38	55	82	NA	NA	NA	50		100	NA	NA	34	29		
Sharpe et al. (1991)[36]	+	+	<2	3	100	58	83	119	77	NA	41		72	21	NA	55	50		
CATS (1994)[35]	+	+	<1	3	298	60	75	134	81	77	44		100	32	NA	13	0		
ECCE (1997)[29]	+	+	<3	3	208	60	80	NA	NA	NA	46		63	61	NA	54	15		
CONSENSUS II (1992)[34]	+	+	<1	6	6090	66	73	134	80	75	NA		56	NA	NA	67	23		
Søgaard (1993)[33]	+	+	7	6	58	59	91	112	NA	65	40		80	100	NA	73	22		
EDEN (1997)[37]	+	+	9	6	356	57	91	119	74	76	48		59	84	18	28	6		
PRACTICAL (1994)[27]	+	+	<1	12	225	64	78	134	NA	NA	45		72	NA	NA	17	17		
AIRE (1993)[28]	+	+	3–10	15	1986	65	74	NA	NA	NA	NA		58	78	NA	22	16		
TRACE (1995)[30]	+	+	3–7	24–50	1749	67	72	121	76	81	<35		45	91	NA	16	28		
SAVE (1992)[31]	+	+	3–16	42	2231	59	83	113	70	78	31		33	73	28	36	42		
HOPE (2000)[32]	+	+	NA	54	9297	66	73	139	79	69	>40		NA	76	NA	40	47		
DAVIT III pilot (1997)[72]	+	–	3–10	3	100	69	85	124	74	75		19	NA	91	NA			NA	AV and sinus block, CHF
DAVIT I (1984)[39]	+	+	<1	6	1436	<76	80	>90	NA	NA		NA	NA	NA	NA			NA	AV and sinus block, CHF
DAVIT II (1990)[38]	+	+	7–15	16	1775	<76	80	>90	NA	>45		83	NA	NA	NA			NA	AV and sinus block, CHF
CRIS (1996)[41]	+	+	7–21	24	1073	55.5	91	121	77	74		71	NA	NA	NA			NA	CHF
DEFIANT II (1997)[42]	+	+	7–10	6	542	58	NA	NA	NA	NA		85	NA	NA	NA	NA		NA	AV and sinus block
SPRINT II (1988 and 1994)[43,45]	+	+	<2	6	828	50–79	NA	>90	NA	NA		NA	NA	NA	NA	NA		NA	
SPRINT I (1988 and 1994)[43,44]	+	+	7–21	10	2276	55	NA	129	77	77		NA	NA	NA	NA	20		NA	AV block, CHF
Ishikawa et al. (1997)[46]	–	+	820	18	1115	60	79	127	75	66		79	NA	64	24	55		16	
INTERCEPT (2000)[48]	+	+	1.5–4	6	874	57	81	124	<120	71		76	65	100	6	13		7	AV and sinus block
MDPIT (1988)[47]	+	+	3–15	25	2466	58	80	NA	NA	<50		74	NA	38	4	54		NA	AV and sinus block

ACE = angiotensin-converting enzyme; AV = atrioventricular; BP = blood pressure; CCB = calcium-channel blocker; CHF = cardiac heart failure; DB = double-blind; DBP = diastolic BP; LVEF = left-ventricular ejection fraction; MI = myocardial infarction; NA = data not available; PC = placebo-controlled; R = randomized; SBP = systolic BP.

Hormone Replacement Therapy

HERS was the first randomized trial designed to investigate the effects of estrogen plus progestin therapy on cardiovascular events in postmenopausal women with established coronary disease.[54,55] Half the women included had a history of MI. The trial revealed no significant differences in total mortality, MI, or any other outcome between 1380 women treated with conjugated equine estrogens 0.625 mg plus medroxyprogesterone acetate 2.5 mg and 1383 women receiving placebo for an average of 4.1 years (Table 3).[54] Subsequent unblinded follow-up of 2321 women for 2.7 years in the HERS II trial also showed no decreases in the rates of MI or death from cardiac heart disease.[54,55] The first HERS trial found an excess of cardiac heart disease events in year 1 and fewer cardiac heart disease events in years 4 and 5. This time trend disappeared after the entire 6.8 years of follow-up of HERS plus HERS II. Venous thromboembolic events occurred more often in women on hormone replacement therapy (HR 2.08; 95% CI 1.12 to 3.40) during the entire follow-up of 6.8 years.[56]

The ERA study was designed to evaluate the effects of hormone replacement therapy on the progression of coronary arteriosclerosis.[57] Half the women included had a history of MI. Treatment with conjugated estrogen 0.625 mg or conjugated estrogen 0.625 mg plus medroxyprogesterone acetate 2.5 mg per day did not alter the rates of cardiovascular mortality, fatal or nonfatal MI, and all-cause mortality compared with placebo (Table 3). In the WAVE study, designed to determine whether hormone replacement therapy influenced the progression of coronary artery disease, the hormone treatment seemed to increase the risk of death (RR 1.8; 95% CI 0.75 to 4.3) or the combined outcome of death, nonfatal MI, and stroke (RR 1.5; 95% CI 0.80 to 2.9) in the treatment group.[58]

Multiple Drug Treatment

Most randomized clinical trials in secondary prevention of MI focused on monotherapy. The only trials that studied the effects of multiple drug treatment evaluated the combination of aspirin and oral anticoagulants.

The meta-analysis by Anand and Yusuf[14] did not reveal significant differences in total mortality or MI between the combination of oral anticoagulants plus aspirin versus aspirin alone (Table 3). Since publication of that meta-analysis, the WARIS II[21] and APRICOT-2[19] studies showed lower risk of reinfarction when aspirin plus oral anticoagulant treatment (INR 2.2 and 2.6, respectively) was compared with aspirin alone. The ASPECT-2 study demonstrated a favorable effect of the combination of aspirin plus Coumadin (INR 2.4) compared with aspirin alone on the composite endpoint of death, MI, and stroke (HR 0.50; 95% CI 0.27 to 0.92).[20] A beneficial effect on mortality has not been demonstrated in these trials.[19-21] The CHAMP study failed to reveal any clinical benefit of low-intensity warfarin therapy (INR 1.8) combined with low-dose aspirin beyond that of aspirin alone (Table 3).[22] The meta-analysis revealed that bleeding complications occurred more frequently in patients who received combination therapy.[14] These findings were confirmed by the ASPECT-2 study,[20] the WARIS II study,[21] and the APRICOT-2 study.[19] However, results from WARIS II indicated a small net benefit on the combined outcome.

To establish the effects of drug combinations other than aspirin and oral anticoagulants, subgroup analyses of trials that investigated a single agent are frequently used. Results from the CCP indicate that β-blocker treatment is beneficial for all patients, regardless of concomitant drug treatment.[74] Subgroup analysis of the first WARIS[75] and the first ASPECT[76] study revealed that oral anticoagulants lowered

Table 5. Characteristics and Main Exclusion Criteria of Long-Term Double-Blind, Placebo-Controlled Trials Evaluating Statin Treatment for Secondary Prevention of MI

Reference	Treatment	Pts. (n)	Mean LDL-C (mg/dL)	Mean TC (mg/d)	Days Between Event and Inclusion	Duration of Follow -Up (y)	Age		Men (%)	Main Exclusion Criteria
							Mean (y)	>70 y (%)		
4S (1994)[49]	simvastatin	4444	188	261	>180	5.4	35–70[a]		81	secondary hypercholesterolemia, unstable angina, recent MI, use of antiarrhythmics, CHF requiring diuretics
LIPID (1998)[50]	pravastatin	9014	150	218	420	6.1	62	15	83	TC >271 mg/dL, cardiac failure, age >75 y
HPS (2002)[51]	simvastatin	20 536	131	228		5		28	75	age >80 y, severe CHF, muscle disease, non–cardiovascular life-threatening conditions, severe psychiatric disorders
CARE (1996)[52]	pravastatin	4159	139	209	300	5	59		86	TC >240 mg/dL, LVEF <25%, symptomatic CHF, age >75 y, fasting glucose >220 mg/dL
MIRACL (2001)[53]	atorvastatin	3086	124	<270	2.6	0.3	65		65	TC >270 mg/dL, planned revascularization, recent cardiac surgery, severe CHF, insulin-dependent diabetes

CHF = cardiac heart failure; LDL-C = low-density lipoprotein cholesterol; LVEF = left-ventricular ejection fraction; MI = myocardial infarction; TC = total cholesterol.
[a]Range.

mortality both in the presence and absence of β-blocker treatment. In the CAPRICORN study, patients with LVEF <40% benefited from β-blocker treatment even when treated concomitantly with an ACE inhibitor.[25] Meta-analysis of β-blocker trials revealed no time trend in risk reduction of cardiovascular events and death among trials performed over several decades, although concomitant drug treatment changed markedly over time.[16]

Studies of ACE inhibitors were performed when the use of aspirin and β-blockers became established and was reported in most cases. In the HOPE trial, beneficial effects of ACE inhibitors were observed whether or not patients were taking aspirin, β-blockers, or lipid-lowering agents.[32] In a retrospective analysis of the SOLVD, HOPE, AIRE, TRACE, and SAVE trials, the benefits of ACE inhibitor treatment were apparent both in the presence and absence of aspirin, although there was a significantly smaller effect of ACE inhibitor treatment on reinfarction.[77] Retrospective analysis of the CONSENSUS II study revealed negative interaction between ACE inhibitors and aspirin,[78] although that interaction was absent in the CATS trial,[79] the JAMIS trial,[61] and the Co-operative Cardiovascular Project. The Heart Protection Study indicated that benefits of simvastatin treatment were largely independent of the use of aspirin, β-blockers, and ACE inhibitors.[51] The considerable use of aspirin in the CARE[52] and LIPID[50] trials (83% of all participants) might indicate that the beneficial effects of statin treatment are independent of aspirin use.

Discussion

Low-dose aspirin (75–150 mg/d), high-intensity oral anticoagulant treatment (INR 2.8–4.8), β-blockers, ACE inhibitors, and statins are effective in lowering the risk of mortality and reinfarction after MI; therefore, these agents are recommended under the conditions shown in Figure 1. These recommendations are based upon the present evidence, regardless of cost effectiveness. The minimal duration of treatment can be derived from results of randomized clinical trials. Therefore, treatment with aspirin, β-blockers, or ACE inhibitors should continue for at least 2–4 years,[13,16,28,30-32] and statin treatment should continue for at least 2–5 years.[51,52] As far as oral anticoagulant treatment is concerned, treatment should continue for at least 6 years, since results from the Sixty Plus Reinfarction study showed that discontinuation of oral anticoagulant treatment in patients receiving oral anticoagulants since their first MI 6 years ago was harmful.[65] As beneficial effects re-

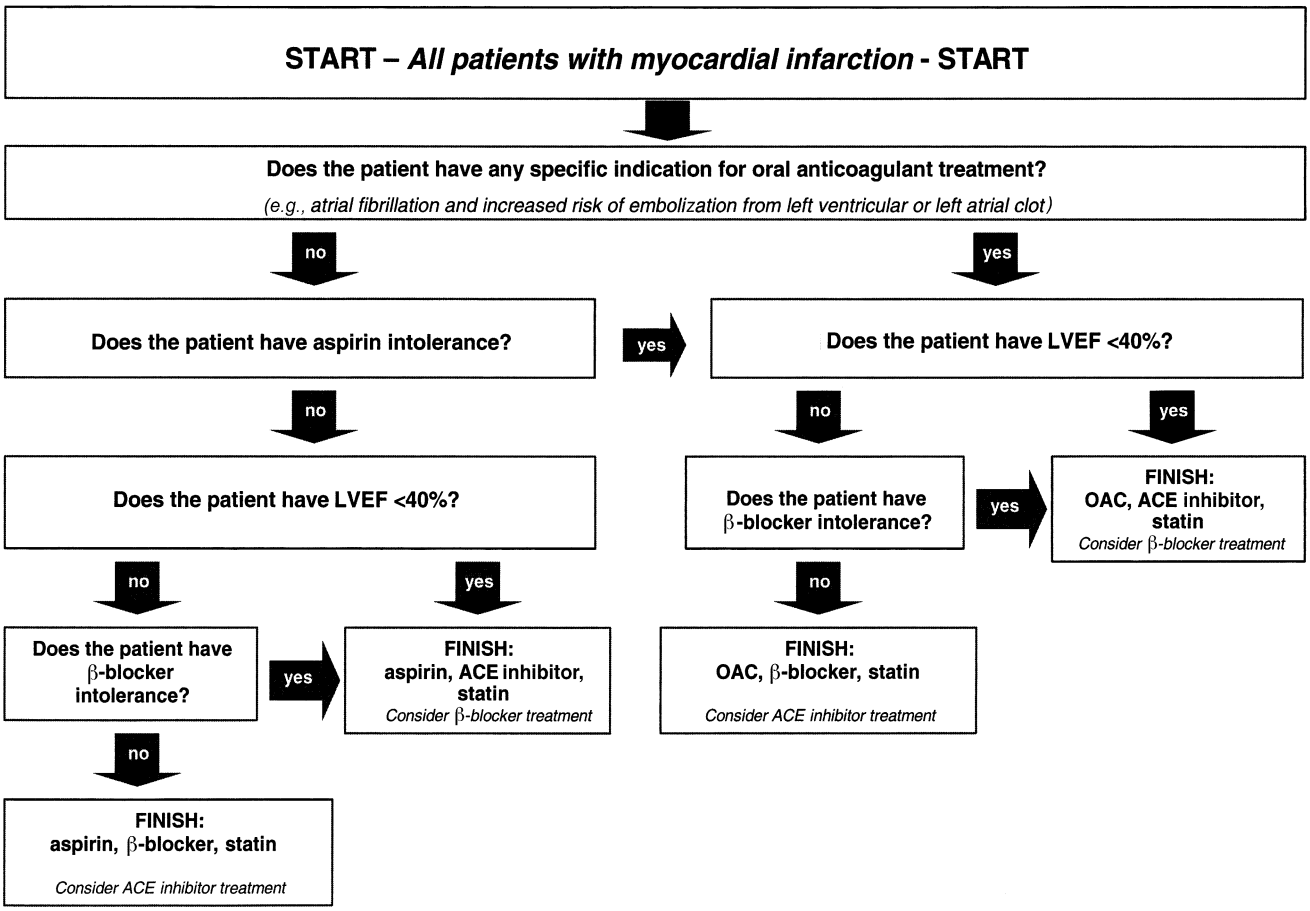

Figure 1. Flowchart for choosing drug treatment for secondary prevention of MI unless contraindications exist. ACE = angiotensin-converting enzyme; LVEF = left-ventricular ejection fraction; OAC = oral anticoagulant.

mained apparent during the entire follow-up period and nothing pointed to the disappearance of the established effects shortly after the end of follow-up, we recommend lifelong treatment.

The expected benefits of lifelong treatment have to be evaluated in observational studies to rule out the absence of benefits in the long term. Clopidogrel treatment could be an alternative or addition to aspirin, but its mortality-lowering properties have yet to be established. The use of ACE inhibitors in patients without reduced LVEF and the use of β-blockers in patients with reduced LVEF probably are beneficial. Addition of an ACE inhibitor to β-blocker treatment or a β-blocker to ACE inhibitor treatment could be considered. Calcium-channel blockers, antiarrhythmics, and hormone replacement therapy should not be recommended for lowering cardiovascular mortality or morbidity after MI, as treatment with these agents did not show benefit for secondary prevention.

Oral anticoagulant and clopidogrel treatment are second-choice agents after low-dose aspirin (75–150 mg/d). The evidence for benefits of clopidogrel above aspirin is poor, although the size of the CAPRIE trial should have had enough power to clearly demonstrate such benefits.[23] Oral anticoagulant treatment seems to provide no additional benefits in reducing MI and mortality compared with aspirin. Furthermore, oral anticoagulant treatment requires monitoring and increases the risk of bleeding complications. Therefore, oral anticoagulants are indicated for patients with other indications specific for this treatment, such as atrial fibrillation or increased risk of embolization from left ventricular or left atrial clot. Low- to medium-intensity oral anticoagulant treatment (INR 2–3) is not suitable after MI, as it did not reduce mortality. Combination therapy of aspirin and oral anticoagulants did not lower total mortality, although the CHAMP study should have had enough power to demonstrate differences in total mortality.[14,22] The effects of combination therapy on reinfarctions as shown in clinical trials are conflicting.[19-22] Therefore, recommendation of concomitant aspirin and oral anticoagulants is inappropriate.

The benefits of β-blockers seem to be a class effect, but most evidence is available for metoprolol, timolol, and propranolol. The dosage of metoprolol should be 100 mg twice daily, as this dose was administered in almost all trials on secondary prevention of MI.[16,71] Timolol should be dosed at 10 mg twice daily as applied in secondary prevention trials. The lack of cardioselectivity probably will prevent broad use of propranolol. In patients eligible for ACE inhibitor treatment, captopril, enalapril, ramipril, and trandolapril should be preferred, as these agents have been shown to be beneficial and the supposed class effect has not been clearly established. The benefits of ACE inhibitors in patients with normal LVEF are less clear, as the positive results from the HOPE study[32] were inconsistent with the negative results from the CONSENSUS II trial.[34] Possibly, the short duration of follow-up or the high rate of concomitant use of β-blockers contributed to the absence of benefits in the CONSENSUS II trial.[34] In patients with reduced LVEF, the addition of carvedilol to ACE inhibitor treatment seems to be appropriate as demonstrated in the CAPRICORN trial.[25]

In randomized clinical trials, long-term statin treatment after MI was beneficial, regardless of gender, age, cholesterol level, and additional cardioprotective treatment after MI. Significant results from the Heart Protection Study were supported by trends from the CARE trial.[51,52] The CARE trial probably lacked statistical significance due to the small number of patients included.[52] Benefits of statin treatment in patients aged ≥70 years have been established in the Heart Protection Study, but statin treatment might be beneficial in patients ≥74 years of age as well, according to the results from the observational Cardiovascular Health Study.[51,81] Results from short-term trials shortly after MI are promising yet inconclusive. Trends revealed by the short-term MIRACL study[53] were supported by observational studies. The RISK-HIA study,[82] a study by Bybee et al.,[83] and a study using data from the GUSTO IIb and PURSUIT trials[84] revealed that prescription of lipid-lowering drugs for patients with MI was associated with reduced short-term mortality of the same magnitude as β-blocker treatment.

Positive results from observational studies using hormone replacement therapy after MI were inconsistent with results from randomized trials that failed to show benefits of hormone replacement therapy.[54,55,57,58,85-88] In these studies, however, patients were not randomly assigned to receive hormone replacement therapy or placebo, so women with healthy behavior probably used postmenopausal hormones more often. A subsequent lower risk of cardiovascular disease in hormone-treated women could thus have been caused by selection bias. At present, hormone replacement therapy should not be offered for the prevention of cardiovascular disease, but could be offered to women with menopausal symptoms or osteoporosis.

Combination therapy is already widespread in daily practice, whereas conclusive evidence from randomized clinical trials that compare different strategies to reduce mortality and morbidity after MI is not yet available. Limited data, however, indicate that the beneficial effects of statins are apparent in the presence of aspirin, β-blockers, and/or ACE inhibitors,[51] as well as the effects of ACE inhibitors being apparent in the presence of aspirin, β-blockers, and/or statins.[77] The combination of oral anticoagulant and aspirin treatment lowered the risk for some combined endpoints but failed to lower total mortality. Given the increase of bleeding complications, combination therapy seems to provide too few benefits. Most data on combination therapy come from subgroup analyses. These results have to be interpreted with great care, as patients were randomly assigned to receive only 1 agent, whereas treatment with the other drug was not distributed by chance. Treatment with this not randomly assigned agent could be indicative for prognosis after MI. While awaiting randomized trials with combination therapy, use of results from subgroup analyses seems to be the best option to help practitioners decide on appropriate therapy, but awareness for bias is required.

Summary

Based upon the present evidence, healthcare professionals should do their utmost to incorporate the use of at least aspirin or an oral anticoagulant, a β-blocker, or an ACE inhibitor, along with a statin in treatment routine. Clopidogrel treatment could be an alternative to aspirin as soon as benefits of clopidogrel on lowering mortality have been established in patients with MI. Addition of a β-blocker to ACE inhibitor–treated patients without reduced LVEF can be considered, although the evidence for advantage over monotherapy is limited. The same applies to the addition of an ACE inhibitor to β-blocker–treated patients with reduced LVEF.

Menno E van der Elst PharmD, PhD Candidate, Utrecht Institute for Pharmaceutical Sciences, Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht University, Utrecht, Netherlands

Henk Buurma PharmD, Director, SIR Institute for Pharmacy Practice Research, Leiden, Netherlands

Marcel L Bouvy PhD PharmD, Senior Researcher, SIR Institute for Pharmacy Practice Research; Utrecht Institute for Pharmaceutical Sciences, Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht University

Anthonius de Boer MD PhD, Professor, Utrecht Institute for Pharmaceutical Sciences, Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht University

Reprints: Menno E van der Elst PharmD, Utrecht Institute for Pharmaceutical Sciences, Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht University, PO Box 80.082, 3508 TB, Utrecht, Netherlands, FAX 31 30 2539166, m.e.vanderelst@pharm.uu.nl

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EXTRACTO

PROPÓSITO: Proveer una revisión basada en evidencia de la terapia farmacológica para la prevención secundaria a largo plazo de infarto al miocardio.

FUENTES DE INFORMACIÓN: Se realizó una búsqueda en MEDLINE (1996 – agosto 2002 a través de Pubmed), Registro Cochrane de Estudios Controlados y lista de referencias de cada estudio identificado.

SELECCIÓN DE FUENTES DE INFORMACIÓN Y MÉTODOS DE EXTRACCIÓN DE INFORMACIÓN: Se incluyeron estudios y análisis meta utilizando los siguientes criterios: (1) estudios aleatorios, (2) descripción del procedimiento de identificación, criterios de inclusión, medidas de resultados, y métodos estadísticos, (3) infartos al miocardio confirmados, (4) tratamiento continuo al menos por 1 mes, y (5) toda causa de mortalidad como resultado primario y otros eventos como resultados secundarios. Todos los autores interpretaron los resultados de los estudios que cumplieron con los criterios de inclusión.

SÍNTESIS: Dosis bajas de aspirina, anticoagulación oral de intensidad alta, bloqueadores beta, inhibidores de la enzima convertidora de angiotensina (ECA), y estatinas disminuyeron el riesgo de mortalidad y reinfarto luego de un infarto al miocardio en estudios clínicos aleatorios. Los estudios clínicos aleatorios con bloqueadores de los canales de calcio, antiarrítmicos, y terapia de remplazo hormonal no demostraron beneficios en pacientes con infarto al miocardio previo. Los efectos del uso combinado de aspirina o anticoagulantes orales con bloqueadores beta o inhibidores de ECA conjuntamente con estatinas tienen que ser derivados de un análisis de subgrupo de los estudios. Sin embargo, estos efectos parecen ser beneficiosos.

CONCLUSIONES: El uso de por lo menos aspirina o un anticoagulante oral, un bloqueador beta o un inhibidor de ECA acompañados de una estatina debe ser incorporado en el tratamiento de rutina. El tratamiento con clopidogrel puede ser una alternativa a la aspirina. La adición estándar de un bloqueador-β a pacientes tratados con inhibidores de ECA sin fracción de eyección del ventrículo izquierdo reducida parece ser prematura.

Juan F Feliú

RÉSUMÉ

OBJECTIF: Revoir la thérapie fondée sur les preuves relativement à la prévention secondaire de l'infarctus du myocarde.

REVUE DE LITTÉRATURE: Une recherche informatisée sur la banque MEDLINE (1966 à août 2002) et la banque Cochrane Controlled Trial Register ainsi qu'une recherche à partir de la liste des références des études identifiées furent effectuées.

SÉLECTION DES ÉTUDES ET DE L'INFORMATION: Les études cliniques et les méta-analyses furent incluses selon les critères suivants: (1) étude randomisée, (2) description de la procédure d'identification, des critères d'inclusion, des mesures de l'effet, et des méthodes statistiques, (3) confirmation d'infarctus du myocarde, (4) le traitement devait continuer pour au moins 1 mois, et (5) l'effet primaire recherché était la mortalité toute cause confondue et les autres étaient secondaires. Les auteurs ont ensuite évalué les résultats des études qui ont satisfait les critères d'inclusion.

RÉSUMÉ: Dans les études randomisées, l'aspirine à faible dose, l'anticoagulothérapie à haute intensité, les β-bloqueurs, les inhibiteurs de l'enzyme de conversion de l'angiotensine (ECA), et les statines diminuent le risque de mortalité et de réinfarction après un infarctus du myocarde. Les études randomisées impliquant les antagonistes du calcium, les anti-arythmiques, et la thérapie hormonale de remplacement n'ont pas montré de bénéfices chez les patients souffrant d'un infarctus du myocarde. L'effet combiné de l'aspirine ou anticoagulation et β-bloqueur ou ECA associé aux statines doit être obtenu à partir de sous groupes d'études. Malgré cela, ces associations semblent être bénéfiques.

CONCLUSIONS: L'utilisation d'au moins l'aspirine ou anticoagulant oral, d'un β-bloqueur ou d'un inhibiteur d'ECA associé à une statine devrait faire partie intégrale d'un plan de traitement. Le clopidogrel peut être une alternative à l'aspirine. L'addition standard d'un β-bloqueur à un régime impliquant un inhibiteur d'ECA chez un patient sans défaillance ventriculaire gauche (fraction d'éjection) ne semble pas encore justifiée.

Marc M Perreault

Appendix I. Acronyms of Clinical Trials

4S	Scandinavian Simvastatin Survival Study
AIRE	Acute Infarction Ramipril Efficacy
APRICOT-2	Antithrombotics in the Prevention of Reocclusion in Coronary Thrombolysis
APSI	Acebutolol et Prevention Secondaire de l'Infarctus
APT	Anti-Platelet Trialists
ASPECT-2	Aspirin and Coumadin After Acute Coronary Syndromes
BHAT	Beta-Blocker Heart Attack Trial
CAPRICORN	Carvedilol Postinfarct Survival Controlled Evaluation
CAPRIE	Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events
CARE	Cholesterol and Recurrent Events
CATS	Captopril and Thrombolysis Study
CCP	Cooperative Cardiovascular Project
CHAMP	Combination Hemotherapy and Mortality Prevention
CONSENSUS II	Cooperative New Scandinavian Enalapril Survival Study II
CRIS	Calcium Antagonist Reinfarction Italian Study
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events
DAVIT	Danish Verapamil Infarction Trial
DEFIANT	Doppler flow and Echocardiography in Functional Cardiac Insufficiency: Assessment of Nisoldipine Therapy
ECCE	Effects of Captopril on Cardiopulmonary Exercise
EDEN	Enalapril in Ventricular Dysfunction After Myocardial Infarction
ERA	Estrogen Replacement and Atherosclerosis
GUSTO IIb	Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries–II
HERS	Heart and Estrogen/Progestin Replacement Study
HOPE	Heart Outcomes Prevention Evaluation
HPS	Heart Protection Study
INTERCEPT	Incomplete Infarction Trial of European Research Collaborators Evaluating Prognosis Post-Thrombolysis
JAMIS	Japanese Antiplatelets Myocardial Infarction Study
LIPID	Long-Term Intervention with Pravastatin in Ischemic Disease
MDPIT	Multicenter Diltiazem Post Infarction Trial
MIRACL	Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering
PRACTICAL	Comparison of Enalapril versus Captopril on Left Ventricular Function and Survival Three Months After Acute Myocardial Infarction
PURSUIT	Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin
RISK-HIA	Swedish Register of Cardiac Intensive Care
SAVE	Survival and Ventricular Enlargement
SOLVD	Studies of Left Ventricular Dysfunction
SPRINT	Secondary Prevention Reinfarction Israeli Nifedipine Trial
TRACE	Trandolapril Cardiac Evaluation
WARIS	Warfarin, Aspirin, Reinfarction Study
WAVE	Women's Angiographic Vitamin and Estrogen Trial