Discharge Policy and Reperfusion Therapy in Acute Myocardial Infarction

Maureen van der Vlugt

Cover design	Maud van Nierop, Erasmus Medical Center, Rotterdam, the Netherlands m.e.vannierop@erasmusmc.nl
Cover photography	Lothar Kort, Studio Kort Photography, Curaçao, Netherlands Antilles info@studiokort.com
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Discharge Policy and Reperfusion Therapy in Acute Myocardial Infarction

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‘…nam qui erudite ad paucorum doctorum iudicium scribunt, quique nec Persium nec Laelium iudicem recusant, mihi quidem miserandi magis, quam beati videntur, ut qui sese perpetuo torquant: addunt, mutant, adimunt, reponunt, repetunt, recudunt, ostendunt, nonum in annum premunt, nec umquam satisfaciunt ac futile praemium, nempe laudem, eamque perpaucorum, tanti emunt, tot vigiliis, somnique, rerum omnium dulcissimi, tanta iactura, tot sudoribus, tot crucibus. Adde nunc valetudinis dispendium, formae perniciem, lippetudinem aut etima caecitatem, paupertatem invidiam, voluptatum abstinentiam, senectutem praeproperam, mortem praematuram, et si qua sunt alia eiusmodi. Tantis malis sapiens ille redimendum existimat, ut ab uno aut altero lippo probetur...’

Erasmi Roterodami, Stultitiae Laus, Bazel, 1515

‘...want zij die bijvoorbeeld een proefschrift schrijven, dat immers alleen bestemd is om aan het oordeel van enige professoren te worden onderworpen, en die de strengste en meest deskundige critici niet vrezen, zijn, dunkt me, meer te beklagen dan te benijden, daar ze zich eindeloos aftobben. Ze voegen toe, veranderen, schrappen, herstellen weer, herzien, werken het weer geheel en al om, laten het graag anderen zien, houden het negen jaar in portefeuille en zijn nooit tevreden met het resultaat. De beloning, die ze er tenslotte voor krijgen - immers de lof van een enkeling - is wel heel duur betaald met al hun zwoegen, zweten en gebrek aan het zoetste, wat er bestaat: de slaap. Voeg hierbij nog dat dit alles gaat ten koste van hun gezondheid, dat ze daardoor humeurig, lelijk, bijziende of zelfs blind worden, tot armoede vervallen, bij ieder uit de gunst zijn, dat ze alle genoegens moeten verzaken, dat ze vóór hun tijd oud zijn, ontijdig sterven en wat dies meer zij. Doch al deze opofferingen getroosten zij zich gaarne om de goedkeuring weg te dragen van één of twee geleerde boekenwurmen...’

Desiderius Erasmus, De Lof der zotheid, Rotterdam, Ad. Donker 1986

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Introduction

INTRODUCTION

Last century has witnessed most dramatic improvements in diagnosis, treatment and management of myocardial infarction (MI). Key elements in this development were the introduction of the external defibrillator[1], closed chest massage[2] followed by the introduction of the Coronary Care Unit (CCU) for monitoring and treatment of life threatening arrhythmia's[3] and subsequently hemodynamic monitoring[4]. Reperfusion therapy as well as the introduction of additional pharmacological therapy such as beta-blockers, antiplatelet and anticoagulant drugs and ACE-inhibition was introduced in clinical practice in the 1980s. These developments resulted in a steady decline in mortality from MI.

Since 1985 reperfusion therapy became the preferred treatment of MI using intracoronary or intravenous thrombolysis.[5] Reperfusion therapy in acute MI reduces infarct size, preserves left ventricular function, and hence increases hospital survival by rapid restoration of coronary flow in the infarct related artery.[5-7] All these parameters mainly determine the prognosis after MI. By the end of the 1990s primary coronary percutaneous intervention (PCI) within the first hours after acute MI turned out to be superior to thrombolytic therapy.[8] Since 1985 reperfusion therapy by thrombolytic treatment increased tremendously first in-hospital and later programs for early pre-hospital thrombolytic therapy in the ambulance were introduced.[9,10] It reached its top at the end of the nineties when gradually primary PCI was introduced. Furthermore, immediate angiography provided additional information like coronary anatomy and left ventricular function.

While nowadays most patients with acute MI in the Netherlands are treated directly with primary PCI, in the previous decade physicians were restricted by lack of resources which necessitated choosing between different modes of reperfusion therapy like Streptokinase, rtPA or PCI.[11] The evolution of reperfusion therapy at the Thoraxcenter is illustrated in Figure 1.1. In Rotterdam a model was developed for optimal allocation of such therapy. The validation of this model is reported in this thesis.

Parallel to the improvement of management of MI significant decrease in hospital stay has been realized. From more than 6 weeks with the "arm-chair" treatment in the late 1950s[12] to less than a week today. Largely driven by the need for cost saving measures and current guidelines recommend early discharge within 4 days after uncomplicated MI.[13] Such efficiency can be achieved through triage and early discharge of patients with MI who have an uncomplicated initial course. The length of hospital stay and early discharge after uncomplicated MI have been a focus of substantial clinical and research interest during the past 30 years. In this thesis a summary is given of the most contributing prospective and retrospective studies in this field. Mainly as a result of advances in management of patients with acute MI and development of sophisticated risk stratification to identify a patient with uncomplicated course, the opportunity for early discharge has increased over the years. Yet, although, the potential economic savings from reduction of

hospital stay for low-risk patients are evident, this should be balanced against the risk. However, defining an acceptable risk it is a challenge and actual care of patients will depend on society and health care systems willingness to pay for the incremental benefit of providing immediate medical attention to a small number of patients who might develop adverse events beyond the planned day of discharge. In this way, we have the opportunity to efficiently deal with our limited resources.

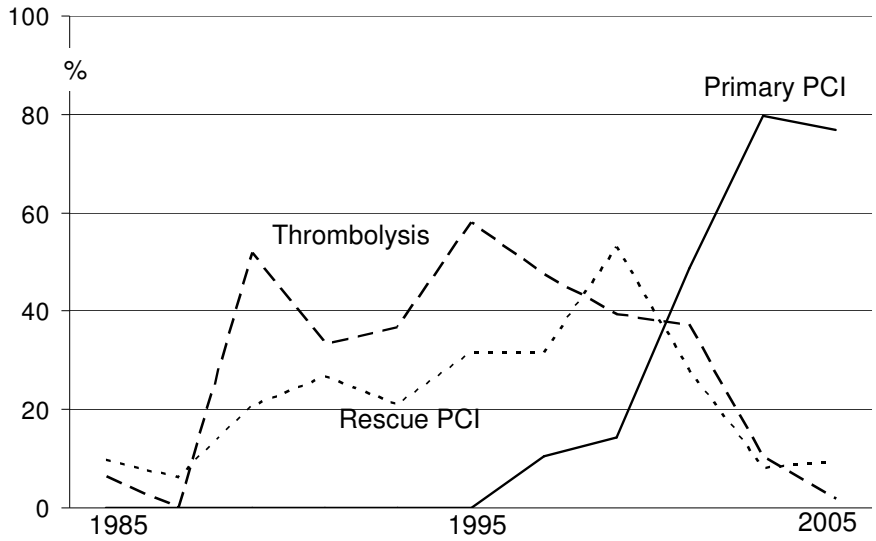

Figure 1.1 Time trend of thrombolysis and PCI for acute myocardial infarction.

These data were collected from the Thoraxcenter Erasmus Medical Center with the use of information from discharge letters and local database in the month March every second year. Note the rise and fall of thrombolytic therapy between 1985 and 2005, while a gradual increase in application of rescue PCI. Since 2000 primary PCI has replaced other modes of reperfusion therapy.

In **chapter 2** this thesis will describe the evolution in length of hospital stay after myocardial infarction during the past decades.

Chapters 3 to 6 explain the development of the decision model for structured discharge management and validation of feasibility and safety of early discharge in several groups of patients with acute myocardial infarction with different modes of reperfusion therapy. Different discharge models are compared.

Chapters 7 and 8 present the psychological effects of patients discharged earlier compared to patients with a complicated course and consequently prolonged hospital stay Outcome of the psychological scores has also shown to be related with mortality.

Chapter 9 evaluates the assumptions on which a decision model for reperfusion therapy in the mid nineties was based with long-term follow-up data of patients with acute myocardial infarction treated according to this decision model.

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2

Early discharge after acute myocardial infarction (review)

Maureen J. van der Vlugt[1]
Eric Boersma[1]
Ineke M. Leenders[2]
Gheorghe A.M. Pop[3]
Rinus J. Veerhoek[4]
Ad Prins[5]
Jaap W. Deckers[1]
Maarten L. Simoons[1]

[1]Thoraxcenter, Erasmus Medical Center, Rotterdam
[2]Haven Hospital, Rotterdam
[3]Vlietland Hospital, Vlaardingen
[4]St. Franciscus Gasthuis, Rotterdam
[5]Department of General Practice, Erasmus University Rotterdam
The Netherlands

based on 'Vroeg ontslag na een hartinfarct'. Hartbulletin 1996;27:62-6.

GENERAL INTRODUCTION

Physicians have to justify their patient management and treatment medically as well as financially. Management should both be effective and efficient as well as cost effective. Pre-arranged decision models may help to achieve these goals.

During the last decades the hospital stay of patients admitted with acute myocardial infarction (MI) has shortened significantly. In the early fifties hospital stay was as long as eight weeks, since pathophysiologic research at that time showed that necrotic myocardium needs 6 weeks to organise into a scar[1]. Therefore, patients had strict orders to stay in bed for 6 weeks where they were completely nursed. The greatest fear then was rupture of the myocardium. It was believed that a sick organ needs rest for healing which lead to immobilisation of a patient with coronary thrombosis.

In 1952 Levine and Lown were pioneers in their attempt to shorten hospital stay by introducing the 'armchair treatment'.[2] Such an early mobilisation procedure had been reported in a case report as early as 1938. The patient described, suffered from serious heart failure and did not respond to any medical treatment available at that time. The patient recovered quickly after placing him in a chair. It was proposed that complete immobilisation has negative physical and psychological implications for recovery. Levine and Lown believed that 'armchair treatment' could also be beneficial for the rehabilitation of patients with MI. They evaluated their hypothesis in a prospective study by placing patients with an uncomplicated myocardial infarction in a chair three days after admission. The 'armchair' treated patients (n = 81) were discharged after approximately four weeks compared to 6 weeks of the control group. No differences were seen between after six months follow-up between these two groups.

In the years that followed much research was performed for further reduction in length of hospital stay, in particular for patients at low risk for complications, resulting in a decrease of length of hospital stay in patients with MI to an average 8.1 (SD $\pm$ 6) days in the USA in 1995.[46] The average length of hospital stay in the Netherlands in 2005 was 8.0 days for all patients with MI. Over the past 25 years (1980 to 2005) the average hospital stay of all MI patients (ICD-9-CM code 410.0-410.9, ICD-10 code I210-229; irrespective of infarct location, survivors and non-survivors) has been reduced with 9.6 days (55%) from 1980 to 2005 (Figure 2.1, resource: 'Prismant, Landelijke Medische Registratie' 2007).

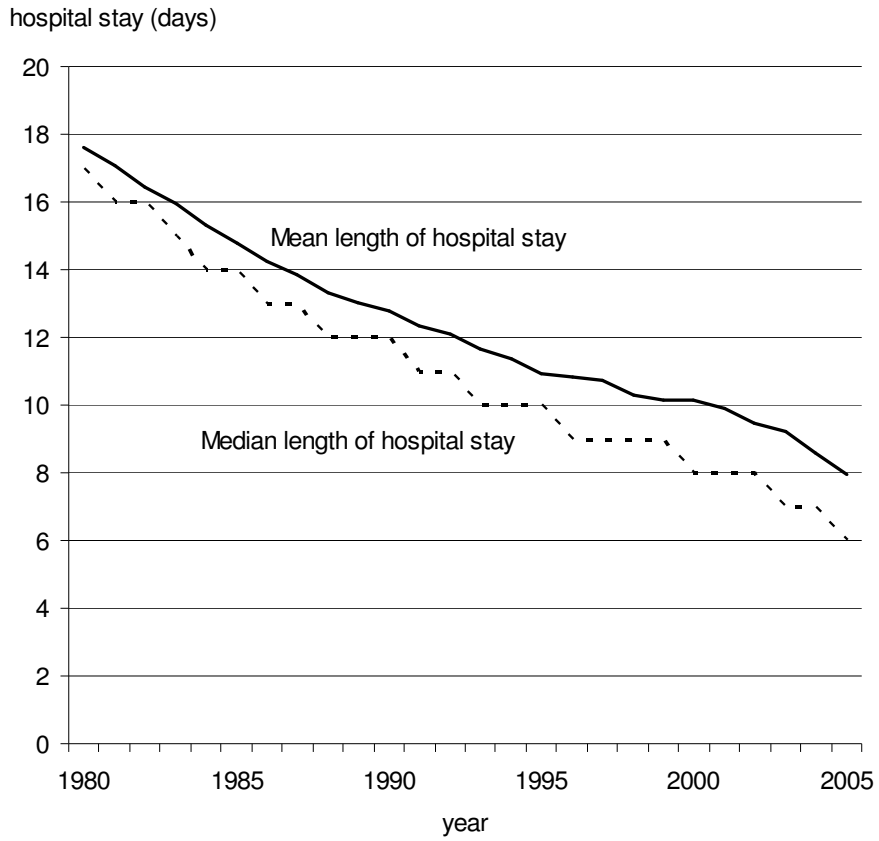

Figure 2.1 Mean and median length of hospital stay of patients with acute myocardial infarction in the Netherlands from 1980 - 2005 ('Prismant, Landelijke Medische Registratie' 2007, ICD-9-CM code 410).

EARLY HOSPITAL DISCHARGE

Most studies concerning, shortening length of hospital stay were performed in the seventies and early eighties.[3,18-29] In prospective studies, patients with uncomplicated myocardial infarction were randomised into two groups: the first group was discharged after the 'usual' number of hospital days (reference group) compared to the second group that was discharged after a shorter hospital stay (Table 2.1). Differences in complications and re-admissions were documented during three to six month follow-up.

For all studies in Table 2.1 the total infarct population is given from which the uncomplicated patients were selected. The percentage of patients with an uncomplicated myocardial infarction eligible for early discharge ranged from 15% to 76%. The percentage

of patients actually discharged early ranged from 7% to 67% of the total population.
The point in time when patients were selected for early discharge varied from time at admission until the sixth hospital day. The definition of uncomplicated MI varied between the investigators. Most common exclusion-criteria for early discharge are: heart failure, recurrent infarction, angina and arrhythmias. Furthermore, Table 2.1 shows a significant decrease in length of hospital stay over the years. In the early seventies, length of hospital stay was about three weeks, which decreased to two weeks at the end of the seventies.
The study of McNeer is often quoted[3]. In 1975, she retrospectively divided the 4th days survivors of 522 (85%) MI patients into two groups (Table 2.2). The uncomplicated group (n = 265, 51%) were patients without heart failure, re-infarction or arrhythmia's during the first four days. These patients experienced no serious complications from day 5 until discharge (average length of hospital stay: 17 days). Mortality of the hospital survivors after six-month follow-up was 8% for patients with an uncomplicated MI. Hospital survivors with a complicated MI had surprisingly a slightly lower mortality of 6%. McNeer concluded that it is safe to discharge a selected group of MI patients after 7 days. Following this description the same investigators performed a prospective study in a smaller number of patients (n=158) of who 67 (42%) patients had an uncomplicated hospital course until day 5. Half of the patients were discharged at one week and the remaining 34 patients had a mean hospital stay of 11 days (range 9 to 20 days).

Author	Year of research	N	Uncompl. (%)	Early discharge (%)	Reference length of hospital stay (days)	Early discharge hospital stay (days)	Cardiac reasons for prolonged stay					
							re-MI	CHF	Rhythm	Recurrent ischaemia	LVEF↓	other
Groden[18]	1966	105	54	39	36	22						
Harpur[19]	1970	262	76	36	28	15		✔	✔			✔
Hutter[20]	1971	925	15	7	21	14		✔	✔	✔		✔
Abraham[21]	1974	129	25	50	19	12		✔	✔	✔		
Lindvall[22]	1978	202	21	19	19	9	✔	✔	✔	✔		✔
Hayes[23]	1973	268	58	38	16	9		✔	✔	✔		
Ahlmark[24]	1978	383	54	28	15	8		✔	✔	✔		✔
Gelson[25]	1975	405	57	67	> 8	8		✔	✔			✔
Mc Neer[26]	1976	158	42	21	11	7	✔	✔	✔			
Boyle[27]	1971	295	62	18	> 9	7		✔	✔	✔		✔
Chaturvedi[28]	1972	275	40	38	9	7		✔	✔	✔		✔
Lau[29]	1978	319	43	39	12	6		✔	✔	✔		✔
Sanz[30]	1988	200	34	9	12	4	✔	✔	✔	✔	✔	✔
Topol[4]	1987	507	35	18	7-10	3		✔	✔	✔	✔	
PAMI-II[50]	1998	908	52	50	7	3	✔		✔		✔	✔
SHORT[51]	2000	1472	39	31	10	7	✔	✔	✔	✔		✔
Yip[52]	2003	898	52	58	≥ 4	< 4	✔	✔		✔		✔
Cadillac[53]	2003	1703	51	25	2-3	1.5-2	✔			✔		✔

Table 2.1 Review of prospective studies about early discharge after acute myocardial infarction.

re-MI = recurrent myocardial infarction; LVEF = left ventricular ejection fraction; Uncompl = uncomplicated; Rhythm = rhythm abnormalities; CHF = congestive heart failure; other = among other things: pericarditis, infarct extension, diabetes, non-cardiac medical problems, age.

Author	Year	N	Uncompl (%)	Proposol early discharge (days)	Exclusion criteria (cardiac)
Mc. Neer-1[3]	1975	522	51	5	re-MI, HF, rhythm- and conduction disorder
TAMI[31]	1991	708	30	4	re-MI, HF, rhythm- and conduction disorder, sinusbradycardia, angina
Sanz-1[6]	1993	406	35	4	re-MI, HF, LVEF > 40%, rhythm- and conduction disorder, angina, pericarditis, non Q-wave infarction, thrombolytic treatment, bypass surgery
GUSTO-I[7]	1996	41 021	57	4	re-MI, HF, rhythm disorder, angina, bypass surgery, emergency angiogram
De Luca[47]	2004	1791	61	< 48 hrs	reocclusion, HF, IABP, rhythm- and conduction disorder, cardiac surgery, pericardial effusion, Zwolle Risk Score ≥ 4 (= 30-day mortality > 0.5%)
Kinjo[48]	2005	3739	20	8	cardiogenic shock, HF, re-MI, angina, ventricular septal perforation, severe mitral regurgitation, cardiac rupture, rhythm- and conduction disorder, left main coronary artery disease, bypass surgery, percutaneous cardiopulmonary support, IABP, mechanical ventilation, prior MI, LAD disease, failed primary PCI
INSPIRE[49]	2006	728	32	?	cardiogenic shock, HF, sustained VT/VF > 24 hrs, angina, primary PCI, LBTB

Table 2.2 Review of retrospective studies about early discharge after acute myocardial infarction.

Year = year of publication of article. Uncompl = uncomplicated; re-MI = recurrent myocardial infarction; LVEF = left ventricular ejection fraction; IABP = intra-aortic balloon pump; HF = heart failure; LAD = left anterior descending artery; PCI = percutaneous coronary intervention.
Zwolle Risk Score with independent predictors of 30-day mortality including: age, anterior infarction, Killip class, ischaemic time, post procedural TIMI flow and multivessel disease.

Reperfusion therapy

In the eighties reperfusion therapy was introduced in the acute phase of MI. Thrombolytic therapy administered in the early hours of an acute MI reduces mortality and infarct size and results in better preservation of left ventricular function.[45]

The ICIN study showed improved survival after early thrombolysis in acute myocardial infarction.[4] From 1981 to 1985, 533 patients with confirmed myocardial infarction were included. These patients with a mean age of 56 years (< 71 years) were admitted to the CCU within 4 hours after symptom onset with a median of 90 minutes. Streptokinase (intracoronary or intravenous and intracoronary) was administered in 269 patients. The clinical course was much better in patients allocated to thrombolytic therapy compared to the control group. Mortality rates at 28 days were 6% and 12%, respectively. Cumulative survival at 1 year was 91% after thrombolysis versus 84% in the control group. Event-free survival without re-infarction was similar in both groups (78%). In patients without pre-treatment with streptokinase intravenously 82% of the infarct-related vessel was occluded and re-canalisation was achieved in 79%. After intravenous streptokinase the infarct-related vessel was occluded in 59% and re-canalisation was achieved in 78%.

The GISSI study, reported in 1986, was an open trial of intravenous or conventional therapy streptokinase in 11 806 patients with acute myocardial infarction within 12 hours after symptom onset.[5] At 21 days overall hospital mortality was reduced significantly by 18%: 10.7% in streptokinase recipients compared to 13.0% in the control group. Effectiveness of Streptokinase was only measured by hospital mortality figures. The extent of the beneficial effect appeared to be a function of time from onset of pain and streptokinase administration, with greater effect for earlier therapy. At 12 months follow-up the significant difference in mortality was maintained: 17.2% in the streptokinase group compared to 19.0% in the controls.[6]

The ISIS-2 reported 17 187 patients with acute myocardial infarction who where treated by four different treatment regimens.[7] One group received Streptokinase, a second group received aspirin, another group received both and the last group received neither. A reduction of 24% in 5-week mortality was seen in the Streptokinase group alone (9.2%) and the aspirin group alone (11.8%). Vascular deaths among allocated patients were both 8%. There was evidence of benefit from each agent even for patients treated late after onset of pain. Even, after the median follow-up of 15 months the differences in vascular and all-cause mortality produced by Streptokinase and aspirin remained highly significant.

In 1993 in 41 021 patients with evolving myocardial infarction, the GUSTO study, showed mortality reduction in four different treatment groups. Mortality figures were as follows: Streptokinase and subcutaneous heparin 7.2%; Streptokinase and intravenous heparin 7.4%; accelerated t-PA and intravenous heparin 6.3%; and the combination of both thrombolytic agents with intravenous heparin, 7.0%. This represented a 14% significant reduction in mortality for accelerated t-PA versus previous standard thrombolytic regimen of Streptokinase.

Zijlstra et al. showed comparative efficacy of thrombolytic drugs and primary angioplasty.[8,9] After 31 months of follow-up primary angioplasty compared to Streptokinase resulted in decreased cardiac mortality (5 versus 11%, respectively) as well as less re-infarction and increased left ventricular function.

These and several other studies have established that timely reperfusion therapy in patients with evolving myocardial infarction (1) restore myocardial perfusion in the area at risk, thereby (2) limits infarct size, (3) preserves left ventricular function and (4) improves outcome.[10] Groups of patients with increased benefits have been established.[11,12] Such risk-benefit assessment may help in selected patients for specific mode of reperfusion therapy (Streptokinase, r-tPA and PTCA).

Early discharge after reperfusion therapy

Topol showed in 1988 that it is possible to discharge a selected group of myocardial infarction patients after 3 days.[13] Patients were defined as uncomplicated if they had proven reperfusion after thrombolytic therapy and a negative thallium exercise scintigraphy on day three (35%). These uncomplicated patients were randomised into two groups. The early discharge group was sent home at day 3 and the reference group was discharged after seven to ten days. Only 18% of all patients were discharged as early as 3 days. No differences were observed in complications between the two groups at three-month follow-up.

To develop a decision rule for early discharge it is necessary to investigate the most important risk factors for early complications (Table 2.3). Important clinical features for complications after myocardial infarction have been described in several large trials.[33-35,37,39-44] The most important risk factors for early complications are shown in Table 2.3. Every risk factor has its estimated prevalence and contribution to early or late mortality. Some relatively common parameters are associated with high mortality risk: older age, heart failure, previous myocardial infarction, anterior infarction and right ventricle infarction. The significance of arrhythmias remains controversial.

Some studies used multivariate analysis to identify independent predictors for short-term complications to select patients for early discharge after myocardial infarction. In a retrospective study of 6746 patients aged below 65 years, Parsons et al developed a regression model for predicting survival at 28 days after myocardial infarction based on: heart rate $\leq$ 100 beats/min, age $\leq$ 60 years, no diabetes, no previous history of myocardial infarction, and no Q-wave on the admission electrocardiogram.[14] This prognostic model had a specificity of 95% and a sensitivity of 33%. One third of the patients were classified in the low risk group according to the chosen model and these patients had a 99.2% chance of survival at 28 days. Patients in this group should be considered for early discharge. The model has not been prospectively validated.

Sanz et al. used a multivariate model in a group of patients characterized by a Q-wave infarction not treated with thrombolytic therapy (Table 2.2).[15] Patients free from complications on the fourth day were eligible for early discharge (n=142; 40%). In

multivariate analysis, diabetes, low ejection fraction and elevated age, showed to be independent predictors for major complications in this cohort. During validation of this decision rule post infarction angina was added to the model (Table 2.1). This risk stratification also had a high sensitivity (91%) but a low specificity (34%). Prospective validation showed that only 13% of all patients admitted with MI were classified at low risk group and eligible for early discharge according to this model.

Wilkinson et al. described in 1995 the advantages and disadvantages of early discharge.[16] In their study of 608 myocardial infarction patients, patients were divided over two groups with and without heart failure. Major adverse events (death, recurrent myocardial infarction, unstable angina and secondary ventricular fibrillation) during admission were recorded at the time. The risk of major events in the first 10 days was 32.3% in patients with heart failure and 7.3% in those without. In patients eligible for early discharge the complication risk decreased beyond a certain point that may be acceptable for patient and physician. The authors emphasize that benefit must be weighted against the risk for every individual patient. Early discharge will have a slightly increased risk for a few patients and shortens time for rehabilitation, education and risk factor modification but on the other hand early discharge has also physical and psychological advantages.

The largest study is the retrospective analysis of the GUSTO-I investigators.[17] This sub-analysis showed that 57% of the patients are at very low risk with a low probability of cardiovascular complications or death beyond four days after admission. The GUSTO-I investigators concluded that this low risk group could be discharged 4 days after myocardial infarction. The low risk group is characterised by absence of the following complications during the first four days after myocardial infarction: re-infarction, heart failure, rhythm abnormalities, angina, bypass surgery or emergency angiogram.

Recently several prospective studies on early discharge in patients with acute MI treated with primary percutaneous coronary intervention (PCI) have been published (Table 2.1).[49,51,52] These studies select low risk patient groups with known prognostic factors for 30-day or 1-year mortality. Half of all MI patients treated with primary PCI have an uncomplicated in-hospital course. Nearly all selected, uncomplicated patients could be discharged after a surprisingly very short term varying between 1.5 and 4 days in the different studies. The investigators found no difference in 30-day, 6-month or 1 year outcome between the usual care and the intervention group with much shorter hospital stay.

Prognostic factors	Prevalence	Prognosis
Age (>70 yrs)	30%	Mortality decreases with 8% per 10 year (ISIS-2)[32]
Prior infarction	15-20%	Mortality risk at least 1.5 x [33]
Diabetes	13-15%	Mortality risk 2 x increased (TAMI, GISSI-2)[34,35]
Anterior infarction	35-40%	Mortality risk approximately 50% increased (GISSI)[36]
Right ventricular infarction	15%	Inferior infarction with right ventricle extension gives up to 5 times increased in-hospital mortality[37]
Intracranial haemorrhage	1%	Intracranial haemorrhage has a 50% mortality[38]
Re-infarction	2-5%	Mortality risk approximately 4 x increased (SPRINT)[39]
Heart failure (Killip > II)	15-20%	Mortality risk 6 x increased (TIMI-2)[40]
Early VT/ VF (< 24uur)	7%	Early mortality increased; no influence on long term outcome (TIMI-2)[41]
Late VT/ VF	2%	At least 2 x increased risk of sudden death after discharge[42]
Heart block	8%	2 x increased in-hospital mortality risk (Worcester)[43]
Early ischaemia	20%	10 x increased risk of re-MI or intervention during hospital stay (GISSI-2)[44]

Table 2.3 Well known prognostic factors and their mortality risk.

Killip class I to IV: class I no clinical signs of heart failure; class II diagnostic criteria include: rales; class III diagnostic criteria include: S3 gallop and venous hypertension, frank pulmonary oedema; class IV cardiogenic shock. VF, ventricular fibrillation; VT, ventricular tachycardia.

CONCLUSIONS

Due to better pathophysiological knowledge and new medical (for example thrombolytics) and interventional treatment modalities (including PCI or bypass surgery) the prognosis of patients with MI has improved significantly. Due to this progress the average hospital stay for patients with myocardial infarction has decreased with 55% from 17.6 to 8 days in the Netherlands (Figure 2.1, resource: 'Prismant, Landelijke Medische Registratie' 2007). It is reasonable to assume that further diagnostic or therapeutic developments will lead to further decrease of hospital stay.

Although many studies have been published on early discharge after acute myocardial infarction these have some limitations. First, most previous studies were small and did not

represent a complete infarct population. The number of patients selected for early discharge was low. Second, decisions for early discharge were often based on factors derived at admission or within the first hours after admission. Some investigators used additional tests like an angiogram or thallium scintigraphy to discharge patients as early as three to six days after myocardial infarction were needed in some studies. Finally the larger studies are only retrospective and have not been prospectively validated.

In conclusion a prospective study is needed which develops a decision rule that can be widely used in a non-selected patient group using simple clinical characteristics. Prospective validation should show that the model works and that it is applicable to a large group of patients that can be discharged early. Early hospital discharge may improve utilization of health care resources at considerable cost savings.

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3

Prospective study of early discharge after acute myocardial infarction (SHORT)

Maureen J. van der Vlugt[1]
Eric Boersma[1]
Ineke M. Leenders[2]
Gheorghe A. M. Pop[3]
Rinus J. Veerhoek[4]
Maarten L. Simoons[1]
Jaap W. Deckers[1]

[1]Thoraxcenter, Erasmus Medical Center, Rotterdam
[2]Haven Hospital, Rotterdam
[3]Vlietland Hospital, Vlaardingen
[4]Sint Franciscus Gasthuis, Rotterdam
The Netherlands

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ABSTRACT

Aims

To identify, without additional investigation, a large group of myocardial infarction patients at low risk who would qualify for early discharge.

Methods

The decision rule was developed in 647 un-selected patients with consecutively admitted myocardial infarction, and validated in 825 others. Daily event-rates were calculated for major (death, ventricular fibrillation, recurrent infarction, heart failure, advanced AV-block) and minor (unstable angina and rhythm-abnormalities) cardiac complications.

Results

Patients free from major complications until day 7 (44% of all patients) were found to constitute a very low risk group and thus would qualify for discharge at day 7. Of the 39% of patients with an uncomplicated infarction (low risk) in the validation group, 31% were discharged at day 7, while 8% stayed longer because of non-cardiac co-morbidity, for social reasons or logistic problems. No major adverse event occurred within 7 days after hospital discharge and only 1.8% developed complications within 1 month. The median duration of hospital stay for all in-hospital survivors was 7 days compared to 10 days in the control group.

Conclusions

Prospective application of the early discharge decision rule, based upon simple clinical variables and without the need for additional non-invasive and/or invasive tests, resulted in a significant reduction of hospital stay. The decision rule correctly classified patients into high and low risk groups and appeared feasible and safe. Its efficacy was demonstrated by its ability to identify a large group of post infarction survivors at low risk for complications during follow-up.

INTRODUCTION

Management of patients with acute myocardial infarction continues to evolve. Early reperfusion therapy limits infarct size, preserves left ventricular function and thus reduces post-infarction complications such as heart failure, secondary (late) ventricular fibrillation and death.[1,2]

Early discharge of infarct patients is cost effective, and may be beneficial for physical as well as psychological betterment. A first step towards a reduction in hospital stay was made in 1952 by Levine and Lown with the introduction of 'armchair treatment'.[3] At that time, early mobilization and rehabilitation of the infarct patient was of particular interest, not the early discharge policy itself. During the following decades, the hospital stay of patients with myocardial infarction has been reduced gradually from an average of more than 6 to less than 2 weeks. Nowadays patients are mobilized within 24 h and early discharge management is of major interest compared with early mobilization.

In selected myocardial infarction survivors, discharge on day 3 may be an option, for instance in the presence of proven reperfusion and negative thallium exercise scintigraphy. Also, patients who have undergone successful direct PTCA with proven reperfusion can be discharged as early as 2 days after PTCA.[4] Other myocardial infarction patients with or without reperfusion therapy and an uneventful course can also be discharged relatively early. A third group of patients requires longer hospitalization to allow for stabilization of heart failure and/or planning of invasive therapy. Furthermore longer in-hospital observation is warranted in patients at increased risk for sudden life threatening complications, such as late ventricular fibrillation, cardiac arrest or re-infarction.

Recently, the GUSTO-I trial identified, on the basis of simple clinical variables, a group of low-risk post-infarction patients treated with thrombolytic therapy.[5] Presumably, such patients could be discharged safely by hospital day 4 with a very low complication risk. The results of this GUSTO substudy are promising but retrospective and applicable only to a minority of infarction patients, namely those treated with thrombolytic therapy.

In contrast, the aim of the present study (SHORT: acronym for Short Hospital Rehabilitation Trial) was to develop and validate prospectively an early discharge decision rule suitable for all or most myocardial infarction patients and widely applicable in clinical practice. The decision rule is based on clinical assessment without the need of pre-discharge exercise testing or other non-invasive or invasive tests.

METHODS

Patients and data collection

The SHORT study consisted of two parts. First, a decision rule was developed to identify patients for early discharge using data from all patients consecutively hospitalized for acute myocardial infarction between May 1993 and May 1994 in three community hospitals and one tertiary referral hospital. Subsequently, the rule was validated in the same four hospitals from November 1994 until November 1995.

All patients (n = 1472) hospitalized within 24 h after onset of symptoms because of a confirmed myocardial infarction were eligible. The clinical diagnosis myocardial infarction was confirmed by the presence of creatine1 phosphokinase levels of at least 200 U/L (approximately twice the normal level in all hospitals), but no specific ECG inclusion criteria were required. Patients with a history of acute ischaemia and electrocardiographic evidence of transmural infarction, who received thrombolytic therapy but did not develop abnormal enzyme levels, ('aborted infarctions') were also eligible as were patients transferred to one of the study hospitals within 24 h following admission at another hospital. Patients who developed an infarction while in hospital were also included. Some patients (3% of all infarcts) had an infarction during or shortly following PTCA.

Medical history and cardiovascular risk profile at admission were recorded in each subject. In addition, the following parameters were registered during each subsequent day in hospital: presence of angina, clinical evidence of heart failure, rhythm abnormalities, blood pressure, heart rate and (cardiovascular) medication. Electro-cardiograms at admission and discharge were evaluated to determine the site of the infarction. Routine monitoring of the patient's heart rhythm was limited to their stay at the CCU. Results from non-invasive tests and invasive procedures were registered, although such procedures were not required. Complications, (invasive) procedures and re-admissions that occurred within the first month after admission were also collected.

Data-analysis

To develop a decision rule for early discharge, univariate and multivariate analyses were employed to predict short term mortality and other complications as defined hereunder. In these analyses, the following variables known to affect prognosis adversely were considered: age over 65 years, female gender, prior myocardial infarction, diabetes, peak creatine phosphokinase level, heart failure, anterior infarction.[6] In-hospital complications were ranked hierarchically as major in case of death, cardiac arrest, recurrent infarction, heart failure (defined as Killip class II, III, IV)[7] and advanced AV block, and as minor in the presence of recurrent ischaemia (chest pain with ECG changes) requiring intravenous administration of nitroglycerin and symptomatic ventricular or atrial tachycardia of at

least 30s duration. Daily new event rates were calculated, defined as the ratio of patients with complications occurring at a specific hospital day and those without complications until that day, as well as freedom from new events. From these data a decision rule was developed which distinguished patients with a very low incidence of major events during the subsequent course (candidates for early discharge) and those at higher risk requiring additional investigation or therapy.
In the second part of the study, all patients categorized at low risk (defined as absence of factors with negative prognostic impact) were eligible for early discharge and attempts were made to discharge such patients in the morning of the 7th day. If an uncomplicated patient was not discharged on that day, the reason for overruling the protocol was specified. Complications were assessed during the 1 month follow-up.
The day of hospital admission was defined as day 1. Because the first and last hospital day combined comprised on average approximately 24 h of hospitalization, the length of hospital stay was calculated by subtracting the date of discharge from the date of admission.

RESULTS

Characteristics of the registration (n = 647) and the validation (n = 825) groups are presented in Table 3.1. The subjects represented a typical population of unselected patients with myocardial infarction. Ages ranged from 22 to 95 years. Both groups were similar in baseline features, risk factors and previous history. Thrombolytic therapy was administered in approximately 40%. Coronary angiograms were made in 22-25% of patients, half of these resulted in PTCA and a quarter in bypass surgery during the same hospitalization. In-hospital mortality was 11% and 12%, respectively. Recurrent infarction was observed in 5% in both cohorts.

Development of decision rule

In univariate analysis, the strongest predictors for mortality by 1 month were the presence of heart failure (Killip class $\geq$ II) and age over 65 years (Table 3.2).
Mortality risk was lower in patients treated with thrombolytic therapy. In multivariate analysis, heart failure was the major determinant of a fatal outcome. The association of heart failure with poor outcome remained significant when ventricular fibrillation and recurrent myocardial infarction were added as end-points. The presence of chest pain and ventricular or supraventricular tachycardia during days 1 and 2 were not predictive of subsequent major complications and these symptoms were considered subsequently only if they developed on day 2 or thereafter.

	Registration set	Validation set
Number of patients	647	825
Females (%)	28	34
Mean age (years) (range)	65 (22-91)	65 (31-95)
Age < 60 years (%)	30	33
Age > 80 years (%)	10	14
History (%)		
Angina > 4 weeks	24	23
Prior MI	32	29
Risk factors (%)		
Current smokers	40	39
Diabetes	14	13
Hypertension	26	31
Hospitalization (%)		
Thrombolytic treatment	40	41
Anterior infarction	41	38
Inferior infarction	41	44
Procedures (%)		
Angiogram	25	22
PTCA	12	11
CABG	6	6
In-hospital mortality (%)	11	12

Table 3.1 Characteristics of the two groups of myocardial infarction patients.

Not surprisingly, event rates were highest early following hospitalization (Table 3.3). On the first day, 40.5% of the patients experienced a major complication, most often heart failure. The event rate subsequently declined and the rate of new major complications was below 1% on day 6. The rate of all new events (major and minor) was below 1% at day 8 and beyond. The number of patients without major events at the beginning of day 7 amounted to 44% of all patients admitted, and to 47% of those alive by day 6.

1 month outcome

None of the 284 patients without complications by day 6 died during the 1 month follow-up. Their rate of major complications (re-admission for recurrent myocardial infarction or heart failure) in this time period was only 1.4%. Re-admission for minor complications was required in 7.0%: because of elective intervention in 2.8%, for angina pectoris in 2.1% and related to non-cardiac morbidity in 2.1%.

Validation of the decision model

Application of the decision rule in clinical practice involved identification of patients without initial (major) complications in the morning of day 3. These patients were scheduled for early discharge if no complications would occur prior to that time.

	Relative risk for in-hospital mortality				Relative risk for death or VF or re-MI			
	Univariate		Multivariate		Univariate		Multivariate	
	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
Killip > I	9.0	(4.7-17.3)**	7.7	(4.0-15.1)**	5.2	(3.4-7.9)**	5.0	(3.3-7.7)**
Age > 65 years	3.2	(1.8-5.7)	2.0	(1.0-3.8)	1.8	(1.2-2.6)	1.3	(0.9-2.1)
Female sex	1.6	(0.9-2.8)	1.2	(0.7-2.3)	1.1	(0.7-1.7)	1.0	(0.6-1.7)
Prior MI	1.3	(0.7-2.2)	1.2	(0.6-2.2)	1.3	(0.9-1.9)	1.3	(0.8-2.0)
Anterior MI	1.2	(0.7-2.1)	1.2	(0.7-2.2)	1.1	(0.8-1.7)	1.1	(0.7-1.6)
Diabetes	1.1	(0.5-2.3)	0.8	(0.4-1.8)	0.9	(0.5-1.6)	0.7	(0.4-1.3)
Thrombolysis	0.5	(0.6- 99)*	0.6	(0.3-1.2)	1.1	(0.7-1.6)	1.2	(0.8-1.9)

Table 3.2 Predictors for in-hospital death and death/ ventricular fibrillation/ recurrent myocardial infarction in 647 myocardial infarction patients (registration group).

VF = ventricular fibrillation; MI = myocardial infarction
**P<0.001
*P<0.05

	Hospital day												Total events
	1	2	3	4	5	6	7	8	9	10	11	12	(%)
Patients with no events	647	385	354	316	297	289	284	279	277	275	272	272	
% of patients with no events	100	60	55	49	46	45	44	43	43	43	42	42	
Mortality	18	-	-	-	-	-	-	-	-	-	-	-	9.6
VF	43	1	-	2	-	-	-	-	-	-	-	-	9.0
re-MI	1	1	5	4	2	1	-	-	-	-	-	-	4.6
Killip II / III / IV	191	28	12	3	2	1	-	1	-	-	-	-	45.4
AV block	9	1	3	-	-	-	-	-	-	-	-	-	5.6
AP			12	6	2	3	1	1	-	3	-	1	22.4
VT			-	-	-	-	2	-	-	-	-	-	8.8
SVT			6	4	2	-	2	-	2	-	-	-	16.2
Total events	262	31	38	19	8	5	5	2	2	3	0	1	58.1
Daily new event rate (%)	40.5	8.1	10.7	6.0	2.7	1.7	1.8	0.7	0.7	1.1	0	0.4	74.4
New major events (%)	40.5	8.1	5.6	2.8	1.3	0.7	-	0.4	-	-	-	-	59.4
New minor events (%)	(4.9)	(7.4)	5.0	3.2	1.3	1.0	1.8	0.4	0.7	1.1	-	-	26.8

Table 3.3 First events in 647 patients of the registration set.

Major events = death, ventricular fibrillation, re-infarction, heart failure, advanced AV-block.
Minor events = unstable angina, ventricular- and supraventricular tachycardia.
Total events: only first event counted for heart failure, AV-block, supraventricular tachycardia; all events counted for VF, re-MI, AP, VT.
VF = ventricular fibrillation; re-MI = re-infarction; AV = atrioventricular; AP = angina; VT = ventricular tachycardia; SVT= supraventricular tachycardia.

Author	Year	N	Uncompl (%)	Early discharge (%)	Length of hospital stay		Other cardiac reasons for prolonged stay				
					Reference	Early discharge	Re-MI	CHF	Rhythm	Ischaemia	Other
Groden[13]	1966	105	54	39	36	22					
Harpur[14]	1970	262	76	36	28	15		✔	✔		✔
Hutter[15]	1971	925	15	7	21	14		✔	✔	✔	✔
Abraham[16]	1974	129	25	50	19	12		✔	✔	✔	
Lindvall[17]	1978	202	21	19	19	9	✔	✔	✔	✔	✔
Hayes[18]	1973	268	58	38	16	9		✔	✔	✔	
Ahlmark[19]	1978	383	54	28	15	8		✔	✔	✔	✔
Gelson[20]	1975	405	57	67	>8	8		✔	✔		✔
McNeer[21]	1976	158	42	21	11	7	✔	✔	✔		
Boyle[22]	1971	295	62	18	>9	7		✔	✔	✔	✔
Chaturvedi[23]	1972	275	40	38	9	7		✔	✔	✔	✔
Lau[24]	1978	319	43	39	12	6		✔	✔	✔	✔
Sanz[25]	1988	200	34	9	12	4	✔	✔	✔	✔	✔
Topol[4]	1987	507	35	18	7-10	3		✔	✔	✔	

Table 3.4 Review of prospective studies on early discharge after acute myocardial infarction.

Re-MI = re-infarction; LVEF = left ventricular ejection fraction; uncompl = uncomplicated; Rhythm = rhythm abnormalities; CHF = congestive heart failure; other = amongst others: pericarditis, infarct extension, diabetes, non-cardiac medical problems, age.

The decision rule was validated in 825 patients consecutively admitted to the same four hospitals during a 12-month period. Of the 750 patients that were alive by day 6, 319 (43%) were candidates for early discharge, of whom 252 (34%) were actually discharged on the morning of day 7 (hospital stay 6 days). The major reasons for non-compliance with early discharge were logistic factors (4.9%), non-cardiac co-morbidity (1.9%), non-infarct related cardiac problems (0.8%) and social (0.5%) factors. The total number of patients discharged at or prior to day 8 was 282, and 295 for discharge at or prior to day 9 (88% and 92% of the 319 low-risk patients, respectively). The cumulative distribution of patients discharged is presented in Figure 3.1. None of the patients who qualified for early discharge died during the 1-month follow-up. The rate of major complications (re-admission for recurrent myocardial infarction or heart failure) was 1.8%. Re-admission for minor complications was necessary in 4.7%.

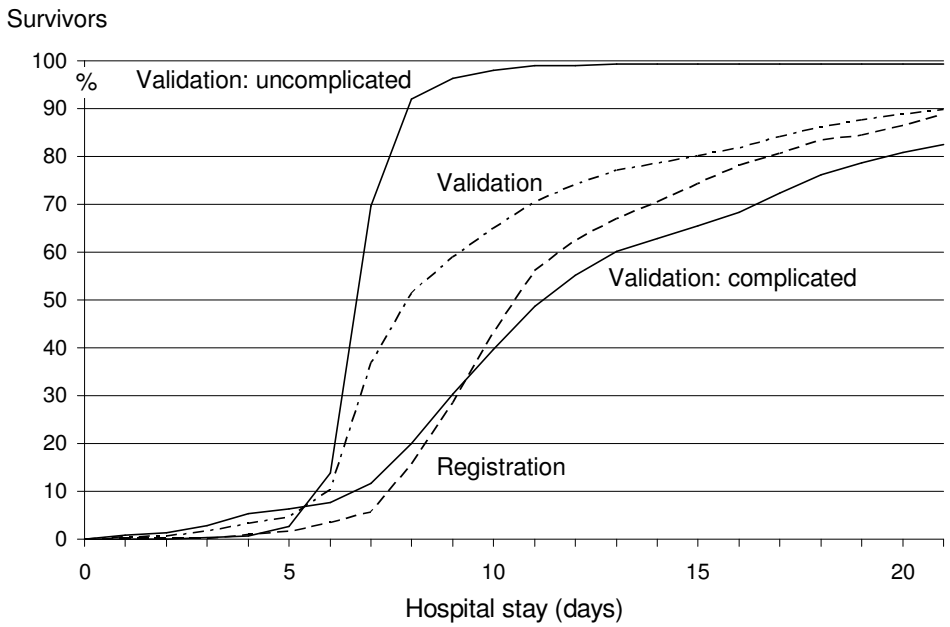

Figure 3.1 Length of hospital stay in number of days for patients with a myocardial infarction before (registration) and after (validation) the application of the early discharge algorithm, as well as for patients from the validation phase with a complicated and uncomplicated myocardial infarction.

Length of hospital stay

In the first part of the study, the median number of days spent in-hospital by the low risk group was 9 days. This was reduced by 33% to 6 days in the second part of the trial (Figure 3.1). The median time spent in hospital by all patients in the registration group was 10 days, which was reduced to 7 days in the validation set.

DISCUSSION

Early discharge after acute myocardial infarction remains a subject of considerable interest due to changes and improvements in the management of myocardial infarction patients. This is even more true now that need for efficiency is a major topic in current health care management and physicians have to justify their management and treatment both medically as well as financially.[8] Hospital length of stay is the most important determinant of total cost.

During the last decades, the mean length of hospital stay of patients admitted with acute myocardial infarction has been reduced dramatically. In the early 1950s, when it became known that necrotic myocardium needs 6 weeks to organise itself into a scar,[9] the hospital stay was as long as 8 weeks. In 1952 Levine and Lown pioneered to shorten hospitalization by introducing the so-called 'armchair treatment'.[4] This early mobilization procedure was the beginning of new rehabilitation programmes for patients with acute myocardial infarction. Since that time, series of observational studies and controlled trials tried to shorten hospital stay further (Table 3.4). As a result, the length of hospital stay has decreased to less than 6 days in patients with no complications in the U.S.A. In European countries, hospital length of stay has decreased more slowly. In The Netherlands in 1995, the mean duration of hospitalization amounted to 10·9 days for all infarct patients, hospital survivors and non-survivors included[11]. In the early 1950s, early mobilization was a major point of interest in contrast to early discharge at the present. Nowadays patients admitted with acute myocardial infarction are hardly immobilized so there is little need for elaborate mobilization programmes, particularly not for uncomplicated myocardial infarction patients. Prolonged hospitalization should only be necessary for patients with uncontrolled symptoms and/or other findings.

Which patient candidate for early discharge?

Most investigators do agree on the clinical parameters associated with favourable or poor outcome. Patients admitted for acute myocardial infarction are candidates for early discharge if they have no congestive heart failure, no persistent major rhythm abnormalities and no recurrent ischaemia (Table 3.4). These same clinical variables were also used for the decision model in the present study. Some investigators added a few parameters to their discharge policy but the requirement for expensive or complex tests like thallium scintigraphy or coronary angiography limits the general applicability of such models. In our perception, a decision model works best if it is applicable to a relatively unselected group of patients and can be applied without additional non-invasive or invasive tests. The aim of the SHORT study was to develop and validate a decision rule which is applicable to a large group of myocardial infarction patients in hospitals with different resources. Candidates for early discharge are patients at low risk for short term complications. This group of patients can be selected easily by simple clinical variables. The algorithm, with its clinical criteria and decision moments, is depicted in Figure 3.2. In

practice, almost 50% of in-hospital survivors are eligible for early discharge as shown in this study. This compares favourably with most other studies (Table 3.4), which were often limited to selected patient groups, for example proven reperfusion, non-Q wave infarction or reperfusion therapy.

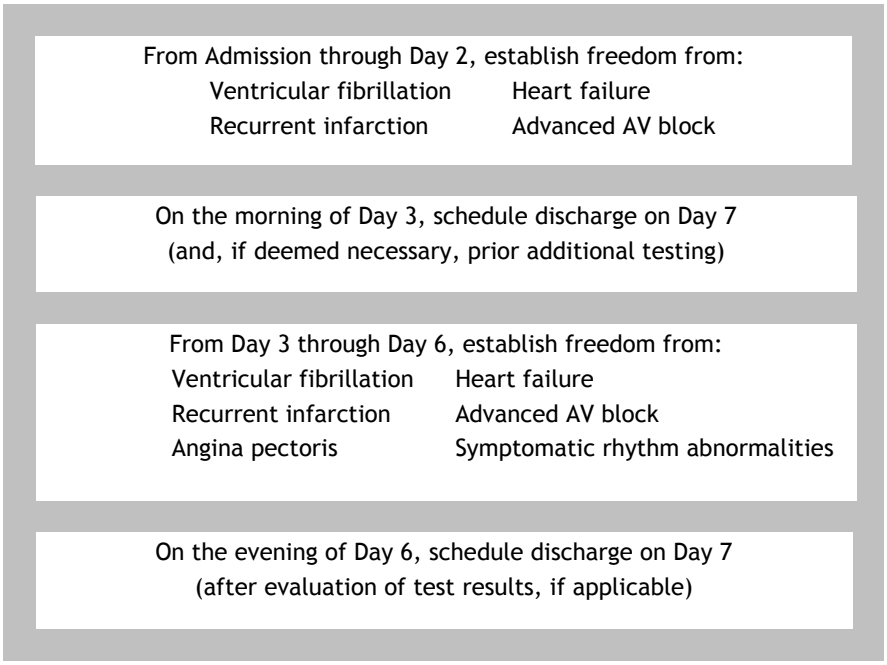

Figure 3.2 The algorithm for early discharge after myocardial infarction.

What is early: 5 or 7 days?

The most recent report on this topic is a retrospective analysis of the GUSTO-I data. These investigators showed that, on the basis of simple clinical features, 57% of these patients were at very low risk for cardiovascular complications beyond 4 days after admission. Accordingly, this low risk group would be eligible for early hospital discharge at day 4 which, due to another method of calculating the duration of hospitalization, would be comparable to discharge at day 5 day according to our method of counting. The SHORT study proposed and validated a decision rule for all infarct patients, with or without reperfusion therapy (40% thrombolytic treatment), where early discharge candidates leave hospital in the morning of day 7, after a hospital stay of about 6 days. The difference in hospital stay between these two studies of one day seems reasonable in view of the slightly higher risk population in the SHORT study. For clarity's sake, it should be noted that the definition and calculation of length of hospital stay are seldom described in the

various publications. Often one or two more days need to be added to the figure provided when the day of admission and discharge are counted as in the present study. Before the SHORT study started, most physicians practising in the participating hospitals believed that a considerable number of patients were already being discharged at day 6. However, the results of the first part of the SHORT study demonstrated a major gap between opinion and reality in clinical practice.

Preparing patient for early discharge?

The moment of selection of uncomplicated myocardial infarction patients eligible for early discharge is very relevant. In the literature this varied from preliminary decisions at admission until the 6th day. An important restriction of many studies is the fact that assessments were made at admission only, and that therefore important complications that develop in the course of the hospitalization, such as ventricular fibrillation, recurrent myocardial infarction, heart failure and post-infarction angina, could not be taken into account. As shown in the present study, the rate of these events is high during the first 2 days and a considerable proportion of presumed uncomplicated patients at admission would have an event during the first days. Continuous clinical monitoring and evaluation of patients, as in the SHORT trial, provides very powerful prognostic information and allows better selection of patients at high and low risk than a decision shortly after admission.

In the SHORT study, patients eligible for early discharge were selected on the morning of day 3, which often is the day of transfer from a high care to a medium care or step-down unit. Over 80% of patients uncomplicated at day 3 remained uncomplicated and were candidates for early discharge at day 7. In the days between selection and discharge simple tests like echo and exercise test can be performed. However, in these uncomplicated patients an exercise test has little prognostic value and might safely be performed in an out-patient setting, for example 1 week after discharge. This practical approach would also settle any scheduling problems during admission. However, in order for an early discharge policy to work, continuous attention and efficient scheduling on a day-to-day basis is required.

Early discharge triage

Until quite recently, the management of myocardial infarction consisted of observation and treatment of complications. Due to better pathophysiological insights and new active treatment modalities, the prognosis of these patients has improved significantly. It is reasonable to assume that future therapeutic developments will improve prognosis further, and it is clear that more effective stratification will decrease the duration of hospitalization further.

Three groups of patients may be distinguished with different length of hospital stay. First, angiography and direct PTCA after acute myocardial infarction give insight into the patency of the coronary vessel and extent of coronary artery disease. Risk stratification

can easily be performed on the basis of these findings. Although direct PTCA is only performed in a minority of myocardial infarction patients, patients with successful PTCA can be discharged shortly after the intervention and those with a patent coronary vessel are also candidates for very early discharge[12].

A second group of patients, with or without reperfusion therapy, can safely be discharged after acute myocardial infarction by day 7 if their hospital course is uncomplicated by day 6 as demonstrated. Patients who experienced a major complication during the first 2 days after myocardial infarction require further observation. If the current findings in patients with an uncomplicated course are extended, complicated patients could be discharged if they are free of major complications (chronic heart failure, serious rhythm abnormalities) for at least 3 subsequent hospital days, or after a revascularization procedure, if appropriate.

Benefit must be weighted against the risk for every patient. Early discharge may confer physical and psychological advantages in addition to financial savings, but may also carry a slightly increased risk for a few patients. Nurses and physical therapists may indicate that early discharge shortens time for rehabilitation, education and risk factor modification during hospitalization. However, rehabilitation is usually not required in early discharge patients, and attention to risk factor modification should continue beyond hospitalization.

We believe that application of formal decision rules, as described, will lead to more efficient use of hospital resources and increase physical and psychological well-being of the patient. The proposed and tested decision rule was shown to be applicable in all myocardial infarction patients with simple clinical characteristics and is thus a powerful tool for efficient management of patients with myocardial infarction.

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4

Length of hospital stay after uncomplicated acute myocardial infarction in Europe can be significantly reduced: Observations from the Euro Heart Survey of Acute Coronary Syndromes. The Euro Heart Survey of Acute Coronary Syndromes (Euro Heart Survey ACS)

Maureen J. van der Vlugt[1]
Sanne E. Hoeks[1]
Wilma Scholte op Reimer[1]
David Hasdai[2]
Alexander Battler[2]
Lars Wallentin[3]
Anselm K. Gitt[4]
Uwe Zeymer[4]
Frans van de Werf[5]
Eric Boersma[1]
Maarten L. Simoons[1]

[1]Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands.
[2]Rabin Medical Centre, Petah Tikva, Israel.
[3]University Hospital of Uppsala, Uppsala, Sweden.
[4]Herzzentrum Ludwigshafen, Ludwigshafen, Germany.
[5]University Hospital Gasthuisberg, Leuven, Belgium.

Submitted

ABSTRACT

Aims

Efficient use of medical resources is a priority for society. Evidence exists that hospital stay might still be too long after uncomplicated MI. The aim was to study the length of hospital stay in patients with an uncomplicated MI across Europe, and to identify those patients who are eligible for earlier discharge.

Methods and Results

During 2001 the Euro Heart Survey of ACS enrolled 6086 patients with acute MI, mean age 65 years. Serious post MI adverse events were recorded. For each day after admission we determined the daily event rate. The median length of hospital stay was 9 days (6-13). During the first 6 hospital days the event rate decreased from 34.3% to 1.9% at day 6. From day 7 on daily event rates stabilized around 1.0 to 1.5%. After primary PCI event rate stabilised below 1.5% from day 4. Yet, at day 7 still 40% of all patients were admitted, eligible for early discharge. If early discharge would be achieved 20% of all days spend in hospital might have been avoided.

Conclusions

Current guidelines recommend discharge within 4 days for patients with uncomplicated MI. Our data suggest that this is appropriate after primary PCI, but might be too early in others, since event rate continued to decrease beyond this 4-day period. However, even if patients would be discharged at day 7 a considerable reduction in length of hospital stay can be achieved compared to current practice with an acceptable small risk that might contribute to a significant reduction in costs.

INTRODUCTION

Early hospital discharge after uncomplicated MI has been of interest for over 25 years.[1,2] The search for further reduction in hospital stay is motivated by a general principle not to hospitalise unless clearly necessary, by the desire of health care payers to reduce expenses and is supported by the belief that part of the current hospitalization is due to inefficiency. Also early discharge has, especially in the elderly patient, positive psychological and physical consequences for the patient.[3] Accordingly, the European Society of Cardiology (ESC) and other organisations have formulated guidelines for the management of MI. These guidelines recommend patients with uncomplicated acute MI to be considered for early discharge within 4 days of admission.[4]

Indeed, early discharge of low-risk patients with acute MI has shown to be feasible and can be achieved at no additional risk of adverse events.[5-7] Patients can be discharged if: 1. No complications occurred so far requiring additional therapy; 2. The expected complication risk in coming days is low. After earlier complications discharge can be effectuated if problems are managed and stabilised.

Risk stratification for early discharge or prolonged hospitalization can be performed with non-invasive techniques like echocardiography and stress testing to estimate important prognostic factors as left ventricular function and ischaemia respectively. Our group developed and validated prospectively an early discharge decision rule that is suitable for all or most myocardial infarction patients and widely applicable in clinical practice. The decision rule is based on clinical assessment without the need of pre-discharge exercise testing or other non-invasive or invasive tests.[5-7] However nowadays, primary PCI, as the most effective reperfusion therapy, is performed in many patients with an early acute MI. In such patients when coronary anatomy and left ventricular function are known and re-infarction is infrequent, usually no further risk stratification is needed, such that discharge can be appropriate in an early stage.

In contrast, patients treated with thrombolysis have an open infarct related artery in approximately only 70% of the cases and are at increased risk for re-infarction.[8,9] In these patients more hospital days might be needed for further risk stratification with echocardiography and stress testing.[10]

The Euro Heart Survey Acute Coronary Syndromes (EHS-ACS) demonstrated the discordance between existing guidelines for ACS and current practice across a broad spectrum of hospitals in Europe.[11] In this report we assess the duration of hospital stay and the discharge policy in patients with acute MI in hospitals with different medical resources with focus on those patients with an uncomplicated course. Furthermore, we verify our earlier developed decision model for safe discharge policy of patients with an acute MI, and verify whether discharge policy should be adjusted to the mode of initial reperfusion therapy of any.

METHODS

The EHS-ACS enrolled 10484 patients from 25 countries in Europe in 103 hospitals with or without facilities for cardiac catheterization and cardiac surgery. The design and methods of the Euro Heart Survey for Acute Coronary Syndromes have been presented in detail.[11]

Patient population

In summary, between September 2000 and May 2001, in each hospital all consenting patients admitted during a period of up to 4 months were registered with a suspected acute coronary syndrome. Patients were included in the survey based on the initial diagnosis and classified according to the initial electrocardiographic pattern with or without persistent ST-segment elevation. At the end of the hospital stay a data collection officer recorded the discharge diagnosis in the following categories: Q wave MI, non-Q wave and unstable angina. For this study we focused on 6086 patients with a final diagnosis at discharge of Q-wave or non Q-wave MI.

Definition of event rate

For calculation of the daily complication rate we defined each complication per patient per day as described earlier.[5] Ten most common post MI complications were identified and ranked in order of clinical importance: death, cardiac arrest by asystole or ventricular fibrillation, ventricular tachycardia, heart failure / cardiogenic shock (Killip IV), re-infarction, severe heart failure (Killip III), high grade AV-block (2^{nd} or 3^{rd}), mild heart failure (Killip II) and recurrent ischaemia.[12] If a patient had more than one event within one day, the clinically most important event of interest was used. Daily new event rates were calculated, defined as the rate of patients with complications occurring at a specific hospital day. Furthermore, patients free from any of these complications until that hospital day were identified. The number of event-free patients at the beginning of a specific hospital day was calculated by: the number of event-free patients at the beginning of the preceding day subtracting from the number of patients having a new complication or discharged on this day.

Length of hospital stay

Calculation of the length of hospital stay was performed by subtracting the date of discharge from the date of admission, adding one. The day of admission as well as the day of discharge was counted as one hospital day each. The day of hospital admission was defined as day 1. Patients admitted after 9 p.m. were not counted for that hospital day. Time of discharge was assumed to be in the morning before 10 a.m. In-hospital death was treated as end of hospitalization (i.e. discharge) in the calculations.
Discharge of patients after MI might be considered if no complications have occurred which require additional in-hospital therapy, and as soon as the predicted daily event rate of new major complications stabilises at an acceptable low rate.

Statistical analysis

Statistical analysis was performed with the SPSS 10.1 statistical package. Continuous data were expressed as mean ± SD and discrete variables by percentages. The non-normal distribution of hospital stay was described by medians with 25th and 75th percentiles. For the predictive model ANOVA was used for continuous variables, and the chi-square test was used for categorical variables. Univariable and multivariable logistic regression analyses were applied to evaluate the relations between baseline demographic characteristics and the occurrence of in-hospital complications after 6 complication-free hospital days (i.e.: discharge at day 7). Furthermore, logistic regression was applied to recognise predictors for length of hospital stay before versus beyond day 7 (i.e. eligible day for discharge). All variables entered the multivariable stage, irrespective of the results of univariable analyses. The final multivariable model was constructed by stepwise backward deletion of the least significant characteristics associated with longer or shorter hospital stay than the eligible day of discharge (i.e. day 7). A probability value < 0.05 was considered statistically significant.

RESULTS

Patient characteristics were comparable with other registries (Table 4.1).[13,14] The majority of patients admitted with an acute MI had Killip class I (72.2%), and only 7.2% of the patients had Killip III or IV at admission. Reperfusion therapy within 24 hours after admission was administered in 39.7% of the patients (thrombolysis 25.6% and primary PCI 14.1%). Coronary angiography was performed in 52.9% of the patients at any time during the index admission for acute MI followed by PCI in 69.2% of these patients.

Length of hospital stay

Median hospital stay after MI was 9 days (Figure 4.1) with significant difference in median length of stay between patients received thrombolysis versus no lysis and primary PCI versus no PCI (p value < 0.001) (Figure 4.2). Three-quarter of all patients were discharged within 13 days, but only a minority of patients, only 21.5%, were discharged alive within 7 days (Table 4.2). Predictors known at admission for prolonged stay beyond day 7 from stepwise multivariable logistic regression model included: female gender, hypertension, diabetes, no prior PCI, history of valvular disease or peripheral vascular disease (Table 4.1). Paradoxically, Killip class III and IV were associated with a shorter hospital stay, because of high mortality in these patients during the first few days. Survivors after admission with serious heart failure or shock (n = 173) had a longer hospital stay (median 11, 25th and 75th percentiles 6 - 16 days respectively).

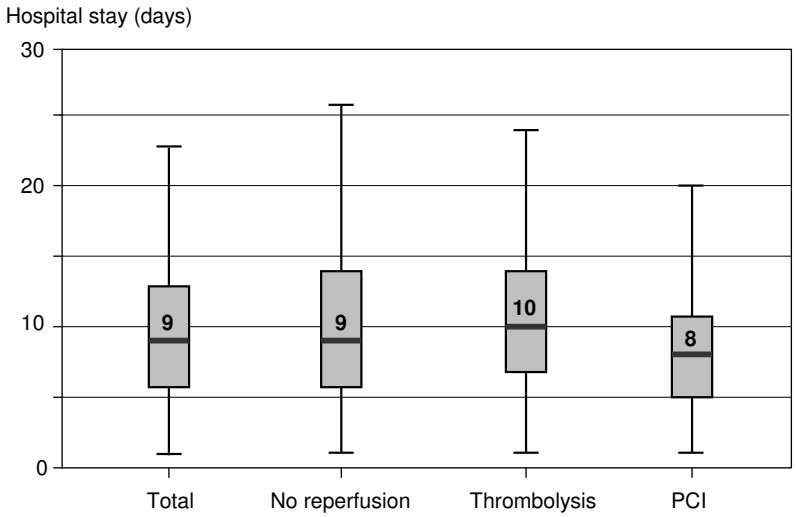

Figure 4.1 Median length of hospital stay in days for all patients with acute myocardial infarction treated with and without reperfusion therapy.

Length of hospital stay is presented as median (25^{th} . 75^{th} percentiles). In hospital death was treated as end of hospitalization (discharge) in the calculations for length of hospital stay.
PCI = percutaneous coronary intervention;

In-hospital complications

The first occurrence of the ten most important complications after acute MI is shown in (Table 4.2 – 4.5). Overall, the rate of a first new complication decreased from 34.3% on day 1 to 1.5% at day 7 (Table 4.2). Patients with an uncomplicated course up to day 6 had only 1.5% or fewer complications from day 7 on (Figure 4.2). Patients with this low rate of new complications, including ≤ 0.2% per day mortality, can be reasonably discharged at day 7. Yet, at day 7 2406 patients (39.5%) with an uncomplicated course remained hospitalized. Discharge of these patients at day 7, would have saved 13209 hospital days, representing 19.9% reduction in length of hospital stay (Table 4.6). In-hospital complication rates of patients yet not discharged at day 10 were even lower, 0.5% per day and death rate 0.1% per day. Yet, 1288 low risk patients remained in hospital beyond day 10.

Characteristics	Distribution	Univariable			Multivariable		
		OR	(95% C.I)	p-value	OR	(95% C.I)	p-value
Age £	64.8 ± 13.1	1.0	(1.0-1.1)	.249			
Male gender	69.8	0.8	(0.7-1.0)	.006	0.9	(0.8-1.0)	.043
BMI *	27.0 ± 4.2	1.0	(1.0-1.0)	.067			
Hypertension	52.6	1.2	(1.1-1.3)	.003	1.2	(1.0-1.3)	.021
Diabetes	22.0	1.3	(1.1-1.5)	.001	1.2	(1.1-1.4)	.007
Hyperlipidaemia *	45.2	1.0	(0.8-1.1)	.479			
Smoking-ever *	60.9	0.9	(0.8-1.0)	.070			
Prior angina	56.5	1.0	(0.9-1.1)	.598			
Prior MI	22.5	0.9	(0.8-1.1)	.206			
Prior CHF	6.4	0.8	(0.8-1.3)	.783			
Prior PCI	6.4	0.8	(0.6-1.0)	.021	0.7	(0.6-0.9)	.005
Prior CABG	4.3	0.9	(0.6-1.1)	.247			
Prior CVA/ TIA	7.4	0.9	(0.7-1.1)	.251			
Valvular disease	4.1	1.6	(1.2-2.2)	.005	1.6	(1.1-2.2)	.006
Pacemaker	1.3	1.0	(0.6-1.6)	.973			
PVD	8.6	1.4	(1.1-1.7)	.007	1.3	(1.1-1.7)	.014
Renal failure	4.8	1.2	(0.9-1.6)	.248			
COPD	8.4	1.2	(0.9-1.5)	.159			
Cancer ever	5.3	0.9	(0.7-1.2)	.429			
Prior GI bleed	4.6	1.2	(0.9-1.6)	.261			
Killip class (> II)	7.5	0.7	(0.6-0.9)	.002	0.7	(0.5-0.8)	.000

Table 4.1 Baseline demographic and clinical characteristics as predictors for length of hospital stay before versus beyond day 7 (day 7 = eligible day for discharge) in a univariable analysis and a stepwise multivariable model.

In the second column continuous variables are presented as mean ± SD. All other variables as percentage (%). BMI = body mass index (kg/m2); MI = myocardial infarction; CHF = congestive heart failure. CABG = coronary artery bypass grafting surgery; PCI = percutaneous coronary intervention; CVA = cerebrovascular accident; TIA = transient ischaemic attack; COPD = chronic obstructive pulmonary disease; PVD = peripheral vascular disease; GI = gastrointestinal. "Killip class (> II)" is a heart failure classification at admission. In the third and fourth column: OR = odds ratio; CI = confidence interval. Significant p-value defined as ≤ 0.05

£ Age is divided into 10 years intervals.

* Missing values >10%: BMI (15.0%). smoking (11.6%). hyperlipidaemia (10.1%).

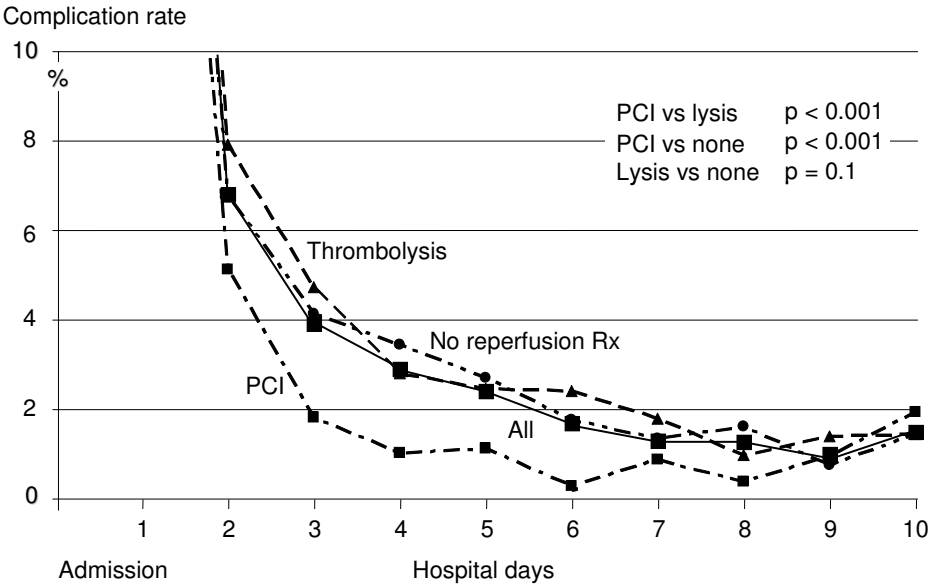

Figure 4.2 In-hospital daily complication rate for different patient groups with and without reperfusion therapy.

PCI = percutaneous coronary intervention; Rx = therapy; Lysis = thrombolysis.

If the patients are grouped according to received reperfusion therapy different complication rates become apparent (Table 4.2 – 4.5). Patients (n = 859) with primary PCI are more likely to be eligible for early discharge because event rate decreased to 1.2% on day 4 and remained low after day 4 between 0.4 - 1.3% (Table 4.4). In contrast, patients after thrombolytic therapy had more frequent complications, and stabilized at a low rate, between 0.9 - 1.9%, after day 7 (Table 4.3). Also patients without reperfusion therapy stabilized at a low event rate only after day 8, and accordingly might be considered for discharge at that day. If all patients with an uncomplicated course up to day 4 (primary PCI), day 7 (thrombolysis) or day 8 (no reperfusion therapy) would have been discharged at those days, a total of 13205 hospital days would have been avoided, which corresponds to 19.9% of current hospitalization. In these patients during subsequent hospitalization 23 death, 7 cardiac arrests, 13 re-infarction and 14 other major complications occurred, corresponding to 1.1%, 1.2% and 0.9% per day respectively.

	Hospital day									
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Number of complication-free pts	6086	3973	3616	3354	3116	2771	2406	1986	1610	1288
Death	1.9	0.6	0.3	0.2	0.3	0.3	0.2	0.2	0.1	0.2
Asystole	0.8	0.1	-	0.1	-	-	-	-	-	-
VF	2.3	0.2	0.1	-	-	-	-	0.1	-	0.1
VT	2.8	0.6	0.2	0.1	0.1	-	-	0.1	-	0.1
HF (Killip IV)	2.8	0.3	0.1	0.1	0.1	0.1	-	-	0.1	-
Re-infarction	0.2	0.4	0.4	0.4	0.1	0.1	0.2	0.1	0.1	0.2
HF (Killip III)	6.3	0.7	0.3	0.2	0.1	0.1	0.1	-	0.2	-
AV-block (2^{nd} or 3^{rd})	1.2	0.3	0.2	0.2	0.1	-	-	-	0.1	-
HF (Killip II)	16.0	2.2	1.1	0.6	0.8	0.5	-	0.1	0.2	0.2
Post-MI angina	0.9	1.8	1.4	1.2	0.8	0.7	0.7	0.8	0.4	0.6
Any first complication rate	**34.3**	**7.1**	**4.2**	**3.1**	**2.5**	**1.9**	**1.5**	**1.3**	**1.0**	**1.4**
Discharged w/o complications	0.4	1.9	3.1	4.0	8.5	11.3	16.0	17.7	19.0	16.9

Table 4.2 Daily in-hospital hazard rate (%) of new cardiac events for patients admitted with an acute myocardial infarction.

Post-MI complications are ranked sequentially in order of clinical importance. Patients could only score once for the clinically most serious adverse event during hospital stay. For example: a patient with an AV-block at day 5 had none of any of the complications above in the column of day 5 and had none of any of the complications mentioned in this table during the preceding four days.
VT = ventricular tachycardia; VF = ventricular fibrillation; MI = myocardial infarction; HF = heart failure; "any complication rate" = sum of all first single complications during that hospital day. "w/o" = without
For better reading of the table values ≤ 0.0 are replaced by a hyphen

	Hospital day									
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Number of complication-free pts	1560	1007	916	848	800	729	633	538	445	356
Death	1.9	0.9	0.2	-	-	-	0.3	0.2	0.2	-
Asystole	0.8	-	-	-	-	-	0.2	-	-	-
VF	4.4	0.2	0.2	-	0.1	0.1	-	-	-	0.3
VT	2.9	0.9	0.1	0.1	0.3	0.1	-	-	-	-
HF (Killip IV)	2.9	0.4	-	0.1	-	0.1	0.2	-	-	-
Re-infarction	0.4	0.5	0.5	0.6	-	0.1	0.2	-	-	-
HF (Killip III)	4.0	0.8	0.2	0.1	-	-	-	-	0.2	-
AV-block (2^{nd} or 3^{rd})	2.3	0.3	0.1	0.1	-	-	-	-	0.2	-
HF (Killip II)	14.6	2.8	2.0	0.8	1.6	0.8	-	-	0.4	-
Post-MI angina	1.0	1.7	1.9	1.3	0.6	1.5	1.1	0.7	0.4	1.1
Any first complication rate	**35.0**	**8.4**	**5.2**	**3.2**	**2.6**	**2.9**	**1.9**	**0.9**	**1.6**	**1.4**
Discharged w/o complications	0.4	0.6	2.2	2.5	6.3	10.3	13.1	16.4	18.4	17.1

Table 4.3 Daily in-hospital hazard rate (%) of new cardiac events for patients admitted with an acute MI treated with thrombolytic therapy.

Post-MI complications are ranked sequentially in order of clinical importance. Patients could only score once for the clinically most serious adverse event during hospital stay. For example: a patient with an AV-block at day 5 had none of any of the complications above in the column of day 5 and had none of any of the complications mentioned in this table during the preceding four days.
VT = ventricular tachycardia; VF = ventricular fibrillation; MI = myocardial infarction; HF = heart failure; "any complication rate" = sum of all first single complications during that hospital day. "w/o" = without
For better reading of the table values ≤ 0.0 are replaced by a hyphen

	Hospital day									
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Number of complication-free pts	859	598	548	502	455	385	348	273	215	157
Death	1.4	0.3	0.2	0.2	-	-	0.3	-	-	-
Asystole	1.3	-	-	-	-	-	-	-	-	-
VF	4.0	-	-	-	-	-	-	-	-	-
VT	3.5	1.3	0.2	0.2	-	-	-	0.4	-	0.6
HF (Killip IV)	3.5	0.3	-	-	-	-	-	-	0.5	-
Re-infarction	0.1	0.2	0.2	0.4	-	-	0.3	-	0.5	0.6
HF (Killip III)	3.5	0.3	0.5	-	-	-	-	-	-	-
AV-block (2^{nd} or 3^{rd})	1.0	0.2	-	0.2	-	-	-	-	-	-
HF (Killip II)	11.1	1.2	0.4	0.2	0.7	0.5	-	-	-	-
Post-MI angina	0.6	1.3	0.4	-	0.4	-	0.3	-	-	-
Any first complication rate	**30.0**	**5.2**	**1.8**	**1.2**	**1.1**	**0.5**	**0.9**	**0.4**	**0.9**	**1.3**
Discharged w/o complications	0.3	3.2	6.6	8.2	14.3	9.1	20.7	20.9	26.0	22.9

Table 4.4 Daily in-hospital hazard rate (%) of new cardiac events for patients admitted with an acute MI treated with primary PCI.

Post-MI complications are ranked sequentially in order of clinical importance. Patients could only score once for the clinically most serious adverse event during hospital stay. For example: a patient with an AV-block at day 5 had none of any of the complications above in the column of day 5 and had none of any of the complications mentioned in this table during the preceding four days.
VT = ventricular tachycardia; VF = ventricular fibrillation; MI = myocardial infarction; HF = heart failure; "any complication rate" = sum of all first single complications during that hospital day. "w/o" = without
For better reading of the table values ≤ 0.0 are replaced by a hyphen

	Hospital day									
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Number of complication-free pts	3667	2368	2152	2004	1861	1657	1425	1175	950	775
Death	2.1	0.5	0.4	0.2	0.5	0.5	0.2	0.2	-	0.4
Asystole	0.6	0.1	-	0.1	-	-	-	-	-	-
VF	1.0	0.3	0.1	-	-	-	-	0.2	-	-
VT	2.6	0.3	0.2	0.1	0.1	-	-	-	-	-
HF (Killip IV)	2.6	0.3	0.1	0.2	0.1	0.1	-	-	-	-
Re-infarction	0.1	0.4	0.5	0.3	0.2	0.1	0.3	0.2	-	0.3
HF (Killip III)	8.0	0.7	0.2	0.3	0.2	0.2	0.2	-	0.2	-
AV-block (2^{nd} or 3^{rd})	0.8	0.4	0.4	0.2	0.2	0.1	-	-	-	-
HF (Killip II)	17.8	2.2	0.9	0.6	0.5	0.4	0.1	0.2	0.1	0.3
Post-MI angina	0.9	2.0	1.5	1.4	1.0	0.5	0.6	0.9	0.4	0.5
Any first complication rate	**35.0**	**7.0**	**4.3**	**3.5**	**2.8**	**1.8**	**1.4**	**1.6**	**0.7**	**1.4**
Discharged w/o complications	0.4	2.1	2.6	3.6	8.1	12.3	16.1	17.5	17.7	15.6

Table 4.5 Daily in-hospital hazard rate (%) of new cardiac events for patients admitted with an acute MI treated with no reperfusion therapy.

Post-MI complications are ranked sequentially in order of clinical importance. Patients could only score once for the clinically most serious adverse event during hospital stay. For example: a patient with an AV-block at day 5 had none of any of the complications above in the column of day 5 and had none of any of the complications mentioned in this table during the preceding four days.
VT = ventricular tachycardia; VF = ventricular fibrillation; MI = myocardial infarction; HF = heart failure; "any complication rate" = sum of all first single complications during that hospital day. "w/o" = without
For better reading of the table values ≤ 0.0 are replaced by a hyphen

	Hospital day								
	2	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Complication-free patients	3973	3616	3354	3116	2771	2406	1986	1610	1288
Mean hospital stay (days)	8.6	7.7	6.9	6.2	5.8	5.5	5.5	5.7	6.0
Median hospital stay (days)	7	6	5	4	3	3	3	3	3
Extra hospital days (days)	34088	27952	23277	19350	15878	13209	10923	9113	7754
Extra/ total hospital days (%)	51.3	42.0	35.0	29.1	24.2	19.9	16.4	13.7	11.7
Daily first new complication rate (%)	**7.1**	**4.2**	**3.1**	**2.5**	**1.9**	**1.5**	**1.3**	**1.0**	**1.4**
Complications/ extra days (%)	0.024	0.019	0.016	0.014	0.012	0.011	0.010	0.009	0.008

Table 4.6 Length of hospital stay patients with uncomplicated acute MI and the total number of hospital days spent by these patients in hospital after that specific day.

Day 1 = day of admission; complication free patients = number of patients without any post-MI complication at the beginning of that hospital day. Extra hospital days = number of added hospital days these complication-free patients stayed longer than that specific day.

DISCUSSION

Prospective clinical registries are the link between randomized clinical trials, guidelines and clinical practice.[15] The Euro Heart Survey ACS is one of the largest registries of acute coronary syndromes in the "real world scenario" in Europe. This survey shows important opportunities to improve management and efficiency in acute MI care.

Early discharge

Opportunities and criteria for early discharge have been intensively studied for the past decades and have driven calls for progressively earlier discharge of uncomplicated MI in European and other guidelines.[4,16] The present analysis confirms that earlier discharge is appropriate indeed in a large group of patients who currently remain hospitalized.

Patients with acute coronary syndromes require hospital admission for several reasons like: immediate reperfusion therapy, arrhythmia monitoring, as well as assessment and treatment of complications. Efficient discharge management could be achieved through a systematic approach, including assessment of patients status at predefined times after admission. Within this perspective the most important question which the treating physician should address every single hospital day is: "why should this patient remain in hospital? Does he/she require specific further treatment in hospital, and is the risk of life threatening complications so high that it requires continued observation, or so low that discharge is appropriate?" Our results present an accurate estimate of new events for uncomplicated post-MI patients, a helpful tool in answering this important question. A

patient can be discharged if the event rate is decreased to a low level and further decrease in event rate is not expected. The event rate is high during the first 48 hours and decreases rapidly after the third day with a complication rate < 4%. After day 6, complication rate stabilised (Figure 4.2) with a hazard rate between 0.9 to 1.9% (Table 4.2 – 4.5). Such stable, low event risk occurs after different days post MI for distinct patient groups related to the reperfusion therapy (Table 4.2 – 4.5, Figure 4.2).
Accordingly, patients treated with primary PCI and an uncomplicated course during the first 3 days, are eligible for discharge at day 4, following the recommendations of the guidelines (Table 4.4). However, patients after thrombolytic treatment have at day 4 still a relatively high daily complication rate that stabilises after day 6 (Table 4.4).
The threshold below which hazard rates are clinical acceptable is, of course, arbitrary. Patients after MI remain at risk for new coronary events including (sudden) death, cardiac arrest and re-infarction. We decided that patients do not need to remain hospitalized when the risk has stabilized, and does not change significantly in the subsequent days or weeks. In addition to life threatening events, we also considered less severe events such as heart failure, AV-block and angina. However, it should be appreciated that such complications, if occurring out of hospital, can easily be managed through re-admission.

Other studies of early discharge

The safety and feasibility of early discharge after 4 days has been advocated based on large data sets from clinical trials.[2,6,7] It should be appreciated that these data represent highly selected patients and in most cases a relatively low risk subgroup of patients with acute MI with a favourable risk profile.[17] The relatively low risk of clinical trial populations has been documented by several Euro Heart Surveys on different clinical topics.[18] Discharge at day 4 as suggested is appropriate in low risk patients in the current survey, particularly after primary PCI.
Comparison of duration of hospitalization among different reports is hampered if these do not clearly describe how length of stay is calculated. The difference can be up to 2 days if day of hospital admission and day of discharge are not counted. We included both these days in our calculations and recommend that others use a similar comprehensive definition of hospital stay in future papers concerning discharge policy.

Guidelines

The current data again demonstrate discordance between guideline recommendations and the “real world” situation. Where guidelines advise patients with uncomplicated MI to be eligible for early discharge after 4 days, the observations in EHS-ACS indicate that discharge after 4 days may be too early for many patients since complication rate is still relatively high (2.5% in the overall group, Table 4.2), and decreasing. In particular patients after thrombolytic therapy, and patients managed without reperfusion therapy may benefit from about 7 or 8 days hospitalization. This discrepancy may be related to the fact that other recent papers on this topic were mainly based on lower risk clinical

trial observations, as discussed above. Therefore, these reports do not necessarily reflect the "real world" while a more complete picture is given by the current survey of clinical practice.
The safety and feasibility of our proposed discharge policy is yet not prospectively evaluated but earlier prospective studies nevertheless stated this already.3

Limitations

In the EHS-ACS only in-hospital complications are registered while after discharge only major complications (death, re-infarction, revascularization) were scored up to 1 year. For our analysis we only used 30-day major adverse cardiac events. Since early discharge will mostly influence outcome during the first 30 days post MI. Not all patients in our registry were observed in the hospital for at least 10 days. A minority of patients (n = 924 or 15.2%) were discharged before day 7. This might have underestimated the event rate, especially for the less severe complications. However, it is unlikely that this would have had a major input on the observations.

Further recommendations

It is recommended that surveys and registries are continuing over several years or are repeated at regular time intervals. This will facilitate verification of the recommendations for early discharge in this report. Furthermore, this will provide evaluation of time trends in the quality of care, and adherence of guidelines, as well as evaluation of the implementation of new therapies and the impact of all these components on the outcome of patients with MI.
Patients with acute coronary syndromes require hospital admission for several reasons like: immediate reperfusion therapy, arrhythmia monitoring, as well as assessment and treatment of complications. Discharge is an individual decision of the physician and may be influenced by the medical history and current situation of the patient, but also by social circumstances and patients living conditions. Yet, in our experiences, prolonged hospital stay is often related to lack of coordination and planning in the hospital. Better planning, management and cooperation between physicians, nurses and other health care providers in the hospital and the outpatient clinic can result in a major reduction in hospital days. We purpose that the treating physician after the first 48 hours asks himself every single hospital day whether a longer stay is necessary and elucidates the rationale behind prolonged hospitalization. The discussion should not be *when* the patient may be discharged but rather *why* the patient still benefits from hospitalization. Systematic application of such approach, based on the observations in this report, will contribute to the continuing efforts to improve the quality of care and ultimately the outcome of our patients with acute MI with the most efficient use of our limited medical resources and finally reduction in healthcare costs.[19]

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5

Baseline determinants of 30-day mortality in patients undergoing primary percutaneous coronary intervention provide insufficient information to decide on early hospital discharge without compromising safety

Maureen J. van der Vlugt
Sanne E. Hoeks
Maarten L. Simoons
Eric Boersma

Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands

Submitted

ABSTRACT

Background

Early hospital discharge after myocardial infarction (MI) has been promoted for over 30 years. Indeed, in a cost-conscious environment, evidently, hospitalization should not be extended beyond the patient's clinical needs.

Aim

To validate the Zwolle Risk Score for accurate identification of uncomplicated patients eligible for early discharge.

Methods

The Zwolle Risk Score was developed in a single centre cohort of 1791 patients with ST-segment elevation acute coronary syndrome (ACS) who received primary percutaneous coronary intervention (PCI). The Zwolle Risk Score consists of 6 clinical variables including age, the total ischemic time, infarct location, Killip class at admission, extent of coronary disease and post-procedural coronary blood flow. The Zwolle investigators argue that a group of patients with a 30-day mortality risk not exceeding 0.5% (Zwolle Risk Score ≤ 3) can be discharged safely 48 hours after the procedure. We validated this risk score in the well-characterized Euro Heart Survey of Acute Coronary Syndromes (EHS-ACS). In the EHS-ACS 803 (18%) received primary PCI within 24 hours after symptom onset; they compose the target cohort for this study.

Results

In general, the patients who enrolled the EHS-ACS had a significant less favourable risk profile. The Zwolle Risk Score adequately predicted the probability of 30-day mortality (c-index 0.84). Thirty day mortality in the EHS-ACS cohort was 6.2% and only 3.6% in the Zwolle cohort ($p = 0.002$). Three patients in the EHS-ACS study cohort with a Zwolle Risk Score ≤ 3 died within the first 2 days after hospital admission. During the subsequent 8 days, clinical events requiring prolonged hospitalization in the remaining 409 patients (77%) were not infrequent: two patients died, 4 patients had VT and another 4 had re-MI: altogether 10 patients (2.4%) with severe life-threatening complications. Half of these complications (5/10) occurred during hospital day 3 and 4. The median duration of hospitalization in the EHS-ACS cohort was 8 days, and only 6 days in the Zwolle cohort.

Conclusions

The Zwolle Risk Score is an easy, bedside tool for identification of low risk patients at day of admission after primary PCI. However, the Zwolle Risk Score is not useful for safe

selection of patients eligible for early discharge. We propose a simple hospital discharge policy based on daily evaluation of clinical parameters. According to this policy, a large group of patients with uncomplicated myocardial infarction at the beginning of the fifth hospital day is eligible for discharge which results in a considerable reduction in health care expenses.

INTRODUCTION

Treatment of patients with acute myocardial infarction (MI) has improved over time and, in parallel, the duration of hospital stay has considerably decreased.[1,2] In the early 1980s, before the widespread introduction of reperfusion therapy, MI patients were hospitalized for approximately 3 weeks, whereas nowadays, the average hospital stay in the Netherlands amounts 8 days reflecting a reduction of 55%.[3,4] Early hospital discharge after MI has been promoted for over 30 years. Indeed, in a cost-conscious environment, evidently, hospitalization should not be extended beyond the patient's clinical needs. Furthermore, early hospital discharge has been associated with improved physical and psychological outcome, especially in elderly subjects.[5] Still, it is obvious that a considerable further reduction in length of hospital stay can be achieved compared to current practice. Hospital stay is often unnecessarily prolonged in patients with uncomplicated MI. Formal protocols to evaluate the risk of life-threatening complications requiring hospitalization are not implemented systematically. Hence, patients at low risk, who are candidates for early discharge, will not be identified quickly.

The Zwolle group recently developed a risk-evaluation model for MI patients who underwent primary percutaneous coronary intervention (PCI).[6] Based on a few characteristics, including age, the duration of ischemic symptoms, infarct location, Killip class at admission, extent of coronary disease and post-procedural coronary blood flow, patients can easily be stratified according to their 30-day mortality risk. The Zwolle investigators argue that a group of patients with a 30-day mortality risk not exceeding 0.5% can be discharged safely 48 hours after the procedure. The Zwolle Risk Score excels by simplicity, which is a major potential advantage for its use in clinical practice. However, so far, the risk score, which is based on single-centre experience in 1791 patients, has not been externally validated.

The Euro Heart Survey of Acute Coronary Syndromes (EHS-ACS) was developed to obtain quantitative information on the adherence to guidelines and prognosis in patients presenting with acute coronary syndromes (ACS). The EHS-ACS enrolled 803 consecutive MI patients undergoing primary PCI in a broad range of practices across Europe. We used this well-characterized cohort to validate the performance of the Zwolle Risk Score. Specifically, we studied whether or not it can be used to select patients who can be discharged early after admission without compromising safety.

METHODS

Euro Heart Survey of Acute Coronary Syndromes

The details of the EHS-ACS have been previously described in detail.[7] The survey was performed in clusters composed of academic and non-academic hospitals and hospitals

with and without cardiac catheterisation laboratories and cardiac surgery facilities. The survey was conducted during 2000-2001.
All patients with suspected ACS, screened at the emergency room, chest pain unit, catheterisation laboratory, or otherwise were registered on a screening log (after acquisition of written informed consent if required). Patients who had been in another hospital for a short (< 12 hrs) observation period and were transferred for diagnosis and management were also registered, and information from the referring hospital was sought. However, patients who were referred only for a specific treatment (i.e. cardiac catheterisation or coronary bypass surgery) were not included. A total of 10484 patients were enrolled after the diagnosis of ACS was confirmed. They were classified as ACS with ST elevation, ACS without ST elevation, and ACS with an undetermined electrocardiographic pattern, based on the initial electrocardiographic pattern.

Study cohort

There were 4431 patients (42%) who presented with ST-elevation or with new left bundle branch block. Among these, 803 (18%) received primary PCI within 24 hours after symptom onset; they compose the target cohort for this study. Hereafter we will refer to the study cohort as MI patients.

Adverse events

The EHS-ACS was designed to evaluate the application of treatment guidelines in patients with ACS during routine clinical practice. With regard to patient outcome, the Survey mainly focussed on major adverse cardiac events that occurred during hospital stay, including death, asystole, ventricular fibrillation (VF), ventricular tachycardia (VT), heart failure (HF), recurrent myocardial infarction (re-MI), 2^{nd} or 3^{rd} degree atrial-ventricular (AV) block and post-MI angina. These complications were reported by the local investigators, and not adjudicated by an independent endpoint committee. 30-day follow-up was complete in 778 patients (97%) of our cohort.

Duration of hospital stay

The duration of hospital stay was defined as the number of days on which the patient was hospitalized in the enrolling EHS-ACS centre. The day of admission as well the day of discharge were counted as a complete day. The day of hospital admission was defined as day 1. In-hospital death was considered as discharge on the very same day.

Data analysis

Most continuous variables had non-normal distribution (as evaluated by Kolmogorov-Smirnov tests).[8] For reasons of uniformity, summary statistics for all continuous variables are therefore presented as medians together with the 25^{th} and 75^{th} percentiles. Categorical data are summarized as frequencies and percentages. Differences in baseline characteristics and outcome between our study cohort and the patients who were used to

develop the Zwolle Risk Score were analysed using Wilcoxon-Mann-Whitney tests or Fisher's exact tests, as appropriate.

The Zwolle Risk Score was developed in a cohort of 1791 patients with ST-segment elevation ACS who received primary PCI in hospital De Weezenlanden, Zwolle, The Netherlands, between Augustus 1994 and October 2001.[6] The risk score was retrospectively validated in 747 patients who were treated during October 2001 to February 2003 in the same centre. The Zwolle Risk Score consists of 6 variables, including age, the time from symptom onset to the first balloon inflation (i.e. the total ischemic time), infarct location, Killip class at presentation, extent of coronary disease and post-procedural coronary blood flow, which are available after the PCI has been conducted. In the last two columns of Table 5.1 calculation of the Zwolle Risk Score is shown. We calculated the Zwolle Risk Score for each patient in our dataset, and applied (univariable) logistic regression analysis to study its performance to determine 30-day mortality with respect to discrimination and calibration. Discrimination refers to the ability of the score to distinguish patients who died within 30 days from those who survived. It was quantified by a measure of concordance, the c-statistic. For binary outcomes the c-statistic is identical to the area under the receiver operating characteristic curve. The c-statistic lies between 0.5 and 1, and is better if closer to 1. Calibration refers to whether the predicted mortality (by using the score) agrees with the actually observed mortality. Calibration was measured with the Hosmer-Lemeshow goodness-of-fit test.[9]

We used the method of Kaplan-Meier to describe the incidence of death over time. Log-rank tests were applied to study differences in survival between patients with a Zwolle Risk Score ≤ 3 versus those with a score ≥ 4. (Note that the Zwolle investigators suggested that patients with a score ≤ 3 are at low risk of 30-day death, and can be safely discharged after 48 hours). Additionally, we studied the incidence of non-fatal adverse events in both groups.

Statistical significance of all tests was stated at the 0.05 probability level. All tests were two-sided.

	Zwolle	EHS	p-value	RF	ZRS
Enrolment period	1994 - 2001	2000-2001			
Number of patients	1791	803			
Demographics					
Age, yrs	60 ± 11	61 ± 13	-	**≥60 yrs**	2
Men	79	77	0.24		
Admission					
Ischemic time, hours *	3.5 ± 1.3	5.5 ± 4.2	-	**>4hrs**	1
Anterior infarction #	51	49	0.97	**yes**	1
Killip class I	88	83	<.001	**I**	0
Killip class II		12		**II**	4
Killip class III		3		**III**	9
Killip class IV		2		**IV**	9
Procedure-related and pre-discharge data					
Multivessel disease	54	54	0.98	**>2**	1
LAD disease	50	66	<.001		
Postprocedural TIMI flow 0-1	74	81	<.001	**TIMI 0-1**	2
Postprocedural TIMI flow 2				**TIMI 2**	1
Postprocedural TIMI flow 3	91	86	<.001	**TIMI 3**	0
			Total Zwolle Risk Score		**0 - 16**

Table 5.1 Key characteristics of the Zwolle-derivation and EHS-validation cohorts for the calculation of the Zwolle Risk Score (ZRS).

Continuous data for the Zwolle cohort are presented as mean values ± one standard deviation; continuous data for our EHS study sample are presented as medians (25^{th}, 75^{th} percentiles).
Dichotomous data are presented as percentages.
* Time from symptom onset to first balloon inflation; for the EHS dataset: median time and 25^{th}, 75^{th} percentiles; Zwolle group median time and two standard deviation.
# in the Zwolle group also left bundle branch block (LBBB) is included, for the EHS data only anterior infarction is given.
LAD = left anterior descending artery. RF = risk factor.
TIMI flow = flow grades based on results of the Thrombolysis In Myocardial Infarction trial.

RESULTS

Patients and outcome

There were important differences in baseline and procedure-related characteristics between the EHS-ACS multi-centre and the Zwolle single-centre cohorts. In general, the patients who enrolled the EHS-ACS had a significant less favourable risk profile (all $p \leq 0.001$). Particularly, they had more often diabetes (18% vs. 9%), hypertension (51% vs. 22%), dyslipidaemia (47% vs. 18%), ever smoking (60% vs. 47%), prior MI (19% vs. 11%) and prior coronary revascularisation (12% vs. 8%). Also their Killip class at admission was worse (Table 5.1). There was no difference in the extent of coronary disease between the two cohorts, but the EHS-ACS patients significantly more often had LAD disease (66% vs. 50%). The PCI procedure was less often successful in the EHS-ACS patients (82% vs. 89%; $p < .001$), with less often post-procedural TIMI 3 coronary flow (86% vs. 91%). Stents were used less often in the Zwolle registry (71% vs 50%). In the EHS-ACS cohort a larger proportion of patients has a Zwolle Risk Score ≥ 4 than in the Zwolle cohort (34% vs 27%; p 0.01) (Figure 5.1).

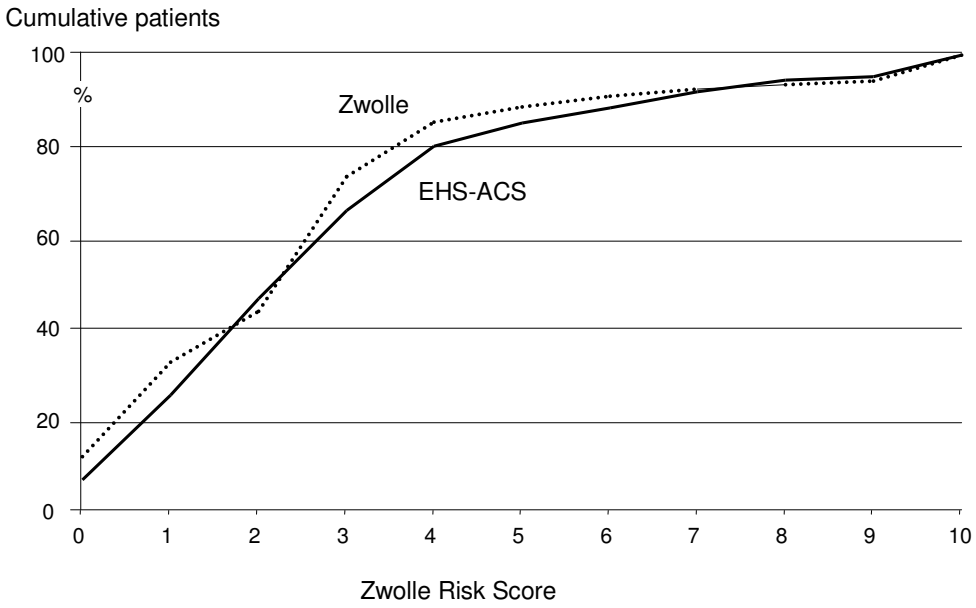

Figure 5.1 Distribution (%) of cumulative patients with primary PCI from the EHS-ACS and the Zwolle group by the Zwolle Risk Score.

In the EHS-ACS cohort the pre-discharge left ventricular ejection fraction (LVEF) was normal (> 50%) in 45%, reduced (40-49%) in 30%, moderate (30-40%) in 16% and poor (< 30%) in 8% of the patients. In the EHS-ACS cohort a total of 50 (6.2%) patients died within 30 days after admission, which is significantly higher than in the Zwolle cohort (3.6%; p 0.002).
The median duration of hospitalization in the EHS-ACS cohort was 8 (5, 11) days, compared to a mean value of 5.9 (± 6.7) days in the Zwolle cohort. The duration of hospital stay increased with an increasing Zwolle Risk Score from a median hospital stay of 8 days in the low Zwolle Risk Score (≤ 3) to 12 days in the highest Zwolle Risk Score (10-16) group. The median duration was 8 (5, 11) days in the 530 patients with a risk score ≤ 3 and 9 (5, 13) days in the 273 patients with a score ≥ 4.

Validation of the Zwolle Risk Score

The power of the Zwolle Risk Score to discriminate between patients who died within 30 days and those who survived was good (c-index 0.84). The test for calibration was not significant (p 0.86), indicating that the risk score adequately predicted the probability of 30-day mortality (Figure 5.2).

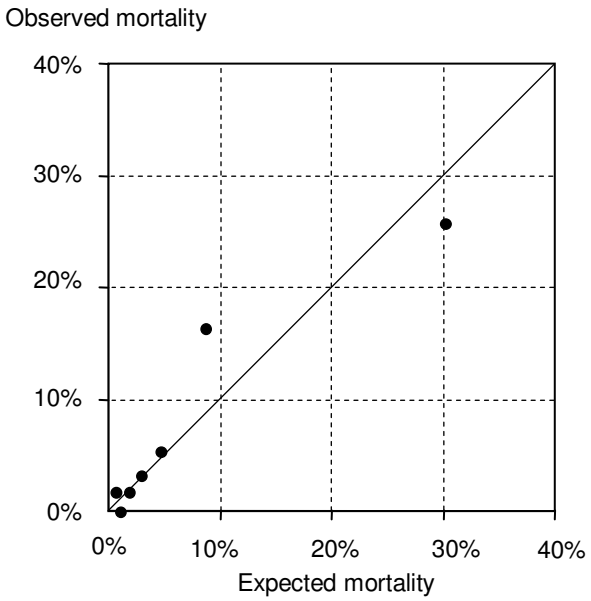

Figure 5.2 Calibration plot of observed versus expected mortality for the EHS-ACS validation set.

Three patients with a Zwolle Risk Score ≤ 3 died within the first 2 days after hospital admission, whereas 121 patients were discharged without complications in the same period. During the subsequent 8 days, clinical events requiring prolonged hospitalization in the remaining 409 (77%) patients were not infrequent: 2 patients died, 4 patients had VT and another 4 had re-MI: altogether 10 patients (2.4%) with severe life-threatening complications. Half of these complications (5/10) occurred during hospital day 3 and 4 (Table 5.2).

Patients with Zwolle Risk Score ≥ 4 had considerable higher 30-day mortality than their counterparts with a lower score (Kaplan-Meier estimate 15.5% vs. 1.8%; p <0.001; Figure 5.3). They also more often had other complications, particularly VF or VT (14.7% vs.9.8%; p 0.041). The 98 patients (36%) who had no clinical complications during the first 2 days also had low incidence of life-threatening complications in the subsequent days (Table 5.3): 2 patients died and another had re-MI.

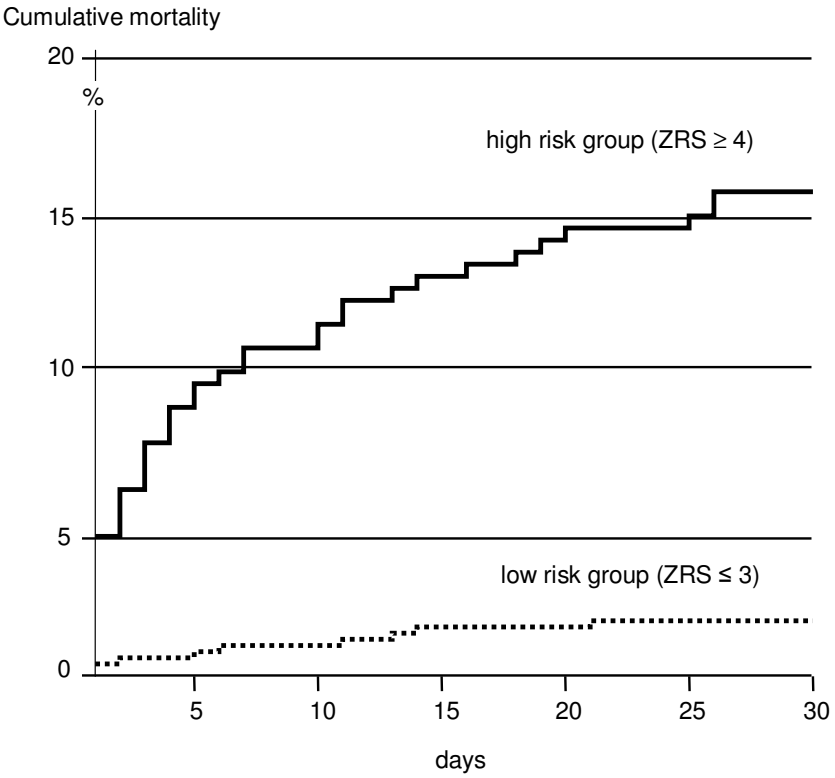

Figure 5.3 Kaplan-Meier survival curves for the EHS validation set for the low and high Zwolle Risk Score (ZRS) during 30-days follow-up.

Day of admission	Patients still hospitalized at the beginning of day/period	Complications justifying hospitalization †							Other compli-cations ‡§
		Death	Asystole	VF	VT	HF (Killip IV)	reMI	Any §	
530 admitted patients with a baseline Zwolle Risk Score ≤ 3									
1	**530**	**2**	**6**	**13**	**19**	**7**	**-**	**47 (8.9)**	**42 (7.9)**
2	526	1	-	-	7	1	1	10 (1.9)	9 (1.7)
3-7	506	2	-	-	2	2	2	8 (1.6)	16 (3.2)
8-14	281	2	-	-	2	-	2	6 #	4#
15-30	44	1	-	-	-	-	-	1 #	2#
439 patients who were still admitted at day 2 and who had no clinical complications at day 1									
2	**439**	**-**	**-**	**-**	**6**	**1**	**1**	**8 (1.8)**	**8 (1.8)**
3-7	423	1	-	-	2	-	2	5 (1.2)	13 (3.1)
8-14	224	2	-	-	2	-	2	6 #	3#
15-30	25	-	-	-	-	-	-	-	1#
409 patients who were still admitted at day 3 and who had no clinical complications at day 1-2									
3	**409**	**-**	**-**	**-**	**1**	**-**	**-**	**1 (0.2)**	**4 (1.0)**
4-7	383	1	-	-	1	-	2	4 (1.0)	8 (2.1)
8-14	215	2	-	-	2	-	2	6 #	3#
15-30	22	-	-	-	-	-	-	-	1#
378 patients who were still admitted at day 4 and who had no clinical complications at day 1-3									
4	**378**	**1**	**-**	**-**	**1**	**-**	**2**	**4 (1.1)**	**2 (0.5)**
5-7	334	-	-	-	-	-	-	-	6 (1.8)
8-14	211	1	-	-	2	-	2	5 #	3#
15-30	21	-	-	-	-	-	-	-	1#
330 patients who were still admitted at day 5 and who had no clinical complications at day 1-4									
5	**330**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**3 (0.9)**
6-7	290	-	-	-	-	-	-	-	3 (1.0)
8-14	210	1	-	-	2	-	2	5 #	3#
15-30	21	-	-	-	-	-	-	-	1#
288 patients who were still admitted at day 6 and who had no clinical complications at day 1-5									
6	**288**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**2 (0.7)**
7	262	-	-	-	-	-	-	-	1 (0.4)
8-14	208	1	-	-	2	-	2	5 #	3#
15-30	21	-	-	-	-	-	-	-	1#

Table 5.2 In-hospital complications for patients with a Zwolle Risk Score ≤ 3.

† In case patients had multiple events, then the most severe event for each day/period of admission is presented

‡ Including heart failure Killip II or III, 2nd or 3rd degree AV-block and post-MI angina

§ Percentages relative to the number of patients who are still hospitalized at the beginning of the day/period

Percentages are omitted because of the steeply decreasing number of hospitalized patients during this period

Day of admission	Patients still hospitalized at the beginning of day/period	Complications justifying hospitalization †							Other compli-cations ‡§
		Death	Asystole	VF	VT	HF (Killip IV)	reMI	Any §	
					273 admitted patients with a baseline Zwolle Risk Score ≥ 4				
1	**273**	**12**	**3**	**17**	**7**	**18**	**-**	**57 (20.9)**	**105 (38.5)**
2	259	5	1	-	1	2	-	9 (3.5)	14 (5.4)
3-7	247	11	-	2	2	2	1	18 (7.3)	14 (5.7)
8-14	154	5	-	-	-	-	-	5 #	1#
15-30	44	5	-	-	-	-	1	6 #	1#
	110 patients who were still admitted at day 2 and who had no clinical complications at day 1								
2	**110**	**2**	**-**	**-**	**-**	**1**	**-**	**3 (2.7)**	**5 (4.6)**
3-7	106	2	-	-	-	-	1	3 (2.8)	5 (4.7)
8-14	57	1	-	-	-	-	-	1 #	-
15-30	16	2	-	-	-	-	1	3 #	-
	100 patients who were still admitted at day 3 and who had no clinical complications at day 1-2								
3	**100**	**1**	**-**	**-**	**-**	**-**	**-**	**1 (1.0)**	**2 (2.0)**
4-7	94	1	-	-	-	-	1	2 (2.1)	4 (4.3)
8-14	52	1	-	-	-	-	-	1 #	-
15-30	13	2	-	-	-	-	-	2 #	-
	92 patients who were still admitted at day 4 and who had no clinical complications at day 1-3								
4	**92**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**1 (1.1)**
5-7	89	1	-	-	-	-	1	2 (3.2)	-
8-14	50	1	-	-	-	-	-	1 #	-
15-30	11	2	-	-	-	-	-	2 #	-
	88 patients who were still admitted at day 5 and who had no clinical complications at day 1-4								
5	**88**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**2 (2.3)**
6-7	68	1	-	-	-	-	1	2 (2.9)	-
8-14	49	1	-	-	-	-	-	1 #	-
15-30	11	2	-	-	-	-	-	2 #	-

Table 5.3 In-hospital complications for patients with a Zwolle Risk Score ≥ 4.

† In case patients had multiple events, then the most severe event for each day/period of admission is presented

‡ Including heart failure Killip II or III, 2nd or 3rd degree AV-block and post-MI angina

§ Percentages relative to the number of patients who are still hospitalized at the beginning of the day/period

\# Percentages are omitted because of the steeply decreasing number of hospitalized patients during this period

DISCUSSION

This analysis of patients presenting with ST-elevation ACS or new LBBB who underwent primary PCI confirmed the applicability's of the Zwolle Risk Score for the prediction of 30-day mortality. The advantage in risk stratification of these patients post primary PCI is that the coronary anatomy and left ventricular function is known. The Zwolle Risk Score adequately discriminated between patients who are at low versus high risk mortality, although the concordance-statistic was somewhat lower than in the cohort that was used to develop the score. Patients with a Zwolle Risk Score ≤ 3 who survived the first 48 hours (409 patients) had 0.2% mortality risk in the remaining week. However, in our view, the incidence of non-fatal life-threatening complications, including asystole and VF, was too high to justify their discharge at that very moment. In fact, short-term mortality risk models are not suitable to predict all life threatening complications during the first few weeks to decide if patients can be safely discharged or should remain hospitalized.[10] Probably a combination of functional assessment (left ventricular function and coronary anatomy as in the Zwolle Risk Score) and observation of clinical events during the first days may be a better approach.

The Zwolle Risk Score is developed on the basis of data that were collected in a single centre that is specialised in the treatment of acute MI patients by primary PCI. Pre-hospital as well as in-hospital logistics are optimised to provide reperfusion therapy as soon as possible after the onset of symptoms. Consequently, total ischemic times are relatively short. Also, the Zwolle Centre acts as a tertiary referral centre for primary PCI, and protocols are in place to help select patients who benefit most of such therapy.[11] In the practice of many other centres primary PCI is predominantly offered to high risk patients, particularly if patients have to be transferred to another hospital for PCI. Indeed, patients who enrolled the Zwolle Risk Score derivation cohort had a more favourable risk profile and lower 30-day mortality than the EHS-ACS patients. Nevertheless, we confirmed that the Zwolle Risk Score can be used to adequately predict 30-day mortality in unselected patients from a broad range of clinical settings. However, even in low risk patients many life threatening events occurred after the first 2 days.

Apparently, determinants of 30-day mortality in patients undergoing primary PCI provide insufficient information to decide on early hospital discharge without compromising safety. At least, we judge that patients who are at serious risk of asystole, VF, VT, heart failure Killip IV and re-MI should remain hospitalized. Although we realise that it will be difficult to agree on a clinically acceptable threshold, the observed short-term incidence of life-threatening complications in patients with suspected low mortality, according to the Zwolle Risk Score, clearly is too high. It should be realised that these patients actually were hospitalized at the time of the complication, and - most likely - survived due to adequate and timely management. Also, it is known that non-fatal complications can hardly be predicted using baseline characteristics, because of the dynamic nature of the disease.[12-15] As an alternative, it seems appropriate to base a hospital discharge strategy

on an pragmatic approach, selecting low risk uncomplicated patients on a day-to-day basis. It appears that patients who were free of complications until day 2 had an incidence of life-threatening complications requiring prolonged hospitalization of approximately 2% in the first week. Interestingly, our data suggests that this incidence is independent of the Zwolle mortality risk score.

In our view, a daily hazard of around 1% is an acceptable level for hospital discharge. Accordingly, at day 5 patients can be discharged safely without life-threatening events in the first few days after discharge. If this policy would have been followed, 358 patients (45%) could have been discharged earlier than observed, irrespectively of the Zwolle Risk Score. It should be appreciated that 3 of these patients (0.7%) who might have been sent home at day 5 according to our model, died unexpectedly after day 5 but within the first 2 weeks after MI. However, the event rate in these patients will never decrease to zero and low event rate has to be accepted. Also, from a cost-effective point of view it is not reasonable to keep all patients admitted for 14 days to prevent 3 unexpected deaths which could not be predicted neither with the Zwolle Risk Score nor by early complications. Although, in a more conservative strategy, patients will be discharged later, our data demonstrates a more or less stable hazard between day 6 and day 30. Obviously, before the suggested policy can be effectuated, its safety should be evaluated in a prospective study.

Study limitations

The EHS-ACS has some limitations that need to be addressed. First, complications were recorded by the attending physician and were not verified by an independent clinical event committee. This might have resulted in an underestimation of the true event rate, particularly, for the less severe complications. Second, because the centres that participated in the survey were predominantly university hospitals with revascularisation facilities, the results of our survey may not necessarily be generalized to a broader spectrum of clinical practices. Third, independent core laboratory analysis for objective TIMI flow measurements were not available.

Conclusions

The Zwolle Risk Score is an easy, bedside tool for identification of low risk patients at day of admission after primary PCI and an accurate predictor for 30-day mortality like several other known risk scores for 30-day mortality in patients with acute myocardial infarction.[16,17] However, the Zwolle Risk Score is not useful for safe selection of patients eligible for early discharge with a low short-term event rate other than death alone.

We propose a simple hospital discharge policy based on daily evaluation of clinical parameters which might help to select candidates for early discharge without compromising safety. According to this policy, a large group of patients with uncomplicated MI at the beginning of the 5th hospital day are eligible for discharge. Appreciation of this policy after primary PCI will result in a considerable reduction in health care expenses, with a low acceptable risk.

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6

Discharge policy of patients with acute myocardial infarction treated with primary angioplasty: a substudy of the RESEARCH and T-SEARCH registries

Maureen J. van der Vlugt
Sanne E. Hoeks
Joost Daemen
Strelitzia Tjon Kon Fat
Farshad Imani
Cihan Simsek
Peter P.T. de Jaegere
Ron T. van Domburg
Maarten L. Simoons
Patrick W. Serruys

Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands

Submitted

ABSTRACT

Background

Since the introduction of primary percutaneous coronary intervention (PCI) in patients with acute myocardial infarction (MI), the length of hospital stay could be further reduced in many patients.

Aim

To validate our developed decision rule, to discharge patients without complications on day 5, in a prospective, consecutive study cohort in patients with ST-elevation myocardial infarction (STEMI) treated with primary PCI in the era of drug eluting stents.

Methods

Between April 2002 and October 2003 342 consecutive STEMI patients were treated with primary PCI with SES (Sirolimus-eluting stents; 40%) or PES (Paclitaxel-eluting stents; 60%). From the hospital medical records major and minor post-infarction complications were documented as well as the exact day at which the event occurred.

Results

The mean age of the study cohort was 58 years, 79% were male. The median length of hospital stay was 7 days. The daily event rate decreased dramatically during the first two days from 28% at day 1 to 8.23% at day 2.
By applying the decision rule, 169 patients (49%) without complications until day 5, could have been sent home at day 5. The mean hospital stay of these patients beyond day 5 was 4.35 days. Early major cardiac complication rate in this period was low (1.8%). With the implementation of the decision rule in total 735 days were saved, or in other words, an average of 2.15 days per admitted patient with acute MI.

Conclusions

Although patients with an STEMI treated with primary PCI remained in hospital 7 days, earlier discharge in the morning of day 5 would be safe and feasible with tremendous cost savings and more efficient use of our resources.

INTRODUCTION

Over the past 2 decades treatment of patients with acute myocardial infarction (MI) has improved considerable and a variety of treatment strategies such as thrombolytic therapy[1,2] and primary coronary angioplasty are now available to restore obstructed coronary blood flow.[3,4] Consequently, length of hospital stay has reduced from 3 weeks to 8 days.[5] While primary angioplasty with direct stenting has demonstrated to be superior to thrombolytic therapy,[6,7] the feasibility and safety of early discharge in STEMI patients who underwent successful PCI has yet to be evaluated.

Our group developed and validated prospectively an early discharge decision rule in STEMI patients which has been shown to be widely applicable in clinical practice.[8] This decision rule is based on repeated clinical assessment during the first days in hospital without the need of pre-discharge exercise testing or other non-invasive or invasive tests. In patients treated by primary PCI, the most effective reperfusion therapy, coronary anatomy and left ventricular function are known and myocardial re-infarction is rare. Therefore, there is little need for prolonged hospitalization in such patients.

The purpose of this study was to assess the length of hospital stay and the discharge policy in patients with acute MI treated by primary PCI. In particularly, we investigated whether patients with an uncomplicated course could safely be discharged at an early stage. Furthermore, we verified our decision model for safety and applicability for patients with acute myocardial infarction treated by primary PCI .

METHODS

Patient population

Between April 2002 to October 2003, all 342 consecutive patients with a ST-elevation acute myocardial infarction were evaluated who have been treated with primary angioplasty using Sirolimus-eluting stents (SES; n=136; Cypher, Johnson & Johnson-Cordis unit, Cordis Europe NV, Roden, The Netherlands) and Paclitaxel-eluting stents (PES; n=206; Boston Scientific, Galway, Ireland) in a single, tertiary hospital (Erasmus Medical Center). This is a substudy of the RESEARCH and the T-SEARCH Registries.[9-11]
All patients were enrolled regardless of the clinical or anatomical presentation, including patients admitted with cardiogenic shock (defined as persistent systolic blood pressure <90mmHg, or the use of vasopressors or intra-aortic balloon pumping to maintain blood pressure >90mmHg with evidence of end-organ failure and elevated left ventricular filling pressures). Patients with rescue angioplasty after failed thrombolytic therapy were excluded from the present analysis. The study protocol was approved by the local ethics committee and written informed consent was given by every patient.

Early discharge decision model

From the hospital charts we re-registered each complication per patient per day as described earlier.[8] Ten most common post MI complications were identified and ranked in order of clinical importance: death, cardiac arrest by asystole or ventricular fibrillation, ventricular tachycardia, heart failure / cardiogenic shock (Killip IV), re-infarction, severe heart failure (Killip III), high grade AV-block (2^{nd} or 3^{rd}), mild heart failure (Killip II) and recurrent ischemia.[12] If a patient had more than one event within one day, the clinically most important event of interest was used. Patients free from any of these complications until that hospital day were identified. The proportion of event-free patients at the beginning of a specific hospital day was calculated by the number of event-free patients at the beginning of the preceding day subtracting from the number of patients having a new complications or discharged on this day. Daily or weekly event rates can be calculated for a specific hospital day or week. New event rates are defined as the hazard of patients with complications occurring at a specific hospital day as a proportion of all patients who had no complication up to that day.
Discharge of patients after acute MI might be considered if no complications had occurred which required additional in-hospital therapy, and as soon as the number of new major daily complications is low.

Length of hospital stay

Length of hospital stay was calculated by subtracting the date of discharge from the date of admission, adding one day. The day of hospital admission was defined as day 1. The day

of admission as well as the day of discharge was counted as one hospital day each. Patients admitted after 9 PM were not counted for that hospital day. Time of discharge was assumed to be in the morning before 10 AM In-hospital death was treated as end of hospitalization (i.e. discharge) in the calculations.

Data collection

As part of the RESEARCH and T-SEARCH registries all baseline characteristics and 30-day outcome were prospectively collected. Being a tertiary hospital, the majority of the patients were referred back to their own hospital a few hours after the coronary intervention. Therefore, it was needed to collect the discharge date and the daily in-hospital cardiac events, needed for the decision rule, in all relevant hospitals. In total, 10 hospitals in the region were visited.

Statistical analysis

Statistical analysis was performed with the SPSS 13.0 statistical package. Continuous data were expressed as mean ± SD and discrete variables by percentages. The non-normal distribution of hospital stay was described by medians with 25th and 75th percentiles.

RESULTS

Mean age was 58 years and 79% were male (Table 1). Previous cardiac events were normally distributed with low prevalence. Smoking was the most common risk factor. Diabetes had a rather low incidence (11%) in this cohort where the majority of patients had type II diabetes (9%). Half of the patients had one vessel disease and the LAD most often was the infarct related artery. Only a minority of patients had three-vessel disease (19%) and a significant left main stenosis was rare (0.5%). The median delay from symptom onset to primary PCI was 115 minutes (= 1.9 hours). One fourth of the patients (25.7%) had heart failure at admission but only a small amount of patients were in cardiogenic shock at admission (10%).
The primary PCI was successful in 98% of the cases with on average 1.5 stents per patient, distributed by 40% SES (n=136) and 60% PES (n=206). Glycoprotein IIb/IIIa inhibitors were administered in 50% of the patients starting before, during or after the procedure. The median CK peak was 3157 U/L. The median hospital stay was 7 days with 25th and 75th percentile of 5 and 8 days respectively and a range of 2 to 30 days.
On the first day 96 patients (28.1%) experienced a complication, in particular death (2.0%), ventricular fibrillation (9.6%), ventricular tachycardia (3.8%) and heart failure (4.7%). The event rate decreased significantly thereafter to 7.3% on day 2, 2.9% on day 3 and event rates of 3.7% and 3.6% on day 4 and 5 respectively. On day 6 the event rate has decreased to 0.7%. Unfortunately, clinical major complications still occurred in those 169 patients (49%) who were still admitted on day 5 and did not experience any clinical

complication until that day. According to our decision rule these patients could have sent home in the morning of day 5. As a consequence three patients (1.8%) would have experienced a recurrent MI between day 5 and day 14 after the acute myocardial infarction. Two patients experienced a VT in this same period. Late severe complications (>7 days) still occurred in 6 patients (3.6%) with an uncomplicated course up to day 5.

The mean hospital stay of the 169 patients, eligible for early discharge according to our decision rule, beyond day 5 was 4.35 days. With the implementation of the decision rule in total 735 hospital days were saved, or in other words, an average of 2.15 days per admitted patient with acute MI.

In the Netherlands 8054 primary PCIs were performed in 2005.[5] Extrapolating our findings nation wide, it was to be expected that about half (49% in our study) of the patients with acute MI treated with primary PCI were uncomplicated and eligible for early discharge in the morning of day 5. Implementation of our early discharge model would have saved 17316 hospital days only in the Netherlands. Overall, 2.15 days per patient with acute myocardial infarction would have been saved by applying the decision rule.

Baseline Characteristic Time of collection data	Primary PCI with DES stenting April 2002 – October 2003
Mean age (yrs)	58 (27 - 89)
Male (%)	79
Risk factors (%)	
Hypertension	31
Current smoking	52
Diabetes mellitus	11
History of dyslipidaemia	47
History (%)	
Prior myocardial infarction	18
Prior PCI	10
Prior CABG	3
Vessel disease (%)	
LAD	55
RCX	18
RCA	39
One-vessel disease	51
Two-vessel disease	30
Three-vessel disease	19
Type of stent (%)	
Sirolimus-eluting stent (SES)	40
Paclitaxel-eluting stent (PES)	60

Table 6.1 Baseline and procedural characteristics of patients with acute myocardial infarction treated with reperfusion therapy by primary stenting with drug-eluting stents (DES) (N = 342).

Hospital day	Patients still hospitalized at the beginning of day/period	Complications justifying hospitalization †							Other compli-cations ‡§
		Death	Asystole	VF	VT	HF (Killip IV)	Re-MI	Any §	
									342 admitted patients
1	**342**	**7**	**-**	**33**	**13**	**16**	**2**	**71 (20.8)**	**25 (7.3)**
2	320	2	-	4	3	4	1	14 (4.4)	12 (3.8)
3-7	306	2	-	1	2	1	6	12 (3.9)	20 (6.5)
8-14	184	3	-	-	2	-	2	7 #	8 #
15-30	46	1	-	-	-	1	-	2 #	1 #
	232 patients who were still admitted at day 2 and who had no clinical complications at day 1								
2	**232**	**-**	**-**	**3**	**3**	**2**	**-**	**8 (3.5)**	**9 (3.9)**
3-7	222	1	-	-	2	1	4	8 (3.6)	16 (7.2)
8-14	129	2	-	-	1	-	1	4 #	5 #
15-30	26	1	-	-	-	1	-	2 #	-
	205 patients who were still admitted at day 3 and who had no clinical complications during day 1-2								
3	**205**	**1**	**-**	**-**	**-**	**-**	**-**	**1 (0.5)**	**5 (2.4)**
4-7	193	-	-	-	2	1	3	6 (3.1)	13 (6.7)
8-14	114	2	-	-	1	-	1	4 #	4 #
15-30	24	1	-	-	-	1	-	2 #	-
	188 patients who were still admitted at day 4 and who had no clinical complications during day 1-3								
4	**188**	**-**	**-**	**-**	**1**	**1**	**1**	**3 (1.6)**	**4 (2.1)**
5-7	176	-	-	-	1	-	2	3 (1.7)	7 (4.0)
8-14	109	2	-	-	1	-	1	4 #	4 #
15-30	21	1	-	-	-	1	-	2 #	-
	169 patients who were still admitted at day 5 and who had no clinical complications during day 1-4								
5	**169**	**-**	**-**	**-**	**-**	**-**	**1**	**1 (0.6)**	**5 (3.0)**
6-7	146	-	-	-	1	-	1	2 (1.4)	1 (0.7)
8-14	104	2	-	-	1	-	1	4 #	4 #
15-30	18	1	-	-	-	1	-	2 #	-
	140 patients who were still admitted at day 6 and who had no clinical complications during day 1-5								
6	**140**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**1 (0.7)**
7	114	-	-	-	1	-	1	2 (1.4)	-
8-14	99	2	-	-	-	-	1	3 #	4 #
15-30	17	1	-	-	-	1	-	2 #	-

Table 6.2 In-hospital complications for acute MI patients treated with primary PCI.

† In case patients had multiple events, then most severe event for each day/period is presented
‡ Including heart failure Killip II or III, 2nd or 3rd degree AV-block and post-MI angina
§ Percentages relative to number of patients, still hospitalized at the beginning of the day/period
# Percentages are omitted due to steeply decreasing number of hospitalized patients in this period

DISCUSSION

Based on our early discharge decision rule we found in the present study that 49% of the 342 patients who experienced an uncomplicated MI and underwent primary PCI with drug-eluting stents were eligible for early discharge on the morning of day 5 with low further cardiac complications in the early days thereafter (event rate until day 7 for major complications is 1.8% (3/169) and for all complications is 5.3% (9/169)). Although late (day 8-30) severe in-hospital complications still occurred, event rate of death is 1.8% over that period. Therefore, the decision model which was developed in the thrombolytic era and based on clinical assessment without pre-discharge testing, turned out to be applicable in patients with acute myocardial infarction treated with primary PCI with drug-eluting stents.

Our decision rule is based on the concept that patients can be discharged if: no complications occurred so far requiring additional therapy up to day 4 since thereafter, the expected complication rate is low. After earlier complications discharge can be effectuated if problems are managed and stabilised.

Treatment of patients with acute myocardial infarction has improved over time,[13] and consequently the length of hospital stay has considerably decreased.[5,14] In the early 1980s, before the widespread introduction of reperfusion therapy, MI patients were hospitalized for at least 3 weeks but today the hospital stay in the Netherlands has decreased to an average hospital stay of 8 days in 2005.[5] From our report it is evident that a further reduction is possible and safe. Median hospital stay can be decreased from 7 days to 6 days which would result in a major cost-savings. The search for further reduction in hospital stay is motivated by a general principle not to hospitalise unless clearly necessary, to reduce expenses and is supported by the belief that part of the current hospitalization is due to inefficiency. Indeed, in a cost-conscious environment, hospitalization should not be extended beyond the patient's clinical needs. Furthermore, early hospital discharge has been associated with improved physical and psychological outcome, especially in elderly subjects.[15,16]

Accordingly, the ESC and ACC/AHA have formulated guidelines for the management of MI. These guidelines recommend patients with uncomplicated acute MI to be considered for early discharge within 4 days after admission.[17] Such, early discharge of low-risk patients with acute MI has been shown to be feasible and can be achieved at no additional risk of adverse events.[8,18] However, the Euro Heart Survey Acute Coronary Syndromes (EHS-ACS) demonstrated a discordance between existing guidelines for ACS and current practice across a broad spectrum of hospitals in Europe.[19,20] Hospital stay is often unnecessarily prolonged in patients with uncomplicated MI. Therefore a considerable further reduction in length of hospital stay can be achieved. Formal protocols to evaluate the risk of life-threatening complications requiring hospitalization should be implemented systematically.

The present study shows that risk stratification for early discharge or prolonged hospitalization can be performed without non-invasive techniques like echocardiography

and stress testing. Based on the decision rule, those patients who experienced an uncomplicated MI in the first 4 days could be discharged. Implementation of our early discharge model would have saved 2.15 hospital days per patient with acute myocardial infarction and contribute to improving physical and psychological outcome and accomplish efficient use of our resources and tremendous cost-savings.

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7

Early discharge of patients with acute myocardial infarction has no adverse psychological consequences

Maureen J. van der Vlugt[1]
Susanne S. Pedersen[2,3]
Eric Boersma[1]
Ruud A. M. Erdman[1,3]
Ineke M. Leenders[4]
Gheorghe A. M. Pop[5]
Rinus J. Veerhoek[6]
Maarten L. Simoons[1]
Jaap W. Deckers[1]

[1]Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands
[2]Institute of Psychology, Aarhus University, Denmark
[3]Department of Medical Psychology & Psychotherapy, Erasmus University, The Netherlands
[4]Haven Hospital, Rotterdam, The Netherlands
[5]Vlietland Hospital, Vlaardingen, The Netherlands
[6]St. Franciscus Gasthuis Rotterdam, The Netherlands

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ABSTRACT

Objective

To investigate whether 1) early hospital discharge results in adverse psychological outcome assessed at three months, and 2) whether patients with a complicated versus an uncomplicated clinical course have different psychological profiles.

Methods

The Heart Patients Psychological Questionnaire was administered to 645 consecutive myocardial infarction patients on the fifth day of hospitalization and at three months. Baseline demographic and clinical variables were sampled from medical records. Patients were divided into four groups according to study phase (registration versus validation) and clinical course (complicated versus uncomplicated).

Results

No differences in psychological outcome were found at three months between patients discharged early and those who remained in hospital for the conventional period. No relation was found between clinical course and psychological profile. Correcting for baseline differences, registration phase patients with a complicated course scored lower on feelings of being disabled at three months than patients with an uncomplicated course.

Conclusions

1. Early discharge had no adverse psychological consequences for patients with myocardial infarction;
2. Psychological profiles of uncomplicated patients and complicated patients were comparable.

INTRODUCTION

The management of acute myocardial infarction (AMI) has changed considerably in recent years with respect to immediate treatment due to the introduction of thrombolytic agents and percutaneous interventions, and with respect to rehabilitation. While prolonged bed rest and hospitalization were previously regarded as the mainstay of treatment, currently patients are mobilized and discharged as soon as possible. The question, however, remains whether early mobilization and discharge have adverse psychological consequences.[17] This question seems particularly relevant with the increasing evidence that psychosocial factors have an impact on prognosis independent of disease severity,[4] and the knowledge that 20 to 40% of cardiac patients suffer from depression, anxiety, and other emotional disturbances up to several years following the event.[10,11] Few studies, however, have addressed this issue.[21,19,1,5,12] A study examining the consequences of early discharge from a Coronary Care Unit found that patients, who are anxiety-prone and have a poor clinical prognosis, might be at risk of adverse psychological consequences.[21] Contradictory results were found in a study assessing anxiety during hospitalization, which showed that levels of anxiety were lowest just prior to discharge.[19] It should be noted that the latter study looked only at psychological outcome until one day prior to discharge. Others have reported a relatively negative mental response to discharge.[1,5,12] However, all of the studies were published more than a decade ago. With the evolution of treatment options, new approaches to rehabilitation, and the increasing evidence that psychosocial variables impact on prognosis independent of disease severity,[4,14] it is therefore appropriate to readdress the issue.

Recently, we developed a strategy for early discharge in a large, unselected group of AMI patients, which has been validated with respect to feasibility and physical safety for the patient.[25] This discharge strategy was developed in 647 patients with AMI and validated in another sample of 825 consecutive patients. All patients were categorized according to clinical course as either complicated or uncomplicated. In the validation phase of this study, patients at low risk - that is with an uncomplicated clinical course - were discharged three days earlier from hospital compared to patients with a similar clinical profile in the registration phase. Low-risk was defined as the absence of clinical factors with negative prognostic impact. All patients were requested to fill in a psychological questionnaire on day five during hospitalization as well as three months later.

Thus, the present study was able to address two issues: 1) to investigate whether early discharge resulted in adverse psychological outcome assessed at three months; 2) to investigate whether patients with an uncomplicated clinical course had a different psychological profile than patients with a complicated course.

METHODS

Patients

The study population consisted of 1,472 consecutive AMI patients admitted to four hospitals in Rotterdam, The Netherlands, participating in the Short Hospital Rehabilitation Trial (SHORT). The design, methods and results of this study have been published elsewhere.[25] Briefly, the aim of the SHORT study was to develop and validate a decision-making strategy for early discharge after AMI in unselected patients. The model was developed in patients in the Registration Phase (RP) and validated in a similar (according to gender, age, medical history, risk factors, in-hospital mortality, and localization of infarction) group of patients in the Validation Phase (VP). Daily new event rates were calculated, defined as the ratio of patients with complications (in order of severity: mortality, ventricular fibrillation, recurrent infarction, heart failure, advanced atrioventricular (AV) block, unstable angina, ventricular tachycardia, and supraventricular tachycardia) occurring at a specific hospital day and those without complications until that day. Thus, uncomplicated patients, who had a daily event-rate close to zero for major events and below 2% for minor events were safe for early discharge after the 5th day of hospitalization. In the validation phase of the study, patients with an uncomplicated clinical course were discharged three days earlier from hospital compared to patients with a similar clinical profile in the registration phase. Figure 7.1 gives an overview of SHORT, the psychological part of the study, and their respective samples.

Patients were excluded from psychological evaluation if they had died within 5 days of hospital admission (RP: *n* = 49 (32%); VP: *n* = 75 (38%)), if they were unable to fill in the questionnaire due to a serious clinical condition (RP: *n* = 41 (26%); VP: *n* = 56 (28%)), were suffering from other incapacitating diseases (RP: *n* = 28 (18%); VP: *n* = 31 (16%)), or had difficulty understanding and reading Dutch (RP: *n* = 37 (24%); VP: *n* = 37 (19%)). On the basis of these criteria, the psychological questionnaire was given to 492 (76%) of the 647 registration phase patients, and 626 (76%) of the 825 validation phase patients. In the registration phase, 292 (59%) patients (221 men and 71 women) completed the psychological questionnaire at, or around day five of their hospitalization, of whom 153 (52%) patients had an uncomplicated course. In the validation phase, 353 (56%) patients (254 men and 99 women) filled in the questionnaire during hospitalization, of whom 140 (40%) had an uncomplicated course. From the initial sample of patients, 149 (51%) RP patients and 244 (69%) VP patients comprised the follow-up sample at three months.

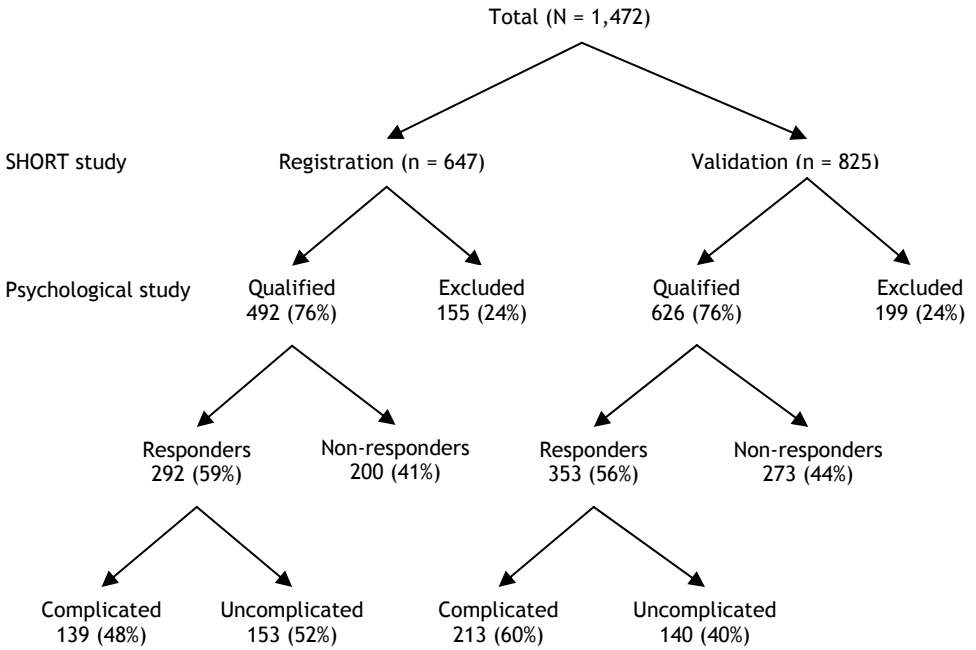

Figure 7.1 Flow chart of participants in the SHORT study and the subsequent psychological study.

Measures

The applied standardized psychological test was the Heart Patients Psychological Questionnaire (HPPQ), which was developed and validated in 1,649 cardiac patients in The Netherlands.[7,8,27] The HPPQ was originally developed to evaluate the psychological health of patients with different cardiac diagnoses. The HPPQ consists of 52 items, and each of the items has a 'Correct / Question Mark / Incorrect' response category. The question mark indicates that the respondent can endorse neither the response category 'correct' nor 'incorrect'. Forty items belong to one of four subscales, whereas 12 items are so-called buffer items: 'Well-being' (W-scale; 12 items; score range from 12 to 36), 'Feelings of being disabled' (F-scale; 12 items; score range from 12 to 36), 'Despondency' (D-scale; 10 items; score range 10 to 30) and 'Social inhibition' (S-scale; 6 items; score range 6 to 18). A high score on 'well-being' reflects that the respondent feels happy, healthy, and self-confident. Conversely, a high score on 'feelings of being disabled' indicates that the respondent feels unable to function as well as prior to the cardiac event, and that this is experienced and perceived as being disabling. A respondent scoring high on 'despondency' is characterized as suffering from anxiety, depression, and worrying, whereas someone scoring high on

'social inhibition' is often introvert and feels ill at ease in the company of people, with whom he or she is not acquainted.
In addition to the HPPQ, baseline characteristics, clinical course, cardiac risk factors, infarct size, and duration of hospital stay for all patients were taken from medical records and collected in a personal interview with the patient, respectively.

Procedure

During both registration and validation phases, the patients were asked to fill in the HPPQ on day 5 in the hospital and three months after the date of admission. A medical doctor (MJV) under conditions of confidentiality and privacy handed out the questionnaire. Patients were instructed how to complete the questionnaire, and were asked to fill it in without any help from friends or family. Patients who did not respond were reminded by mail.

Statistical analyses

Between group comparisons of responders versus non-responders and responders versus excluded were undertaken using chi-square tests for categorical variables and ANOVA for continuous variables. Patients were divided into four groups according to the study phase (registration or validation) and clinical course (complicated or uncomplicated). Analyses of variance were used to evaluate differences between groups, using registration phase patients with an uncomplicated course as reference group. Both crude and adjusted linear regression analyses were performed to evaluate differences in short-(fifth day) and medium-term (three months) psychological outcome between these four groups. We adjusted for possible differences in demographic characteristics, clinical risk factors, and indicators of infarct size. Furthermore, R^2-values are given, reflecting the explained data variance by the regression model ($0 \leq R^2 \leq 1$).

RESULTS

Baseline characteristics of the sample

Baseline characteristics of HPPQ responders, non-responders, and excluded patients are depicted in Table 7.1.
Obviously, baseline characteristics of excluded patients were significantly different from patients eligible to participate in the psychological part of the study. The excluded patients were older, more likely to be female, and had a larger infarct size (Table 7.1). Their in-hospital mortality rate was close to 50%. There were no striking differences between responders and non-responders.
The response rates in the two phases were comparable with 59% completing the HPPQ in the registration phase and 56% in the validation phase, respectively (Figure 7.1). The

number of patients with an uncomplicated course and thus eligible for early discharge was somewhat higher in the registration phase (52%) compared with (40%) the validation phase.

	(1) Responders N(%)	(2) Non-responders N(%)	Comparisons between (1) & (2)	(3) Excluded N(%)	Comparisons between (1) & (3)
Number of patients	645	473		354	
Age (mean, years)	63	64	0.237	68	0.0001 †
Female	170 (26)	116 (25)	0.488	173 (48)	0.0001 †
Prior infarction	149 (23)	105 (22)	0.722	139 (39)	0.0001 †
Prior angina (> 4 weeks)	123 (19)	92 (20)	0.873	73 (20)	0.556
Anterior infarction	227 (35)	158 (34)	0.534	161 (45)	0.0014 §
Large infarct (CK > 1500)	148 (23)	114 (24)	0.652	71 (20)	0.291
Killip class III or IV	64 (10)	53 (11)	0.489	123 (34)	0.0001 †
Complicated MI	282 (44)	217 (46)	0.474	298 (83)	0.0001 †
30 day mortality	2 (0.3)	4 (0.9)	0.226	180 (50)	0.0001 †

Table 7.1 Baseline characteristics of HPPQ responders, non-responders and excluded patients in the SHORT study.

CK: creatine phosphokinase. § $P < 0.01$; † $P < 0.001$.

Psychological outcome

Mean baseline scores for all 645 respondents, irrespective of study phase and clinical course, on the HPPQ subscales were: well-being: 24.85 (SD 7.88); feelings of being disabled: 26.03 (SD 6.40); despondency: 16.54 (SD 5.00); and social inhibition: 11.64 (SD 3.24), respectively. At three months follow-up, psychological data were available for 393 respondents. Again irrespective of study phase and clinical course, their mean scores on the HPPQ subscales were: well-being: 26.82 (SD 8.11); feelings of being disabled: 25.99 (SD 7.10); despondency: 15.88 (SD 5.33); and social inhibition: 11.46 (SD 3.21). These data are comparable to HPPQ scores of 370 patients with mixed cardiac diagnoses prior to rehabilitation.[23]

Analyses of variance showed no differences on psychological outcome at three months between patients discharged earlier and patients, who stayed in hospital for the conventional period. Similar results were found when correcting for baseline characteristics.

No differences were found on psychological profile between patients in the registration versus validation phase, or with a complicated versus an uncomplicated clinical course as measured by the four subscales of the HPPQ at baseline and at three months. Correcting for baseline differences between groups also showed no significant relation between registration versus validation phase, uncomplicated versus complicated course, and

psychological status at baseline, respectively. However, following adjustment for baseline characteristics, a difference on feelings of being disabled was found between registration phase patients with a complicated versus an uncomplicated course at three months. Patients with a complicated course scored lower on feelings of being disabled.

Predictors of psychological outcome at baseline are shown in Table 7.2. Gender was independently related to all HPPQ subscales with women having poorer psychological outcome compared with that of men. Age was also a predictor of three of the sub-scales with older patients scoring higher on well-being and feelings of being disabled, but lower on despondency. History of AMI was associated with decreased well-being and increased feelings of being disabled. Diabetes was a predictor of decreased social inhibition, whereas angina pectoris was associated with increased social inhibition. However, it should be noted that the variance explained by the predictor variables is low with only 6% of the variance being explained. Predictors of psychological outcome at three months are not shown, since only the baseline score on the relevant subscale proved to be a significant predictor of the score on the same subscale at three months.

Dependent Measure	Predictor variables	B	R^2	df	F	*P*
Well-being	Gender[a]	-3.332	0.0347	1	23.139	0.0001
	Age	0.039	0.0034	1	2.202	0.0024
	Previous MI[b]	-1.105	0.0035	1	2.267	0.0441
Feelings of being disabled	Gender	3.167	0.0476	1	32.114	0.0001
	Age	0.139	0.0666	1	45.909	0.0001
	Previous MI	3.024	0.0399	1	26.711	0.0001
Despondency	Gender	0.631	0.0031	1	2.000	0.0034
	Age	-0.072	0.0293	1	19.381	0.0001
Social inhibition	Gender	1.661	0.0510	1	34.548	0.0001
	Diabetes[b]	-0.593	0.0034	1	2.170	0.0157
	Angina > 4 weeks[b]	1.219	0.0107	1	6.939	0.0259

Table 7.2 Predictors of psychological outcome at baseline.

[a]Male = 0, female = 1; [b]No = 0, yes = 1; MI = myocardial infarction.

DISCUSSION

During the last two decades, knowledge of cardiovascular disorders has increased considerably, resulting in an improvement in treatment options.[9] As a consequence, more patients recover, and usually recover more quickly. Several studies have been undertaken to study this possible alteration in rehabilitation policy, and its consequences for cardiac patients (see editorial comment).[13] Most of these studies, however, have primarily looked at the physical consequences of early discharge. Early discharge may also impact on

emotional reactions and psychological adjustment. The extent of this impact, however, is unclear, since few studies have addressed this issue. In addition, most studies have focused primarily on anxiety.[21,19] Thus, the objective of the present study was to examine whether early discharge results in adverse psychological outcome, as determined by four different psychological aspects as measured by the HPPQ.

We found no relation between early discharge and adverse psychological consequences at three months as measured by the four subscales of the HPPQ. This lends further credence to the strategy that we developed in the SHORT study. In indicates that patients at low cardiac risk are suitable for early discharge, and that early discharge has no adverse physical or psychological consequences to the patient.

We also found no association between patients' psychological profiles and clinical course. Patients with an uncomplicated clinical course had a comparable psychological profile to patients with a complicated course at baseline, although it should be appreciated that very severely sick patients were excluded from participation in the psychological study. However, when correcting for demographics (age, gender), cardiac risk factors (smoking, diabetes mellitus, hypertension, prior infarction), and infarct size (creatine phosphokinase), we found a difference between patients with a complicated versus an uncomplicated clinical course in the registration phase, with the former patients scoring lower on feelings of being disabled. The latter finding is surprising, as one might expect patients with a complicated clinical course to score higher on feelings of being disabled. An alternative explanation could be that patients with a complicated course are denying the seriousness of the event, although we have no way of confirming this, since denial was not assessed in this study.

Gender was an independent predictor of outcome on all HPPQ subscales with women having adverse psychological outcome compared with men. One study that looked at gender differences on the HPPQ has found similar results.[6] This also concurs with studies that have shown that women are more likely to have difficulty with emotional adjustment following AMI compared with men.[3,22] Age was an independent predictor of three of the sub-scales, with older patients scoring higher on well-being and feelings of being disabled, but lower on despondency. In other words, older patients felt more disabled, but were generally psychologically better adjusted. As pointed out by other authors, the latter may reflect a more positive and hopeful attitude among older patients with regard to their disease.[2] With advanced age an increase in chronic and acute conditions is to be expected. Thus, the cardiac event may not be so traumatic to older patients as compared to younger patients, who are still raising a family and trying to advance their careers. Patients with a previous AMI suffered from decreased well-being and enhanced feelings of being disabled. This concurs with studies that have found an association between previous AMI and decreased quality of life.[28,18] Diabetes was a predictor of decreased social inhibition, whereas angina pectoris was associated with increased social inhibition. We can offer no interpretation for the former association. However, higher depression scores have been found in patients with angina.[20,16] With apathy or loss of interest being one of

the key symptoms of depression, patients with angina may be plagued by their symptoms to such an extent that it prevents them from expending energy on making social contacts with people they are not acquainted with.

The inconsistent findings in the few studies that have investigated psychological outcome following early discharge can most likely be attributed to differences in clinical circumstances, the applied discharge protocol, and measures selected to assess psychological outcome. As a result of the introduction of reperfusion therapy in the early 1980's, the prognosis of AMI patients has improved dramatically.[9,26] Furthermore, extensive information and education have increased public knowledge of the disease at hand. These circumstances might very well have caused alterations in psychological reactions, which surpass psychological reactions caused by early mobilization or discharge.

The findings of the present study should be interpreted with caution due to the relatively high attrition rate in the psychological part of the study. However, analyses showed no differences between responders and non-responders on demographic baseline characteristics and clinical course. Another limitation is that patients excluded from the psychological part of the study were more likely to suffer from severe cardiac complications, and hence also more likely to suffer from more emotional difficulties than patients, who were included. However, the main objective of the study was to evaluate psychological consequences as a result of early discharge in patients with uncomplicated myocardial infarction. Patients excluded because of complications would in any case not have been eligible for early discharge, and it is thus unlikely that this limitation has had a major impact on the results. Finally, the HPPQ, which was used to assess psychological adjustment in this study, may not have been sufficiently sensitive to detect a difference between groups, since the instrument was originally developed for a mix of cardiac patients rather than for AMI patients alone.[7] Nevertheless, mean HPPQ scores in our study population were comparable with the reference population for whom the HPPQ questionnaire was developed,[7] and with mean scores found in 370 mixed cardiac patients prior to rehabilitation.[23]

In conclusion, the results of the present study indicate that early discharge of patients with AMI had no adverse psychological consequences as measured by the HPPQ. Since female gender was associated with negative psychological outcome, it may be important to investigate in future research whether women are at increased risk of negative psychological sequelae following early discharge. Extant research and the present study show that women are more likely to suffer from emotional difficulties following a cardiac event and thus, may also be more vulnerable to suffer adverse psychological consequences following early discharge.

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8

Feelings of being disabled as a risk factor for mortality up to 8 years after acute myocardial infarction

Maureen J. van der Vlugt[1]
Ron T. van Domburg[1]
Susanne S. Pedersen[1,6]
Rinus J. Veerhoek[3]
Ineke M. Leenders[4]
Gheorghe A.M. Pop[5]
Daan ter Keurs[1]
Jaap W. Deckers[1]
Maarten L. Simoons[1]
Ruud A.M. Erdman[1,2]

[1]Thoraxcenter, Erasmus Medical Center, Rotterdam
[2]Department of Medical, Psychology and Psychotherapy, Erasmus Medical Center, Rotterdam
[3]St. Franciscus Gasthuis, Rotterdam
[4]Haven Hospital, Rotterdam
[5]Vlietland Hospital, Vlaardingen
[6]Department of Psychology and Health, Tilburg University
The Netherlands

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ABSTRACT

Objective

We examined the independent prognostic value of the four subscales of the Heart Patients Psychological Questionnaire (HPPQ) on mortality in acute myocardial infarction (AMI) survivors up to 8 years after the event.

Methods

The HPPQ, which measures well-being, feelings of being disabled, despondency and social inhibition, was administered to 567 AMI patients during hospitalization and at 3 months follow-up. The patients were followed for 8 years.

Results

During follow-up, 157 patients (28%) died. Forty-one percent of the patients had a score indicating at least mild to moderate feelings of being disabled. Patients with feelings of being disabled were at increased risk of mortality compared with those having a low score, adjusted for other cardiac risk factors (HR=1.8, 95% confidence interval (CI)=1.3-2.5) There was no interaction between feelings of being disabled and gender. None of the other HPPQ subscales were related to mortality or recurrent myocardial infarction (MI). When the study population was stratified by low- and high clinical risk (43% vs 57%, respectively), feelings of being disabled was the most prominent predictor of mortality in the low risk group (HR=3.5, 95%CI=1.4-8.8).

Conclusions

Feelings of being disabled measured at baseline and at 3 months was the most prominent predictor of mortality in low-risk patients 8 years post-MI. This finding adds to the existing knowledge that psychosocial variables influence morbidity and mortality in cardiac patients.

INTRODUCTION

The management of acute myocardial infarction (AMI) has changed considerably with the introduction of thrombolytic agents and immediate percutaneous interventions. Early reperfusion therapy limits infarct size, preserves left ventricular function and improves early as well as long-term survival. The long-term outcome after AMI is related to the residual cardiac function, coronary anatomy and established biomedical risk factors. Furthermore, there is increasing evidence that psychosocial factors have prognostic value independent of disease severity and traditional risk factors.[1-6] Psychosocial factors have also been shown to impede the change of health-related behaviour and to moderate the effects of medical and invasive treatment.[4,7]

Several instruments have been used to quantify the psychological functioning of cardiac patients, but few of these are disease specific. Disease-specific instruments are likely to be more sensitive and to cover dimensions that are relevant to cardiac patients, resulting in more valid results.[8] The Heart Patients Psychological Questionnaire (HPPQ) was developed in a heterogeneous group of cardiac patients and measures psychological functioning according to four subscales: well-being, feelings of being disabled, despondency and social inhibition.[9] There is a paucity of studies that have evaluated the prognostic value of the HPPQ. "Feelings of being disabled" measured one year after hospital discharge was a significant predictor of mortality 10 years in men after percutaneous coronary intervention (PCI) and in post-AMI patients.[10,11]

The objectives of the current study were to investigate the impact of the HPPQ subscales in relation to subsequent major adverse cardiac events and to examine the prognostic value of the four HPPQ scales in low- and high-risk patients at 8 years follow-up in post-AMI patients.

METHODS

Study Population

The study population consisted of 567 AMI patients who completed the HPPQ during hospitalization just prior to discharge from hospital. They were recruited from the Short Hospital Rehabilitation Trial (SHORT).[12] The aim of the SHORT study was to develop and validate a decision-making strategy for early discharge after AMI in unselected patients. Between May 1993 and November 1995, 1472 patients were enrolled in four Dutch hospitals. Patients were excluded from the psychological study if they had died in-hospital (n=139), were unable to fill in the questionnaire due to a serious clinical complication (n=199), were suffering from other incapacitating diseases (n=114), or had difficulty understanding and reading Dutch (n=212). Seventy percent of the remaining 808 patients meeting the inclusion criteria agreed to take part and filled in the HPPQ in-hospital. Of

these, 365 patients (64%) also filled in the HPPQ at 3 months.
No differences were found between responders and non-responders on baseline characteristics.[13] Ethical approval was obtained from the hospital ethics committee, and the study was carried out in accordance with the Helsinki Declaration. Written informed consent was provided by every patient.

Measures

The Heart Patients Psychological Questionnaire (HPPQ) was used to assess psychological functioning.[9] The HPPQ is a 52-item questionnaire that was developed and validated in a heterogeneous group of cardiac patients in the Netherlands. The scale consists of 52 items that are answered on a three-point scale (Correct / ? / Incorrect), of which 40 items contribute to four sub-scales: w*ell-being* ("I feel happy") (12 items; score range 12-36), f*eelings of being disabled* ("I quickly feel tired even if I don't do much") (12 items; score range 12-36) (Appendix A), d*espondency* ("I am often in a bad mood without knowing why") (10 items; score range 10-30), and s*ocial inhibition* ("I feel shy in the company of people whom I don't know") (6 items; score range 6-18). The remaining 12 items are so-called buffer items. A high score on feelings of being disabled, despondency and social inhibition indicates psychological maladjustment whereas a high score on well-being suggests adjustment. The internal consistency (Guttman's Lambda) of the subscales is good (*Well-being*=0.93; *Feelings of being disabled*=0.87; *Despondency*=0.80; and *Social Inhibition*=0.64), and test-retest reliability coefficients following 1-2 weeks range from 0.73 to 0.85.[9] The HPPQ has been used to assess psychological functioning in patients with myocardial infarction,[14] chronic heart failure[15] and coronary artery bypass graft surgery.[16] The HPPQ has also been shown to distinguish between relatively small groups of patients with stroke (n = 16), myocardial infarction (n = 20), and matched controls (n = 17).[17]

Follow-up

At the time of follow-up, May 1, 2002, clinical status was documented by approaching general practitioners by mail, review of hospital records, and checking the civil registries. Information on follow-up survival, reinfarction and coronary interventions was obtained for all patients.

Statistical analyses

The chi-square test (or Fisher's Exact Test when appropriate) was used to test the unadjusted association between categorical variables. Continuous variables were compared by Student's t-test. The HPPQ subscales were mainly analysed as continuous variables. Cumulative survival curves were constructed using the Kaplan-Meier method. The log-rank test was used to compare survival curves. Univariate Cox regression analyses, adjusting only for the follow-up period, were used to evaluate the unadjusted relation between baseline characteristics and mortality. To adjust for baseline characteristics, a multivariate Cox proportional hazard regression model was used. In this multivariate

model, the HPPQ scores were entered as dichotomised variables with the highest tertile on the subscale indicating probable psychological morbidity. To investigate the relation between feelings of being disabled and gender a test for interaction was performed. The clinical profile (demographic and procedural details), including complications, was recorded during the index AMI. The following variables were selected a priori and retained in the model irrespective of statistical significance: age, heart failure (as defined by Killip class >I), prior myocardial infarction, treated diabetes (type I or II), current smoking, treated hypertension, treated hypercholesterolemia, and the angiographic parameters multivessel disease (at least 2 stenotic arteries ≥50%) and impaired left ventricular function (ejection fraction <50%). The primary endpoint was all cause mortality; the secondary endpoint was a major adverse cardiac event (death, recurrent myocardial infarction or coronary revascularisation). A decision rule classified patients into high- and low risk patients.[12] Low risk was defined as free from major complications until day 7 (43% of all patients), and these patients would qualify for discharge on day 7. In-hospital complications were defined as death, cardiac arrest, recurrent myocardial infarction, or heart failure (defined as Killip class II, III or IV).

RESULTS

Sample characteristics

The study population consisted of 567 patients of whom 74% were male (Table 8.1). Mean age was 64 years. The mean in-hospital HPPQ subscales were similar to the subscale at three months. Median follow-up for the surviving patients was 8 years (range 6 to 9 years). During the follow-up period 157 patients (28%) had died.

Feelings of being disabled as a predictor of mortality

Patients scoring higher on feelings of being disabled at baseline were at increased risk of mortality at 8 years follow-up (HR=2.1, 95%CI=1.6-2.7) as indicated by univariate Cox regression analysis (Table 8.2). No significant relationships were found between the other HPPQ subscales and mortality. The predictive value of the 3-months' HPPQ scores was not different from the baseline HPPQ scores (Table 8.2). Other univariate predictors were older age (HR=3.0, 95%CI=2.3-3.9), heart failure (HR=2.0, 95%CI=1.5-2.5), prior MI (HR=1.8, 95%CI=1.4-2.4), and diabetes (HR=1.6, 95%CI=1.1-2.2). However, smoking at the time of the event (HR=0.7, 95%CI=0.5-0.9), dyslipidaemia (HR=0.7, 95%CI=0.5-0.9), and thrombolytic therapy (HR=0.7, 95%CI=0.5-0.9) were predictors of lower mortality. At 3-, 5- and 8-years' follow-up, feelings of being disabled remained an independent predictor of mortality after adjustment for other baseline characteristics (8-years: HR=1.8, 95%CI=1.3-2.5) (Table 8.3). The results did not change when using continuous scores on the HPPQ. We investigated the effect size of feelings of being disabled on mortality while entering

covariates by performing a suppression analysis. The results were that only age had some, non-significant effect, on feelings of being disabled. The beta coefficient of feelings of being disabled decreased from 0.85 to 0.68 and the hazard ratio from 2.3 to 1.8. However, the effect of the other cofactors was much less. Furthermore, the correlations between the independent variables and mortality were very low and varied from 0.04 to 0.2.

Although women scored worse on feelings of being disabled, there was no interaction found. Other independent predictors of mortality were older age, heart failure, diabetes, prior MI and treatment delay >3 hours. Cumulative survival rates among patients scoring high (highest tertile) versus those scoring low on feelings of being disabled were 91%, 80%, 70%, and 56% at 1, 3, 5 and 8 years, respectively (Figure 8.1). By comparison, survival rates in patients scoring low on feelings of being disabled were 95%, 89%, 86%, and 78%, respectively. This difference was significant (log-rank p-value<0.0001).

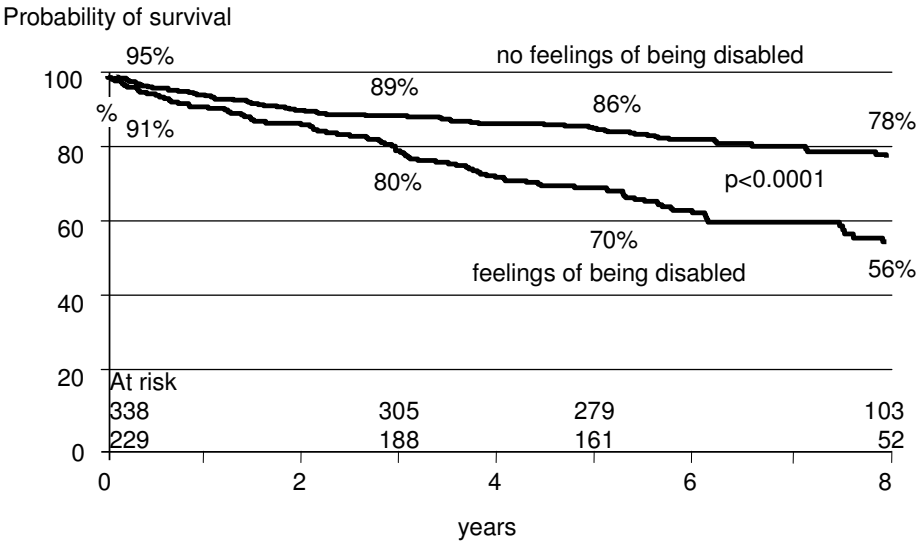

Figure 8.1 Cumulative survival curves according to patients with and without feelings of being disabled in 356 post-MI patients.

	N	%	Mean	SD
Number of patients	567			
Age years ±SD	64	±11.4		
Male	418	74		
History				
Angina > 4 weeks	136	24		
Progressive angina	74	13		
Heart failure (Killip > I)	112	20		
Prior myocardial infarction	124	22		
Prior CABG[a]	28	5		
Prior PCI[b]	21	4		
Risk factors				
Current smoking	247	44		
Dyslipidaemia	142	25		
Diabetes	64	11		
Hypertension	179	32		
Familiar	132	23		
Hospitalization				
Treatment delay >3 hours	373	66		
Thrombolytic treatment	264	47		
Intra-aortic balloon pump	58	10		
Psychological HPPQ* factors				
In-hospital (n=567)				
Feelings of being disabled			26.0	±6.2
Well-being			25.0	±7.7
Despondency			16.4	±4.8
Social inhibition			11.6	±3.1
At 3-months (n=365)				
Feelings of being disabled			26.0	±6.9
Well-being			26.9	±7.9
Despondency			15.8	±5.1
Social inhibition			11.6	±3.2

Table 8.1 Patient characteristics.

[a] CABG = Coronary bypass surgery
[b] PCI = Prior percutaneous coronary intervention
* HPPQ = Heart patients psychological questionnaire

	Feelings of being disabled			
	Yes (N = 202) N (%)	No (N = 365) N (%)	HR[a]	95%CI
Age yrs > 70 years	83 (41%)	92 (25%)	3.0	2.3-3.9
Gender	124 (61%)	294 (81%)	0.9	0.7-1.2
Angina > 4 weeks	75 (37%)	33 (9%)	0.8	0.5-1.3
Heart failure (Killip > I)	52 (26%)	60 (16%)	2.0	1.5-2.5
Prior myocardial infarction	65 (32%)	59 (16%)	1.8	1.4-2.4
Prior CABG	16 (8%)	12 (3%)	0.9	0.5-1.7
Prior PCI	13 (6%)	8 (2%)	1.2	0.6-2.3
Thrombolytic treatment	82 (41%)	182 (50%)	0.7	0.5-0.9
Treatment delay >3 hrs	143 (71%)	230 (63%)	1.6	1.1-2.2
Risk factors %				
Current smoking	76 (38%)	171 (47%)	0.7	0.5-0.9
Dyslipidaemia	53 (26%)	89 (24%)	0.7	0.5-0.9
Diabetes[b]	28(14%)	3 (10%)	1.6	1.1-2.2
Hypertension[b]	76 (38%)	103 (28%)	1.1	0.9-1.5
Psychological HPPQ[c]				
In-hospital				
Feelings of being disabled			2.1	1.6-2.7
No well-being			1.0	0.8-1.4
Despondency			1.2	0.8-1.7
Social inhibition			0.9	0.6-1.2
At 3-months				
Feelings of being disabled			1.7	1.1-2.6
No well-being			1.3	0.8-2.0
Despondency			1.4	0.8-2.4
Social inhibition			1.1	0.7-1.8

Table 8.2 Unadjusted predictors of mortality.

[a] HR = Hazard ratio, 95%CI = 95% Confidence interval.
[b] Treated risk factors.
[c] Highest tertile versus other tertiles.

	3-years		5-years		8-years	
	HR[a]	95% CI[b]	HR[b]	95% CI[b]	HR[b]	95% CI[b]
Feelings of being disabled[c]	1.5	1.1-2.4	1.7	1.2-2.4	1.8	1.2-2.5
Age	1.06	1.04-1.09	1.07	1.05-1.09	1.07	1.05-1.09
Male	1.9	1.1-3.2	1.7	1.1-2.6	1.9	1.3-2.7
Heart failure (Killip > I)	2.3	1.4-3.6	2.1	1.4-3.1	1.8	1.3-2.5
Diabetes	2.1	1.3-3.6	1.9	1.2-3.1	1.7	1.1-2.6
Prior MI	1.4	0.9-2.3	1.5	1.0-2.3	1.5	1.1-2.1
Delay start treatment	1.7	1.1-2.8	1.6	1.0-2.5	1.6	1.1-2.3
In-hospital high risk[d]	1.2	0.6-2.5	1.4	0.4-1.2	1.3	0.8-2.0

Table 8.3 Adjusted[a] feelings of being disabled as a predictor of mortality.

[a] Adjusted for age, prior myocardial infarction, prior coronary intervention, prior angina, progressive angina, Killip class, diabetes, smoking, hypertension, dyslipidaemia, thrombolysis, delay start treatment >3 hours;
[b] HR = hazard ratio, 95% CI = 95% Confidence interval;
[c] Highest tertile versus other tertiles;
[d] In-hospital high risk = in-hospital complications defined as death, cardiac arrest, recurrent myocardial infarction, heart failure (defined as Killip class II, III or IV).

The relation between feelings of being disabled and major adverse cardiac events

During the 8-year follow-up period, 240 patients (38%) experienced one or more major adverse cardiac events. A recurrent infarct was experienced by 9.2% of the patients, 6.5% underwent coronary bypass surgery (CABG), and 5.5% percutaneous coronary angioplasty (PCI). By far, most of the events occurred in the first year. Adjusting for all known baseline characteristics, feelings of being disabled remained an independent predictor of death or recurrent myocardial infarction (HR=1.8; 95% CI=1.3-2.4) and of any major adverse cardiac events (HR=1.4; 95% CI=1.1-1.8). In Figure 8.2 and Figure 8.3 the Kaplan-Meier survival curves of death or myocardial infarction and of any cardiac event are shown for patients scoring high versus those scoring low on feelings of being disabled.

Feelings of being disabled as a predictor of mortality stratified by clinical risk

When the study population was stratified according to low- and high clinical risk (43% and 57%, respectively; late mortality 17% and 29%, respectively), feelings of being disabled was the most prominent independent predictor of mortality in the low risk group (HR=3.5, 95% CI=1.4-8.8). In the high-risk group, feelings of being disabled was also an independent predictor of mortality, although less pronounced (HR=1.4, 95% CI=1.1-2.1).

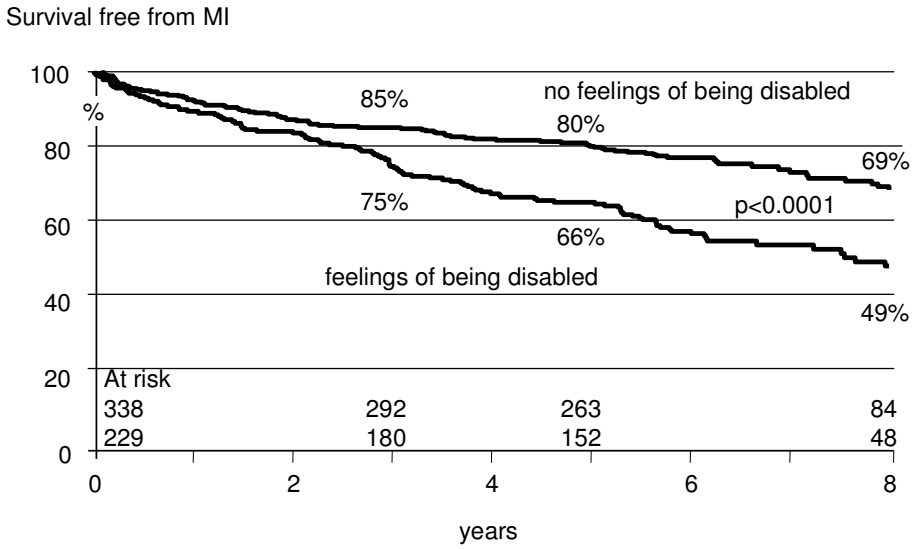

Figure 8.2 Cumulative survival curves free from myocardial infarction according to patients with and without feelings of being disabled in 356 post-MI patients.

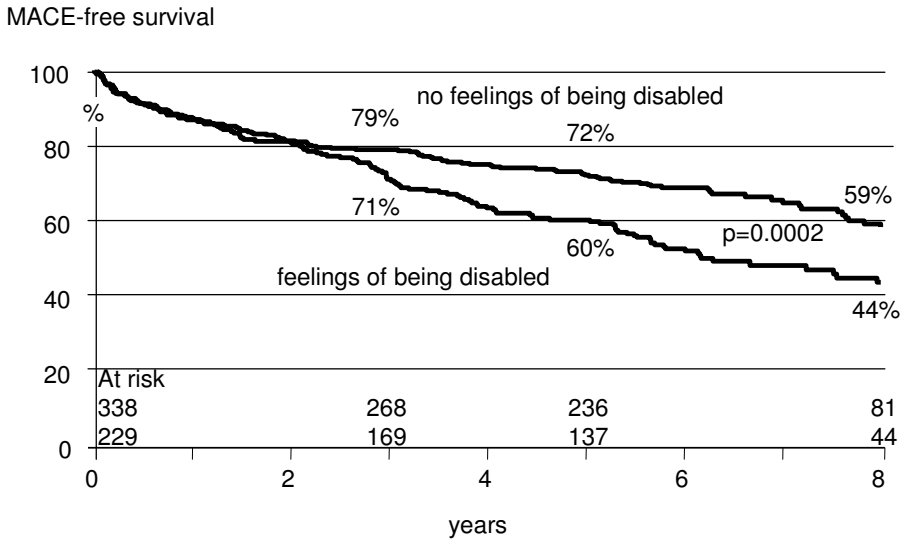

Figure 8.3 Cumulative survival curves free from major adverse clinical events (MACE: death, myocardial infarction, revascularization) according to patients with and without feelings of being disabled.

DISCUSSION

In the current study, feelings of being disabled in post-MI patients was associated with an increased risk of mortality and of major adverse coronary events at 8-year follow-up, independent of established biomedical risk factors. In other words, the effect of feelings of being disabled could not be accounted for by somatic symptoms and clinical impairment, as indicated by heart failure, angina, prior MI, and a larger infarct size. Although we did not investigate its mechanisms, the effect size for feelings of being disabled actually increased substantially when these clinical factors were added to the Cox model. This increase might be the result of a statistical suppressor effect, in which the effect of feelings of being disabled on mortality was partly masked by the association of feelings of being disabled with the other established factors. However, we were not able to find any relation between feelings of being disabled and the other cofactors on mortality. In other words, the suppression effect was marginal.

In contrast to the current study, in which the HPPQ was administered at baseline and early thereafter, the HPPQ was administered much later in the post-PCI study (1-2 years following the procedure).[10] Although we do not know whether feelings of being disabled in the post-PCI patients were present already early on, the findings of the current study suggest that when present, feelings of being disabled may not remit spontaneously. The similarity in the mean HPPQ scores at baseline and at 3 months post-AMI and their respective prognostic impact, which were also of a similar magnitude, supports this notion. A recent study by Blumenthal et al. also indicates that it is not the presence of psychological morbidity per se that renders patients at risk for adverse clinical outcome, but whether these symptoms become chronic.[1] In addition, although it may seem puzzling that there was no decrease in the HPPQ scores between baseline and 3 months in the current study, others have also shown that symptoms such as depression and anxiety may persist up to at least one year in cardiac patients.[1,18]

We were not able to find a relation between the other HPPQ subscales and mortality 8 years later. It may seem surprising that the HPPQ despondency subscale was not a predictor of mortality, given that it has an overlap with depression and that other studies have shown that depression has a prognostic role in patients with established CVD.[19-22] However, the shared variance between the HPPQ despondency and depression, as measured by Zung's Depression Scale is only 40%,[9] indicating that there is an overlap but they do not measure the same construct.

In our opinion, feelings of being disabled may best be construed as a mental state rather than a proxy for clinical symptoms of disease. This can be substantiated by the fact that both in the current study and our previous study,[10] feelings of being disabled was a significant predictor of mortality despite adjustment for clinical symptoms. In other words, it is the patients perception of the extent to which they are affected by the disease rather than clinical symptoms per se that predicts adverse clinical outcome. As such, feelings of being disabled may share some common features with vital exhaustion,

another psychosocial risk factor for adverse clinical outcome.[23,24] Vital exhaustion also reflects a mental state rather than physical symptoms and is defined as unusual fatigue, demoralisation and increased irritability.[23] Although no studies to date have evaluated the overlap between feelings of being disabled and vital exhaustion, studies are now beginning to emerge that seek to disentangle the overlap between psychological constructs.[25,26] Two studies have shown that vital exhaustion and depression are moderately correlated, suggesting that, although there is an overlap, they comprise separate and distinct constructs.[26,27] An earlier study found that the shared variance between depression and feelings of being disabled is 15%.[9] Taken together, these findings suggest that feelings of being disabled comprises a different and distinct construct compared with vital exhaustion and depression.

The findings of the current study have implications for research and clinical practice. Further research is warranted that seeks to disentangle the overlap between psychological constructs to establish a core list of the most "toxic" risk factors. In addition, repeated rather than single assessments of psychological symptoms in research should become the preferred strategy to delineate the most optimal time point(s) to screen for psychological morbidity in clinical practice. The findings by Blumenthal et al.[1] and Poston et al.[28] support this notion. Of note, in the latter study, depression at 1-month postprocedure was a much stronger predictor (OR=27.2) of depression at 6 months than was baseline depression (OR=6.5).[28] In turn, such knowledge would optimise risk stratification in clinical practice and help to identify patients most at need for psychosocial intervention. Finally, research into the mechanisms that may be responsible for the impact of feelings of being disabled on prognosis is required, as feelings of being disabled may only be a risk marker rather than a risk factor. Cytokines and altered haemostasis have been associated with increased symptoms of vital exhaustion[29,30] and may also provide mechanisms for feelings of being disabled. However, until such information is available, the results of the current study and those of our previous study suggest that feelings of being disabled in cardiac patients should be attended to, as they comprise a risk factor on par with diabetes and heart failure. This was especially the case in the low-risk population, i.e. those defined as free from major complications until Day 7 (43% of all patients). In other words, although screening on its own is not sufficient, "'not enough' does not mean 'not at all'", as pointed out in a recent editorial on the screening for depression.[31]

Limitations

Although psychosocial intervention programs would be warranted for patients scoring high on feelings of being disabled, its value is controversial. A trial comparing the effect of an outpatient rehabilitation program with standard medical care in patients with ischemic heart disease showed that rehabilitation patients displayed healthier behaviour than did the controls, as measured by the HPPQ.[32] In other words, the latter trial demonstrated that feelings of being disabled might be reduced through intervention. However, the important question is whether a reduction in psychological morbidity automatically leads

to improved survival. The recent ENRICHD[33] and SADHART[34] trials showed a reduction in depressive symptoms and improvement in social support, but this did not lead to a concomitant increase in event-free survival. Furthermore, the poor prognosis of patients scoring high on feelings of being disabled may well partly be determined by other factors than pure psychosocial factors, such as differences in lifestyle (physical exercise and food habits) during follow-up, which were not assessed in the current study. Finally, other variables not assessed in the current study, such as socioeconomic status,[35] may also serve as confounders on the relationship between feelings of being disabled and mortality.

CONCLUSIONS

This is the first study to look at the prognostic value of the HPPQ on the long-term outcome following MI. The results showed that patients with a high score on feelings of being disabled who experience a MI are at increased risk of mortality and recurrent MI 8 years later. In particular, the subgroup of patients at low clinical risk, who score high on feelings of being disabled, might benefit from psychosocial intervention targeting feelings of being disabled in combination with optimal medical treatment with aspirin, beta-blockers, ACE-inhibitors and statins. Thus, in clinical practice, it would be important to be aware of and intervene in those patients who feel most disabled by their cardiac disease.

Appendix Feelings of being disabled

1. If it's cold and windy outside, I hardly ever leave the house.
2. I could do a lot more work formerly.
3. I don't have enough stamina.
4. I used to be capable of a lot more.
5. I fell tired quicker than I think is normal.
6. I feel tight in the chest quite often.
7. I still feel up to anything.
8. Things often go wrong if I have to do something quickly.
9. I quickly feel tired even if I don't do much.
10. I don't like the idea of doing heavy work.
11. I get out of breath quickly.
12. I still feel quite capable of taking parts in sports.

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9

Validation of a decision model for the treatment of patients with acute myocardial infarction

Maureen J. van der Vlugt[1]
Ron T. van Domburg[1]
Farshad Imani[1]
Alf E.R. Arnold[2]
Tjeerd Germans[2]
Rinus J. Veerhoek[3]
Ineke M. Leenders[4]
Jaap W. Deckers[1]
Maarten L. Simoons[1]
Eric Boersma[1]

[1]Thoraxcenter, Erasmus Medical Center, Rotterdam
[2]Medical Centre Alkmaar, Alkmaar
[3]St. Franciscus Gasthuis, Rotterdam
[4]Haven Hospital, Rotterdam
The Netherlands

Submitted

ABSTRACT

Objectives

Decision models enable physicians to apply available treatment options in a consistent and reproducible manner, resulting in more objective choices, and most likely, better care of patients. The aim of the study was to validate the key model assumptions and predictions of a decision model for selection of reperfusion therapy in patients with acute myocardial infarction (MI) who were treated according this model and followed-up until 10 years after admission.

Methods

During 1993-1996 a total of 983 consecutive patients with an acute MI in four hospitals in the Netherlands were treated in conformance with a formal decision model, developed to guide reperfusion treatment. Decisions on reperfusion therapy were based on the estimated regain of life-expectancy that would be lost if not such therapy was installed. Time from onset of symptoms to treatment, age, previous infarction, infarct location and indicators of the expected infarct size were considered determinants of 1-year morality. Life-expectancies were calculated based on the estimated 1-year and long-term mortality figures, for several clinical scenarios. We compared the 'observed' and calculated life-expectancies to validate our previous developed decision model based on calculated life-expectancies.

Results

During 10-year follow-up, 403 patients (41.0%) had died and 30 patients (3.1%) where lost to follow-up. One-year mortality was underestimated in patients aged ≥ 70 years, and overestimated in patients with multiple risk factors as well as in those treated within3-6 hours after onset of symptoms. Long-term annual mortality probabilities were overestimated in our model, especially the probabilities in the more distant future.
The median value of 'observed' regained life-expectancy by successful reperfusion therapy was close to the median estimated value (5.5 versus 4.9 months). These data indicate that, on average, effects of reperfusion therapy on life-expectancy were adequately estimated by our model. In individual patients, however, 'observed' and estimated effects could be quite different (95% limits of agreement were -15.9 and 12.9) with a negative correlation (r=-0.58) between the estimated regain and the 'observed' minus estimated values. The model underestimated the regain of life-expectancy by reperfusion therapy in elderly patients (lowest estimated values) and overestimated in those with multiple determinants of 1-year mortality (highest estimated values).
Yet, the ranking of patient groups with lower and higher expected regain in life expectancy appeared to be appropriate.

Conclusions

Treatment effects were adequately estimated on the average group level, but the model has several deficiencies that explain the varying accuracy in individual patients. Although, the clinical question is not longer applicable in our environment, where primary PCI is liberally available, the model itself is not obsolete and can, once updated according to the findings of this study, still be used for clinical decision making in acute myocardial infarction patients.

INTRODUCTION

Decision models enable physicians to apply available treatment options in a consistent and reproducible manner, resulting in more objective choices, and most likely, better care of patients.[1] Furthermore, application of decision models can help to focus resources on the most cost-effective treatment strategies. Still, it has to be realized that clinical decision models are only a simplification of daily clinical practice, and there is a serious possibility that their design is inaccurate for the intended purpose. Particularly, the choice of the model structure, data sources that are used to assess model parameters, the time-horizon of treatment outcomes and assumptions that are made about unknown data-elements may influence its external validity and applicability. In view of these considerations, validation exercises are crucial to understand the performance of clinical decision models.

Since it became clear that a myocardial infarction is caused by an acute intracoronary thrombotic occlusion, treatment strategies have been introduced that aim at a rapid, complete and lasting restoration of the coronary blood flow. In the early 1990s, physicians could choose from different pharmacological reperfusion regimens based on non-fibrin-specific (streptokinase, urokinase) or fibrin-specific agents (alteplase, reteplase), whereas in some hospitals, catheter-based interventions also were an alternative. Randomized clinical trials that were conducted in those days demonstrated an important mortality reduction by fibrinolytic therapy compared to control treatment,[2] a further mortality reduction by fibrin-specific agents compared to non-fibrin-specific agents,[3] and an even further reduction by primary percutaneous interventions (PCI) compared to pharmacological reperfusion treatment.[4] Unfortunately, these options were not only increasingly effective, but also increasingly complex and costly. Explorative analyses of clinical trial data, as well as data from observational studies, demonstrated that treatment effects were influenced by the patient's age, area at risk or infarct size, left ventricular function and treatment delay.[1,5-11] In this acute clinical setting, in which there is little time for reflection, adequate decision making appeared a major challenge. With the intention to support the treating physician to make consistent decisions, and to provide optimal therapy in spite of limited resources, a decision model was introduced in 1996, in which suspected treatment effects were expressed in terms of gain in life expectancy.[5] The aim of this study was to validate the key model assumptions and predictions in 983 patients with acute myocardial infarction who were treated according this decision model and who were followed-up until 10 years after admission.

METHODS

Decision model

The development and initial validation of the decision model is described in detail elsewhere.[13] Briefly, the model was developed to guide treatment of patients between 40 and 80 years of age, presenting within 12 hours after the onset of symptoms suggestive of evolving MI, with typical chest pain lasting at least 20 minutes, accompanied by significant electrocardiographic changes. Time from onset of symptoms to treatment, age, previous infarction, infarct location and indicators of the expected infarct size were considered determinants of 1-year mortality. Estimated 1-year mortality in patients not receiving reperfusion therapy ranged from less than 5% in patients with small infarcts presenting early to over 40% in those with large infarcts and multiple risk factors presenting late.

Randomized clinical trials only demonstrated significant heterogeneities in treatment effects of reperfusion therapy for the duration of symptoms (treatment-delay) but not for other clinical baseline characteristics.[1] Based on these observations, proportional 1-year mortality reduction by reperfusion therapy was thought to be similar in low- and high-risk subgroups in our model. Consequently, the largest absolute mortality reductions by reperfusion therapy were expected in patients with the greatest baseline mortality risk. Again, based on clinical trial evidence, it was assumed that initiation of reperfusion treatment within 3 hours from onset of symptoms would reduce 1-year mortality by 50%, while treatment within 3-6 hours and treatment within 6-12 hours would reduce mortality by 25% and 12.5%, respectively.[6,14-16]

Survival tables of the normal Dutch population were used to estimate long-term mortality.[12] For patients with an estimated 1-year mortality < 10%, long-term annual mortality was estimated at age- and sex-specific reference annual mortality plus 1%. For those with an estimated 1-year mortality 10-30% or ≥ 30%, long-term annual mortality was estimated at reference annual mortality plus 2% and plus 3%, respectively.

Based on the estimated 1-year and long-term mortality figures, life-expectancies were calculated for several clinical scenarios. We realized that early treatment outcome could be predicted more accurately than long term outcome. Furthermore, in clinical decision making a higher weight is given to the near future compared to the more distant future. For these reasons, future life years were discounted with a rate of 5% per year.

Table 9.1 summarizes the decision model for a 45 year old patient. In 1990, discounted life expectancy of a 45 year old subject in the Dutch population was 15.6 years. A myocardial infarction would result in a loss of 2.0-8.9 years with a remaining life expectancy of 6.7-13.6 years. Part of this loss can be regained by reperfusion therapy, depending on treatment delay. The expected gain is negligible in patients with small infarctions treated late after onset of symptoms (discounted gain in life expectancy < 1 month), while a considerable benefit is to be expected in those with extensive infarctions

treated within 3 hours (benefit expressed as gain in discounted life expectancy up to 39 months). This and similar tables were used for decision making during the nineties in our study population. It was recommended to refrain from reperfusion therapy in patients with an estimated gain < 1 month, and to initiate reperfusion therapy by streptokinase, alteplase, or primary PCI for patients with an estimated gain of 1-4, 5-11 of ≥ 12 months, respectively. These thresholds were mainly chosen according to the availability of resources and their costs.

Number of determinants of 1-year mortality	ST deviation ≥ 2.0 mV	Life expectancy without therapy (years)	Months regained by reperfusion therapy		
			< 3 h	3-6 h	6-12 h
Life expectancy of a normal reference		**15.6**			
0	no	13.6	3	1	0
0	Yes	13.4	4	2	< 1
1	No	13.1	7	3	1
1	Yes	12.7	10	5	2
2	No	10.8	15	7	3
2	Yes	10.1	20	10	5
3+	No	7.7	30	15	7
3+	Yes	6.7	39	19	9

Table 9.1 Decision model for a 45-year old patient.

Estimated treatment effects depend on the number of risk indicators (history of infarction, anterior location or inferior infarction with right ventricular involvement of the current infarction, congestive heart failure, and QRS > 120 msec), total ST-deviation on the ECG, and duration of symptoms (h=hours).

Patient cohort

The decision model was introduced in four hospitals in The Netherlands (including one university hospital) during 1993-1996, and until December 1996 a total of 1094 consecutive patients was treated correspondingly. There were 111 patients (10.1%) outside the 40-79 years age-window, who were excluded from analysis. The remaining 983 patients compose our study cohort. In 2006 we completed the 10-year follow-up through the Registry Office (median follow-up 10.0 years; interquartile range [IQR] 5.8-11.3). During this period, 403 patients (41.0%) had died and 30 patients (3.1%) were lost to follow-up.

Statistical analysis

The main purpose of this study is to verify the accuracy of the decision model by comparing the key assumptions and estimations with observations in the study cohort. The

decision model distinguishes 96 different clinical scenarios according age (categorized as: 40-49, 50-59, 60-69, and 70-79 years), ST-deviation on the presenting ECG (< 2.0 and ≥ 2.0 mV), number of determinants of 1-year mortality (0, 1, 2 and ≥ 3) and time from onset of symptoms (< 3, ≥3-6, ≥ 6-12 hours). Hence, the mean number of patients who are available for analysis per scenario are too low to obtain reliable results. The 'observed' values were therefore obtained by multivariable regression analyses of the follow up data.
First, the best fit Cox proportional hazard regression model was determined that linked the four variables mentioned above with 1-year mortality. Subsequently, based on this model, the 'observed' probability of 1-year mortality was calculated for each patient of the study cohort. Then the method of Bland and Altman was applied,[17] and estimated values were plotted against the 'observed' minus estimated values and the 95% limits of agreement (limits of agreement: mean value of 'observed' minus estimated values ±2 standard deviations) were determined. Furthermore, patients were classified into quintiles of increasing estimated 1-year mortality, and the average estimated value was plotted against the average 'observed' value in these quintiles.
Second, the best fit Cox regression model was obtained to link the same four variables with 5-year mortality in patients who survived the first year, and with 10-year mortality in those who survived the first 5 years. Based on these regression models, the 'observed' long-term annual mortality probabilities could be determined for each patient in the dataset. The 'observed' values were compared with estimated values, applying the same methodology that was used for the evaluation of 1-year mortality.
Third, the 'observed' life expectancy was calculated using 'observed' mortality probabilities until 10-year follow-up and estimated probabilities for longer term follow-up. 'Observed' life-expectancy, loss in life-expectancy relative to the Dutch reference population and regain of life expectancy by reperfusion therapy are compared with estimated values. We only report on discounted values as explained earlier.
Linear regression analyses were applied to evaluate the relation between 'observed' and estimated values, as well as between differences in 'observed' and estimated values and the variables that compose the model. Two-sided tests of statistical significance were applied, whereas significance was stated at $p < 0.05$. We present Pearson linear correlation coefficients (r), regression coefficients (intercept and slope), and explained variance (R^2).
It should be emphasized that the 'observed' values are composed via regression analyses of true data. Hence, these are not observations in the pure sense of the term.

RESULTS

The baseline characteristics of the study cohort are presented in Table 9.2. The median age was 63 years (IQR 55-71) and 73% were men. Forty-one percent of patients had an anterior infarction and 21% had an inferior infarction with right ventricular involvement. Total ST-deviation on the presenting ECG was ≥ 2.0 mV in 38% of the patients. More than two thirds of patients were admitted within 3 hours after symptom onset. Reperfusion therapy was initiated in 88% of patients: 46% received streptokinase, 52% received alteplase, and 2% underwent primary PCI.

Demographics	
Median age (IQR), years	63 (55, 71)
Age (years categorised) (%)	
40-49	21
50-59	24
60-69	28
70-79	27
Men (%)	73
Risk factors (%)	
Hypertension	16
Diabetes mellitus	18
Current or past smoker	40
Cardiovascular history (%)	
Angina	23
Myocardial infarction	24
Heart failure	18
Percutaneous coronary intervention	19
Coronary artery bypass surgery	20
Stroke or transient ischemic attack	14
Valvular heart disease	9
Atrial fibrillation	11
Presentation (%)	
Localization: Anterior	41
Inferior with right ventricle involvement	21
Bundle branch block (QRS >120ms)	7
Heart failure	11
ST deviation on presenting ECG ≥ 2.0 mV	38
Time from symptom onset to presentation (hours categorised)	
< 3	69
3-6	22
6-12	9

Table 9.2 Baseline characteristics of the study cohort of 983 MI patients.

One-year mortality

One year after admission 11.1% of the patients had died. The median values of 'observed' and estimated 1-year mortality were similar (both 7.8%), but the IQR of 'observed'

mortality was narrower than this estimated mortality (4.5-12.6% versus 3.5-15.1%). The mean difference between 'observed' and estimated 1-year mortality was 0.8%, indicating that, on average, 1-year mortality was adequately estimated by our model (Figure 9.1, upper left panel). However, the 95% limits of agreement were wide apart (-13.4% and 15.0%), and, importantly, there was a negative correlation (r = -0.60) between estimated 1-year mortality and the 'observed' minus estimated values. Thus, the model underestimated 1-year mortality probabilities in patients at relatively low risk, whereas it overestimated 1-year mortality in those at higher risk (Figure 9.1, upper right panel). More specific, 1-year mortality was underestimated in patients aged ≥ 70 years, and overestimated in patients with multiple risk factors as well as in those treated within 3-6 hours after onset of symptoms (Table 9.3).

Long-term annual mortality

Among the 874 1-year survivors 117 (13.4%) patients died during the years 2-5 after admission, whereas among the 757 5-year survivors 147 (19.4%) died during years 6-10. The median value of 'observed' annual mortality probabilities during years 2-5 was lower than the median estimated value (2.9% versus 3.8%), and the IQR was narrower (1.5-5.6% versus 2.0-8.2%). These differences were even more pronounced for the annual mortality probabilities during years 6-10. In that period, median (IQR) 'observed' and estimated values were 3.6% (2.0-7.2%) and 5.0% (2.5-11.3%), respectively. The mean difference between 'observed' and estimated annual mortality during years 2-5 and 6-10 was -1.3% and -1.9% (Figure 9.1, middle and lower left panels). These data indicate that long-term annual mortality probabilities were overestimated in our model, especially the probabilities in the more distant future. Overestimations were largest in patients with high estimated mortality (Figure 9.1, middle and lower right panels), and particularly in elderly subjects (Table 9.3).

	1-year mortality (%)	Annual mortality during years 2-5 (%)	Annual mortality during years 6-10 (%)	Life expectancy (years, discounted)	Loss in life expectancy (months, discounted)	Regain of life-expectancy (months, discounted)
R^2 value	0.47	0.53	0.68	0.31	0.31	0.34
Intercept	-6.4	3.5	6.7	0.07	-0.81	-5.4
Age, year	0.2	-0.1	-0.1	no contribution	no contribution	0.1
ST-deviation ≥ 2.0	no contribution	no contribution	no contribution	no contribution	no contribution	1.6
Determinants of 1-year mortality, range 0-4	-5.8	0.3	0.3	0.40	-4.77	-5.1
Time from onset of symptoms to presentation, h (max. 12h)	-0.2	-0.1	0.1	0.01	-0.18	0.2
Patient received reperfusion therapy	no contribution	0.2	no contribution	0.13	-1.62	does not apply

Table 9.3 Multivariable linear regression models describing the relation between clinical characteristics and the 'observed' minus estimated values.

We present the coefficients of the regression equations. The dependent variable in all equations is defined as 'observed'-estimated value. A positive (negative) regression coefficient implies that the 'observed'-expected value increases (decreases) with increasing values of the variable at hand.
No contribution: the variable at hand does not significantly ($p<0.05$) contribute to the regression model.
Does not apply: regain in life expectancy can only be calculated in patients receiving reperfusion therapy.

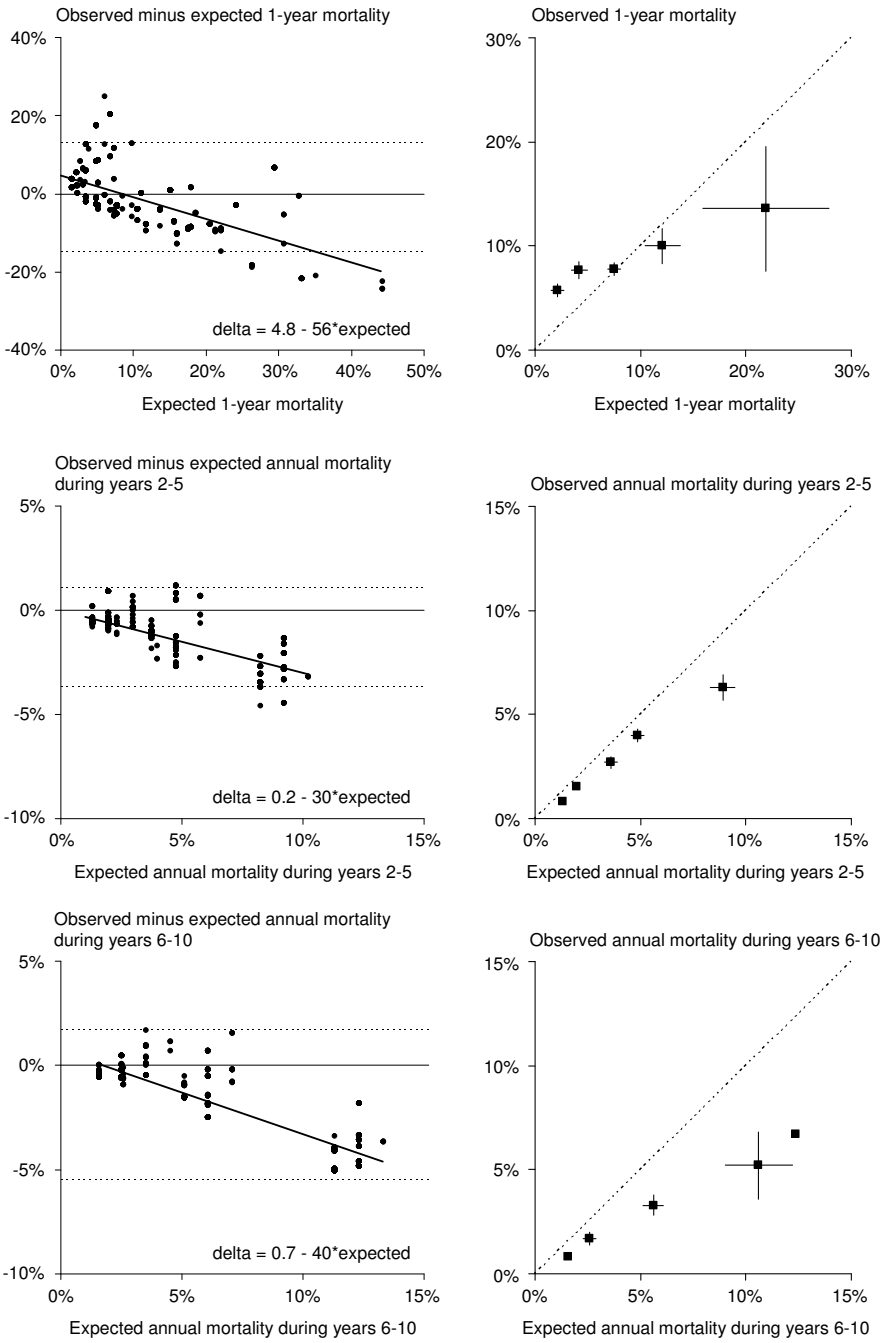

Figure 9.1 'Observed' vs expected annual mortality for three separate time periods up to 10 year after admission.

Life-expectancy

The median 'observed' discounted life expectancy was 9.6 years, which was higher than the median estimated value of 9.0 years. The difference between 'observed' and estimated life expectancy was independent of the estimated value (Figure 9.2, upper panels). The median 'observed' loss in life-expectancy relative to the normal Dutch population was lower than the median estimated value (11.2 versus 17.2 months), while the width of the IQRs was similar (6.7-18.4 versus 14.3-24.7 months). The mean difference in 'observed' and estimated loss in life-expectancy was -7.7 months and the 95% limits of agreement were -21.8 and 6.6. There was a negative correlation (r = -0.61) between the estimated loss in life-expectancy and the 'observed' minus estimated (Figure 9.2, middle left panel). In fact, our model overestimated the loss in life-expectancy in all patients. Overestimations were largest in those with high estimated values of loss in life expectancy or highest mortality (Figure 9.2, middle right panel).

As explained in the method section, decisions on reperfusion therapy were based on the estimated regain of life-expectancy (using discounted values) that will be lost if no such therapy is installed. The median value of 'observed' regained life-expectancy was close to the median estimated value (5.5 versus 4.9 months), whereas the mean difference between the 'observed' and estimated values was 1.5 months. These data indicate that, on average, effects of reperfusion therapy on life-expectancy were adequately estimated by our model. In individual patients, however, 'observed' and estimated effects could be quite different (95% limits of agreement were -15.9 and 12.9). Figure 9.2 (lower left panel) demonstrates a clear negative correlation (r=-0.58) between the estimated regain and the 'observed' minus estimated values. The model underestimated the regain of life-expectancy by reperfusion therapy in patients with lowest estimated values and overestimated the regain in those with highest estimated values (Figure 9.2, lower right panel). The regain was particularly underestimated in elderly patients and overestimated in those with multiple determinants of 1-year mortality (Table 9.3). Yet, the ranking of patient groups with lower of higher expected regain in life expectancy appeared to be appropriate.

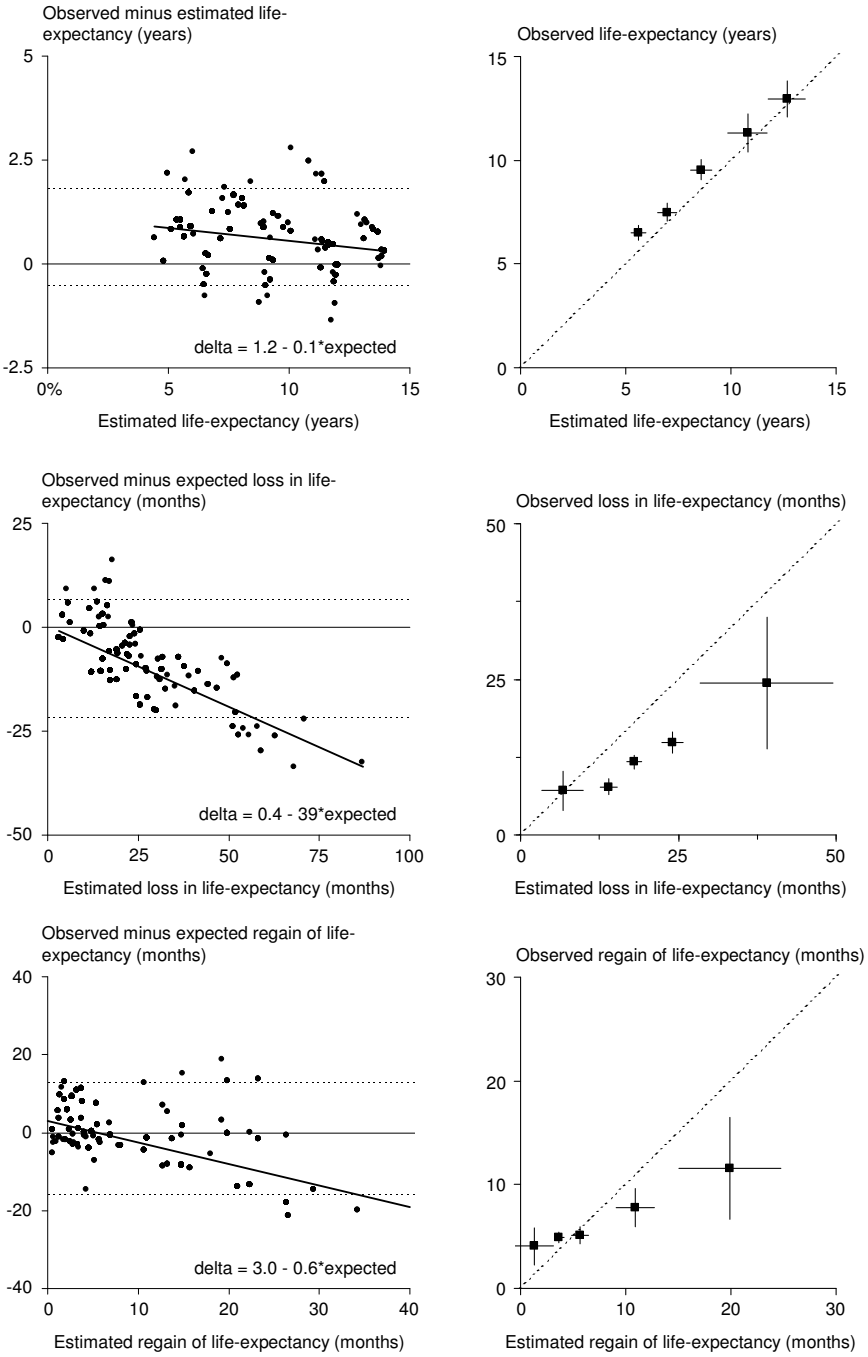

Figure 9.2 'Observed' versus estimated life expectancy data.

Loss (middle panel): life expectancy that is lost due to myocardial infarction
Regain (lower panel): life expectancy that is regained by the installation of reperfusion therapy

In 865 patients (88%) in whom reperfusion therapy was applied, therapy was based on a fibrinolytic agent: streptokinase (N = 398) or alteplase (N = 450). Figure 9.3 shows the difference in estimated (fat line) versus 'observed' (thin line) regain in life expectancy in the subgroups of patients according to these strategies. Clearly, the regain in life expectancy was underestimated in the patients who received streptokinase, and the regain was overestimated in patients who received alteplase. These differences are understandable to some extent, since, according to the protocol, streptokinase was reserved for the lower-risk patients, in whom mortality rates (and thus treatment effects) were underestimated, as we learned above. In contrast, alteplase was reserved for the higher risk patients, in whom mortality was overestimated. Still, the interpretation of the results with respect to applied treatment is complicated by differences in treatment effect, with (accelerated) alteplase being more effective than streptokinase.[3]

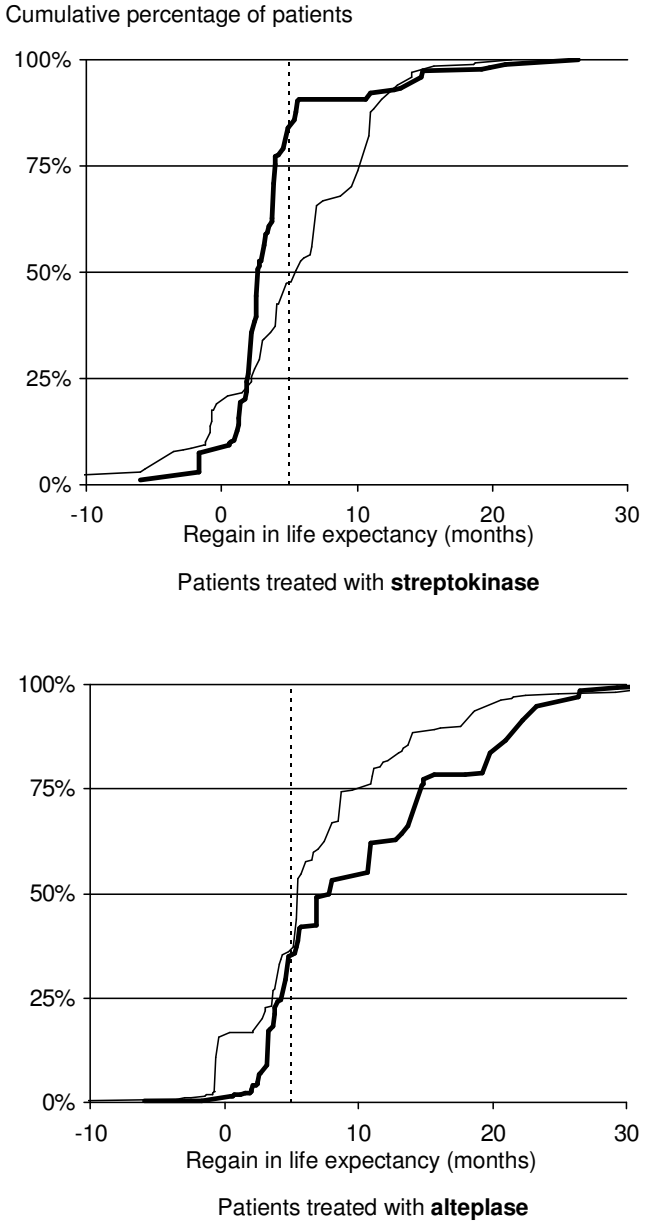

Figure 9.3 Observed versus estimated regain in life expectancy by streptokinase and (accelerated) alteplase.

Vertical dotted line: regain in life expectancy: ≥ 5 months, advised therapy: alteplase, regain in life expectancy: 1-4 months, advised therapy: streptokinase.
Fat line: estimated life expectancy. Thin line: 'observed' life expectancy.

DISCUSSION

In the early 1990s we developed a clinical decision model to allocate scarce reperfusion resources in myocardial infarction patients in a consistent and equitable way. Treatment decisions were based on the estimated regain in life expectancy that would be lost if no reperfusion therapy was given. In this validation study, we demonstrated that, on average, life expectancy after myocardial infarction, as well as the gain in life expectancy by reperfusion therapy - i.e. the treatment effect -, can be adequately estimated by this model. However, there were large variations in expected and 'observed' values between patient groups. In particular, the model presented too pessimistic estimates of treatment effect in lower risk patients, and too optimistic estimates in higher risk groups. Nevertheless, the ranking of patient groups appeared to be appropriate.

Life expectancy estimates are calculated by using estimates of 1 year and subsequent annual mortality. One year mortality estimates were based on a simple regression model that related a limited number of determinants to outcome. When regression models are applied for risk stratification, the best calibration is usually obtained in the patients who belong to the second, third and fourth quintiles of estimated risk, whereas calibration is weaker in the first and fifth quintiles. From that perspective, the results of our analyses were not unexpected. Still, we judge the difference between estimated and 'observed' 1-year mortality too large for the lowest and highest risk patient groups. There are four main factors that may have contributed to these apparent deviations. First, the applied 1-year mortality model was developed on patients who enrolled in clinical trials of fibrinolysis versus control therapy that were conducted in the late 1980s.[6,14-16] These patients constitute a highly selected cohort, and might not be representative for the patients who were admitted during routine clinical practice in the period 1993-1996. Second, the components of the mortality model were considered to be entirely independent, and the regression coefficients were not adjusted to minimize the effects of colinearity. Obviously, this is a simplification of reality, since patient characteristics are usually strongly correlated. Third, patients were classified according to their age into 4 categories with a class-width of 10 years, and mortality was assumed to be similar for all patients in the same age-class. This categorization was too crude, especially for the patients aged 70 years and over. Finally, mortality reduction by reperfusion therapy was estimated at 50% for the entire 0-3 hour period after symptom onset. In retrospect, this was too optimistic. In fact, evidence for such large treatment effect only exists for patients presenting in the first 'golden hour'.[18]

Annual mortality during extended follow-up was overestimated in all patients, particularly for the period 6-10 years after admission. This overestimation was most pronounced in the elderly. In our decision model, long-term mortality estimates were based on survival tables of the Dutch population in 1990. However, during the research period, which lasted until 2006, the life expectancy in The Netherlands has significantly improved. Obviously, our model did not reckon with this development. Also in our model, long-term annual

mortality was proportional to the (estimated) 1 year mortality. Elderly patients, as well as patients with multiple risk factors for 1 year mortality were thought to be at a higher mortality risk throughout the remainder of life than their age- and sex-specific counterparts in the general population. With the data of this study available, we now realize that this assumption was inappropriate. In fact, with increasing age and during extended follow-up, the prognosis of survivors of myocardial infarction gradually diverges to the general population.

Clearly, part of the deficiencies of the model is consequences of our choice to present the entire decision model on a simple paper-chart. To our judgment this was the most useful way to introduce the model in clinical practice, and to enable fast and appropriate decision making. Nowadays, the availability of hand-held computer devices (or personal digital assistants - PDAs), as well as electronic patient record systems (EPS), provide the opportunity to fine tune model parameters. Thus, nowadays individual-based, rather than group-based decision making becomes practicable.

Since the ranking of patient groups according to the estimated regain in life expectancy was appropriate it is unlikely that patients would have been treated differently had other model assumptions been made, cannot be answered with certainty. Indeed, the estimated regain in life expectancy by reperfusion therapy was not treatment-specific. Treatment decisions were based on estimated effects on life-expectancy, and the most effective therapy was reserved for patients with largest estimated benefits (in order to optimize the cost/benefit ratio). Yet, the observed treatment effects are influenced by allocated treatment. Still, in our study, 44% of patients with an expected treatment benefit below the median - most of whom were treated with streptokinase - had an observed benefit above the median. At the other hand, 64% of patients with an expected treatment benefit above the median - most of whom were treated with alteplase - had an observed benefit below the median. The magnitude of these shifts suggests that, in individual patients, treatment choices might indeed have been different had the decision model been adapted according to the insights that we gained from this study.

Conclusions

The decision model that we developed in the early 1990s, which allocated reperfusion therapy in myocardial infarction patients on the basis of its suspected effects on life-expectancy, has contributed to the penetration of evidence-based medicine in clinical cardiology. Treatment effects were adequately estimated on the average group level, but the model has several deficiencies that explain the varying accuracy in individual patients. Although the clinical question is no longer applicable in our environment, where primary PCI is liberally available, the model itself is not obsolete and can, once updated according to the findings of this study, still be used for clinical decision making in myocardial infarction patients.

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10

General discussion

GENERAL DISCUSSION

In this thesis we present the development, validation and implementation of a decision rule for early discharge after acute myocardial infarction in daily clinical practice. Not only clinical parameters but also psychological consequences of early discharge are measured and evaluated. Furthermore, we validated a decision model for reperfusion therapy in patients with acute myocardial infarction based on calculated life expectancy with 10-year follow-up.

Discharge policy after myocardial infarction is part of a complex continuing process of patient management after myocardial infarction. Although, many physicians believe they perform an active and early discharge policy, this thesis showed with data from a prospective study in four hospitals in Rotterdam, with the registry of The Euro Heart Survey and with data from recent primary percutaneous coronary intervention (PCI) registries of the Thoraxcenter that this is not true in daily clinical practice. In the Euro Heart Survey 39.5% of patients remained longer in hospital than medically required and 49% in the PCI registries. Early after admission the patient with an acute myocardial infarction should be identified for the appropriate discharge policy. Daily evaluation of several simple clinical parameters without using other complex diagnostic resources can identify patients who are candidates for early discharge. (Table 10.1)
In clinical practice we experienced difficulties to implement the early discharge policy. Only during the SHORT study, when the investigator was daily at the clinical ward, early hospital discharge was achieved for the majority of uncomplicated patients. The study ended and so did the early hospital discharge policy and length of hospital stay increased. Apparently, daily attention to this matter is required to maintain an active early discharge policy.
Discharge policy is not homogenous for all patients after acute myocardial infarction. For example, various lengths of hospital stay is appropriate after different kind of reperfusion therapies. In particular, after primary PCI with additional prognostic information, patients with uncomplicated myocardial infarction can be discharged earlier than patients treated with thrombolytic reperfusion therapy.
For effective implementation of the developed and validated early discharge policy in clinical practice we propose to select nurses at the ward who are responsible for the early discharge policy. They would have to check every day including the weekend whether patients after a myocardial infarction are eligible for early discharge. Selected nurses from the CCU and the ward should assist execution of this discharge protocol starting at the day of admission. Only by an active cooperation between wards with constantly changing staff this will succeed. The nurse or physician should frequently ask “why is this patient still admitted” rather than from the contrary point of view “how many days should this patient still be admitted”. The decision rule should be checked by the nurse every day and communicated with the treating physician. If, in the near future, an electronic

patient database (EPD) is incorporated in daily clinical practice the early discharge tool could pop up every day in the patients' record. Daily reminders are needed in successful early discharge policy. In perspective, similar models could be introduced for patients with non ST-elevation acute coronary syndromes or transient ST-elevation with only positive Troponin (small infarcts) and other patient groups.

In this thesis also the psychological consequences of patients with acute myocardial infarction who are discharged early have been investigated. We found no differences in psychological outcome between patients with an uncomplicated course discharged early and those who remained in hospital for the conventional time of period in the SHORT study. Furthermore, no relation was found between clinical course and psychological profile. Nevertheless, patients with a complicated course scored lower on feelings of being disabled at three months than patients with an uncomplicated course. Although, no psychological benefit is found in patients who are discharged earlier.

Long term follow-up of more than 8 years showed that feelings of being disabled on the four subscales of the Heart Patients Psychological Questionnaire (HPPQ) was a prominent predictor of mortality in a group of patients at low risk. This finding adds to the existing knowledge that psychological factors influence morbidity and mortality in cardiac patients.

In the previous decade a decision model was developed and used in Rotterdam Rijnmond to allocate different modes of reperfusion therapy to specific patients with myocardial infarction. The decision model was based on the expected effects on life-expectancy of reperfusion therapy in these patients and has contributed to the penetration of evidence-based medicine in clinical cardiology. Long-term follow-up of a patient cohort in which this model was applied revealed that indeed treatment effects were adequately estimated on the group level and succeeded in properly ranking patients according to longer or shorter survival. Nevertheless, the model has several deficiencies that explain the varying accuracy in individual patients.

Our experience will help the development of similar models to allocate scarce resources in similar or other settings.

Although this thesis took too many years to be accomplished, time was an important factor for its completion as a consequence. Discharge policies could be evaluated over time in a period with major changes in acute treatment of patients with myocardial infarction. Furthermore, time was needed to evaluate the influence of psychological factors on long-term outcome in these patients. Finally, all those years gave us the opportunity to validate a decision model for reperfusion time based on calculated expected life expectancy based on several correct and inaccurate assumptions.

Day 1: admission of patient with acute ST-elevation myocardial infarction

Day 2: on the morning of the second day:

1. Establish freedom until that time from:
    a. Cardiac arrest (asystole, ventricular fibrillation)
    b. Ventricular tachycardia
    c. Heart failure (Killip > I)
    d. Re-MI
    e. Advanced AV-block (2^{nd} or 3^{rd})
2. If none of the above: inform patient about the fast track discharge policy

Day 3: on the morning of the third day, schedule discharge

1. Establish freedom until that time from:
    a. Cardiac arrest (asystole, ventricular fibrillation)
    b. Ventricular tachycardia
    c. Heart failure (Killip > I)
    d. Re-MI
    e. Advanced AV-block (2^{nd} or 3^{rd})
2. If none of the above: inform patient about date of discharge.
    a. Patients with no reperfusion therapy or thrombolytic therapy are scheduled for discharge at day 7
    b. Patients with primary PCI are scheduled for discharge at day 5.
3. Inform secretary about preliminary date of discharge
4. If necessary, plan additional testing to avoid delay.

Day 5: on the morning of the 5^{th} day after PRIMARY PCI

1. Establish freedom until that time from:
    a. Cardiac arrest (asystole, ventricular fibrillation)
    b. Ventricular tachycardia
    c. Heart failure (Killip > I)
    d. Re-MI
    e. Advanced AV block (2^{nd} or 3^{rd})
    f. Post-MI angina
2. If none of the above: patients treated with primary PCI are discharged today
3. If complications act accordingly

Day 7: on the morning of the 7^{th} day after THROMBOLYTIC THERAPY

1. Establish freedom until that time from:
    a. Cardiac arrest (asystole, ventricular fibrillation)
    b. Ventricular tachycardia
    c. Heart failure (Killip > I)
    d. Re-MI
    e. Advanced AV block (2^{nd} or 3^{rd})
    f. Post-MI angina
2. If none of the above: patients with no reperfusion therapy or after thrombolytic therapy are discharged today
3. If complications act accordingly

Table 10.1 Discharge policy after acute myocardial infarction.

Summary

SUMMARY

Treatment of patients with acute myocardial infarction (MI) has improved over time and the duration of hospital stay has considerably decreased. Early hospital discharge after acute MI has been promoted for over 30 years (**chapter 1 and 2**). However, the meaning of "early" has evolved over time. In the early 1980s, before the widespread introduction of reperfusion therapy, patients were hospitalized for approximately 3 weeks and an early discharge rule was a reduction to 7 days. Today, the average hospital stay in the Netherlands is 8 days with a median of 6 days and "early" discharge is after 3-5 days. Evidently, in a cost-conscious environment, hospitalization should not be extended beyond the patients clinical needs. Still, evidence exists that further reduction in length of hospital stay can be achieved compared to current practice. In particular, after primary percutaneous coronary intervention (PCI) that nowadays is the choice of reperfusion therapy especially in the Netherlands, when coronary anatomy and left ventricular function are known, discharge can be safely effectuated after a few days. In particular, because such early hospital discharge has been associated with improved physical and psychological outcome, especially in elderly patients.

We developed and validated different early discharge strategies in unselected patients with acute myocardial infarction in different cohorts. Over time, reperfusion therapy changed and we evaluated the consequences for discharge policy.

In **chapter 3** we present the basics of our model. In the SHORT (Short Hospital Rehabilitation Trial) study we developed en validated our first decision model for early discharge. The decision rule is based on the calculated daily event rate of simple clinical variables which proved to correctly classify patients into high and low risk groups. The decision rule appeared to be feasible and safe, and patients with uncomplicated myocardial infarction can be safely discharged in the morning of day 7. This resulted in a reduction of the median length of hospital stay from 10 days in our control group to 7 days in our validation set for all in-hospital survivors. Subsequently, we validated our decision model in the Euro Heart Survey of Acute Coronary Syndromes, one of the largest registries of acute coronary syndrome in the "real world scenario" (**chapter 4**). Patients with an acute myocardial infarction were selected and categorized for no reperfusion therapy, thrombolytic therapy and primary PCI. Current guidelines recommend discharge within 4 days for patients with uncomplicated myocardial infarction. Our data suggest that this is appropriate after primary PCI but might be too early in others, since event rate continued to decrease beyond this 4-day period. However, even if patients would be discharged at day 7 a considerable reduction in length of hospital stay (20% of all hospital days) can be achieved compared to current practice with an acceptable small risk that might contribute to a significant reduction in costs.

Furthermore, in **chapter 5** we validated the Zwolle Risk Score for accurate identification of uncomplicated patients with acute MI eligible for early discharge, with our decision model for early discharge. The Zwolle Risk Score is a model using baseline determinants of

30-day mortality in patients with acute myocardial infarction undergoing primary PCI. The Zwolle Risk Score consists of 6 clinical variables including age, Killip class at admission, post-procedural coronary blood flow, extent of coronary disease, infarct location and the total ischaemic time. The Zwolle investigators argue that a group of patients with a 30-day mortality risk not exceeding 0.5% (Zwolle Risk Score ≤ 3) can be discharged safely 48 hours after the procedure. We validated this risk score in the well-characterized patients of the 'Euro Heart Survey of Acute Coronary Syndromes' (EHS-ACS) who received primary PCI. Although, the Zwolle Risk Score adequately predicted the probability of 30-day mortality, 3 patients (0.6%) in the EHS-ACS study cohort with a Zwolle Risk Score ≤ 3 (n = 530) died within the first 2 days after hospital admission. During the subsequent 8 days, clinical events requiring prolonged hospitalization occurred in 409 of the remaining patients (77%) with 2.4% severe life-threatening complications. Half of these severe complications (5/10) occurred during hospital day 3 and 4. Although, the Zwolle Risk Score is an easy bedside tool for identification of low risk patients at day of admission after primary PCI, the score is not adequate for safe selection of patients eligible for early discharge. We propose a hospital discharge policy based on daily evaluation of simple clinical parameters. According to this policy, a large group of patients with uncomplicated myocardial infarction at the beginning of the fifth hospital day is eligible for discharge which results in a considerable reduction in health care expenses.

Since the introduction of primary PCI in patients with acute myocardial infarction, the length of hospital stay can be further reduced in many patients (**chapter 6**). We evaluated discharge policy in a prospective, consecutive study cohort of patients with ST-elevation myocardial infarction (STEMI) treated with primary PCI in the era of drug eluting stents. From 2002 to 2003 342 consecutive STEMI patients were treated with primary PCI with SES (Sirolimus-eluting stents; 40%) or PES (Paclitaxel-eluting stents; 60%). From the hospital medical records daily major and minor post-infarction complications were documented. The median length of hospital stay was 7 days. The daily event rate decreased dramatically during the first two days from 28% at day 1 to 8.2% at day 2 and stabilizes after 2 days (± 3.5%). About half of the patients with acute myocardial infarction treated with primary PCI are uncomplicated in the morning of day 5 and eligible for early discharge according to our decision model. In the Netherlands 8054 primary PCIs were performed in 2005. With the implementation of the decision rule in total 735 days would have been saved, or in other words, on average 2.15 days per admitted patient with acute myocardial infarction. This will result in tremendous cost savings and more efficient use of our resources.

In **chapter 7** we investigated whether early hospital discharge results in adverse psychological outcome assessed at 3 months, and whether patients with a complicated versus an uncomplicated clinical course have different psychological profiles. The Heart Patients Psychological Questionnaire (HPPQ) which measures well-being, feelings of being disabled, despondency and social inhibition, was filled-out by 645 consecutive patients of the SHORT study on the fifth day of hospitalization and at 3 months. No differences in

psychological outcome were found at 3 months between patients discharged early and those who remained in hospital for the conventional period. Psychological profiles of uncomplicated and complicated patients were comparable. Correcting for baseline differences, registration phase patients with a complicated course scored lower on feelings of being disabled at 3 months than patients with an uncomplicated course.

Furthermore, we examined the independent prognostic value of the four subscales of the HPPQ on mortality in patients of the SHORT study up to 8 years after the event (**chapter 8**). Forty-one percent of the patients had a score indicating at least mild to moderate feelings of being disabled and were at increased risk of mortality compared with those having a low score, adjusted for other cardiac risk factors (hazard ratio 1.8). None of the other HPPQ subscales were related to mortality or recurrent myocardial infarction. When the study population was stratified in patients at low (43%) and high (57%) risk for in-hospital complications after MI, feelings of being disabled measured at baseline and at 3 months were the most prominent predictor of mortality in the low-risk patients 8 years post-MI. This finding adds to the existing knowledge that psychosocial variables influence morbidity and mortality in cardiac patients.

The aim of the study in **chapter 9** was to validate the key model assumptions and predictions of a decision model for selection of reperfusion therapy in 983 consecutive patients with acute myocardial infarction who were treated according to this model during 1993-1996 and followed-up until 10 years after admission. Decisions on reperfusion therapy were based on the estimated regain of calculated life-expectancy that would be lost if no such therapy was installed. Time from onset of symptoms to treatment, age, previous infarction, infarct location and indicators of the expected infarct size were considered determinants of 1-year mortality and life-expectancies were calculated. For validation of the decision model we compared the 'observed' and calculated life-expectancies. During 10-year follow-up, 403 (41.0%) patients had died and 30 patients (3.1%) were lost to follow-up. One-year mortality was underestimated in patients aged ≥70 years, and overestimated in patients with multiple risk factors as well as in those treated within 3-6 hours after onset of symptoms. Long-term annual mortality probabilities were overestimated in our model, especially the probabilities in the more distant future. The median value of 'observed' regained life-expectancy by successful reperfusion therapy was close to the median estimated value (5.5 versus 4.9 months). These data indicate that, on average, effects of reperfusion therapy on life-expectancy were adequately estimated by our model. In individual patients, however, 'observed' and estimated effects could be quite different (95% limits of agreement were -15.9 and 12.9) with a negative correlation (r = -0.58) between the estimated regain and the 'observed' minus estimated values. The model underestimated the regain in life-expectancy by reperfusion therapy in elderly patients (lowest estimated values) and overestimated in those with multiple determinants of 1-year mortality (highest estimated values). Yet, the ranking of patient groups with lower or higher expected regain in life expectancy appeared to be appropriate. Although the clinical question is no longer applicable in our

environment, where primary PCI is liberally available, the model itself is not obsolete and can, once updated according to the findings of this study, still be used for clinical decision making in patients with acute myocardial infarction.

In conclusion, we developed and validated a decision rule for early discharge in non-selected patients with acute myocardial infarction admitted in different hospitals, academic as well as non-academic hospitals. We showed that the decision model for early discharge is safe and feasible in daily clinical practice. The decision rule resulted in a decrease in length of hospital stay and better use of our resources. We compared our model to an other early discharge model based on a 30-day mortality risk score in patients with acute myocardial infarction treated with primary PCI. This Zwolle Risk Score was adequate in predicting 30-day mortality with only clinical variables collected at admission and during primary PCI but not useful for clinical decision making for early discharge. Ultimately, we validated our decision model in two registries of consecutive patients with acute myocardial infarction treated by primary PCI with drug-eluting stents. Our decision model is able to select almost half of all patients (49%) with an uncomplicated in-hospital course who can be discharged safely in the morning of day 5. With the implementation of this decision rule on average 2.15 days per admitted patient with acute myocardial infarction would have been saved. In 2005, 8054 primary PCIs were carried out in the Netherlands. This would mean, with the implementation of our decision model, for patients with acute MI treated with primary PCI, a reduction of 173161 hospital days per year, only in the Netherlands could be accomplished. This will result in tremendous cost savings and more efficient use of our resources.

In a psychological substudy we demonstrated that early discharge had no adverse psychological consequences for patients with acute MI. Psychological profiles of patients with an uncomplicated versus complicated course post-MI are comparable. Otherwise in our long-term follow-up study we substantiated that feelings of being disabled measured at baseline and after 3 months, is the most prominent predictor of mortality in low-risk patients 8 years post-MI. This finding adds to the existing knowledge that psychosocial variables influence morbidity and mortality in cardiac patients.

Finally, we validated the key model assumptions and predictions of a decision model for selection of reperfusion therapy in patients with acute myocardial infarction who were treated according this model and followed-up until 10 years after admission. We compared the ‘observed’ and calculated life-expectancies to validate our previous developed decision model for selection of reperfusion therapy based on calculated regain in life-expectancies. Life-expectancy that would be lost if no such therapy was installed. Treatment effects were adequately estimated on the average group level, but the model has several deficiencies that explain the varying accuracy in individual patients.

Decision models enable physicians to apply available treatment options in a consistent and reproducible manner, resulting in more objective choices, and most likely, better care of patients.

Samenvatting

SAMENVATTING

De behandeling van patiënten met een acuut hartinfarct is de afgelopen jaren sterk verbeterd en telijkertijd is hierdoor de opnameduur van deze patiënten afgenomen. Vervroegd ontslag na een hartinfarct staat in de internationale literatuur al meer dan 30 jaar in de belangstelling (**hoofdstuk 1 en 2**). De definitie ´vervroegd´ is echter in de loop van de tijd veranderd. In het begin van de jaren tachtig, voor de wereldwijde introductie van reperfusietherapie, werden patiënten gemiddeld 3 weken opgenomen in het ziekenhuis. Onder ´vervroegd ontslag´ verstond men toen een afname van de opnameduur tot 7 dagen. Tegenwoordig is de gemiddelde opnameduur in Nederland 8 dagen met een mediaan van 6 dagen. 'Vervroegd´ ontslag betekent nu na 3-5 dagen. In een kostenbewuste omgeving moet de opnameduur niet langer zijn dan voor de patiënt medisch noodzakelijk is. Er zijn echter aanwijzingen dat verdere afname van de opnameduur – in vergelijking met de huidige, dagelijkse praktijk - kan worden bereikt, vooral bij patiënten na een Primaire Coronaire Interventie (PCI), hetgeen tegenwoordig de eerste keus van reperfusietherapie is, met name in Nederland. Als de coronaire anatomie en de linker-ventrikelfunctie bekend zijn, kan ontslag binnen enkele dagen volgen. In het bijzonder daar vervroegd ontslag geassocieerd wordt met verbeterde fysieke en psychologische uitkomsten, voornamelijk bij de oudere patiënt.

In **hoofdstuk 3** presenteren wij de basis van ons vervroegd-ontslagmodel. In de SHORT studie (Short Hospital Rehabilitation Trial) hebben we ons eerste beslismodel ontwikkeld en gevalideerd. De beslisregel voor vervroegd ontslag is gebaseerd op de berekende, dagelijkse 'hazard ratio' van eenvoudig meetbare klinische variabelen, waarmee patiënten correct kunnen worden ingedeeld in hoog- en laag-risicogroepen. Deze beslisregel blijkt veilig en toepasbaar in de dagelijkse praktijk. Patiënten met een ongecompliceerd hartinfarct kunnen veilig in de ochtend van de 7de ziekenhuisdag worden ontslagen. Dit heeft geleid tot een afname van de mediane opnameduur van 10 dagen in de controlegroep naar 7 dagen in de validatiegroep.

Vervolgens hebben we onze beslisregel gevalideerd in the 'Euro Heart Survey of Acute Coronary Syndromes' (EHS-ACS), een van de grootste observationele onderzoeken onder patiënten met acuut coronair syndroom in de dagelijkse praktijk (**hoofdstuk 4**). Patiënten met een acuut hartinfarct werden geselecteerd en ingedeeld in 3 behandelgroepen: één zonder reperfusietherapie, één met trombolytische behandeling en een groep met primaire PCI. De huidige internationale richtlijnen adviseren om patiënten met een ongecompliceerd beloop na een hartinfarct binnen 4 dagen te ontslaan uit het ziekenhuis. Onze onderzoeksbevindingen tonen aan dat dit inderdaad mogelijk is voor patiënten met een hartinfarct die in de acute fase zijn behandeld middels primaire PCI. Maar voor de andere groepen patiënten lijkt dit te vroeg, aangezien de frequentie op complicaties zelfs na dag 4 nog een dalende trend laat zien. Indien deze groepen patiënten zouden worden ontslagen op dag 7, zou nog steeds een opmerkelijke afname in de opnameduur kunnen worden geëffectueerd in vergelijking met de huidige dagelijkse praktijk met een

acceptabel klein risico op complicaties na ontslag. Dit ontslagbeleid zal leiden tot een significante afname in de zorgkosten.
Vervolgens hebben we in **hoofdstuk 5** de Zwolle Risico Score voor accurate identificatie van patiënten met een ongecompliceerd beloop na een acuut hartinfarct gevalideerd met onze beslisregel. Deze risicoscore bevat een zestal klinische variabelen: leeftijd van de patient, lokalisatie van het infarct, Killip klasse bij opname, ischaemietijd, meertaks coronairlijden en TIMI flow (Thrombolysis In Myocardial Infarction) na de primaire PCI. De Zwolle Risico Score is een model dat gebruik maakt van genoemde variabelen als onafhankelijke voorspellers voor sterfte binnen 30 dagen bij patiënten met een acuut hartinfarct, die worden behandeld middels primaire PCI. Volgens de Zwolse onderzoekers zou een groep patiënten met een zeer laag risico op sterfte binnen 30 dagen (< 0.5%; Zwolle Risico Score ≤ 3) binnen 48 uur na PCI uit het ziekenhuis kunnen worden ontslagen. Wij valideerden deze risicoscore in de goed omschreven populatie van de EHS-ACS die een primaire PCI ondergingen. Hoewel de Zwolle Risico Score adequaat het risico op sterfte binnen 30 dagen voorspelt, stierven drie patiënten (0.6%) uit de EHS-ACS cohort studie met een Zwolle Risico Score van ≤ 3 (n = 530) binnen de eerste 2 dagen na opname. Gedurende de volgende 8 dagen traden bij 409 van de overgebleven patiënten (77%) complicaties op die een langere ziekenhuisopname vereisten, waarbij het bij 2.4% ernstige, levensbedreigende complicaties betrof. De helft van deze ernstige complicaties (5/10) manifesteerde zich op dag 3 en 4. Niettegenstaande het feit dat de Zwolle Risico Score een eenvoudig, aan het bed van de patiënt bruikbaar hulpmiddel is voor het identificeren van laag-risicopatiënten op de dag van opname na de primaire PCI, is de score niet geschikt voor een veilige selectie van patiënten die in aanmerking komen voor vervroegd ontslag. Wij stellen een ontslagbeleid voor gebaseerd op de dagelijkse evaluatie van eenvoudige klinische parameters. Met dit ontslagbeleid zal een grote groep patiënten met een ongecompliceerd beloop na een hartinfarct aan het begin van dag 5 geschikt zijn voor ontslag, hetgeen zal resulteren in een aanzienlijke reductie van de gemiddelde opnameduur en derhalve ook in een daling van de zorgkosten.
Sinds primaire PCI een reperfusietherapie is bij patiënten met een acuut hartinfarct, kan de opnameduur voor veel patiënten verder worden verkort (**hoofdstuk 6**). Wij evalueerden het ontslagbeleid in een prospectieve studie van opeenvolgende patiënten met ST-elevatie myocard infarct (STEMI) behandeld middels primaire PCI met 'drug-eluting stents' (DES). Van 2002 tot 2003 werden middels primaire PCI met SES (Sirolimus-eluting stents; 40%) of PES (Paclitaxel-eluting stents; 60%) 342 opeenvolgende patiënten met STEMI behandeld. Uit het patiëntendossier werden alle ernstige en minder ernstige complicaties per ziekenhuisdag geregistreerd. De mediane opnameduur bedroeg 7 dagen. De dagelijkse frequentie van complicaties daalde gedurende de eerste twee dagen fors van 28.1% op dag 1 naar 7.3% op dag 2 om vervolgens te stabiliseren rond de gemiddeld 3.4%. Bijna de helft van alle patiënten (49%) met een acuut hartinfarct behandeld d.m.v. primaire PCI heeft een ongecompliceerd beloop tot dag 5 en is geschikt voor vervroegd ontslag conform ons beslismodel. In 2005 werden in Nederland 8054 primaire PCI's

verricht. Middels ons beslismodel kunnen in totaal 735 ziekenhuisdagen worden voorkomen, dat is gemiddeld 2.15 ziekenhuisdagen per opgenomen patiënt met een acuut hartinfarct. Dit betekent dus voor de Nederlandse situatie een besparing van 173161 ziekenhuisdagen per jaar voor patiënten met een acuut hartinfarct die worden behandeld middels een primaire PCI.

In **hoofdstuk 7** hebben wij onderzocht of vervroegd ontslag mogelijk negatieve psychologische gevolgen zou kunnen hebben 3 maanden na ontslag en tevens of er een verschillend psychologisch profiel bestaat bij patiënten met een gecompliceerd beloop versus patiënten met een ongecompliceerd beloop na een hartinfarct. Met behulp van de Medisch Psychologische Vragenlijst voor Hartpatiënten (MPVH), die werd ingevuld op de 5de dag van de ziekenhuisopname en na 3 maanden door 645 opeenvolgende patiënten uit de SHORTstudie, werd welbevinden, invaliditeitsbeleven, ontstemming en sociale geremdheid gemeten. Er werd geen verschil in psychologische uitkomst gevonden tussen de patiënten die vervroegd werden ontslagen en die, die de conventionele opnameduur genoten. Het psychologisch profiel was vergelijkbaar voor patiënten met een gecompliceerd dan wel een ongecompliceerd beloop na een hartinfarct. Indien gecorrigeerd voor verschillen in patiëntenkarakteristieken scoorden patiënten uit de registratiefase met een gecompliceerd beloop lager voor invaliditeitsbeleven na drie maanden dan patiënten met een ongecompliceerd beloop.

Verder hebben wij gekeken naar de afzonderlijke 4 schalen van de MPVH als onafhankelijke, prognostische voorspeller van sterfte bij patiënten uit de SHORTstudie met 8 jaar follow-up na het hartinfarct (**hoofdstuk 8**). Eenenveertig procent van de patiënten had een score die tenminste een mild tot matig gevoel van invaliditeitsbeleven aangaf. Deze patiënten hadden daarmee een verhoogd risico op sterfte vergeleken met patiënten die een lage score hadden, indien gecorrigeerd voor andere cardiale risicofactoren (hazard ratio 1.8). Geen van de andere MPVH schalen was gecorreleerd aan sterfte of aan een recidief hartinfarct. Als de studiepopulatie werd ingedeeld in laag en hoog risico op een ziekenhuiscomplicatie bij patiënten met een acuut hartinfarct, dan was het invaliditeitsbeleven - gemeten zowel tijdens opname als na 3 maanden - de meest belangrijke voorspeller voor sterfte in de laag-risicogroep 8 jaar na het hartinfarct. Deze waarneming sluit aan bij de kennis die reeds bestaat, namelijk dat psychosociale kenmerken morbiditeit en mortaliteit beïnvloeden bij hartpatiënten.

Het doel van de studie in **hoofdstuk 9** was het evalueren van de belangrijkste aannames en voorspellingen van een beslismodel voor de selectie van reperfusietherapie bij 983 opeenvolgende patiënten met een acuut hartinfarct, die conform dit beslismodel gedurende 1993-1996 werden behandeld en die gedurende 10 jaar werden gevolgd. De beslissing voor reperfusietherapie werd gebaseerd op het geschatte terugwinnen van de berekende levensverwachting die verloren zou zijn gegaan indien geen reperfusietherapie werd toegediend. Factoren die van invloed zijn op de éénjaarssterfte en de vervolgens daaruit te berekenen levensverwachting, zijn: de tijd die verstreken is sinds het ontstaan van de klachten; de leeftijd van de patiënt; een eerder hartinfarct; de lokalisatie van het

hartinfarct en de factoren die de omvang van het bedreigde myocard weefsel bepalen. Voor de validatie van het beslismodel hebben we de 'geobserveerde' en de berekende levensverwachting met elkaar vergeleken. In het 10 jaar durende vervolgonderzoek, zijn 403 patiënten (41%) overleden en zijn 30 patiënten (3.1%) uit het oog verloren ('loss to follow-up'). Eénjaarssterfte werd onderschat bij patiënten met een leeftijd ≥ 70 jaar en overschat bij patiënten met meerdere risicofactoren en bij patiënten die tussen de 3-6 uur na het ontstaan van de klachten werden behandeld. De schatting van de langetermijn jaarlijkse sterfte werd overschat in ons model, vooral de schatting voor de verre toekomst. De mediaan van de 'geobserveerde', herwonnen levensverwachting bij succesvolle reperfusietherapie lag niet ver van de mediaan van de geschatte waarde (5.5 versus 4.9). Dit houdt in dat gemiddeld genomen het effect van de reperfusietherapie op de levensverwachting door ons model adequaat werd ingeschat. Maar voor de individuele patiënt kunnen het 'geobserveerde' en het te verwachten effect sterk van elkaar verschillen (95% ´limits of agreement´ zijn 15.9 and 12.9) met een negatieve correlatie (r = -0.58) tussen de geschatte terugwinst in levensverwachting en de ´geobserveerde´ min de geschatte waarde. Het model onderschat de terugwinst in levensverwachting door middle van reperfusietherapie bij de oudere patiënt (laagste verwachte waarde) en overschat het bij patiënten met meerdere determinanten voor éénjaarssterfte (hoogste verwachte waarde). Maar de rangschikking van patiëntengroepen in lager en hoger te verwachten, terug te winnen levensverwachting lijkt adequaat. Hoewel de klinische vraagstelling van destijds tegenwoordig niet meer relevant is in onze klinische setting, waar primaire PCI in iedere regio in Nederland voor elke patiënt beschikbaar is, is het model op zich niet obsoleet en het kan, indien aanpast aan de bevindingen van het beschreven onderzoek, nog steeds gebruikt worden als klinische beslisregel bij patiënten met een acuut hartinfarct.

Concluderend hebben wij een beslisregel voor vervroegd ontslag ontwikkeld en gevalideerd in een niet-geselecteerde patiëntengroep met een acuut hartinfarct, opgenomen in verschillende - zowel academisch als perifere - ziekenhuizen. Wij hebben aangetoond dat de beslisregel voor vervroegd ontslag veilig en toepasbaar is in de dagelijkse klinische praktijk. Met behulp van deze beslisregel was het mogelijk de opnameduur te verlagen en een efficiënter gebruik van onze middelen te bewerkstelligen. Wij vergeleken onze beslisregel met een ander vervroegd-ontslagmodel dat gebaseerd is op onafhankelijke voorspellers van sterfte binnen 30 dagen bij patiënten met een acuut hartinfarct, behandeld middels primaire PCI. Deze Zwolle Risico Score bleek adequaat in het voorspellen van de dertigdagensterfte gebruikmakend van klinische variabelen die werden verkregen op de dag van opname en gedurende de primaire PCI. Het model is echter niet bruikbaar als klinische beslisregel voor vervroegd ontslag. Bovendien valideerden wij onze beslisregel in twee observationele cohortstudies van opeenvolgende patiënten met een acuut hartinfarct, die werden behandeld met primaire PCI met ´drug-eluting stents´. Met behulp van onze beslisregel waren wij in staat bijna de helft van alle patiënten (49%) met een ongecompliceerd beloop te selecteren die in aanmerking kwamen

voor veilig vervroegd ontslag op de ochtend van dag 5. Met de invoering van deze beslisregel in de dagelijkse praktijk kunnen gemiddeld 2.15 dagen per patiënt, die wordt opgenomen met een acuut hartinfarct, worden bespaard. Dit zal leiden tot een enorme kostenbesparing in de zorg en een efficiënter gebruik van onze middelen.
In een psychologische substudie hebben we aangetoond dat vervroegd ontslag van patiënten met een acuut hartinfarct geen negatieve psychologische consequenties heeft. Het psychologisch profiel van patiënten met een ongecompliceerd, dan wel gecompliceerd beloop na een hartinfarct, is vergelijkbaar. Anderzijds hebben we in het langetermijn onderzoek vastgesteld dat het invaliditeitsbeleven bij patiënten met een acuut hartinfarct, tijdens opname en na drie maanden, de belangrijkste gemeten psychologische voorspeller is van sterfte in de laag-risicogroep 8 jaar na het hartinfarct. Deze bevinding sluit aan bij de bestaande kennis over de invloed van psychosociale variabelen op de morbiditeit en mortaliteit van hartpatiënten.
Tot slot hebben we de belangrijkste aannames en voorspellingen gevalideerd van een beslismodel voor de selectie van reperfusietherapie bij patiënten met een acuut hartinfarct die conform het beslismodel werden behandeld en gedurende 10 jaar werden gevolgd. Wij hebben de ´geobserveerde´ en berekende levensverwachting vergeleken om het beslismodel, dat gebaseerd is op het herwinnen van levensverwachting middels reperfusietherapie, te kunnen valideren. Het behandelingseffect werd adequaat ingeschat voor de gemiddelde groep patiënten, maar het model heeft verschillende tekortkomingen die de wisselende accuraatheid bij de individuele patiënt verklaren.
Klinische beslismodellen maken het de medicus mogelijk om beschikbare behandelingsopties op een consistente en reproduceerbare manier toe te passen, resulterend in een meer objectieve keuze en meest waarschijnlijk in een betere zorg voor de patiënt.

Dankwoord

DANKWOORD

Een promotieonderzoek is vooral het resultaat van doorzettingsvermogen, toewijding en de wil een wetenschappelijke bijdrage te leveren. Tijd is in deze slechts een zijdelingse factor die, indien goed besteed, kwaliteitsverhogend werkt. Moge dit proefschrift daar het bewijs van zijn. Bij de totstandkoming van mijn proefschrift heb ik de hulp gehad van velen: sommige waren sturend, andere ondersteunend en weer andere actief participerend met het uiteindelijke doel mij te helpen met het promotieonderzoek. Dank aan jullie allen!
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Lieve jongens: Olav en Sven, jullie zijn mijn alles!

CURRICULUM VITAE

The author of this thesis was born on January 12th 1967 in Rotterdam, the Netherlands. She graduated from secondary school in 1986 at the C.S.G. Comenius in Capelle a/d IJssel. From 1986-1990 she studied Medicine at the Erasmus University of Rotterdam. With the Dr E. Dekker programme of the Netherlands Heart Foundation she spent in 1991 four months at The Johns Hopkins University in Baltimore, Maryland, U.S.A. where she followed the Graduate Summer Program in Epidemiology at the School of Hygiene and Public Health, and performed research at The Johns Hopkins Precursors Study (head dr. Michael J. Klag), Departments of Medicine, Epidemiology and Health Policy and Management.
She obtained her medical degree in May 1993.
From 1993-1997 she started the studies described in this thesis as a research fellow at the Department of Clinical Epidemiology (KLEP-groep) of the Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands (head dr. J.W. Deckers), supported by the Netherlands Heart Foundation.
In 1998 she moved with her family to Curaçao where she started her medical residency Internal Medicine (1998-2000) at the Sint Elisabeth Hospitaal, Willemstad, Curaçao, Netherlands Antilles (prof. dr. R.A. Rojer), followed by the Cardiology fellowship (2000-2004) at the Department of Cardiology of the University Medical Center St. Radboud, Nijmegen, the Netherlands (head Prof. dr. F.W.A. Verheugt). In October 2004 she was registered as a cardiologist and became a staff member at the same institution with fields of interest: Cardiac Imaging and Cardiovascular Medicine.
Maureen is married to Erik de Haas and they have two sons, Olav (1998) and Sven (2002).

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