DRUG THERAPY OF ACUTE MYOCARDIAL INFARCTION

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September 29, 1994

In the classic paper by James B. Herrick (1912) describing the clinical presentation of a non-fatal myocardial infarction attributed to sudden obstruction of the coronary arteries he indicated his familiarity with an earlier publication by Obraztsov and Strazhesko (1910). The first case of acute myocardial infarction (AMI) whose findings were confirmed by autopsy was described as follows[1].

G.E. A 49 year old artillery man was admitted to the medical division of the Aleksandrovsky Hospital on December 5, 1899. For twelve days prior to admission, he had experienced substernal pain radiating to the throat, head and left arm. The attacks lasted 2-4 hours and after a brief pause would begin again. During the attacks he experienced shortness of breath and the inability to breath deeply. The chest pain was so severe that the intern on my service, who was young and inexperienced, in response to my question as to the patient's admitting diagnosis responded "rheumatism of the chest".

Objective findings: He was well nourished and well developed. There was moderate cyanosis of the mucous membranes. His facial expression revealed distress from the substernal pain which radiated to the neck and head. No vessel motion was visible in the neck. The respiratory and abdominal organs were without abnormalities. The cardiac impulse was not visible, but was weakly palpable in the fifth intercostal space in the left mammary line. The heart sounds were distant and there were no murmurs. Direct auscultation revealed presystolic splitting of the first sound. Pulse 90 and barely palpable. Rhythm regular. *At the initial examination the diagnosis of coronary thrombosis was made.* The patient died four days later on December 9, 1899.

Autopsy Findings: On cross section of the left ventricle its' entire thickness was of a muddy-gray yellowish color as seen with necrosis. These changes occurred in almost the entire wall of the left ventricle and septum. Near the origin of the right coronary artery there was a 1 cm long yellowish projection from the wall of the vessel producing some luminal narrowing. The changes in the left coronary were more severe. The left anterior descending coronary artery was occluded by grayish-red thrombus 1 cm long and 1 mm in diameter. The left circumflex was occluded by 3 cm long soft yellow thrombus.

Most MI's result from atherosclerosis of the coronary arteries generally with superimposed coronary thrombus. However coronary occlusion can occur in the absence of AMI when the collateral circulation is adequate[2] and AMI can also occur in the absence of coronary occlusion[3]. Most transmural MI's occur distal to a totally occluded coronary artery.

Drug therapies are aimed at (1) "reducing infarct size" by either increasing oxygen or nutrient supply (e.g., thrombolytic agents) or by reducing the need for nutrients or oxygen (e.g., beta blockers, nitrates, etc.); and (2) preventing sudden death (presumably

arrhythmic), non-sudden death (progressive cardiac dysfunction), and reinfarction.

Ultimately, **the most important determinant of prognosis following AMI is the cumulative amount of myocardial damage accrued.** Meta-analyses suggest certain common drug treatments favorably influence the course of AMI[4].

AMI : INFLUENCE OF DRUG TREATMENT ON MORTALITY

DRUG	MORTALITY
ACUTE	
THROMBOLYTIC AGENT	-25%
ASPIRIN	-21%
ANTICOAGULANTS	-22%
IV BETA-BLOCKERS	-13%
IV NITRATES	-35%
IV MAGNESIUM SULPHATE	-20%(?)
LIDOCAINE	+11%
CALCIUM ANTAGONISTS	+10%
LONG-TERM	
BETA-BLOCKERS	-22%
CALCIUM ANTAGONISTS	+6%
ANTI-PLATELET AGENTS	-11%
AFTERLOAD REDUCTION	-19%

Certain trends have occurred in the use of drug therapies over the last few years [5]. Between 1988 and 1990 the overall thrombolysis rate increased rapidly but stabilized at 19% between 1990 and 1992. Soon after t-PA was approved by the FDA in November 1987 it was used in 90% of patients receiving thrombolysis and streptokinase was used in only 10%. Since 1991 t-PA has been used in 60% of patients and streptokinase in almost 30%. Use of thrombolytic therapy has increased in the elderly (75-79 years) from 3% in 1988 to 11% in 1992. In the same years the use of calcium channel

blockers decreased from 63% to 47%, whereas the use of beta blockers increased from 29% to 38%. Even though virtually all patients are eligible to receive aspirin therapy in the setting of AMI, usage in 1987 was only 39% and in 1989 was 72% [6].

ASPIRIN.

ISIS-2 showed that administration of aspirin up to 24 hours after the onset of symptoms of acute suspected MI, in a dosage of 160 mg per day, reduced five-week vascular mortality to 9.4% compared with placebo (11.8%). In patients receiving both SK and aspirin therapy, five-week mortality was reduced to 5% compared with patients receiving neither therapy (13%), representing odds reductions of 23% and 42% respectively. This survival advantage persisted during two years of follow-up [7]. In AMI patients treated with thrombolysis aspirin also reduces recurrent myocardial ischemia and the likelihood of coronary reocclusion [8]. Aspirin, or other antiplatelet agents, started days, months, or years after MI reduce the risk of vascular death, non-fatal MI, and non-fatal strokes [9]. This benefit of aspirin (and antiplatelet treatment) observed both early and late after MI is consistent with the results of trials of patients with cerebrovascular diseases (22% risk reduction, $p < 0.001$) and unstable angina (36% risk reduction, $p < 0.002$). The data suggest that the use of aspirin alone is just as effective as using aspirin plus either dipyridamole or sulfinpyrazone. The benefits of aspirin appear to be similar in the trials at differing doses, i.e., 160 mg per day, 300 to 325 mg per day, or 900 to 1500 mg per day and, therefore, the dose of aspirin 160 mg per day, or on alternate days, is recommended for patients with AMI, starting early and continuing indefinitely.

PAIN RELIEF.

Pain relief is very important [10]. There is a relationship between the severity of chest pain and the heart rate-blood pressure product soon after arrival in hospital.With reduced sympathetic nervous system activity the major determinants of myocardial oxygen demand can also be reduced (Blood pressure and heart rate). Patients with more severe chest pain appear to have a higher hospital mortality, and an increased incidence of ventricular fibrillation and heart failure.

Morphine sulphate (or other narcotic analgesics) induce symptomatic hypotension in 2-3% of patients [11]. When this occurs the heart rate may be inappropriate for the degree of blood pressure fall i.e. heart rate decreases or fails to appropriately increase. Marginal decreases in pO2, and increases in pCO2 have also been described and respiratory failure can occur in approximately 1% of patients [10].
Intravenous beta-blockers also relieve pain within several minutes, and reduce the requirement for subsequent analgesics by approximately 30% [12]. This effect is most pronounced in patients with a high initial heart rate-blood pressure product [10]. Indeed

administration of beta blockers does not reduce the requirement for analgesics in patients with a low heart rate or low initial blood pressure.

Sublingual nitroglycerin will provide temporary pain relief but intravenous nitroglycerin has a prolonged effect [13].

Finally, thrombolytic therapy (rt-PA) has been demonstrated to reduce pain severity and duration as well as requirement for narcotics compared with placebo-treated patients. Again the beneficial effect on pain relief is most marked in patients with ST elevations on their initial cardiograms suggesting relief of ischemia is the mechanism[14].

THROMBOLYTIC AGENTS

Thrombolytic agents act by converting the pro enzyme plasminogen to the active enzyme plasmin, which lyses fibrin clot [15]. Plasminogen is a single-chain glycoprotein. Plasminogen is converted to plasmin by cleavage of the Arg-Val (residues 560-561) peptide bond. Plasmin, the active two-chain polypeptide, is a non-specific serine protease which is capable of breaking down fibrin as well as fibrinogen, and factors V and VIII. The plasmin(ogen) molecule has lysine binding sites, particularly in the homologous triple-loop structures "kringle regions" which bind to and degrade fibrin. In the circulation, the action of plasmin is rapidly neutralized by circulating plasmin inhibitors. Thrombolytic agents are plasminogen activators with the ability to activate plasminogen to plasmin, and result in fibrinolysis and varying degrees of depletion of circulating fibrinogen and factors V and VII [16].

Streptokinase (SK) is not a fibrinolytic agent itself. It combines with plasminogen to form an activator complex that combines with additional plasminogen and converts the latter into plasmin, which then lyses the fibrin in the thrombus. A systemic lytic state is produced since both circulating and fibrin-bound plasminogen are converted to plasmin. SK, a protein produced from ultrafiltrates of Group C streptococci, may be antigenic. Consequently, allergic or anaphylactic reactions can occur in 1% of patients receiving short-term high-dose therapy. SK is acted upon by plasmin inactivators; it has a plasma half-life of 10 to 18 minutes.

Tissue-type plasminogen activator (t-PA) is a naturally occurring protein produced by endothelial cells which has a much higher affinity for bound fibrin than for circulating plasminogen. The binding of t-PA to fibrin already in a thrombus causes local activation of plasminogen to plasmin. Recombinant t-PA (rt-PA) is produced in pharmacologic quantities by recombinant DNA technology. The plasma half-life of rt-PA is 5 to 10 minutes.

Anisoylated plasminogen-streptokinase activator complex (APSAC) is inert in serum since the active serine site is acylated. APSAC binds actively to fibrin, however, and, once bound, deacylation by hydrolysis commences, activation of APSAC occurs, and this

continues in a controlled fashion. Therefore, the activation and plasma clearance half-life of APSAC (70 minutes) are longer than those of SK, resulting in a more sustained fibrinolytic activity. APSAC is not fibrin specific.

When assessing the results of trials with thrombolytic agents, the primary end-points studied need to be reviewed critically. The common end-points include: (1) reperfusion (occlusion of the infarct-related coronary artery is documented angiographically prior to therapy and subsequent reperfusion is documented angiographically); (2) patency of coronary arteries (some time after therapy, patency of coronary arteries is documented; however, there is no proof of pre-treatment occlusion in such patients); and (3) mortality. The benefits of thrombolytic therapy seem related to "re-opening" the infarct-related artery". There may be both time-dependent and time-independent benefits. Early opening of an infarct related artery is likely to have the most impact on the limitation of infarct size whereas time-independent re-opening of an occluded artery may improve myocardial healing or remodeling, prevent infarct expansion and reduce aneurysm formation.

In major randomized trials of patients with suspected AMI, SK, t-PA, and APSAC have all been shown to reduce early mortality rates of patients compared to patients treated with placebo.
The Fibrinolytic Therapy Trialists collaborative Group [17] have analyzed 9 randomized trials of patients with suspected AMI with over 1000 patients [GISSI-1, ISAM, AIMS, ASSET, USIM, ISIS-3 ("uncertain indication" group), EMERAS AND LATE].

The nine trials included 58,600 patients examined during the first 5 weeks after AMI. There were 10.5% deaths, 1.0% strokes and 0.7% major non-cerebral bleeds.

It was found that

1. Fibrinolytic therapy was associated with an excess of deaths during days 0-1 (especially in the elderly and patients presenting more than 12h after symptom onset) but this was outweighed by a much larger benefit during days 2-35.

2. Benefit was observed amongst patients presenting with ST-segment elevation or LBBB.

3. Mortality reductions were greatest for patients presenting early.

4. Fibrinolytic therapy was associated with 0.4% extra strokes during days 0-1.

Neither the GISSI-2 or ISIS-3 trials of >60,000 patients found differences in mortality between SK, t-PA or anistreplase. In these trials the use of subcutaneous heparin (regimens of heparin 12,500

U per 12 hours) did not reduce mortality compared to the use of no heparin.

The GUSTO trial [18] was designed to see whether more aggressive regimens would achieve more rapid and effective infarct-artery patency (using an accelerated t-PA dosing regimen of intravenous administration of t-PA over 90 minutes - with two thirds of the dose given in the first 30 minutes), and whether combination thrombolytic therapy would be associated with lower rates of reocclusion. 41,021 patients presenting within 6 hours of the onset of at least 20 mins of chest pain and ≥ 1mm ST-elevation in two or more limb leads or ≥ 2mm ST-elevation in two or more contiguous precordial leads were enrolled from December 1990 until February 1993. The primary end point was 30 day mortality.

GUSTO TRIAL

Treatment	Number of Patients	30-day Mortality	CVA All types	Hemorrhagic Stroke
Accelerated t-PA with IV heparin	10,344	6.3%	1.6%	0.7%
t-PA and SK with IV heparin	10,328	7.0%	1.6%	0.9%
SK with subcutaneous heparin	9,796	7.2%	1.2%	0.5%
SK with IV heparin	10,377	7.4%	1.4%	0.5%

N Engl J Med 1993; 329:673-82.

The combined end point of death or disabling stroke was also significantly lower in the accelerated t-PA group than in the pooled SK groups (6.9% versus 7.8%; $P < 0.001$). The GUSTO study confirms that t-PA is slightly more effective than SK in treating patients with AMI.

The GUSTO angiographic study (2431 patients) supported the hypothesis that more rapid and complete restoration of coronary flow through the infarct-related artery results in improved ventricular performance and lower mortality among patients with AMI 19.

GUSTO TRIAL ANGIOGRAPHY

Treatment (2431 patients)	IRA 90' Patency	IRA Normal Flow	IRA 180' Patency	Mortality 30 days
Accelerated t-PA with IV heparin	**81%**	54%	**76%**	5.3%
t-PA and SK with IV heparin	**73%**	38%	**85%**	7.8%
SK with subcutaneous heparin	**54%**	29%	**73%**	6.5%
SK with IV heparin	**60%**	32%	**74%**	7.5%

N Engl J Med 1993; 329:1615-22.

GUSTO TRIAL ANGIOGRAPHY

Flow in IRA (TIMI Grade)	Mortality 30 days	LVEF 90 mins	LVEF 5-7 days
Grade 0 = Absent antegrade flow	**8.9%**	55%	56%
Grade 1 = Incomplete distal filling		55%	54%
Grade 2 = Filling with washout delay	**5.7%**	56%	56%
Grade 3 = Normal Flow		62%	61%

N Engl J Med 1993; 329:1615-22

It is noteworthy that the 30-day mortality was low (6.3%) compared with the mortality of 10.7% in the GISSI-1 Trial (1986). The GUSTO Angiographic Substudy confirms the open infarct-related artery theory (early reperfusion of the infarct-related coronary artery results in myocardial salvage, which preserves ventricular function and such preservation in turn is responsible for improved survival). The study re-emphasizes the importance of early

reperfusion. However, even with the most effective regimen (accelerated t-PA, aspirin and intravenous heparin) 46% of the patients in the GUSTO Angiographic Study did not have full patency at 90 minutes.

According to data from a national registry 39% of AMI patients were treated with thrombolytic therapy [20]. Patients are often excluded because they do not meet the criteria for age, chest-pain duration, and a qualifying electrocardiogram such as used in major trials [12]. Furthermore, of those patients receiving thrombolytic agents very few are treated within the first hour (TIMI-II 3%, GUSTO 2.6%, GISSI-1 10.9%). Late arrival at hospital is a frequently cited reason for not giving a thrombolytic drug [22].

Delays can be attributed to:

1) Patient/by-stander factors: The factors that keep the patient from seeking immediate medical care through the emergency response system.

2) Pre-hospital delays: Those that occur from the time the patient decided to seek medical attention by accessing emergency medical services until arrival at a hospital emergency department.

3) Hospital factors: Those delaying care (specifically reperfusion therapy) once the patient has arrived at the emergency department.

There is a dramatic relationship between the time of symptom onset, the time of reopening of an occluded coronary artery and benefit of thrombolytic therapy. The time to reperfusion versus benefit curve is steep in the first 1-2 hours but then levels off and reaches a plateau [23]. The greatest reduction in mortality occurs among patients treated early with thrombolytic therapy, especially those treated within an hour of the onset of symptoms. Nevertheless, patients who are treated between 1 and 12 hours also have lower mortality than control patients. Available evidence suggests that thrombolytic drug treatment reduces AMI mortality if administered in the first 12 hours after symptom onset.

The angiographic sub-study of 2,431 GUSTO patients corroborated the findings of animal studies suggesting early patency resulting in myocardial salvage is the key benefit of thrombolytic therapy. In GUSTO preserved left ventricular function was associated with significantly lower mortality and both 24-hour and 30-day endpoints were related to angiographic patency at 90 minutes [19]. In most studies improvements in left ventricular function have been small, although significant, but the associated mortality reduction has been substantial in the treated groups [16]. In clinical trials of thrombolytic agents left ventricular ejection fraction may be an insensitive endpoint for a number of reasons:- Measurements are not available in many patients who die early; a substantial number of surviving patients do not have the measurement performed; survivors with significantly impaired left ventricular function who might

have died had they not been treated with a thrombolytic agent contribute to a lower average ejection fraction in the treated group as compared to the control group; the phenomenon of myocardial "stunning".

Myocardial stunning refers to prolonged, but temporary, post-ischemic ventricular dysfunction without myocyte necrosis. Typically, a brief period of acute ischemia followed by restoration of coronary perfusion results in prolonged contractile dysfunction. The features of this are that abnormal systolic and diastolic function can be observed, the myocardium is viable, the myocardium exhibits contractile reserve and there is absence of myocyte necrosis with routine microscopy (and subtle changes noted with electron microscopy). Abnormalities have been described in high energy phosphate metabolism. This phenomenon has been demonstrated to be relevant in patients with AMI [24].

Even in the early, major randomized trials evaluating whether coronary angioplasty should follow the use of lytic therapy in patients with AMI patency of the infarct-related vessel at 90 minutes after administration of lytic therapy (administered 3 hours after the onset of symptoms) was an important determinant of in-hospital mortality [25]. The TAMI investigators found hospital mortality was 7% for patients with AMI eligible for thrombolytic therapy; 5.2% for patients with a patent infarct-related coronary vessel 90 minutes after lytic therapy and 10.4% for those with an occluded infarct-related artery. Similar observations have been made in subsequent trials.

Certain angiographic observations made approximately one month after AMI are also determinants of long term prognosis. They are:

1) Left ventricular ejection fraction.

2) Left ventricular end-systolic volume index.

3) Patency of the infarct-related artery.

The area of supply of the infarct-related artery and ventricular dysfunction are independent, related factors prognostic determinants of outcome [26]. That is, patency of the infarct-related artery is an important determinant of prognosis if it supplies more than 25% of the left ventricle when the left ventricular ejection fraction is normal (LVEF $\geq$ 50%). A smaller area of supply of the infarct-related artery is an important determinant of adverse outcome if the LVEF is $<$ 50%.

Thrombolytic therapy and vessel patency also have important independent. but complementary beneficial effects on remodeling of the left ventricle [27]. After AMI there are changes in ventricular architecture in both non-infarcted and infarcted zones of the heart. Infarct expansion occurs (almost exclusively in patients with large transmural infarcts) because of disruption of

normal myofibrils which leads to thinning and dilation of the necrotic zone of myocardium [28].
Left ventricular end-systolic volume has been shown to be a major determinant of survival after MI [29] and is also a sensitive index of change in ventricular geometry even as early as Day 1 after an AMI [27]. Patients treated with thrombolytic therapy have smaller left ventricular end systolic volumes and higher ejection fractions as early as Day 1 after AMI. Thrombolysis even has a beneficial effect on left ventricular size in patients who subsequently develop an occluded infarct-related artery. Patency of the infarct-related artery approximately one month after infarction influences subsequent dilation of the heart.

HEPARIN

The use of full dose heparin therapy as an adjunct to thrombolytic therapy, especially with t-PA, seems important. The European Cooperative Study Group (ECSG) showed a correlation between the level of heparinization and patency of the infarct-related artery after treatment of AMI with alteplase (rt-PA) [30].

ECSG
281 MI pts treated with rt-PA and ASA
Randomized to fixed dose Heparin or Placebo. .

		6 day IRA Patency
PLACEBO		
N=132		71 %
HEPARIN		
N=149	All patients	80%
N=48	**Optimal APTT** (>2x Baseline)	90%
N=40	**Suboptimal APTT** (1.3 to 2x Baseline)	80%
N=61	**Inadequate APTT** (< 1.3x Baseline)	72%
	Arnout J et al,	JACC1992;20:513

There is substantial evidence that heparin dosage nomograms which are not based on the patients weight can lead to suboptimal heparinization [31].

APTT VALUES WITH DIFFERENT HEPARIN NOMOGRAMS

	Standard Care	Weight Based	P Value
Within first 24 hrs			
Above therapeutic	7 %	27 %	< 0.001
Therapeutic	35 %	57 %	< 0.001
Subtherapeutic	58 %	15 %	< 0.001
Within first 48 hrs			
Above therapeutic	8 %	18 %	< 0.001
Therapeutic	44 %	65 %	< 0.001
Subtherapeutic	49 %	18 %	< 0.001

Ann Int Med 1993; 119 : 874-881.

TYPICAL DOSES USING HEPARIN NOMOGRAMS

	Standard Care	Weight Based	85 kg
Initial Dose	5000u bolus +1000 u/hr	80u/kg bolus, then 18u/kg/hr	6800u bolus +1530 u/hr
APTT < 35s (<1.2X control)	5000u bolus +200 u/hr	80u/kg bolus, then 4u/kg/hr	6800u bolus +340u/hr
APTT 35 to 45s (1.2-1.5X control)	2500u bolus +100 u/hr	40/kg bolus, then 2/kg/hr	3400u bolus +170u/hr
APTT 46 to 70s (1.5-2.3 X control)	No change	No change	No change
APTT 71 to 90s (2.3 -3 X control)	Decrease rate by 100u /hr	Decrease rate by 2u /kg/hr	Decrease rate by 170u/hr
APTT >90s (>3 X control)	Hold infusion 1hr then decrease rate by 200u /hr.	Hold infusion 1hr then decrease rate by 3u /kg/hr	Hold infusion 1hr then decrease rate by 255u /hr

Ann Int Med 1993; 119 : 874-881.

The ACC/AHA Task Force [32] suggests a number of management strategies using anticoagulants (and platelet inhibitory agents) in patients with AMI.

1. The use of low-dose subcutaneous heparin is recommended in all patients for the prevention of deep venous thrombosis and pulmonary embolism early after the onset of acute infarction when the patient is relatively immobile.

2. Anticoagulants are also used to prevent arterial embolism. The formation of LV mural thrombus is most common after Q-wave anterior myocardial infarction and is less common after inferior infarction or non-Q wave infarction. The incidence of mural thrombus formation after anterior infarction is reported to be approximately 30%. Severe depression of LV ejection fraction is not a prerequisite for thrombus formation, however an apical wall motion abnormally is almost always present. While the incidence of systemic embolization from mural thrombus in the ventricle is low, the result can be devastating. Embolic events tend to occur within 2-3 months after acute infarction, and especially within the first 10 days. Thrombus that has a protruding configuration or is freely mobile is more likely to embolize.

OTHER ANTIPLATELET AGENTS AND ANTITHROMBIN AGENTS

There are several direct thrombin inhibitors under investigation in patients with unstable angina and AMI including hirudin, hirulog and argatroban.The most widely studied is hirudin the naturally occurring anticoagulant secreted by the salivary glands of the leech Hirudo medicinalis. It exerts its action by directly binding to the active catalytic site of thrombin and can inhibit clot bound thrombin [33].It is better able to inhibit thrombin mediated platelet activation than heparin [34]. Because hirudin is not inhibited by activated platelets or other proteins that are known to neutralise heparin it may result in greater consistency of anticoagulation [35,36]. Unlike heparin it does not require a cofactor(antithrombin), and does not appear to cause thrombocytopenia. Recombinant desulhatohirudin (r-hirudin) is being used extensively in clinical trials since it has been shown experimentally to enhance thrombolysis and reduce reocclusion [37]. In the pilot dose-ranging TIMI 5 Trial patients with AMI were given aspirin, front-loaded tissue-type plasminogen activator and either heparin or hirudin [38]. The primary endpoint (TIMI grade 3 flow in the infarct related artery at 90 minutes and 18-36 hours without death or reinfarction) was achieved in 62% of 157 evaluable hirudin treated patients and 49% of 79% evaluable heparin treated patients(p=0.07).There was decreased late occlusion and improved late reperfusion.There have

been concerns with bleeding and dosage adjustments have been required in ongoing trials.

Antiplatelet agents under study (particularly after coronary angioplasty) include c7E3 Fab a monoclonal-antibody FAB fragment directed against the integrin platelet glycoprotein IIb/IIIa receptor - the final common pathway of platelet aggregation [39]. This binds circulating adhesive macromolecules, especially fibrinogen and von Willebrand factor, which can then cross-link receptors on adjacent platelets leading to aggregation. Pilot studies in patients suggest 7E3, a mouse monoclonal antibody, inhibited platelet aggregation by more than 80% [40]. In patients a bolus of c7E3 Fab reduced ischemic complications in high-risk angioplasty but increased the risk of bleeding [41].

INTRAVENOUS BETA BLOCKERS.

Experimental studies have demonstrated that beta blockers may lead to a reduction in infarct size, decrease myocardial wall stress, and prevent cardiac rupture in addition to elevating the threshold for ventricular fibrillation. These studies have led to the use of early beta blockers following AMI and the expectation that early mortality rates, reinfarction rates, and the onset of ventricular fibrillation following may be diminished.

Pooling the results of over 25 available randomized trials suggests that the use of acute beta blocker following infarction reduces mortality by 13% in the first week and that the benefit is most marked in the first 48 hours. Hospital rates of non-fatal reinfarction and non-fatal cardiac arrests are reduced by about 19% and 16% respectively. Analyses of the causes of deaths in ISIS-1 suggested that the reduction in mortality was due chiefly to the prevention of cardiac rupture and ventricular fibrillation.

In the TIMI-II trial, 3,262 patients were treated with intravenous rt-PA within four hours of the onset of chest pain thought to be caused by AMI (as well as being given therapy with aspirin, heparin, and lidocaine). Patients were randomized to an early invasive strategy (coronary angiography between 18 and 48 hours after the onset of chest pain with PTCA if arteriography demonstrated suitable anatomy) and a conservative strategy (angiography and PTCA were performed for unstable angina or a positive exercise test). A subgroup of 1,434 patients were eligible for short-term intravenous beta blockade and were randomly assigned to receive either immediate beta blocker (15 mg of intravenous metoprolol followed by oral metoprolol) or deferred beta blocker (oral metoprolol begun on Day 6) [42].

TIMI IIB : BETA-BLOCKADE POST AMI

IMMEDIATE VERSUS DEFERRED

EVENTS AT 6 DAYS	IMMEDIATE Rx N=720	DEFERRED Rx N=714	P VALUE
Death	2.4%	2.4%	NS
Non-fatal reinfarction	2.4%	4.7%	p=0.02
Fatal or non-fatal reinfarction	2.7%	5.1%	p=0.02
Recurrent chest pain	18.8%	24.1%	p=0.02

Retrospective analyses of the Miami trial patients suggested that the highest risk patients might benefit from intravenous beta blockade.

MIAMI TRIAL

RETROSPECTIVE ANALYSIS OF MORTALITY

PREDICTORS		**PLACEBO**	**METOPROLOL**
- Age > 60			
- Abnormal ECG			
- Prior MI	< 3 PREDICTORS	55/1874	62/1866
- Angina		**= 2.9%**	**= 3.3%**
- CHF			
- Hypertension	> 2 PREDICTORS	87/1027	61/1011
- Diabetes		**= 8.4%**	**= 6.0%***
- Prior diuretics			
- Prior digitalis			

Eur Heart J 6:199,1985.

The ACC/AHA Task Force recommended early intravenous blockade for (a) patients with reflex tachycardia or systolic hypertension (including those receiving thrombolytic therapy); (b) patients with recurrent ischemic pain; (c) tachyarrhythmias with a rapid ventricular response, e.g., atrial fibrillation. Contraindications include a heart rate of less than 50 to 60 bpm, a systolic blood pressure less than 100 mm Hg, LV failure or rales greater than 10 cm from the lung bases, AV conduction abnormalities, severe chronic obstructive pulmonary disease (and asthma or wheeze), and peripheral hypoperfusion.

INTRAVENOUS NITROGLYCERIN.

The biochemical mechanism of organic nitrate action has been largely defined [43]. The final pathway for vascular dilation (of veins and arteries) occurs when the enzyme guanylate cyclase (GC) is activated and initiates the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). Since nitric oxide (NO) actively stimulates guanylate cyclase it was thought logical that organic nitrates might act similarly through the production of NO. It is now believed that organic nitrate action does result from the metabolic conversion to NO in the vascular smooth muscle cell [44]. Organic nitrates interact with sulfhydryl groups to produce NO or S-nitrosothiols which then activate guanylate cyclase. In addition, activation of GC increases platelet cGMP; leading to inhibition of platelet aggregation responses [45].
Intravenous nitrates reduce afterload and preload, and thus reduce oxygen demand and myocardial wall stress. In addition, they may increase blood supply to the myocardium by relieving coronary vasoconstriction. It has been suggested that the use of intravenous nitroglycerin following AMI results in a 35% mortality reduction with the greatest benefit in the first week after infarction [4].

Data are inadequate to recommend the use of nitroglycerin in all patients with AMI but clearly it is useful therapy for patients with post myocardial infarction angina. It should be used with extreme caution in patients with right ventricular infarction who may be particularly preload dependent [46].

Tolerance develops quickly [47-49]. Tolerance is the attenuation, or loss, of one or several of the effects of organic nitrates administered chronically e.g. diminished hypotensive effect, diminished headache, increase in frequency of myocardial ischemia "noisy" or "silent". All organic nitrate regimens using continuous delivery systems (transdermal nitroglycerin patches or continuous intravenous infusions of nitroglycerin), frequent doses of long-acting nitrates (3 or more times daily) or long acting (sustained release) preparations will result in partial or complete nitrate tolerance.

There are several proposed mechanisms:

Neuro hormonal activation: In normal volunteers continuous administration of organic nitrates has been associated with increases in plasma norepinephrine, plasma renin activity and arginine vasopressin [50]. These hormonal changes are accompanied by plasma volume expansion and sodium retention [51].

Sulfhydryl group depletion: To activate organic nitrates the presence of cysteine is required. In some circumstances the development of tolerance has been associated with depletion of intra-cellular sulfhydryl co-factors (cysteine) required in the metabolic conversion of nitroglycerin to NO or S-nitrosothiols. In humans the administration of N-acetylcysteine and methionine (which are converted into cysteine) have reversed tolerance [52,53].

Plasma volume expansion: Prolonged administration of nitroglycerin by the intravenous route [54] in patients with AMI and in normal volunteers [50] leads to a decrease in hematocrit, sodium retention and plasma volume expansion. It is possible that tolerance is partially related to an increase in intra-vascular volume resulting from the activation of the renin-angiotensin system. This may limit the ability of the drug to decrease filling pressures. In normal volunteers diuretic therapy does not prevent the plasma volume expansion seen during continuous therapy with nitroglycerin [55]. This suggests that the plasma volume expansion is caused primarily by a shift from the extravascular fluid compartment to the intravascular space following continuous therapy with organic nitrates [56].

MAGNESIUM.

Reasons to consider Magnesium therapy in AMI

IV magnesium salts appear to reduce mortality.

Magnesium protects myocardium from experimental ischemia-reperfusion injury perhaps by inhibiting mitochondrial calcium overload and preserving intracellular ATP and creatine phosphate reserves.

Magnesium causes coronary and systemic vasodilation, platelet inhibition and antiarrhythmic effects..

A retrospective meta-analysis of seven, blinded, placebo controlled trials assessed the benefits of magnesium infusions given within 12 hours of suspected AMI and continued for 24 to 48 hours. In the control group of 644 there were 53 deaths (8.2%) and in the treated group of 657 there were 25 deaths (3.8%) [57]. The improved survival appeared to result from arrhythmia suppression. Two major prospective trials address magnesium therapy [58,59].

LIMIT-2

2316 pts within 24 hours of suspected AMI
given Saline or IV $MgSO_4$

	Saline	**$MgSO_4$**		**RR**
LVEF in CCU	14.9%	11.2%	2p =0.009	25%
28-day Mortality	10.3%	7.8%	2p = 0.04	24%
2.7-year Mortality	13.2%	11.4%	p = 0.03	16%

Lancet 1992; 339: 1553-58

Lancet 1994; 343: 816-19

The ISIS-4 investigators randomized 58,000 patients with signs or symptoms suggestive of suspected or definite MI (with or without ECG changes) who presented within 24 hours of the onset of symptoms. The investigators utilized a 2 x 2 x 2 factorial design in which each of the study treatments was compared with a placebo or, in the case of magnesium, open control (the transient flushings associated with magnesium infusion precluded effective use of a placebo). Magnesium was administered as intravenous bolus of 8-mmol over 15 minutes followed by a 72 mmol infusion over 24 hours. Mortality at 35 days was the principal pre-specified endpoint.

ISIS-4 STUDY : 35 Day Mortality

Placebo	**IV Magnesium**	
N=1,897	N=1,997	
6.9%	**7.3%**	**NS**

NY Times, Monday Nov 8, 1993

The possible reasons for ISIS-4 failing to a beneficial effect on mortality include:

1) The time from onset of symptoms to randomization with therapy in ISIS-4 was longer than in LIMIT- 2 i.e. 8 hours rather than 3 hours.

2) The ISIS-4 protocol specified that thrombolytic therapy should be given and completed before trial randomization. 30% of patients not given thrombolytic therapy were randomized at a median of 12 hours after symptom onset. The likelihood of reperfusion (either induced or spontaneous) occurring during magnesium treatment was therefore low.

3) The sample size of patients included in this portion of the trial (3,894 patients) might have been too small to show a benefit when the mortality in the control group of patients was approximately 7%.

Some feel that the most likely mechanism by which magnesium could exert a benefit is by protecting the myocardium from reperfusion injury. If this is true, early administration of magnesium following the onset of chest pain would be a requirement for observing a beneficial effect. Currently, magnesium therapy is not routinely used in the early hours of AMI and we await the results of other trials to decide its therapeutic role.

LIDOCAINE.

There are at least 11 randomized trials with a total of 8,527 patients studying the use of lidocaine. The incidence of ventricular fibrillation and fatal asystole among the untreated patients in these trials is 1.4% and 0.2% respectively, and lidocaine reduced the risk of developing ventricular fibrillation by 36% without altering overall mortality [32].

Findings :

Prophylactic lidocaine may reduce incidence of VF by 33% without altering mortality.

"There appears to be an **increased incidence of asystole** with lidocaine".

Lidocaine is usually indicated with PVC's if they are > 6/min , R on T, multiform configuration or ventricular tachycardia.

Lidocaine is usually indicated for survivors of CPR for VT or VF.

Prophylactic use controversial : Risk of VF highest in first 6 hours. Younger patients (without CHF) have less toxicity.

LONG TERM ANTICOAGULANTS

Meta-analyses suggest that anticoagulants may reduce mortality following AMI by approximately 22% ($p < 0.001$, 95% confidence limits between 8 and 35% reduction). Two recent, well designed studies address the issue of long-term anticoagulants [60,61].

Warfarin Re-Infarction Study.

1,214 patients assigned Warfarin/placebo for 3 years

EVENTS	PLACEBO	WARFARIN	RISK REDUCTION	P VALUE
Deaths	123	94	24%	0.027
Reinfarctions	124	82	34%	0.0007
CVA's	44	20	55%	0.0015

Treatment started 27 days post AMI.
Target INR=2.8-4.8 (PT approx 1.5-2.0)

Smith P et al. N Engl J Med 323:147,1990.

Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis Research Group (ASPECT)

3,404 patients followed for 37 months assigned nicoumalone or phenprocoumon / placebo

EVENTS	PLACEBO	ANTICOAG	HAZARD RATIO	95% CI
Deaths	189	170	90%	NS
Reinfarctions	242	114	47%	38-59%
CVA's	62	37	60%	40-90%
Major Bleed	19	73		

Treatment started within 6 weeks post AMI.
Target INR=2.8-4.8 (PT approx 1.5-2.0)

In AMI survivors **oral anticoagulation** reduces reinfarction and cerebrovascular episodes and appears to reduce all-cause and vascular mortality. The long term influence of **antiplatelet** therapy on AMI survivors has been recently re-examined. In 11 trials of antiplatelet therapy (mainly aspirin) among about 20,000 patients with a mean follow-up of 27 months there was a reduction in recurrent vascular events (1.6 per 100 patient years) and all-cause mortality (0.53 per 100 patient years). Major extra-cranial hemorrhage was more frequent with oral anticoagulants than with aspirin. [In two trials where aspirin and oral anticoagulation have been directly compared there were no differences in mortality [62].

EVENT RATE PER 100 PATIENT YEARS

	REDUCTION				INCREASE
	Recurrent MI	CVA's	Vascular events	Death	Major bleed
Anticoagulants					
WARIS 1990	2.2*	1.33*		1.6*	0.4
ASPECT 1995	2.8*	0.5*	3.1*	0.4	0.8
Antiplatelet agents					
APT 1994			1.6*	0.53*	

Cairns JA, Lancet 1994;343 :497.

Both aspirin and oral anticoagulants have been shown to reduce overall mortality, recurrent myocardial infarction and cerebrovascular accidents [62] in AMI survivors. Oral anticoagulants have an increased rate of non-fatal major hemorrhage. Most would agree that myocardial infarct survivors with mobile mural thrombus, atrial fibrillation or congestive heart failure who are thought to be at high risk of systemic embolization should receive oral anticoagulant prophylaxis.

It has been suggested that oral anticoagulation could offer greater efficacy than aspirin, and its bleeding risk be reduced by the use of more conservative INR values. This has prompted two trials

directly comparing warfarin and aspirin. The CARS Trial of AMI Survivors is randomizing them to aspirin 160 mg daily; aspirin 80 mg daily plus warfarin 3 mg daily; and aspirin 80 mg daily plus warfarin 1 mg daily. The CHAMP Trial is randomizing AMI survivors to aspirin 160 mg a day or aspirin 80 mg daily plus warfarin to achieve a INR value of 1.5-2.5.

Until the results of these trials are known aspirin is recommended in a dose of 160-325 mg daily [63].

CALCIUM ANTAGONISTS.

In a meta-analysis of 28 randomized trials composed of 19,000 patients who received calcium antagonists in the setting of AMI there was no evidence that mortality was reduced [64,65]. The three major randomized trials examining this issue include the Diltiazem and Reinfarction Study in patients with non-Q wave myocardial infarction treated for two weeks [66], the Multi Center Diltiazem Post Infarction Trial Research Group which examined the effect of Diltiazem on mortality and reinfarction during a two year treatment period [67] and the Danish Study Group of Verapamil in myocardial infarction [68] of patients treated from 14 days to 18 months after infarction.

AMI : INFLUENCE OF CALCIUM ANTAGONISTS [66-68]

	TREATMENT	REINFARCT	DEATH	DEATH or REINFARCT
REINFARCTION STUDY	Placebo	9.3%	3.1%	
Non-Q-MI treated 2 weeks	Diltiazem	5.2% *	3.8%	
POSTINFARCTION TRIAL	Placebo	9.4%	13.5%	
AMI's treated 2 years	Diltiazem	8.0%	13.5%	
DAVIT-II	Placebo		13.8%	21.6%
AMI's treated 14 days-18mnths	Verapamil		11.1%	18.0% **

* p=<0.03

**p=0.02

No mortality advantage was seen in MDPIT or DAVIT-II. The Reinfarction Study showed early reinfarction was reduced in patients with non-Q wave MI treated for two weeks with Diltiazem.

The ACC/AHA Task Force [32] stated "there is no clear evidence to support the routine use of calcium channel blockers in the treatment of AMI except in the subset of patients with non-Q wave infarction in whom diltiazem was found effective in preventing early reinfarction and recurrent severe angina." The Multicenter Diltiazem Postinfarction Research Group reported that diltiazem treatment was harmful in patients with low ejection fractions and pulmonary congestion [67].

LONG-TERM BETA BLOCKERS.

Secondary prevention trials of survivors of acute infarction indicate that prophylactic beta-blockade has a favorable effect on sudden death and possibly reinfarction [69-71]. Pooling the results of the major randomized, prospective, placebo-controlled trials shows a 20% reduction in mortality (95% confidence limits 12-28%).

INFLUENCE OF BETA-BLOCKERS ON MORTALITY AFTER AMI

TRIAL	FOLLOWUP	PLACEBO	BETA-BLOCKER	% RISK DIFFERENCE	RELATIVE REDUCTION
BHAT Propranolol N=3,837	25 mo	9.8%	7.2%	2.6%	26%
NORWEGIAN Timolol N=1884	17 mo	13.9%	7.7%	6.2%	45%
SWEDISH Metoprolol N=1395	90 days	8.9%	5.7%	3.2%	36%

Such therapy is cost effective [72]. Detailed analyses of the results of beta-blocker therapy based on various patient subgroups (by age, sex, site of myocardial infarction, initial heart rate, risk category, presence or absence of ventricular arrhythmias on Holter monitors) fails to reveal any preferential treatment effect in any category. Subdivision of the data by the mode of death (sudden or non-sudden) suggests benefit in preventing sudden death (32% risk reduction) and, to a lesser extent, non-sudden death (12% risk reduction). Combining information on non-fatal reinfarction from the various trials indicates a 27% risk reduction from treatment (5.6% in the beta blocker group compared with 7.5% amongst controls).

BETA-BLOCKERS POST MYOCARDIAL INFARCTION
2.5 YEAR RISK OF DEATH & CHF

	RISK of DEATH		Risk of CHF	
LVEF	**No BB**	**BB**	**No BB**	**BB**
> 39%	13%	8%	20%	11%
30-39%	19%	9%	44%	24%
< 30%	45%	24%	61%	46%

MDPIT Study (Placebo Group)
J Am Coll Cardiol 1990;16:1327-32.

LONG-TERM ANTIARRHYTHMIC DRUGS.

Most of the randomized, controlled trials of empirical long-term antiarrhythmic therapy confirm that the Type I antiarrhythmic agents reduce premature ventricular beats following myocardial infarction, although no consistently beneficial survival advantage has been demonstrated. Indeed, meta-analyses of these studies suggest that, despite reducing premature ventricular contractions, the Type I antiarrhythmic agents may shorten survival after myocardial infarction

The CAST (Cardiac Arrhythmia Suppression Trial) was initiated in 1987 to test the hypothesis that suppression of asymptomatic or mildly symptomatic ventricular arrhythmias would reduce the incidence of sudden cardiac death. Three drugs were evaluated: encainide, flecainide, and moricizine. Twenty-two months after its initiation, part of the study was prematurely halted because of excessive mortality in the group of patients randomized to treatment with encainide or flecainide [73]. Despite effective suppression of PVCs, flecainide and encainide significantly worsened the total sudden death mortality compared with placebo overall and across all subgroups analyzed. The use of moricizine also proved to be harmful [74].

Amiodarone is an FDA approved drug for life threatening ventricular tachyarrhythmias when other drugs are not tolerated or ineffective. Its actions include Class I (blocks Na channel), Class II (antiadrenergic) and Class IV (blocks Ca^{++} channel) actions.

In AMI survivors with contraindications to beta-blockers (heart failure, asthma, treated diabetes or peripheral arterial disease with claudication) amiodarone (800mg per day for 7 days-starting 5-

7 days after AMI- then 400mg 6 days a week for 12 months) reduced the incidence of cardiac death [75] (sudden death) in patients who did not necessarily have high density ventricular arrhythmias.Adverse drug effects led to withdrawal of amiodarone in 18% of treated patients.

AMI : Effect of Amiodarone on 1 Year Mortality

Patients ineligible for Beta-Blockers

	Placebo (N=308)	**Amiodarone (N=305)**	**Odds Ratio**
Deaths	n=33	n=21	0.62 p=0.048
Serious ventricular arrhythmias (Lown Class 4)	19.7%	7.5%	p=<0.01
Adverse drug effects	10%	30%	

Amiodarone 800mg/day for 1 week
then 400mg 6 days per week for 1 year

Ceremuzynski et al J Am Coll Cardiol 1992;20:1056-62.

Current data do not support the routine use of antiarrhythmic agents in asymptomatic or mildly symptomatic patients. Many studies confirm that ventricular ectopy and reduced ventricular function are independent predictors of increased risk for death after myocardial infarction. Salvos or non-sustained ventricular tachycardia may be more hazardous than a high frequency of PVCs per hour. When left ventricular ejection fraction falls below 40%, cardiac mortality following infarction increases substantially. Untreated patients with sustained ventricular tachycardia have a very high mortality and it is unknown whether antiarrhythmic therapy will have a salutary effect in such patients. For salvos of premature ventricular contractions, non-sustained VT and sustained VT, the risk to benefit ratio of antiarrhythmic drug therapy long term remains unresolved.

LONG-TERM AFTERLOAD REDUCTION.

Following AMI both acute and chronic alterations in ventricular shape occur ("remodeling") which are influenced by the size of the myocardial infarction, ongoing ventricular wall stress and the healing process [76]. In general, moderate and large myocardial

infarctions can lead to progressive ventricular enlargement and both experimental and clinical studies have demonstrated that long term therapy with an angiotensin-converting-enzyme (ACE) inhibitor can attenuate this process.The major clinical trials were a logical consequence of the results of experimental animal studies. In rats with coronary artery ligations long-term administration of Captopril resulted in attenuation of the observed time-dependent increase in ventricular size [77]. Subsequently, a one year placebo-controlled mortality trial was conducted in rats and demonstrated that Captopril prolonged survival following experimental myocardial infarction and that this effect was most pronounced in the animals with moderate (rather than small or large) sized infarctions [78].

	Consensus II	Isis-4	SAVE	AIRE
Time of RZ	Within 24 hours.	Within 24 hours.	3-16 days; mean=11 days.	3-10 days;mean=5 days
LVEF	Unknown.	Unknown.	40% or less, Mean=31%	Unknown.
Agent used.	Enalapril	Captopril	Captopril	Ramipril
Presence of heart failure	Possible	Possible	Overt heart failure absent	Present (NYHA class IV excluded)
Follow-up	6 months	35 days	Average = 42 months	Average = 15 months
Endpoints	Mortality and morbidity	Mortality	Mortality and morbidity	Mortality and morbidity
Results	Survival not improved Reduced need for therapy change for heart failure	Survival improved	Survival improved	Survival improved

A highly focused clinical trial was performed in patients with first, anterior myocardial infarctions and ejection fractions of 45% or less (in the absence of overt congestive heart failure) which revealed that ventricular enlargement was progressive and that Captopril appeared to reduce cardiac filling pressures, attenuate the process of ventricular enlargement and improve exercise tolerance [79]. In another clinical study serial echocardiograms were performed in patients with anterior and inferior Q-wave myocardial infarctions (all with left ventricular ejection fractions of less than 45%) and demonstrated that patients treated with placebo or Lasix exhibited progressive ventricular

enlargement which was not observed in patients treated with Captopril [80].
Thus, experimental studies and focused clinical studies suggested a salutary effect of ACE inhibitors following AMI and larger trials were initiated to see whether such therapy would influence mortality in patients after AMI.
The GISSI-3 protocol [81] was designed to test the effects of transdermal glyceryl nitrate and lisinopril in a wide range of patients with AMI. Patients were eligible if they had been admitted to a participating coronary care unit within 24 hours of onset of chest pain accompanied by elevation, or depression, of the ST segment of at least 1mm in one or more non-precordial leads of the ECG or of at least 2mm in one or more precordial leads. There was no age exclusion (27% patients were > 70 years). Patients with severe CHF, or Killip Class 4, were excluded. Approximately 5% of patients had an echocardiographic ejection fraction of ≤ 35%.

GISSI - 3
19,394 pts within 24 hours of onset of chest pain accompanied by electrocardiographic ST changes.

6 week Endpoints	**Controls** (n=4729)	**Nitrates** (n=4731)	**Lisinopril** (n=4731)	**Lisinopril + Nitrates** (n=4722)
Death	**7.2%**	**7.0%**	**6.6%***	**6.0%***
Odds Ratio	1.0	0.97	0.91	0.83
Combined Endpoints	**17%**	**17.0%**	**16.4%***	**14.8%***
Odds Ratio	1.0	1.0	0.96	0.85
CHF	3.7%	3.8%	4.0%	3.7%
EF< 36%	5.5%	5.7%	5.0%	4.6%
AD > 44%	0.6%	0.5%	0.8%	0.5%
Death	7.2%	7.0%	6.6%	6.0%

Lancet 1994; 343: 1115-22

[Protocol : An IV infusion of GTN starting at 5µg/min and rising by 5-20µg/min every 5 min for the first 30 min until systolic BP

fell by at least 10%, provided it remained above 90 mm Hg. After 24 h the IV infusion was replaced with a patch providing 10 mg daily GTN transdermally applied in the daytime and removed to allow a nitrate free interval. If the patch was not tolerated a single oral dose of 50mg isosorbide mononitrate was given daily) and an ACE inhibitor (lisinopril, 5mg at randomization, 5 mg after 24h, 10 mg after 48h, then 10mg daily for 6 weeks)]

In differing populations of patients suffering suspected, or definite, Q-wave, or non-Q wave, myocardial infarctions the SAVE [45], AIRE [82], ISIS-4 and GISSI-3 [81] studies suggest that Captopril ,Ramipril or Lisinopril may reduce early (ISIS-4, GISSI-3) and longer term (SAVE, AIRE) mortality following AMI. The SAVE trial focused on patients who had moderate to severe left ventricular dysfunction as a consequence of acute infarction in the absence of overt heart failure whereas the AIRE study focused on post-infarction patients with transient or ongoing heart failure believed to be at high risk of premature death (Patients with severe heart failure were excluded). In both studies the earliest oral ACE inhibitors were initiated was 3 days after infarction and the mean time to randomization to therapy was 11 and 5 days after infarction, respectively. In the Consensus II [83], ISIS 4 and GISSI-3 studies therapy was initiated within 24 hours of definite (or suspected) myocardial infarction. In Consensus II an aggressive treatment protocol was used and the authors suggested that hypotension occurring in some patients given enalapril may have led to increased mortality. Mortality was not improved by enalapril in Consensus II whereas with a less aggressive oral regimen within 24 hours of definite, or suspected, infarction in the ISIS 4 and GISSI-3 studies Captopril and Lisinopril were associated with a small survival advantage at 5-6 weeks. In the SAVE trial the mortality benefits appeared modest during the first year of therapy but appeared to increase with time (the mortality curves diverged with time) suggesting an accrued and continuing benefit of therapy. Inspection of the mortality curves in the AIRE study suggested earlier benefits perhaps because heart failure was a requirement for entry into the study (in contrast to the SAVE trial where patients with overt heart failure were excluded.).

In each of the SAVE, AIRE and Consensus II studies clinical heart failure was an endpoint and ACE inhibitor therapy was associated with fewer episodes of clinical heart failure. The SAVE Trial [84] also assessed whether captopril would attenuate progressive left ventricular enlargement in patients with left ventricular dysfunction. Irrespective of treatment assignment baseline left ventricular systolic area and percent change in area were strong predictors of cardiovascular mortality and adverse cardiovascular events. At one year, left ventricular end-diastolic and end-systolic areas were larger in the placebo than in the captopril group. At one-year 111 out of 420 (26%) of survivors with serial echocardiographic measurements experienced a major cardiovascular event and these patients had more than a three-fold greater

increase in left ventricular cavity areas than those with an uncomplicated course.

The SAVE trial also suggested that Captopril therapy reduced recurrent myocardial infarction [85]. In a post infarction population potential mechanisms by which ACE inhibitors may exert an anti-ischemic effect include reducing blood pressure and favorably altering remodeling of the heart (thereby reducing wall stress), blocking the coronary vasoconstrictor influences of angiotensin-II, regulating the production of bradykinin and modifying the vascular response to injury. It has also been observed that the DD genotype of the ACE gene which is associated with higher levels of circulating ACE, than ID and II genotypes, can be found more frequently in patients with myocardial infarction than in controls [86]. Recently, It is then possible that patients with this "risk factor" may derive increased benefit from ACE inhibitor therapy. Furthermore, it is of interest that the SOLVD investigators have reported a reduction in the occurrence of myocardial infarction and unstable angina in populations of patients with low left ventricular ejection fractions (with and without overt heart failure) treated with enalapril [87]. These observed reductions in recurrent myocardial infarction with different ACE inhibitors, in different populations, are of interest and deserve further investigation.

Taken together, these clinical trials suggest that attenuation of the acute and chronic alterations in ventricular shape ("remodeling") by ACE inhibitors that had been observed following moderate and large myocardial infarctions in animal, and human studies, will result in improved survival. Patients with transient, or persistent, mild to moderate heart failure following AMI also appear to have a survival advantage if ACE inhibitors are employed. Escalating oral doses of Lisinopril and Captopril administered within 24 hours of AMI and of Captopril and Ramipril administered 3-16 days after AMI have been safely administered to patients and improved survival has been demonstrated. The safety of more aggressive regimens is a matter of concern. Last, the possibility that ACE inhibitors exert an anti-ischemic effect has been raised and deserves further attention.

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