MEDICAL GRAND ROUNDS

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"UNSTABLE ANGINA PECTORIS"

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Unstable angina pectoris poses one of the most vexing issues currently facing the clinical cardiologist. This vexation can be attributed to a number of reasons, among them: the lack of a clear understanding of the pathophysiology and natural history of unstable angina, the lack of an ideal medical treatment, and the controversies over whether and which of these patients should have coronary artery bypass surgery as part of their treatment, and if so at what stage of their illness or recuperation. The purpose of this review is to analyze the state of our current knowledge and to formulate a tentative recommended approach to the management of these patients.

HISTORICAL BACKGROUND AND NOMENCLATURE:

Heberden, (58,59) in his classic and still unsurpassed clinical description of angina pectoris alluded to unstable angina as he briefly mentioned non-exertional angina. Parry (101) mentioned it in 1799. But an appreciation of a syndrome intermediate to chronic stable angina pectoris on the one hand and myocardial infarction on the other was delayed by the long interval (until the early part of this century) between Heberden's description of angina and an appreciation of its pathophysiology (68) and the description of myocardial infarction (61,96). Both of these pioneer descriptions of myocardial infarction also vaguely referred to what was probably unstable angina. However, attention was drawn to unstable angina as a distinct entity first in the 1930's in the German literature (15,16,30,129) and in the United States by Sampson and Eliaser (115) and Feil (40). These latter descriptions referred to this variety of pain as precursor phenomena and preliminary pains of coronary thrombosis. Since then, this syndrome has been described under a number of terms. Some of these are listed in Table I. Unstable angina pectoris and intermediate coronary syndrome seem to be the most appropriate terms. They are broad enough to effectively encompass the spectrum of disorders that make up the syndrome and draw attention to its position between chronic stable angina and myocardial infarction. The term acute coronary insufficiency is flawed chiefly because it has been used in so many different ways since its first use over 30 years ago, even by Dr. Master who coined the term. Currently it is generally used to mean a single episode of severe angina mimicking infarction, but without evidence of necrosis of myocardium. The large number of terms that have been included in the last group in this table all connote that unstable angina is a premonitory phase of acute myocardial infarction. Since it is clear from a review of the literature that most patients with unstable angina do not develop a myocardial infarction in the immediately following period and since a diagnosis using these terms can be made correctly only in retrospect, it has been

suggested recently that the use of such terms be avoided. It must be conceded, however, that they have been useful in pointing out the potential seriousness of unstable angina. When viewed "from the opposite direction", it is clear from a number of studies over the last few decades following Wearns initial observation in 1924 (135), that patients with a clearly documented myocardial infarction frequently have had a premonitory, unstable period. Some of these studies are summarized in Table II. Although these studies span 34 years, agreement is remarkable in that all reported that a substantial percentage of their patients had a distinct prodrome, ranging from 16-84%. Probably the most sensible taxonomical approach is to use "unstable angina" as a general term to include all patients in a rather broad spectrum of disorders and to subdivide this into smaller groups with descriptive terms as was suggested by Papp and Smith (100) in 1960 and more recently by Hurst and Logue (65).

Since its recognition as a distinct entity, it has become increasing obvious that it is quite common. In 1955 (26), it was estimated to be "at least half as common as acute transmural myocardial infarction" and the percentage of all patients in the coronary care unit who have this syndrome have been stated to be 10.5% (82), 19% (73), and 30% (91). Wood (139) found that 10% of 1000 consecutive patients with ischemic heart disease fell into this category.

DEFINITION:

The difficulties in naming this syndrome point up the even greater difficulties in defining it. This has caused particular difficulty in trying to compare patients in one study with those of another. This led Fowler (43) in 1971, almost 40 years after the description of unstable angina as a distinct clinical entity, to make an editorial plea for an objective definition! While there is still no uniformity of definition, most would agree to a definition similar to the following:

> Unstable angina includes patients with the following clinical presentations (in the absence of precipitating events, anemia, severe congestive heart failure, thyrotoxicosis, etc.):
>
> 1. New onset or recurrence of angina pectoris that is progressive (accelerated, crescendo) in nature or that occurs at rest poorly relieved by rest or nitroglycerine.
>
> 2. Deterioration of chronic angina pectoris that was formerly stable in that it becomes more frequent, more easily provoked, more severe, longer in duration, or less readily relieved by rest and nitroglycerine.

3. One or more bouts of angina pectoris that last in excess of 15 minutes with poor or no relief by rest and nitroglycerine.

Further, the absence of a myocardial infarction must be confirmed by demonstration of:

1. No new pathologic Q waves or permanent loss of R wave forces pathognomonic for myocardial infarction.

2. No diagnostic serum enzyme alterations.

Some, but not all, would include in the definition demonstration of fluctuating ischemic ST or T wave changes in the electrocardiogram. Fowler (43) has suggested that the definition also include arteriographic evidence of a significant atheromatous narrowing of one or more coronary arteries to make the definition truly objective. This addition to the definition has advantages and disadvantages that will be discussed in subsequent sections.

DIAGNOSIS:

The diagnosis rests, after establishment that the pain is ischemic in nature, on excluding stable angina pectoris on the one hand and myocardial infarction on the other. In the case of the latter, one must rely heavily on the electrocardiogram and laboratory evaluation, especially serum enzymes released from damaged myocardium, CPK, SGOT, and LDH. Pathognomonic ECG changes and evolution of a transmural infarction rarely cause any difficulty in recognition and proper diagnosis. Characteristic ECG changes and diagnostic enzyme rises distinguish clear-cut subendocardial infarctions. Differentiation of unstable angina from small amounts of subendocardial necrosis may be difficult, however. An absolute distinction is probably impossible. When one considers that ischemic heart disease includes a broad spectrum of clinical presentations, it is only logical that the border between unstable angina and subendocardial infarction would be imprecise. Minor degrees of serum enzymic evidence of cell necrosis have been reported in 37% (130) and 74-93% (108) of patients with unstable angina. Willerson and his colleagues at this institution have recently reported that 35% of patients with unstable angina have mild myocardial uptake of technetium-99m stannous pyrophosphate raising the possibility of minor degrees of cell necrosis in these patients not detected by other methods (32). In a pathologic study of patients dying shortly after coronary artery bypass surgery, 4 of 12 patients with unstable angina were found to have evidence of pre-operative infarction that had not been detected clinically, whereas this was not found in any of 35 patients with stable angina.

In general it seems more appropriate to consider these patients as having unstable angina rather than a myocardial infarction. Serum enzyme levels not exceeding 140% (25) or 150% (7) of the upper limit of normal have recently been suggested as arbitrary cut-off points in this distinction. Since marked hypotension, shock, and marked degrees of congestive heart failure are not uncommon with subendocardial infarctions but absent (by definition) from unstable angina, presence of these complications of the acute episode also allow prompt distinction.

Differentiation of unstable from stable angina is largely a function of a carefully obtained history. Some of the helpful features are outlined in Table III. While provoking factors such as exertion or emotional upsets are present in stable angina, they are absent or cause pain with progressively lesser degrees in unstable angina. Unstable angina occurs more frequently than stable angina. While stable angina is predictable with regard to frequency and ease of provocation, unstable angina is not. While rest and/or nitroglycerine provide relief for stable angina, in unstable angina they provide only partial or less prompt or no relief.

Electrocardiographic ST and T wave abnormalities of ischemia are worthy of special comment. In general they are often missed in stable angina and frequently observed in unstable angina. In both cases they are found in direct proportion to how frequently and diligently the physician looks for them. While some investigators have demanded these abnormalities for the diagnosis for inclusion into a particular group for study, it is important to realize for therapeutic purposes that a large number of patients with unstable angina do not have ischemic ECG changes at the time of their presentation. Table IV summarizes the frequency of normal or non-diagnostic ECG's in these patients in the experience of several investigators. Since this reported frequency is as high as 50%, it is a serious mistake to fail to make the diagnosis of unstable angina when the history warrants it but the ECG is negative for ischemic changes.

PATHOPHYSIOLOGY:

The pathophysiologic basis (bases) for unstable angina remains an enigma. Early it was assumed that patients with unstable angina with a more abrupt onset had sustained a coronary thrombus complicating an atheromatous lesion and patients with a more insidious onset had progressive narrowing of the involved vessel (139). As early as 1956, Master et al (86) cautioned against assuming acute thrombosis without frank infarction as the cause. He reviewed the frequency of sudden death and myocardial infarction in patients with ischemic heart disease without pathological evidence of coronary thrombosis.

Probably, there is a degree of myocardial ischemia in unstable angina in which the coronary flow is barely sufficient for the oxygen needs at rest. In stable angina, the flow to the ischemic segments of the heart is presumably adequate at rest but inadequate during exertion. What causes the development of the former state is far from clear. With the advent of coronary arteriography in the 1950's, it was hoped that accurate delineation of the coronary circulation in life would provide anatomical information to explain the etiology of this syndrome. Unfortunately, this has not been the case. Proudfit and his colleagues at the Cleveland Clinic (106) have reported on the distribution of arterial lesions of 627 patients with clinically presumed or suspected ischemic heart disease. One hundred seventy patients had unstable angina. The distribution of lesions in these patients was similar to that encountered in patients with stable angina pectoris. Herman and Gorlin (60) compared the distribution, severity, and site of atheromatous disease and left ventricular function of 19 patients with unstable angina to those with chronic coronary disease and noted that they were similar. Similar findings were obtained in a study of the coronary arteries at autopsy in 12 patients with unstable angina, 20 with stable angina, and 15 with stable moderate angina (53). These studies did not find a high incidence of left main coronary artery lesions in patients with unstable angina, but in one retrospective analysis of 28 patients who had left main disease, 23 had presented with unstable angina (70). Some investigators (116, 132) have noted a paucity of collateral vessels to the ischemic area subserved by the diseased vessels. Others (25,60) have not confirmed these findings, so that a potential etiologic role for inadequate collateral vessel formation remains uncertain. Occlusion of a coronary collateral vessel and thus diminishing the blood supply to the ischemic area it served has been suggested as a potential mechanism (125). A particularly vexing finding is a large number of patients with symptoms identical to patients with demonstrable arteriographic lesions with normal coronary arteriograms. The number of such patients relative to the total group has been remarkably similar in most reports, ranging from about 10-25%. Some of these results are itemized in Table V. The significance of this finding and the etiology of the symptoms in these patients remains completely unclear.

As mentioned above (see DIAGNOSIS), some of these patients probably have microscopic islands of myocardial necrosis. Multiple micro-infarctions cannot be dismissed as a possible cause for the instability in some of these patients.

There has been recent interest in a potential role of platelet aggregates in unstable angina. Further occlusion of an already stenotic vessel by platelet aggregates could acutely further diminish flow to the already compromised myocardium. This aggregate might either break up or lead to the formation of a thrombus. In experimental animals, intracoronary adenosine disphosphate (ADP) (66) and systemic epinephrine (54) have been demonstrated to cause intracoronary platelet aggregation and myocardial necrosis. Prevention of platelet aggregation in the former case by induced thrombocytopenia and in the latter with the use of aspirin or dipyridamole prevented induction of myocardial necrosis due to ADP or epinephrine in these models.

In an interesting recent report, Caulfield and his associates (18) found that in 13 of 15 autopsied patients who were admitted with unstable angina followed by acute myocardial infarction and death, there were multiple plaque hemorrhages in two or more coronary arteries and occlusive thrombosis at the site of infarction. This was a distinctly more common finding in this group than in 12 patients with acute infarction not preceded by unstable angina and 11 patients with no history of coronary artery disease.

It is well established that classical exertional angina is virtually always due to an imbalance between myocardial oxygen demand (MVO_2) and coronary oxygen delivery and that the hemodynamic changes preceding effort angina can be clearly defined and are reproducible in a given patient (110). Unstable angina has been studied similarly (17,80,113) and also was preceded almost invariably by increases in the heart rate and/or blood pressure to yield a pulse-pressure produce similar to those proceding angina during exertion. Consequently, in some patients, unstable angina may be the result of a dynamic imbalance between MVO_2, coronary oxygen delivery and the cardiac mechanical activity state. The causes of the hemodynamic changes occurring before the onset of spontaneous angina could be multiple.

Variant (Prinzmetal's) angina pectoris is discussed at greater length below but a few comments are in order here, since some would include this order as a sub-group of unstable angina. (For most references in this paragraph, see the section VARIANT ANGINA below). It appears well demonstrated from several studies that coronary artery spasm, focal or diffuse, in association with an atheromatous lesion or in a vessel without such plaques may be the cause of the myocardial ischemia and angina. This has been demonstrated in patients totally free of atheromatous disease. In some of these patients the ST segment elevation and pain at rest that is characteristic of this disorder have been demonstrated to occur without a rise in blood pressure or pulse rate.

It seems appropriate to add coronary artery spasm as a potential pathophysiologic mechanism to at least some patients. However, variant angina is quite rare compared to all cases of unstable angina and this mechanism would presumably account for only a small percentage of all such cases. It is interesting to speculate that coronary spasm may have played some role in the disease of the four patients of Scanlon et al (116) who had unstable angina, a previous MI and normal coronary arteriograms, and the 1 of Conti et al (25) who had unstable angina, normal coronary arteriograms and died suddenly several months after his initial evaluation. It is well documented that patients with normal coronary arteries with the Prinzmetal variant angina may develop a myocardial infarction or die suddenly in marked contrast to the benign course of patients with stable angina pectoris and normal coronary arteries (78, 69). Whether spasm is involved in myocardial infarctions in other rare patients with normal coronary arteries (77, 36, 121) is unknown.

NATURAL HISTORY:

Although reports on the natural history of unstable angina date to 1937, our understanding is still limited. There are several identifiable reasons for the great disparity in the reported natural history studies. First, the heterogeneity of the patient population, even within a single study, has not been taken into account properly. Sampson and Eliaser (115) in the initial natural history study in 1937 noted that they suspected that the prognosis in patients with a single prolonged episode of pain resembling an acute infarction was different from patients with progressive angina pectoris. Yet only recent studies have attempted to look at the prognosis of patients within well defined subgroups as well as the total group. Second, earlier studies, which generally reported a worse prognosis than recent ones, almost certainly included some patients with subendocardial infarctions. Prior to the late 1950's separation of unstable angina from subendocardial infarction rested on the serial evaluation of fever, leukocytosis, and various tests of systemic reaction such as erythrocyte sedimentation rate and C-reactive protein. Introduction of SGOT in 1955 (1,95) as a diagnostic tool for myocardial infarction, and later of LDH and CPK substantially sharpened this distinction. Third, different investigators have defined unstable angina differently, adding further to the heterogeneity of the population groups. Fourth, the follow-up periods have varied from acute hospitalization to over 10 years. Fifth, coronary arteriography has been available for only the last few years. Dunkman and his coworkers (35) have pointed out that differentiation of the coronary anatomy considerably sharpened our understanding of the natural history of stable angina pectoris and is likely to do so for unstable angina as well. Finally, the patients often were treated quite differently, even within a single study, until recent years, further adding to the heterogeneity of the study group. Given these drawbacks, it is somewhat remarkable that the data do not differ more than they do. For the reader inclined toward "splitting", the data from 20 studies are abstracted in as much detail as feasible

in Table VI. For the "lumper", the overall incidence of myocardial infarction and mortality regardless of the follow-up period is itemized from these studies in Table VII. Except for the work of Sampson and Eliaser, which is included because of its historical value, data from studies derived from patients who were admitted with a myocardial infarction preceded by a prodrome are excluded for their obvious bias. It would not be valid to attempt to precisely condense these data to a single incidence of infarction or mortality figure because of the multiple reasons mentioned above. However, if one makes an "educated guess" based on these data, there appears to be an overall chance of about 20-25% of the patients with unstable angina developing an infarction and a similar chance of dying in the year following destablization. The annual infarction rate is 5% and the death rate is 4% in the total population with ischemic heart disease (67) and the annual death rate is 10% in the highest risk group, the group with 3-vessel disease (14). This stark contrast alone makes recognition of this group of patients as a separate entity important for prognostic and therapeutic purposes. If one looks only at more recent studies, however, where the definitions of unstable angina were sharper and more comparable and where treatment of the patients were more nearly comparable, further tentative conclusions about the natural history seem justified. The studies of Krauss et al (73), Fischl et al (41), Bertolasi et al (7), See et al (118), Watkins et al (134), and especially Gazes et al (47) are helpful in this regard. From these studies, it appears that the clinical profile of those patients with unstable angina pectoris who are particularly high risk patients is beginning to emerge. Gazes and his associates (47) found that those patients who had angina beyond the first 48 hours of hospitalization had a much worse prognosis and likelihood of a myocardial infarction than those who did not. (Table VI). Most of those patients had prior stable angina pectoris and ischemic ECG changes during pain. Prior bundle branch block was a marker for poor prognosis. Within this high risk subgroup, those patients who had ischemic ECG changes prior stable angina, or a previous myocardial infarction had the highest incidence of acute infarction and associated death. The single in-hospital death in the patients reported by Krauss et al (73) was one of the 3 patients who had recurrent pain in spite of medical treatment. In that study and in those of Beamish and Storrie (5), and See et al (118), there were more cardiac deaths in patients who had had a previous myocardial infarction or previous angina pectoris. In those patients studied by Bertolasi et al, the mortality of patients treated medically was seven-fold that in the group with "intermediate syndrome" as opposed to "progressive angina". In several ways, the group with "intermediate syndrome" corresponded to the "high risk" group of Gazes although both groups (by design) had comparable numbers of previous myocardial infarctions. It seems highly likely then that persistent pain despite medical therapy, previous MI or stable angina, ischemic

ECG changes during pain and prior bundle branch block are indeed bad prognostic markers in these patients.

A higher mortality rate in patients with hypertension, multiple-vessel disease, and diabetes mellitus (118,134) and with a third heart sound (134) have been reported, also.

It seems likely that the natural history of this disorder can be even better defined as more studies with more homogeneous and well defined subgroups with carefully defined coronary anatomy become available. As will be discussed subsequently, this is of paramount importance in order to define which patients should be considered candidates for coronary artery surgical reconstruction in order to avoid subjecting patients to a treatment with a higher morbidity and mortality than the disease itself.

VARIANT (PRINZMETAL'S) ANGINA:

Prinzmetal et al (104,105) described a variant form of angina pectoris characterized by non-exertional, non-preinfarctional chest pain associated with ST segment elevation. He noted that the location of the ST segment elevation corresponded closely to the site of ischemic muscle that later was involved in infarction. He postulated that the angina and ECG changes were due to a focal stenotic coronary artery lesion with superimposed spasm causing severe ischemia in a well localized area. While not rare, this variant is not nearly as common as classic angina pectoris.

While Prinzmetal noted that ventricular arrhythmias and heart block occurred in some of his patients and two died suddenly, he distinguished this syndrome from "pre-infarctional angina". Subsequently, some case reports have tended to suggest a more grave prognosis with a rather high frequency of rapid progression to infarction and death (121) while others have noted a more chronic, benign course (31,57). The occurrence of ventricular arrhythmias (8,50,55,57,94,114) and atrioventricular conduction defects (8,13,31,48) have been confirmed in a number of reports. The nature of the pain, with occurrence at rest and with transient, often dramatic, ST segment elevation tend to weigh in favor of its inclusion in the overall category of unstable angina.

Recently it has been emphasized that variant angina pectoris, too, represents a rather heterogenous group of patients (117). While most of the reports have substantiated Prinzmetal's hypothesis that variant angina is associated with proximal, single-vessel arteriosclerotic plaques, it has become clear that this syndrome may occur in the absence of significant coronary artery disease (9,20,21,26,31,74,84,97,141). Numerous

cases of variant angina have been reported recently with coronary artery spasm (20,22,28,29,55,88,97,114,141) with and without significant coronary artery disease. This spasm has been shown to be discrete or segmental. Different amounts of the vessel may be involved with spasm at different times (31). While the pain and ST segment elevation may be preceded by an increase in the pulse rate and/or blood pressure, carefully documented cases have been reported (46,52,84) where they are preceded by no change or a drop in the pulse-pressure product or the "triple product" (left ventricular mean systolic pressure x pulse x systolic ejection period) which contrasts sharply with the nearly invariable presence of an increase preceding classical angina. It is tempting to speculate that the pathophysiologic abnormality in these latter cases is reduction of coronary flow due to spasm rather than an increase in MVO_2. A recent study (141) suggested that the etiology of this spasm may be enhanced activity of the parasympathetic nervous system which is involved in initiating the episode by stimulating the sympathetic nerve which then induces coronary artery spasm by activation of alpha receptors in these vessels.

While ST segment elevation cannot be elicited during exercise in the typical patient with variant angina pectoris, there are some patients who have exercise-induced transient ST segment elevation (42). Other patients, "a variant of the variant" have ST segment elevation without pain (20,50). In a recent comparison of 82 patients with unstable angina (102) clinical and arteriographic data were compared in 64 patients with ST segment depression ("group I") and ST segment elevation ("group II"). While there was no significant difference in the angiographic extent, location or severity of the coronary artery disease or collateral development, single vessel disease was encountered twice as frequently in group I and left main disease was found only in group II. More of the group I patients presented with recent onset angina. Life-threatening arrhythmias were uncommon in both groups, but were present more often in group I.

In the approach to these patients, their marked heterogeneity (117) must be kept in mind. Careful evaluation of the hemodynamic changes preceding and accompanying pain and an early documentation of the nature and extent of coronary artery disease in these patients is obviously of great importance. Only the presence of coronary artery spasm in many of these patients appears to be a unifying feature (83).

TREATMENT:

General

From the data outlined in NATURAL HISTORY, it is clear that these patients should be hospitalized in a coronary care unit in order to detect dangerous arrhythmias and conduction defects, define precisely the clinical nature of the pain pattern and establish the nature of any ECG changes during and in the absence of pain. During the first 2-3 days, many will require careful evaluation to distinguish between a subendocardial infarction and unstable angina. They should be treated with bedrest, quietude, oxygen and sedation when appropriate and correction of any complicating abnormalities viz. arrhythmias, electrolyte abnormalities, etc. Hypertension should be treated vigorously. Nitroglycerine and long-acting nitrates may be very useful, but pain that is not relieved within 5 minutes by nitrates should be treated with intravenous opiate analgesics. The vast majority of patients will become pain-free on this regimen alone. Liberalization of the patients' activity should be postponed until there has been a pain-feee interval of at least 48 hours and resumption of activity should be gradual. It is obvious that discharge prior to a 10-day stay should be unusual; the practice of discharging "rule-out myocardial infarction" patients after 3 days of observation is hard to defend in most cases.

Anticoagulation

Since the report of Wood in 1948 (138), the literature has been replete with glowing but poorly documented reports of the efficacy of anticoagulation in unstable angina. The results of most of the large studies utilizing anticoagulation in unstable angina are tabulated in Table VIII. Only the studies of Master (85) and Vakil (131) were truly controlled and neither study was randomized or double-blinded. While Vakil stated that the infarction and mortality rates were significantly lower in the treated group, no details of this analysis were given. In Master's study, anticoagulated patients appear to have fared worse than the controls. While anticoagulation would appear to be beneficial in preventing both infarctions and mortality, the design of the studies prevent drawing any firm conclusions. In recent years, anticoagulants in this syndrome have been used less frequently (142). The current practice in the Coronary Care Unit at the VA Hospital is to use them in this setting only when the patient is at greater than ordinary risk for venous thrombosis (previous venous thrombosis, venous disease, obesity, need for prolonged bedrest, etc.).

In view of the recent necropsy findings (18) of widespread coronary artery plaque hemorrhages, one might question whether anticoagulation in these patients is hazardous. However, in a large number of autopsies of patients treated with anticoagulants post-myocardial infarction, the Committee on Anticoagulants of the American Heart Association did not find an increased frequency of subintimal hemorrhage in the coronaries (140).

A final tentative note of caution regarding the use of heparin is in order. There is current interest in a possible deleterious role of free fatty acids in patients with acute myocardial infarction and unstable angina (103). The use of heparin causes a significant rise in the level of circulating free fatty acids (112).

Because of the interest that platelet aggregates may be important in the pathophysiology of this disorder in some of these patients, and because there are now suggestive although not conclusive data that patients with ischemic heart disease on chronic aspirin therapy a reduced incidence of myocardial infarctions (12,37), a randomized, controlled, double-blind trial of aspirin in this disorder has been suggested (142), and a cooperative study involving 10 hospitals including the VA Hospital has been underway for about one year. No preliminary data are available yet from that study.

β-Adrenergic Blockade

Cardiac β-adrenergic blockade lowers MVO_2 by diminishing the heart rate and inotropic state of the heart and, in some patients, by some diminution in blood pressure (afterload). Since its introduction as a therapeutic modality (33), it has become second in importance only to nitrates in medical management of angina pectoris. Fischl et al (41) found good control of angina in 17 of 20 patients with unstable angina of a "high risk" type (47), with propranalol. In 7 patients with unstable angina with continued pain after 14 days of hospitalization, Papazoglov (98) found that all could be rendered pain-free with propranalol.

The use of propranalol in unstable angina must be accompanied by a diligent watch for the development of insidious left ventricular decompensation. During the initial evaluation some will be found to have already sustained a non-transmural infarction; others will go on to develop an infarction. Clinically unsuspected left-sided failure is common in patients with an uncomplicated myocardial infarction (56). Some patients with unstable angina without infarction have depressed left ventricular function (19). The use of propranalol in these patients should generally be avoided since it would worsen the congestive failure and the attendant increase in cardiac size would increase left ventricular wall stress and MVO_2.

The role of β-adrenergic blockade in variant angina in unclear. While there are several reports of successful management of such patients with a regimen including propranalol (31), precipitation of variant angina with propranalol and sympatholytic antihypertensives have been reported (114,141). If the hypothesis of Yasue (141) is correct regarding the initiation of coronary artery spasm in these patients (activation of coronary artery alpha receptors - see VARIANT (PRINZMETAL'S) ANGINA), β-adrenergic blockade might well further aggravate the spasm or allow its development.

Coronary Artery Surgical Reconstruction

In 1967, Favaloro and his associates (38) introduced saphenous vein aorto-coronary bypass surgery for patients with chronic severe stable angina; in 1971, he and others (39,75,132) reported extending this procedure to patients with unstable angina. Since then, there have been many such reports. The data from most of these studies are outlined in Table IX. Hegel's comments on history and people* have been borne out in the approaches to coronary artery surgery in the last 4 years. All the mistakes made in the studies of the natural history of unstable angina and in the studies of the treatment of unstable angina with anticoagulants have been repeated. Most of the studies are uncontrolled. Most of the "controlled" studies are far from truly being controlled. In most, the definition of unstable angina have differed or were vaguely stated. The populations have been heterogeneous and specific subgroups have not been separated for analysis. The approaches to surgery have differed widely. Once again, we must try to make "educated guesses" from the literature. First, it is clear that even in this unstable group bypass surgery can be undertaken with much less than a prohibitively high risk such as that seen in such surgery immediately following acute myocardial infarction. The greater issues are, of course, whether surgical or medical management will hold the lesser risk of subsequent infarction and death and reduction in the frequency and severity of angina pectoris. The only means to obtain conclusive evidence of the superiority of surgical versus non-surgical management of unstable angina pectoris is with the use of carefully designed, prospective, randomized, controlled studies utilizing sharply drawn definitions (43).

*Georg Wilhelm Friedrich Hegel in Philosophy of History (1832) Introduction. "People and governments never have learned anything from history, or acted on principles deduced from it."

Two such studies are underway and merit special consideration. One is a cooperative study involving several of the former Myocardial Infarction Research Units which were set up by the National Heart and Lung Institute. These preliminary data are itemized in Table IX under Conti et al, 1975 (24). Seventy-three patients received non-surgical treatment and 65 had bypass grafts. There were 4 surgical (3 peri- and 1 postoperative) and 7 medical in-hospital deaths. There have been 2 surgical and 3 medical late deaths after a mean follow-up of 7 months. There were 14 in-hospital myocardial infarctions, 3 pre-, 9 peri-, and 2 post-operative and 5 late infarctions. Non-surgically treated patients had significantly fewer infarctions with 6 occurring in-hospital and 5 late. It is, of course, possible that with longer follow-up, the non-surgically treated patients will evenutally have more infarctions than the surgically treated group.

Bertolasi and his associates in Buenos Aires have undertaken a similar study (7). In addition (see above under NATURAL HISTORY), they have subdivided their patients into two groups prior to randomization. The intermediate syndrome was classified as recurrent, prolonged, intense, non-exertional angina and at least two of the following: little or no relief by nitrates, transitory ST or T wave ECG changes, transitory arrhythmias, and an interval of less than one month between onset of angina and admission to the study. Their other subgroup, progressive angina was defined as a change in the evolutionary pattern of angina within 3 months of admission to the study with an increase in the intensity, duration and frequency of pain. As noted above, the intermediate syndrome patients have many aspects in common with Gazes' (47) high-risk group. Their preliminary data after a mean follow-up period of 8.3 months also are tabulated in Table IX. While they found no significant difference in the mortality rate between surgically and non-treated patients in the progressive angina group, surgically treated patients in the intermediate syndrome group fared much better than the non-surgically treated group. Theroux and Campeau (127) have also noted differences in the surgical mortality of patients with unstable angina when various subgroups are investigated. They found a higher incidence of surgical mortality in patients with "crescendo angina" than in patients with "acute coronary insufficiency".

It has been an almost uniform finding that surgically treated patients have less frequent and less severe angina than those patients treated non-surgically. Because patients with more diffuse and severe coronary disease and more severe left ventricular dysfunction would tend not to come to surgery, these findings must be viewed skeptically in non-randomized, controlled studies. However, this finding has also been borne out by the two randomized studies mentioned above. In Bertolasi's study, the difference between the two was much more marked in the patients with the intermediate syndrome. In the group with progressive angina, both groups improved, but the medically treated patients did so to a lesser extent.

Whether left ventricular function can be improved in patients with chronic stable angina pectoris remains uncertain with conflicting reports. There are fewer data available regarding this question in patients with unstable angina. If some of these patients have severely ischemic but viable myocardium, it is conceivable that revascularization might restore more nearly normal function. Chatterjee and his coworkers (19) have reported such reversal in six patients with unstable angina, but there was no comparison to similar patients treated medically. Further work will be necessary before it can be concluded that surgical treatment of patients with unstable angina and depressed ventricular function will experience improvement in this dysfunction.

There are some conflicts in these reports regarding the risks of surgery in these patients compared to similar surgery on patients with stable angina. It is of concern that in large groups of patients with unstable angina treated surgically at Johns Hopkins (25) and Stanford (89), the operative mortality is several-fold higher than that for the same surgeons operating on patients with stable angina. While this has not been uniformly noted in all centers, it argues for discerning what steps might be taken to lower the operative mortality in this group. It has been noted by several centers that stabilization of the patients medically for several days (6,72,41) or weeks (128) leads to a diminution in the surgical mortality rate. Other centers have reported a lack of untoward results, however, in spite of early catheterization and operation (11).

The selection of patients who are suitable for surgery does not differ from that for patients with stable angina. Patients with proximal coronary disease with large, patent distal vessels represent good candidates; those with diffusely diseased vessels or markedly diminished ventricular function represent poor candidates.

The role of coronary artery surgery in the Prinzmetal's variant angina is not yet clear. Certainly in those patients with proximal, high-grade coronary artery stenosis, and well preserved ventricular function they would appear to be ideal surgical candidates. That spasm of the coronaries may contribute to the disorder clouds the rationale of this therapeutic approach. Coronary spasm may occur distally as well as proximally in the vessel and surgical bypass of a fixed lesion would not provide relief if the distal anastomosis is occluded by spasm. Further experience will be necessary before final conclusions can be drawn. Certainly, surgery has no place in the management of those patients with variant angina and normal coronary arteries.

In the last few years, there has been considerable interest in applying various therapeutic manuevers that "unload" the left ventricle by lowering the systolic blood pressure or increase coronary flow by raising the diastolic blood pressure or both to patients with acute ischemic episodes. For the most part, these have been applied to patients with acute myocardial infarctions. One of these modalities, the intraaortic balloon pump has been used in patients with unstable angina. An inflatable balloon is placed in the descending thoracic aorta and is rapidly inflated during diastole and rapidly deflated during systole causing an increase in the diastolic pressure and an increased coronary flow and a decreased systolic pressure causing decreased MVO_2. The use of this modality in patients with unstable angina who are resistant to intensive medical management has recently been reported by 2 groups (49,136). They reported excellent results in relief of pain in this high-risk group. Both groups used this counterpulsation to support the patient through coronary arteriograms and induction of anesthesia and surgery. In similar patients, this has been the practice of the cardiovascular surgeons at this institution recently. Other modalities such as pharmacologic unloading of the left ventricle with nitroprusside or other hypotensive agents and external counterpulsation (rapid compression of the lower extremities with an inflatable bag enclosed in a rigid box during diastole and rapid decompression during systole) have been used on a few occasions in several centers, but no studies have been reported as yet.

A TENTATIVE PLAN FOR MANAGEMENT:

Given the current state of knowledge, it seems possible to formulate a tentative recommendation for the management of the patient with unstable angina, recognizing that changes will be necessary as further information becomes available. This plan is presented schematically in Figure I. After it seems clear that the patient's pain is due to myocardial ischemia and that a myocardial infarction has not occurred, these patients can be divided into three general groups based on the ECG and the clinical presentation and course. Those patients with ST segment elevation associated with pain make up the relatively small subgroup with variant angina pectoris. The remainder can be divided into two groups based on their clinical course in the first 48 hours of hospitalization. Those who are pain-free after this period of medical management should be considered a lower risk subgroup and those with pain beyond this period a higher risk subgroup (47). Each of these two subgroups can be further subdivided depending on the presence or absence of additional risk factors, namely previous myocardial infarction or angina pectoris, ischemic ST or T wave changes during pain, and possibly, a third heart sound, hypertension, or diabetes mellitus. Those in the low-risk subgroup without additional risk factors can be managed medically with a low risk of myocardial infarction and death relative to the total group. Elective coronary arteriography will be indicated in most to identify the 10-25% with normal coronary arteries and to accurately define the location and severity of the disease in those patients with coronary atherosclerosis.

This will also allow division of these patients into groups who are suitable and unsuitable candidates for coronary artery surgery. My own preference currently is to manage these patients as patients with stable angina, operating on the suitable candidates who have disabling angina on a good medical regimen or on those patients with particularly threatening lesions, especially those with high-grade left main coronary disease or a combination of lesions that is tantamount to left-main disease. Those low-risk subgroup patients with additional risk factors will require individualization of their management. Depending on the number and nature of the risk factors, they might logically be managed similarly to low-risk patients without other risk factors or as patients in the high-risk subgroup.

Patients in the high-risk subgroup for myocardial infarction and death should generally have semi-urgent coronary arteriography. When it seems possible in a given patient, aggressive attempts to stabilize the patient for several days may lower the risks of coronary arteriography and surgery. Surgical candidates in this group probably are best managed by semi-urgent by-pass grafts, although it must be kept in mind that we do not yet have conclusive evidence that surgery will lower their mortality rate.

The key to the proper management of patients with variant angina is a proper understanding of the extent of the patient's coronary disease. Consequently after several days of stabilization, they should generally undergo semi-urgent coronary arteriography. This will allow division of these patients into groups with significant proximal coronary disease, diffuse disease, and without significant disease. Spasm may also be documented at the time of the study. Only the group with significant proximal disease of a major vessel can now be thought of as suitable candidates for by-pass surgery and it must be kept in mind that the role for surgery even in this setting is still somewhat uncertain. Spasm may still occur in the coronary arteries of these patients and treatment with nitrates should be continued in these patients if there is further pain or ST segment elevation.

In all of these groups, those patients who are not suitable candidates for surgical treatment should have aggressive medical management. With such therapy, the vast majority should show at least some improvement in their angina. One of the unfortunate side-effects of the surgical treatment of coronary disease is the tendency to consider patients who are not surgical candidates as hopeless in spite of a half-century of evidence that sound medical treatment can reduce angina in most patients. In addition to the sound use of nitrates and β-adrenergic blockade, this treatment includes a sensible restriction of the patient's activity, weight loss, cessation of smoking, and physical training.

TABLE I

Some terms applied to symptoms intermediate between stable angina pectoris and myocardial infarction.

	Reference No.
Unstable angina pectoris	(45)
Intermediate coronary syndrome	(51)
Acute coronary insufficiency	(86)
Crescendo angina pectoris	
Accelerated angina pectoris	
Acute atypical coronary artery insufficiency	(81)
Status anginosus	(100)
Slight coronary attacks	(99)
Coronary failure	(44)
Pre-infarctional angina	
Impending myocardial infarction	
Threatening myocardial infarction	
Pilot anginal attacks	(122)
Premonitory pain to coronary occlusion	
Precursor phenomena to coronary occlusion	(115)
Preliminary pains to coronary occlusion	(40)
Pre-thrombotic syndrome	
Pre-occlusive syndrome	

TABLE II

Prodromes to Myocardial Infarction

			Ref.
50%	Feil	1937	(40)
48.1%	Sampson & Eliaser	1937	(115)
49%	Yater et al	1948	(146)
16%	Behrmann et al	1950	(143)
29%	Mounsey	1951	(90)
39%	Maurice et al	1955	(87)
39%	Vakil	1961	(131)
45%	Wood	1961	(139)
50%	Moss et al	1969	(145)
65%	Solomon et al	1969	(123)
84%	Hochberg	1971	(63)
60%	Fulton et al	1972	(45)

TABLE III

	Stable Angina	Unstable Angina
History-provoking factors	Exertion, Emotion, Meals, etc.	None or pain with lesser provation
Frequency	Less often	More often
Predictability	Present	Absent
Duration	Usually < 5min	>15min
Effect of rest, TNG	Relief	Partial, less prompt, or none
EKG changes (ST and T)	Often missed	Frequently observed

TABLE IV

Unstable angina patients without ischemic ECG changes.

			Ref.
29%	Maurice et al	1955	(87)
48%	Nichol et al	1959	(93)
17%	Beamish & Storrie	1960	(5)
10%	Papp & Smith	1960	(100)
12%	Wood	1961	(139)
10%	Krauss et al	1972	(73)
17%	Gazes et al	1973	(47)
20%	Lopes et al	1973	(82)
7%	Huetgren et al	1974	(64)
50%	Amsterdamm et al (of patients with arteriographically significant disease)	1975	(4)

TABLE V

Unstable angina in the absence of significant athermatous disease.

				Ref.
25%	(54/216)	Proudfit et al	1966	(107)
19%	(15/79)	Scanlon et al	1973	(116)
5%	(1/19)	*Herman & Gorlin	1972	(60)
7%	(10/142)	Bertolasi et al	1974	(7)
25%	(10/40)	Amsterdam et al	1975	(4)
10%	(29/182)	Alison et al	1975	(2)
10%	(3/31)	Donsky et al	1975	(32)

*All the patients in this group were "high risk" patients.

TABLE VI

Natural History of Unstable Angina

Reference	Ref.#	No. Pts.	Early MI	Early Mort.	Follow-up Period	Late MI	Late CV	Angina Improved	Follow-up Period	SEMI's inc.?	Angios?	Comments
Sampson & Eliaser 1937	115	29	100%	34.5%	in-hosp.	NS	NS	NS	NS	Yes	No	Study of patients with MI prodrome who developed MI
Littman & Barr 1952	81	29	3.5%	6.9%	in-hosp.	NS	NS	100% (27/27)	in-hosp.	Possibly	No	
Levy 1956	76	158	NS *	NS	NS	* 23.4%	32%	NS	6	Yes (prob. C.40%)	No	Excluded patients with a single long episode of pain. Patients not hospitalized. *Most of the 23.4% appear to have occurred within few weeks/mos.
Cutts et al 1957		69	NS	NS	NS	*26%	20%	26%	<1 to >6 yrs	Yes (Many probably)	No	*Total of early and late. Timing N.S. Unusually large % of women
Beamish & Storrie 1960	5	100 100	14%	9%	0-6wks	5% (overall 24%)	4% (overall 42%)	NS	7wks-6mos >1yr	Probably	No	Includes data from the anticoagulated and non-anticoagulated groups

N.S.=Not Specified.

Reference	Ref.#	No. Pts.	Early MI	Early Mort.	Follow-up Period	Late MI	Late CV	Angina Improved	Follow-up Period	SEMI's inc.?	Angios?	Comments
Papp & Smith 1960	100	20	15%	10%	<2wks	15% 20%	10% 30%	100% (11/11 survivors) for >1yr	2wk-3mos >3mos. 1-12yrs	?-No indices of systemic response recorded at 2u	No	Fairly severe cases by selection.
Vakil 1961	130	251	NS*	*NS	*NS	36%	0.8%	NS	3mos	Probably not	No	Author comments that the hospital course was usually uneventful.
Wood 1961	139	150	NS	NS	NS	9.3%	12%	NS	2mos	Probably not	No	Combining data from anti-coag. & non-anticoag. patients.
Resnik 1962	108	31	0	0	in-hosp.	3.2%	NS (?0)	NS	5 or more mos.	No	No	
Vakil 1964	131	360	NS	1.1%	4days	40.6%	15.3%	NS	3mos	Probably 10-15%		
Murnaghan et al 1970	91	78	NS	0	in-hosp.	NS	NS	NS	6yrs	No	No	Author comments that mortality in patients admitted with UA worse at 6 yrs than pts adm at same time with MI.

Reference	Ref.#	No. Pts.	Early MI	Early Mort.	Follow-up Period	Late MI	Late CV	Angina Improved	Follow-up Period	SEMI's inc.?	Angios?	Comments
Fulton et al 1972	45	167 45	NS 17.8%	1% 2.2%	4wks NS	*13.8% NS	1.2% NS	50% NS	3mos NS	No No	No No	Prospective study.*Total MI's. Time NS 122 patients not hospitalized(presumably very "mild" destabilization).45 hospitalized (High Risk?)
Krauss et al 1972	73	100 --	6% --	1% --	in hosp. --	9% --	21% 10%	NS --	$\bar{x}$20mos 1yr	No --	No (in only 5) --	
Robinson et al 1972	111	38	NS	NS	NS	*31.6%	18.4%*	41.9% (13/31)	$\bar{x}$6.4 mos	No	Yes	*Total early and late. Timing NS
See et al 1972	118	90	16.7%	8%	hospitalization	5.6%	4%	66%	1yr	No	Yes	
Watkins et al 1972	134	47	8%	8%	in-hosp	NS	17%	NS	14mos	No	NS	
Fischl et al 1973	41	9	0%	0%	NS	33.3%	33.3%	100% (6/6)	$\bar{x}$32mos	No	Yes	High Risk Group. Patients of an initial group of 23 who were stabilized w/ propranalol.

Reference	Ref.#	No Pts.	Early MI	Early Mort.	Follow-up Period	Late MI	Late CV	Angina Improved	Follow-up Period	SEMI's inc.?	Angios?	Comments
Gazes et al 1973	47	140	12%	6%	2wks	--	--	--	--	No	No	Total Group
			17%	8%	4wks	--	--	--	--	No	No	
			21%	10%	12wks	--	--	--	--			
			--	--	--	NS	*18%	74%	1yr			*Deaths from all causes
						--	25%	--	2yrs			
						--	31%	--	3yrs			
						--	39%	--	5yrs			
						--	52%	--	10yr			
		54	22%	15%	2wks	--	43%	--	1yr			High Risk Gr.
			28%	20%	4wks	--	53%	--	2yrs			*Deaths from all causes
			35%	26%	12wks	--	63%	--	3yrs			
							73%	--	5yrs			
							81%	--	10yrs			
Lopes et al 1973	82	170	NS	NS	NS	NS	15.4%	NS	$\bar{x}$ 17.9mos	No	No	Retrospective analysis of patients admitted to CCU who had MI ruled out
Bertolasi et al 1974	7											*Total for early & late.
"Intermediate Syndrome" (High Risk)		20	NS	NS	--	NS	35%*	No	$\bar{x}$ 8.3mos	No	Yes	
"Progressive Angina"		20	NS	NS	--	NS	5%*	Slight		No	Yes	

TABLE VII

Myocardial Infarction and Mortality Complicating Unstable Angina
(Condensed from TABLE VI)

Paper	Ref.	#Patients	MI	Mortality	Follow-up
Sampson & Eliaser, 1937	115	29	100%	35%	N.S.
Littman & Barr, 1952	81	29	4%	7%	in-hospital
Cutts et al, 1957	144	69	26%	20%	<1 to >6 yrs
Beamish & Storrie, 1960	5	100	42%	24%	7wk - 6mos
Papp & Smith, 1960	100	20	50%	50%	1 - 12 yrs
Vakil, 1961	130	251	36%	1%	3 mos
Wood, 1961	139	150	9%	12%	3 mos
Vakil, 1964	131	360	41%	16%	3 mos
Murnaghan et al, 1970	91	78	N.S.	0%	in-hospital
Fulton et al, 1972	45				
Total		167	14%	1%	3 mos
Hospitalized		45	18%	2%	N.S.
Krauss et al, 1972	73	100	15%	22%	$\bar{x}$ 20 mos
Robinson et al, 1972	111	38	32%	18%	$\bar{x}$ 6.4 mos
See et al, 1972	118	90	22%	12%	1 yr
Watkin et al, 1972	134	47	8%	25%	14 mos
Fischl et al, 1973	41	9	33%	33%	$\bar{x}$ 32 mos
Gazes et al, 1973	47				
Total		140	21%	18%	1 yr
"High Risk"		54	35%	43%	1 yr
Lopes, et al, 1973	82	170	N.S.	15%	$\bar{x}$ 17.9 mos
ertolasi, et al, 1974	7				
"Intermediate Syndrome"		20	N.S.	35%	$\bar{x}$ 8.3 mos
"Progressive Angina"		20	N.S.	5%	

TABLE VIII

Use of Anti-coagulants in Unstable Angina

Reference	Ref.#	No. Controls	No. Treated	†Anti-coag.	Cont. % MI	Rx % MI	Cont. % Mort.	Rx % Mort.	Follow-up Period	SEMI's Incl.	Comments
Wood 1948	138	25	33	--	48%	6%	20%	0%	---	---	
Nichol 1959	93	0	318	Both	---	6.6%	---	1.6%	30 days	Possibly a few	48% had no EKG evidence of ischemia
Beamish & Storrie 1960	5	15**	85	C*	80% 67% (2/3)	2% 17.5% (10/57)	60% 67% (2/3)	0% 2.5% (2/80) 12% (7/57)	0-6 wks 7wk-6mos 76mos		*21 also received H. **"Controls" were patients in whom recommendation of anti-coag. was not carriet out.
Wood 1961	139	50**	100	C*	22%	3%	6%	30%	2mos	Probably Not	*A few also received H. **only first 20 controls were true controls
Master 1963	85	80	55	N.S.	21%	C.57%	--- 5.0% 10.0%	--- 7.3% 12.7%	N.S. 3mos 1yr	Probably Not	
Vakil 1964	131	156	190	C*	49.4%	36.3%	48.1%	26.1%	3mos.	Probably 10-20%	*Sometimes Both

†H - Heparin

C - Coumarin family

TABLE IX

Surgical Coronary Artery Reconstruction for Unstable Angina

Reference	Ref.#	No. Pts.	Cont?	Rand?	Group	Early or Op. Mort.	Early Non-Fatal M.I.	Early M.I. Total	Late M.I.	Late Mort.	Relief of Angina	Follow-up	Comments
Favaloro et al 1971	39	18	No	No	Surg	2/18	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	
Lambert et al	75	52	No	No	Surg	5.3%*	3.8%	5.8%	N.S.	N.S.	82.4%*	N.S.	*Includes with the 52 patients 5 others operated for arrhythmia. Separate data N.S.
Vogel et al 1971	132	5	No	No	Surg	0	20%	20%	0	0	100%	2-5 1/2mos	
Bolooki et al 1972	10	3	No	No	Surg	0	0	0	0	0	100%	8-20mos	
Dumesnil et al 1972	34	8	No	No	Surg	12.5%	N.S. (?0)	N.S.	N.S. (?0)	N.S. (?0)	100%	"Early"	
Hill et al 1972	62	3	No	No	Surg	0	0	0	0% (0/2)	0% (0/2)	100% (2/2)	1 "several mos" 1 6mos 1 not followed	

N.S.=Not Specified

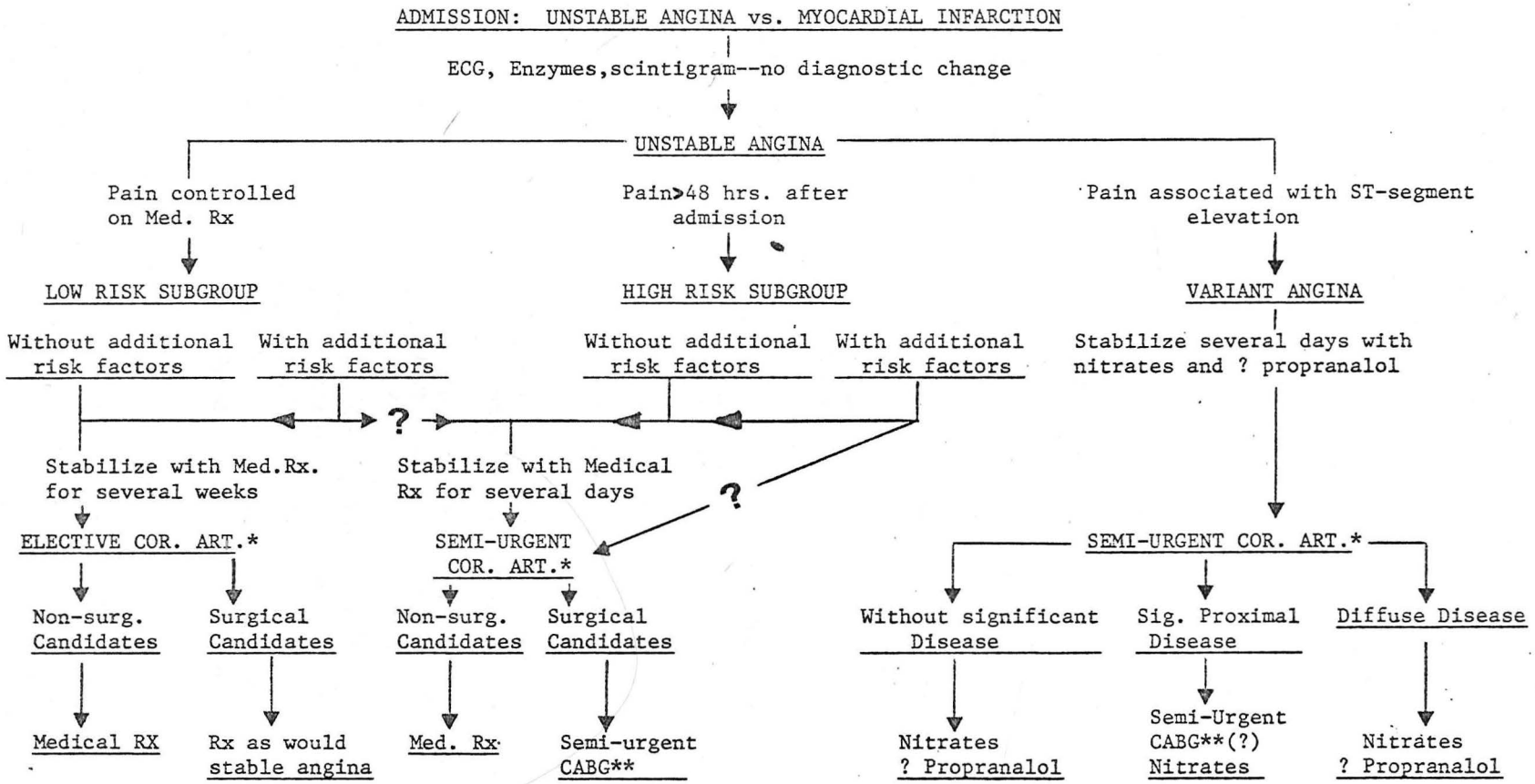
Reference	Ref.#	No. Pts.	Cont?	Rand?	Group	Early or Op. Mort.	Early Non-Fatal M.I.	Early M.I. Total	Late M.I.	Late Mort.	Relief of Angina	Follow-up	Comments
Linhart et al 1972	79	5	No	No	Surg	0	0	0	N.S.	N.S.	N.S.	in hosp.	
Robinson et al 1972	111	38	Yes	No	Med	NS	NS	NS	*31.6%	*18.4%	41.9% (13/31)	$\bar{x}$ 6.4mos	Prospective *Total early and late.
		21			Surg	1	NS	NS	*14.3%	9.5%	67% (12/18)		
Segal et al 1972	119	17	No	No	Surg	11.8%	N.S.	N.S.	17.6%	0	100%	5-16mos	
Conti et al 1973	25	15	"Yes"	No	Med	0	1	1	1	1	67% (6/9 surg candidates)	N.S.	Prospective "Controls" 10 refused 1 nl.cor.art. 3 LV Dysfunction 1 MI Post-cath
		40			Surg	9	N.S.	N.S.	1	0	97% (30/31)	$\bar{x}$ 16.7mos	Both were High Risk Patients
Fischl et al 1973	41	14	No	No	Surg	7%	7%	7%	0	0	12/13 survivors	$\bar{x}$ 22mos	High Risk Patients
Scanlon et al 1973	116	22	"Yes"	No	Med	27%	32%	59%	N.S.	N.S.	6/19	("Late")	
		39			Surg	10%	N.S.	25%	N.S.	N.S.	36/41	("Late")	
Sustaita et al 1973	126	15	"Yes"	No	Med	46.7%	40%	N.S.	N.S.	N.S.	N.S.	2 weeks	
		36			Surg	8.3%	N.S.	8.3%	N.S. (?0)	0	91% (30/33)	4-25mos	

Reference	Ref.#	No. Pts.	Cont?	Rand?	Group	Early or Op. Mort.	Early Non-Fatal M.I.	Early M.I. Total	Late M.I.	Late Mort.	Relief of Angina	Follow-up	Comments
Theroux & Campeau 1973	128	31	"Yes"	No	Med	6%	N.S.	N.S.	N.S.	N.S.	N.S.	3-12wks from adm.	
		25			Early Surg	28%	11%	N.S.	N.S.	N.S.	N.S.	in hosp	Op. within 3wks adm.
		39			Late Surg	5%	21.6%	N.S.	N.S.	N.S.	N.S.	in hosp	Op.3-12 wks from adm.
		64			Total Surg	14.6%	15.6%	23.4%	N.S.	N.S.	N.S.	in hosp	
Bertolasi et al 1974	7		Yes	Yes									
Intermediate Syndrome		20			Med	N.S.	N.S.	N.S.	N.S.	35%*	No	$\bar{x}$8.3mos	*Total for early & late
		24			Surg	8.5%	N.S.	N.S.	N.S.	0%	Yes		
Progressive Angina		20			Med	N.S.	N.S.	N.S.	N.S.	5%*	Slight	-	
		33			Surg	6.0%	N.S.	N.S.	N.S.	0%	Yes		
Bonchek et al 1974	11	55	No	No	Surg	5%	11%	11%	5%	2%	84% (42/50)	12-52mos $\bar{x}$ 24mos	"High Risk"
Huetgren et al 1974	64	34	No	No	Surg	3%	N.S.	N.S.	N.S.	N.S. (?0)	61%	$\bar{x}$ 6mos	
Amsterdam et al 1975	4	13	"Yes"	No	Med	0	0	0	7.7%	7.7%	N.S. (22% had repeat U.A.)	$\bar{x}$ 10mos	Med. Rx successful
		17			Surg	12%	6%	N.S.	0	0	100%	$\bar{x}$ 10mos	Op. because Med.RX unsuccessful. "High Risk"

Reference	Ref.#	No. Pts.	Cont?	Rand?	Group	Early or Op. Mort.	Early Non-Fatal M.I.	Early M.I. Total	Late M.I.	Late Mort.	Relief of Angina	Follow-up	Comments
Berndt et al 1975	6 (See also 23,89)	81	No	No	Surg	8.6%	N.S.	16%	14.8%	2.5%	94.5% (70/74 survivors)	5-34mos $\bar{x}$ 18mos	
Conti et al 1975	24	73 65	Yes	Yes	Med Surg	9.6% 6.2%	N.S. N.S.	8.2% 21.5%	6.8% 7.7%	4.1% 3.1%	N.S.* N.S.*	$\bar{x}$ 7mos	Prospective MIRU Co-op Study. *Less angina in surg group $p < 0.01$
Kouchoukos et al 1975	72	65	No	No	Surg	0	14%	14%	15%	6.2%	75% (24/32)	$\bar{x}$ 8mos	
Vogel 1975	133	7	"Yes"	No	Med	*85.7%	*14.3%	*100%	*	*	N.S.	.2-13mos	All patients "High Risk"
		20			Surg	5%	N.S.	25%	0	0	18/19	1-36mos $\bar{x}$ 10mos	*Late and Early data not separated.

FIGURE I

A TENTATIVE PLAN FOR THE MANAGEMENT OF UNSTABLE ANGINA PECTORIS



* Coronary Arteriography

** Coronary Artery Bypass Graft

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