# Medical Grand Rounds: Rational Drug Therapy for Primary Unstable Angina

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The term "unstable angina," proposed by Fowler in 1971, refers to patients with one or more of three general categories of ischemic chest discomfort: 1) new onset angina, 2) angina at lower levels of exertion or with reduced sensitivity to nitroglycerin, and 3) angina at rest. These patients are a heterogeneous group in terms of symptoms, ECG abnormalities, associated clinical circumstances, and clinical outcome. This reported variability in prognosis is undoubtedly due to differences in definition. For example, new onset angina pectoris during exertion or a change in the pattern of chronic angina has an annual mortality of approximately 2-5%. At the other end of the spectrum is angina at rest associated with ST and T wave abnormalities in spite of maximal medical therapy which has a substantially higher mortality. However it is defined, patients with unstable angina have a significant risk of progression to acute myocardial infarction and death.

*The goal of therapy is to relieve symptoms and prevent progression to MI and death*, and a secondary goal may be to improve left ventricular systolic and diastolic function. The diagnosis is purely clinical and carries no mechanistic implications for therapy. Consequently, clinical trials and therapeutic recommendations have been guided by our evolving concepts of the pathogenesis of unstable angina. It's arbitrary, but recommendations to achieve these goals may be divided historically into three categories. Initially, unstable angina was managed with $\beta$ adrenergic blockers and nitrates; the underlying pathophysiology was considered to be primary but small increases in oxygen demand, perhaps in a subpopulation with occluded coronary arteries and inadequate collateral perfusion. Later, coronary artery spasm, that is, primary reduction in perfusion, was thought to play a critical role in unstable angina, and calcium channel blockers assumed a major role in clinical trials and therapeutic recommendations. Most recently, the importance of acute platelet aggregation and intraluminal thrombus formation has been emphasized, and aspirin and heparin have assumed central roles in routine therapy.

Thus, five classes of drugs have been recommended for therapy: antiplatelet agents, heparin and other anticoagulants, nitrates, $\beta$ adrenergic blockers, and calcium channel blockers. Some agents became widely accepted in clinical practice in the absence of controlled clinical trials, and others have been studied only in relatively small populations with low statistical power. Nevertheless, combination of all five classes is widely recommended even when the actual efficacy of a particular class of agents may be unclear. For example, a meta-analysis of calcium channel blockers indicated adverse effects in patients with unstable angina, a worrisome conclusion in view of their widespread use (Held, 1989). To complicate matters, a sixth class, thrombolytic agents, is currently under investigation.

Selecting proper drug therapy for an individual patient somewhere in the spectrum of unstable angina may be difficult because therapeutic recommendations have become layered, one on another, as concepts have evolved. The purpose of this review is to reexamine the efficacy of each class of drugs in randomized clinical trials, where possible, and to determine the relative importance of each agent for the relief of symptoms and prevention of myocardial infarction or death in patients with unstable angina.

## 1. Pathophysiology and principles of therapy for primary unstable angina

The final mechanism of unstable angina is an imbalance in myocardial oxygen demand compared to supply which occurs under three clinical conditions (Braunwald, 1989). *Secondary* unstable angina refers to patients with conditions not involving the coronary vasculature which cause a primary increase in myocardial oxygen demand or reduced capacity for oxygen delivery. These conditions include, but are not limited to, uncontrolled tachyarrhythmias or hypertension, infection, thyrotoxicosis, as well as profound anemia, hypotension, or hypoxemia. Therapy is directed at removing or alleviating the extracardiac condition. *Primary* unstable angina refers to patients who develop an unstable pain pattern without a significant increase in myocardial oxygen demand or a significant reduction in oxygen delivery. Although obvious changes in oxygen demand are not present, this definition does not imply that therapeutic reduction in oxygen demand is not beneficial. *Postinfarction* unstable angina refers to patients with recent myocardial infarction who develop unstable angina.

Primary unstable angina has been attributed to altered myocardial oxygen consumption, abnormal platelet reactivity or aggregation, thrombus formation, progression of atheroma, or coronary artery spasm. Although evidence for each factor has been reported, the most comprehensive hypothesis states that disruption of the endothelium overlying an atheroma stimulates platelet aggregation and thrombus formation which reduces lumen diameter and releases vasoactive metabolites. The evidence for an association between intracoronary thrombosis and unstable angina is diverse and may be grouped as follows.

First, *plaque rupture and luminal thrombus are common in patients dying of acute ischemia*. A series of studies reported between 1978 and 1985 shape much of our current thinking regarding unstable angina. In 1978 Horie showed that intraluminal thrombus frequently occurs at the site of ruptured plaque. Levin and Fallon later showed that pathological abnormalities such as thrombus formation and plaque disruption can be inferred from the coronary arteriogram. Specifically, intraluminal lucencies and irregular borders correlated with thrombus and plaque disruption. In 1984 Falk reported on 25 patients with MI and sudden death. Layered intracoronary thrombus consistent with repeated episodes of thrombosis and partial healing were noted. Simultaneously, Davies and Thomas, in a study of 100 patients which died abruptly of ischemic heart disease, found either intraluminal or intraintimal thrombus in 95 patients. Together, these landmark studies indicate that thrombosis on a site of endothelial injury (which have variously been termed erosions, fissures, tears, ruptures or ulcers) plays a central role in fatal coronary disease, and that these lesions might be detected in patients using standard coronary arteriography.

Second, angiographic and angioscopic studies of patients with unstable angina often show that *the ischemia-related lesion is complex and associated with thrombus*. Typically, the ischemia-related artery is patent; total occlusion is uncommon, and thrombus is detected in approximately 60-70% of patients with unstable angina if arteriography is carried out early in the hospitalization. The variability in prevalence could certainly be attributed to differences in the time elapsed between symptoms and arteriography, and, indeed Table 1 strongly suggests that after 24 hours the frequency of detectable thrombus decreases substantially. There also may be limitations of the x-ray imaging chain, and the decision as to what represents a clot is subjective. The absence of detectable clot could also be due to small size, mural layering, or spontaneous endogenous fibrinolysis.

The morphology of coronary atheroma in patients with unstable angina has been described in detail (Ambrose, 1985, 1986, 1987a). The essential observation is that the morphology of the ischemia-related atheroma is different in patients with unstable angina compared to patients with stable angina. Specifically, attention was directed to lesion shape and symmetry. Asymmetric stenoses with irregular borders and overhanging edges are detected in 60-70% of patients with unstable angina. Ambrose initially classified lesions as concentric, eccentric or multiply irregular, and further subdivided "eccentric" lesions into types I and II. Fortunately, he has revised this classification scheme and now refers to "simple" and "complex" lesions.

**Table 1.** Angiographic studies of the prevalence of intracoronary thrombus in patients with unstable angina.

| Reference | Number of patients | Time between symptoms and angiography | Thrombus demonstrated |
|---|---|---|---|
| Gotoh, 1988 | 37 | 0 | 57% |
| TIMI IIIA | 215 | < 11.5 hours | 18%: occlusion<br>11%: thrombus<br>≈40%: ? thrombus |
| Cowley, 1989 | 69 | 1 hour to 5 days | 58% |
| Capone, 1985 | 44 | 24 hours | 52% |
| Williams, 1988 | 93 | < 5 days | 28% |
| Capone, 1985 | 75 | < 14 days | 28% |
| Vetrovec, 1982 | 129 | 28 days | 6% |
| Zack, 1984 | 83 | 12 weeks | 12% |
| Holmes, 1981 | 1202 | 12 weeks | 1% |

Third, *endothelial injury may cause abnormal vasoconstriction and increased reactivity.* There is probably no simple relation between the angiographic morphology of an atheromatous plaque and the associated clinical syndrome. Some atherosclerotic lesions have a small central core of fatty debris covered by a dense fibrous cap. Other lesions have a large central core of fatty and cellular debris with little, if any, fibrous cap. Both types of lesions could be associated with stable angina, but the latter may be more prone to instability because of its physical features. The lesions described by Ambrose are presumably due to deep subintimal injury. However, superficial intimal injury has been characterized in anatomical terms. Patients with atherosclerotic coronary artery disease vasoconstrict in response to acetylcholine, in contrast to normals where acetylcholine causes vasodilation. Human coronary artery segments studied in vitro show impaired relaxation in response to NO compared to normal segments. These observations suggest that even minor intimal injury may disrupt the normal control of coronary vascular tone.

Fourth, *markers of platelet activity are increased.* Apart from understanding pathophysiology, it would be quite attractive to monitor platelet activation for clinical purposes. Thromboxane metabolites have been studied intensively for this purpose. Thromboxane $A_2$ is released from activated platelets and is converted in the plasma to thromboxane $B_2$ which provides an index of $A_2$ synthesis. Using this approach, Hirsch, Willerson and colleagues found evidence for intracoronary platelet activation in patients with unstable angina. Breakdown products of thromboxane detected in the urine (such as 2,3-dinorthromboxane $B_2$) are also thought to represent *in vivo* platelet activation. This urinary metabolite correlates with both unstable angina and intracoronary thrombus (Hamm, 1987).

Finally, *degradation products of fibrin are increased.* Cleavage of fibrinogen by thrombin yields fibrin monomer, fibrinopeptide A and fibrinopeptide B. Fibrin monomer polymerizes to form a clot. Circulating levels of fibrinopeptide A (FPA) are normally low, but become elevated in acute myocardial infarction. Levels of FPA in patients with unstable angina is similar to that in patients with acute MI, and higher than in controls or in patients with stable angina. Theroux reported on 16 patients with reversible ECG changes and no evidence of infarction by cardiac enzyme criteria. Plasma FPA, measured about 18 hours after admission, was significantly higher compared to matched controls with stable angina and similar severity of coronary disease. Since the half-life of FPA is so short (5 minutes) these observations are consistent with continuous fibrinogen cleavage in patients with unstable angina.

**Table 2.** Pathophysiology of unstable angina and therapeutic options.

| Pathophysiology | Therapeutic option |
|---|---|
| $O_2$ supply/demand imbalance | increase supply<br>correct anemia and hypoxemia<br>treat hypotension<br>intra-aortic balloon pump<br>angioplasty<br>coronary artery bypass surgery |
| | reduce demand<br>reduce cardiac output (rest)<br>decrease heart rate<br>control blood pressure<br>reduce afterload (IABP)<br>treat preload (control CHF)<br>reduce contractility |
| rupture → platelet aggregation + thrombosis | aspirin<br>heparin<br>thrombolytics |
| minor endothelial injury, increased coronary vascular reactivity, spasm | calcium channel blockers, nitrates |

The evidence is overwhelming for a role of intracoronary thrombosis, directly or through vasoactive products, causing diminished oxygen delivery. Simple plaque progression (Moise, 1983) is unlikely to play a role, but the independent contribution of endothelial dysfunction is uncertain. Although much remains to be learned, it is reasonable to expect that therapeutic benefit might be derived from modifying the oxygen supply/demand balance, interrupting intracoronary platelet aggregation or thrombosis, and preventing coronary artery spasm.

## 2. Definition of unstable angina pectoris and trial endpoints

Therapy for unstable angina must be individualized (Table 2). The challenge is to identify those clinical trials which are relevant to a particular patient. Much of the uncertainty surrounding therapy for unstable angina is due to difficulty in establishing a definition which is both precise and clinically practical. The heterogeneity of patient populations enrolled in various trials make comparison, interpretation and integration rather complex. Different definitions of unstable angina have been used across categories of trials for unstable angina (for example, natural history, medical therapy, surgical therapy, etc.) as well as within each category. Table 3 is an abbreviated summary of the enrollment criteria for some of the major trials of medical therapy for unstable angina. It is far from exhaustive, and only serves to illustrate that completely consistent results should not be expected when comparing results of these studies.

Table 3. Definition of unstable angina, patient populations, and associated clinical data in drug therapy trials of unstable angina.

| reference | duration of pain (minutes) | Did every patient have pain at rest? | MI ruled out?* | post MI allowed?** | ECG changes required or observed in all patients? | coronary anatomy defined? |
|---|---|---|---|---|---|---|
| Lewis, 1983 | > 15 | no | yes | no | no | no |
| Cairns, 1985 | ? | no | yes | no | no | no |
| Muller, 1984 | < 45 | no | no | yes | no | no |
| Andre-Fouet, 1983 | ? | no | yes | no | yes | no |
| Curfman, 1983 | < 15 | no | yes | no | no | no |
| Rentrop, 1981 | > 20 | yes | yes | yes | yes | yes |
| Gotoh, 1988 | 30-60 | yes | yes | ? | ? | yes |
| Gold, 1987 | ? | yes | yes | no | yes | yes |
| Schreiber, 1992 | > 10 | no | yes | yes | yes | no |
| HINT, 1986 | > 15 | yes | no | no | no | no |
| Parodi, | <15 | yes | yes | no | yes | yes |
| Chaudry, 1992 | ? | ? | yes | no | no | no |
| Fischl, 1983 | > 20 | yes | yes | no | yes | yes |
| Théroux, 1988 | ? | no | yes | yes | no | yes |
| DeZwaan, 1988 | > 20 | no | yes | no | no | yes |
| Gerstenblith, 1982 | ? | yes | yes | no | yes | no |
| TIMI IIIA, 1993 | 5-360 | yes | yes | no | no*** | yes |

* MI ruled out prior to either enrollment or data analysis.
** Defined as MI within 2 to 12 weeks prior to enrollment; definition varied among studies.
*** Enrollment required at least one of the following: ECG changes during ischemia, prior MI, or documented coronary disease by angiography.

Precise definition of both the patient population and therapy in a trial is quite important in developing an integrated approach to unstable angina. Many clinical trials, particularly those with $\beta$ blocker, calcium channel blockers or thrombolytic therapy, are relatively small. Therefore, conclusions are based on synthesis of results from several trials. Pooling of results assumes, among other things, that patient populations and concurrent medications are equivalent and that the clinical effect of a drug is the same in all trials. Thus, even if a trial is too small to detect an effect, a real effect will emerge from the combination of several trials. If pooled results show no effect, two explanations should be considered. First, there is no effect, and the agent should not be used. Second, the agent is beneficial in some subgroups but detrimental in others. In this case the challenge is to identify patients which will benefit. Several questions might be asked to guide the interpretation of a particular study.

First, *what was the severity of unstable angina?* Clinically severe unstable angina (such as chest pain at rest associated with deep anterior T wave inversion and ST depression in a patient on medical therapy) has a different prognosis compared to a patient experiencing their first episodes of exertional angina which

is relieved by rest and no medical therapy. It is possible that a trial which accepts patients with new onset angina but no pain at rest (and therefore without ECG changes documented during pain) could have a different conclusion compared to a trial where severe coronary disease is more likely.

*How was conventional care defined, and was it continued after enrollment?* The stated goal of many trials is to examine the efficacy of one agent. Typically, however, patients often are enrolled after failing to respond well to one or more drugs which are then continued. Thus, the actual trial may be a comparison of the efficacy of multiple drugs.

Third, *was myocardial infarction ruled out prior to enrollment?* Trials of initial therapy with early endpoints are important. However, trial interpretation may be complicated because patients with an admission diagnosis of unstable angina may in fact have an evolving infarction. If the trial focuses on early therapy, typically required within 12-48 hours after admission, then cardiac enzymes are by definition not available. Further, admission cardiac enzymes may be normal but later evolution could document that the patient was admitted very early in the course of a non-Q infarction. Inevitably, patients will be enrolled who, in spite of best efforts, in retrospect are found to have an evolving myocardial infarction. For example, although suspicion of MI was an explicit exclusion criteria in one large, well-designed trial (HINT, 1986), 12% of patients were later shown to have MI. These early entry trials typically have early endpoints (typically 2-7 days). It is also critical in early entry trials to monitor both symptoms and infarction, since one way of reducing symptoms is to cause an infarction. On the other hand, trials which enroll patients who have had MI excluded typically have a longer time frame and focus on endpoints months after enrollment.

Fourth, *was coronary arteriography performed in every patient?* Subgroup analysis based on coronary anatomy (e.g., the presence of left main coronary artery disease or normal coronary arteries) may be helpful.

Finally, *what were the endpoints?* Five endpoints have been used in the studies to be described: 1) reduction in symptomatic ischemia, 2) reduction in total ischemia (symptomatic plus asymptomatic, defined by continuous ECG monitoring), 3) prevention of myocardial infarction, 4) improved survival, and 5) alteration in coronary morphology. The relevance of asymptomatic ST deviations to therapy of unstable angina is uncertain and will not be considered further. It is obviously critical to determine the rate of progression to myocardial infarction, since one method for stabilizing symptoms is to inadvertently increase the rate of infarction.

## 3. Nitrates

Nitroglycerin and isosorbide dinitrate are organic nitrate esters, that is, they contain the $-ONO_2$ group. The mechanism of action appears to be a cascade of events beginning with a reaction involving sulfhydryl groups. This produces HO (or possibly S-nitrosothiols) which activate production of cyclic GMP by guanylate cyclase. cGMP is the intracellular second messenger causing vasodilation in peripheral arterioles, coronary arteries, and venous capacitance vessels. This series of biochemical events has direct consequences for myocardial oxygen demand and supply. There is also some evidence for direct antiplatelet effect.

*Myocardial oxygen demand* is reduced by three direct and indirect effect of nitrates. The predominant antianginal effect is generally attributed to direct venodilation which reduces left ventricular end diastolic volume and oxygen demand. Consequently, stroke volume is reduced, and, if peripheral resistance remained the same, systemic pressure and afterload would be decreased. Finally, nitrates have direct systemic arteriolar vasodilator effects which further serve to reduce oxygen demand.

*Myocardial oxygen supply* is increased by both direct and indirect effects of nitrates. Epicardial vessels stenotic sites, collateral vessels and vessels in spasm are all dilated by nitroglycerin. An indirect effect of decreased preload is improved subendocardial blood flow.

Nitrates have an important but surprisingly ill-defined role in the therapy of unstable angina. Although they are certainly part of routine clinical practice, there are no controlled trials demonstrating their efficacy in unstable angina. Of course, andy trial to address this question would require withholding acutely administered nitrates for chest pain, which would be unacceptable. Although there is no question that various nitrate preparations effectively treat chest pain, the goal of using prolonged exposure to nitrates to prevent further events is complicated by the development of nitrate tolerance.

**Table 4.** Studies of intravenous nitroglycerin for therapy in patients with unstable angina pectoris.

| reference | number of patients | control group? | prior nitrates? | prior calcium channel blocker? | prior β adrenergic blocker? | # of patients with significant pain relief |
|---|---|---|---|---|---|---|
| Distante, 1979 | 12 | crossover | yes | no | yes | 80% dec in pain |
| Dauwe, 1979 | 14 | no | yes | no | yes | 12/14 |
| Brodsky, 1980 | 14 | no | yes | no | yes | 5/14 |
| Mikolich, 1980 | 45 | no | yes | no | ? | 40/45 |
| Squire, 1980 | 42 | no | yes | no | yes | 19/42 |
| Roubin, 1982 | 16 | no | yes | yes | yes | 16/16 |
| Gaskin, 1982 | 16 | no | yes | no | yes | 16/16 |
| DePace, 1982 | 20 | no | yes | yes | yes | 17/20 |
| Kaplan, 1983 | 35 | no | yes | no | yes | 25/35 |
| Curfman, 1983 | 14 | yes* | yes | no | yes | 14/14 |
| Thadani, 1987 | 43 | no | ? | ? | ? | 14/43 |
| Horowitz, 1988 | 46 | yes† | yes | yes | yes | not reported |

* i.v. nitroglycerin compared to oral isordil and nitroglycerin ointment
† i.v. nitroglycerin with or without N-acetylcysteine

Nitrate therapy for unstable angina typically includes sublingual nitroglycerin (or oral spray) for rapid treatment of chest pain. Additional nitrate therapy with nitroglycerin ointment, nitroglycerin transdermal patches or oral isosorbide nitrate is then used to prevent recurrent ischemia. Because of

recurrence of chest pains or concerns about maintenance of continuous prophylaxis against ischemia, i.v. nitroglycerin has become the *de facto* standard for nitrate therapy in unstable angina.

Sublingual and cutaneous nitrates formed the basis of antianginal therapy in the 1970s. There are no randomized trials of the efficacy of i.v. nitroglycerin compared to placebo (no nitrates) in the treatment of unstable angina. Nevertheless, results from 9 uncontrolled trials, one crossover trial and two others indicate that i.v. nitroglycerin provides rapid and often dramatic relief of pain even in patients maximally treated with cutaneous and oral nitrates plus $\beta$ adrenergic blockers. As shown in Table 4, in these uncontrolled trials 178/259 or about 70% of patients had substantial and often very rapid relief of pain. There is no information on the effect of i.v. nitroglycerin on subsequent MI or death. Less well-studied is the effect of nitrates in the presence of calcium channel blockers, but it also appears effective. Together, these studies strongly suggest that i.v. nitroglycerin is effective in reducing symptoms. However, no randomized trials of nitrates compared to placebo have been performed, and their effect on infarction and mortality is unknown. Because of long clinical experience, benefits demonstrated in uncontrolled trials, and compelling pharmacology, there is a strong consensus that nitrates and particularly i.v. nitroglycerin are indicated for unstable angina.

## 4. $\beta$ adrenergic blocking agents

$\beta$ adrenergic antagonists reduce myocardial oxygen demand by reducing heart rate and contractility. These favorable effects stimulated the initial studies of $\beta$ adrenergic blockade for unstable angina which were reported in the early 1970s. At the time the dominant paradigm of angina, both stable and unstable, was increased oxygen demand relative to supply. For example, Gorlin's group (Fischl, 1973) reported 25 patient with unstable angina (pain > 20 min at rest associated with ECG changes) who were managed with propranolol (average dose, 170 mg/d). They found prompt relief of pain in 22/25 patients including some with clinical left heart failure. A major conclusion of this study was that relief of chest pain correlated well with reduction in rate-pressure product. Similarly, unstable angina refractory to nitrates and heparin respond to $\beta$ blocker in 13/15 patients (Mizgala, 1970). Thus, propranolol was safe and effective in most patients, even those with mild congestive heart failure. These early uncontrolled trials showed that increasing doses of propranolol were associated with pain relief which correlated well with decreased indices of oxygen.

The first randomized prospective trial (Norris, 1978) recruited patients with chest pain consistent with myocardial infarction but no ST elevation on the ECG. The risk of infarction was reduced by a combination of early intravenous propranolol and later oral propranolol. Two randomized trial with atenolol have also been reported. Early intravenous atenolol was studied in 79 patients with ischemic chest pain without ST elevation. Atenolol appeared beneficial, but there was a total of 8 nonfatal cardiac arrests in the study, about 10% of the study population, which is consistent with a large portion of those patient having non-Q MI. Atenolol was also studied by Telford and Wilson in a 2x2 design of placebo, atenolol, heparin and atenolol plus heparin. Assuming no interaction of heparin with atenolol, there was no effect of atenolol on the risk of infarction, and there were 2 deaths in the control group compared to 0 in the atenolol group. This study has been criticized because of the large number of patients (186 out of 400) who were randomized but dropped out of the study.

Table 5. β blockers, diltiazem, verapamil or the combination for unstable angina.

| reference | duration (days) | # pts. | study groups and comedications | reduction in angina at 48-72 hours | MI | CABG | Death |
|---|---|---|---|---|---|---|---|
| β adrenergic blockers | | | | | | | |
| Norris, 1978 | ≈ 1 | 20 | propranolol (i.v. within 4 followed by p.o.) | | 11* | | 0 |
| | | 23 | control | | 22 | | 0 |
| Yusuf, 1980 | ≈ 10 | 35 | atenolol (i.v. within 4 hours, followed by p.o.) | | 11* | | 4 |
| | | 44 | control | | 27 | | 9 |
| Telford, 1981 | 7 | 109 | atenolol (p.o.) | | 10 | | 0 |
| | | 105 | control | | 10 | | 2 |
| Calcium channel blockers | | | | | | | |
| Mauritson, 1983 | 2 | 5 | verapamil (80 mg p.o. q 6 hr) | 70%* | | | |
| | | 6 | control | no change | | | |
| Mauri, 1988 | | 12 | verapamil or diltiazem + heparin + nitrates | both CCB reduce angina | | | |
| β blocker vs. diltiazem | | | | | | | |
| Andre-Fouet, 1983 | ≈ 5 | 34 | diltiazem | ≈ 70% | diltiazem superior for pain at rest | | |
| | | 36 | propranolol | ≈ 70% | | | |
| Théroux, 1985 | 150 | | pretreatment | | | | |
| | | 50 | diltiazem | 28% | 5 | 19 | 2 |
| | | 50 | propranolol | 26% | 4 | 21 | 2 |
| β blocker vs. verapamil | | | | | | | |
| Parodi, 1986 | 2 | 9 | crossover | | | | |
| | | | propranolol 300 mg/d | ≈10% | 9 | - | - |
| | | | verapamil 400 mg/d | ≈100%* | 6 | - | - |
| Capucci, 1983 | 4 | 20 | crossover | | | | |
| | | | propranolol 240 mg/d | ≈50% | - | - | - |
| | | | verapamil 480 mg/d | ≈90%* | - | - | - |

* significant decrease compared to control or propranolol

In these three early trials using i.v. β blocker, a large fraction of patients may have presented with non-Q MI. There was suggestive evidence of a beneficial effect in reduced mortality and subsequent infarction. A later meta-analysis by Yusuf indeed found a small (13%) beneficial effect. Supporting this conclusion was a subset of a later trial (HINT, 1986) which compared metoprolol to control. There was a strong trend to reduction in mortality by metoprolol (risk ratio, -24% compared to control), but this effect was not statistically significant.

It has been argued that β blockers are contraindicated if coronary artery spasm is primarily responsible for reduced perfusion. Unopposed α adrenergic receptor activity could in principle further impair perfusion. However, the HINT

trial (HINT, 1986) which included monotherapy with metoprolol *vs.* monotherapy with nifedipine found a strong trend toward improved survival with metoprolol but no effect (an adverse trend) of nifedipine. These observations coupled with reasonable evidence for both mortality and symptomatic benefit suggest that β blockers should be a component of medical therapy if there is no contraindication.

β blockers such as metoprolol and atenolol appear to relieve symptoms, and there is suggestive evidence of reduced progression to MI in patients with unstable angina. In the absence of contraindications (hypotension, frank congestive heart failure, heart block, bradycardia, etc.), β blockers do not have adverse effects. They probably reduce symptoms when oxygen consumption is elevated, and may have weak beneficial effects on subsequent infarction and mortality. If the diagnosis is unclear on admission (MI *vs.* unstable angina), the favorable effects of β blockers also support their use.

## 5. Calcium channel blockers

Three types of calcium channels have been identified, and one of them, the L type, is present in cardiovascular tissue and interacts with a group of drugs known as calcium channel blockers. These agents interfere with the movement of calcium into the cell during the action potential and thereby inhibit calcium-induced calcium release. Action potential generation in automatic tissues such as the sinoatrial node also depends on the slow inward calcium current. Thus, these agents have the potential to relax vascular smooth muscle, reduce myocardial contractility, and slow the sinoatrial node. The overall impact of three calcium channel blockers - nifedipine, verapamil and diltiazem - should in principle be quite favorable. Oxygen demand should be reduced by beneficial effects on heart rate, contractility and afterload. Oxygen supply should be improved by dilation of epicardial coronary arteries and prevention of spasm.

In practice, each calcium channel blocker has different specificity. Nifedipine is a potent coronary and peripheral vasodilator with relatively minor direct effects on contractility. Reflex stimulation of heart rate and contractile state is usually observed with agents such as nifedipine without significant negative chronotropic effects, and could have a significant adverse effect on myocardial oxygen demand. The hemodynamic differences among calcium channel blockers are substantial. Therefore, sweeping conclusions about the utility of this class of drugs must be interpreted cautiously.

The concept of primary reduction in blood flow due to epicardial coronary artery spasm, refined in the late 1970s, was quite attractive because the major determinants of myocardial oxygen demand were not dramatically elevated in patients with unstable angina (Maseri, 1978; Chierchia, 1980). Typically, in these studies ECG evidence of ischemia occurred more frequently than episodes of chest discomfort, and also preceded hemodynamic evidence of regional ischemia (such as dP/dT and elevated left ventricular filling pressure). These observations and supporting studies using provocative maneuvers were interpreted as evidence for epicardial coronary artery spasm which caused a primary decrease in perfusion. In retrospect, of course, these studies could not distinguish the complex interactions of thrombus formation from coronary supersensitivity to vasoconstrictor stimuli. Nevertheless, this hypothesis was the stimulus for numerous trials (Andre-Fouet, 1983; Parodi, 1986; Capucci, 1983) which indeed found a significant symptomatic benefit of monotherapy with diltiazem or verapamil compared to β blockers for unstable angina.

Table 6. β blockers, nifedipine, and their interaction in unstable angina. Abbreviation, n.s., not significantly different.

| Reference | duration (days) | # pts. | study groups and comedications | relief of angina | MI | CABG | Death |
|---|---|---|---|---|---|---|---|
| Gerstenblith, 1982 | 120 | 68 | nifedipine + propranolol +nitrates | 44% treatment failures | | | |
| | | 70 | control + propranolol + nitrates | 61% treatment failures, p<0.03 | | | |
| Muller, 1984 | 14 | 63 | propranolol + isosorbide | ≈ 50% | 9 | 13 | |
| | | 63 | nifedipine | ≈ 50% | 9 | 14 | |
| | | | | MI or recurrent ischemia (risk ratio) | | | |
| HINT, 1986 | 2 | 89 | nifedipine | + 15%, n.s. | | - | - |
| | | 79 | metoprolol | - 24%, n.s. | | - | - |
| | | 86 | nifedipine + metoprolol | - 20%, n.s. | | - | - |
| | | 84 | control (nitrates only) | | | | |
| | | 81 | nifedipine + prior β blocker | - 32%, p < 0.01 | | - | - |
| | | 96 | control prior β blocker | | | | |
| Gottleib, 1986 | 28 | 42 | propranolol + nifedipine | yes, some | 6 | 14 | 1 |
| | | 39 | control + nifedipine | | 3 | 17 | 0 |
| Quyyumi, 1987 | - | 9 | crossover | | | | |
| | | | atenolol | yes | - | - | - |
| | | | isosorbide mononitrate | no | - | - | - |
| | | | nifedipine | yes | - | - | - |

One of the earliest trials of nifedipine therapy for unstable angina was reported by Gerstenblith in 1982. Conventional therapy plus nifedipine was compared to conventional therapy alone (β blocker plus nitrates). This placebo controlled, double blind study used "failure of therapy" as the primary endpoint which was defined as bypass surgery, death or myocardial infarction. There were significantly more treatment failures in the control group. Since the study was double blind, the results appear valid. However, there was no difference in the frequency of sudden death or infarction in the nifedipine compared to control group. The only difference was in the rate of bypass surgery which implies that in the presence of a β blocker, nifedipine is useful in reducing symptoms.

In 1984 Muller reported a double blind randomized clinical trial of conventional therapy (nitrates plus propranolol) compared to nifedipine. There was no difference in the time to relief of angina, the frequency of subsequent angina, or the risk of myocardial infarction. In *post hoc* subgroup analysis, there was a benefit of using nifedipine among patients already receiving a β blocker compared to increasing the dose of a β blocker.

The Holland Interuniversity Nifedipine-Metoprolol Trial (HINT, 1986) enrolled 515 patients in a trial of nifedipine, metoprolol, both, or neither for the treatment of un-stable angina. This study was multicenter, prospective, randomized, double blind and placebo controlled. It was terminated because of a trend towards an adverse effect of nifedipine. A major effort was made to reflect real clinical practice. Thus, for example, an evolving MI was an exclusion criterion, but patients were enrolled prior to results of cardiac enzymes. Prior therapy with β blockers (usually metoprolol) was recognized: patients on β blockers were randomized separately from patients on no β blockers, and were randomized only to

nifedipine or placebo. The baseline characteristics of these patients is shown in Table 7.

**Table 7.** Baseline characteristics of 515 patients enrolled in the HINT.

| | | |
|---|---|---|
| age | < 55: 36% | 56-65: 48% |
| sex | female: 25% | male: 75% |
| history of prior MI | yes: 34% | no: 66% |
| angina for > 4 weeks | yes: 40% | no: 60% |
| prior β blocker | yes: 34% | no: 66% |
| pain free interval prior to therapy | < 1 hour: 26% | 1-3 hours: 36% |
| ECG changes during pain | yes: 51% | (baseline ECG often unavailable) |

The major result of the HINT was a trend towards an adverse effect of nifedipine which virtually excludes any possibility of this drug having a beneficial effect in this population of patients. There was a strong trend favoring monotherapy with metoprolol, and that addition of nifedipine to new metoprolol therapy had little additional effect. However, when nifedipine was added to prior $\beta$ blocker therapy, the combination seemed beneficial, as shown in table 6.

A somewhat worrisome observation from the HINT is the remarkably poor efficacy of drug therapy in high-risk subgroups. Retrospectively, the investigators grouped patients into low, intermediate and high-risk groups based on the pattern of chest pain and associated ECG abnormalities (Table 8). In the highest risk group there was a trend towards excess Q wave infarction in patients treated with nifedipine, but there was virtually no benefit of the other treatment protocols in this study.

**Table 8.** Risk of recurrent ischemia or infarction (RI+MI) or Q wave MI (Q MI) according to treatment group and clinical risk status.

| | low risk | | moderate risk | | high risk | |
|---|---|---|---|---|---|---|
| Treatment group | RI+MI | Q MI | RI+MI | Q MI | RI+MI | Q MI |
| control | 23% | 4% | 59% | 27% | 83% | 17% |
| nifedipine | 28% | 8% | 70% | 20% | 81% | 38% |
| metoprolol | 19% | 4% | 38% | 13% | 75% | 25% |
| metoprolol + nifedipine | 16% | 5% | 60% | 10% | 50% | 20% |
| prior β blocker | 24% | 6% | 67% | 0% | 72% | 14% |
| prior β blocker + nifedipine | 19% | 0% | 30% | 9% | 57% | 19% |

RI+MI, recurrent ischemia or myocardial infarction; Q MI, Q wave MI.

Another study reported in 1986 by Gottlieb et al. took a different approach to understanding the interaction of $\beta$ blockers with nifedipine. In this study all patients received nifedipine and nitrates, and the effects of propranolol were compared to placebo. In propranolol-treated patients there was a statistically significant benefit in controlling angina at rest and the number of episodes of angina during the first 4 days of therapy. This study is quite useful since it demonstrates no evidence of an adverse effect of $\beta$ blockade which might be due to induction of vasospasm.

Thus, there are three well-designed prospective, blinded, placebo controlled studies of nifedipine compared to conventional therapy. Nifedipine added to conventional therapy including $\beta$ blockers significantly reduces symptoms, but has no beneficial effect on progression to infarction or death as monotherapy. If nifedipine is combined with prior $\beta$ blocker, there is a significant reduction in the risk of infarction or recurrent angina.

## 6. Antiplatelet therapy

In 1974 the Veterans Administration cooperative study on aspirin for the treatment of unstable angina was initiated. This study, reported 9 years later, was performed because several trials of aspirin therapy after myocardial infarction had shown a trend to beneficial effects. It was felt that reversible limitation of myocardial perfusion could be interrupted by aspirin (Lewis, 1983). This trial, summarized in Table 9, demonstrates about 50% reduction in nonfatal MI which was highly significant ($p<0.005$), and a strong trend toward reduces mortality ($p=0.059$). The beneficial effect at 1 year persisted in spite of discontinuation of therapy at 12 weeks. There was no evidence of adverse effects of the dose and delivery used: 325 mg of aspirin in "effervescent buffered powder (Alka-Seltzer)".

The Canadian multicenter trial enrolled patients somewhat later (8 days *vs.* 2 days after admission) compared to the VA trial, and sulfinpyrazone and aspirin were studied in a 2x2 design. No benefit was detected for sulfinpyrazone. Aspirin at high doses (1300 mg/d) was associated with about 50% reduction in cardiac death or nonfatal MI ($p=0.0087$) by control therapy . By intention to treat analysis, cardiac death of nonfatal myocardial infarction tended to be reduced by 30% ($p=0.072$) with aspirin.

The third of the landmark aspirin trials was reported in 1988 (Theroux, 1988). In contrast to the other aspirin studies, this was an early entry, early endpoint trial. Patients were randomly assigned to aspirin, full dose i.v. heparin, the combination, or placebo within an average of 8 hours after the last episode of chest pain. Therapy was continued for about 6 days. Refractory angina occurred in about 23% of the placebo-treated population, and was significantly reduced by heparin or the combination of aspirin and heparin. Aspirin alone was not useful as prophylaxis against pain. Regarding the risk of infarction, there was a trend favoring heparin or heparin plus aspirin compared to aspirin alone, but this did

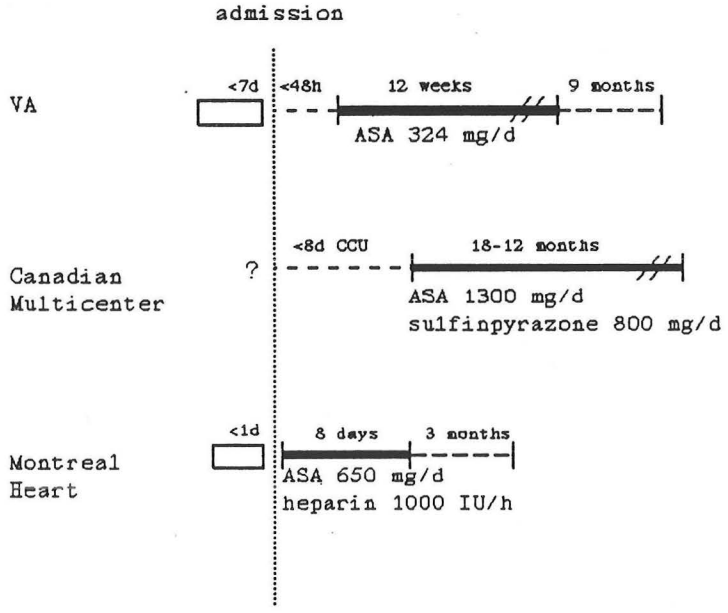


**Figure 1.** Trial design of three studies of aspirin for unstable angina. After Lorenz, 1990.

not reach statistical significance. Thus, this trial showed the efficacy of heparin for control of symptoms and aspirin for reduction of subsequent infarction.

Later reports based on this trial have also appeared. The abrupt withdrawal of heparin is associated with reactivation of unstable angina (Theroux, 1992). Interestingly, the original trial was expanded, and the trend towards benefit of heparin compared to aspirin for prevention of infarction reached statistical significance (Qiu, 1992). Other trials confirm the efficacy of aspirin. Wallentin, using a trial design similar to Theroux et al. but a lower dose (75 mg/day) found a reduction in death or infarction with aspirin of about 60%.

The overall consistency of results across dose and trial design is remarkable. Practice standards with regard to medical interventions, advisability and timing of catheterization and other factors are constantly evolving. However, three trials with very short, intermediate and prolonged treatment periods with different doses all found benefit (Figure 1). Together, these studies provide very strong evidence not only that aspirin is helpful, but that platelet activation plays a central role in the progression of unstable angina to infarction and death. In view of the unequivocal benefit in early intervention trials such as ISIS-2 as well as the Montreal Heart trial, it is prudent to administer aspirin as early as possible after admission.

Other agents also inhibit platelet function. Sulfinpyrazone inhibits cyclooxygenase, but the inhibition is less prominent than observed with aspirin. No benefit was found in the study by Cairns, et al. Ticlopidine differs from aspirin since it interferes with ADP-mediated platelet activation and does not block cyclooxygenase. A randomized, unblinded study of ticlopidine in unstable angina found significantly reduced progression to infarction in the treatment group which was equally effective as aspirin (Balsano, 1990), but side effects were significant.

In sum, antiplatelet agents (aspirin, ticlopidine, sulfinpyrazone) also have a reasonable theoretical foundation. Aspirin reduces MI and mortality in patients with unstable angina, and it has been carefully scrutinized in randomized prospective trials. Ticlopidine, a less well studied agent, may have similar benefits to aspirin, but has greater side effects. Sulfinpyrazone has been studied prospectively, and has no role in therapy for unstable angina. There is a strong consensus that either aspirin or heparin should be used in all patients with unstable angina. In view of the high reinfarction rate when heparin is discontinued without concomitant aspirin, it should be used in all patients.

## 7. Anticoagulation

If thrombus formation plays a role in the pathogenesis of unstable angina, then anticoagulation would seem to be beneficial. The first report on a clinical trial was not blinded, and patients were alternately assigned to control or therapy with phenindione for at least 6 weeks (Wood, 1961). Midway through the trial, patient selection was altered, and control patients were selected solely on the basis of a contraindication to anticoagulation or other factors. In this way 50 controls (20 from patient alternation and 30 from the latter phase) were compared to 100 treated patients. After 2 months, the risk of myocardial infarction and death in the control population was 22% and 30%, respectively. Anticoagulation provided dramatic benefits: infarction occurred in only 3%, and death in 6% of the

**Table 9.** Aspirin, heparin, and their interaction in patients with unstable angina.

| reference → | Telford, 1981 | Lewis, 1983 | Cairns, 1985 | Théroux, 1988 | Zwerner, 1987 | Wallentin* |
|---|---|---|---|---|---|---|
| A.K.A. → | Northern Ireland | VA Cooperative | Canadian Multicenter | Montreal Heart | | |
| study groups | control<br>heparin | control<br>ASA | control<br>ASA | control<br>ASA<br>ASA + hep<br>heparin | control<br>heparin | control<br>ASA<br>ASA + hep<br>heparin |
| total number of patients | 214 | 1266 | 555 | 479 | 62 | 794 |
| time to endpoint (days) | 7 | 84 | 550 | 7 | 8 | 90 |
| men only? | no | yes | no | no | ? | yes |
| heparin dose | 20,000 U/d | - | - | 5000 U bolus<br>1000 U/hr;<br>titrate to<br>PTT of 1.5 to<br>2.0 x control | ? | 30,000 U/d<br>for 5 days |
| aspirin dose/day | - | 325 mg | 1300 mg | 650 mg | - | 75 mg |
| time to medication start | ≈ 6-24 hrs | < ≈ 2 d | < ≈ 8 d | ≈ 8 hours since pain | ? | 24-72 hours |
| **endpoints** | | | | | | |
| ANGINA | | | | | | |
| control | - | - | - | 23.0% | - | |
| ASA | - | - | - | 16.0% | - | |
| ASA + heparin | - | - | - | 10.6%* | - | |
| heparin | - | - | - | 8.5%* | n.s. | |
| DEATH | | | | | | |
| control | 2% | 3.3% | 7.9% | 1.7% | 3% | |
| ASA | - | 1.6%* | 2.2%* | 0 | - | |
| ASA + heparin | - | - | - | 0 | - | |
| heparin | 0 | - | - | 0 | 9% | |
| MI (nonfatal) | | | | | | |
| control | 15% | 6.9% | 5% | 10.0% | 10% | |
| ASA | - | 3.4% † | 4% | 3.0% † | - | |
| ASA + heparin | - | - | | 1.6% † | - | |
| heparin | 3%* | - | | 1.0% † | 12% | |
| DEATH or MI | | | | | | risk ratio |
| control | 17% | 10.1% | 12.9% | - | 13% | |
| ASA | - | 5.0% ‡ | 6.2% † | - | - | A 0.41* |
| ASA + heparin | - | - | - | - | - | A+H 0.23 † |
| heparin | 3% | - | - | - | 21% | H 0.87 |
| statistical significance: value of p compared to control | * < 0.03 | * 0.059<br>† < 0.002<br>‡ < 0.0002 | * 0.004<br>† 0.008 | * < 0.01<br>† ≈ 0.01 | | * < 0.05<br>† ≈ 0.01 |

Abbreviations: ASA, aspirin, hep, heparin. *, included patients with non-Q MI

treated patients. Apparently, this study was widely accepted, but anticoagulation therapy for unstable angina fell out of favor about 10 years later.

In 1981 Telford and Wilson reported the Northern Ireland study, described previously. This was an early entry trial (Table 9) which found a significant reduction in the progression to infarction with heparin therapy, but there was a very large drop-out from the study, and cannot be considered conclusive. Nevertheless, this report probably stimulated later trials of heparin. In 1988 Theroux reported results of the 2x2 study design involving aspirin, heparin, both or neither for treatment of unstable angina. There was a clear beneficial effect of heparin for prophylaxis against recurrent angina and against progression to myocardial infarction. Interestingly, myocardial infarction was associated with Q waves in 86% of control patients, but significantly fewer of treated patients with infarction had a Q wave infarction.

In 1989 Wallentin briefly reported results of a similar study design which included patients with non-Q wave myocardial infarction. The aspirin dose was small, 75 mg/day. Nevertheless, at 5 days patients treated with heparin and aspirin had significantly reduced risk of death or myocardial infarction. This benefit persisted to 30 and 90 days. The risk ratio for aspirin alone was reduced at 30 and 90 days, but not at 5 days. Interestingly, heparin alone did not show a significant effect, in contrast to the observations by Theroux. Heparin alone was also studied in a trial reported briefly by Zwerner in 1987. Again, heparin did not confer any benefit in terms of reduced death or infarction.

In sum, heparin reduces MI risk very effectively. It is well-studied, and appears to be associated with a significant risk if discontinued without aspirin. There are some discrepancies in results with heparin monotherapy, but the most fully-reported study found substantial benefit. The role of combined heparin and aspirin has not been shown to be favorable compared to either agent alone in one study, but it was better than heparin in another. In my view, the combination is appropriate, and the risk of complications due to coadministration for a few days is small.

## 8. Thrombolytic therapy

Coronary thrombosis plays a role in the development of unstable angina, and the presence of thrombi correlates with adverse outcomes. Therefore, it is reasonable to determine if the symptoms of unstable angina or the risk of myocardial infarction is diminished by thrombolytic therapy. Perhaps at the outset it should be emphasized that the risk/benefit relationship of thrombolytic agents must be very carefully scrutinized since there are well-documented risks of major complications. Generally, most clinical trials of thrombolytic agents for unstable angina have taken this into account by reducing the dose or limiting the systemic exposure by intracoronary infusion.

Results of several small to medium size trials are summarized in Table 10. The most consistent result is that various thrombolytic agents and routes of administration lead to *angiographic* improvement, that is, the presence of intraluminal thrombi or the severity of coronary artery stenosis is reduced. However, the fact that only limited data are available regarding *clinical* improvement must be emphasized. Thrombolytic therapy for unstable angina remains investigational.

**Table 10.** Thrombolytic therapy for unstable angina.

| reference | randomized? | agent | # pts | angio-gram in all pts? | thrombus detected? | clinical and angiographic results |
|---|---|---|---|---|---|---|
| Rentrop, 1981 | no | ic sk | 5 | yes | ? | no angiographic improvement |
| Lawrence, 1980 | yes | iv sk | 20 | no | - | ↓ cardiovascular events at 6 months in patients given sk plus longterm coumadin |
| Vetrovec, 1982 | no | ic sk | 12 | yes | | angiographic improvement |
| Mandelkorn, 1983 | no | ic sk | 9 | yes | 44% | angiographic improvement |
| Ambrose, 1987 | no | ic sk | 37 | yes | 67% | nonoccluded arteries only; no angiographic improvement |
| Gold, 1987 | yes | t-PA, 12 hour infusion | 24 | | - | no arteriography prior to therapy; no clot found in patients given t-PA; decreased angina with t-PA |
| Gotoh, 1988 | no | ic uk | 37 | yes | 57% | angiographic improvement |
| de Zwaan, 1988 | no | ic sk or t-PA | 41 | yes | 68% | angiographic improvement |
| Topol, 1988 | no | t-PA | 40 | yes | 40% | improved pacing threshold |
| Chaudry, 1992 | yes | cont<br>tpa rd | 24<br>26 | - | - | stabilization of symptoms |
| Schreiber, 1992 | yes | uk + hep<br>uk + asa<br>pla+ hep | 149 | no | - | no clinical difference in outcome. |
| TIMI IIIA, 1993 | yes | t-PA, rd, + heparin | 209 | yes | 29% | 15% (t-PA) had > 2 TIMI grade improvement, compared to 5% of control; clinical outcome not yet reported. |
| Bär, 1992 | yes | apsac | 159 | yes | - | angiographic improvement - reopening of occluded vessels |

Abbreviations: ic, intracoronary; rd, reduced dose, t-PA, tissue plasminogen activator; sk, streptokinase; uk, urokinase; APSAC, anistreplase; pla, placebo; cont, control.

## 9. Combination medical therapy for unstable angina

The rationale for combination therapy of unstable angina is based on one or more goals. *First*, the pathogenesis of the syndrome may be multifactorial. Since a single drug may modify only a one or a few determinants, multiple drug therapy may be logical. Over the last decade unstable angina has been attributed to multiple pathogenic factors including increased oxygen demand, coronary artery vasomotion, or coronary artery thrombus formation on an ulcerated atheroma. Although the pathogenesis is probably multifactorial in some patients, therapy targeted to simply reducing oxygen demand or dilating epicardial coronary arteries appears to improve symptoms but to have no effect on progression to MI or death. Drugs which have distinct effects on platelet aggregation, thrombus generation and maintenance, coronary artery dimension and myocardial oxygen demand can be logically combined.

*Second*, low doses of two drugs with overlapping beneficial effects but different side effects may have a more favorable risk/benefit ratio. It is more difficult to rationalize combining drugs with overlapping effects. Among the drugs listed in Table 10, this principle applies only to combining $\beta$ adrenergic blockers and calcium channel blockers, since both classes can have favorable effects on heart rate, afterload and myocardial contractility.

*Third*, a drug may be used to counteract the adverse effects of another agent. The combination of $\beta$ adrenergic blockers with nifedipine has been advocated because the $\beta$ blocker will blunt a reflex tachycardia of nifedipine.

A useful conceptual framework is to classify treatments in terms of their documented effects on therapeutic goals: relief of symptoms, and reduction of MI or death (Table 11). *Aspirin* has consistently shown a favorable effect on reduced progression to infarction or death in patients with unstable angina, and should therefore be used in all patients without clear contraindications. Results of studies with *heparin* are not completely consistent, but it appears to both improve symptoms and prevent progression to infarction. Again, in the absence of contraindications, it should be used concomitantly with aspirin. *Nitroglycerin* is clearly effective for acute control of symptoms, but the consequences of longer term (days) prophylactic therapy, particularly intravenously at high doses, are uncertain. It is probably reasonable to use relatively low dose intravenous nitroglycerin and titrate it up in response to ischemic chest pain rather than arbitrary blood pressure goals. *$\beta$ adrenergic blockade* should be initiated early because it has favorable although less well-documented effects on both mortality and symptoms. Intravenous therapy is supported in two early trials. Calcium channel blockers are useful for control of symptoms, and may be particularly helpful when angina occurs at rest with ST elevation. Nifedipine when administered to patients already taking $\beta$ blockers is beneficial, and it should not be used in the absence of well-established $\beta$ blockade. Both verapamil and diltiazem are effective for symptomatic relief, and can be used in combination with $\beta$ blockers to achieve optimal heart rate and blood pressure control.

**Table 11.** Effects of drug therapy for unstable angina. Each entry refers to the documented or probable results of monotherapy with that agent.

| THERAPY | RELIEVES SYMPTOMS? | REDUCES MI OR DEATH IN UNSTABLE ANGINA? | FAVORABLE EFFECT IN MYOCARDIAL INFARCTION? |
|---|---|---|---|
| i.v. nitroglycerin | yes | unknown | probably yes |
| metoprolol, atenolol, or propranolol | yes | probably yes | yes |
| diltiazem or verapamil | yes | unknown | possibly yes |
| nifedipine | yes, if combined with a $\beta$ blocker | no | no, possible adverse effects |
| aspirin | no | yes | yes |
| heparin | probably yes | yes | yes |
| thrombolytic therapy | probably no | probably no | yes |

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