Management Policies and Prognosis in Unstable Angina Pectoris

Use of Coronary Angiography in Different Practice Settings

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Management Policies and Prognosis in Unstable Angina Pectoris

Use of Coronary Angiography in Different Practice Settings

Behandelingsstrategieën en Prognose bij Patienten met Onstabiele Angina Pectoris
Gebruik van Coronairangiografie in Verschillende Praktijksituaties

Proefschrift

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Moreel, economisch en fiscaal wordt een promotie aangemerkt als leidende tot een niveauverhoging. Het gezin, dus ook de echtgenoot, moet daar veel voor over hebben. Maar "at what price glory"?
Uit: "Memoires van een Promovendus", Dr. R.E.M. van den Brink, 1988

Voor Bart Jan

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INTRODUCTION

INTRODUCTION

Unstable angina encompasses a wide range of clinical presentations of myocardial ischemia, usually caused by sudden deteriorations of coronary lesions. Sometimes, extracardiac conditions disturbing the oxygen balance, such as severe anaemia, fever or thyrotoxicosis, may cause myocardial ischemia. In this thesis unstable angina is referred to as myocardial ischemia due to obstructive atherosclerotic coronary artery disease. In the literature and in clinical practice a variety of definitions is used to describe this particular clinical situation. These definitions are characterised by the description of chest pain, the clinical circumstances under which unstable angina occurs, the presence or absence of concomitant ECG changes during pain, and the intensity of treatment before pain occurs [1,2]. Patients with anginal symptoms of unstable character, and no signs of acute myocardial infarction, are admitted with an *initial* diagnosis of unstable angina pectoris. An observation period is necessary to come to a definite *final* diagnosis, as myocardial infarction may have already occurred in a number of such patients, but can not be recognised until an increase in cardiac enzyme concentrations can be detected in the circulation [3]. Thus in addition to the characteristics of clinical signs and symptoms also the time of definition is of importance to characterise the patient population. Treatment of unstable angina is directed to relief of acute symptoms and to prevent progression to myocardial infarction or death. Various drugs are available, acting upon different underlying pathophysiologic mechanisms, and thereupon bypass surgery and angioplasty may be used to improve the coronary blood supply.

In the present study the application of these treatment options in the management of patients hospitalized for suspected unstable angina is described. Furthermore it was assessed how physicians in different hospital settings apply each of the alternative management strategies in their practice. Finally, the prognosis under the current management strategy is described.

Chapter 1 is a literature review of the various aspects of the syndrome unstable angina. The diversity of definitions is described and the underlying pathophysiology related to these definitions. An overview of anti-anginal drugs is provided. Prognostic studies are summarised with identified risk factors for development of myocardial infarction or death, and the effect of different treatment strategies upon prognosis is delineated.

A prospective study was performed in order to establish how physicians approach the syndrome unstable angina. In two hospitals in Rotterdam 417 patients with suspected unstable angina at hospital admission, were followed during hospital stay and during the subsequent six months. In chapter 2 the patient population of this study is described in terms of clinical characteristics of the initial presentation at admission, and the final diagnosis after observation. The treatment given to these patients is documented in terms

of medical treatment and the rate of angiography procedures initiated to decide on subsequent coronary interventions. In addition, the occurrence of myocardial infarction and death is reported, with special interest to those events occurring during a waiting period between a decision to perform angiography and coronary interventions and the actual performance of these procedures (see figures 2.1 and 2.2.). Chapter 3 gives an overview of the events occurring within six months in patients with a final diagnosis of unstable angina and the number of interventions after discharge. Events during follow-up in patients with a final diagnosis of myocardial infarction and other causes of chest pain are described separately.

A comparison of management strategies in each of the two hospitals is made in chapter 4. As both hospitals differ with respect to availability of angiography facilities, special attention is given to the difference in use of angiography with a view to subsequent interventions. Multivariate analyses are performed in order to describe which factors can explain the observed difference in angiography rate between the two hospitals. Chapters 5 and 6 focus on understanding the management policies of individual cardiologists. Cardiologists were interviewed to reveal their opinion on the definition of unstable angina and the indications for several further treatment options (chapter 5). In addition, individual judgments were examined using paper case vignettes in a so-called 'policy analysis' (chapter 6). Chapter 7 provides an example of an intervention study which was directed to improve the safety of angioplasty procedures in patients with unstable angina. In chapter 8 a general discussion of the findings and a comparison with other long term follow-up studies is provided, followed by some recommendations for future research.

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CHAPTER 1

UNSTABLE ANGINA PECTORIS
A REVIEW OF PATHOPHYSIOLOGY, CLINICAL COURSE AND MANAGEMENT

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Introduction

Current understanding and recent literature on unstable angina are reviewed in this chapter. After a description of the various definitions of the syndrome 'unstable angina' an overview of the pathophysiologic mechanisms leading to unstable angina is provided. The 'natural history' of patients with unstable angina and their prognosis is described by summarizing several older studies. Results of more recent studies illustrate how this prognosis has been altered by modern treatment, including intravenous medication and, in selected patients, angioplasty an bypass surgery.

I. Definition

Angina pectoris is often described as: "chest discomfort caused by myocardial ischemia in the absence of infarction"[1]. Angina pectoris is commonly provoked by effort and is said to be stable when there has been no change in the frequency, duration or precipitating factors during a longer period of time. All other presentations of angina pectoris are subsumed under the heading 'unstable angina'[2]. In this way unstable angina is defined as an ischemic syndrome intermediate between stable angina pectoris and myocardial infarction. Within this wide spectrum several categories can be distinguished, based on clinical presentation and on prognosis. Conti described three modes of presentation[3]: 1. recent onset angina pectoris, 2. changing pattern (progression of frequency or duration) of preexisting stable angina pectoris, and 3. angina at rest. Within these clinical presentations several subgroups can be distinguished, based on the clinical circumstances in which the unstable period develops. Pain at rest can be the first presentation or angina, or it can develop in patients with chronic stable angina[4]. Also, pain which develops during recovery from a myocardial infarction (24 hours to 4 weeks after the infarct) is usually described separately as post infarction angina pectoris[5]. Braunwald[6] speaks of subacute angina when the most recent pain episode occurred more than 48 hours ago, whereas the situation in which the most recent episode occurred within 48 hours is called acute angina.

In various studies the definition 'unstable angina' is based on typical symptoms with concomitant ST-T changes on the ECG as objective evidence of ischemia[7]. The label 'intermediate coronary syndrome' is applied to the situation in which pain at rest of longer duration ($\geq$ 15 min) occurs with concomitant ST-segment or T-wave changes[8]. Furthermore a subcategory is distinguished as 'variant angina', used to describe angina at rest accompanied by ST-elevations on the ECG in patients with normal exercise tolerance[5]. The severity of the condition depends on the level of maintenance pharmacologic treatment at the time of the development of unstable angina. Persisting pain episodes despite extensive antianginal therapy is called 'refractory' angina[6].

It is clear that the term 'unstable angina' is insufficient to delineate the exact situation of a patient. Important aspects of the clinical description of unstable angina are: the clinical circumstances in which unstable angina occurs, the severity of the clinical manifestations, the presence of transient ECG changes during pain and the level of medication at the onset of ischemia[6]. Therefore, it is necessary to describe the clinical situation of patients with 'unstable angina' in more detail such as, for example, 'post infarction angina', 'unstable angina of recent onset, pain at rest', 'progressive unstable angina occurring at minimal exertion' or 'unstable angina at rest with concomitant ST-depression despite treatment with ß-blockers and intravenous nitrates'.

II. Pathophysiology

Presentations of acute ischemic cardiac diseases include unstable angina pectoris, myocardial infarction and sudden death. These manifestations are usually expressions of a similar dynamic pathophysiologic process in the coronary arteries impeding myocardial oxygen supply (primary unstable angina)[9,10]. Myocardial ischemia may also be precipitated by non-coronary causes such as severe anaemia, hypotension or tachyarrhythmia: secondary (unstable) angina[6]. This review focusses on the primary forms of unstable angina, based on coronary artery disease.

In patients with atherosclerosis, progression of an atherosclerotic plaque may lead to obstruction of the coronary lumen. Severe stenoses may result in inadequate coronary blood flow to the myocardium during periods of increased oxygen demand. This situation with a limited 'coronary flow reserve' corresponds with stable angina on effort. In contrast, unstable angina pectoris is caused by a sudden increase of the degree of obstruction in the coronary artery, followed by a (transient) reduction of coronary flow, unstable angina is not directly related to an increased oxygen demand[11], although ischemic episodes may occur 5-30 minutes after a temporary increase of heart rate or blood pressure[12]. The conversion of a clinically stable situation into an unstable episode is initiated by rupture or ulceration of an atherosclerotic plaque, often in combination with increased vasomotor tone (or even spasm) and platelet aggregation[9]. Such sudden progression of the coronary obstruction may progress to total thrombotic occlusion and myocardial infarction[13]. Alternatively, the increase of obstruction can be of temporary character without myocardial necrosis (unstable angina)[9,14]. The plaque rupture can recover after some time resulting in a new, stable situation[15]. The thrombus may disappear by internal thrombolysis and fragmentation, but often thrombus material is incorporated in the plaque. In the new stable situation the plaque will then be more severe than before the unstable period, which may manifest as stable angina at a lower threshold. By means of serial angiography progression of coronary obstruction was observed in 28/38 patients with unstable angina, whereas this was seen in only 12/38

patients with stable angina pectoris[16]. Similarly, a pathologic study of 25 patients who died suddenly after an episode of unstable angina, revealed intraluminal thrombus in all patients, while a layered structure of the thrombus was observed in 81% of these patients. In most cases the underlying plaque showed rupture of the plaque surface and haemorrhage in the plaque. In 73% of the patients small thrombus fragments and microinfarcts were found in the myocardium distal to the coronary thrombi[15].

Angiographically, the severity of coronary atherosclerosis appears to be similar in patients with stable and unstable angina[17,18]. However, the morphology of the stenosis differs. Ambrose[18] reported eccentric stenoses with convex intraluminal obstruction and narrow neck due to one or more overhanging edges or irregular scalloped borders in 71% of patients with unstable angina versus 16% of patients with stable angina pectoris. In post mortem studies this morphology appeared to be associated with ruptured atherosclerotic plaques, intraintimal haemorrhage and thrombus formation[19]. Rehr[20] and Cowley[21] described complex lesions, corresponding with the presence of intima rupture and thrombus formation, on the angiograms in 70% and 84% of patients with unstable angina and in only 21% and 15% of patients with stable angina.

Using coronary angioscopy the lesions of patients with stable and unstable angina could be observed directly during angiographic procedures and during bypass surgery. In patients with stable angina pectoris the plaque surface was smooth and intact. In patients with progressive angina on effort the plaque surface was irregularly ragged, and showed intramural haemorrhage, while in patients with angina at rest thrombus was observed distal to the stenosis[22,14].

These findings support the concept that conversion from stable- to unstable angina is initiated by plaque rupture or endothelial ulceration. Rupture of the plaque surface probably is a random event in the evolution and growth of an atherosclerotic plaque. The bending and twisting of the arteries which occur during every heart beat, haemodynamic stress such as pulsatile flow and variations in blood pressure, or changes in the vascular tone may be sufficient to disrupt the very thin cap of fibrous tissue. Direct contact of the lipids in the plaque and blood initiates platelet aggregation. Furthermore, a ruptured plaque surface allows platelets and red blood cells to enter into the plaque resulting in rapid plaque expansion. Further narrowing of the lumen may be caused by stimulation of the vascular smooth muscle (spasm) via break-down products of extravasated platelets and by progression of platelet aggregation and thrombus formation. This may progress to total occlusion and cause myocardial infarction. Thrombus fragmentation and embolization may result in distal microinfarcts causing cardiomyopathy or (fatal) ventricular arrhythmias. The extent and severity of the preexisting stenosis, the duration and completeness of the coronary obstruction and of the presence of collateral vessels determine the subsequent clinical presentation[10].

III. Diagnosis of acute coronary syndromes

When a patient presents with symptoms compatible with acute coronary insufficiency, the patient's history, physical examination and an ECG are immediately available to make a diagnosis. During the first hours a differentiation between myocardial infarction and unstable angina can often not be made based on the clinical characteristics. Thus, an initial diagnosis will be made at the time of admission. After observation and new information is obtained this initial diagnosis will be confirmed or revised and a final (discharge) diagnosis is made.

The most important information for the initial diagnosis at admission is a careful assessment of the patient's history. The major attributes of the history are the character and location of the pain, the mode of onset and the course of symptoms as well as the reaction to medical therapy (sublingual nitrates)[23]. A history of coronary artery disease and the presence of risk factors (hypertension, smoking, hypercholesterolemia and a positive family history) may influence the interpretation of the presenting symptoms[24,25]. Unfortunately a patient with acute coronary disease will often present with symptoms that do not meet the criteria for typical angina pectoris. On the other hand, symptoms suggestive for myocardial ischemia are sometimes caused by non-cardiac disease, such as gastrointestinal problems, gall bladder disease or pulmonary embolism[26].

Physical examination is of little help for the diagnosis 'unstable angina'. A patient with angina pectoris usually exhibits no abnormalities on physical examination, although a third heart sound or a murmur of mitral incompetence may be present during ischemia[23]. Signs of impaired left ventricular function (heart failure) or vegetative symptoms, such as severe perspiration are often associated with myocardial infarction[27,28].

Electrocardiographic information is of great value for the diagnosis, especially when serial electrocardiograms are recorded during and after pain. At admission often only an ECG without pain can be obtained. The value of such resting electrocardiogram is limited, because it is often normal or it shows abnormalities that give little information about the actual situation, such as abnormal Q-waves, intraventricular conduction disturbances or left ventricular hypertrophy, all of which may be accompanied by secondary ST-T abnormalities. Transient ECG changes during pain, particularly depression or elevation of the ST-segment or T-wave inversion indicate myocardial ischemia, whereas the absence of ECG changes during pain makes an ischemic cause less likely, but does not exclude ischemia[1].

When a patient is admitted with severe, typical chest pain of long duration (>30 minutes) with concomitant ST-elevation on the electrocardiogram, the 'admission' or 'initial' diagnosis is myocardial infarction. In a small percentage of these patients (2-3%) the diagnosis 'infarction' is not confirmed by serial enzyme assays[29,30] and in

retrospect the final diagnosis 'unstable angina' will be made and treatment will be continued accordingly. For patients with symptoms, suspected of unstable angina without signs of acute infarction (pain of shorter duration, without vegetative symptoms and without persisting ECG changes) a clinical observation period is warranted to make a definite diagnosis. In about 10% of such patients myocardial infarction may be present although it can not be recognised with certainty at that moment[25]. In another 30% the symptoms appear in retrospect due to non-cardiac or non-specific causes[31]. These findings were confirmed in a prospective registry in two hospitals in Rotterdam, which is described in this thesis (chapter 2).

During a period of 7 months in 1988/89, 417 patients were admitted to the Thoraxcenter of the University Hospital Dijkzigt or to the Sint Franciscus Gasthuis for observation because of chest pain suspected of acute ischemia, 'unstable angina',

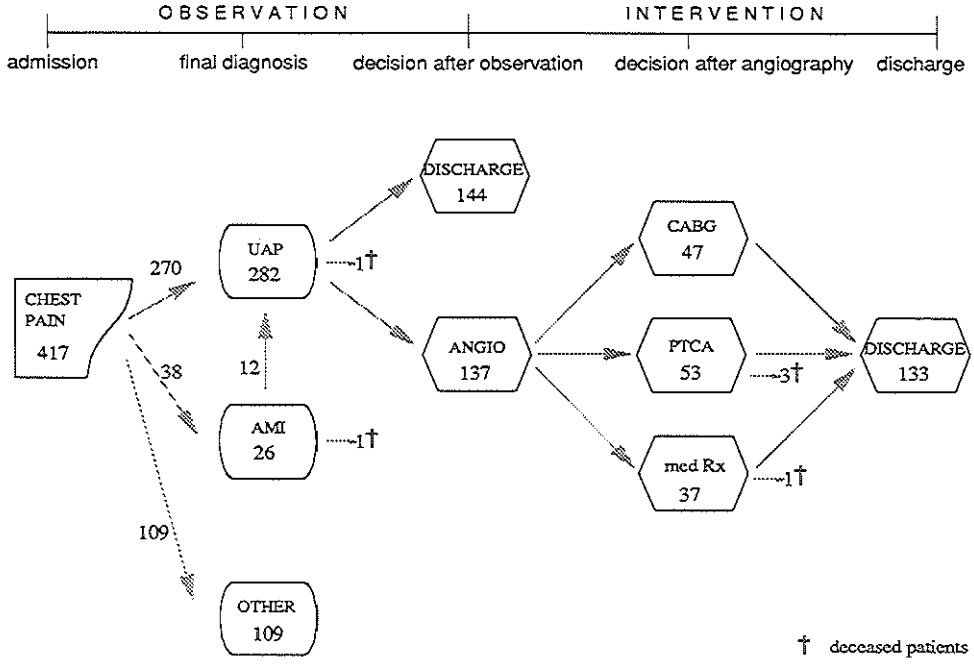

Figure 1.1. *In-hospital course for 417 patients, admitted for chest pain suspected of unstable angina pectoris. A definitive diagnosis was made after an observation period of 24-48 hours. For patients with definitive unstable angina the subsequent course and management strategy is shown. Six patients died in hospital (†), 1 after infarction, 1 after infarction and post infarction angina, 3 in relation to PTCA and 1 during medical treatment after angiography. Myocardial infarction occurred in 15 patients, 8 during observation or while waiting for an intervention and 7 during an intervention (4 during CABG and 3 during PTCA).*

without signs of acute infarction or other diseases at the time of admission. In figure 1.1 the in-hospital course of these patients is depicted. After an observation period of 24 to 48 hours serial electrocardiographic and enzymatic measures showed that myocardial infarction had already occurred in 38 patients (9%). In 109 patients (26%) the symptoms were attributed to other or non-specific causes. In the other 270 patients (65%) the initial diagnosis unstable angina was maintained. This diagnosis was supported by objective ECG changes during observation or exercise tolerance tests or by a history of coronary disease in 256 patients (95%). The typical character of the pain was sufficient for the diagnosis in the other 14 patients. Furthermore, 12 out of 38 patients with myocardial infarction at admission still developed unstable post infarction angina with recurrence of pain 24 hours or more after the infarction.

Additional diagnostic tools, such as exercise tolerance tests, scintigraphy and angiography are of importance for the assessment of prognosis and for the choice of suitable therapy. In the Rotterdam registry an exercise tolerance test was performed in about 50% of all patients, usually to confirm the suspicion of non-specific origin of the pain or to assess the need for intervention. Eventually, a decision to perform angiography was made for 137 patients, and subsequent PTCA or CABG was performed in 53 and 47 patients, respectively. More details are provided in chapter 2.

IV. Natural history / prognosis

When patients present with unstable angina, there is danger for progression to infarction or sudden death. The pathophysiologic mechanisms underlying each of these three expressions of coronary disease are in fact different stages of the same process[14,15]. Prognostic studies on unstable angina vary depending on the definition used, the duration of follow-up and treatment. These studies do not provide information on the real natural history, because most patients received treatment, including nitrates, ß-blockers and calcium-antagonists. In the surgical studies[42-43] patients were included only if there had been neither 'medical failure', nor main stem disease or impaired left-ventricular function. As a consequence, the patients with the worst prognosis were excluded.

While the studies vary with respect to definitions and inclusion criteria, it appears that most infarctions in patients admitted for unstable angina pectoris occur in an early stage. On average 9% of the patients develop myocardial infarction within the first six months, most of which occur within the first month. After 1 year an average of 14% of the patients has developed infarction. Mortality figures increased during follow-up. The mean percentages vary from 2% after 1 month to 4%, 6% and 10% after 3 and 6 months and 1 year, respectively (figure 1.2).

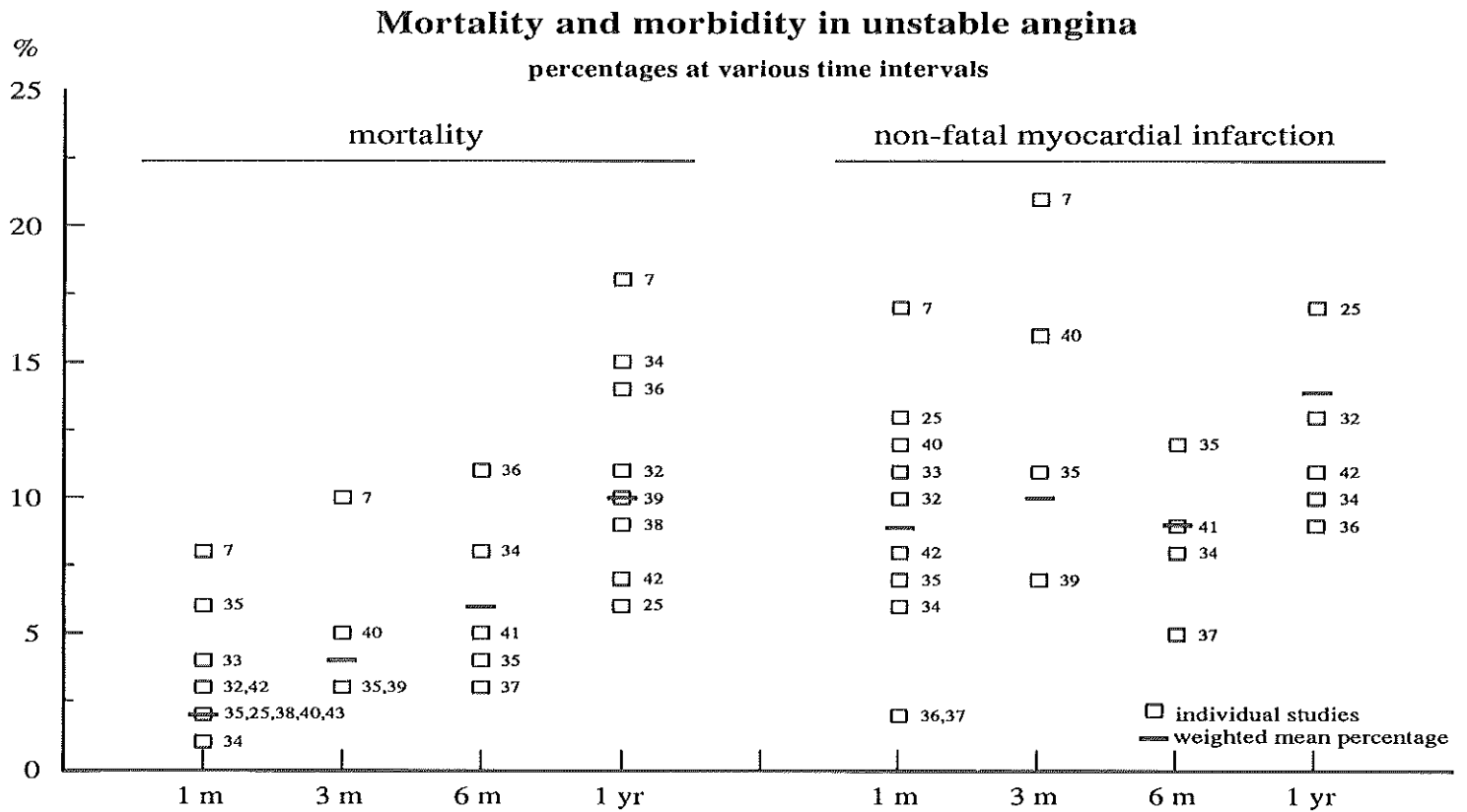

Figure 1.2. *Complications in unstable angina, derived from observational studies[7,32-38] and randomised trials[25,39-44]. The results of placebo controlled trials with platelet inhibitors are given for the placebo group[39-41]. The results of randomised studies of surgical versus medical therapy are given for the medically treated patients[42-44]. The high mortality figures after 1 and 3 months and 1 year and the infarction rates after 1 and 3 months are from one, relatively small study from 1973[7]. The lowest 1 year mortality was reported in the HINT study (6%) while in that study a high infarct percentage at 1 year (17%) was found[25].*

A number of clinical, electrocardiographic and angiographic factors are related to the prognosis. An increased infarction or mortality risk is found in patients with frequent pain episodes and in patients with limited response to medical therapy (refractory angina)[7,33], with progression of preexisting stable angina[34,36], with persistent ST-T abnormalities or transient ECG changes during pain[7] or with angiographically extensive coronary lesions and impaired left ventricular function[17]. Prognostic models derived from the Rotterdam registry are presented in chapter 3.

Prognosis of patients with unstable angina is also determined by additional interventions. The proportion of revascularisation procedures during follow-up varies from 8 to 50%[32,37,40,45]. The 'cross-over' percentage of medical therapy to surgery in randomised studies amounts to 8% in the acute phase, 19% after 1 year and 31-34% after 2 years[42,43]. In the Rotterdam registry a revascularisation procedure was performed in 100 out of 417 patients (24%), which corresponds to 35% of patients with a definite diagnosis of 'unstable angina'.

V. Medical therapy

Initial treatment of patients with unstable angina pectoris is directed to relieve pain and ischemia in the acute phase and to establish a new stable situation. Long term treatment is aimed to prevent recurrence of ischemic episodes and specifically to prevent infarction or death.

Several drugs are included in the management strategy with different working mechanisms, representing the complex pathophysiology of unstable angina, consisting of a combination of changes in the underlying atherosclerotic plaque, increased coronary vasomotor tonus, (transient) platelet aggregation and thrombosis[14].

The classical management of (unstable) angina pectoris is directed to the reduction of oxygen demand of the myocardium with nitrates and ß-blockers. Later calcium-antagonists were added to inhibit increased coronary vasomotor tone. During the recent years, since the role of platelet aggregation and thrombus formation in unstable angina was established, treatment has been extended with aspirin, heparin and thrombolytic therapy.

Nitrates. Nitrates predominantly induce venous dilation, resulting in a reduction of the 'preload' of the heart and in a decrease of the myocardial oxygen demand. At higher doses also relaxation of the coronary arteries will occur, resulting in better myocardial perfusion, as well as arterial dilation, resulting in a reduction of the 'afterload'. Such peripheral vasodilation may cause side effects, including reflex-tachycardia, flushes and headache. Relaxation of smooth muscle tissue by nitrates appears to be based on a similar mechanism as the so-called endothelium related relaxing factor (EDRF). EDRF is nitric oxide (NO) which accomplishes muscle relaxation by conversion of GTP into

Table 1.1. Summary of the efficacy of antianginal drugs in unstable angina pectoris.

Author	n	Description of the study	Results / conclusion
NITRATES			
Kaplan [48]	35	Pts with angina at rest despite oral nitrates and ß-blockers - open study	Reduction of the number of pain episodes after iv-NTG.
Curfman [49]	40	Pts with angina at rest + ECG changes or other evidence for coronary disease - iv-nitroglycerin vs oral isosorbide dinitrate + 2%nitroglycerin ointment	In both groups a similar significant reduction of the number of pain episodes in the acute phase.
ß-BLOCKERS			
Gottlieb [50]	81	Pts with angina at rest + ECG changes, treated with nitrates and nifedipin - propanolol vs placebo	Addition of propanolol to vasodilating drugs reduces the number symptomatic- and silent ischemic episodes.
Wallis [51]	23	Pts with angina at rest and objective evidence of coronary disease - iv-metoprolol vs oral propanolol	In both groups a similar improvement of haemodynamic parameters and a reduction of the number of pain episodes.
HINT [25]	515	338 pts with suspected UAP at admission, without ß-blocker therapy at admission - metoprolol vs placebo	Metoprolol reduces the incidence of recurrent ischemia and infarction within the first 48 hours.
CA-ANTAGONISTS			
nifedipin			
HINT [25]	515	338 pts with suspected UAP at admission, without ß-blocker therapy at admission - metoprolol, nifedipine or both vs placebo 117 pts with suspected UAP at admission, with existing ß-blockade - nifedipine vs placebo	Combination no additional effect to ß-blocker alone. Mono therapy with nifedipine increases the frequency of recurrent ischemia / infarction. Addition of nifedipine to ß-blocker therapy reduces the frequency of recurrent ischemia / infarction.
Gerstenblith [52]	138	Pts with angina at rest + ECG changes, treated with nitrates and ß-blockers - nifedipine vs placebo	Addition of nifedipine reduces the need for bypass surgery in order to control persisting symptoms.
Muller [53]	126	Pts with angina at rest + ECG changes or other evidence for coronary disease - conventional (nitrates+ß-blockers) vs nifedipine	In pts without maintenance treatment with ß-blockers conventional therapy is more effective control ischemia. In pts with maintenance treatment with ß-blockers nifedipine is more effective to control ischemia.

diltiazem			
Andre-Fouet [54]	70	Pts with angina at rest + ECG changes; Prinzmetal's angina not excluded - propanolol vs diltiazem	In both groups a similar significant reduction of the number of pain episodes. Diltiazem is possibly more effective in angina at rest without previous angina of effort.
Theroux [55]	100	Pts with progressive angina or angina at rest + ECG changes; Prinzmetal's angina excluded- diltiazem vs propanolol	In both groups a similar significant reduction of the number of pain episodes. Bypass surgery, infarctions and mortality during follow up (5 months) similar.
ANTICOAGULANTS / ANITPLATELET DRUGS			
heparine			
Telford [56]	214	Pts with progressive angina ± ECG changes or subendocardial infarction - heparin, atenolol, or both vs placebo	Reduction of infarction risk with heparin compared to atenolol and placebo.
Theroux [40]	479	Pts with progressive angina or angina at rest + ECG changes - heparin, aspirin, or both vs placebo	Reduction of persisting pain (refractory angina) with heparin. Reduction of infarction risk with heparin and aspirin. Combination no additional effect, but more bleeding complications.
RISC group [58]	796	Pts with progressive angina + ECG changes or non-Q-wave infarction - heparin, aspirin or both vs placebo	Reduction of infarction and mortality risk with aspirin alone and in combination with heparin, not with heparin alone.
Semeri [45]	97	Pts with persisting (refractory) angina 48 hours after admission - heparin continuous infusion or heparin bolus injections vs aspirin	Reduction of the number of pain episodes with heparin infusion compared to heparin bolus or aspirin.
aspirin			
Lewis [39]	1266	Pts with progressive angina or angina at rest + ECG changes or other evidence of coronary disease - aspirin vs placebo	Reduction of the infarction and mortality risk with aspirin, both short term (12 weeks) and long term (1 year).
Cairns [57]	555	Pts with ischemic chest pain, after exclusion of infarction or other diseases - aspirin, sulfinpyrazone, or both vs placebo	Long term (18 months) reduction of infarction and mortality risk with aspirin. No effect of sulfinpyrazone.
Ticlopidine			
Balsano [41]	652	Pts with progressive angina or angina at rest + ECG changes - conventional (nitrates, ß-blockers and calcium antagonists) vs conventional therapy + ticlopidine (=platelet inhibitor)	Reduction of infarction and mortality risk with ticlopidine.

THROMBOLYTIC AGENTS			
urokinase			
Gotoh [66]	37	Pts with recurrent angina at rest despite triple therapy (nitrates, ß-blockers and ca-antagonists) in whom angiography during pain was possible - open study	Angiographically: thrombus in 57%, reduction after ic-UK. Clinically: recurrence of pain / infarction associated with the presence of thrombus, independent of thrombolysis.
rt-PA			
Gold [59]	24	Pts with angina at rest + ECG changes - rt-PA vs placebo (continuous infusion during 12 hours)	Angiographically: fewer thrombi with rt-PA after 1-3 days. Clinically: reduction of recurrent pain after rt-PA; recurrence of pain is associated with thrombus; bleeding risk high after rt-PA infusion.
Topol, Nicklas [60,61]	40	Pts with angina at rest and coronary stenosis > 60% - rt-PA vs placebo after diagnostic angiogram	Angiographically: no reduction in diameter stenosis. Pacing threshold increases after rt-PA when thrombus present. Clinically: no difference in revascularisation procedures.
vd Brand [62]	36	Pts with angina at rest + ECG changes - rt-PA vs placebo after diagnostic angiogram; PTCA after 24 hours	Angiographically: no difference. Clinically: no difference in pain episodes or infarctions. PTCA: rt-PA no effect on procedural complications.
Williams [63]	67	Pts with angina at rest + ECG changes and coronary stenosis > 80% - high dose rt-PA (100 mg), low dose rt-PA (0.75 mg/kg, max 60 mg) vs placebo after diagnostic angiogram	Angiographically: no difference between groups. Clinically: no difference in pain, infarctions or emergency operations; increased bleeding risk in both rt-PA groups.
streptokinase			
de Zwaan [64]	41	Pts with angina at rest ± ECG changes - open study: IC-SK or rt-PA iv after diagnostic angiogram	Angiographically: in both groups a reduction of the number of thrombi and a reduction of diameter stenosis. Clinically: number of pain episodes and revascularisation procedures independent of angiographic improvement.
Saran [65]	48	Pts with angina at rest + ECG changes, persisting after 48 hrs despite treatment with triple-therapy + iv-nitroglycerin - iv-SK vs placebo	Clinically: earlier pain relief and reduction of the number of pain episodes after SK; infarct reduction after 6 months.
anistreplase			
Bär [83]	159	Pts with a typical history of unstable angina + ECG changes + significant coronary lesions - anistreplase vs placebo	Angiographically: significant reduction of diameter stenosis. Clinically: no difference in angina severity, infarction and mortality rate; increased bleeding risk after anistreplase.

All studies are randomised trials unless mentioned otherwise.

cGMP. Dissociation of NO from nitrates results in vasorelaxation independent of endothelial EDRF, also in an atherosclerotic environment without intact endothelium[46].

ß-blockers. ß-blockers reduce the incidence of new ischemic episodes by reducing heart rate and blood pressure and depressing myocardial contractility, all of which lower myocardial oxygen demand. A low heart rate also results in a prolonged diastole and thus provides more time for coronary perfusion. ß-blockers without intrinsic sympaticomimetic activity (ISA) are generally preferred because they are more effective to reduce heart rate. However, the clinical efficacy of the various ß-blockers is not significantly different[46,47]. Side effects of ß-blockers include heart failure, hypotension, peripheral vasoconstriction and bronchospasm, and seldom coronary artery spasm.

Calcium-antagonists. The three most important representatives of this group are nifedipine, diltiazem and verapamil. These drugs act through a blockade of the calcium influx into the (muscle) cells. The anti-ischemic effect is established by improvement of the oxygen balance on both the supply side and on the demand side: by coronary vasodilation, peripheral arterial vasodilation and afterload reduction, by reducing the heart rate (except nifedipine) and by depressing contractility[46,1]. The three drugs vary in their potency to affect the different components of the cardiovascular system. Nifedipine has a strong vasodilating effect and a modest negative inotropic effect. Side effects due to vasodilation may occur as reflextachycardia and hypotension and even 'coronary steal', which can aggravate the anginal symptoms[47]. In addition to a vasodilating effect, diltiazem also inhibits the sinoatrial node and AV-conduction, reducing heart rate. Verapamil has an even stronger inhibiting effect on the AV-node and reduces myocardial oxygen demand by negative inotropic action. This drug is often used to treat supraventricular arrhythmias.

Both ß-blockers and calcium-antagonists are effective in alleviating acute symptoms (table 1.1), but reduction in infarction rate by ß-blocker treatment has only been shown in the HINT study[25], and no reduction in mortality rate has been reported[50,52].

Platelet inhibitors and anticoagulants. Platelet aggregation and thrombus formation are the key factors in an evolving unstable situation. Accordingly, a favourable effect of platelet inhibitors and anticoagulants may be expected to prevent progression to infarction or sudden death in patients with unstable angina. Indeed, aspirin and heparin have been shown to reduce infarction and sudden death in patients with unstable angina pectoris (table 1.1). These drugs are of value for both short term treatment (reduction of ischemic episodes by heparin) and long term treatment (reduction of the risks for infarction and death by both heparin and aspirin)[39,40,57,58].

Thrombolytic agents The recognition of intracoronary thrombus formation in unstable angina pectoris, as well as the efficacy of thrombolytic agents in treatment of acute infarction[67-70] have been a reason to investigate the clinical effect thrombolytic agents

in unstable angina. However, no salutary effect of these drugs has been found in patients with unstable angina, neither angiographically nor clinically (table 1.1). Some authors report an association between recurrence of pain and the presence of thrombus[59,66]. Possibly thrombolytic therapy might be effective in this subgroup of patients, but this has not yet been shown.

A stepwise approach to treatment of unstable angina is generally recommended[71]. The first step is admission to hospital, bed rest and pain relief with sublingual nitroglycerin or morfinomimetic drugs. Additional problems, such as high blood pressure and heart rate, arrhythmias, anaemia or thyrotoxicosis should be treated when present. The second step includes administration of heparin and ß-blockers immediately at admission, even when the ECG is normal. Nitrates (oral or intravenous) are administered at the same time. Finally, calcium-antagonists can be added. It should be noted that nifedipine is only beneficial for patients who are already on maintenance treatment with ß-blockers, while its administration is discouraged without concomitant ß-blocker therapy[25,53]. Addition of aspirin to heparin treatment in the acute phase may provide extra protection although it may also be reserved for long term therapy[40,58].

Such stepwise combination therapy will control the symptoms in 80-90% of the patients admitted to the hospital with unstable angina[47,71]. In case of persisting symptoms in spite of intensive pharmacological therapy, coronary angiography is indicated to prepare subsequent angioplasty or bypass surgery. Although a thrombus is frequently present, especially early after the most recent pain episode and in the presence of concomitant ST-T changes[72], thrombolytic therapy has at present no place in the treatment strategy for unstable angina, unless complete coronary occlusion has been documented by angiography[66]. If the patient has stabilised it is often suggested to perform angiography after several weeks, either after or without intermediate exercise testing, and to decide for elective angioplasty or bypass surgery, depending on the angiographic results[47,71].

VI. Coronary angiography, angioplasty and bypass surgery

Coronary angiography is performed to assess the possibilities for revascularisation if such intervention is being considered. In addition, in some patients an angiogram may be helpful to establish the diagnosis of coronary disease, when the symptoms are suggestive for coronary artery disease, but without concomitant ECG changes. Clear indications for angiography are post infarction angina (within 4 weeks after infarction), 'refractory' angina (persisting despite extensive medical therapy), angina at rest with ECG changes indicative for ischemia in a large myocardial area, or the development of deep negative T-waves in the anterior leads (suggestive of proximal LAD obstruction)[73]. The frequency of angiography procedures in patients admitted for unstable angina varies

considerably between regions and institutions[74], depending in part on descriptions and patient referral patterns. In the Rotterdam study a decision to perform angiography was made for 31% of the patients admitted with an initial diagnosis of unstable angina (chapter 2). In the hospital with in-house angioraphic facilities the decision for angiography was made twice as often as in the hospital without a catheterisation laboratory (chapter 4). The intensity of medication at the onset of the unstable period appears to be an important factor for this variability[74], but also considerable variation in the decision making process is observed between individual cardiologists (chapter 5).

It should be appreciated that the risk of coronary angiography is low but not negligible, varying from 0.1 to 0.5%[75]. Procedural mortality is positively associated with elderly age and with severe coronary artery disease, especially left main disease. Thus, a decision to perform angiography should not be made lightly.

Although the angiographic appearance of the culprit lesion in patients with unstable angina may differ from the appearance of the lesions in patients with stable angina, the extent of coronary artery disease appears similar in both patient groups, independent of the clinical presentation[16,18]. In approximately 5-10% of patients no significant lesions are found. Left main disease is observed in about 5%, and 1-, 2-, and 3-vessel disease are present in equal amounts. Apparently, the dynamic obstruction in unstable angina, as described in paragraph 2, is responsible for the unstable situation and not the severity of the fixed obstruction per se.

Both bypass surgery and angioplasty are often performed in patients with unstable angina pectoris. However, if possible, such interventions should be deferred until symptoms have been stabilised[76,77]. In patients with three-vessel disease and impaired left ventricular function survival may be improved by surgery[44]. Angioplasty of the culprit lesion may be efficacious in case of failure of medical therapy as well as after initial stabilisation[78,79]. Initially angioplasty was performed only in patients with single vessel disease and circumscript lesions with smooth borders. More recently also irregular 'unstable' lesions in patients with multivessel disease have been treated by PTCA. Such angioplasty procedure of the ischemia-related, 'culprit' lesion is successful in 85-90% of the patients[80,81]. Complications occur more often in patients with unstable angina than in patients with stable angina, especially when intracoronary thrombus is present and also if the procedure is performed within one week after the most recent pain episode[82]. Restenosis after initially successful procedures occurs in 25-35% of the patients in the first 6-8 months[81]. The choice between PTCA or surgery in practice will be based on the angiographic findings, as well as on the availability of both procedures, and waiting list. A formal of PTCA comparison with medical therapy or with surgery is not yet available. Therefore, the long term effects of PTCA and CABG in patients who are eligible for either procedure are currently being compared in several randomised trials (CABRI,BARI,EAST,RITA,GABI)[84,85].

Conclusion

The term 'unstable angina pectoris' encompasses a broad spectrum clinical presentations of coronary artery disease and has to be specified in greater detail when the clinical condition of an individual patient is described. The pathophysiology of unstable coronary disease includes abrupt disruption of an atherosclerotic plaque, often with an increase in vasomotor tone, platelet aggregation and thrombus formation. In patients with prolonged complete coronary occlusion myocardial infarction will develop. The risk of progression to infarction in patients presenting with symptoms compatible with unstable angina varies form 1-6% in the acute phase and from 5-15% within 1 year. This risk depends in part on patient selection and on the definition of unstable angina, as well as on the intensity of medication. Presently available medication for short-term and long-term treatment acts on different pathophysiologic mechanisms. Besides the traditional nitrates and ß-blockers, calcium-antagonists, heparin and aspirin have been added to the treatment regimen. So far, thrombolytic drugs have not shown a salutary effect in patients with unstable angina. Angioplasty and bypass surgery are efficacious to prevent of complications in selected patients. However, is has not been determined by controlled studies in which cases angioplasty or surgery should be preferred and in which cases medical therapy would be the best option.

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CHAPTER 2

IN-HOSPITAL MANAGEMENT AND COMPLICATIONS IN UNSTABLE ANGINA

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ABSTRACT

A follow up study was performed in order to examine the management and clinical course in unstable angina. 417 consecutive patients admitted to the Thoraxcenter (TXC) or Sint Franciscus Gasthuis (SFG) for chest pain denoted as unstable angina, suspected of reversible ischemia, without signs of acute myocardial infarction, were followed during hospital stay.

After an initial observation period the final diagnosis was myocardial infarction in 38 patients (9%), unstable angina in 270 patients (65%) and non-cardiac or non-specific pain in 109 patients (26%).

All patients received medical therapy as indicated. A key question in unstable angina is whether medical therapy will suffice, or whether coronary angiography and additional interventions are required. During hospital stay it was decided to perform angiography in 137 patients (33%), including 16 patients for whom this decision was made immediately at admission, because of the history and the severity of symptoms. Subsequently, 100 patients (24%) were scheduled for angioplasty or bypass surgery. Angiography was performed more often in the TXC (47%) than in the SFG (25%). During follow-up 211 patients (53%) had recurrent pain episodes. New myocardial infarction occurred in 16 patients (4%), 9 during observation or waiting for an intervention and 7 related to PTCA (3) or CABG (4). Six patients died (1.4%), of which 3 during observation and 2 in relation to PTCA. Mortality was associated with advanced age (≥ 70 years) and recent infarction.

We conclude that patients admitted for suspected unstable angina have benign in-hospital course if intensive therapy is available. Recurrent ischemia occurs frequently but it can be treated with low morbidity and mortality.

INTRODUCTION

The syndrome unstable angina pectoris encompasses a variety of clinical presentations caused by transient episodes of myocardial ischemia. These episodes are precipitated by changes in the degree of coronary flow obstruction caused by different pathophysiological mechanisms, including intracoronary atheromatous plaque rupture, platelet aggregation and thrombus formation, and increased vasomotor tone[1,2]. Other terms that have been used to describe the syndrome, such as impending myocardial infarction, pre-infarction angina, acute coronary insufficiency or intermediate coronary syndrome[3], indicate concern for progression to myocardial infarction. However, morbidity and mortality in patients with unstable angina vary[4-6], which occur in 1-6% respectively 2-12% in the acute phase. Accordingly the 'label' or diagnosis can change over time[7,1].

In a patient with chest pain severe enough to warrant hospital admission an *early* working diagnosis of suspected unstable angina is made when symptoms and signs are such that transient myocardial ischemia is believed to be the underlying cause. New information acquired during admission, such as the occurrence or absence of new episodes of chest pain, ECG changes or elevated serum enzyme levels, will contribute to a *final* diagnosis which can be either acute myocardial infarction, unstable angina, non cardiac disease, or 'non-specific' chest pain.

Most reports address specific selected subgroups of patients with unstable angina, such as patients in whom myocardial infarction has been 'ruled out' by serial enzyme determinations[8,9], or patients referred for angioplasty[10,11] or bypass surgery[12,13]. Accordingly, data on the clinical course and management in the whole spectrum of patients with unstable angina are scarce.

In an attempt to collect such data we conducted a prospective two-center follow-up study in 417 consecutive patients who were primarily admitted to hospital for chest pain of suspected ischemic origin, labelled 'unstable angina', without signs of acute infarction or other diseases at the time of admission. The specific aim of the study was to assess the diagnostic and therapeutic procedures used in various subgroups and to assess the incidence of in-hospital events, including development of myocardial infarction and mortality and the need for emergency revascularisation procedures. Also the management strategy in the two hospitals was compared.

PATIENTS AND METHODS

Study site

The study was conducted in the Thoraxcenter (TXC) of the University Hospital Dijkzigt and the Sint Franciscus Gasthuis (SFG) in Rotterdam. The TXC is a

teaching hospital with facilities for diagnostic angiography, angioplasty, and cardiac surgery, where approximately 1100 patients are admitted to the CCU per year. The SFG is a large community hospital with about 1700 CCU admissions per year, but without in-house angiography facilities. Most diagnostic catheterization procedures in patients admitted to the SFG are performed by cardiologists from the SFG who have their own schedule in the TXC and in another hospital in Rotterdam. Most emergency angiograms, as well as the majority of revascularisation procedures are performed in the TXC.

Patient selection and definitions

All patients admitted to the cardiac department for chest pain diagnosed as unstable angina by the physician on duty, were included in the registry. The initial diagnosis *suspected unstable angina* was based on a history of severe chest pain at rest or at minimal exertion, probably of ischemic basis without electrocardiographic signs of acute infarction or signs of other causes of chest pain such as aneurysm or arrhythmia. ST-T changes were not required for inclusion. Patients admitted for suspected myocardial infarction were also included as unstable angina when subsequent enzyme levels remained below twice the normal value. Patients who were referred to the TXC from other hospitals for further treatment were excluded.

The final diagnosis *definite unstable angina* was based on the evaluation of symptoms and on the documentation of objective ECG criteria during observation or exercise testing. Patients with initial infarction who had recurrent anginal pain after 24 hours were included as post infarction unstable angina.

Data collection and follow-up

The data were prospectively collected and recorded on a form which was designed in such a way that registration followed the various decision moments during a patient's hospital stay.

The in-hospital stay was divided in three periods: an *observation period* lasting from admission until the decision either to discharge or to initiate coronary angiography; a *waiting period* lasting from the moment of decision to perform angiography until the execution of the procedure; in patients for whom the decision was made to perform angioplasty or bypass surgery a *second waiting period* was distinguished between the decision and the procedure; in patients for whom was decided to continue medical therapy a *second observation period* was distinguished between this decision and discharge.

Demographic data, history and characteristics of presentation were recorded at admission. During all follow-up periods a log was kept of new pain episodes, new infarctions or death. The following diagnostic and therapeutic measures were

recorded: electrocardiograms, exercise tests, and medication. After an observation period of 24-48 hours the final diagnosis was noted. Furthermore the frequency of and reasons for changes of initial decisions were recorded.

Electrocardiograms were coded with respect to the presence or absence of Q-waves, indicating old infarction (Q-waves > 0.03 sec or Q-wave equivalents: R-wave > 0.03 seconds in V1 and R > S in V2), signs of left ventricular hypertrophy (R ≥ 2.6mV in V5 or V6, or R in V5 or V6 plus S in V1 ≥3.5mV), intraventricular conduction disturbances (QRS > 0.12 seconds) or neither of these[14]. The ST-segment was scored as ST elevation or ST depression ≥ 0.1mV and/or T-wave inversion. If an electrocardiogram during pain was obtained, the occurrence of ST elevation/depression ≥ 0.1mV or T-wave deviation ≥ 0.1mV was described.

Serum creatine kinase levels and other enzymes were determined at various moments during hospital stay according to local routine. Myocardial infarction was defined as the presence of serum creatine kinase levels above twice the local upper limit of normal. The time of onset of infarction was determined from analysis of history, ECG and enzyme changes.

Statistical analysis

Comparisons between groups were analyzed with a student t-test for continuous variables and χ-square test for discrete variables.

RESULTS

Patient flow and final diagnosis

Between October 1988 and September 1989, 148 patients were admitted for suspected unstable angina to the Thoraxcenter (TXC), University Hospital Dijkzigt and 269 to the Sint Franciscus Gasthuis (SFG). This includes 11 patients with an initial diagnosis of myocardial infarction but without serial enzyme changes. A flow chart of these 417 patients with respect to the final diagnosis and clinical events between admission and the decision to perform angiography is given in figure 2.1.

For 16 patients the decision to perform angiography was made immediately at admission because of the history and the severity of symptoms, including 7 with a history of recent infarction or angioplasty. For the other 401 patients a final diagnosis was made after a 24-48 hour observation period. In 270 patients the final diagnosis was definite unstable angina, 38 patients appeared to have an infarction at the time of admission, according to enzyme levels that became available after several hours and for 109 other patients the final diagnosis was non-specific chest pain or chest pain of other causes, including gall bladder and liver disease (2),

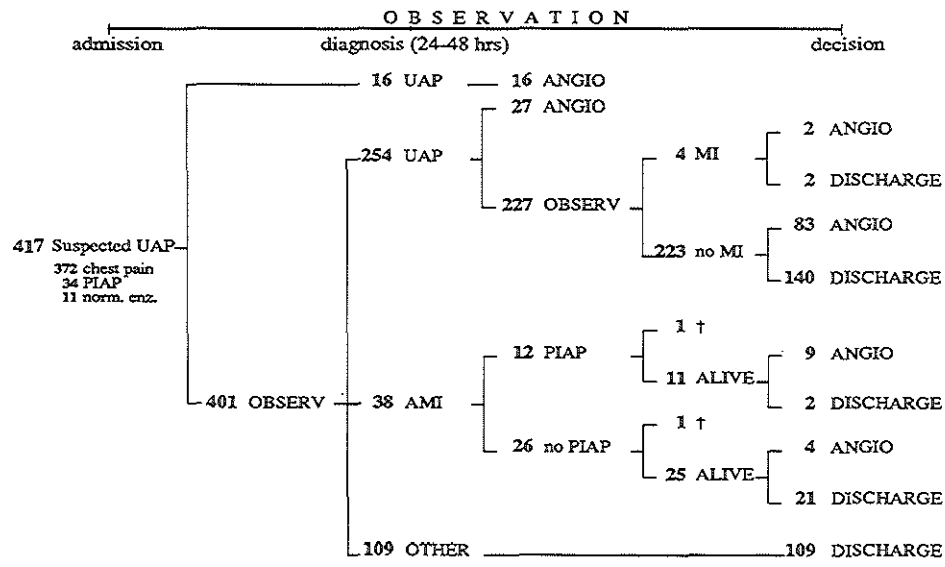

Figure 2.1. *Flow of patients admitted for chest pain suspected of unstable angina from admission until the decision either to perform angiography or to discharge without angiography. PIAP = post infarction angina; norm. enz. = normal enzymes: patients admitted for suspected myocardial infarction without elevated enzyme levels.*

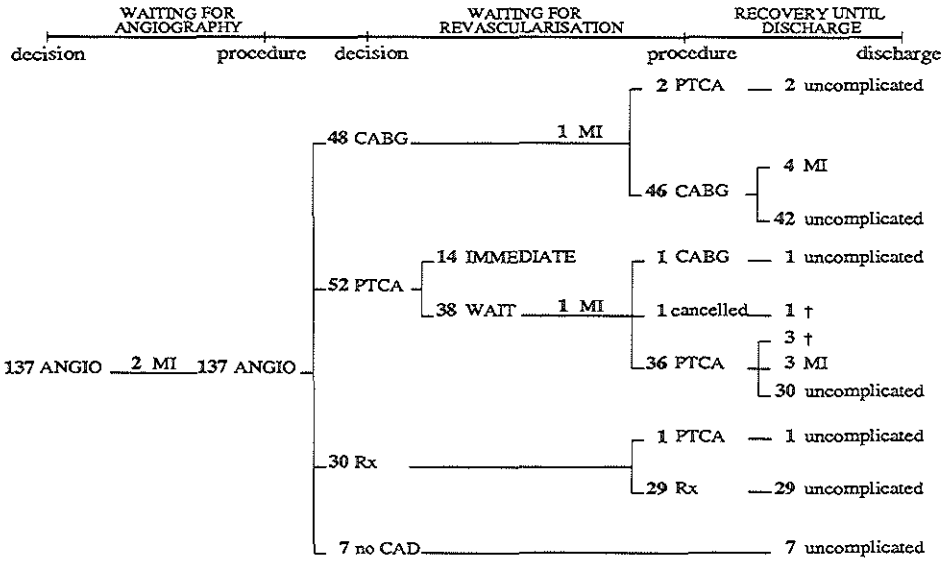

Figure 2.2. *Flow of all patients with definite of unstable angina from the time of decision to perform angiography until the eventual procedure, subsequent interventions and discharge. CAD = coronary artery disease*

gastrointestinal problems (4), musculoskeletal pain (1), heart failure (5), arrhythmias (3), and pericarditis (1). Twelve out of 38 patients with initial infarction developed post infarction angina, bringing the total number of patients with unstable angina to 282.

Patients with 'definite' unstable angina.

After the diagnosis unstable angina was made, 52 out of 282 patients were scheduled for angiography without further delay and angiography was scheduled for another 85 patients after recurrent ischemic episodes. The subsequent course of these 137 patients with unstable angina scheduled for angiography is illustrated in figure 2.2. All planned angiography procedures were performed without complications. After angiography 100 patients were scheduled for revascularisation procedures, 37 patients were treated medically including seven patients in whom the angiogram did not show significant coronary disease. Two patients scheduled for surgery eventually underwent angioplasty, because of infectious disease in one patient and because of recurrent pain episodes that warranted an emergency procedure in the other patient. Angioplasty was performed during the same session as the angiography in 14 patients, including 8 patients undergoing a repeat procedure within six months of an earlier angioplasty. One patient who waited for angioplasty underwent surgery instead after revision of the angiogram. One other procedure was cancelled because of fever. This patient subsequently died after reinfarction despite medical therapy. Medical treatment failed in one patient who subsequently underwent angioplasty because of recurrent pain episodes with ECG changes.

Table 2.1 In hospital mortality

	gender	age	symptoms	time after admission	cause of death
1	female	85	infarct at admission -recurrent ischemia	4 days -observation period	reinfarction
2	female	75	infarct at admission -recurrent ischemia	31 days -waiting for PTCA (cancelled)	reinfarction
3	male	70	angina after recent infarct and PTCA	0 days -during PTCA	heart failure, asystole -thrombus formation
4	male	73	recent onset angina	5 days -2 days after PTCA	retroperitoneal bleeding
5	male	79	infarct at admission	1 day -observation period	infarction and heart failure
6*	female	73	angina after recent infarct	12 days -during PTCA	intracerebral bleeding

* Decision for angiography was made immediately at admission.

Mortality and morbidity.
Six out of 417 patients (1.4%) died in hospital. All six patients were 70 years or older. Five of these six patients died after recent infarction. Three patients died during observation, while the three other deaths were related to angioplasty procedures. Details are provided in table 2.1.
Myocardial infarction occurred in 16 patients (3.8%). This was associated with prehospital acceleration of angina and ST-T abnormalities on the baseline ECG. Four patients developed infarction during initial observation (figure 2.1). Four patients suffered infarction during a waiting period, two waiting for angiography, one for surgery and one other for angioplasty and seven infarctions were related to revascularisation procedures, four to surgery and three to angioplasty (figure 2.2).

Baseline characteristics
Demographic and historical data of the 417 patients who were admitted for observation are presented in table 2.2. There was no difference in mean age between patients with a final diagnosis of unstable angina, myocardial infarction or chest pain of other causes. However there were less patients younger than 50 years with unstable angina (16%) compared to the other two groups (29%, $p<0.01$). Patients with unstable angina had more often a history of documented coronary artery disease than patients who in retrospect had an infarction or other diagnosis. At hospital entry 42% of all patients were without antianginal medication. Medication before admission was more extensive in patients with unstable angina since only 31% entered the hospital without medication against 63% of the other patients, $p<0.001$. Thirty percent of all patients had one, 20% two and 7% three antianginal drugs (nitrates, ß-blockers or calcium antagonists) before admission.

A short history of pain was seen more often in patients with acute infarction or other causes than in patients with unstable angina. In half of the patients with other causes the pain was of sudden onset (table 2.3). In case of myocardial infarction the pain was usually still present at admission and lasted for more than one hour. However a high number of patients with unstable angina (33%) had pain of long duration. This may partly be due to interpretation of a sequence of many shorter episodes. However, it is not a sensitive indicator for myocardial infarction on its own. Patients with unstable angina and myocardial infarction had more pain episodes during 24 hours before admission than patients with other causes (46% and 29% respectively with multiple episodes, $p<0.05$).

The initial diagnosis of suspected unstable angina in the 417 patients who were admitted for initial observation was supported by dynamic ECG changes during or shortly after pain in 147 patients, and by abnormal repolarisation considered as ischemia on the painfree ECG in 67 patients (28 patients had ST-T abnormalities on

Table 2.2 Baseline characteristics

	Total n=417	final diagnosis: UAP n=270	AMI n=38	Other n=109
	n (%)	n (%)	n (%)	n (%)
age				
≤ 50 years	80 (21)	44 (16)	11 (29)	32 (29)
50-70 years	203 (49)	145 (54)	18 (47)	40 (37)
> 70 years	127 (30)	81 (30)	9 (24)	37 (34) †
male	267 (64)	172 (64)	29 (76)	66 (61)
hypertension[1]	152 (36)	93 (34)	19 (50)	40 (37)
diabetes mellitus	49 (12)	35 (13)	4 (11)	10 (9)
hypercholesterolemia[2]	59 (14)	45 (17)	6 (16)	8 (7)
smoking[3]	142 (34)	95 (35)	13 (34)	34 (31)
positive family history[4]	151 (36)	108 (40)	9 (24)	34 (31)
previous history				
unstable angina	95 (23)	78 (29)	6 (16)	11 (10) †
myocardial infarction	193 (46)	133 (51)	15 (39)	41 (38) *
angiography (documented CAD)	112 (27)	87 (32)	8 (21)	17 (16) †
angioplasty	51 (12)	45 (17)	1 (3)	5 (5) †
bypass surgery	63 (15)	49 (18)	4 (11)	10 (9)
one of above	230 (55)	165 (61)	20 (53)	45 (41) †
medication before admission[5]				
long acting nitrates	104 (24)	82 (30)	7 (18)	15 (14) †
beta blockers	167 (39)	130 (48)	12 (32)	25 (23) †
calcium antagonists	113 (25)	89 (33)	9 (24)	15 (14) †
platelet inhibitors	87 (21)	66 (24)	5 (21)	16 (15) *
oral anticoagulants	55 (13)	29 (11)	4 (11)	22 (20) *

* $p<0.05$ † $p<0.01$; UAP=unstable angina pectoris; AMI=acute myocardial infarction; Other=non-specific chest pain or chest pain of other causes.
[1] Blood pressure >160/90 or current treatment. [2] serum cholesterol >6.5 mmol/l or current treatment. [3] current smoking and smoking until less than a year ago. [4] infarct or cardiac death at age under 60 in first or second degree relative. [5] total number of antianginal drugs is displayed in figure 2.3.

Table 2.3 Presentation at admission

	Total n=417	final diagnosis: UAP n=270	AMI n=38	Other n=109
	n (%)	n (%)	n (%)	n (%)
pain before presentation[1]				
none	133 (32)	61 (23)	15 (39)	57 (52)
≤ 4 weeks, progressive	105 (25)	77 (29)	13 (34)	15 (14)
> 4 weeks, stable	77 (18)	50 (19)	6 (16)	21 (19)
> 4 weeks, progressive	101 (24)	81 (30)	4 (11)	16 (15) †
pain still present at admission	227 (54)	138 (51)	33 (87)	56 (51) †
duration of pain episodes				
<15 min	109 (26)	83 (31)	4 (10)	22 (20)
15-60 min	126 (30)	88 (32)	3 (8)	35 (32)
≥60 min	169 (41)	89 (33)	31 (82)	49 (45)
unknown	13 (3)	10 (4)	0 (-)	3 (3) †
thalamonal for pain relief	63 (15)	38 (14)	13 (34)	12 (11) †
electrocardiogram				
QRS				
Q-wave	131 (31)	91 (34)	12 (32)	28 (26)
intraventricular conduction disturbances	37 (9)	20 (7)	7 (18)	10 (9) *
left ventricular hypertrophy	24 (6)	15 (6)	1 (3)	8 (7)
none of the above	225 (54)	144 (53)	18 (47)	63 (58)
ST-T segment				
ST-elevation > 0.1mV	47 (11)	29 (11)	6 (16)	12 (11)
ST-depression > 0.1mV	73 (18)	47 (17)	8 (30)	18 (17)
T-wave inversion	137 (33)	101 (37)	10 (26)	26 (24) *
ST-T segment judged as ischemia[2]	95 (23)	73 (27)	10 (26)	12 (11) †
ST-T change during pain				
Δ ST-elevation > 0.1mV	31 (7)	24 (9)	7 (18)	0 (0) *
Δ ST-depression > 0.1mV	79 (19)	59 (22)	15 (39)	5 (5) †
Δ T-wave > 0.1mV	31 (7)	24 (9)	3 (8)	4 (4)
ST-T change judged as ischemia[2]	147 (35)	110 (41)	25 (66)	12 (11) †

* $p<0.05$ † $p<0.01$. [1] none=no pain before present episode; ≤ 4 weeks=pain for less than four weeks with progression; > 4 weeks, stable=chronic stable chest pain before admission without acceleration before present episode; > 4 weeks, progressive=chest pain present for more than four weeks with gradual acceleration. [2] interpretation of the ST-T segment by the attending physician. Δ = difference in ST-segment or T-wave deviation in comparison to the ECG without pain.

both ECGs). In 203 patients it was based on history alone. Although a history of myocardial infarction was more frequent in patients with UAP, this was not reflected in the frequency of Q-waves on the electrocardiogram. Ischemic ST-T abnormalities on the admission electrocardiogram at rest and/or ST-T changes during or after pain were seen at admission in more than half of the patients, while 20 percent of the patients with 'other' causes had ST-T abnormalities.

Clinical course

Observation from admission until the decision for angiography or discharge.

New episodes of chest pain in hospital were frequent in all categories of patients (table 2.4). The pain was accompanied by ST-T changes and was reason for additional medication in one third of the patients with unstable angina. Two third of the patients with infarction had new episodes of pain in hospital, although post infarction angina (> 24 hours after initial infarct) occurred in only 12 patients. An exercise test was performed in half of the patients in all categories. Pain or ECG changes were observed in 54% of the tests in patients with unstable angina while but also in 10% of the patients with chest pain of other causes.

Patients in whom the decision was made to perform angiography differed from the other subjects in the following respects: they had more often post infarction angina, more recurrent pain episodes during the initial observation, which were accompanied by ECG changes and treated with additional medication more often. Fewer patients underwent an exercise test, but if exercise testing was performed, pain and ECG changes during the test were observed more frequently.

Waiting period for angiography.

Angiography was followed by angioplasty or bypass surgery in similar frequencies, although emergency angiography was followed by angioplasty more often (table 2.5). This was due in part to the relatively high number of patients (8) with clinical suspicion of restenosis after recent angioplasty.

Multiple pain episodes occurred more frequently in patients who were later scheduled for bypass surgery, and ECG changes during pain were observed less often in patients were treated medically after angiography. The severity of coronary artery disease was a decisive factor for subsequent management. Among the patients who were subsequently treated medically or with angioplasty 47% had single vessel disease, whereas 58% of the patients who were scheduled for bypass operation had three vessel or left main disease. Still, nine out of 37 patients with three vessel disease were treated medically. Eight of them had undergone bypass surgery in the past and non-invasive management was chosen because of technical difficulties related to renewed surgical procedures or angioplasty, or because of the relative mildness of the symptoms.

Table 2.4 Clinical course during observation period

	Total n=401	final diagnosis UAP n=254	AMI n=38	Other n=109
	n (%)	n (%)	n (%)	n (%)
medication in hospital[1]				
oral nitrates	79 (20)	66 (26)	1 (3)	12 (11) †
intravenous nitrates	231 (58)	146 (57)	34 (89)	51 (47) †
ß-blockers	229 (57)	171 (67)	25 (66)	33 (30) †
calcium-antagonists	125 (31)	97 (38)	13 (34)	15 (14) †
platelet inhibitors	147 (37)	102 (40)	15 (39)	30 (28)
heparin	273 (68)	185 (73)	32 (84)	56 (51) †
new pain episodes[2]	193 (48)	125 (49)	27 (71)	41 (38) †
number (>1)	101 (25)	69 (27)	16 (42)	16 (15) †
max duration (>15 min)	58 (14)	35 (14)	11 (30)	12 (11) *
ECG changes				
during pain	104 (26)	78 (31)	19 (30)	7 (6) †
without pain	18 (4)	18 (7)	0 (-)	0 (-)
no pain or ECG changes	190 (47)	111 (44)	11 (29)	68 (62) †
thalamonal for pain relief	43 (11)	18 (7)	16 (42)	9 (8) †
additional medication after pain	121 (30)	86 (34)	20 (53)	15 (14) †
oral medication	107 (27)	73 (29)	19 (50)	15 (14) †
(re)start intravenous medication	42 (12)	33 (13)	7 (18)	2 (2) †
thrombolytic therapy	8 (2)	7 (3)	1 (3)	0 (-)
exercise test	199 (50)	120 (47)	19 (50)	60 (55)
no ischemic signs	117 (29)	55 (22)	13 (34)	49 (45)
chest pain only during test	16 (4)	11 (4)	0 (-)	5 (5)
ECG changes during test	66 (17)	54 (21)	6 (16)	6 (5) †

* $p<0.05$ † $p<0.01$; 1 total number of antianginal drugs is displayed in figure 2.3.
2 progression to infarction or death is displayed in figures 2.1 an 2.2.

Table 2.5 Clinical course during waiting period for angiography and subsequent results by decision after angiography.

	Total (n=137)	med Rx (n=37)	PTCA (n=52)	CABG (n=48)
	n (%)	n (%)	n (%)	n (%)
priority of angiography[1]				
emergent	20 (15)	4 (11)	11 (21)	5 (10)
urgent	100 (73)	28 (76)	35 (67)	37 (77)
elective	17 (12)	5 (13)	6 (12)	6 (13)
infarction	2 (1)	-	-	2 (4)
new pain episodes	58 (42)	12 (32)	22 (42)	24 (50)
number (>1)	27 (19)	4 (11)	8 (15)	15 (31) *
duration (>15 min)	12 (9)	1 (3)	6 (12)	5 (10)
ECG changes	31 (23)	5 (14)	12 (23)	14 (29) †
no ECG changes	16 (12)	6 (16)	6 (12)	4 (8)
no ECG available	11 (8)	1 (3)	4 (8)	6 (13)
ECG changes without pain	2 (1)	-	-	2 (4)
no pain or ECG changes	77 (56)	25 (68)	30 (58)	22 (46)
additional medication	31 (23)	8 (22)	10 (19)	13 (27)
oral medication	21 (15)	5 (14)	6 (12)	10 (21)
(re)start intravenous medication	11 (8)	3 (8)	5 (10)	3 (6)
thrombolysis	2 (1)	-	1 (2)	1 (2)
angiography results				
no significant lesions	7 (5)	7 (19)	-	-
one vessel disease	44 (32)	18 (49)	24 (46)	1 (2)
two vessel disease	42 (31)	3 (8)	21 (40)	18 (38)
three vessel disease	40 (29)	9 (24)	7 (14)	24 (50)
left main disease	4 (3)	-	-	4 (8) †

* $p<0.05$ † $p<0.01$

1 emergent=on the same day or the next day; urgent=during the present admission period; elective=after discharge, according to waiting list.

Medication.

The number of antianginal drugs (nitrates, ß-blockers, calcium-antagonists and platelet inhibitors) prescribed at each decision moment in hospital is illustrated in figure 2.3 for patients with chest pain from other causes and unstable angina. Forty-six percent of all patients discharged without angiography and 23% of the patients who underwent angiography entered the hospital without medication ($p<0.001$). However, four of the 16 infarctions and three of the six deaths in hospital occurred in patients without medication before admission. At admission and during hospital stay more drugs were prescribed in unstable patients than in patients with chest pain from other causes ($p<0.01$), although half of the patients with 'other causes' were temporarily treated with intravenous nitroglycerin and heparin.

At the time of the decision to perform angiography or not the number of medications was significantly higher for patients who underwent angiography than for those who were discharged ($p<0.001$). Of the former patients 84% were treated with heparin or aspirin and 47% of the patients were treated with intravenous nitrates.

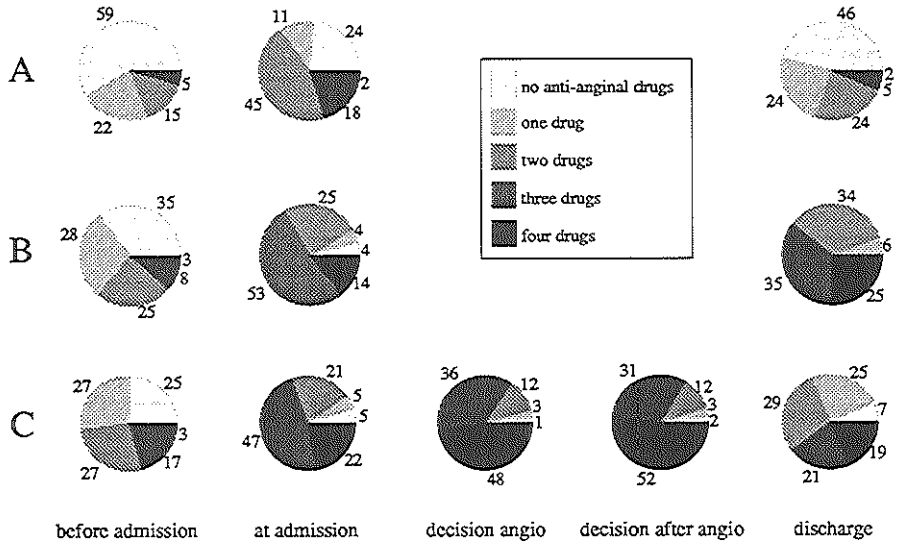

Figure 2.3. *Anti anginal drugs (nitrates, ß-blockers, calcium antagonists and platelet inhibitors) at each decision moment for patients with chest pain of other causes (A), patients with definite unstable angina who were discharged without angiography (B) and patients with definite unstable angina who underwent angiography (C).*

The medication patterns were similar for those who were treated medically after angiography and those who were scheduled for angioplasty or bypass surgery. Nitrates were usually continued intravenously in the latter two groups until the intervention, while these were replaced by oral nitrates in the medically treated group. These medically treated patients left the hospital with slightly more medication than unstable patients who were discharged without angiography (not statistically significant).

Duration of observation and waiting periods

The time in hospital until the final diagnosis was made and subsequent management strategy was determined is depicted in figure 2.3. The median observation period was 2 days in both hospitals, with a maximum of 32 and 14 days for TXC and SFG respectively. Ninety-five percent of patients with 'other causes' were discharged within seven days.

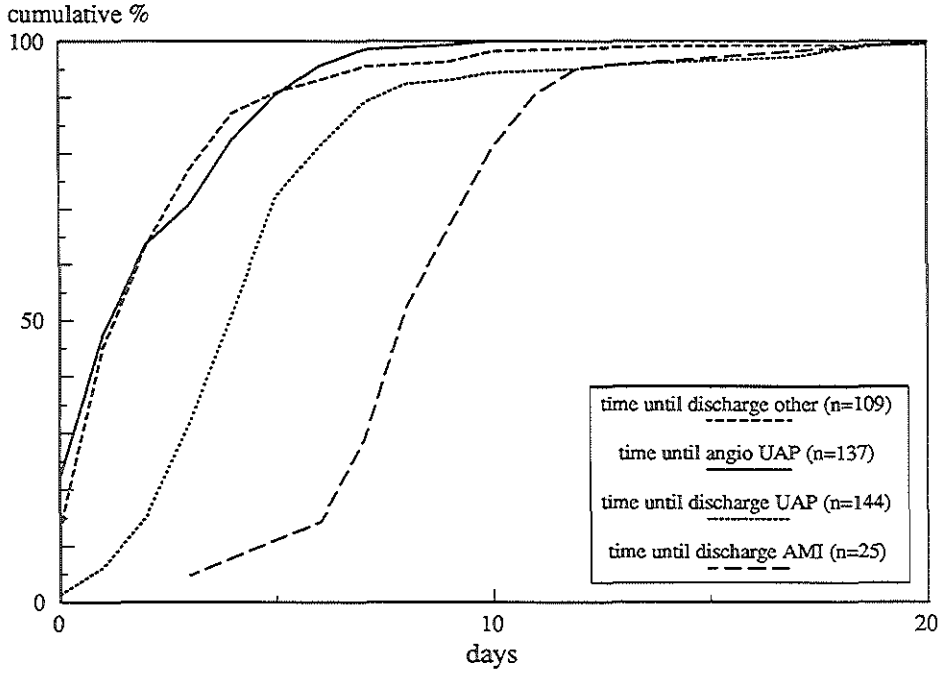

Figure 2.4. *Observation time in days until the decision to perform angiography or to discharge without angiography was made, separated by final diagnosis. From left to right the curves represent*

- *time until discharge in patients with "other diagnoses"*
- *time until angiography in patients with unstable angina*
- *time until discharge in patients unstable angina who did not undergo angiography*
- *time until discharge in patients with myocardial infarction.*

The decision to perform angiography was made on average two days earlier than the decision to discharge without angiography in patients with 'definite' unstable angina (p=0.001). The median time until discharge without angiography was similar for both hospitals (4 and 5 days). The decision to perform angiography was made on average one day earlier in the TXC than in the SFG (p<0.04), with median times of 1 (max. 7) and 2 (max. 10) days respectively. Twenty-two percent of these decisions were made on the day of admission, 34% in the TXC and 9% in the SFG.

Angiography was performed within a median of two (max. 48) days after the decision. The waiting time was significantly shorter in the TXC than in the SFG, 1 (max. 9) day and 5 (max. 48) days respectively (p=0.0001). All procedures in the TXC were done during the same admission period, but 24% of the procedures in the SFG were done after discharge, although the decision had been made during admission. Eight angiography procedures were performed earlier than planned because of aggravation of symptoms, which progressed to infarction in one patient who waited at home. Seven procedures were delayed two to seven days, because of myocardial infarction, fever, temporary stabilization of symptoms and side effects of medical treatment. In three cases organizational problems in the catheterization laboratory caused delay, without serious consequences.

The median waiting time for angioplasty was 2 (max. 8) day. Eleven out of 32 procedures in the TXC and 2 out of 20 in the SFG were done during the same session as the angiography procedure, eight of these for restenosis following previous angioplasty. Angioplasty was performed earlier than planned in 2 patients, because of increasing angina. Three procedures were delayed three to nine days, because of other ailments and organisational problems.

The waiting time for bypass surgery was similar for both hospitals, median 10 (max. 140) days. Seven percent of the bypass operations were emergency procedures and 30% were performed electively. Five bypass operations had to be performed earlier because of increasing symptoms. One of these patients developed myocardial infarction while waiting at home. Four procedures were delayed one to 24 days, for medical or organizational problems. In one patient the waiting period of one day was covered with intra-aortic balloon counterpulsation. None of these delays led to serious consequences such as myocardial infarction or death.

A total of 33 procedures were planned electively, after discharge. Two patients developed infarction as described above. Another 10 patients were readmitted and the procedures were performed earlier than planned because of recurrent chest pain without infarction.

Difference between both hospitals

During the study period twice as many patients were admitted to the SFG compared to the TXC. In both hospitals 65% of the patients were male. Patients admitted in the TXC were on average 4 years younger. Seventeen percent of patients in the TXC and 38% in the SFG were older than 70 years ($p<0.01$). There was no difference between both hospitals with respect to the final diagnosis (table 2.6), although more TXC patients had a history of coronary disease (prior infarction, angioplasty of bypass surgery) or the risk factors hypertension and hypercholesterolemia. Antianginal medication at admission was more extensive in this hospital. Forty-four percent of patients were admitted without antianginal medication in the SFG and 29% to the TXC, ($p<0.01$). The initial diagnosis was based on history alone in more patients in the TXC ($p<0.05$).

Table 2.6 Diagnosis in each hospital

	Total n=401	TXC n=134	SFG n=267	
	n (%)	n (%)	n (%)	
Initial diagnosis				
suspected unstable angina, based on				
history alone	198 (49)	76 (57)	122 (46)	
ECG abnormalities	203 (51)	58 (43)	145 (54)	*
Final diagnosis				
unstable angina	254 (64)	89 (67)	165 (62)	
myocardial infarction	38 (9)	14 (10)	24 (9)	
other	109 (27)	31 (23)	78 (29)	

* $p<0.05$; TXC = Thoraxcenter, University Hospital Rotterdam, Dijkzigt
SFG = Sint Franciscus Gasthuis.

The clinical course until the decision to perform angiography for patients with unstable angina did not differ between hospitals. Angiography was performed in 47% of all patients in the TXC and in 25% in the SFG. The waiting period for angiography was on average 4 days shorter in the TXC, with fewer pain episodes or ECG changes during this period. In both hospitals medication was increased after pain in half of the patients, but intravenous therapy was started more frequently in the SFG. At the time of the decision to perform angiography 23% of the patients in the TXC and 34% of the patients in the SFG had intravenous nitrates (not significant). In both hospitals angiography revealed similar severity of coronary

artery disease. Five percent had no significant coronary disease, 33% had single vessel disease, 30% two-vessel disease, 30% three-vessel disease and 2.% left main disease. Also the strategy following angiography was not significantly different between both hospitals, although physicians in the TXC tended to do more angioplasty procedures, whereas in the SFG bypass surgery was the preferred option for revascularisation.

The number of emergency procedures was significantly higher in the TXC than in the SFG for angiography (20% and 9%) as well as for angioplasty (52% and 10%). One patient from the SFG who underwent immediate angioplasty because of restenosis after previous angioplasty died during the procedure. During hospital stay the total number of events was small and not significantly different for both hospitals. New infarction occurred in 4 patients in the TXC and in 12 patients in the SFG (3 resp 4%). Two patients in the TXC and four patients in the SFG died during the study period (both 1.5%).

DISCUSSION

During one year in two hospitals all patients admitted for chest pain, suspected for unstable angina pectoris were followed prospectively with respect to clinical course and management strategy. This wide entry criterium and the selection of patients immediately at admission ensured that the whole spectrum of unstable angina was included in this registry. This is in contrast with most other studies on unstable angina, where only selected patients were included, restricted by age[15,9], absence of recent myocardial infarction or bypass surgery[16-18,9], duration of pain episodes[17,16,19] or the presence of objective ischemic signs on the electrocardiogram[18-20], or to patients with confirmed coronary artery disease after angiography[18,21], or those selected for angioplasty[10,11] or bypass surgery[12,13]. In most studies patients were selected 24 to 48 hours after admission when myocardial infarction was ruled out by serial enzyme analysis. Such delay also excludes most patients who in retrospect had chest pain of other causes and who were included in the present study. The only exclusion criterium in the present study was evidence of other disease which was believed to cause the chest pain, e.g. aneurysm dissecans, and referral from other hospitals for further treatment of patients in whom already a complete diagnostic workup was performed.

The full spectrum of suspected unstable angina at admission represents a patient population with a dynamic pattern of diagnoses. New information during observation revealed three major diagnostic groups: myocardial infarction that had already occurred but was not recognized as such at admission, a definite diagnosis of

unstable angina, and other causes of chest pain. In one quarter of all patients, after observation the complaints were attributed to causes other than coronary insufficiency. This proportion is much lower than Duncan[15] reported in an out-patient study of 616 men aged under 70 who were referred for chest pain, suggestive for myocardial ischemia, by general practitioners. After a cardiological analysis 365 patients (60%) did not satisfy the criteria for unstable angina. This suggests that a considerable proportion of patients with chest pain from other causes may be filtered before admission. At the other side of the spectrum, myocardial infarction had already occurred in 9% of all admitted patients, which could only be recognized from the serum enzyme assays that became available six to eight hours after admission. Similarly, in the HINT study[19] myocardial infarction had occurred in retrospect at the time of admission in 12% of patients with prolonged chest pain and concomitant ECG changes.

ECG changes were not required for the final diagnosis of unstable angina. In 55 out of 282 patients with unstable angina as final diagnosis no ECG changes were observed during the clinical observation period or during exercise testing. Forty-three of these 55 patients (78%) had a history of coronary disease (myocardial infarction or prior angiography, angioplasty or bypass surgery) and in the other twelve patients the diagnosis of definite unstable angina was made on the present history alone.

Morbidity and mortality.

The in-hospital infarction rate was low. New myocardial infarctions occurred in 16 patients (4%) during the registry period. One of these occurred after initial infarction at admission and two infarctions occurred in patients waiting at home for angiography or bypass surgery. The overall mortality rate was low: 1.2% for the total group and 1.5% in patients with 'definite' unstable angina. These figures are comparable with earlier prognostic studies which mention in-hospital infarction rates from 4-20% and mortality rates from 1-6%[15,22,8,4,16]. In other recent studies these figures are 1.7-11.9% and 1.1-1.7% for infarction and mortality rates respectively[23,9,24]. The infarction rate of 11.9% in the study of Theroux[24] applies to patients treated with placebo, whereas this number was 1.9% for patients treated with aspirin, heparin or both. These drugs were prescribed in more than 80% of the patients with unstable angina in our registry. Mulcahy reported in hospital morbidity and mortality rates of 10.1% and 3.2%[25] in patients without routine medical treatment of ß-blockers, calcium antagonists or anticoagulants. The extensive medication in the present study may explain the lower numbers infarctions and death. In hospital 78% of all patients received oral or intravenous nitrates, 58% received ß-blockers, 33% calcium-antagonists and 78% of the patients was initially treated with either aspirin or heparin. It should be noted that in the present study many infarctions and deaths were related to interventions, and such cases were

usually not included in the above mentioned studies. Furthermore all deaths occurred in patients older than 70 years, a group that is excluded in many other studies.

Within the group of 'definite' unstable angina coronary angiography was performed in only 137 out of 282 (49%) patients and in 100 patients a subsequent revascularisation procedure was scheduled (figure 2.2). Although many patients had recurrent pain episodes in hospital they could often be treated satisfactorily with medication, at a low risk for infarction or death. Angiography was performed predominantly in patients with multiple new pain episodes and ECG changes in hospital and in patients with post infarction angina. These patients have relatively high risks for death or myocardial infarction[8,16,5,26]. Other characteristics at admission associated with a high risk of infarction or death were a gradual acceleration of pain before admission and abnormal repolarisation on the admission ECG without pain. Within the group of patients with a definite diagnosis of unstable angina only an abnormal admission ECG indicated higher risk. Deterioration of angina and ST-T abnormalities were also found to be associated with a more complicated clinical course in the studies of Krauss and Roberts[22,21].

Some infarctions occurred during the waiting period for angiography or intervention. However, it remains doubtful whether all of these infarctions could have been prevented by earlier intervention. Four infarctions during the initial observation period occurred between one and four days after admission, while on average three days were needed before a decision for an intervention was made and another five days until the procedure was performed. On the other hand two infarctions while waiting at home for angiography and for bypass surgery. These complications might have been prevented by an earlier intervention.

Differential diagnosis at admission.

The differentiation between unstable angina or infarction and other causes of chest pain remains difficult[27-29]. Based on symptoms and signs available at admission that do not suggest acute infarction one has to accept a considerable false positive diagnostic rate. About ten percent will turn out to have acute infarction after all on the basis of cardiac enzyme levels. An ever higher percentage does not suffer ischemic disease at all. Predictive rules that have been developed based on admission criteria still leave 30% of all admissions without a final diagnosis of ischemia[29].

Although in the present study patients with chest pain of other causes differed from patients with myocardial ischemia with respect to the previous history of ischemic disease, medication, presentation at admission and electrocardiographic signs of ischemia, the admission characteristics were of little value to differentiate patients with and without ischemic heart disease. In many patients careful clinical observation is required to rule out ischemic disease or to assess the severity of angina for further treatment. Nevertheless the amount of medication that was started

in hospital was less in patients with other causes of chest pain than in those with 'definite' unstable angina. This indicates that the attending physicians recognized the symptoms as less severe in the former group.

Difference between both hospitals.

The patient populations in both hospitals differed with respect to cardiac history, risk factors and medication before admission. The proportion of patients older than 70 years was twice as high in the SFG, while patients in the TXC had more often a history of known coronary artery disease. However there was no difference in the final diagnoses and the clinical course in hospital. The most prominent difference between the two hospitals was the management strategy. In the TXC nearly twice as many patients underwent angiography. Decisions were made earlier and the procedures were performed earlier than in the SFG. Whether this is only due to the availability of facilities for angiography, angioplasty or bypass surgery, or also to specific patient characteristics and personal decision making processes remains uncertain. As a consequence of the longer waiting period for angiography and further interventions in the SFG patients suffered more new pain episodes and more intravenous medication was needed. Nevertheless no difference was observed with respect to infarction rate or mortality.

Conclusion.

Unstable angina is a relatively benign syndrome under the current management strategy. Many patients can be stabilized on medication, in particular with iv-heparin and long-term treatment with aspirin, which have become 'standard' treatment during the past years in addition to ß-blockers and nitrates. In clinical practice further intensive treatment is requested in a quarter of hospitalized patients with unstable angina. Although these procedures are not free of risk the morbidity and mortality in hospital is low. Further studies will attempt to reduce the rate of these complications further by, for example, more intense antiplatelet therapy[30]. Such therapy may also prevent complications of PTCA as were observed in a few patients in this study. Currently, angiography and revascularisation can be reserved for selected patients, particularly patients with post infarction angina, elderly patients and patients with recurrent chest pain and concomitant ECG changes.

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CHAPTER 3

SIX MONTHS FOLLOW-UP AFTER HOSPITALISATION FOR UNSTABLE ANGINA

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ABSTRACT

A six months follow-up study was performed in 417 patients hospitalised for suspected unstable angina in the Thoraxcenter (TXC) and the Sint Franciscus Gasthuis (SFG). Six patients died in hospital and 411 patients were discharged alive with a final diagnosis of unstable angina in 277 patients, myocardial infarction in 25 patients and non-cardiac or non-specific chest pain in 109 patients. Coronary angiography was initiated in 60% of the patients with a final diagnosis of unstable angina. Forty-eight percent of these procedures were performed within 28 days after admission and 9% after 28 days. Angioplasty and bypass surgery were performed in 22% each. Six months mortality rate for patients with a final diagnosis of unstable angina was 4.3%, 2.1% within 28 days and 2.2% after 28 days. Non-fatal infarction occurred in 9.6% of these patients, 7.4% within and 2.1% after 28 days. Age over 70 years, a history of myocardial infarction, and ECG changes during pain were identified as independent predictors of death or myocardial infarction. Male gender, hypertension and the absence of ß-blocker use served as additional predictors for mortality alone. For patients with chest pain of other causes the six month mortality rate was 5% and non-fatal infarction occurred in 2% of these patients. These results indicate a favourable prognosis of unstable angina, with a risk for infarction predominantly during the early phase, and a high intervention rate.

INTRODUCTION

Patients hospitalised for unstable angina can usually be stabilised during the in-hospital period. Nevertheless, in spite of initial 'stabilisation' patients remain at risk for future events. Progression of unstable angina to myocardial infarction or death within the first six months has been reported in 5-12% and 3-11%, respectively, of patients admitted for unstable angina, depending on the selection criteria and the time of diagnosis[1-5]. Many prognostic studies were performed in early years, when medical treatment was limited to nitrates and ß-blockers. During the last decade medical treatment with nitrates and ß-blockers has been extended with the use of calcium-antagonists[6-9], heparin[10,11] and aspirin[12,13]. Furthermore, bypass surgery and angioplasty are being used on larger scale[14-18]. More recent studies have described the prognosis with the use of the newer drugs, bypass surgery and angioplasty[5,13-15,19-21]. However, mortality and morbidity figures in these studies apply to selected patient groups who were treated according to a fixed study protocol, and few data are available regarding prognosis in unselected patients with unstable angina.

This study aimed at assessment of the risk of death and myocardial infarction in patients with unstable angina in present clinical practice. All patients admitted for chest pain suspected for unstable angina, without signs of acute infarction or of other diseases at the time of admission, were followed for six months after admission. Patients were treated according to local practice without the restrictions of a study protocol. The in-hospital clinical course and management strategies were described in the previous chapter. In this chapter the prognosis up to six months after admission is presented of patients who were discharged with a diagnosis of unstable angina, and of those patients with a discharge diagnosis of myocardial infarction or chest pain of other causes. The analysis included mortality, morbidity as well as the frequency of revascularisation procedures after hospital discharge.

PATIENTS AND METHODS

Patients

During a seven months study period in 1988 and 1989, 417 consecutive patients admitted for suspected unstable angina to the Thoraxcenter (TXC) of the University Hospital Dijkzigt or to the Sint Franciscus Gasthuis (SGF) in Rotterdam were included in the registry.

Patients entered the study as soon as the attending physician decided to admit them for observation of 'unstable angina'. This initial diagnosis *suspected unstable angina* was based on a history of chest pain at rest or at minimal exertion, probably of ischemic

origin without signs of acute infarction or of other causes of chest pain. ECG changes were not required for inclusion. Patients admitted for suspected myocardial infarction were also included as unstable angina when subsequent enzyme levels remained below twice the normal value. Patients who were referred to the TXC from other hospitals with a definite diagnosis of unstable angina in order to undergo invasive treatment were excluded.

Since patients were included immediately upon admission the final diagnosis as registered 24-48 hours after admission often differed from the initial diagnosis. A final diagnosis of *myocardial infarction* (AMI) was determined by analysis of enzyme changes in 38 patients. *Definite unstable angina* (UAP), based on evaluation of symptoms and on the documentation of objective ECG criteria during observation or exercise testing, was present in 270 patients. Furthermore 12 of the 38 patients with initial infarction had recurrent anginal pain after 24 hours and were included as post infarction unstable angina. A final diagnosis of *atypical chest pain or pain of other causes* (other) was made in 109 patients.

Data collection and analysis

In-hospital clinical course and management strategy were registered. Details are provided in chapter two.

Follow-up data after discharge were acquired by review of the clinical records or through a simple questionnaire sent to the general practitioner. The occurrence of myocardial infarction, death or any coronary intervention was recorded until six month after admission.

Mortality, morbidity and frequency of revascularisation procedures are reported in relation to the *final* diagnosis, making a distinction between the in-hospital period and the time after discharge. Myocardial infarction followed by death was defined as non-fatal infarction when both events did not occur during the same admission. In case of fatal infarction only death is reported. For multiple events or interventions only the first infarction or procedure is reported in the tables. The period after discharge was divided in 'early' period, i.e. within 28 days after admission, and 'late', i.e. between 28 days and 6 months. Combined end points are presented in terms of 'survival without myocardial infarction' and 'survival without infarction or revascularisation'.

Clinical variables known at admission and during the first 24-48 hours (until the final diagnosis was made) were examined for a relationship with complications during six months. Univariate analysis of categorical data was performed using a χ-square test and differences in continuous variables were evaluated with Student's t-test. The probability of survival and survival without infarction was estimated using the Kaplan Meier method. A stepwise proportional hazard model was used to select predictors of survival. Variables were entered into the model or removed at a significance level of

0.10. The following variables were considered: age at admission, gender, a history of myocardial infarction, pattern of presentation of angina (gradual acceleration of angina or sudden exacerbation), hypertension (blood pressure >165/90 or current treatment for hypertension), medication at admission, pathologic QRS-complex on the baseline electrocardiogram, recurrent pain in hospital, and ECG-changes during pain.

RESULTS

After hospitalisation for suspected unstable angina 411 patients were discharged alive, 277 with final diagnosis of unstable angina (UAP), including 10 patients with post infarction angina after initial infarction at admission, 25 patients with myocardial infarction (AMI), and 109 patients with non-specific chest pain or chest pain from other causes. Follow-up data after discharge were available for 276 patients with definite unstable angina, for 25 patients with myocardial infarction and 106 patients with chest pain of other causes. Four patients were lost to follow-up.

Patients with definite unstable angina

Mortality and morbidity

Mortality and non-fatal infarctions during hospitalisation and follow-up after discharge are summarised in table 3.1, separated for the in-hospital period, 'early' (28 days) and 'late' (28 days to 6 months) after discharge. One in-hospital event occurred after 31 days. Early death occurred in 6 patients (2.1%) and late death in 6 patients (2.2%). Total six months mortality was 4.3%.

Myocardial infarction occurred predominantly during the first months after admission. A total of 21 patients (7.6%) developed non-fatal myocardial infarction

Table 3.1. Number of events in hospital, at 28 days and 6 months in patients with a final diagnosis of unstable angina (n=282).

	in-hospital	28 days	6 months	total (%)
events				
mortality	5*	2	5	12 (4.3)
non-fatal infarction	14	7	6†	27 (9.6)
TOTAL patients with events¶	19	8	9	36 (12.7)

* 1 death occurred after 31 days. † 1 infarction occurred after 53 days during elective PTCA for which the decision had been made in-hospital.

¶ Three patients sustained non-fatal infarction and died later during follow-up.

Table 3.2. Determinants of mortality and/or myocardial infarction within six months in patients with a final diagnosis of unstable angina (n=282).

		N	'event' (%)	crude RR	(95% CI)	adjusted RR	(95% CI)
mortality							
age	≤70 yrs	199	(2.0)	-		-	
	>70 yrs	83	(9.6)	5.2	(1.4-21.2)	7.1	(2.0-12.2)
gender	female	101	(3.0)	-		-	
	male	181	(5.0)	1.7	(0.4-14.5)	5.1	(1.2-22.9)
hypertension	no	180	(3.0)	-		-	
	yes	102	(6.9)	2.6	(0.7-9.7)	6.2	(1.7-22.5)
history of MI	no	201	(3.0)	-		-	
	yes	216	(6.0)	2.1	(0.7-6.3)	-	
ß-blocker use	yes!	134	(1.5)	-		-	
	no	148	(6.8)	4.8	(1.0-24.2)	7.5	(1.5-38.6)
QRS-complex	normal	151	(2.7)	-		-	
	abnormal	131	(6.1)	2.4	(0.6-9.7)	-	
ΔECG during pain	no	103	(1.0)	-		-	
	yes	179	(6.2)	6.7	(0.9-54.9)	6.2	(0.8-48.3)
non-fatal infarction							
ca-antagonist use	no	304	(6.3)	-		-	
	yes	113	(11.5)	1.9	(0.9-4.3)	-	
pain in-hospital	no	145	(5.5)	-		-	
	yes	137	(13.9)	2.8	(1.1-7.2)	2.6	(1.2-6.02)
ΔECG during pain	no	103	(6.8)	-		-	
	yes	179	(11.2)	1.7	(0.7-4.7)	-	
death or infarction							
age	≤70 yrs	199	(10.0)	-		-	
	>70 yrs	83	(19.3)	2.1	(1.0-4.6)	2.0	(1.0-3.78)
history of MI	no	133	(9.8)	-		-	
	yes	149	(15.4)	1.7	(0.8-3.7)	-	
ca-antagonist use	no	191	(11.0)	-		-	
	yes	91	(16.5)	1.6	(0.7-3.5)	-	
pain in-hospital	no	145	(10.0)	-		-	
	yes	137	(16.1)	1.8	(0.8-3.9)	-	
ΔECG during pain	no	103	(7.8)	-		-	
	yes	179	(15.8)	2.2	(0.9-5.5)	2.1	(1.0-4.56)

crude rate ratios (crude RR) were estimated by univariate analysis; adjusted rate ratios were calculated with multivariate Cox analysis; 95% CI = 95% confidence interval, test-based.

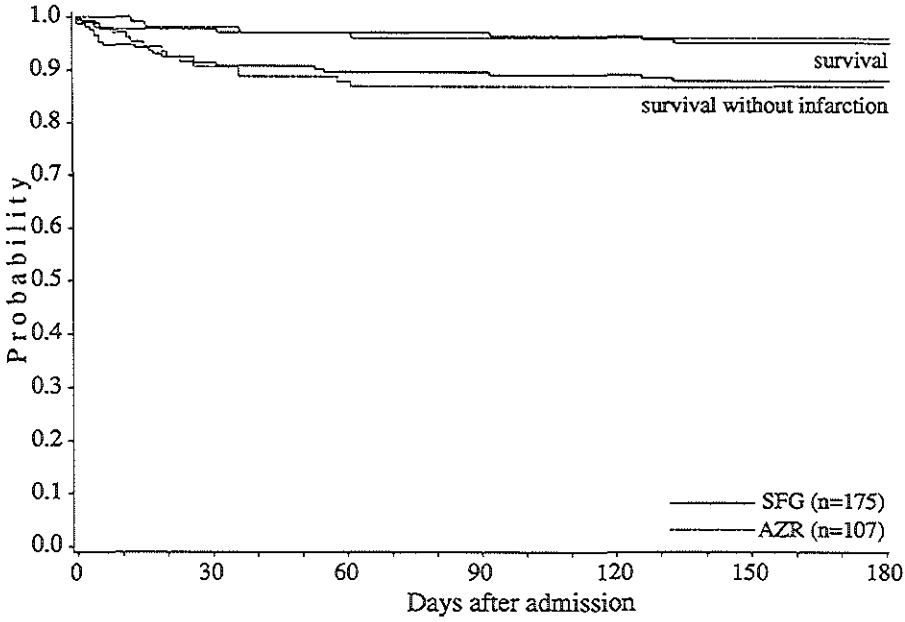

Figure 3.1. *Kaplan-Meier survival curves in patients with unstable angina for both hospitals. Six months survival was 96% and survival without infarction was 87%*

within 28 days after admission and 6 patients (2.2%) between 28 days and six months. Total infarction rate was 9.6% for patients with unstable angina. Three patients died several weeks after non-fatal infarction. Thus the infarct free survival of patients with unstable angina was 87% after six months.

Despite the different management strategies, as described in chapter 2, patients treated for unstable angina in the two participating hospitals had a similar prognosis. The Kaplan Meier curves for survival and for infarct free survival are depicted for both hospitals in figure 3.1. The six month survival was 96.3% and 95.4% for the TXC and the SFG respectively, infarct free survival at six months was 86.9% and 87.4%.

Univariate analysis revealed age over 70 years, abnormal QRS-complex on the baseline ECG, and the absence of ß-blocker use before admission as significant risk factors for death, while male gender, hypertension, a history of infarction and ECG changes during pain indicated increased risk with confidence intervals overlapping 1 (table 3.2). Patients who died were on average 11 years older than the survivors, respectively 72±6 and 61±11 years (means±SD, p=0.0001). Only one patients died younger than 65 years, 3 patients were between 65 and 70 years old, and 8 patients were older. A history of myocardial infarction as such was not associated with mortality.

However, all but two patients who died had documented vascular disease before admission, either cardiac (previous myocardial infarction), peripheral (CVA, claudication or kidney disease) or both. In particular 4 of the 5 in-hospital deaths occurred after myocardial infarction at admission or shortly before admission (post infarct angina), and one death after discharge was associated with post infarct angina.

Three in-hospital deaths were related to a PTCA procedure (see chapter 2). None of the patients who died after discharge was treated invasively during or before admission. One patient underwent PTCA after discharge because of recurrent angina and died while waiting for subsequent CABG. The relation between clinical characteristics and the occurrence of myocardial infarction was weak, and only in-hospital recurrent pain and ECG changes during pain were significantly associated with subsequent infarction (table 3.2). Mean age of patients who developed myocardial infarction and those who did not were respectively 65±10 and 61±12 years (p=0.09). More than half of the patients who developed myocardial infarction were younger than 65 years and 27% older than 70 years.

Stepwise multivariate Cox analysis identified elderly age, male gender, hypertension, absence of the use of ß-blockers, and ECG changes during pain as independent predictors for mortality, with wide confidence intervals because of the small number of deaths (table 3.2). Recurrent pain and ECG changes predicted non-fatal infarction. Survival without infarction was impaired for elderly patients, with a history of infarction, and in the presence of ECG changes during pain.

Interventions

A total of 169 patients underwent coronary angiography during the first six months after admission (table 3.3). Several procedures were performed after discharge while the decision had been made in-hospital (see chapter 2). The total number of angiography procedures within 28 days was 135 (48%) and 34 (12%) during the late phase, followed by revascularisation in 44% of the patients. Fifty of the 63 angioplasty procedures could be performed within 28 days, whereas nearly half of the bypass operations were performed after more than one month.

Thirty-two patients (12%) who were initially discharged without (a decision for) angiography underwent as yet coronary angiography because of recurrent symptoms after discharge, followed by revascularisation in 24 patients (9%).

Patients who had undergone a revascularisation procedure in hospital, or for whom this was decided during hospital stay, had a better prognosis after discharge than patients without revascularisation, since none of these patients died and fewer infarctions occurred during follow-up. However, the rate of revascularisation procedures during follow-up was similar for those with and those without in-hospital initiation of revascularisation (table 3.4).

Table 3.3. Number of interventions in hospital, at 28 days and 6 months in patients with a final diagnosis of unstable angina (n=282).

	in-hospital	28 days	6 months	total (%)
Interventions				
Coronary angiography	121	14^{10}	34^{6}	169 (60)
PTCA	45	5^{3}	13^{5}	63 (22)
CABG	33	3^{1}	25^{13}	61 (22)

The numbers in superscript indicate the number of procedures that were performed after discharge, while the decision was made in-hospital

Table 3.4. Prognosis of hospital survivors with UAP related to in-hospital revascularisation.

	revascularisation		no revascularisation	total
total	97		179	276
mortality	0		7	7
non-fatal MI	2		10	12
death or MI	2	*	14	16
revascularisation	11		24	35

* p=0.04

During the six month follow-up period 124 patients underwent a revascularisation procedure (table 3.3). Twenty-two of these patients died or developed myocardial infarction within these six months. After six months a total of 144 patients (51%) was alive without myocardial infarction and without coronary interventions.

Patients with myocardial infarction and chest pain of other causes

The number of patients with acute infarction was small. Four patients (15%) developed reinfarction and/or died within six months (table 3.5). One in hospital death occurred after reinfarction. Coronary angiography and revascularisation were performed in 19% and 15% of these patients, respectively.

A total of five patients (5%) with 'other' diagnosis at discharge died during follow-up (table 3.5) including two with a final diagnosis of heart failure and three with symptoms of non-specific cause. The group of patients with chest pain of other causes included 46 patients with known coronary heart disease such as previous myocardial

Table 3.5. Number of events and interventions related to hospital stay, at 28 days and 6 months in patients with myocardial infarction and patients with chest pain of other causes.

	in-hospital	28 days	6 months	total
AMI (n=26)				
mortality	1	1	-	2 (8)
non-fatal re-MI*	2	-	1	3 (12)
Coronary angiography	2	2[1]	1	5 (19)
PTCA	1	1	1	3 (12)
CABG	-	-	1[1]	1 (4)
Other (n=109)				
mortality†	-	1	4	5 (5)
non-fatal MI†	-	2	-	2 (2)
Coronary angiography	-	1	4	5 (5)
PTCA	-	1	-	1 (1)
CABG	-	-	2	2 (2)

AMI = acute myocardial infarction; * One patient sustained non-fatal infarction and died later during follow-up; † One late death and both infarctions occurred in patients without a history of coronary artery disease before admission; The numbers in superscript indicate the number of procedures that were performed after discharge, while the decision was made in-hospital.

infarction or revascularisation, and 63 patients without a history of coronary disease. Four patients with previous infarctions died during follow-up. Furthermore, one of 63 patients without known coronary artery disease died of unknown cause 6 months after discharge, and 2 other patients developed myocardial infarction 8 and 18 days after discharge respectively. Neither of them had a cardiac history or showed ECG changes during hospital stay, although both patients had several risk factors for coronary disease.

In spite of a final diagnosis of 'chest pain of other causes' five patients underwent angiography during follow-up, two of them after a myocardial infarction and another three because of recurrent angina. Three of these procedures were followed by coronary revascularisation.

DISCUSSION

The in-hospital course of patients admitted to hospital for suspected unstable angina was favourable, with a mortality rate of 1.4% and infarction rate of 3.8% (chapter 2). This was similar for both hospitals despite differences in patient population and management strategy. After six months survival and infarct free survival were still identical. Total mortality and infarction rate after six months were respectively 6.0%, and 7.7%. In contrast to most other studies, the present study included all patients admitted for suspected unstable angina. As a consequence patients with a discharge diagnosis of myocardial infarction, non-specific chest pain or other diseases were included in this registry. For those patients in whom the diagnosis unstable angina was maintained after observation in hospital, six month mortality and infarction rates were 4.3% and 9.6% respectively.

The low mortality rate in the present registry compares favourably with other reports[1,2,4-6,10,22-24]. This is particularly noteworthy since 25% of patients were older than 70 years, while in many studies patients older than 70 or 75 years as well as patients with recent infarction were excluded[1,2,4,5,10,12,13,19,22,23,25]. Advanced age was identified as an independent predictor of death or infarction. Other risk factors by multivariate analysis were hypertension and ECG changes[23,26,27], while other authors also mentioned persistent pain, or previous MI[1,23,26,28]. In this study a history of myocardial infarction alluded to an increased risk in the univariate analysis, but this association was not apparent after adjustment for other factors by multivariate analysis. As in other studies[2,26,29], patients with multiple episodes of recurrent pain and ECG changes in hospital were at increased risk for development of myocardial infarction. These infarctions occurred predominantly in the first 28 days, which is consistent with the observations reported in earlier studies[6,10,26,28]. The prognostic factors were calculated for patients with a final diagnosis of unstable angina. The same models were also calculated for all patients, which resulted in similar prognostic factors. In addition a separate analysis was performed to establish which factors could differentiate between death and mocardial infarction in the 36 patients died or experienced myocardial infarction. Advanced age, male gender and the absence of ß-blocker use remained in the model as independent determinants for death in these patients.

The relatively good prognosis in the current registry may be related to intensive medical therapy and high intervention rates. After hospital admission 78% of all patients received either oral or intravenous nitrates, 58% received ß-blockers, 33% calcium-antagonists and 78% of the patients was initially treated with either aspirin or heparin. For comparison, Mulcahy reported in hospital mortality rates of 3.2% within one month and 10.1% after 1 year[24]. Similarly, Theroux reported an infarction rate of 11.9% in patients treated with placebo whereas this was only 1.9% for patients treated with

aspirin, heparin, or both[10]. Patients receiving ß-blockers before admission had a lower mortality risk (table 3.2) which was in agreement with the need of ß-blockers for treatment of unstable angina[6] and secondary prevention as established in other studies[30,31].

In addition to medical therapy 35% of the patients with a final diagnosis of UAP underwent a revascularisation procedure, mostly during the hospital period. Similar rates of additional revascularisation procedures after extensive medical treatment were reported by Cairns and Theroux[13,10], while others reported lower numbers of 4% and 18% within the first 3-8 months[19,23].

Patients who underwent or were scheduled for PTCA or CABG in-hospital had a relatively better prognosis than those without revascularisation. However, this does not imply that revascularisation should be performed in all, or most, patients. It should be noted that despite the favourable course after discharge, the revascularisation procedures themselves were not free of risk, nor was this therapy fully satisfactorily in a number of patients. Three in-hospitals deaths and seven infarctions were related to interventions (chapter 2). Eleven patients (11%) underwent a new PTCA or CABG after initial revascularisation in hospital.

The group of patients not revascularised included elderly people and patients who were not suitable for PTCA or CABG because of anatomical reasons, either known before admission or found during in-hospital angiography, or because of concomitant diseases (44%). On the other hand this group also comprised patients whose symptoms were not severe enough to warrant revascularisation therapy (56%). In fact this group represents the patients at high risk for complications in combination with the patients with the mildest symptoms. Seven of the 14 patients who died or sustained myocardial infarction belonged to the high risk group in whom revascularisation was judged to be not suitable.

The current management of unstable angina results in a favourable prognosis. Six months after admission for unstable angina 87 percent of the patients survived without myocardial infarction, while 50 percent had an uncomplicated course with medical therapy alone. Patients discharged with a diagnosis of chest pain of other causes had a good prognosis, although still 5 percent had died and two percent had developed myocardial infarction after six months. This was partly due to the presence of earlier cardiac disease, but myocardial infarction occurred in patients without any history of coronary disease.

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CHAPTER 4

DECISIONS FOR CORONARY ANGIOGRAPHY AND INTERVENTIONS IN PATIENTS WITH UNSTABLE ANGINA. A COMPARISON BETWEEN TWO HOSPITALS.

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ABSTRACT

Medical services are being used in different rates between countries and regions. The use of coronary angiography in patients with unstable angina differs with a factor 2 to 4. We examined the management strategies in two hospitals that differed with respect to angiography facilities and served a different patient population. Patients in the hospital with angiography facilities where younger and had a more severe history of coronary artery disease. Data of a prospective registry of 314 patients admitted to the two hospitals were analyzed in order to explain an observed difference in angiography rate between both hospitals. Angiography was performed more often in the hospital with angiography facilities (crude odds ratio: 2.3 with 95% confidence interval of 1.4-3.7). Multivariate analysis identified the following clinical variables as independent predictors for angiography: age under 70 years, hypercholesterolemia, progression of angina, multiple pain episodes, ß-blocker or calcium-antagonist use before admission, ST-T deviations on the baseline ECG and ECG changes during pain present at admission. When corrected for the patient characteristics the odds ratio for hospital was lowered to 1.8 but still significant. Examination of interaction terms of clinical characteristics and hospitals revealed no indication of different interpretation of these variables between physicians in each hospital.

Thus, the difference in angiography rate for unstable angina could be explained in part by a difference of patient population and of hospital resources, but not by a difference of the physicians' assessment of patient characteristics.

INTRODUCTION

Delivery of heath care services varies considerably among countries and regions[1,2]. For example, rates for coronary angiography differed two to fourfold between areas in recent studies from the USA and The Netherlands[3,4]. Variation between practices can be explained by a difference in patient populations[5,3], by the lack of consensus on indications for particular services because of insufficient knowledge about treatment outcomes[6,7], and by the (limited) availability of resources[4,8]. However, the relative contribution of these factors is often unclear.

Considerable differences were observed in treatment of patients with unstable angina between two hospitals in the same city (chapter 2). Treatment of unstable angina is directed to the relief of symptoms and to prevention of recurrent ischemic episodes or progression to infarction or death. Initially, hospitalization and medical treatment is recommended for these patients[9]. In 80-90% of patients, the unstable situation can be stabilized by combination therapy with various drugs[10-12]. In case of failure of medical therapy physicians agree about the need for (urgent) angiography followed by angioplasty or bypass surgery, if feasible[13,14]. Also coronary angiography is often recommended for patients who stabilize on medical therapy, either to confirm the diagnosis or to assess whether the patient may benefit from angioplasty or bypass surgery[10,12,15].

In order to examine the differences in management strategy in patients with unstable angina data were analyzed from two hospitals, one with and one without facilities for angiography and coronary interventions. Special attention was paid to the decision to initiate coronary angiography, because this is the key decision in view of subsequent angioplasty or bypass surgery. The analysis was directed to answer the questions: 1) which clinical variables do doctors respond to when they make a decision about angiography and interventions; 2) do doctors at the two hospitals respond differently to clinical variables; and 3) how much practice variation is explained by the difference in the patients' characteristics at the two hospitals, by differences in how doctors respond to those characteristics, or by other factors, such as the availability of angiography facilities.

PATIENTS AND METHODS

Study site

Two hospitals participated in a prospective registry of patients with unstable angina: the Thoraxcenter (TXC) of the University Hospital Rotterdam and the Sint Franciscus Gasthuis (SFG) in Rotterdam. The TXC is a teaching hospital with in-

house facilities for coronary angiography, angioplasty, and cardiac surgery. The SFG is a large community hospital without in-house angiography laboratory. Patients are transported for diagnostic angiography procedures, either to the TXC or to another hospital in Rotterdam. In both the TXC and the SFG usually several physicians (staff, residents) are involved in the decision making process.

Patient selection and definitions

Consecutive patients admitted for chest pain, suspected of unstable angina, without electrocardiographic signs of acute infarction and without signs of other causes of chest pain were included in the registry. The admission diagnosis *suspected unstable angina* was made by the physician on duty. The presenting symptoms were classified as pain of recent onset (within the last four weeks), pain progressive in frequency or duration, and pain at rest. Type of onset of the present episode was described as 'sudden' (without previous acceleration) or 'progressive' (gradually accelerating of pre-existing angina). ST-T changes or other ECG abnormalities were not required for inclusion. A final diagnosis was made after evaluation of in hospital symptoms, electrocardiograms, and cardiac enzyme assays. Three categories of the final diagnosis were distinguished: myocardial infarction (AMI), unstable angina (UAP), and other causes of chest pain.

Myocardial infarction was defined by serum creatine kinase levels above twice the upper limit, in addition to typical chest pain, and/or compatible ECG changes. Other causes included non-cardiac illnesses or chest pain of other cardiac- or uncertain etiology.

Patients with a definite diagnosis of unstable angina referred from other hospitals for further treatment in the TXC were not included in the registry. For the comparison of strategies between the two hospitals, patients older than 80 years were excluded, as well as patients with an infarction within the last four weeks or with angioplasty or bypass surgery within the previous six months.

Analysis of the data

Univariate analysis

Univariate analysis of the baseline characteristics, the in-hospital course and the applied mode of treatment was used to compare patients and management strategy in both hospitals. Differences were tested by Student's t-test for continuous variables and by chi-square test for discrete variables.

Multivariate analysis

In order to correct statistically for the variable case-mix, multivariate models were built to describe the relation between clinical variables and the decision to initiate coronary angiography or to discharge and continue medical treatment. The selection

of clinical variables was based on the results of the univariate analysis. Differences in policy, or physicians' assessment of clinical characteristics, between hospitals were then analyzed using interaction terms. Hospital was also used in the model as a main effect, to test the hypothesis of a different threshold for angiography in each hospital. To study the impact of clinical course during admission, such as recurrent pain episodes in hospital and the timing of these pain episodes as well as of the eventual decision, the same data were used to test this hypothesis with a proportional hazards model for competing risks.

LOGISTIC REGRESSION

A logistic regression model was built using patient characteristics available at admission. The following variables were used: age under 70 years, hypercholesterolemia (cholesterol more than 6.5 mMol/L), diabetes mellitus, smoking, gradual progression of angina (vs sudden onset or sudden increase of previously stable symptoms), multiple pain episodes during 24 hours before admission, use of ß-blockers or calcium antagonists prior to admission, QRS abnormalities -and normal ST segment- on the baseline ECG (pathologic Q-waves, signs of left ventricular hypertrophy or of intraventricular conduction disturbances), ST-T deviation -and normal QRS complex- on the baseline ECG, both QRS- and ST-T abnormalities, and the absence of ST-T changes while pain still present at admission (as opposed to the presence of ST-T changes during pain or the absence of pain or a pain ECG). All variables were coded as indicator variables, which assume the value 1 if the property at issue is present and 0 if otherwise. The hospital variable was coded 1 for the TXC and 0 for the SFG.

After such a model was built, we tested the hypothesis of different judgment strategies by testing all interaction terms of hospital and the respective clinical characteristics for significance, using the generalized likelihood ratio test statistic. If, for example, the presence of multiple pain episodes in the 24 hours interval prior to admission had been selected in the first stage, we tested whether the coefficient for this term had significantly different values in one hospital compared to the other. Interaction terms were tested in a stepwise inclusion strategy, selecting the one with the largest contribution to the likelihood first. After this stepwise procedure, we tested whether the addition of the hospital as a single term in the regression equation led to a significant improvement of the likelihood. If any of the interaction terms was included in the regression equation, we would conclude that judgment of the importance of patient characteristics differed between the two hospitals. If the hospital was included in the model as a main term, it would be interpreted as a lower threshold for ordering angiography and interventions in one of the hospitals.

PROPORTIONAL HAZARDS MODEL

The same three questions concerning the origin of the difference in angiography rates

between hospitals were also studied using proportional hazards regression. In this case the data were studied as if they were competing risks data[16]. This means that the hazard, or the inclination of the physician at any moment in time, that a decision will be taken in a particular patient in a particular hospital *h* hours after admission is modelled as a sum of two hazards, each one related to the outcome of the decision:

hazard (decision; h, patient, hospital) =

hazard (angiography; h, patient, hospital) + hazard (discharge; h, patient, hospital)

We assume that at each point in time, *h* hours after admission, a choice may be made between two decisions: either to initiate angiography in order to prepare an intervention (the first component) or to discharge the patient on medication, without ordering angiography (the second component). The "hazard" in this case can be interpreted as the cardiologists' inclination to make either decision. The higher the overall hazard at *h* hours, the more likely it is that a decision will be taken at that time. The relative balance between the hazard for angiography and the hazard for discharge denotes the more likely direction of the decision, if any. If for a patient with a specified profile the hazard for discharge is relatively high compared to that for angiography, the cardiologists in that particular hospital seem more inclined towards discharging on medication without coronary intervention.

Using proportional hazards modelling, regression equations were defined to model each of the two components of the hazard:

$$\lambda_{angio}(h,x_1..x_n,hosp) = \lambda_{0,a}(h) * \exp(\beta_{a1}x_1 + \beta_{a2}x_2 +...+ \beta_{an}x_n + \gamma_a hosp)$$

$$\lambda_{disch}(h,x_1..x_n,hosp) = \lambda_{0,d}(h) * \exp(\beta_{d1}x_1 + \beta_{d2}x_2 +...+ \beta_{dn}x_n + \gamma_d hosp),$$

where $\lambda_0(h)$ indicates the baseline hazard for each of the decisions at time *h*. The expression '$\beta_1x_1 + \beta_2x_2 +...+ \beta_nx_n + \gamma hosp$' indicates the risk function for a patient with a specified set of characteristics in one of the hospitals. The coefficients ($\beta_1..\beta_n,\gamma$), indicating the weight of the terms in the risk function, depend on the type of the decision and may be different for each hospital. A positive coefficient β_{ai} indicates that for a patient with characteristic x_i present it is more likely that the decision for angiography will be made compared to patients with x_i absent. A negative coefficient means the opposite. Similarly a positive coefficient β_{dj} indicates that for a patient with characteristic x_i present it is more likely that the decision for discharge will be made compared to patients with x_i absent, and a negative coefficient means the opposite.

This proportional two-component hazards approach has two advantages: it allows us to correct statistically for unmatched in-hospital histories (recurrent pain episodes and ECG changes during pain), in addition to the differences in patient characteristics at admission. Furthermore, it allows us to study the relation between the inclination to order angiography and the availability of relevant facilities over time, after admission.

Recurrent pain was introduced as a time-dependent variable (see appendix). This means that once pain recurs, one, or both components of the hazard rate are multiplied by the relative risk factor. Since this effect on the hazard probably does not remain constant over time, it is hypothesised that after some time the hazard will return to its initial value. Several models were compared to explore the time elapsed until this 'normalisation' has taken place. Using the likelihood as a criterion, the approach was selected which best fitted the data.

The same three-stage strategy discussed for logistic regression was used. In the first stage a model was built to correct statistically for the difference in case-mix. This resulted in two sets of variables with corresponding coefficients: one set of variables for the hazard for angiography, another for the hazard for discharge. If a variable contributes to the inclination to make a decision, its contribution to the hazard for angiography is not necessarily related to its contribution to the hazard for discharge and vice versa. It may very well be that a patient characteristic increases the inclination to order angiography, without affecting the inclination to discharge without angiography. In a second stage, all interactions of the selected variables with the hospital variable were tested in a stepwise strategy. In the third stage, the threshold hypothesis was tested by adding the hospital term to the model.

Comparison of the proportional hazard models with the actual angiography rate

After derivation of the models the risk functions were calculated for each individual patient, resulting in two scores, one for angiography and one for discharge. Both set of scores were ranked from the lowest to the highest score. For each score, patients were assigned to four groups, according to the quartiles, leading to a total of 16 possible groups. For each group the percentage of angiography procedures actually performed was calculated.

RESULTS

During the study period a total of 417 patients were admitted for suspected unstable angina in the two hospitals. Seventy six patients were excluded from this analysis, 23 patients because of advanced age, 33 with post infarction angina, and 20 patients because of recent revascularization procedures. Thus 341 patients were available for the present analysis, 118 patients in the Thoraxcenter (TXC) and 223 patients in the Sint Franciscus Gasthuis (SFG).

Baseline characteristics

Patient characteristics at admission are listed for each hospital in table 4.1. Patients in the TXC were on average 2.3 years younger than in the SFG, had a more severe

Table 4.1 Baseline characteristics

	Total n=431	TXC n=118	SFG n=223	
	n (%)	n (%)	n (%)	
age ≥ 70 years	93 (27)	20 (17)	73 (33)	†
male	126 (66)	77 (66)	149 (67)	
previous history of				
unstable angina	76 (22)	40 (34)	36 (16)	†
myocardial infarction	140 (41)	57 (49)	83 (37)	*
angiography	96 (28)	53 (45)	43 (19)	†
angioplasty	31 (9)	23 (20)	8 (4)	†
bypass surgery	53 (16)	29 (25)	24 (11)	†
hypertension[1]	123 (36)	54 (46)	69 (31)	†
diabetes mellitus	40 (12)	16 (14)	24 (11)	
hypercholesterolemia[2]	51 (15)	31 (27)	20 (9)	†
smoking[3]	120 (35)	40 (34)	80 (36)	
positive family history[4]	124 (36)	51 (44)	73 (33)	*
medication before admission				
long acting nitrates	83 (24)	37 (32)	46 (21)	*
ß-blockers	128 (30)	52 (44)	76 (34)	
calcium antagonists	92 (27)	46 (39)	46 (21)	†
platelet inhibitors	55 (16)	15 (13)	40 (18)	
pain before presentation[5]				
none	108 (31)	36 (31)	72 (32)	
≤ 4 weeks, progressive	91 (26)	22 (18)	69 (31)	
> 4 weeks, stable	63 (18)	29 (25)	34 (15)	
> 4 weeks, progressive	79 (23)	31 (27)	48 (22)	*
baseline ECG				
QRS				
Q-wave	92 (27)	41 (35)	51 (23)	
IV-conduction disturbance[6]	31 (9)	14 (12)	17 (8)	
left ventricular hypertrophy	18 (5)	8 (7)	10 (4)	
none of above	200 (59)	55 (46)	145 (65)	*
STT-abnormalities	175 (51)	66 (56)	109 (49)	
ECG during pain				
ECG recording during pain present	180 (53)	52 (45)	127 (57)	
ST-T changes	108 (32)	33 (28)	75 (34)	

Table 4.2 In-hospital course

	Total n=341	TXC n=118	SFG n=223	
	n (%)	n (%)	n (%)	
Clinical course				
recurrent pain	154 (45)	52 (44)	102 (46)	
multiple pain episodes	85 (25)	27 (23)	58 (26)	
ECG changes during pain	104 (30)	32 (27)	72 (32)	
Interventions				
medication				
oral nitrates	65 (19)	49 (42)	16 (7)	†
intravenous nitrates	198 (58)	45 (38)	153 (69)	†
ß-blockers	194 (57)	68 (58)	126 (57)	
ca-antagonists	106 (31)	47 (40)	59 (26)	*
platelet inhibitors	117 (34)	10 (8)	107 (48)	†
heparin	232 (68)	73 (62)	159 (71)	
exercise test	175 (51)	49 (42)	126 (57)	†
angiography	105 (31)	50 (43)	55 (25)	*
PTCA	37 (11)	20 (17)	17 (8)	*
CABG	39 (11)	17 (14)	22 (9)	
Final diagnosis[7]				
AMI	34 (10)	13 (11)	21 (9)	
UAP	211 (62)	78 (66)	133 (60)	
Other	96 (28)	27 (23)	69 (31)	

(tables 4.1 and 4.2)
* p<0.05 † p<0.01; TXC=Thoraxcenter; SFG=Sint Franciscus Gasthuis; [1] blood pressure > 160/90 or current treatment. [2] serum cholesterol >6.5mmol/l or current treatment with cholesterol lowering drugs. [3] current smoking or smoking until less than a year ago. [4] infarct or cardiac death at age under 60 in first or second degree relative.
[5] none=no pain before present episode; < 4 weeks=pain for less than four weeks with progression; > 4 weeks, stable=chronic stable chest pain before admission without acceleration before present episode; > 4 weeks, progressive=chest pain present for more than four weeks with gradual acceleration. [6] IV=intraventricular.
[7] AMI = acute myocardial infarction; UAP = unstable angina pectoris; Other = non-cardiac or non-specific chest pain.

history of coronary artery disease and a longer history of symptoms. However, there was no difference in signs of acute ischemia on the electrocardiogram at admission. A history of either unstable angina, myocardial infarction or revascularisation was present in 60% of the patients in the TXC and in 43% of the patients in the SFG (p=0.003). This is compatible with the difference in risk factors for coronary disease, and explains the difference in medication before admission between the hospitals.

In-hospital course and management

Despite the differences at admission the clinical course in-hospital was similar in both hospitals with respect to recurrent pain and ECG changes. Also the distribution of final diagnoses after observation was similar in both hospitals (table 4.2). Nevertheless, the management differed between hospitals, particularly with respect to medical therapy, the use of exercise testing, and the frequency of angiography and interventions.

Nitrates were predominantly administered intravenously in the SFG, with supplementary ß-blockers and both aspirin and heparin, while oral nitrates were prescribed more often by physicians in the TXC. The number of antianginal drugs (nitrates, ß-blockers and calcium antagonists) was similar.

Table 4.3 Management strategies in each hospital in relation to angiography.

	TXC		SFG	
	angio	discharge	angio	discharge
	n (%)	n (%)	n (%)	n (%)
<2 antianginal drugs	8 (21)	31 (79)	15 (16)	78 (84)
≥2 antianginal drugs	42 (53)	37 (47)	39 (30)	91 (71)
additional medication				
none	27 (33)	56 (67)	23 (14)	137 (86)
oral medication	13 (54)	11 (46)	11 (31)	24 (69)
iv-medication	10 (91)	1 (9)	21 (75)	7 (25)
no exercise test	39 (57)	30 (43)	43 (44)	54 (56)
exercise test	11 (22)	38 (78)	12 (10)	114 (90)
pain during test	6 (43)	8 (57)	8 (40)	12 (60)
ECG changes	9 (39)	14 (61)	12 (24)	38 (76)

TXC = Thoraxcenter; SFG = Sint Franciscus Gasthuis; angio = decision for angiography and interventions; discharge = decision for discharge without coronary interventions.

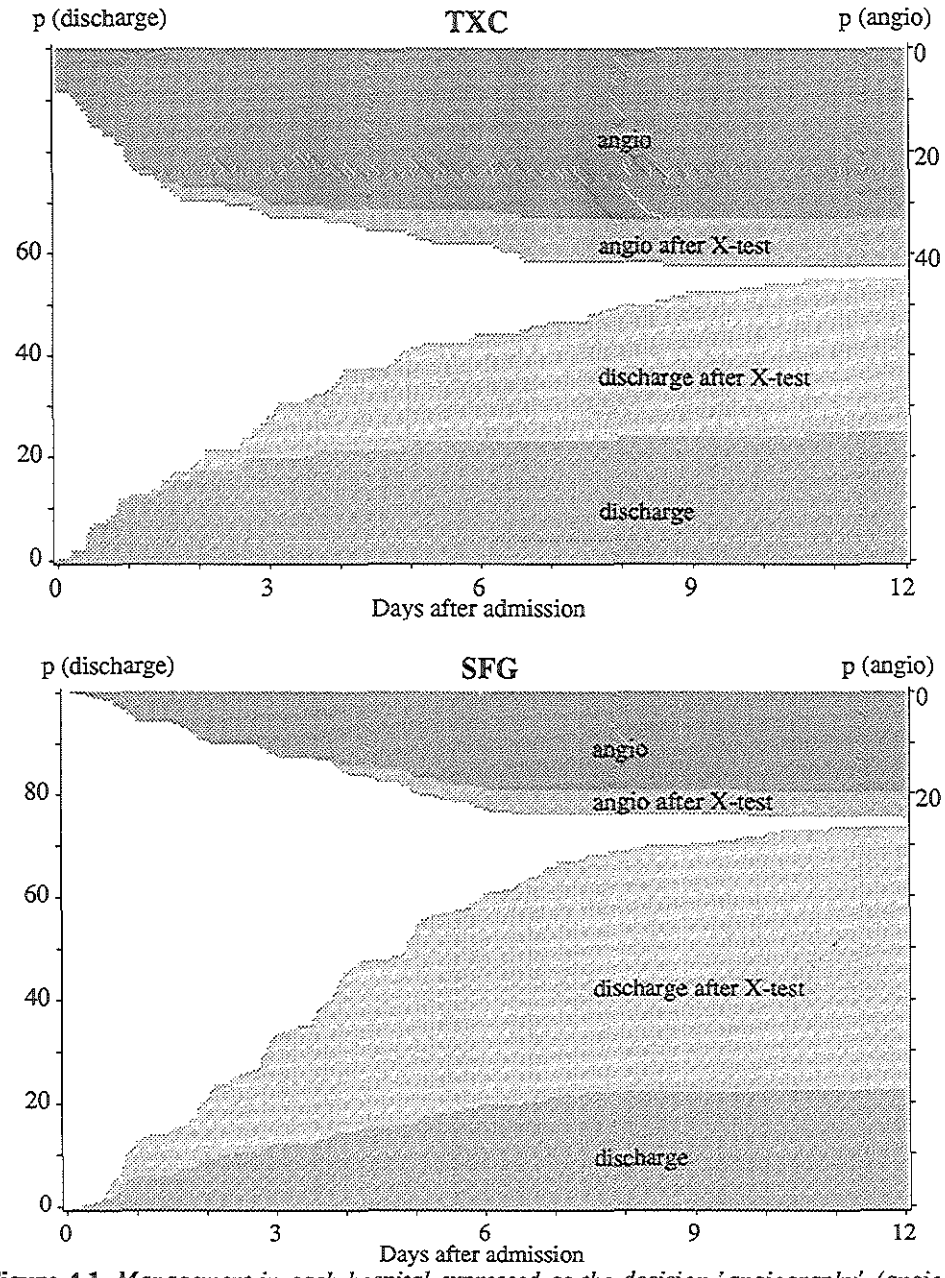

Figure 4.1. *Management in each hospital expressed as the decision 'angiography' (angio) or 'discharge without angiography' (discharge) in relation to the time since hospital admission. The white area represents the proportion of patients for whom no decision has been made yet at each moment in time. The upper and lower grey areas represent the proportion of patients for whom the decision 'angiography' or 'no angiography' has been made. Decisions made after exercise testing (X-test) are indicated in the lighter areas.*

In patients who were stabilised with medical treatment an exercise test was performed to assess the level of exertion and to evaluate the effect of medication before discharge. Exercise testing was used less often in the TXC than in the SFG, but more tests were positive (pain or ECG changes during the test) in the TXC (table 4.3). After the test more angiography procedures were ordered in the TXC than in the SFG, especially when ECG changes were present during the test.

The angiography rate was higher in the TXC, especially for patients treated with multiple anti-anginal drugs and for patients who needed additional medication after recurrence of pain (table 4.3). Furthermore the decision for angiography was made earlier in the TXC. Figure 4.1 shows the proportion of patients for whom a decision to initaite angiography, 'angiography', or the decision to discharge on medical treatment, 'discharge', had been made in the course of time. The median time until the decision for angiography was made was 1 day (range 0-8.5 days) in the TXC and 3 days (range 0-12 days) in the SFG. The time until the decision to discharge was similar in both hospitals, with respective median times of 3.0 and 3.5 days in the TXC and the SFG.

The angiography decision

Detailed analysis of the difference in angiography rates between both hospitals was performed with two multivariate analyses.

1. *Logistic regression*

The contribution of clinical variables known at admission to the decision to initiate angiography was explored in a logistic regression model. The decision to perform angiography was made more often for patients with the following characteristics: age under 70 years, hypercholesterolemia, progression of angina, multiple pain episodes before admission, the use of antianginal medication before admission, ST-T deviations on the baseline ECG and ST-T changes during pain present at admission (table 4.4). No interaction terms of clinical variables and hospital were selected. Thus, overall there was no difference in judgement of the importance of clinical variables between physicians in one or the other hospital. The hospital as a main effect variable was included into the model, indicating a difference in threshold for ordering angiography. The crude odds ratio for angiography was 2.25 (95% CI 1.4-3.7). Statistical correction for the difference in patient population changed this odds ratio to 1.8 (table 4.4).

2. *Proportional hazards model*

Results of the proportional hazards analysis of the association between patient characteristics and the physicians' inclination at any moment in time to perform angiography or to discharge without angiography, are given in table 4.5. Results are presented as hazard rate ratios, after exponential transformation of the coefficients

Table 4.4 Association between clinical characteristics and hospital with the decision for angiography.

		N	angio (%)	crude OR	(95% CI)	adjusted OR	(95% CI)
admission variables							
age	≥ 70 years	93	(20)	-		-	
	< 70 years	248	(35)	2.2	1.2-4.1	1.9	1.0-3.8
hypercholesterolemia							
	no	290	(26)	-		-	
	yes	51	(57)	3.7	1.9-7.1	2.1	1.0-4.4
progression of angina							
	no	171	(19)	-		-	
	yes	170	(43)	3.3	1.9-5.5	3.0	1.7-5.2
> 3 pain episodes during last 24 hours							
	no	298	(27)	-		-	
	yes	43	(58)	3.7	1.8-7.2	2.7	1.2-5.8
use of ß-blockers or ca-antagonists before admission							
	no	171	(19)	-		-	
	yes	170	(42)	3.1	1.8-5.1	2.8	1.6-4.9
abnormal STT on baseline ECG, normal QRS							
	no	255	(26)	-		-	
	yes	86	(45)	2.3	1.3-3.9	1.9	1.1-3.5
ECG changes during pain or no ECG recording during pain							
	no	72	(18)	-		-	
	yes	269	(34)	2.3	1.2-4.7	2.5	1.1-5.0
hospital							
	SFG	223	(25)	-		-	
	TXC	118	(43)	2.3	1.4-3.8	1.8	1.0-3.1

Seven variables, known at admission, were retained in the model with independent association with angiography. After selection of the clinical variables the hospital term was added and served a significant determinant for angiography after adjustment for clinical characteristics. Crude odds ratios (OR) were estimated by univariate analysis; adjusted OR were calculated with multivariate logistic regression; 95% CI = 95% confidence interval, test-based.

($ß_1..ß_n$). Two sets of hazard rate ratios are reported, one for the angiography decision and one for the discharge decision. A hazard rate ratio greater than one indicates an increased inclination to make the respective decision, while a hazard rate ratio less than one indicates a decrease of inclination. For example, age under 70 years is associated with an increased inclination to decide for angiography. This means that, conditional on the other characteristics in the model, a decision for angiography will be made more often for younger patients, compared to elderly patients.

Thus the decision for angiography will be made more often in patients younger than 70 years, with a history of progression of angina before admission and multiple pain episodes in spite of use of ß-blockers or calcium antagonists, with ST-T abnormalities on the baseline ECG, with one or more recurrent pain episodes in hospital, and with accompanying by ECG changes. On the other hand for patients with nausea at admission and abnormal QRS complex on the baseline ECG, both characteristics which are often associated with infarction or other disease, the decision for angiography is less likely.

Table 4.5 Association between patient characteristics and hospital with the inclination over time to decide for angiography or to decide for discharge without angiography.

	angio		discharge	
	HRR	95%-CI	HRR	95%-CI
admission variables				
age under 70 years	2.1	1.2-3.6	-	
hypercholesterolemia	-		0.6	0.4-1.0
progression of angina	2.4	1.6-3.8	-	
use of ß-blockers or ca-antagonists	2.2	1.4-3.4	0.7	0.5-0.9
>3 pain episodes during last 24 hours	1.4	0.8-2.2	-	
nausea	0.5	0.3-0.9	-	
BASELINE ECG				
abnormal STT, normal QRS	1.5	0.9-2.5	0.7	0.5-1.0
abnormal QRS, normal STT	0.7	0.3-1.4	0.6	0.4-1.0
abnormal QRS & STT	0.4	0.2-0.7	0.7	0.5-0.9
no ST-changes while pain present	-		1.5	1.1-2.0
in-hospital variables				
nr of pain within last 24 hours				
1	2.6	1.6-4.3	0.6	0.4-1.1
2	4.5	2.2-9.1	-	
3	17.2	6.4-46.5	-	
ECG-changes during pain	2.5	1.6-3.8	0.4	0.3-0.6
hospital				
TXC vs SFG (first 36 hours)	7.4	3.7-15.0	-	

HRR (hazard rate ratio) : inclination over time for the respective decision, given the presence of the characteristic divided by the same inclination given the absence of the charachteristic; estimated by exponential transformation of the coefficient of the relevant characteristic in the proportional hazard models; 95% CI = 95% confidence interval, test-based.

Cardiologists were more inclined to decide for discharge without angiography if ECG changes during pain at admission were absent. Factors influencing the inclination for discharge decisions negatively were known hypercholesterolemia, ß-blocker or calcium antagonist use, abnormal baseline ECG, and recurrent pain or ECG changes in hospital.

There was an increased inclination for angiography in the Thoraxcenter, even after correction for the patient characteristics mentioned above. The hospital site did not affect the inclination for discharge. The proportionality assumption of the proportional hazard model was checked for the hospital variable. As can be seen in figure 4.1 the rate of angiography was higher in the TXC, particularly during the first days. This was confirmed by allowing the effect of the hospital site in the model to vary over time. If no decision was reached in the first 36 hours the difference between the two hospitals disappeared.

Comparison of the proportional hazard models with the actual angiography rates.

In figure 4.2 the proportion of actually performed angiography procedures is depicted for patients within each quartile of angiography score and within each quartile of discharge score. It shows that in patients within the same quartile of angio score the decision for angiography was made more often with decreasing discharge score. Otherwise within the same quartile of discharge score, the decision to perform angiography was made less often when the discharge score increased.

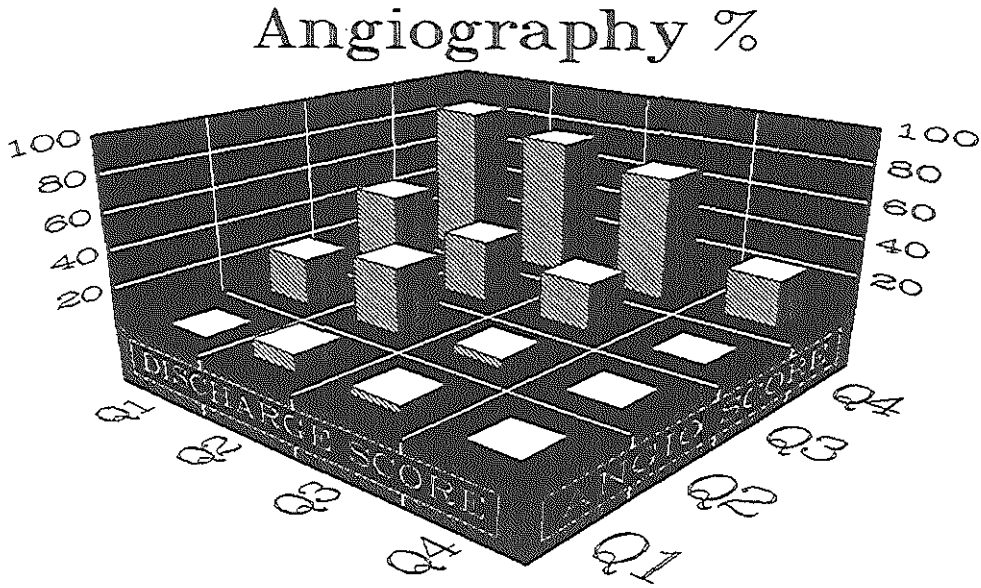

Figure 4.2. *Percentage of angiograpgy performed in patients with low scores (Q1), intermediate low (Q2), intermediate high (Q3) and high (Q4) scores for angiography and discharge, respectively.*

DISCUSSION

The management strategy applied to patients with unstable angina was studied in two hospitals in Rotterdam, that differed with respect to the patient population served, the availability of resources, and teaching responsibilities. Both statistical models revealed a basic difference in management strategy between the two hospitals. This difference was most apparent with respect to the use of diagnostic procedures, while therapeutic measures were similar. In the hospital with in-house catheterisation facilities the proportion of exercise tests was lower and of angiography procedures higher. Medical therapy was similar in both hospitals, as were the proportions of revascularisation procedures after angiography.

Several clinical characteristics could be identified as independent predictors for subsequent decisions by either model. In fact the results obtained by both models were remarkably similar, which supports the validity of the observations. People of younger age were referred to angiography earlier and more often[17]. Progression of angina and the presence of multiple pain episodes were interpreted as indications of severe angina[18,19], and increased the hazard for angiography. In the same way the level of medication and the presence of ST deviations on the baseline ECG increased inclination for the decision to initiate angiography. The presence of nausea implies infarction or other non-cardiac disease[20], and delayed the decision and lowered the hazard for angiography. QRS abnormalities on the baseline ECG delayed the decision without giving direction to either of the two decisions. This property indicates earlier infarction and complicates the decision making process. Finally when a normal ECG was present during pain at admission, the situation was judged as mild and these patients were sent home in an early phase. The presence of hypercholesterolemia increased the odds toward angiography in the logistic model, and reduced the inclination for discharge without angiography in the proportional hazards model. It was tested whether this surprising finding was a proxy of known coronary artery disease, but neither the presence of a previous infarction, nor earlier revascularisation procedures were associated with hypercholesterolemia. Possibly, symptoms are interpreted in a different manner, and more often as a sign of coronary disease in the presence of this risk factor[21].

None of the interaction terms was included into either model, suggesting that clinical variables were judged similarly by physicians in both hospitals. The hospital site was still an independent predictor for coronary angiography, even after adjustment for differences in clinical characteristics.

Wennberg has suggested that variation in practice styles derives from lack of consensus and from diversity of accepted opinions on the need and value of alternative treatments[22]. Other studies do not confirm this idea[3,4]. Contrary to belief

that population differences are not related to variation of medical services[6,8] our data suggested the opposite. The relation between a number of patient characteristics and the decision for angiography persisted after adjustment for other patient characteristics and for hospital site. Thus, although we found a difference in threshold for angiography between the two hospitals, physicians did attend to clinical variables when making decisions.

The exercise test was used more selectively in the presence of a catheterisation laboratory. An exercise test was ordered less often in the Thoraxcenter and was followed by angiography in a larger proportion of patients. This implies that the exercise test played a different role in each hospital. In the Thoraxcenter the test served as an intermediate argument to decide whether or not to proceed to angiography, whereas in the Sin Franciscus Gasthuis it was more often used as an evaluation of the status of a patient before discharge.

Comparison with other studies

Variability in use of diagnostic measures has been described with respect to different regions[2], different specialities[23] as well as different practice settings[5,11]. Conti[11] compared data of 111 patients admitted for unstable angina in a University hospital and interviews with cardiologists in a community hospital, which revealed a higher angiography rate in the community hospital. Similarly, Hlatky et al.[5] reported a higher rating of the need for coronary angiography by community cardiologists when reviewing case summaries. These reports seem to contrast the findings of the present study. However, the before mentioned studies did not mention explicitly the availability of angiography facilities in the different practices, which was the major difference between the two hospitals in the present study. In fact, it is likely that the financial rewards of angiography in private practice in USA hospitals may have contributed to a tendency toward angiography and intervention in that setting.

Limitations of this investigation

Data were collected prospectively in order to achieve a complete database with equal information for all patients. However, no detailed information was collected on the type of pain, and no attempt was made to decide in an objective manner whether the symptoms were typical for angina or not. In the present study the decisions of the physician on duty at the time of admission and those of the hospital staff during admission were accepted at face value. It was appreciated that the history was sometimes interpreted differently at different times by the various physicians who were involved with the decision making process. Nevertheless, this approach was chosen because we were interested in the factors which contributed to the medical decisions, and less in the correctness of the decisions per se.

The multivariate analyses were confined to patient characteristics only. Although the level of medication and the results of an exercise test were important factors for the subsequent decisions, they were omitted from the models because of the nature of this information. In fact these factors are intermediate decisions made by the same physicians who eventually decide whether to order angiography or not, and are likely to be influenced by the same patients characteristics as the final decision to perform or not to perform angiography. Therefore, inclusion of these variables would dilute the weights of the patient characteristics in the analysis.

The present analysis provides information on hospital-based utilisation rates. The presented rates represent the average rate of the physicians in each hospital, and do not supply information about individual clinical decisions. Neither were differences in weights of patient characteristics between physicians considered. Statistical analysis of these data did not reveal a difference in judgment of the importance of clinical characteristics. Furthermore, other factors than those in the models, may have played a role in the decision making process, and were not accounted for in the analysis.

Quality of care

A vital question is whether the difference in practice between hospitals implicates a difference in quality of care. The most important measure for quality of care is mortality and infarction rate, and no difference in this outcome was observed either with or without statistical correction for differences between the patient populations (chapter 3). Although the rates of angiography differed, the findings during angiography and the decisions for interventions after angiography were similarly distributed. Thus the more restricted use of angiography in the Sint Franciscus Gasthuis did not result in selection of a subset of patients with more advanced coronary disease. Less frequent use of angiography and coronary interventions will reduce the number of complications due to performing an invasive procedure, but may also identify fewer patients with severe coronary artery disease who may benefit form subsequent revascularisation. We therefore cannot determine whether the more aggressive or the more conservative approach represents the best quality of care for these patients.

Conclusion

The observed difference in angiography rate between two hospitals can be attributed to differences in patient populations and in availability of facilities for angiography and interventions, and not by different judgment of patient's characteristics. Angiography was performed more often in younger patients, with known hypercholesterolemia, who present with a progression of angina and multiple pain

episodes prior to admission and with ECG deviations, and are already treated with ß-blockers or calcium antagonists. After adjustment for patient characteristics the hospital site was still an important factor, associated with the decision for angiography. However, this effect was most prominent during the first 36 hours after admission. Thus the decision to perform angiography was made rapidly early after admission in the presence of angiography facilities. When the decision had not been made in the first 36 hours then physicians in the Thoraxcenter followed a similar policy as physicians in the Sint Franciscus Gasthuis.

APPENDIX

Definition of time dependent variables.

The effect of recurrent pain in hospital on either hazard was modelled as one where the occurrence of pain acts directly on the hazard rate[24]. This variable was therefore included as a time-dependent variable and the covariate function for each decision becomes

$$\lambda_{angio}(h,x_1..x_n,hosp) = \lambda_0(h) * \exp(\beta_1 x_1 + \beta_2 x_2 + ... + \beta_n x_n + \gamma_a hosp)\exp(\theta Y * g\{t-T\})$$

where $g\{t-T\}$ is some function of T, the failure time of the pain to occur, with $g\{t-T\}=0$ for $t \leq T$ and Y=1 if pain occurred and Y=0 otherwise. Thus if g is such that $g\{0\}=1$ the model assumes that the respective hazard rate is multiplied by $\exp(\theta)$ on the recurrence of pain. The functional forms of g can be considered as an immediate increased risk which remains thereafter or, alternatively, a temporary increase of the hazard which disappears after some time.

Table 4.6 Values of Log-Likelihood (LogL), the hazard rate ratio (HRR) of recurrent pain in-hospital with 95% confidence interval (CI) for each hypothesis adjusted for covariates age, clinical presentation, medication and ECG.

	angiography		discharge		
	LogL	HRR (95% CI)	LogL	HRR (95% CI)	Σ(LogL)
T= 6 hrs	-468.76	3.14 (1.9-5.2)	-1065.95	0.33 (0.1-1.0)	-1534.71
T=12 hrs	-466.84	2.26 (1.4-3.7)	-1064.60	0.35 (0.2-0.8)	-1531.44
T=24 hrs	-464.09	2.57 (1.6-4.1)	-1065.43	0.62 (0.4-1.0)	-1529.52
T=36 hrs	-463.80	2.23 (1.4-3.7)	-1066.21	0.67 (0.4-1.1)	-1530.01
T=48 hrs	-462.65	1.95 (1.2-3.3)	-1068.07	0.87 (0.6-1.3)	-1531.72
T=unlimited	-466.97	1.41 (0.8-2.5)	-1068.18	0.94 (0.7-1.3)	-1535.15

T=x hrs: various time periods of the effect of recurrent pain upon the hazard funtions for the decision to perform angiography and for discharge without angiography, respectively.

To test the hypothesis that the effect of pain on the hazard rate was a temporary increase, the duration of this effect was explored in various models varying the time period from 6, 12, 24, 36, 48 hours to continuous effect after the occurrence of pain. The results are described in the table. For both 'angiography' and 'discharge' the LogLikelihoods are reported for the models including all other variables mentioned in table 4.6 and the hazard rate ratio for the recurrence of pain in-hospital. The sum of both values of the LogLikelihood represents a measure of fit of each model. The higher the total LogLikelihood, the better the fit. This means that the best description could be made by considering the occurrence of pain within the previous 24 hours.

In a similar way it was hypothesised that the effect of the hospital site upon the inclination at any moment in time to decide for angiography was most prominent immediately after admission and declined after some time. A series of models where compared where the hospital effect was allowed to differ before and after 12, 24, 36, 48 and 60 hours. According to the likelihood criterion the hospital effect had disappeared after 36 hours.

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CHAPTER 5

PHYSICIANS' OPINIONS ABOUT DEFINITION AND MANAGEMENT OF UNSTABLE ANGINA.

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ABSTRACT

Definitions of unstable angina and management strategies vary in different reports. Twenty cardiologists were interviewed in order to explore areas of individual variability in definitions, in judgment of symptoms and signs during hospitalisation, and in treatment options for unstable angina. Definitions varied from the whole spectrum of angina between stable angina and myocardial infarction to the more restricted, severe conditions, as pain at rest accompanied by ECG changes. Judgment of the clinical course was predominantly based on the recurrence or absence of angina by some physicians, whereas others paid more attention to the presence of ECG changes. Different time periods, varying from a painfree period of 1-3 days to several weeks, were mentioned until the situation would be stabilised. Transient ECG changes in patients without pain (silent ischemia) were considered as a sign of instability and would be treated more aggressively by more than half of the physicians. The pattern of pain and the level of medication were important criteria for angiography for all physicians, as was a positive exercise test result. Exercise tests were performed more often by physicians in hospitals without angiography facilities. The presence of facilities for angiography would result in more procedures according to all physicians, while the attitude towards exercise testing seemed not to be influenced by the presence of a catheterisation laboratory. Differences in interpretation by individual physicians may be reduced in part by more detailed descriptions of patients with unstable angina.

INTRODUCTION

Unstable angina pectoris consists of a number of conditions intermediate between chronic stable angina and acute myocardial infarction, characterized by severe transient myocardial ischemia[1-3] as summarised in chapter 1. The attitude of physicians towards patients presenting with chest pain of unstable character can be influenced by the various definitions of 'unstable angina' and by the many treatment options, including medical therapy with nitrates, ß-blockers, calcium antagonists, heparin and aspirin, and coronary interventions, which are performed in part of the patients. It is therefore not surprising that treatment regimens vary between different countries and regions[4,5]. An earlier analysis of the management of unstable angina in two hospitals in Rotterdam (chapter 4) indicated that availability of angiography facilities was associated with more frequent use of coronary angiography and subsequent revascularisation procedures.

In order to explore areas of variability among individual physicians, 20 cardiologists were asked to give their opinion on the importance of various aspects of unstable angina, pertaining to diagnosis and treatment of this syndrome. The differences in response to this open interview, in combination with the structured policy analysis (chapter 6) may help to explain differences in management strategies between hospitals with and without angiography facilities.

METHODS

Twenty physicians were asked a structured series of open-ended questions concerning several aspects of unstable angina (see appendix). Physicians were selected for participation because they worked in one of the two hospitals where the prospective study, described in chapter 4, was performed or because of close relationship with these hospitals. Eleven of the cardiologists worked in a university hospital with angiography facilities and the other nine worked in four hospitals without such facilities. Most of the cardiologists had received their cardiology training in the same centre and were working in closely related practices in the city of Rotterdam. The interview was divided in five subsections, dealing with 1. the definition of unstable angina and criteria for admission of patients with suspected unstable angina, 2. initial management after admission, 3. the importance of electrocardiographic signs, 4. indications for angiography, and 5. the role of exercise tests in these patients. The answers in the interviews were categorised and described according to these subdivisions and analyzed for fields of differences between individual cardiologists as well as for differences between hospital settings.

Table 5.1 Opinions of 20 physicians with respect to definition and management of unstable angina.

Definition	
recent onset, progressive- and rest angina	14
angina at rest only	6
ECG changes required	7
ECG changes NOT necessary	2
Admission	
ECG changes	4
level of medication	9
cardiac history	13
risk factors	10 *
Stabilisation	
painfree during 1-3 days	12
painfree during 4-5 days	4
painfree during more than 5 days	2
Silent ischemia	
regarded unstable	13
reason for angiography	8
Multiple pain episodes; all with concomitant ECG changes or only once	
no difference for management	11
difference: more aggressive therapy	9
Indication for elective angiography	
pattern of pain, reduced exercise tolerance	20
level of medication	15
ECG changes	12
history of coronary disease	5
Purpose of elective angiography	
coronary interventions	20
diagnostic purpose and risk estimation	6
Indication for exercise test	
diagnostic purpose	8
treatment evaluation, risk estimation	16
CLINICAL COURSE	
pain without ECG changes	19
pain + ECG changes	9 *
no pain + ECG changes	11 *

RESULTS

Definition of unstable angina and admission criteria

The pattern of symptoms was mentioned as a major criterium for the definition of unstable angina and for hospital admission by all physicians. Most physicians referred to a wide definition, including recent onset angina, progressive angina and angina at rest, although six physicians restricted their definition to pain at rest only. The presence of ECG changes in relation to pain at rest was required by seven doctors, while two others explicitly stated that ECG changes were *not* necessary for the definition (table 5.1).

Progression of angina and pain at rest would be a reason for admission according to all physicians, while patients with recent onset angina would only be admitted in case of pain at rest or in the presence of ECG changes. The presence of ECG changes was not a strong criterium for admission and the physicians who mentioned it, said to use it as additional information. They stressed that the ECG could be normal after a recent episode of myocardial ischemia. Half of the physicians referred to the level of medication as an important factor for admission. When explicitly asked, 13 physicians agreed to admit a patient earlier when a history of coronary artery disease was present and ten would be more inclined to admission in the presence of risk factors for coronary artery disease. Eight of the latter ten cardiologists worked in hospitals without angiography facilities.

Physicians were not able to give a precise estimation of the one-year risk of myocardial infarction in patients with unstable angina. Ten interviewees mentioned a percentage, which ranged from 10% to 60% (median 30%).

In-hospital management

Medical treatment was said to be started after admission according to local protocols. Periods of unstable angina were said to have stabilised after medical treatment when the patient would be free of pain for a certain time period, or if the pain pattern would become predictable. The length of this period varied from 24 hours to several weeks (table 5.1). This difference was in part related to the department where the physicians worked. The shortest periods were mentioned by physicians working predominantly at a coronary care unit.

(table 5.1) * difference in opinion between physicians in hospitals with and without angiography facilities. Risk factors lowered the admission threshold in respectively 2 out of 11 and 8 out of 9 physicians in hospitals with and without angiography facilities. Exercise testing was performed after occurrence of pain with ECG changes during clinical observation by respectively 3 and 6 physicians and after observation of ECG changes without pain by respectively 3 and 9 physicians in hospitals with and without angiography facilities.

The interviewed cardiologists disagreed about the importance of silent ischemia. ECG changes without chest pain were considered as unstable by 13 physicians, and eight of them would perform angiography, depending on the location of the ECG changes for four doctors. The other seven physicians relied predominantly on the presence or absence of symptoms. They would continue medical treatment and start a mobilization scheme in patients without pain, despite ECG changes.

The occurrence of multiple pain episodes was judged to be more severe when concomitant ECG changes were present during all episodes than when ECG changes were observed only once. Eleven physicians said to be more aggressive in the first situation and to decide earlier for angiography. For the remaining nine, the pain was of major importance for management decisions, while ECG changes served as mere confirmation of the diagnosis.

Angiography

The pattern of pain and level of medication were mentioned as the most important criteria for elective angiography. ECG changes were required by twelve physicians.

The intention of angiography should be directed to subsequent interventions, according to all interviewees. Six physicians said to use angiography also for diagnostic purposes without need for intervention, and for risk estimation in patients with post infarction angina or in young patients.

All physicians in hospitals without angiography facilities said they would perform angiography more often if they would have access to a catheterisation laboratory in their own hospital, and nine of eleven physicians in the hospital with angiography facilities thought they would perform fewer angiography procedures if they worked in a hospital without catheterisation laboratory.

The role of the exercise test

An exercise test is predominantly used after stabilisation of symptoms, for evaluation of medical therapy, for risk assessment at the time of discharge, and to a lesser extent for diagnostic purposes. Exercise testing was indicated less often according to physicians working in a hospital with angiography facilities, when ECG changes had been observed during pain in hospital. Physicians in hospitals without angiography facilities used the test frequently, also when pain and ECG changes had been recorded during observation.

Consequences of the exercise test would depend on its results, independent of the previous clinical course. A positive test result would be followed by angiography for all but two physicians. All but one cardiologists, who said to perform an exercise test, would discharge the patient on medical treatment after a negative test result.

In hospitals without angiography facilities, all physicians but one said that they would not do fewer exercise tests if they had their own catheterisation laboratory. On the other hand, in the hospital with angiography facilities six physicians thought they would do more exercise tests if they worked in a hospital without catheterisation laboratory.

DISCUSSION

The interviewed physicians expressed different opinions about diagnosis and management of unstable angina. It is surprising to find such differences between physicians working so closely together.

Definition

Many physicians referred to the traditional classification as described by Conti[6] (recent onset angina, progressive angina and angina at rest). Others mentioned definitions as used in clinical trials[7] (angina at rest with ECG changes during pain) or more recent classifications as proposed by Braunwald[8]. Braunwald described three important aspects for classification of unstable angina, including the *severity* of clinical manifestation (progressive angina of effort, angina at rest occurring within 2 months but more than 48 hours before presentation, or angina at rest occurring within the previous 48 hours), the clinical *circumstances* in which unstable angina occurs (secondary angina, due to external conditions disturbing the oxygen balance, primary angina, and post infarction angina) and the absence or presence of transient *electrocardiographic changes* during pain. In addition the intensity of treatment at the onset of angina is regarded as helpful information to classify the patients (no antianginal medication, oral antianginal medication or maximally tolerated doses of triple medication, including intravenous nitrates). Most physicians in the present survey included the whole spectrum of clinical manifestations in their definition, whereas one third of the cardiologists emphasised the more severe conditions including pain occurring at rest, accompanied by ECG changes. The time interval after the most recent pain episode became important in the judgment of the clinical course.

Objective evidence of ischemia

The presence of ECG changes was not included in the definition or required for admission by the majority of physicians. Cardiologists reacted differently to frequency of ECG changes during multiple pain episodes. Nine physicians said to rely on the ECG signs whereas others emphasized the importance of pain, and

regarded the presence of ECG changes as additional information. Similarly, ECG changes without pain (silent ischemia) were regarded as a sign of continuing instability by 13 physicians, who would start invasive therapy in this situation, whereas others relied specifically on pain for management decisions. The presence of silent ischemia in patients with unstable angina is indeed associated with impaired prognosis[9-11], and treatment with antianginal medication or with PTCA result in a reduction of the ischemic episodes[12-15]. However, no data are available on the effect of treatment of silent ischemia with respect to prognosis.

Thus similar patients would receive different treatment, depending of the judgment strategy of the treating physician. For proper understanding, management discussions about individual patients with unstable angina should be clarified with a description according to the absence or presence of the various clinical characteristics as mentioned by Braunwald (the severity of symptoms, the clinical circumstances, the absence or presence of ECG changes and the level of medication), and not just as 'patients with unstable angina', as physicians interpret the characteristics of the syndrome differently.

Time until stabilisation

Twelve of 20 respondents indicated that they consider a patient as stabilised after 1 to 3 days. The others mentioned periods of one week or several weeks. Braunwald suggested a stepwise indication of stabilisation, referring to subacute angina after a painfree period of 48 hours and to a stable situation after an asymptomatic period of two months[8]. In the registry described in chapter 2 it was observed that indeed most recurrent pain episodes occurred within the first 24-48 hours. Still, 30% of the patients developed new pain after a painfree interval of more than 24 hours, 20% after 48 hours, and less than 10% after a painfree interval of 5 days or more (fig. 5.1). Also, in angiographic studies a higher frequency of the presence of nonocclusive thrombi has been reported on angiograms performed early after the occurrence of pain compared to angiograms made after several days[16]. The gradual decrease of symptoms as well as pathophysiologic signs of instability does not allow us to indicate exactly when the unstable episode would be over. Clinically, the risk of recurrent pain has been reduced to less than 10% after 5 days (fig. 5.2), and pathophysiologically the presence of intracoronary thrombi had been reduced to 20% after this period[16]. The distribution of the occurrence of a new pain episode over time was similar for the first interval since admission, as well as for the occurrence of a second episode after a first pain episode, and a third after a second pain episode. This similarity in clinical course suggests similar pathophysiologic mechanisms of each pain episode. These findings indicate that a period of at least 4-5 days after the

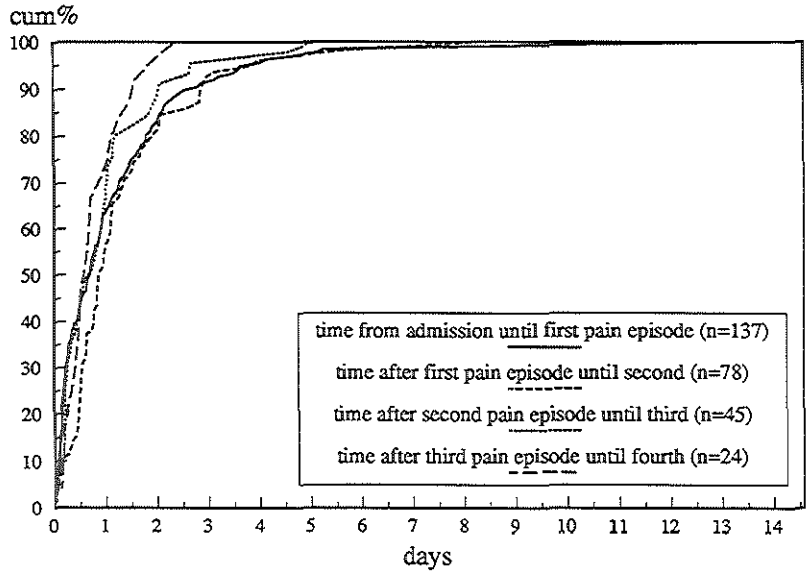

Figure 5.1. *Cumulative incidence of recurrent pain over time. The time interval since admission until the first pain in hospital is given for patients who experienced ≥ 1 recurrent pain episodes. The time interval between the first and second pain episode is given for patients who experience ≥ 2 recurrent pain episodes, the interval between the second and third episode for patients who had ≥ 3 episodes, and the interval between the third and fourth interval for patients with ≥ 4 pain episodes.*

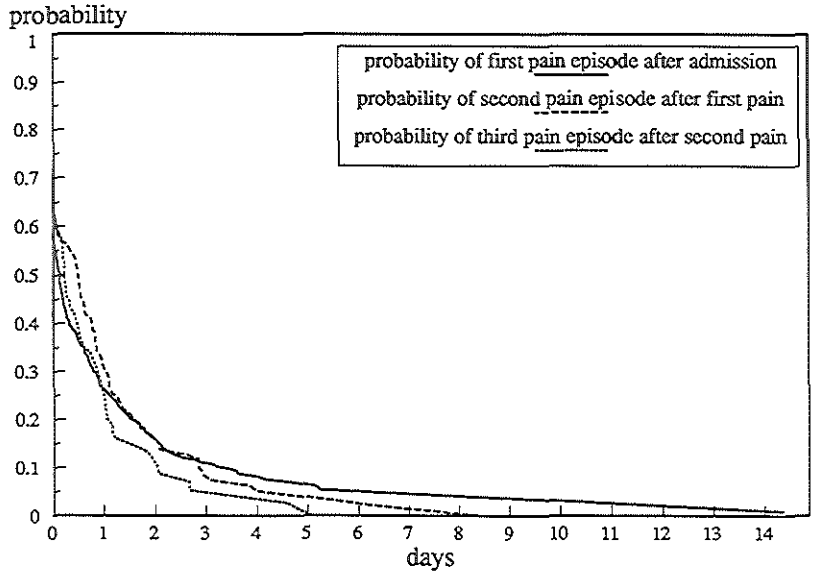

Figure 5.2. *Probability of the occurrence of pain after admission, recurrence after a first pain episode, and after a second pain episode. Probabilities are calculated using Kaplan Meier estimates, where patients who were discharged without recurrent pain were considered as censored observations.*

last pain episode is needed for stabilisation of the pathophysiologic process responsible for the unstable episode and the risk of new episodes of chest pain.

Prognosis

Although the estimated risk for myocardial infarction depends on the definition of unstable angina, and of the individual perception of the severity of a clinical situation, the risk of progression to myocardial infarction angina was highly overestimated. Six of the ten estimates exceeded 30%, with a maximum of 60%. Although it was appreciated that prognosis depends on the definition used, 1 year infarction risk varies from 9% to 17% in the literature[17,7]. Follow-up data of the patients in two hospitals, where most of the interviewed physicians worked, indicated a cumulative infarction risk of 10% after 6 months (chapter 3). No subgroup could be identified with an infarction risk between 30 and 60%. Only recurrent pain was associated with myocardial infarction, and the presence of recurrent pain resulted in a risk of 14%. The high risk estimates be could explained by misinterpretation of data describing the association between unstable angina and myocardial infarction and vice versa. It has been reported that 30-60% of the patients who present with acute myocardial infarction experience a prodrome of unstable angina before reaching the hospital[18]. These numbers are not to be reversed, and do not imply that such high frequency of patients admitted for unstable angina will develop myocardial infarction. A excessive estimation of the infarction risk may increase the use of coronary interventions in patients with unstable angina, although the interviewed physicians with high risk estimates did not express a higher likelihood for coronary interventions.

Assessment of prognosis

Both exercise testing and angiography were mentioned as methods for risk assessment, although it was not specified which factors were considered to be associated with prognosis. It should be appreciated that exercise testing in patients with unstable angina is contraindicated within 48 hours of the most recent pain episode[19], which is consistent with the high risk of recurrent pain during this period. On the other hand, exercise testing before discharge, after a painfree period of several days, adds prognostically important information to several clinical and electrocardiographical descriptors in patients with unstable angina[20]. A low rate-pressure product (product of heart rate and systolic blood pressure at peak exercise) and ECG changes during the test are independent predictors of cardiac events during follow-up. Furthermore, exercise tests may be helpful in clinical decisions on the necessity for further investigation and coronary revascularisation. Although mentioned less often by the physicians, exercise testing is especially useful for

diagnostic purposes in patients without objective evidence of ischemia in hospital[19].

Several angiographic findings are associated with increased risk of future complications, such as the number and the severity of the coronary lesions (stenoses $\geq$ 70% or left main disease)[21-23], and are used to assess the need for revascularisation. Still, it should be appreciated that revascularisation studies of patients with stable angina pectoris have shown that symptoms are reduced after bypass surgery but that prognosis is improved only in patients with severe multivessel coronary disease and with impaired left ventricular function[24]. Similarly, angioplasty in patients with stable angina, and single vessel disease, resulted in a reduction of recurrent pain, but not in improvement of prognosis[25].

Physicians' opinions and actual practice

While physicians said to proceed to angiography if the exercise test was positive, this was not observed in clinical practice. In the registry of patient management, only 40% of the patients with pain or ECG changes during the test were referred for angiography (chapter 4). Such discrepancies between physicians descriptions of their own policy and what they really do in clinical practice have been described by Kirwan et al.[26], and invite caution in interpreting physicians' opinions about the importance of different measures of disease severity. Opinions expressed in surveys and conferences may differ from actual practice. Clinical judgment analysis provides a more accurate method for modelling judgment policies of physicians, a method which will be described in chapter 6.

Implications of the availability of angiography facilities

All physicians admitted that their use of coronary angiography would change in different practice settings, which is in agreement with the finding that the availability of facilities served as a major explanatory factor for differences in angiography rates between two hospitals (chapter 4). In contrast physicians expressed different opinions with respect to their change of use of the exercise test. In the hospitals without angiography facilities physicians were inclined to perform this test routinely in all patients, whereas their colleagues in the hospital with angiography facilities used the exercise test predominantly in patients for whom the diagnosis was not confirmed by ECG changes. On the other hand, the physicians indicated that the availability of angiography facilities would have little effect upon the use of exercise tests, although the results of an exercise test were of more importance in the decision making process for coronary angiography for physicians who worked in a hospital without angiography facilities, than for physicians in a hospital with angiography facilities.

Conclusion

Physicians expressed different opinions with respect to unstable angina and its management. Part of the physicians relied mainly on symptoms when making their management decision, whereas others based their decisions on the presence of objective signs of ischemia on the ECG. When describing patients with unstable angina more detailed information has to be provided in order to reduce differences in individual interpretations. Patients may be considered as 'stable' after 5 days since the most recent pain episode. Such a waiting period is also recommended for the performance of an exercise test in order to assess the need for further treatment.
The difference in opinions could explain management variation between physicians. Some differences were related to hospital setting. In particular, physicians agreed that the availability of angiography facilities lowered the threshold to perform invasive procedures.

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APPENDIX

The purpose of this interview is to assess cardiologists' opinions on unstable angina pectoris and contains a number of open questions. Although several aspects of the management are related to each other we aim to handle them separately. The issues we would like to discuss are: definition of unstable, medication treatment, electrocardiographic changes, coronary angiography, and the use of exercise testing.
Sometimes, the questions seem easy or it looks like we already know the answers. However, an earlier study in the Thoraxcenter of the University Hospital Rotterdam and the Sint Franciscus Gasthuis revealed considerable differences in the management of unstable angina (chapter 4). Coronary angiography was performed more often in the Thoraxcenter (43%) than in the Sint Franciscus Gasthuis (25%).
The answers of the interview will be used to explore variability among individual cardiologists.

1. The syndrome 'unstable angina'

1) How would you define unstable angina?
2) Based on your definition, which percentage of patients do you think will develop myocardial infarction within one year?
3) Which criteria are important for you to decide for admission when a patient presents with chest pain?
4) Do you change your admission policy when a patient has a history of coronary artery disease?
5) Does the presence of risk factors influence your decision for admission?

2. Medical treatment

Could you describe briefly a patient you admitted for unstable angina recently.

6) Once you have decided for admission do you act according to a certain protocol? Which are the first measures you take for such patient?
7) Imagine that you visit the patient the next day.
   -The patient had no more pain episodes. What would you do in this situation?
   -What would be your next step if the patient had recurrent pain?
   (an ECG during pain has been recorded and shows ST-depression in lead V5-V6 of 0.5mm)
8) When do you consider the unstable episode *stabilised*?
9) Imagine that the patient is painfree for a period of 24 hours, but the ECG has changed compared to earlier recordings, e.g. T-wave inversion. Would you consider this situation as "stable"?
   -What would you do in that situation?

3. ECG-changes

10) What kind of ECG changes during pain are most important to prove ischemia?
-What consequence do these changes have?
11) Do you interpret ECG changes differently when they are recorded during *all* pain episodes than when several pain episodes are accompanied by ECG changes only once?

4) Coronary angiography

12) What do you consider as the most important criteria for coronary angiography?
13) Are there any contra-indications for angiography?
14) When do you consider *acute* angiography (on the same day)?
When acute intervention is not indicated, but you still decide to perform an *elective* angiography, within what period has an angiography to be done?
15) What is the main purpose that you want to achieve with angiography in patients with unstable angina who initially responded to medical therapy, and in patients who do *not* respond to medical therapy?
16) Do you think you would decide for angiography more often when you have immediate access to an in-house catheterisation laboratory than when you are working in a hospital without catheterisation facilities?

5. Exercise tolerance test

17) What is an indication for a exercise test after stabilisation for a patient admitted for unstable angina?
18) Would you perform an exercise test (after initial stabilisation)
-if ECG changes have been observed during pain in the previous clinical observation period?
-if pain has occurred without ECG changes?
-if no pain has occurred, but the ECG has changed (silent ischemia)?
19) What are the consequences of a positive test result in each of the situations mentioned in the previous question?
-what are the consequences of a negative result test in the same situations?
20) Do you think you would do more exercise tests when you have no in-house catheterisation laboratory, or fewer exercise tests when you do have in-house catheterisation facilities?

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CHAPTER 6

PHYSICIANS' USE OF CLINICAL INFORMATION FOR THE DECISION TO INITIATE ANGIOGRAPHY IN PATIENTS WITH UNSTABLE ANGINA. A POLICY ANALYSIS.

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ABSTRACT

A previous study of management in unstable angina revealed substantial differences in management between two hospitals in the same city, especially with respect to the use of coronary angiography. Physicians in the hospital with angiography facilities were more inclined to perform angiography than physicians in the hospitals without these facilities, even when differences in patient population were taken into account. In order to assess individual variability between physicians we examined management strategies of 18 cardiologists. A series of paper case summaries with different patient characteristics was used to establish how physicians in different practice settings respond to similar medical problems. Individual cardiologists showed considerable differences in likelihood of using various medical services. Differences in individual policies could be explained by different weight given to clinical information. Three subgroups of physicians with similar policies could be identified. The first group (n=4) of physicians based their decisions predominantly on the prehospital history, the second group (n=5) used mainly the in-hospital course, and the third group (n=6) considered both the prehospital history and the in-hospital course equally important. Independent of the patient description, physicians who worked in a hospital with in-house angiography facilities were more inclined to perform angiography procedures and coronary interventions. These results confirm that the same patient's medical problem would be evaluated and treated differently by physicians in different practice settings.

INTRODUCTION

Uncertainty about optimal treatment results in heterogenous management for many diseases[1]. Unstable angina is such an area of uncertainty, because different definitions are used[2-4] and because many new modes of therapy have been introduced in the past two decades. Medical treatment with nitroglycerin and ß-blockers has been extended with calcium antagonists, platelet inhibitors and anticoagulants[5-7]. Furthermore, cardiac catheterization followed by bypass surgery or angioplasty is used frequently in addition to medical treatment[8,9].

The analysis in chapter 4 it showed that the management of unstable angina varied considerably between two hospitals in the city of Rotterdam. Both hospitals served a different patient population, but apart from the variability of case-mix the availability of angiography facilities appeared to be a major explanatory factor for this difference. In this analysis of 'overall' hospital policies it was not feasible to account for individual differences between cardiologists in the decision making process. Individual variability and differences in use of clinical information have been demonstrated for many conditions[10-12]. Therefore a separate study was set up to establish how physicians in different practice settings respond to case summaries of identical patients in a management simulation: a so-called 'policy capturing' or 'judgment analysis'[13].

Cardiologists were asked to rate the need for admission, angiography and exercise testing for a series of written case vignettes and to indicate the medication they would prescribe. Linear regression models portray judgments as the sum of important factors either for or against a decision multiplied by the relative importance (weight) of each factor, and were used to study the apparent weighing physicians gave to clinical information and to explore reasons for variability among the physicians. The purpose of this study was to assess the inclination to use of the various services of individual cardiologists, and to estimate the relative importance of a number of elements in the patient's history, the presentation of angina, and in the in-hospital course on the management strategy in unstable angina, especially on the decision to order coronary angiography. Second it was estimated to what extent individual variability among cardiologists contributed to the difference in angiography rates in hospitals with and without angiography facilities.

METHODS

Participating physicians

Eighteen physicians in Rotterdam took part in this study. Physicians who were selected worked in either of the two hospitals, where the follow-up study, reported in chapters 2, 3, and 4 was performed, and two other related community hospitals in Rotterdam. Eleven physicians worked as cardiologists in the university hospital with in-house angiography facilities, the other 7 were cardiologists working in 3 different hospitals without angiography facilities.

Design of the case summaries

Each cardiologist evaluated twelve case vignettes, describing different patient profiles (see appendix for example). The patient profiles varied on seven clinical variables, which were elicited from the analysis presented in chapter 4 and the clinical experience of a senior cardiologist, and were modified after six try-out policy analyses. These clinical variables included (a) presence or absence of a history of myocardial infarction, (b) presence of risk factors for cardiovascular disease (none, hypercholesterolemia only, or smoking and a positive family history for coronary disease) (c) the amount of anti-anginal medication at presentation (none, ß-blockers only, or multiple drug therapy), (d) the mode of onset of the present complaints (i.e. sudden onset versus gradual progression of pain), (e) presence or absence of ECG changes during pain at presentation, (f) recurrence or absence of pain during the first 48 hours in hospital, and (g) presence or absence of ECG changes in hospital.

Representation of all possible combinations of these seven variables at two and three levels would require 288 cases. However, if the possibility to explain interaction terms is abandoned, a fractional factorial design of 12 cases can be used[14]. A fractional factorial design selects out cases so that each level of any given factor appears in combination with all levels of every other factor. Thus the independent main effect of each factor on the decision can be established.

The same set of twelve case vignettes was presented to all physicians. For each case they were asked to indicate what type of management was indicated for a patient with a specific profile. The decision to initiate coronary angiography was of primary interest, because this is the key decision in view of subsequent angioplasty or bypass surgery. This decision was embedded in a presentation of the cases describing the various steps made in daily practice. Three decision moments were simulated in the case presentation (figure 6.1). First, each physician was asked to indicate the propensity for admission based on the data available at presentation and the inclination to decide for angiography immediately at admission. Second, physicians were asked to indicate which medication they would start or continue

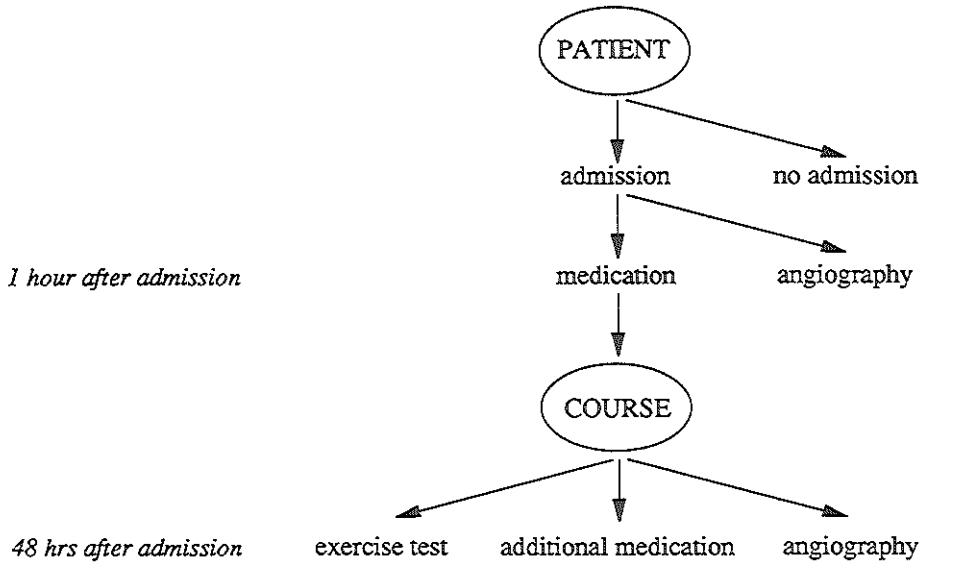

Figure 6.1. *Flow chart illustrating the structure of the case summaries. PATIENT : description of clinical characteristics at presentation. COURSE : description of the in hospital course during the first 48 hours. Three decision moments were simulated: 1. admission or not, 2. (after 1 hour) medical therapy or immediate angiography and 3. (after 48 hours observation) exercise test, additional medication or angiography.*

in-hospital. Then information was given about the in-hospital course and thereupon three policies were given for consideration: exercise testing, intensification of medical treatment, and angiography. For each decision a seven-point scale, ranging from 1:'definitely not' to 7:'definitely', was used to indicate the inclination for each alternative.

Statistical analysis

Frequency of use of medical services

Since 18 physicians participated in the study, 216 ratings were obtained for each decision. The initial analysis of these responses involved tabulating of the ratings. Results were then summarized as the number of ratings lower than or equal to four and those greater than four for each decision. Frequencies were compared between physicians in hospitals with angiography facilities and those in hospitals without angiography facilities. Differences between hospital sites were analyzed with chi-square tests.

The decision to order angiography after clinical observation was analyzed in detail. For each case the mean rating was calculated and the amount of variation among cardiologist was assessed. The results are presented for each hospital setting separately.

Judgment of clinical variables

In addition to examining the levels of utilization of various treatment options and the (dis)agreement among physicians, a second purpose of the study was to determine the symptom profiles associated with a specific decision. Thus, having found the amount of variability, it was attempted to understand why physicians differed in their choices.

The relation between clinical information and the initiation of angiography after clinical observation was explored using linear regression analysis, with the response on the 7-point scale as dependent variable and the seven clinical characteristics as independent variables. The five variables with two levels were coded as indicator variables, assuming the value 1 if the property at issue is present and 0 if otherwise. The risk factors appeared to have a linear relationship to the decision and were coded as one discrete variable on 3 levels. The medication level was coded as two separate indicator variables, because of the absence of a linear relationship. The Policy PC®[15] program was used for policy analysis, applying the EXTRACT module for the regression analysis. The weight of each clinical variable was calculated for each physician. Weights were expressed as a percentage of the total weighing.

Cluster analysis was applied to identify groups of physicians with similar policies[16,17], using the actual answers of the question whether angiography was preferred or not. This analysis was performed with the BMDP program 1M, where variables are grouped according to the minimum distance criterium[18]. A policy profile was calculated for each cluster, using the mean response of the individual cardiologists in each cluster as dependent variable.

RESULTS

Frequency of use of medical services

Wide variation in ratings was found between individual cardiologists. In table 6.1 the responses are summarized as the number of answers greater than four for each individual physician and combined for the physicians at each hospital type. The physicians agreed upon the need for admission and immediate angiography, but they showed a wide variation with respect to the management after admission. Some physicians have a basic tendency towards angiography and coronary interventions whereas others appear reluctant to initiate invasive therapy. For example, physician 2

Table 6.1 Answers given at each decision moment by 18 physicians

	At admission		After 48 hours of observation		
	admission	immediate angiography	angiography	exercise test	additional medication
physician					
1	7	2	4	8	5
2	12	3	8	4	10
3	8	2	4	5	5
4	10	2	3	8	3
5	9	2	0	6	5
6	12	0	2	10	10
7	12	0	2	6	6
8	12	0	7	4	4
9	12	0	2	1	3
10	12	1	7	4	7
11	12	1	6	4	7
12	12	0	8	3	2
13	9	0	1	5	7
14	11	3	6	3	5
15	12	2	6	3	9
16	9	5	5	2	6
17	12	1	6	0	6
18	12	2	5	5	5
Hospital; angiography facilities					
no (n=84)*	70 (83)	11 (13)	23 (27)	47 (56)	44 (52)
yes (n=132)	125 (95)	15 (11)	59 (45)	34 (26)	61 (46)
p-value (χ^2 test)	0.006	0.703	0.011	0.000	0.377

numbers indicate frequency of answers greater then 4 at each decision moment
physicians 1 to 7 represent cardiologists in hospitals without angiography facilities, and physicians 8-18 represent cardiologists in a hospital with angiography facilities.
* number of cases evaluated by physicians at respective hospital type
For hospital types absolute numbers and percentages (between brackets) are given.

would perform coronary angiography in almost all patients, while physicians 5 and 9 were very restrictive and choose for watchful waiting. The physicians' mean answer for all 12 cases varied between 4.9 and 7.0 for admission, and between 1.0 and 3.8 for immediate angiography. After the clinical course was available, the average rating for angiography varied from 1.3 to 5.0, for exercise testing from 1.0 to 5.6 and for prescription of additional medication from 2.3 to 5.6.

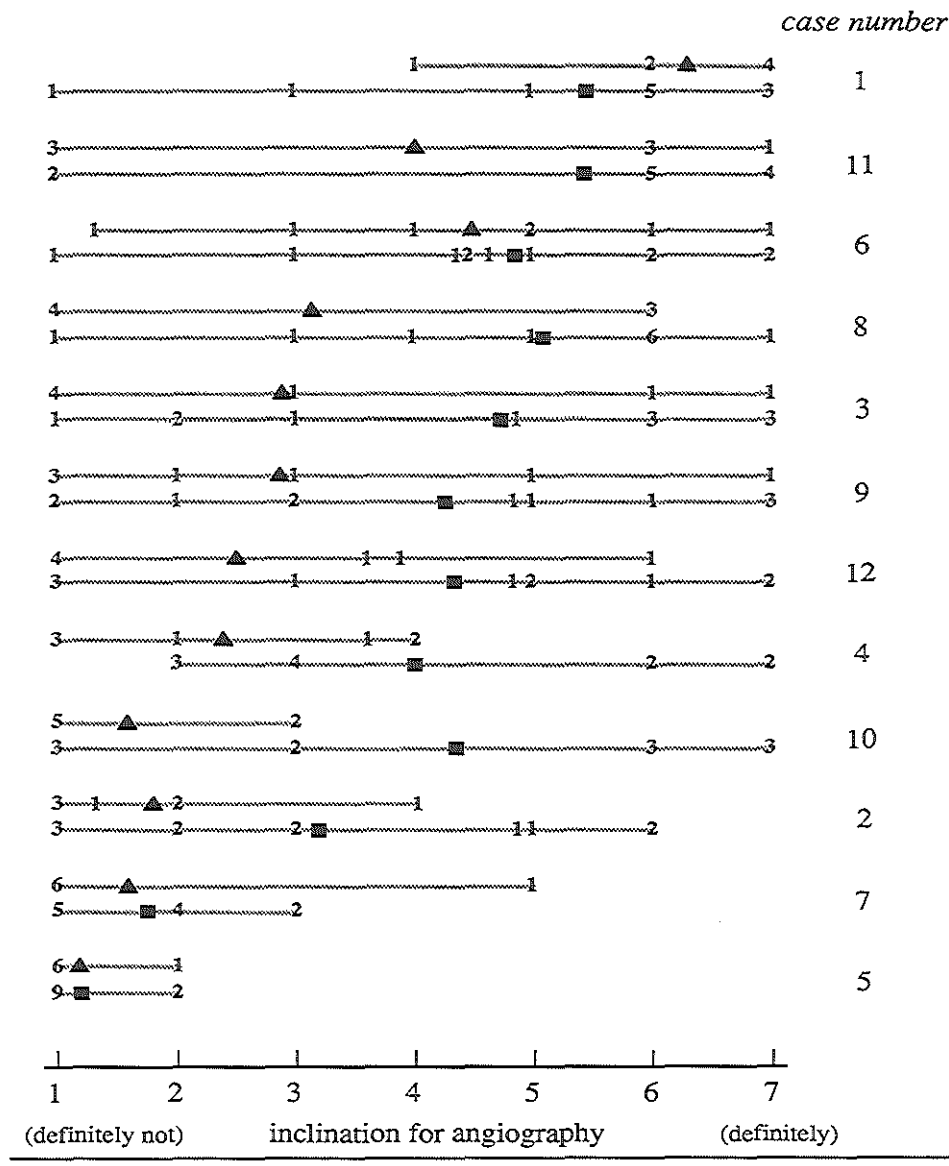
means and individual deviation for each case
case number
1
11
6
8
3
9
12
4
10
2
7
5
1
2
3
4
5
6
7
(definitely not)
inclination for angiography
(definitely)

Figure 6.2.

Combining the data for each hospital type revealed that physicians in hospitals with catheterization facilities were more inclined to admit patients and to initiate angiography after clinical observation, while in the hospitals without angiography facilities more physicians would order an exercise test. However, there was no difference between the hospital types with respect to the decision for early angiography, or to the decision to increase medical therapy during observation.

The decision to initiate angiography was analyzed in detail. Figure 6.2 shows for each case the ratings of the individual physicians and the mean answers in each hospital setting. The individual variation was wide for both groups of physicians, and there were only a few cases in which all physicians agreed. Nevertheless a systematic difference was apparent between the two hospital types when the variables in the cases were varied. On average physicians in a hospital with angiography facilities rated the need for angiography 1 point higher than physicians in a hospital without these facilities. The mean rating was 4.0 in the former group, with a range of 1.8 to 5.0 for the individual physicians, and a mean rating of 2.9 in the latter group, with a range from 1.3 to 5.0.

Judgment of clinical variables

Individual judgment analyses revealed wide variation between physicians with respect to the weights they gave to the clinical variables when making a decision for coronary angiography. On average, this decision was based for 27% on the use of ß-blockers before admission. The relative contribution was 15% for the use of multiple drug therapy, 18% for the presence of risk factors, 11% for the presence of ECG changes during observation, 9% for the recurrence of pain during observation, 8% for the presence of a coronary history, 7% for progression of angina before presentation and 5% for the absence of ECG changes at admission. Similarity between individual policies was explored with cluster analysis, using the actual ratings for each case. Three clusters resulted, including respectively 4, 5 and 6 physicians. Three physicians could not be grouped into one of the clusters, implying a highly individual policy.

Figure 6.2. *Means and individual ratings for coronary angiography per case for each hospital. For each case two lines represent the range of ratings. The lower line represents the variation of physicians in the hospital with catheterization facilities, with mean values for each case represented as black squares. The upper line represents the variation of physicians in the hospitals without catheterization facilities, with mean ratings for each case indicated by black triangles. The numbers along the line indicate the number of individual physicians giving one specific answer. The cases were ordered according to the overall likelihood for angiography, with the lowest likelihood on the bottom and the highest likelihood at the top.*

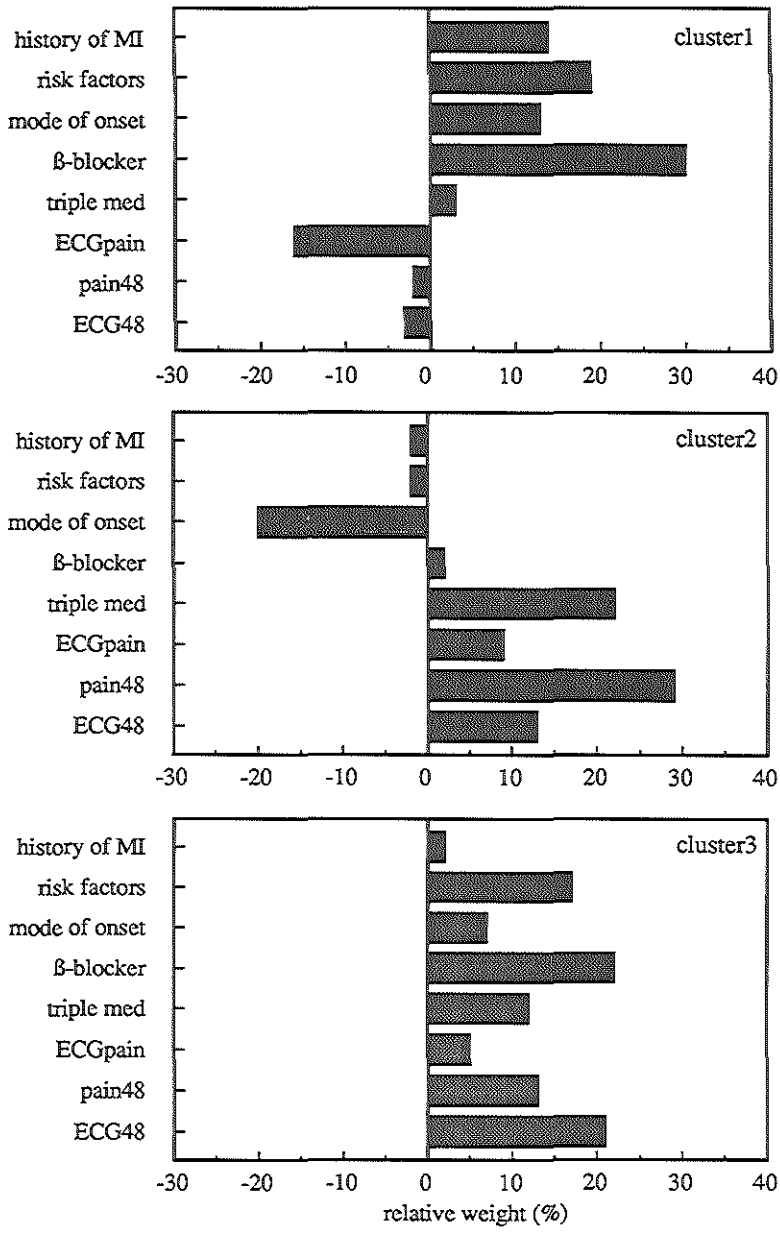

Figure 6.3. *Relative weights of clinical variables for groups of physicians with similar policies, as determined with cluster analysis. The clusters included respectively 6, 5, and 4 physicians. Three physicians could not be included in any cluster. For description of the policies, see text. MI=Myocardial infarction; ECGpain=ECG changes during pain at presentation; pain48=recurrence of pain within 48 hours; ECG48=ECG changes within first 48 hours.*

For each of the three clusters a policy analysis was performed, using the cluster mean rating for each case as dependent variable. Results are presented as relative weights in figure 6.3. Physicians included in cluster 1 based their policy predominantly upon prehospital characteristics. Cluster 2 represents physicians whose policy was predominantly based on medication level and in-hospital events. The third cluster represents physicians whose policy was based on a combination of both prehospital and in-hospital characteristics. The clusters included respectively 1, 3 and 4 physicians working in a hospital with angiography facilities, and 3, 2, and 2 physicians from hospitals without such facilities. The three physicians not included in one of the clusters worked in a hospital with angiography facilities.

DISCUSSION

In this study physician's decisions in the management of unstable angina were characterized, in order to assess interindividual variability with respect to the frequency of use of various management options. In addition it was attempted to identify factors influencing the decision to initiate coronary angiography. The first issue concerns the *likelihood* of a decision by a certain physician, while the second issue concerns the *reason* of that decision in a particular patient.

Differences in the likelihood of use of certain medical services have been reported between countries[19,20], between regions within countries[21,22], within different practice settings[23,24] and also among physicians in different specialties[25]. These differences were attributed to cultural differences, different patient populations, specialty, and organization and size of practices. In addition, Gillis et al.[26] demonstrated that physicians working in the same psychiatric institution not only use various drugs in different frequencies, but also show little agreement on prescriptive strategies. Similarly, we observed a wide variability among cardiologists working in the same city in the likelihood of performing coronary angiography in patients with unstable angina. Apparently some physicians had a basic tendency to choose for medical therapy, while others were more inclined to proceed to invasive treatment.

Several studies have suggested that the degree of variation in medical care for a particular procedure is linked directly to the degree of consensus concerning the indications for its use[27-29]. Uncertainty in diagnosing illness and choosing the appropriate treatment may stem from difficulties to classify a particular patient, lack of information on the probabilities of treatment outcome and divergence among physicians on the value they assign to different outcomes. Indeed, the physicians had expressed in an earlier interview (chapter 5) variations in the definition of unstable angina, and in the assessment of the risk of progression to myocardial infarction.

However, the present study indicated that the observed variability is also due in part to the judgment of patient characteristics and to the availability of angiography facilities. Similarly, in two other studies[21,22] variability between physicians were attributed to lack of consensus, but also to difference in severity of patients' conditions and to the number of physicians in a certain department.

In general, physicians working in a hospital with angiography facilities were more inclined to perform angiography. This was also found in a prospective registration of consecutive patients admitted for unstable angina (chapter 4) in two hospitals, where 15 of the 18 physicians who participated in the present study worked. Thus the availability of angiography facilities lowered the threshold for invasive procedures. This may be due to self selection of physicians who decide to work in a certain hospital. However, it is more likely that the threshold for invasive procedures is a property of the organizational structure itself, since individual variability of the likelihood to perform angiography exceeded the variability among practice settings, as is clearly shown in figure 6.2. The observation that physicians responded to variation of patient characteristics, and that their response is modified by practice settings supports the conclusions of other reports indicating that comparisons of the use of health services in different populations should be controlled for patient variability[22,23,30].

In the second part of the study, having found *how* physicians vary in their decisions, we explored *why* they made different management decisions, by determining which patient profiles were associated with the decision to perform coronary angiography. Although guidelines for angiography have been proposed[31], there are no well-established rules for weighing the pertinent factors, except for so-called 'refractory angina', where medical treatment fails to control the symptoms[32,33]. The relative importance of clinical variables was assessed using linear regression analysis, as described by Hammond[34]. Linear regression models portray judgment as the sum of important factors either for or against a decision multiplied by the relative importance (weight) of each factor. A judge's strategy can be inferred from decisions over a series of cases where the status of these factors is known. For example, one can calculate the weight a physician assigns to the presence or absence of ECG changes during pain by observing how his decision changes as ECG patterns vary over a sample of cases, while controlling for other factors. This method is called 'policy capturing' or 'judgment analysis'[13].

Similar to analyses of other technologies[10-12,16,26,35] the present study confirmed that physicians used different weights for clinical variables when they decide to perform coronary angiography or not. Three groups of physicians with similar policies could be identified: physicians whose decision was predominantly directed by the patient's prehospital history, physicians who based their decisions on recent

in-hospital information, and physicians who balanced both the prehospital data and the in-hospital course. All physicians based their decision in part on the use of medication before admission. However, physicians in cluster 1 were influenced predominantly by the use of ß-blockers, while physicians in cluster 2 would perform angiography only if multiple drug therapy was given.

The importance assigned to clinical variables was not related to the overall preference for angiography. For example, the physicians in clusters 2 and 3 expressed similar tendencies for coronary angiography, but based their decisions on different patient characteristics. Similarly Holzman et al[10] showed little relationship between the regression weights and the likelihood of prescription of estrogen replacement therapy for menopausal women, and Gillis et al.[26] described that physicians who relied on the same psychoactive drugs for psychiatric illnesses base their decision whether or not to give those drugs on different patient characteristics. In our study physicians from different clusters were present in both types of hospitals. Accordingly, decision policies in each hospital type were an amalgamation of the three cluster policies, while the likelihood of performing angiography was significantly different. This is in accordance with the analysis of the patient registry, where no difference in weighing of clinical variables was found (chapter 4).

Recognition of judgment strategies is of interest for several reasons. First, this allows individual physicians to gain insight in their own decision making process, which may help them to reflect on and modify their policies. Second, it provides insight in the factors which could cause disagreement, and thus may facilitate communication between clinicians when discussing indications for coronary angiography in a specific patient, for example when a patient in a hospital without angiography facilities has to be referred to a hospital with those facilities. Third, it may be of help in medical teaching, when it is perceived that part of the whole set of textbook variables may be rejected as superfluous by subsequent experience.

All variables which were included in the case vignettes were used indeed in the decision making process, although to a different extent by various physicians. Most physicians based their decision on four or five variables only. This is consistent with earlier studies showing that only a small number of clinical variables is needed to describe judgment policies adequately[11,35]. Nevertheless, the analysis did not reduce the number of clinical variables which were related to the decision to initiate angiography. This is not surprising, because the important variables were derived form earlier analysis of actual patients, but it supports the validity of the representation of real patients by the written case descriptions.

Limitations of the study

The use of 'paper' case summaries have been applied in many studies on practice variation[11,12,16,23,36]. One might question whether decisions made about case vignettes represent actual behaviour, since the case vignettes do not mimic the complicated interaction between doctor and patient. It does not allow the physician to obtain additional patient information, which he or she might request otherwise, and which might change his or her approach. On the other hand the presentation of paper cases isolates judgment from the process of gathering information and allows comparison between physicians in their judgment of similar cases. Kirwan et al.[38] indicated a remarkable similarity between judgments of disease activity in rheumatoid arthritis made on 'paper' cases with those made on actual patients. This is supported by our findings: the likelihood of angiography shifted appropriately when patient characteristics were varied; the same patient characteristics were used as those used for real patients (chapter 4); the trend towards more angiography in hospitals with angiography facilities was observed in clinical practice (chapter 4) as well as in this policy analysis. Therefore the marked variations in management in this study is unlikely to be due to the design of the paper cases, but appeared to reflect existing trends in clinical practice.

The study population was small and limited to 18 cardiologists working at various departments in a few hospitals in one city. Therefore it remains uncertain whether these observations will be applicable to other groups of cardiologists.

The number of 12 cases was small for assessment of individual weights. This small number was deliberately chosen for practical purposes. First the number of cases was restricted to make sure that the physicians were able to complete the set in a reasonable amount of time, and second of the purposes of this study was to establish the feasibility of the method. However, the present data were sufficient study the individual inclination of using the various medical services, and by using the actual responses in as selection criterium in the cluster analysis the combined weights could be established by using a larger number of responses provided by the physicians included in each cluster.

Conclusion

Physicians varied considerably in the *likelihood* to use coronary angiography and in the reason *why* it is used. Physicians in a hospital with angiography facilities were more inclined to perform coronary angiography, although similar individual variability in the likelihood to initiate coronary angiography was observed in both hospital settings. Variability in the use of coronary angiography could be explained in part by differences in weighing clinical information. Three groups of physicians with similar policies could be identified, who emphasized the prehospital history, the

recent in-hospital course or both.
These results demonstrate a wide variability in preference and in decision strategies for coronary angiography among cardiologists and support earlier observations of a different management in hospitals with or without facilities for angiography. Judgment analysis provides a means of elucidating important physician and patient related factors in medical decisions and may be helpful to improve co-ordination between clinicians and clinical investigators in different hospitals.

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APPENDIX

Two case examples. The bold sections indicate the variable parts of the descriptions.

EXAMPLE 1

The 57 years old man R.J. is referred to your department because of chest pain, radiating to the left arm. The pain was accompanied by severe perspiration, but without shortness of breath, and lasted for approximately 30 minutes.
According to R.J. these pain attacks existed for several weeks now. The attacks occurred during daily activities, such as car driving, but stopped after a period of rest. Recently, the pain attacks became more severe and occurred more frequently. Today's pain was so severe, that he called the family doctor.
The family doctor sent the patient to hospital, with the diagnosis of suspected unstable angina pectoris. The pain subsided after nitroglycerin sublingual. After arrival at the hospital, a pain ECG was made.
Mr J was admitted for unstable angina pectoris four years ago as well. He then developed myocardial infarction. At this moment he uses beta blockers.
Furthermore, the patient is in a good condition.

PHYSICAL EXAMINATION

heart rate	: 60/min
blood pressure	: 130/80 mmHg
ECG without pain	: normal
pain ECG	**: no changes compared to the previous routine ECG**

1 : WOULD YOU ADMIT THIS PATIENT?

definitely not definitely
|----------|----------|----------|----------|----------|----------|

2 : WOULD YOU IMMEDIATELY DECIDE FOR ANGIOGRAPHY?

definitely not definitely
|----------|----------|----------|----------|----------|----------|

3 : WHICH MEDICATION WOULD YOU START?
(encircle those drugs you would prescribe)

a : none
b : ß-blockers
c : calcium antagonists
d : oral nitrates
e : intravenous nitrates
f : aspirin
g : heparin

We follow the patient at your department. Mr. R.J. is treated with the therapy, you have indicated at question 3.
Within 48 hours after admission, R.J suffers another attack of dull chest pain.
The ECG shows ST depression of 1.5 mm in leads V5 and V6.
The other findings, like pulse and blood pressure remain stable.

4 : WHICH OF THE FOLLOWING WOULD BE YOUR NEXT STEP?

a : coronary angiography

definitely not definitely
|---|---|---|---|---|---|

b : exercise tolerance test

definitely not definitely
|---|---|---|---|---|---|

c : additional medication

definitely not definitely
|---|---|---|---|---|---|

(encircle the drugs you would prescribe - both existing and additional medication)

a : none
b : ß-blockers
c : calcium antagonists
d : oral nitrates
e : intravenous nitrates
f : aspirin
g : heparin

EXAMPLE 2

The 57 years old man R.J. is referred to your department because of chest pain, radiating to the left arm. The pain was accompanied by severe perspiration, but without shortness of breath, and lasted for approximately 30 minutes.
The pain occurred at rest on the day of admission. He did not have any anginal complaints during the previous period.
The family doctor sent the patient to hospital, with the diagnosis of suspected unstable angina pectoris. The pain subsided after nitroglycerin sublingual. After arrival at the hospital, a pain ECG was made.
Mr J has no cardiac history, but he is known with high cholesterol levels (most recent value 7.8 mmol/l). He uses no medication.
Furthermore, the patient is in a good condition.

PHYSICAL EXAMINATION

heart rate	: 60/min
blood pressure	: 130/80 mmHg
ECG without pain	: normal
pain ECG	**: 1.5 mm ST depression compared to the ECG without pain**

1 : WOULD YOU ADMIT THIS PATIENT?

definitely not — definitely
|----------|----------|----------|----------|----------|----------|

2 : WOULD YOU IMMEDIATELY DECIDE FOR ANGIOGRAPHY?

definitely not — definitely
|----------|----------|----------|----------|----------|----------|

3 : WHICH MEDICATION WOULD YOU START?
(encircle those drugs you would prescribe)

a : none
b : ß-blockers
c : calcium antagonists
d : oral nitrates
e : intravenous nitrates
f : aspirin
g : heparin

We follow the patient at your department. Mr. R.J. is treated with the therapy, you have indicated at question 3.
Within 48 hours after admission, R.J suffers another attack of dull chest pain.
The ECG shows no changes compared to the ECG without pain.
The other findings, like pulse and blood pressure remain stable.

4 : WHICH OF THE FOLLOWING WOULD BE YOUR NEXT STEP?

a : coronary angiography

definitely not definitely
|----------|----------|----------|----------|----------|----------|

b : exercise tolerance test

definitely not definitely
|----------|----------|----------|----------|----------|----------|

c : additional medication

definitely not definitely
|----------|----------|----------|----------|----------|----------|

(encircle the drugs you would prescribe - both existing and additional medication)

a : none
b : ß-blockers
c : calcium antagonists
d : oral nitrates
e : intravenous nitrates
f : aspirin
g : heparin

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CHAPTER 7

AN EXAMPLE OF AN INTERVENTION STUDY IN PATIENTS WITH UNSTABLE ANGINA:

Tissue plasminogen activator in refractory unstable angina. A randomized double blind placebo controlled trial in patients with refractory unstable angina and subsequent angioplasty.

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Tissue plasminogen activator in refractory unstable angina. A randomized double-blind placebo-controlled trial in patients with refractory unstable angina and subsequent angioplasty

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KEY WORDS: Unstable angina, tissue plasminogen activator, angioplasty.

To evaluate the effect of recombinant tissue plasminogen activator (alteplase) on the clinical course, angiographic changes and the outcome of subsequent coronary angioplasty, 36 patients with angina at rest, despite bedrest and medical treatment including heparin, and with concomitant ECG changes, were studied. After diagnostic angiography, patients were randomized to receive either alteplase 100 mg in 3 h (19 patients), or placebo (17 patients). The mean interval between qualifying anginal episode and initial angiography was 10 and 9 h for the alteplase and placebo group, respectively. Angiography was repeated and angioplasty was performed within 24 hours.

Between the first and the second angiogram, five patients in the alteplase and seven in the placebo group had recurrent ischaemic episodes, while four alteplase and three placebo patients showed signs of myocardial necrosis (creatine kinase (CK) rise ≥twice the upper limit for normal). Intracoronary clots were recognized in three alteplase patients and one placebo patient at the first angiogram, while two alteplase patients and one placebo patient showed total occlusion of the ischaemic-related vessel. After infusion, thrombi were present in four alteplase patients and one placebo patient, and total occlusion in three alteplase patients and one placebo patient. Quantitative coronary angiography showed no change in the percentage diameter stenosis of the ischaemia-related segment after drug infusion, (alteplase 67 ± 16 to 69 ± 16%; placebo 65 ± 11 to 63 ± 12%). Angioplasty was successful in 14 of 19 alteplase and 14 of 16 placebo patients. Three patients after alteplase and two placebo patients developed myocardial necrosis during percutaneous transluminal coronary angioplasty (PTCA), and one alteplase patient required urgent bypass surgery. Minor bleeding complications were observed in six alteplase patients before the second angiogram and in five alteplase patients and one placebo patient after PTCA. One patient after alteplase developed a fatal retroperitoneal haemorrhage.

In patients with unstable angina refractory to medical treatment, including heparin, alteplase has no beneficial effect on the severity of coronary stenosis, on the clinical course, or on the success of a subsequent angioplasty procedure. Thus thrombolytic therapy with alteplase for unstable angina cannot be recommended on the basis of this investigation.

Introduction

In patients with unstable angina pectoris, intracoronary thrombus has been documented by angiography[1–5] and angioscopy[6], while biochemical studies have suggested the presence of thrombi in the circulation[7]. In some patients intracoronary thrombi can be resolved by intracoronary administration of streptokinase[3,8,9]. Resolution of such thrombi by thrombolytic therapy may be expected to improve coronary blood flow, and to prevent or reduce subsequent ischaemic episodes.

A few studies have reported a reduction in recurrent ischaemic episodes, in the incidence of sudden death and an improvement in the ischaemic threshold during atrial pacing[10–13]. Furthermore, it might be expected that thrombolytic therapy could reduce acute thrombotic occlusion during PTCA of the ischaemia-related segment, which occurs in approximately 10% of patients who undergo PTCA for unstable angina[14,15].

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In order to assess the value of thrombolytic therapy with alteplase in patients with ongoing unstable angina despite medical therapy including heparin, a randomized trial was undertaken. Quantitative analysis of the coronary arteriogram was performed in order to verify whether the culprit lesion was improved by thrombolytic therapy. Furthermore the clinical course and outcome of the subsequent PTCA procedures were compared in patients treated with alteplase or placebo.

Patient selection and methods

Included in the study were patients between 21 and 75 years with: (a) Recurrent episodes of chest pain after hospital admission, despite bedrest and medical treatment, with at least one episode with concomitant reversible ST-T segment changes or persistent negative T waves on the electrocardiogram. (b) A diagnostic coronary arteriogram, within 24 h after the last episode of chest pain. (c) The 'culprit' coronary lesion suitable for PTCA. Total occlusion of an ischaemia-related vessel, which supposedly was of recent date, was considered acceptable for angioplasty. (d) Ability to perform a second coronary

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angiogram, followed by PTCA within 24 h after the diagnostic angiogram.

Excluded were patients with known bleeding disorders, recent major trauma, including resuscitation, or a bleeding history in the past 3 months, including cerebrovascular, gastric or genito-urinary tract bleeding. Patients with persistent hypertension and patients unable to give informed consent were also excluded, as were patients with previous angioplasty of the same coronary segment now judged to be related to the ischaemic myocardial zone, the so-called 'culprit' lesion. Informed consent was obtained after completion of the first (diagnostic) angiogram.

Reversible ST-T segment changes were classified in one of four categories: ST segment elevation or depression of at least 0·1 mV, persistent negative T-waves, or minimal ST-T segment changes not fulfilling the criteria for the other categories.

All patients were treated with the following combination of medication: (1) Heparin 1000 IU.h^{-1}, or a dose sufficient to prolong the activated partial thromboplastin time to twice the normal value, after a bolus injection of 5000 IU of heparin. (2) Beta-blockers, metoprolol 50–200 mg, in order to reduce heart rate to 60 beats.min^{-1}. (3) Calcium antagonists, nifedipine, in a dose of 40–120 mg.day^{-1}. (4) Intravenous nitroglycerin in a dose between 50 to 300 μg.min^{-1}.

The patients were randomized to receive either alteplase infusion (Actilyse^{R}) or placebo, supplied by Boehringer Ingelheim International. The study medication was started as soon as possible after the first coronary angiogram, in a double-blind manner. An injection of 10 mg i.v. was followed by an infusion of 50 mg in the first hour and 20 mg.h^{-1} for the subsequent 2 h. Thus, a total dose of 100 mg alteplase or placebo was administered in 3 h.

Coronary angiography was performed using the Judkins technique as soon as possible after the qualifying anginal attack and repeated within 24 h after the start of the study medication. The coronary artery responsible for the ischaemia was identified by means of electrocardiographic location of the reversible ST segment changes during chest pain. In patients with multiple lesions in the ischaemia-related vessel, the most severe lesion was considered the 'culprit' lesion. At least two orthogonal projections were made of the coronary artery segment with the culprit lesion, after intracoronary injection of 1 to 3 mg isosorbide dinitrate. The culprit lesion was filmed in exactly the same projections in the first and second angiogram. Low osmolar contrast medium (iopamidol) was employed. Intracoronary clot was defined as an intraluminal filling defect surrounded by contrast material. A totally occluded vessel was considered as representing intracoronary thrombus, only if the distal margin had a convex, irregular or hazy shape, and contrast retention or staining occurred. All coronary angiograms were scored by at least two observers who were blinded with respect to the treatment.

The angiograms were analysed in a quantitative manner with the Cardiovascular Angiography Analysis System[16]. Minimal lumen diameter (Dm) and interpolated reference diameter (Dr) were calculated in mm[16] using the catheter tip as a calibration measure. Percent diameter stenosis was calculated.

The extent of the obstruction was determined from the diameter function on the basis of curvature analysis and expressed in millimeters. 'Plaque area' is the difference in area in mm^2 between the reference and detected contours over the length of the lesion[17]. Area stenosis was calculated by videodensitometry. The densitometric profile was measured at the site of maximal narrowing of the vessel, and compared with the area of a reference segment.

The second angiogram to be followed by angioplasty was scheduled between 12 and 24 hours after the first angiogram. If patients had recurrent ischaemia, the second angiogram and angioplasty were performed on an emergency basis. Before the start of the PTCA procedure, 250 mg of acetyl salicylic acid and 100 mg of heparin were administered intravenously. An extra dose of 50 mg of heparin was administered every hour after the start of the procedure. Monorail Piccolino (Schneider-Shiley, Zürich) balloons were employed, introduced over high torque floppy 0·014" guide wires, (Advanced Cardiovascular Systems, Billerica, Ma). In case of abrupt occlusion of a dilated lesion, oversized balloons, longer inflation duration and intracoronary streptokinase infusion were attempted in this order. Primary success was defined as a less than 50% residual diameter stenosis in the culprit lesion, without signs of myocardial infarction or recurrent ischaemia within 24 hours, and without urgent coronary bypass surgery.

The efficacy of treatment was assessed in several ways:

1. Frequency of recurrent ischaemic events between the first and the second angiogram (maximal 24 hours).
2. Incidence of myocardial infarction during this observation period as assessed by serial serum enzyme measurements. For this purpose, serum CK was measured every 12 hours until at least 72 hours after the first angiogram, and 6 hours after each episode of chest pain. Myocardial necrosis was considered to be present when serum CK content was at any time more than twice the local upper limit for normal (i.e. $\geq$200 IU.l^{-1}).
3. Quantitative angiographic differences between the first and the second coronary angiogram.
4. Presence or absence of intracoronary filling defects in both angiograms.
5. Procedural complications during angioplasty, such as death, myocardial infarction, abrupt closure of the dilated vessel and the need for emergency coronary bypass surgery.

STATISTICAL ANALYSIS

Differences between groups were analysed with a two-tailed Student t-test. Changes in quantitatively measured coronary artery stenosis in each group were compared with a two-tailed paired t-test. Differences in incidence of recurrent ischaemic attacks, myocardial infarction, presence of intracoronary clots and the occurrence of abrupt occlusion during angioplasty between groups

Table 1 Clinical, haemodynamic, electrocardiographic and angiographic characteristics of each patient group

Group	Alteplase	Placebo
N	19	17
Male/female	16/3	13/4
Mean age (years)	59	62
Previous infarct	7	10
Previous CABG	0	1
ECG changes during ischaemia		
ST-T elevation ≥0·1 mV	5	9
ST-T depression ≥0·1 mV	5	4
Persistent negative T waves	5	2
Other ST-T changes	4	2
Ischaemia-related vessel		
Left anterior descending artery	11	6
Right coronary artery	6	7
Left circumflex artery	2	4
Multi vessel disease	5	5
Ejection fraction:		
<0·50	3	2
≥0·50	16	14
Missing	0	1

CABG, coronary artery bypass graft.

treated with alteplase or placebo were determined with Fisher's exact test.

Results

Between November 1987 and April 1989, 38 patients with refractory unstable angina pectoris were enrolled in the study. Two placebo patients were excluded from the analysis because bleeding disorders, already present at the time of randomization, had been overlooked. One patient had a groin haematoma, and did not receive trial medication. In the other patient haematuria and bleeding from a subclavian vein puncture were disclosed after a bolus injection of 10 mg of trial medication, which was subsequently discontinued.

Clinical characteristics of the remaining 36 patients are summarized in Tables 1 and 2. The 17 preceding infarctions had occurred more than 1 month before admission to the trial. At the time of the qualifying episode 50% of patients were treated with intravenous nitroglycerin, while 92% received oral anticoagulants, heparin or aspirin. At the time of the first angiogram all patients except two were on intravenous nitroglycerin, while 94% were on intravenous heparin or antiplatelet drugs. Antiplatelet therapy before the qualifying attack and at the time of the first angiogram consisted of aspirin 80 to 500 mg per day, except in one placebo patient who received dipyridamol, 300 mg per day, before the qualifying attack.

RECURRENT ISCHAEMIA AND MYOCARDIAL NECROSIS

Between the start of drug infusion and the second angiogram, 11 patients had one or more episodes of chest pain, five in the alteplase group and six in the placebo group (NS). Severe recurrent ischaemia, not subsiding with medical measures, necessitated urgent PTCA in five patients, four in the alteplase and one in the placebo group. In these patients angiography and PTCA were performed between 4·5 and 8·5 h after the first angiogram. Four of these five patients developed myocardial infarction, with peak CK values between 257 and 2019 $IU.l^{-1}$. Clinical and electrocardiographic evidence, as well as the timing of CK peaks indicate that myocardial infarction occurred prior to the angioplasty procedure. Another eight patients had signs of myocardial necrosis, four in the alteplase and four in the placebo group. In retrospect, two of these had already a CK rise before the first angiogram, one had a CK rise before angioplasty, and five developed myocardial infarction during or directly after angioplasty (Table 3).

QUALITATIVE AND QUANTITATIVE CORONARY ANGIOGRAPHIC DATA AND THE PRESENCE OF INTRACORONARY CLOTS

The sites of the culprit lesions are presented in Table 1. In the first angiogram three patients had an occluded ischaemia-related segment, and thrombi were recognized in four patients. The occlusions were resolved at the time of the second angiogram in all but one patient, but three other new occlusions appeared (Fig. 1). Thrombi resolved in two patients in the alteplase group, while at the same time new clots appeared in two other patients from the same group (Fig. 1).

Data obtained by quantitative angiography are summarized in Table 4. Twenty-nine patients showed non completely obstructed vessels in all three angiograms, 15 in the treatment and 14 in the placebo group. No significant differences were found between the two groups at any time, i.e. during the first angiogram, or before or after angioplasty. A significant reduction in obstruction diameter and percentage diameter obstruction was found in both groups after angioplasty. Changes in diameter stenosis, obstruction length and plaque area between the first and second angiogram were not significant neither within, nor between both groups.

ANGIOPLASTY PROCEDURE

Angioplasty was performed in all 19 alteplase patients and in 16 patients of the placebo group. One placebo patient did not undergo angioplasty because the second angiogram showed extensive clotting in the right coronary artery, without a significant localized stenosis. In this patient streptokinase $1{\cdot}5 \times 10^6$ IU was subsequently administered i.v., without effect on the proximal intracoronary thrombus but with some resolution of a peripheral embolus in the posterolateral branch of the right coronary artery. After elective administration of 100 mg of alteplase i.v., all clots resolved, leaving a virtually normal coronary artery.

Dilatation was angiographically successful in all 16 patients in the placebo group and in 17 out of 19 patients in the alteplase group. One patient with unsuccessful PTCA had a totally occluded right coronary artery at the beginning of an emergency angioplasty procedure, which

Table 2 Medical therapy at the time of occurrence of angina at rest and at the time of the first angiogram

Medical therapy	At the time of the qualifying anginal episode		At the time of the first angiogram	
	Alteplase	Placebo	Alteplase	Placebo
Oral anticoagulants	0	2	0	0
Intravenous heparin	11	10	16	16
Antiplatelet drugs	5	5	1	1
i.v. nitroglycerin	9	9	18	16
Oral nitrates	4	5	1	0
Beta blocker	16	9	17	10
Calcium antagonist	7	11	10	15
No therapy	0	0	0	0

Table 3 Incidence of myocardial necrosis with maximal CK rise in IU.l^{-1} in the alteplase and placebo group

Alteplase group (n = 19)		Placebo group (n = 17)	
Before PTCA (n = 4)	After PTCA (n = 3)	Before PTCA (n = 3)	After PTCA (n = 2)
257*	288	222	636
348	357	275*	656
824*	758	490	
2019*			

*Indicates patients who underwent urgent angioplasty.

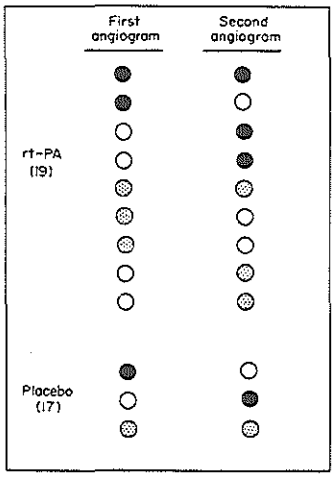

Figure 1 Qualitative coronary angiographic data before and after alteplase or placebo infusion. ○, Non-totally occluded coronary artery without intracoronary filling defect; ●, totally occluded coronary artery; ◎, intracoronary filling defect. Non-totally occluded vessels, without intracoronary clots in both angiograms, are not depicted.

could not be reopened permanently. The other patient had an occlusion of the left anterior descending artery immediately after angioplasty and was operated on as an emergency. Two other patients in the alteplase group and two patients in the placebo group had a CK rise after angioplasty. Thus the primary success rate of dilatation of the ischaemia related vessel was 74% and 88% in the alteplase and placebo groups, respectively. A second stenotic site was successfully dilated in three out of four vessels in the alteplase and in four out of four vessels in the placebo group. A third stenotic vessel was successfully dilated in one patient in the alteplase group.

In the alteplase group transient reocclusion was seen in two patients. Both were treated successfully with oversized balloons, longer inflation duration and intracoronary infusion of streptokinase, 500 000 IU, but nevertheless necrosis developed, documented by elevated serum enzymes. One other patient sustained a side branch occlusion complicated by ventricular fibrillation. In the placebo group three patients had transient reocclusion, all treated successfully with standard procedures, although ventricular fibrillation occurred in one patient. Two of these patients developed elevated enzymes after the angioplasty procedure.

BLEEDING COMPLICATIONS

Bleeding between the first and second angiogram occurred in five alteplase patients, but not in the placebo

Table 4 Quantitative angiographic data. The extent of the obstruction and plaque area could only be measured in non-occluded vessels. Values are given as mean values ± standard deviation. All differences between and within groups were not significant before angioplasty

	Extent obstruction (mm)		Plaque area (mm^2)		Obstruction diameter (mm)		Percentage diameter obstruction		Percentage area stenosis	
	A	P	A	P	A	P	A	P	A (n = 10)	P (n = 9)
First angiogram (1)	7·4 ± 2·1	8·8 ± 3·8	10·2 ± 5·3	11·8 ± 7·0	1·0 ± 0·4	1·1 ± 0·4	67 ± 16	65 ± 11	87 ± 11	84 ± 8
Second angiogram prePTCA (2)	7·4 ± 2·4	7·9 ± 3·5	10·0 ± 6·9	9·6 ± 5·3	0·9 ± 0·4	1·0 ± 0·4	69 ± 16	63 ± 12	90 ± 9	84 ± 14
Post PTCA (3)	6·8 ± 3·1	7·1 ± 2·7	5·7 ± 4·7	6·1 ± 3·6	1·9 ± 0·6	1·9 ± 0·2	37 ± 19	36 ± 8	48 ± 17	49 ± 11
Δ 1–2	−0·0 ± 1·4	−0·9 ± 2·1	−0·2 ± 3·0	−2·2 ± 3·7	−0·1 ± 0·6	−0·1 ± 0·5	3 ± 17	−2 ± 17	3 ± 15	0 ± 12

PTCA = percutaneous transluminal coronary angioplasty; A = alteplase; P = placebo.

group. Four had a haematoma at the puncture site in the groin, one at another site.

Bleeding was observed after angioplasty in six other patients after alteplase and in one in the placebo group. One patient in the alteplase group died of the sequelae of intimal dissection, which occurred when the guiding catheter was advanced through the common iliac artery. The other femoral artery was punctured and a proximal LAD lesion was successfully dilated. At the end of the procedure blood pressure dropped, a retroperitoneal haematoma was diagnosed and the patient underwent laparotomy. After drainage of this haematoma the circulation seemed to be restored and the abdomen was closed. He was treated with blood transfusions and measures to restore normal coagulation. The next day the patient was in good haemodynamic condition but showed signs of occlusion of the right femoral artery. Embolectomy and a crossover operation from the left iliac artery were performed. However, bleeding in the retroperitoneum progressed with subsequent ischaemia of the bowel and the right leg. The patient died 48 h after the angioplasty procedure.

The other five patients had local haematoma in the groin, three of them with prolonged bleeding from the puncture site after removal of the sheaths, and one with combined microscopic haematuria. One patient in the placebo group had haematemesis and localized haematoma at a previous puncture site. In two patients with bleeding in the alteplase group, 6 and 7 units of blood were administered while the patient in the placebo group was treated with Haemacel®. One patient who was excluded from the analysis had an uncomplicated course. The other patient was entered in the trial for recurrent ischaemia 3 days after a myocardial infarction. Eight hours after diagnostic angiography and again 2 days later he exhibited signs of reinfarction with cardiogenic shock. He died one week later in spite of treatment with intracoronary streptokinase, emergency angioplasty, alteplase and intra-aortic balloon counterpulsation.

Discussion

In spite of previous reports that patients with unstable angina might benefit from thrombolytic therapy[9,12,14,15,19–22] no beneficial effect was observed in the present study. Administration of alteplase neither reduced the angiographic severity of the culprit lesions, improved the clinical course, nor facilitated subsequent PTCA in patients who were already treated with heparin and/or aspirin.

Quantitative analysis of coronary artery stenosis was used in the present study because this is the most sensitive method of detecting changes in diameter stenosis or other characteristics of the lesion. Nevertheless, we observed no significant decrease in the severity of the underlying coronary artery stenosis, either after alteplase, or in the placebo group. The extent of the obstruction, plaque area, minimal lumen diameter and obstruction area revealed no significant change in either group. Similar findings were reported by others[15,18], while one recent report demonstrated a small improvement in percent diameter stenosis in patients treated with alteplase and/or heparin[22]. In these studies the calculated diameters of 'culprit' stenosis were similar to those in the present study.

Measurement of percent diameter stenosis might not be the optimal indicator of the remaining lumen in cases of intracoronary thrombus or asymmetric lesions[23]. However, densitometric measurements did not disclose a change in severity of stenosis after alteplase infusion in our study population. Similarly, videodensitometric measurements of area stenosis did not improve after intracoronary infusion of 100 000 to 300 000 IU of streptokinase in another study of 37 patients with unstable angina or non Q infarction[19].

The lack of a beneficial effect of thrombolytic therapy raises the question whether intraluminal thrombosis is indeed a major cause of 'instability' of the symptoms in these patients. The presence of intracoronary thrombus has been reported in 1 to 52%[1–5] of patients with unstable angina, using coronary arteriography as a diagnostic criterion. However, the individual criterion in these studies differed widely, ranging from occlusion, supposedly caused by thrombus, intraluminal defects and intraluminal staining, to a reduction of stenosis severity after streptokinase infusion. Intraluminal defects, suggestive of clots, were observed in four patients in this study, while three other patients had a total occlusion suggesting recent clot formation. Two out of three patients treated with alteplase showed resolution of clots in the second angiogram, and in one other patient, initially given placebo, extensive clotting in the right coronary artery resolved when alteplase was administered after the second angiogram. Thus thrombolytic therapy with alteplase may be beneficial in a few selected patients with unstable angina and extensive clots visible on the angiogram[20]. However, systematic therapy with thrombolytic drugs in patients with unstable angina does not seem warranted. In fact new clots appeared in three patients in spite of preceding treatment with alteplase.

The lack of efficacy of thrombolytic therapy in the current study may be related to the fact that 92% of the patients were treated with oral anticoagulants, heparin, or antiplatelet drugs at the time of the qualifying episode of angina. It is likely that factors other than intracoronary thrombosis contribute to the acute coronary syndrome in those patients who remain 'unstable' in spite of anticoagulation and anti-platelet therapy. This also explains the relatively low incidence of visible intracoronary clots in our study.

In three studies which reported higher incidences of intravenous thrombosis, between 41% and 68%, the patients were not pre-treated with heparin[20,21,24].

ANGIOPLASTY PROCEDURAL COMPLICATIONS

Major complications of angioplasty, defined as procedure-related death, myocardial infarction or urgent surgery are infrequent (5%) in patients with stable angina. Complications are more frequent (10%) in patients with unstable angina, and may amount to 20% of patients requiring urgent angioplasty for intractable angina[10,25].

as in the present study. It should be noted that after the first coronary arteriogram all patients were treated with i.v. nitroglycerin and heparin, while the majority were already receiving heparin and/or aspirin at the time of the qualifying episode of angina. Despite this intensive medical treatment, seven patients developed a myocardial infarction before the second angiogram. In four of these and one other patient urgent angioplasty was performed.

Successful angiographic dilatation (diameter stenosis after angioplasty of less than 50%), was achieved in 89 and 100% of patients in the alteplase and placebo groups respectively, although five patients developed a moderate CK rise after intermittent reocclusion during the procedure. Thus the primary success rate was 74 and 88%. It should be noted that no intracoronary clot was observed prior to the angioplasty procedure in the patients with transient reocclusion. All five patients with intracoronary clots pre angioplasty and three patients with a totally occluded ischaemia-related vessel had successful uncomplicated angioplasty procedures.

Conclusion

Intravenous administration of alteplase in this patient group with unstable angina, in spite of extensive medical therapy, did not have any favourable effect, either on the culprit lesion, the clinical course, or the outcome of subsequent angioplasty. On the contrary one fatality occurred, which might be ascribed to a complication of the procedure and the administration of a thrombolytic drug. It is possible that thrombolytic therapy is beneficial in selected patients with angiographically demonstrated intracoronary clots as observed in one patient. However, based on the presently available data, thrombolytic therapy cannot be recommended in patients with unstable angina.

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CHAPTER 8

GENERAL DISCUSSION

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Introduction

In this chapter the main results of the studies described in the previous chapters are summarised. The findings with respect to diagnosis, prognosis and management strategies are compared with another large dutch study[1] and with two other large studies form the recent literature[2,3]. Finally, suggestions for future research are given.

Definitions used in studies on unstable angina

A major concern in studying the clinical entity, described as 'unstable angina' is the definition of this disease entity. As noted in chapter 1 definitions of unstable angina vary from wide criteria as "all forms of angina, which are not presumed to be 'stable', i.e. when there has been no change in the frequency, duration, or precipitating factors during the preceding 60 days"[4], to "persisting angina at rest, despite intensive medical treatment, with reversible ECG changes during pain"[5,6]. Patients with anginal patterns, recognised as unstable angina at presentation in the emergency unit, represent a different population than patients who have been observed in hospital and in whom the nature of the symptoms has been determined by objective signs of reversible ischemia and myocardial infarction has been ruled out by serial electrocardiograms and enzyme assessments. Specifically, as indicated in the flowchart depicted in figure 1.1, several subgroups can be indicated, all of which are denoted as 'unstable angina'. First, the entry of the flowchart represents all patients presenting with symptoms, suspected of unstable angina at hospital admission, either with or without concomitant ECG changes. Some patients with evolving myocardial infarction will be included in this classification, but can only be recognised when enzyme assays have become abnormal, which may take several hours. The HINT trial[1] is an example of application of such 'admission diagnosis', which was defined as symptoms (prolonged pain at rest) and signs (evidence for myocardial ischemia and absence of signs of acute myocardial infarction) indicating acute but reversible myocardial ischemia. A second category includes patients with symptoms of unstable angina according to specified criteria, in whom myocardial infarction has been ruled out by normal serum enzyme values. In these situations patients are usually included 12 to 24 hours after admission, and include a subgroup, indicated as UAP in the flowchart. This starting point is used in many observational studies and clinical trials[2,3,7]. Third, further narrowing of the definition may be applied by including the in-hospital course. For example, intervention studies, as described in chapter 7, define unstable angina as pain at rest despite intensive medical treatment, with concomitant ECG changes, where coronary intervention is indicated. These subgroup of patients is indicated as 'ANGIO' in the flowchart, followed by the arrow directed to 'PTCA', or to 'CABG' when it concerns studies evaluating the efficacy of bypass operations[8,9]. A fourth subgroup can be identified as 'stabilised after a period of unstable angina', indicated as 'DISCHARGE' respectively 'med Rx' after angiography.

These patients are discharged on medical therapy and are of interest for studies evaluating certain therapeutic strategies providing 'secondary prevention'. For example, trials on aspirin treatment for long-term prevention of future complications start treatment 3 days after admission and continue treatment for on year or longer[10].

Which definition is chosen in a particular clinical trial depends in part on the nature of the treatment option under study. The studied disease entity is defined in terms of a homogeneous clinical indication, with patient characteristics which are representative for the indication at issue, but it should also refer to a particular stage in the development of the disease. Given the rapidly changing nature of relevant diagnostic and other clinical information in patients with unstable angina, it is of importance to define the time of inclusion.

In contrast to studying how a certain drug or intervention affects outcome for a specific group of patients, the present study was directed to study how certain drugs and interventions were applied in clinical practice to patient with (suspected) unstable angina. It was attempted to assess which patient characteristics were used to make certain decisions. Patients admitted to hospital for suspected unstable angina, according to the physician in charge, were followed during hospitalisation, and all information which became available over time was used to describe the decision making process. It was appreciated that, for example, a patient's history might be interpreted as 'typical' angina by one physician, and could be judged as 'atypical chest pain' by another physician or at a later moment in time. The data used for the analyses described in this thesis were all based on judgments of the treating physicians, and were not directed by objective external criteria.

The initial diagnosis of suspected unstable angina, according to the physicians in charge, was revised into myocardial infarction in 10% of the patients after a period of observation, which was not recognised at admission, but became apparent after several hours, when results of enzyme determinations indicating myocardial infarction became available. This percentage was similar to the HINT trial[1]. In another 25% of the patients, the presenting symptoms appeared later to be due to other causes, including non-cardiac disease or non-specific chest pain.

Based upon admission diagnosis medical treatment, including nitrates, aspirin and/or heparin, was started in the majority of patients. This treatment strategy was adapted over time depending on new diagnostic and prognostic information. Medical treatment was considered adequate in 50% of the patients with a *final* diagnosis of unstable angina, while after a period of observation and medical treatment coronary angiography was initiated in 50% of these patients with a view to subsequent coronary interventions. Given this treatment strategy patients with a definite diagnosis of unstable angina according to the treating physicians have a relatively good prognosis. Hospital mortality rate and infarction rate were respectively 2% and 5%. After 6 months 4% of

the patients with definite unstable angina had died and 10% had developed myocardial infarction.

Comparison with other trials

In order to compare the outcome of unstable angina in the current registry (chapters 2 and 3) with other studies, three recent large trials will be reviewed. The HINT study[1] reported the effect of ß-blockers, calcium antagonists and the combination of the two with respect to recurrent ischemia and myocardial infarction during the first 48 hours. These patients were followed until 2 years after admission. Both HINT, which was also conducted in the Netherlands, and our prospective registry included patients immediately upon admission, and did not include patients with possible non-coronary cause of angina, such as anaemia (table 8.1). Patients over 70 years, patients with recent infarction, and patients with maintenance treatment with nifedipine were excluded in the HINT trial. Accordingly, patients in the UAP registry were older than in the HINT study. For comparison, the numbers of those patients younger than 70 years in the UAP registry are given separately in table 1. These patients had more often a history of coronary artery disease, and a shorter painfree interval at admission. However, both populations were comparable with respect to gender, duration of angina before admission, electrocardiographic characteristics and use of nitrates and ß-blockers. Although a wider entry criterium was used, 95% of the patients with a definite diagnosis of unstable angina met the HINT criteria, i.e. ST-T changes had been observed or a documented history of coronary artery disease was present. In both studies 10% of all patients had in retrospect a myocardial infarction at admission. New infarctions occurred in 17% of the HINT patients, and in 10% in the present study. Mortality rates were similar for all patients, but was lower in the UAP registry when elderly people were excluded. Despite differences in baseline characteristics, some of which are associated with increased risk for myocardial infarction, the prognosis of patients with unstable angina has improved in the Netherlands over the past ten years.

In table 8.2 the main features of HINT and two other recent trials are described[2,10]. All three studies excluded patients of elderly age and required objective evidence of ischemia for inclusion. However, enrolment was restricted to patients with pain at rest only in HINT, included both crescendo angina and angina at rest in the 'Theroux' trial, and encompassed recent onset, increasing angina, angina at rest, and non-Q-wave infarction in RISC. It is important to note that the interval between the most recent pain episode and start of the study medication varied considerably between these studies. As was shown in the HINT trial, the interval between pain and the start of the trial medication is strongly related to the rate of recurrent ischemia or myocardial infarction within the first 48 hours. (see also figure 5.2). In HINT 10% of all patients had myocardial infarction at admission, but still 9% of the patients developed

Table 8.1 Comparison of baseline characteristics and outcome of patients in the presented registry and in the HINT study

	UAP registry	HINT[1]
Baseline characteristics		
	n=417 (n=290)*	n=515
age > 65 years	44% (20%)	16%
men	64% (70%)	75%
history of CAD		
myocardial infarction	46% (46%)	34%
PTCA	12% (14%)	-
CABG	15% (17%)	7%
history of angina > 4 weeks	43% (49%)	40%
pain free interval		
< 1 hour	63% (62%)	26%
1-3 hours	15% (15%)	35%
≥ 3 hours	21% (23%)	38%
ECG		
baseline: ST↓ > 0.1 mV	18% (23%)	18%
pain: ST-T changes	35% (35%)	61%
medication before admission		
nitrates	24% (22%)	19%
ß-blockers	40% (42%)	34%
calcium antagonists†	25% (24%)	1%
aspirin†	21% (21%)	3%
Outcome		
mortality	4% (2%)	4%
myocardial infarction	10% (9%)	17%

* Numbers between brackets indicate the percentages for patients younger or equal to 70 years. † Maintenance treatment with nifedipine and aspirin use were exclusion criteria in the HINT trial

myocardial infarction within 48 hours after admission. As most infarctions occur early after admission, the differences in time interval between pain and start of the study may explain the high infarction rate in the HINT study, but does not explain the higher infarction rate in the RISC study compared to the study of Theroux. The RISC study patients included patients with non-Q-wave infarction, which accounted for 49% of the study population, and might have resulted in higher event rates.

The reported figures are the combined event rates of the treatment groups and the placebo groups. HINT reported a beneficial effect of ß-blocker use in patients not

Table 8.2 Summary of treatment strategy and prognosis in patients with unstable angina in three recent large trials

	HINT[1]	Theroux[2]	RISC[3,10]
Design features			
n	515	479	796
patient description	age≤70 yr chest pain at rest reversible ST-T changes or documented CAD	age≤75 yr chest pain at rest or with minimal exercise ischemic ECG changes	men aged < 70 yr non-Q-wave MI angina at rest increasing angina recent onset angina ischemia on ECG or ET
time between start of study and most recent pain	<12 hours	<24 hours	<72 hours
treatment	nifedipine ß-blocker both	heparin- continuous infusion aspirin both	heparin- intermittent injections aspirin both
follow-up	1 year	3 months	1 year
Outcomes			
cardiac events			
non-fatal infarction			
in hospital / 1 mnth	13%	4.4%	7.5%
during follow-up	4%	2.9%	5.0%
death			
in hospital / 1 mnth	1.7%	0.4%	1.2%
during follow-up	2.4%	1.3%	2.4%
interventions			
PTCA or CABG			
in hospital / 1 mnth	14%	n.d.	1.8%
during follow-up	25%	49%	11.8%
Conclusion	*pts not on ß-blocker:* metoprolol beneficial, nifedipine detrimental, combination no additional effect *pts on ß-blocker:* nifedipine beneficial	heparin and aspirin beneficial. heparin favoured over aspirin. combination no additional effect	risk reduction after aspirin treatment. no effect of heparin or combination.

on previous ß-blocker treatment, and a beneficial effect of addition of calcium blockers in patients who already used ß-blockers before admission. Theroux reported an improved prognosis after heparin and aspirin treatment compared to placebo, but heparin was favoured over aspirin. RISC found a favourable effect of aspirin treatment, but not of heparin. The lack of efficacy of heparin in RISC is probably due to the dosage scheme of intermittent injections, resulting in insufficient anticoagulation. In patients with myocardial infarction it was found that patency after thrombolytic therapy was related to the dosage of concomitant heparin treatment. Patency after 2-5 days was 72% after inadequate heparin levels, 80% after suboptimal dosage schemes and 90% after optimal treatment[11]. In the UAP registry 80% of all patients were treated with nitrates and heparin and/or aspirin after admission, and more than half of the patients with ß-blockers, which may account for the good prognosis. Based on the results of the above described studies it is recommended to start initial treatment of patients hospitalised for unstable angina with intravenous heparin and ß-blocker treatment in addition to nitrates. Only if a ß-blocker was already being taken before admission addition of a calcium antagonist is to be considered. If this pharmacologic management strategy fails and angina recurs, coronary angiography is performed followed by angioplasty or coronary bypass surgery, if feasible. Long term preventive treatment may include platelet aggregation inhibiting drugs or a ß-blocker, or both.

Timing of interventions

Despite intensive medical treatment coronary revascularisation is performed in a large proportion of patients. Coronary interventions in patients with unstable angina are directed to prevent new episodes of ischemia as well as progression to myocardial infarction or death. As most infarctions in patients admitted for unstable angina occur early, it seems preferable to perform angiography and subsequent revascularisation as soon as possible. On the other hand, it has been reported that emergency procedures have a greater risk in patients with unstable angina[12,13]. Acute coronary occlusion after PTCA occurred more frequently in patients with unstable angina, with multivessel disease in patients with complex lesion in an observational study of 1423 consecutive patients in the Thoraxcenter[14]. Such complex lesions, indicating plaque rupture and/or thrombosis, are found more often shortly after a period of unstable angina[15]. In the present UAP registry 137 of 282 patients with a definite diagnosis of unstable angina underwent angioplasty followed by PTCA or CABG in 100 patients. Ten of these revascularisation procedures (10%) were complicated by procedural myocardial infarction of death. While these complications were not associated to emergency procedures, the complication rate remains high. On the other hand, 6 infarctions occurred during the waiting period for angiography or revascularisation. Two of these 6 infarctions occurred in patients who waited at home for the procedure. Another 10

patients who waited at home were readmitted during this period because of recurrent pain, and needed earlier intervention, and 1 other patient, who was treated medically, subsequently needed angioplasty because of recurrent pain. Thus the timing of interventions has to be balanced between 'too early' and 'too late'. It seems beneficial to wait several days after the unstable period before performing coronary interventions, but also to try to perform the procedures before hospital discharge.

Based upon available evidence it is concluded that prognosis in unstable angina is better prognosis than thought in general. Many patients can be managed with non-invasive measures. Revascularisation procedures are not without risk. However, patients have a good prognosis after successful revascularisation (chapter 3), but also a high rate of reinterventions. Coronary intervention can be reserved for a specified subset of 'high risk' patients. This 'high risk' group includes patients with recurrent pain with ECG changes, post infarction angina, and patients with severe multivessel coronary artery disease and impaired left ventricular function.

Difference in angiography rate and subsequent intervention

A major difference is observed with respect to the frequency of coronary interventions (table 8.2). The HINT trial was conducted between 1980 and 1984, whereas the other two trials were performed between 1985 and 1988. During the last decade the use of coronary interventions in patients with unstable angina has increased substantially[16,17]. The inclusion of patients after 72 hours may introduce a selection of patients who have stabilised with medical treatment, and thus reducing the need for addition interventions. In addition, the location of the studies is of importance as revascularisation rates are known to be different among countries[16]. The Canadian study[2] confirmed the high intervention rate in this area, and the Scandinavian study[10] the lower rates. The latter revascularisation rate may be underestimated, as a waiting time of 6 to 8 months between the time of referral to angiography and the intervention and several interventions occurred after conclusion of the study.

Apart from these regional differences in the use of coronary interventions, considerable differences were found between in the two participating hospitals in Rotterdam in the UAP registry. The finding of these differences in one city was explained in part by the availability of angiography facilities. Such 'supply-driven' use of facilities have also been described for other resources, such as available hospital beds[18,19]. Neither the follow-up data from our UAP registry (chapter 3) nor the event rates described in table 2 show differences in prognosis. Whether the supply is too large can not be established with these data, but there is no indication that more facilities are needed. The present facilities seemed to be sufficient to treat the patients with an indication for coronary intervention. As all physicians admitted that the availability would increase the number of procedures, more interventions would be performed if

more facilities were available, without evidence for better outcome. However, the waiting time for patients referred from other centres was significantly longer than in the hospital with in-house facilities. To prevent events in the waiting time these periods should be reduced.

Suggestions for future research

Evaluation of current practice in treatment of patients with unstable angina pectoris is useful to assess the effect of treatment strategies and to explore areas where further improvement is required. Although the prognosis of unstable angina is better than generally thought, there is still a considerable morbidity and mortality. The results of the present study suggest three fields of possible management improvement.

The diagnostic phase, or the time until definitive therapy has been selected, varied between several hours to over 7 days. After 48 hours in 50-70% of all patients no decision for definitive treatment had been made yet (figure 4.1). After admission 50% of the patients remains free of pain, while 55 to 70% of the recurrent pain episodes evolved within 24 hours[20] (chapter 5). It is known that recurrent chest pain is associated with cardiac events. Early recognition of the patients who are likely to remain free of pain could shorten the hospital period for these low risk patients. Additional measures, such as continuous 12-lead ECG monitoring[21], biochemical markers indicative for unstable processes in an atherosclerotic plaque[22] or pharmacological stress testing[23], may be of value to identify of low-risk patients, and thus shorten the time needed to make a definitive treatment decision.

Although medical treatment of unstable angina has been extended during the last years, and prognostic improvement has been demonstrated, some contradictions have to be explained. It has been described earlier that the effect of heparin use depends in the level of anticoagulation. More detailed analysis of the effect of heparin in patients with unstable angina, by careful monitoring of haematologic variables, may offer an optimal dosage regimen. To date, the value of thrombolytic therapy has not been confirmed in patients with unstable angina (chapter 7). However, it has been suggested that subgroups of patients, with evidence of intracoronary clots on the angiogram, may benefit from this therapy. These subgroups have to be defined in further studies. Further work is needed to define comparative effectiveness of various drugs reducing platelet activation in patients with unstable angina in order to reduce episodes of myocardial ischemia and to improve prognosis[24].

The complication rate of coronary interventions is still a matter of concern. Angioplasty procedures are often complicated by acute occlusion, leading to death, infarction or emergency surgery. Until now no adequate solution has been found to improve the complication rate. Additional measures should be sought to protect the patients more effectively during these interventions[24].

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SUMMARY

This thesis provides a description of the clinical syndrome 'unstable angina pectoris' and of the patients who are admitted and treated for unstable angina in two hospitals in the city of Rotterdam. In chapter 1 a literature review is given of the definitions, the underlying pathophysiologic mechanisms of unstable angina and the treatment options available. Unstable angina consists of a wide range of conditions intermediate between chronic stable angina an acute infarction, all characterised by severe transient ischemia. Definitions vary from 'each form of deteriorating angina, including recent onset angina and progressive angina' to 'severe angina at rest with concomitant reversible electrocardiographic (ECG) changes'. In addition, the level of medication and the time interval between the last pain episode and presentation are considered in several definitions. Plaque rupture or endothelial ulceration followed by platelet aggregation or a thrombotic process, often in combination with coronary spasm, are considered to be the pivotal factors in sudden changes in the degree of flow obstruction and hence in the conversion from clinical stability to clinical instability. Coronary obstruction by these mechanisms may develop and regress rapidly, inducing reversible episodes of myocardial ischemia (unstable angina). Sometimes the obstruction progresses to total coronary occlusion, inducing irreversible myocardial injury (infarction) or death. When a patient presents with symptoms suspected of unstable angina it takes some time after admission to make a definite diagnosis. Differentiation between reversible ischemia and irreversible ischemia is only possible when the cardiac enzyme values are known, which are released from irreversibly injured myocardial cells into the circulation during a period of several hours. On the other hand patients may present with chest pain, which is initially suspected of unstable angina, but appears in retrospect to be of non-cardiac or non-specific causes.

In patients with definite unstable angina the risk of progression to myocardial infarction or death is on average 14% and 10% respectively. This risk is increased for patients with recurrent pain and with concomitant ST-T changes on the electrocardiogram. Treatment of unstable angina is directed to initial relief of the pain and to prevention of progression to infarction or death. Medical therapy of nitrates, ß-blockers, calcium-antagonists, heparin and aspirin are usually given in various combinations, and thereupon coronary revascularisation procedures (bypass surgery and angioplasty) are available to manage the syndrome unstable angina.

In a prospective registry 417 consecutive patients were followed after admission for suspected unstable angina in two hospitals in Rotterdam. After observation 9% of these patients had in retrospect myocardial infarction and in 26% the symptoms appeared to be non-cardiac or non-specific. In 65% of the patients had a definite

diagnosis of unstable angina. Medical therapy was started in the majority of the patients, including heparin and aspirin. In addition 137 patients (33%) underwent angiography, followed by subsequent bypass surgery of angioplasty in 100 patients (24%). Despite frequent recurrent pain episodes during admission (53% of all patients) only 4% of the patients developed myocardial infarction and 1.4% of the patients died in hospital. The occurrence of death was related to elderly age and recent infarction (chapter 2).
During a follow-up period of six months the infarction rate was 9.6% for patients with a definite diagnosis of unstable angina and the mortality rate was 4.3%. The occurrence of infarction or death was associated with elderly age and the presence of ECG changes during pain. The risk of death was also increased for men, for hypertensive patients and for patients who already used ß-blockers before admission. Ten percent of the patients underwent as yet an angiography after discharge, followed by angioplasty of bypass surgery in 7% of the patients (chapter 3).

A difference between the two hospitals was found with respect to the angiography rate. In chapter 4 an analysis of the origin of this difference is presented. The angiography rate for patients younger than 80 years without recent infarction or revascularisation procedure was nearly twice as high in the Thoraxcenter of the university hospital Dijkzigt, a hospital with in-house angiography facilities, compared to a community hospital without such facilities, the Sint Franciscus Gasthuis. The patients in the Thoraxcenter were younger and had a more severe history of coronary artery disease than the patients in the Sint Franciscus Gashuis. Multivariate analyses were used to assess the patient characteristics associated with a subsequent decision for angiography. Patients younger than 70 years, with known hypercholesterolemia, with progression of angina and multiple pain episodes before admission, who were already treated with ce-blockers, and had ECG abnormalities at admission underwent angiography more often. After adjustment of the patient characteristics the hospital site still remained an independent factor associated with subsequent angiography. This difference disappeared 36 hours after admission. This means that for comparable patients in the hospital with angiography facilities the decision to initiate angiography is made more often and also earlier in time.

In chapter 5 the results of an open interview are reported. Physicians were asked to describe their definition of 'unstable angina' and the preferred treatment strategy. Individual cardiologists used different definitions and expressed different risk estimates for progression to myocardial infarction. These risk estimates were significantly higher than the rates reported in the literature. In addition individual differences existed in the judgment of the clinical course, in particular of the painfree period until the situation is no longer considered unstable. The individual differences in opinions were independent of the hospital situation. All cardiologists admitted that they would decide for angiography more often and earlier when they worked in a hospital with

angiography facilities.
In addition, a series of paper cases, varying on seven clinical factors, were given to the cardiologists. For each case description they were asked to indicate what kind of treatment they would prefer. Using linear regression analysis the relative importance of clinical variables for the decision to initiate angiography was calculated. Three groups of physicians, who used similar information, could be identified. The first group of physicians (27%) made their decision predominantly upon the prehospital information, the second group (33%) relied on the new events in hospital, and the third group (40%) based their decision on both the prehospital and in hospital information. Recognition of these patterns may be helpful in the communication between physicians and can explain why individual cardiologists come to a different decision in the same patient (chapter 6).

Finally in chapter 7 a clinical trial is presented on new treatment options. A double-blind randomised placebo-controlled trial was performed in order to assess the efficacy of thrombolytic therapy before angioplasty in patients with unstable angina, despite intensive medical therapy. Angiographic nor clinical endpoints revealed any differences between the placebo group and the treatment group. Based on these results and those reported in other trials thrombolytic therapy can not be recommended in patients with unstable angina.

In the general discussion the results are summarised and compared to several large studies from the recent literature, which were performed in different countries under similar circumstances. The described results lead to suggestions for future research are given, such as the evaluation of diagnostic measures to come to earlier recognition of 'low risk' patients and earlier decisions for the definite therapy and hence shorten the admission period. Additional medical therapy should be further evaluated and for presently used drugs, such as heparin, optimisation of the efficacy may be obtained by improved dose regimens. Finally, the complication rate of revascularisation procedures is still a matter of concern and additional measures to reduce these complications may further improve the prognosis of patients with unstable angina.

SAMENVATTING

Dit proefschrift bestaat uit een beschrijving van het ziektebeeld 'onstabiele angina pectoris' en de patiënten die als zodanig opgenomen en behandeld werden in twee Rotterdamse ziekenhuizen. In het eerste hoofdstuk wordt een overzicht gegeven van de kennis die de literatuur verschaft omtrent de definitie, de pathogenese en de behandeling van onstabiele angina. De definities van onstabiele angina lopen uiteen van 'elke vorm van angina pectoris die in ernst is toegenomen' tot 'langdurige pijn op de borst in rust met reversibele electrocardiografische (ECG) veranderingen zonder enzymstijgingen'. Aanvullend worden het niveau van de medicatie waaronder de pijn ontstaat en de tijdsduur tussen de laatste pijnaanval en de presentatie in de definitie betrokken. Een periode van onstabiele angina pectoris wordt veroorzaakt door een ruptuur van een atherosclerotische plaque in een kransslagader, mogelijk gevolgd door vaattonus-verhoging en thrombocytenaggregatie, waardoor de bloedtoevoer naar de hartspier wordt belemmerd. Wanneer dit proces reversibel is en er geen blijvende schade aan het hartspierweefsel is ontstaan spreekt men van onstabiele angina. Voortschrijding van kransslagadervernauwing kan leiden tot totale afsluiting met als gevolg een hartinfarct (permanente beschadiging van een deel van de hartspier) dat tot de dood kan leiden. Bij opname van een patiënt met klachten die verdacht zijn voor onstabiele angina, zijn de anamnese en het ECG de belangrijkste diagnostische middelen. Er is na opname enige tijd nodig om tot een definitieve diagnose van onstabiele angina of een andere diagnose te komen. De klachten bij opname kunnen achteraf blijken te berusten op een infarct op grond van verhoogde enzymwaarden die op weefselversterf duiden en die pas na enkele uren aantoonbaar zijn in het bloed. Anderzijds kunnen de klachten berusten op niet-cardiale of aspecifieke oorzaken.

Patiënten met onstabiele angina hebben een risico om binnen een jaar alsnog een infarct te krijgen of te overlijden van gemiddeld 14% respectievelijk 10%. Dit risico is verhoogd bij patiënten met frequente pijnaanvallen en met ST-afwijkingen op het ECG. De behandeling van onstabiele angina is erop gericht nieuwe aanvallen van pijn en de ontwikkeling van een hartinfarct te voorkomen. Medicamenteuze therapie bestaat uit (een combinatie van) nitraten, ß-blokkers, calcium-antagonisten, heparine en aspirine. Daarnaast kunnen een bypass operatie of ballondilatatie worden uitgevoerd teneinde de bloedtoevoer naar de hartspier te verbeteren.

In een prospectief onderzoek werden 417 opeenvolgende patiënten in twee ziekenhuizen in Rotterdam gevolgd, die opgenomen werden onder verdenking van onstabiele angina pectoris. Na observatie werd bij 9% van de patiënten alsnog een myocardinfarct gediagnostiseerd, bij 26% was de diagnose niet-cardiaal of aspecifieke borstpijn en bij 65% werd de diagnose 'onstabiele angina' gehandhaafd. De patiënten

werden met intensieve medicamenteuze therapie behandeld, inclusief heparine en aspirine. Aanvullend werd bij 137 patiënten (33%) een angiografie verricht, gevolgd door ballondilatatie of bypass chirurgie bij 100 patiënten (24%). Ondanks frequent voorkomende recidief pijnaanvallen tijdens opname (53% van de patiënten) ontstond bij slechts 4% van de patiënten een hartinfarct en overleed 1.4% van de patiënten tijdens opname. Bijna de helft van de infarcten was gerelateerd aan een revascularisatie-procedure. Overlijden was geassocieerd met een hoge leeftijd en met een recent infarct voor opname (hoofdstuk 2).

Gedurende een vervolgonderzoek van zes maanden werd een totale infarct frequentie van 9.6% en een mortaliteit van 4.3% geregistreerd voor patiënten met een definitieve diagnose 'onstabiele angina'. Het risico voor een infarct of overlijden was verhoogd voor patiënten boven de 70 jaar en voor patiënten met ECG veranderingen tijdens pijn. Het overlijdensrisico was bovendien verhoogd voor mannen, voor mensen met hypertensie en bij ß-blokker gebruik vóór opname. Na ontslag onderging 10% van de patiënten met onstabiele angina alsnog een angiografie, gevolgd door bypass chirurgie of een ballondilatatie bij 7% van de patiënten (hoofdstuk 3). Het ziektebeeld onstabiele angina pectoris zoals dat in de twee deelnemende ziekenhuizen werd gezien heeft een goede prognose onder het huidige beleid, met intensieve medicamenteuze behandeling en een groot aantal interventies.

De registratie liet een verschil zien tussen de twee ziekenhuizen in het aantal patiënten waarbij een hartcatheterisatie werd verricht. In hoofdstuk 4 is een analyse verricht naar de mogelijke oorzaken voor dit verschil. Bij patiënten onder de 80 jaar zonder een recent infarct of een recente revasularisatieprocedure werd in het academisch ziekenhuis Dijkzigt ruim 2 maal zo vaak een angiografie verricht als in het Sint Franciscus Gasthuis. Het eerste ziekenhuis beschikt over eigen hartcatheterisatie-faciliteiten, terwijl het tweede ziekenhuis deze faciliteiten niet heeft en zijn patiënten moet verwijzen voor angiografisch onderzoek. De patiëntenpopulaties in beide ziekenhuizen verschilden met betrekking tot de leeftijd en de cardiale voorgeschiedenis. Patiënten in het Dijkzigt ziekenhuis waren gemiddeld jonger, hadden vaker een voorgeschiedenis van coronairlijden en hadden een langere periode van angina voor opname. Multivariate analyses werden toegepast om na te gaan welke patiënten-karakteristieken konden voorspellen welke patiënten een angiografie zouden ondergaan. Patiënten jonger dan 70 jaar, met bekende hypercholesterolemie, met progressie van bestaande angina, met meerdere pijnaanvallen recent voor opname, die al behandeld werden met ß-blokker therapie, en met ECG afwijkingen bij opname werden vaker geangiografeerd. Het verschil tussen de twee ziekenhuizen bleef aanwezig, nadat gecorrigeerd was voor de verschillende patiëntenkarakteristieken. Dit verschil verdween 36 uur na opname. Dit betekent dat bij vergelijkbare patiënten in het ziekenhuis met angiografie faciliteiten vaker en vooral eerder tot een angiografie werd besloten.

In hoofdstuk 5 is onderzocht hoe individuele cardiologen het ziektebeeld 'onstabiele angina' definiëren en behandelen. In open interviews werd duidelijk dat er verschil is in de definitie die de cardiologen hanteren en de prognose die ze aan het ziektebeeld toekennen. Voor zover aangegeven werd gevreesd voor een hoger infarct risico dan in de literatuur en in de beschreven registratie is gerapporteerd. Er werd tevens verschillend gedacht over de situatie waarin en wanneer een patiënt 'gestabiliseerd' genoemd mag worden na een onstabiele periode. De individuele verschillen waren niet gerelateerd aan de ziekenhuissituatie waarin men werkte. Echter, alle cardiologen gaven aan dat zij vaker en eerder een angiografie zouden verrichten wanneer zij beschikten over een catheterisatie laboratorium of minder vaak wanneer zij hier niet over zouden beschikken. Aanvullend werd aan de cardiologen een serie beschrijvingen van 'papieren' patiënten voorgelegd, waarin een zevental klinische gegevens werden gevarieerd. Voor elke casus werd een uitspraak gevraagd naar het te voeren beleid in de gegeven situatie. Met lineaire regressie analyse werd voor elke cardioloog bepaald welke gegevens hij/zij belang achtte om tot angiografie over te gaan. Drie groepen van cardiologen, die hun besluit namen op grond van vergelijkbare combinaties van gegevens, konden onderscheiden worden. De eerste groep kan worden beschreven als cardiologen die tot angiografie besloten voornamelijk op grond van gegevens met betrekking tot de voorgeschiedenis en de presentatie bij opname (27%). De tweede groep nam dit besluit voornamelijk op grond van nieuwe gebeurtenissen tijdens opname (33%) en de derde groep gebruikte zowel de voorgeschiedenis als het beloop in het ziekenhuis om tot een besluit te komen (40%). Herkenning van dergelijke patronen kan behulpzaam zijn bij de discussie over het beleid voor een bepaalde patiënt en kan verklaren waarom cardiologen in een gegeven situatie tot een ander besluit komen (hoofdstuk 6).

Tot slot wordt in hoofdstuk 7 een klinisch onderzoek gepresenteerd naar het gebruik van een nieuwe therapievorm om de bestaande behandelingsmogelijkheden te verbeteren. In een dubbelblind gerandomiseerd placebo-gecontroleerd onderzoek is nagegaan of een behandeling met trombolytische therapie voorafgaand aan een ballondilatatie bij patiënten met onstabiele angina ondanks intensieve medicamenteuze therapie de complicaties bij deze procedure kan verminderen. Angiografische noch klinische eindpunten lieten een verschil zien tussen de patiënten behandeld met trombolyse en de patiënten behandeld met placebo. Op grond van deze en andere onderzoeksresultaten is er geen reden om trombolytische therapie toe te passen bij patiënten met onstabiele angina.

In een afsluitende discussie worden bovenstaande resultaten samengevat en vergeleken met enkele grote onderzoeken uit de recente literatuur die in verschillende landen werden uitgevoerd onder vergelijkbare omstandigheden. De beschreven resultaten leiden tot mogelijke onderzoeksvelden in de toekomst. Met betrekking tot de diagnostiek

zouden aanvullende procedures een eerdere herkenning van de 'laag risico' patiënten kunnen bieden en zodoende kunnen leiden tot een snellere besluitvorming ten aanzien van de definitieve behandelingsvorm en verkorting van de opnameduur. Uitbreiding en aanscherping van medicamenteuze therapie dient verder te worden onderzocht. Aanvullende mogelijkheden om complicaties bij bypass operaties en ballondilataties te voorkomen kunnen in de toekomst mogelijk leiden tot een nog verdere verbetering van de prognose bij patiënten met onstabiele angina pectoris.

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CURRICULUM VITAE

Addy van Miltenburg-van Zijl werd geboren op 17 december 1959 te Uithoorn. Zij behaalde in 1978 het eindexamen gymnasium-ß aan het Aloysius College te Den Haag. In hetzelfde jaar begon zij aan de studie Pedagogiek aan de Rijks Universiteit te Leiden. Na het propaedeuse examen pedagogiek werd in 1979 de studie Geneeskunde aangevangen, eveneens in Leiden. Na het artsexamen in 1986 werkte zij enkele maanden op de afdeling verloskunde van het Academisch Ziekenhuis Leiden. In januari 1987 trad zij in dienst van de Erasmus Universiteit te Rotterdam voor een opleiding tot klinisch onderzoeker. Daar was zij verbonden aan de afdelingen Klinische Epidemiologie van het Thoraxcentrum en de afdeling Klinische Besliskunde. In 1987 werkte zij aan de opzet van het REPAIR onderzoek (de toepassing van prehospitale trombolyse bij het acute hartinfarct) en van 1988 tot eind 1991 aan het in dit proefschrift beschreven onderzoek. Sinds januari 1992 is zij werkzaam als onderzoekscoördinator by Cardialysis te Rotterdam.