PREVENTION OF CARDIOVASCULAR DISEASES

opportunities for pharmaceutical care

Cover design: Martin Hoogmoed

CIP-gegevens Koninklijke Bibliotheek, Den Haag

van der Elst, Menno Eduard

Prevention of cardiovascular diseases, opportunities for pharmaceutical care /
Menno Eduard van der Elst
Thesis Utrecht – with ref.- with summary in Dutch
ISBN-10: 90-9020292-7
ISBN-13: 978-90-9020292-1

PREVENTION OF CARDIOVASCULAR DISEASES

opportunities for pharmaceutical care

Preventie van hart- en vaatziekten

kansen voor farmaceutische patiëntenzorg

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit van Utrecht op gezag van de Rector Magnificus Prof. dr. WH Gispen, ingevolge het besluit van het College voor Promoties in het openbaar te verdedigen op donderdag 16 februari 2006 des namiddags om 12.45 uur

door

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Geboren op 1 maart 1974 te Rotterdam

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The work in this thesis was performed at the Division of Pharmacoepidemiology and Pharmacotherapy of the Utrecht Institute for Pharmaceutical Sciences (Utrecht), in collaboration with the SIR Institute for Pharmacy Practice and Policy (Leiden).
The research presented in this thesis was funded by the Scientific Institute of Dutch Pharmacists (WINAp) and the SIR Institute for Pharmacy Practice and Policy. The study presented in chapter 6.2 was funded by an unrestricted grant from Astra Zeneca BV, Zoetermeer, the Netherlands.

Financial support from the Stichting KNMP fondsen and the Netherlands Heart Foundation for the publication of this thesis is gratefully acknowledged.

Contents

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INTRODUCTION

Introduction

Since decades, cardiovascular disease has been the most prevalent cause of death in developed countries, with myocardial infarction as its most prevailing manifestation. Therefore, strategies to reduce mortality and cardiovascular morbidity in patients with myocardial infarction have been studied extensively. Especially in the field of the acute management of cardiovascular disease important progress has been made. Early thrombolysis after myocardial infarction, advances in percutaneous transluminal coronary angioplasty (PTCA) techniques, the introduction of (drug eluting) stents, and wider use of coronary artery bypass grafting (CABG) have remarkably decreased cardiovascular mortality. [1-5] Recent advances in the emergency treatment of myocardial infarction may probably further decrease mortality and morbidity. [6] Furthermore, agents used for long-term secondary prevention of coronary heart disease following myocardial infarction have proven to decrease mortality and morbidity after myocardial infarction. [7-13]

Several international and national guidelines for the management of acute myocardial infarction have been developed. These guidelines have a strong focus on the in-hospital management of myocardial infarction and less attention is paid to long-term secondary prevention. Implementation of guidelines is reported to have resulted in decreased mortality rates early after myocardial infarction. [14] However, cardiovascular disease still remains the leading cause of death and myocardial infarction contributes most to it. Survivors of myocardial infarction have high death rates in the absence of preventive treatment. In the first year, the death rate is 10% and remains 5% in subsequent years, which persists for at least 15 years and probably for life. [15] These death rates are six times higher than those for people of the same age without coronary artery disease. Consequently, further improvement of the prognosis of patients with a history of myocardial infarction seems to be needed. Like appropriate treatment during hospital admission can decrease in-hospital mortality rates, long-term drug treatment can lower mortality rates after hospital discharge. Most randomised clinical trials (RCTs) studied the effects on morbidity and mortality during two to five years. Based upon the results of these randomised clinical trials, guidelines recommend lifelong benefits. International studies on the use of preventive medication in daily practice reported that long-term secondary prevention is sub-optimal. A considerable proportion of patients discontinues therapy early during treatment. Although the use and persistence of preventive drug treatment in the

Netherlands has not been estimated precisely, there is no indication that drug utilisation will differ appreciably from other countries. Therefore, it seems quite probable that there is still considerable potential to lower cardiovascular disease and mortality.

Traditionally, adequate treatment was the domain of general practitioners and consultant specialists. However, with the increasing number of therapeutic agents and the ageing of the society, the number of patients eligible for long-term prophylactic treatment has risen considerably. Moreover the complexity of prophylactic therapy has increased. Furthermore, physicians' and specialists' time for systematic and critical reappraisal of patients' drug use is limited. Therefore, in several countries other healthcare providers, such as nurses and pharmacists, are involved in patient care. Pharmacists increasingly play an important role in maintaining the quality of drug therapy, both directed at physicians and patients. Pharmacists can help physicians managing patients' treatment through pharmacotherapy updates and feedback on prescribing in 'peer review groups' or 'quality circles'. In relation to the patient, 'pharmaceutical care' is emerging as a patient-centred process through which a pharmacist, in cooperation with other health professionals, designs, implements, and monitors a pharmaceutical care plan to promote health, to prevent disease and to assess, monitor, initiate and modify medication use. The goal of pharmaceutical care is to optimize the patient's health-related quality of life and achieve positive clinical outcomes. Given the sub-optimal medication use in patients with a history of myocardial infarction and the goals of pharmaceutical care, research on the role of pharmacists in secondary prevention after myocardial infarction seems timely.

Aim and outline of the thesis

This thesis deals with the secondary prevention of cardiovascular diseases, with a special focus on myocardial infarction. It covers an overview of evidence based medicine after myocardial infarction, describes the quality of long-term secondary prevention after myocardial infarction in the Netherlands, assesses the effects of sub-optimal secondary prevention in daily practice on adverse outcomes, evaluates the reasons for non-persistence with evidence based medication, and provides examples of pharmaceutical care interventions both directed at physicians and patients to improve preventive drug treatment in patients with cardiovascular disease.

Evidence based medicine after myocardial infarction

Chapter 2 gives an overview of drug therapy for the prevention of recurrent myocardial infarction. The use in the general population of drugs that proved to be effective in lowering mortality and morbidity as established in Chapter 2 is studied in Chapter 3. Chapter 3.1 deals with the use of oral antithrombotics over the period 1988-1998. The use of oral antithrombotics, beta-blockers, ACE-inhibitors, statins and their combinations during a 12-year follow-up is presented in Chapter 3.2.

Effects of drug treatment on cardiovascular outcomes

Chapter 4.1 describes the effects of different exposure to drugs and combinations of several drugs after myocardial infarction on the incidence of non-fatal recurrent myocardial infarction. The acute effects of the discontinuation of statin treatment on the occurrence of myocardial infarction are described is Chapter 4.2.

Reasons for non-persistence with prescribed medication

Chapter 5 deals with non-persistence with prescribed medication in daily practice and attempts to establish the proportion of patients that discontinues treatment while having no good reason to do so. Reasons for non-persistence with statin treatment according to both patients and general practitioners are described in Chapter 5.1. Discontinuation of beta-blocker treatment and reasons as reported by patients are described in Chapter 5.2.

Interventions to improve drug treatment in patients with cardiovascular disease

Two examples of interventions to improve the quality of drug treatment are given in Chapter 6. Chapter 6.1 describes an intervention in a peer review group of general practitioners and pharmacists to improve the quality of secondary prevention in patients with a history of myocardial infarction. In Chapter 6.2 the effect of a pharmaceutical care program on the compliance with statin treatment is assessed in a randomized clinical trial that is carried out in 26 community pharmacies in the Netherlands.

The results presented in this thesis will be discussed in chapter 7.

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DRUG THERAPY FOR PREVENTION OF RECURRENT MYOCARDIAL INFARCTION

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The Annals of Pharmacotherapy. 2003;37:1465-77

Summary

Objective: To provide an evidence-based overview of drug treatment for long-term secondary prevention of myocardial infarction.

Data Sources: We conducted searches of Medline (1966-August 2002 through Pubmed), the Cochrane Controlled Trial Register, and the reference list of each identified study.

Study Selection and Data Extraction: Trials and meta-analyses were included using the following criteria; 1) Randomized trials 2) Description of identification procedure, inclusion criteria, outcome measures, and statistical methods 3) Confirmed myocardial infarctions 4) The treatment had to continue for at least one month 5) All cause mortality as primary outcome; other events as secondary outcomes. All authors interpreted the results from trials that met the inclusion criteria.

Data synthesis: In randomized clinical trials, low-dose aspirin, high intensity oral anticoagulants, beta-blockers, ACE-inhibitors and statins decreased the risk of mortality and reinfarction after myocardial infarction. Randomized clinical trials on calcium channel blockers, anti-arrhythmics, and hormone replacement therapy did not show benefits in patients with prior myocardial infarction. Effects of the combined use of aspirin or oral anticoagulants with beta-blockers or ACE-inhibitors along with statins have to be derived from subgroup analysis of trials, but seem to be beneficial.

Conclusions: The use of, at least, aspirin or an oral anticoagulant, a beta-blocker or an ACE-inhibitor, along with a statin should be incorporated in treatment routine. Clopidogrel treatment might be an alternative to aspirin. Standard addition of a beta-blocker to ACE-inhibitor-treated patients without reduced LVEF seems to be untimely.

Introduction

Myocardial infarction is one of the most prevalent causes of death worldwide. [1-3] Therefore, strategies to reduce mortality and cardiovascular morbidity in patients with myocardial infarction have been studied extensively. Investigation of the in-hospital management of acute myocardial infarction [4-7] has lead to the ACC/AHA and ESC guidelines for the management of acute myocardial infarction. [8,9] Despite the progress in the acute management, survivors of myocardial infarction are still at increased risk of cardiovascular mortality and morbidity. In the first year after myocardial infarction, the mortality rate is ten percent and remains five percent for each subsequent year. These death rates are six times that in people of the same age without coronary artery disease. [10,11] Guidelines for secondary prevention after myocardial infarction remain inconclusive concerning combination therapy. [8,9,12]

Given the importance of long-term secondary prevention of myocardial infarction, the lack of clear recommendations concerning combination therapy in guidelines, and the wide spread practice of it, an overview of evidence-based medicine after myocardial infarction is timely.

Objective

The objective is to present an overview of pharmacological strategies for long-term secondary prevention which has shown to be effective in lowering mortality and morbidity after myocardial infarction.

Methods

Medline searches were conducted (1966-August 2002 through Pubmed) with search terms 'myocardial infarction', 'secondary prevention', 'aspirin', 'antiplatelet', 'beta-blocker', 'ACE-inhibitor', 'anticoagulant', 'statin', 'calcium channel blocker', 'anti-arrhythmic', 'hormone replacement', 'estrogen' and the Cochrane Controlled Trial Register was used. We reviewed the reference list of each identified study. All studies on pharmacological long-term secondary prevention of myocardial infarction were identified. Trials and meta-analyses were included using the following criteria; 1) Randomized trials 2) Description of identification procedure, inclusion criteria, outcome measures, and statistical methods 3) All patients had to have a confirmed myocardial infarction or a subgroup analysis of data on these patients was performed 4) The treatment had to continue for at least one month 5) Primary outcome had to be all cause

mortality; reinfarction, death from cardiac causes, stroke or combined endpoints could be secondary outcomes. Both placebo controlled trials and comparative studies were included in order to assess the effects of monotherapy, combination therapy, and to differentiate specific pharmacological regimens. All authors interpreted the results from individual trials that met the inclusion criteria.

Results

Aspirin and other antiplatelet agents

The beneficial effects of antiplatelet agents including aspirin after myocardial infarction have been well established by the Antiplatelet Trialists' Collaboration. [13] Their overview comprised data from 12 randomized clinical trials containing 20,006 patients with a history of myocardial infarction. Baseline characteristics and exclusion criteria are shown in Table 1. Overall, antiplatelets reduced the risk of all cause mortality and non-fatal reinfarction when compared with placebo (Table 2A). Antiplatelet treatment also reduced the risk of vascular death (odds ratio [OR]=0.85, 95 percent confidence interval [CI 95%] 0.75-0.95), non-fatal stroke (OR=0.61, CI 95% 0.39-0.83), and all vascular events (OR=0.75, CI 95% 0.67-0.83). Vascular deaths comprised deaths from a cardiac, cerebrovascular, venous thromboembolic, hemorrhagic, and other vascular or unknown causes. Vascular events included non-fatal myocardial infarction, non-fatal stroke, and vascular deaths. Low aspirin doses (75-150 mg/day) seemed to be as effective as aspirin doses of 160-325 mg and 500-1,500 mg daily. [13,19-21] It is unclear whether doses below 75 mg are as effective as higher doses. [13] Bleeding complications were the main adverse effects of aspirin, with intra-cerebral hemorrhage as the most serious manifestation, followed by gastro-intestinal bleeding. The gastrointestinal side effects seldom result in withdrawal from treatment and fatalities are rare. Two meta-analyses on the adverse effects of aspirin indicate that gastrointestinal side effects of aspirin were probably dose-related. [22,23] A third meta-analysis did not confirm this tendency, probably due to different definitions of adverse events. [24]

Dipyridamole, sulfinpyrazone, or suloctidil, showed no advantages above aspirin. [13] The CAPRIE trial assessed the efficacy of clopidogrel compared to aspirin in 19,185 patients with myocardial infarction, stroke or peripheral artery disease. [25] Clopidogrel treatment for an average of 1.9 years lowered the risk of the

Table 1. *Characteristics and main exclusion criteria of meta-analyses on secondary prevention of myocardial infarction.*

Study	Treatment	Year of publication of trials included	Number of trials included	Number of patients included	Placebo controlled	Time between event and inclusion	Duration of follow-up (months)	Age (years)	Male sex	Main exclusion criteria
APT (2002) [13]	Antiplatelet	1974-1995	12	20,006	+	1-5 days	12-72	30-80	++	Aspirin intolerance, history of GI bleeding, former cardiac surgery, severe hypertension
Anand and Yusuf (1999) [14]	OAC	1960-1998	31	10,056	+	< 90 days	3-24	61	++	Increased risk for bleeding, need for oral anticoagulant treatment
Yusuf (1985) [15]	Beta-blockers	1972-1985	23	20,312	+	days to months	1.5-48	< 70	++	AV-block, bradycardia, hypotension, severe heart failure, COPD, age > 70
Freemantle (1999) [16]	Beta-blockers	1967-1997	31	24,974	+	days to months	1.5-48	< 70	++	AV-block, bradycardia, hypotension, severe heart failure, COPD, age > 70
Teo (1993) [17]	Class I anti-arrhythmics	1961-1992	51	23,229	+/-	hours to days	N/A	N/A	N/A	AV block, hypotension, heart failure, ventricular arrhythmia
Connolly (1997) [18]	Amiodarone	1987-1997	8	5,101	+	< 60	1.34	61	81%	AV-block, severe heart failure or angina, severe hypotension, thyroid dysfunction, bradycardia

Table 2A. *Results from meta-analyses on secondary prevention of myocardial infarction. Statistical significant results are boldfaced.*

Reference	Treatment	Control	Sample size	Total mortality OR	(95% CI)	Non-fatal re-infarction OR	(95% CI)	All re-infarctions OR	(95% CI)
APT (2002) [13]	Antiplatelet agents	Placebo	20,006	0.88	(0.78-0.98)	0.70	(0.58-0.82)	N/A	
Anand and Yusuf (1999) [14]	OAC (INR 2.8-4.8)	Placebo	10,056	0.78	(0.69-0.87)	N/A		0.58	(0.52-0.66)
Anand and Yusuf (1999) [14]	OAC (INR 2-3)	Placebo	1,562	0.82	(0.63-1.06)	N/A		0.48	(0.36-0.63)
Anand and Yusuf (1999) [14]	OAC (INR 2-4.8)	Aspirin	3,457	0.93	(0.69-1.28)	N/A		0.88	(0.63-1.24)
Anand and Yusuf (1999) [14]	OAC (INR 2-4.8) + aspirin	Aspirin	480	0.74	ns	N/A		0.55	ns
Yusuf (1985) [15]	Beta-blockers	Placebo	20,312	0.77	(0.70-0.85)	0.74	(0.66-0.83)	N/A	
Freemantle (1999) [16]	Beta-blockers	Placebo	24,974	0.77	(0.69-0.85)	N/A		N/A	
Teo (1993) [17]	Class I anti-arrhythmics	Placebo	23,229	1.14	(1.01-1.28)	N/A		N/A	
Connolly (1997) [18]	Class III anti-arrhythmics (amiodarone)	Placebo	5,101	0.92	(0.78-1.08)	N/A		N/A	

CI = confidence interval, INR = international normalized ratio, N/A = data not available, ns = non-significant, OAC = oral anticoagulants, OR = odds ratio

Table 2B. *Results from randomized clinical trials on secondary prevention of myocardial infarction.*

Reference	Treatment		Control	Sample size	Total mortality (95% CI)	Non-fatal re-infarction (95% CI)	All re-infarctions (95% CI)
APRICOT-2 (2002) [26]	Aspirin + coumarin (median INR 2.6)		Asp	308	∞	N/A	RR 0.28 (0.08-0.98) *
ASPECT-2 (2002) [27]	Aspirin + coumadin (mean INR 2.4)		Asp	999	RR 0.60 (0.26-1.36)	N/A	RR 0.70 (0.31-1.58)
WARIS II (2002) [28]	Aspirin + warfarin (mean INR 2.2)		Asp	2,414	RR 1.03 (0.78-1.36) *	N/A	RR 0.56 (0.41-0.78)
CHAMP (2002) [29]	Aspirin + warfarin (median INR 1.8)		Asp	5,059	RR 0.98 (0.87-1.11)	N/A	RR 1.02 (0.88-1.17) *
CAPRIE (1996) [25]	Clopidogrel		Asp	19,185	RR 0.98 (0.87-1.10)	RR 0.84 (0.70-1.00) *	RR 0.82 (0.70-0.97) *
CURE (2001) [30]	Clopidogrel + aspirin		Asp	12,562	RR 0.93 (0.80-1.07) *	N/A	RR 0.77 (0.67-0.89)
CAPRICORN (2001)	Beta-blocker	cavedilol	P	1,959	RR 0.77 (0.60-0.98)	RR 0.59 (0.39-0.90)	N/A
Nabel (1991) [31]	ACE-inhibitors	captopril	P	38	OR 0.29 (0.01-7.44)	N/A	N/A
PRACTICAL (1994) [32]		enalapril	P	225	OR 0.46 (0.20-1.06)	N/A	N/A
AIRE (1993) [33]		ramipril	P	1,986	RR 0.70 (0.56-0.87)	N/A	OR 0.93 (0.66-1.32)
ECCE (1997) [34]		captopril	P	208	OR 0.71 (0.14-3.67)	N/A	N/A
TRACE (1995) [35]		trandolapril	P	1,749	OR 0.73 (0.60-0.88)	N/A	OR 0.86 (0.66-1.13)
SAVE (1992) [36]		captopril	P	2,231	OR 0.79 (0.64-0.96)	N/A	OR 0.75 (0.60-0.95)
HOPE (2000) [37]		ramipril	P	9,297	OR 0.84 (0.75-0.95)	N/A	OR 0.80 (0.70-0.90)
Sogaard (1993) [38]		captopril	P	58	OR 1.00 (0.10-10.20)	N/A	N/A
CONSENSUS (1992) [39]		enalapril	P	6,090	RR 1.10 (0.93-1.29)	RR 1.01 (0.85-1.21)	N/A
CATS (1994) [40]		captopril	P	298	OR 1.31 (0.57-3.05)	N/A	OR 2.48 (0.83-7.43)
Sharpe (1991) [41]		captopril	P	100	OR 1.43 (0.27-7.61)	RR 0.24 (0.03-2.18)	N/A
EDEN (1997) [42]		enalapril	P	356	OR 1.48 (0.06-36.56)	N/A	N/A

DAVIT II (1990) [43]	Calcium channel blockers	verapamil	P	1,775	RR 0.80	(0.61-1.05)	N/A		RR 0.77	(0.58-1.03) ⋆
DAVIT I (1984) [44]			P	1,436	OR 0.91	(0.67-1.24)	N/A		N/A	
DAVIT III (1997) [45]			P	100	OR 0.96	(0.06-15.79)	N/A		OR 0.14	(0.01-1.02) ⋆
CRIS (1996) [46]			P	1,073	RR 1.06	(0.64-1.77)	N/A		RR 0.81	(0.53-1.24)
DEFIANT II (1997) [47]	Calcium channel blockers	dihydropyridines	P	542	OR 0.14	(0.02-1.15)	N/A		OR 0.78	(0.35-1.76) ⋆
SPRINT I (1988) [48 49]			P	2,276	OR 1.02	(0.71-1.45)	N/A		N/A	
SPRINT II (1988) [48 50]			P	1,358	RR 1.33	(0.98-1.80)	N/A		N/A	
Ishikawa et al. (1997) [51]			P	936	OR 1.36	(0.88-2.10)	OR 1.75	(0.25-12.48)	OR 2.02	(0.73-5.62)
MDPIT (1988) [52]	Calcium channel blockers	diltiazem	P	2,466	RR 1.02	(0.82-1.27)	RR 0.84	(0.64-1.12)	N/A	
INTERCEPT (2000) [53]			P	874	OR 1.03	(0.36-2.97)	RR 0.79	(0.41-1.50)	N/A	
Ishikawa (1997) [51]			P	774	OR 1.14	(0.65-2.01)	OR 1.67	(0.15-18.48)	OR 3.42	(1.18-9.88)
4S (1994) [54]	Statins	simvastatin	P	4,444	RR 0.70	(0.58-0.85)	RR 0.63	(0.54-0.73)	N/A	
LIPID (1998) [55]		pravastatin	P	9,014	RR 0.78	(0.69-0.87)	N/A		RR 0.71	(0.62-0.82)
HPS (2002) [56]		simvastatin	P	20,536	RR 0.80	(0.81-0.94)	RR 0.62	(0.54-0.70)	N/A	
CARE (1996) [57]		pravastatin	P	4,159	N/A		RR 0.77	(0.61-0.96)	RR 0.63	(0.38-1.05)
MIRACLE (2001) [58]		atorvastatin	P	3,086	RR 0.94	(0.67-1.31)	RR 0.90	(0.69-1.16)	N/A	

HERS (1998) [59]	Hormone replacement therapy	P	2,763	RR 1.08 (0.84-1.38)	RR 0.91 (0.71-1.17)	N/A	
HERS II (2002) [60 61]		P	2,321	RR 1.14 (0.89-1.46)	RR 0.98 (0.69-1.40)	N/A	
HERS I+II (2002) [60 61]		P	2,321	RR 1.10 (0.92-1.31)	RR 0.94 (0.77-1.15)	N/A	
ERA (2000) [62]		P	309	RR 0.94 (0.36-2.47) ⋆	RR 0.88 (0.36-2.17) ⋆	N/A	
WAVE (2002) [63]		P	423	RR 1.8 (0.75-4.3)	RR 1.01 (0.26-4.00) ⋆	N/A	

CI = confidence interval, INR = international normalized ratio, N/A = data not available, OAC = oral anticoagulants, OR = odds ratio , RR = relative risk ⋆ = RR or OR and CI 95% calculated based upon trial data

combined endpoint of ischaemic stroke, myocardial infarction, or vascular death in all patients (risk ratio [RR]=0.93, CI 95% 0.83-0.99), but failed to lower total mortality (Table 2B). In a subgroup of myocardial infarction patients (33 % of all patients), clopidogrel treatment tended to lower both fatal and non-fatal myocardial infarction. Data on total mortality for the subgroup of myocardial infarction patients were absent. Severe gastrointestinal bleedings were more frequent in the aspirin group (RR=1.49, CI 95% 1.17-1.89). [25]

Anticoagulants

The effects of oral anticoagulants after myocardial infarction have been studied since the 1960's. Anand and Yusuf classified 31 randomized trials by the intensity of oral anticoagulant treatment and the kind of control treatment. [14] They did not perform one meta-analysis including all trials, but performed separate meta-analyses for high intensity trials (international normalized ratio [INR] 2.8-4.8) and moderate intensity (INR 2-3) trials. [14] Baseline characteristics and exclusion criteria are shown in Table 1. High intensity treatment in 10,056 patients reduced total mortality, fatal and non-fatal reinfarctions (Table 2A), stroke (OR=0.56, CI 95% 0.43-0.72), and the combined outcome of death, reinfarction, and stroke (OR=0.59, CI 95% 0.54-0.66). Moderate intensity treatment in 1,562 patients reduced fatal and non-fatal reinfarction (Table 2A) and stroke (OR=0.47, CI 95% 0.27-0.85), but failed to lower total mortality. [14]

The Sixty Plus Reinfarction study showed that discontinuation of high intensity oral anticoagulant treatment in patients on treatment for up to six years after their first myocardial infarction was harmful. [65] No significant differences in total mortality or myocardial infarction between oral anticoagulant treatment of any intensity and aspirin were noted in the meta-analysis by Anand and Yusuf. [14]

The meta-analysis of Anand and Yusuf revealed that bleeding complications occurred more frequently in oral anticoagulant-treated patients than in placebo-treated patients (OR was 4.7 (CI 95% 4.0-5.6) for total bleeds and OR was 6.0 (CI 95% 4.4-8.2) for major bleeds). The increase in bleeding complications was related to the intensity of oral anticoagulant treatment. Compared to aspirin, OR was 2.4 (CI 95% 1.6-3.6) for high or moderate intensity oral anticoagulant treatment. [14]

Beta-blockers

The BHAT trial, the Norwegian Multicentre Study Group, Hjalmarson, the APSI trial, and the CAPRICORN study all found reduced risk of all cause mortality in patients treated with a beta-blocker compared with placebo. [31,66–70] A meta-analysis by Yusuf was published in 1985 and another by Freemantle was published in 1999. [15,16] Baseline characteristics and exclusion criteria are shown in Table 1. The Yusuf meta-analysis of 23 trials involving 20,312 patients showed a reduction in both total mortality and non-fatal reinfarction when beta-blocker treatment was compared to placebo. [15] In the Freemantle meta-analysis, data on 4,662 patients from 8 long-term trials were added to the data from the Yusuf analysis. Again, beta-blocker treatment was associated with a significant reduction in mortality (Table 2A) when compared to placebo. [16] The CAPRICORN trial differed from the other beta-blocker trials, as only patients with reduced LVEF were included. Carvedilol treatment provided additional benefits to ACE-inhibitor treatment in lowering mortality or non-fatal myocardial infarction (Table 2B). [31] Although individual trials only established the benefits of acebutolol, metoprolol, propranolol, carvedilol and timolol, both meta-analyses indicate that benefits of beta-blocker treatment are a class effect. Nevertheless, beta-blockers with intrinsic sympathomimetic activity appear to be associated with reduced benefits. [16] It is unclear if cardio selectivity is a predictor of benefit, as both meta-analysis showed contradictory associations between cardio selectivity and outcome measures. Doses of beta-blockers studied varied between trials and most frequent adverse effects in the treatment groups were bradycardia and hypotension. Dizziness, depression, cold extremities, and fatigue were less common. [10,16] Adverse effects were significantly more common in treatment groups than in control groups. [66,71]

ACE-inhibitors

The effects of ACE-inhibitors after myocardial infarction have been investigated in a number of randomized clinical trials, but no complete meta-analysis is available. Eleven trials, including 13,339 patients, met the criteria. [32–37,39–43] The design, baseline characteristics of randomized patients, and the use of non-study drugs are shown in Table 3. The results of these trials are summarized in Table 2B. In the PRACTICAL, AIRE, HOPE, TRACE, and SAVE studies the use of enalapril, ramipril, trandolapril, or captopril caused a significant reduction in total mortality. [33,34,36–38] Risk of cardiac death was significantly reduced in the

PRACTICAL, HOPE, SAVE, and TRACE studies. The HOPE and SAVE studies also showed a significant reduction in reinfarctions in the ACE-inhibitor group. The HOPE study revealed consistent benefits of ramipril on recurrent myocardial infarction in both patients using non-study aspirin, beta-blockers, or statins, and patients not using other drugs. [74] In other, mostly small, studies, the use of ACE-inhibitors did not cause a statistical significant effect on total mortality or cardiac death. [32,35,39-43] Hypotension was reported as the most frequent adverse effect. Other adverse drug reactions, like cough, rash, dizziness, and loss of taste, were reported less frequently.

Statins

The benefits of hydroxy-methylglutaryl coenzyme A inhibitors (statins) in subjects with elevated cholesterol levels have been clearly established in the 4S study. [55] Baseline characteristics of randomized patients and exclusion criteria of the trial are shown in Table 4. In 4,444 patients with angina pectoris or previous myocardial infarction, simvastatin treatment reduced the risk of all cause mortality and reinfarction (Table 2B). [55] The results from the 4S study have been confirmed by the LIPID study. [56] The recently published Heart Protection Study included 20,536 patients with coronary disease and a broad range of cholesterol levels (total cholesterol > 135 mg/dL), who were randomly allocated to receive simvastatin 40mg daily or placebo. Baseline characteristics of randomized patients and exclusion criteria are shown in Table 1. Simvastatin treatment reduced all cause mortality, non-fatal myocardial infarction, stroke, and the need for revascularisation (Table 2B). There was no excess of death from non-cardiovascular causes or cancer in the treatment group. Event rates were similarly and significantly reduced among both patients with and without prior myocardial infarction, patients with and without elevated cholesterol levels, men and women, and patients of all ages. The benefits of simvastatin were in addition to aspirin, beta-blockers, and ACE-inhibitors. [57] The Cholesterol And Recurrent Events (CARE) trial enrolled 4,159 patients with a normal cholesterol level and prior myocardial infarction. Baseline characteristics and exclusion criteria are shown in Table 4. Pravastatin treatment for a mean period of five years reduced the combined endpoint of death from coronary heart disease and nonfatal myocardial infarction (RR=0.76, CI 95% 0.64-0.91). The death rate from coronary heart disease was not reduced significantly (RR=0.80, CI 95% 0.61-

1.05). Data on total mortality were absent. [58] The MIRACL trial studied the short-term (16 weeks) effects of atorvastatin in 3,086 patients who recently experienced unstable angina or myocardial infarction. Baseline characteristics and exclusion criteria are shown in Table 4. Atorvastatin treatment reduced the combined endpoint of death, nonfatal acute myocardial infarction, cardiac arrest with resuscitation, and a recurrent ischaemic event requiring hospitalization (RR=0.84, CI 95% 0.70-1.00). Atorvastatin treatment did not reduce the risk of each endpoint component, except for recurrent ischemic events requiring hospitalization. [59]

Calcium channel blockers

The effects of calcium channel blockers after myocardial infarction have been investigated in many randomized clinical trials and none of them, except for the DAVIT III pilot study, showed any statistical significant benefit concerning total mortality, cardiac mortality or reinfarction. No meta-analysis that met our inclusion criteria was available. Ten randomized clinical trials evaluated the long-term calcium channel blocker treatment in patients with myocardial infarction. [44,45,47,48,51,53,54,72,75] The design of the randomized clinical trials and the baseline characteristics of randomized patients are shown in Table 3. Results of these trials are summarized in Table 2B.

Anti-arrhythmics

The preventive effects of anti-arrhythmics on mortality and morbidity after myocardial infarction have been investigated, as a substantial proportion of deaths after myocardial infarction is due to ventricular fibrillation. Anti-arrhythmics can be subdivided into four major classes. The effects of class II anti-arrhythmics (beta blockers) and class IV anti-arrhythmics (diltiazem and verapamil) have been discussed separately. A meta-analysis of class I anti-arrhythmics performed by Teo et al. reviewed 51 trials of class I anti-arrhythmics that included 23,229 patients with a history of confirmed or suspected myocardial infarction (Table 1). [17] The risk of mortality was significantly increased in patients assigned to class I agents compared with placebo (Table 2A). No differences were found between early and late intervention trials. [17]

Meta-analysis of the class III anti-arrhythmic, amiodarone, comprised 8 trials including 5,101 patients with a history of myocardial infarction. Baseline

Table 3. *Design of long-term trials evaluating ACE-inhibitors treatment or calcium channel blocker treatment for secondary prevention of myocardial infarction.*

	Design		Baseline characteristics										Use of non-study drugs at study entry				Exclusion criteria
	Randomized, double-blind	Placebo controlled	Days between event and inclusion	Mean follow-up (months)	Number of patients included	Mean age (years)	Male sex (%)	Mean systolic BP (mmHg)	Mean diastolic BP (mmHg)	Mean heart rate (bpm)	LVEF (%)	Q-wave (%)	Thrombolytic therapy (%)	Aspirin (%)	Anticoagulants (%)	Beta-blockers (%)	Calcium channel blockers (%)
Nabel (1991) [31]	+	+	<1	3	38	55	82	N/A	N/A	N/A	50		100	N/A	N/A	34	29
Sharpe (1991) [41]	+	+	<2	3	100	58	83	119	77	N/A	41		72	21	N/A	55	50
CATS (1994) [40]	+	+	<1	3	298	60	75	134	81	77	44		100	32	N/A	13	0
ECCE (1997) [34]	+	+	<3	3	208	60	80	N/A	N/A	N/A	46		63	61	N/A	54	15
CONSENSUS II (1992) [39]	+	+	<1	6	6,090	66	73	134	80	75	N/A		56	N/A	N/A	67	23
Søgaard (1993) [38]	+	+	7	6	58	59	91	112	N/A	65	40		80	100	N/A	73	22
EDEN (1997) [42]	+	+	9	6	356	57	91	119	74	76	48		59	84	18	28	6
PRACTICAL (1994) [32]	+	+	<1	12	225	64	78	134	N/A	N/A	45		72	N/A	N/A	17	17
AIRE (1993) [33]	+	+	3-10	15	1,986	65	74	N/A	N/A	N/A	N/A		58	78	N/A	22	16
TRACE (1995) [35]	+	+	3-7	24-50	1,749	67	72	121	76	81	<35		45	91	N/A	16	28
SAVE (1992) [36]	+	+	3-16	42	2,231	59	83	113	70	78	31		33	73	28	36	42

HOPE (2000) [37]	+	+	N/A	54	9,297	66	73	139	79	69	> 40		N/A	76	N/A	40	47	
DAVIT III pilot (1997) [71]	+	-	3-10	3	100	69	85	124	74	75		19	N/A	91	N/A	-		AV- and sinus block, CHF
DAVIT I (1984) .[44]	+	+	< 1	6	1,436	< 76	80	> 90	N/A	N/A		N/A	N/A	N/A	N/A	-		AV- and sinus block, CHF
DAVIT II (1990) [43]	+	+	7-15	16	1,775	< 76	80	> 90	N/A	> 45		83	N/A	N/A	N/A	-		AV- and sinus block, CHF
CRIS (1996) [46]	+	+	7-21	24	1,073	55.5	91	121	77	74		71	N/A	N/A	N/A	-		CHF
DEFIANT II (1997) [47]	+	+	7-10	6	542	58	N/A	N/A	N/A	N/A		85	N/A	N/A	N/A	N/A		AV- and sinus block
SPRINT II (1988) [48 50]	+	+	< 2	6	828	50-79	N/A	> 90	N/A	N/A		N/A	N/A	N/A	N/A	N/A		
SPRINT I (1988) [48 49]	+	+	7-21	10	2,276	55	N/A	129	77	77		N/A	N/A	N/A	N/A	20		AV-block, CHF
Ishikawa (1997) [51]	-	+	820	18	1,115	60	79	127	75	66		79	N/A	64	24	55		
INTERCEPT (2000) [53]	+	+	1½-4	6	874	57	81	124	< 120	71		76	65	100	6	13		AV- and sinus block
MDPIT (1988) [52]	+	+	3-15	25	2,466	58	80	N/A	N/A	< 50		74	N/A	38	4	54		AV- and sinus block
MI Study Group (1979) [72]	-	N/A	N/A	60	N/A	N/A	N/A	N/A	N/A	N/A		N/A	N/A	N/A	N/A	N/A		AV-block, CHF

AV = atrioventricular, BP = blood pressure, CHF = cardiac heart failure, LVEF = left ventricular ejection fraction, MI = myocardial infarction, N/A = data not available

Table 4. *Characteristics and main exclusion criteria of long-term trials evaluating statin treatment for secondary prevention of myocardial infarction.*

	Treatment	Number of patients included	LDL cholesterol level (mean, mg/dL)	Total cholesterol level (mean, mg/dL)	Placebo controlled and double blind	Days between event and inclusion	Duration of follow-up (months)	Age (mean, years)	Age > 70 years (%)	Male sex (%)	Main exclusion criteria
4S (1994) [54]	Simvastatin	4,444	188	261	+	> 180	5.4	35-70		81	Secondary hypercholesterolaemia, unstable angina, recent MI, use of antiarrhytmics, CHF requiring diuretics.
LIPID (1998) [55]	Pravastatin	9,014	150	218	+	420	6.1	62	15	83	Total cholesterol > 271 mg/dL, cardiac failure, age > 75
HPS (2002) [56]	Simvastatin	20,536	131	228	+		5		28	75	Age > 80, severe CHF, muscle disease, non cardiovascular lifethreatening conditions, severe psychiatric disorders.
CARE (1996) [57]	Pravastatin	4,159	139	209	+	300	5	59		86	Total cholesterol > 240 mg/dL, LVEF < 25%, symptomatic CHF, age > 75, fasting glucose level > 220 mg/dL
MIRACLE (2001) [58]	Atorvastatin	3,086	124	< 270	+	2.6	0.3	65		65	Total cholesterol > 270 mg/dL, planned revascularization, recent cardiac surgery, severe CHF, insulin-dependent diabetes.

characteristics and exclusion criteria of these patients are shown in Table 1. Amiodarone treatment tended to lower the risk of total mortality (Table 2A). [18]

Hormone Replacement Therapy

The Heart and Estrogen/Progestin Replacement Study (HERS) was the first randomized trial designed to investigate the effects of estrogen plus progestin therapy on cardiovascular events in postmenopausal women with established coronary disease. [60,61] Half the women included had a history of myocardial infarction. [60,61] The HERS trial revealed no significant differences in total mortality, myocardial infarction, or any other outcome between 1,380 women treated with 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate and 1,383 women receiving placebo for an average of 4.1 years (Table 2B). [60] Subsequent unblinded follow-up of 2,321 women for 2.7 years in the HERS II trial also showed no decreases in the rates of myocardial infarction or death from cardiac heart disease. [60,61] The first HERS trial found an excess of cardiac heart disease events in year 1 and fewer cardiac heart disease events in years 4 and 5. This time trend disappeared after the entire 6.8 years of follow-up of HERS plus HERS II. Venous thromboembolic events occurred more often in women on hormone replacement therapy (RH=2.08, CI 95% 1.12-3.40) during the entire follow-up of 6.8 years. [62] The ERA study was designed to evaluate the effects of hormone replacement therapy on the progression of coronary arteriosclerosis. [63] Half the women included had a history of myocardial infarction. Treatment with 0.625 mg conjugated estrogen or 0.625 mg conjugated estrogen plus 2.5 mg of medroxyprogesterone acetate per day did not alter the rates of cardiovascular mortality, fatal or non-fatal myocardial infarction, and all cause mortality, compared with placebo (Table 2B). [63] In the WAVE study, designed to determine whether HRT influenced the progression of coronary artery disease, HRT seemed to increase the risk of death (RR=1.8, CI 95% 0.75-4.3) or the combined outcome of death, non-fatal myocardial infarction, and stroke (RR=1.5, CI95% 0.80-2.9) in the treatment group. [64]

Multiple drug treatment

Most randomized clinical trials in secondary prevention of myocardial infarction focused on monotherapy. The only trials that studied the effects of multiple drug treatment, studied the combination of aspirin and oral anticoagulants.

The meta-analysis by Anand and Yusuf did not reveal significant differences in total mortality or myocardial infarction between the combination of oral anticoagulants plus aspirin versus aspirin alone (Table 2A). [14] Since the publication of the meta-analysis by Anand and Yusuf, the WARIS and APRICOT-2 study showed lower risk of reinfarction when aspirin plus oral anticoagulant treatment (INR 2.2 and INR 2.6 respectively) was compared with aspirin alone.[26,28] The ASPECT-2 study demonstrated a favorable effect of the combination of aspirin plus coumadin (INR 2.4) compared with aspirin alone on the composite endpoint of death, myocardial infarction and stroke (HR=0.50, CI 95% 0.27-0.92). [27] A beneficial effect on mortality has not been demonstrated in these trials. [26–28] The CHAMP study failed to reveal any clinical benefit of low intensity warfarin therapy (INR 1.8) combined with low-dose aspirin beyond that of aspirin alone (Table 2B). [29] The Anand and Yusuf meta-analysis revealed that bleeding complications occurred more frequently in patients who received combination therapy. [14] These findings were confirmed by the ASPECT-2 study [27], the WARIS study [28], and the APRICOT-2 study. [26] However, results from WARIS-2 indicate a small net benefit on the combined outcome.

To establish the effects of other drug combinations than aspirin and oral anticoagulants, subgroup analyses of trials that investigated a single agent are frequently used. Results from the Cooperative Cardiovascular Project (CCP) indicate that beta-blocker treatment is beneficial for all patients, regardless of concomitant drug treatment. [76] Subgroup analysis of the first WARIS and the first ASPECT study revealed that oral anticoagulants lowered mortality both in the presence and absence of beta-blocker treatment [77,78] In the CAPRICORN study, patients with left-ventricular ejection fraction of less than 40 % benefited from beta-blocker treatment even when treated concomitantly with an ACE-inhibitor. [31] Meta-analysis of beta-blocker trials revealed no time trend in risk reduction of cardiovascular events and death among trials performed over several decades, although concomitant drug treatment changed markedly over time. [16]

ACE-inhibitor trials were performed when the use of aspirin and beta-blockers became established and was reported in most cases. In the HOPE trial, beneficial effects of ACE-inhibitors were observed whether patients were taking aspirin, beta-blockers, or lipid lowering agents or not. [38] In a retrospective analysis of the SOLVD, HOPE, AIRE, TRACE, and SAVE trials, the benefits of ACE-inhibitor treatment were apparent both in the presence and absence of aspirin,

although there was a significantly smaller effect of ACE-inhibitor treatment on reinfarction. [79] Retrospective analysis of the CONSENSUS II study revealed negative interaction between ACE-inhibitors and aspirin [80] although the interaction was absent in the CATS trial, the JAMIS trial, and the Co-operative Cardiovascular Project. [21,81,82] The Heart Protection Study indicated that benefits of simvastatin treatment were largely independent of the use of aspirin, beta-blocker and ACE-inhibitor. [57] The considerable use of aspirin in the CARE and LIPID trial (83 % of all participants) [56,58] might indicate that the beneficial effects of statin treatment are independent of aspirin use.

Discussion

Low-dose aspirin (75-150 mg/day), high intensity oral anticoagulant treatment (INR 2.8-4.8), beta-blockers, ACE-inhibitors, and statins are effective in lowering the risk of mortality and reinfarction after myocardial infarction: therefore, these agents are recommended under the conditions as stated in Figure 1. These recommendations are based upon the present evidence, irrespective of cost-effectiveness. The minimal duration of treatment can be derived from results of randomized clinical trials. So treatment with aspirin, beta-blockers or ACE-inhibitors should continue for at least 2 to 4 years [13,16,34,36-38] and statin treatment should continue for at least for at least 2 to 5 years. [57,58] As far as oral anticoagulant treatment is concerned, treatment should continue for at least six years, since results from the Sixty Plus Reinfarction study showed that discontinuation of oral anticoagulant treatment in patients receiving oral anticoagulants since their first myocardial infarction six years ago was harmful. [65] As beneficial effects remained apparent during the entire follow-up period, and nothing pointed to the disappearance of the established effects shortly after the end of follow-up, we recommend lifelong treatment. The expected benefits of lifelong treatment have to be evaluated in observational studies to rule out the absence of benefits in the long term. Clopidogrel treatment could be an alternative or addition to aspirin, but its mortality lowering properties have to be established yet. The use of ACE-inhibitors in patients without reduced LVEF and the use of beta-blockers in patients with reduced LVEF probably are beneficial. Addition of an ACE-inhibitor to beta-blocker treatment or a beta-blocker to ACE-inhibitor treatment could be considered. Calcium channel blockers, anti-arrhythmics, and HRT should not be recommended for lowering cardiovascular mortality or morbidity after myocardial infarction. Treatment

with these agents did not show benefit in patients with prior myocardial infarction.

Oral anticoagulant treatment and clopidogrel treatment are second choice agents after low-dose aspirin (75-150 mg/day). The evidence for benefits of clopidogrel above aspirin is poor, although the size of the CAPRIE trial should have had enough power to clearly demonstrate such benefits. Oral anticoagulant treatment seems to provide no additional benefits concerning reducing myocardial infarction and mortality compared to aspirin. Furthermore, oral anticoagulant treatment requires monitoring and oral anticoagulant treatment increases risk of bleeding complications. Therefore, oral anticoagulant treatment is indicated for patients with other indications for oral anticoagulants only, like patients with atrial fibrillation or patients at increased risk of embolization from left ventricular or left atrial clot. Low to medium intensity oral anticoagulant treatment (INR 2-3) is not a suitable treatment after myocardial infarction, as it did not reduce mortality. Combination therapy of aspirin and oral anticoagulants did not lower total mortality, although the CHAMP study should have had enough power to demonstrate differences in total mortality. [14,29] The effects of combination therapy on re-infarctions as shown in trials are conflicting. [26-29] Therefore recommendation of combination therapy of aspirin and oral anticoagulants is inappropriate.

The benefits of beta-blockers seem to be a class effect, but most evidence is available for metoprolol, timolol, and propranolol. Dosage of metoprolol should be 100mg twice daily, as this dose was administered in almost all trials on secondary prevention of myocardial infarction. [16,71] Timolol should be dosed 10 mg twice daily as applied in secondary prevention trials after myocardial infarction. The lack of cardio selectivity probably will prevent broad utilization of propranolol. In patients eligible for ACE-inhibitor treatment, captopril, enalapril, ramipril and trandolapril should be preferred as these agents have been shown beneficial and the supposed class effect has not been clearly established. The benefits of ACE-inhibitor treatment in patients with normal LVEF are less clear as the positive results from the HOPE study [38] were inconsistent with the negative results from the CONSENSUS II trial. [40] Possibly, the short duration of follow-up or the high rate of concomitant use of beta-blockers contributed to the absence of benefits in the CONSENSUS II trial. [40] In patients with reduced

LVEF, addition of carvedilol to ACE-inhibitor treatment seems to be appropriate as demonstrated in the CAPRICORN trial. [31]

In randomized clinical trials, long-term statin treatment after myocardial infarction was beneficial, irrespective of sex, age, cholesterol level and additional cardio protective treatment after myocardial infarction. Significant results from the Heart Protection Study were supported by trends from the CARE trial. [57,58] The CARE trial probably lacked statistical significance due to the small number of patients included. [58] Benefits of statin treatment in patients 70 years or older have been established already in the Heart Protection Study, but statin treatment might be beneficial in patients 74 years or older as well, according to the results from the observational Cardiovascular Health Study. [57,83] Results from short-term trials early after myocardial infarction are promising yet inconclusive. Trends revealed by the short-term MIRACL study were supported by observational studies. The RISK-HIA study, a study by Bybee, and a study using data from the GUSTO IIb and the PURSUIT trial revealed that prescription of lipid-lowering drugs for patients with myocardial infarction was associated with reduced short-term mortality of the same magnitude as beta-blocker treatment. [84-86]

Positive results from observational studies on hormone replacement therapy after myocardial infarction were inconsistent with results from randomized trials that failed to show benefits of hormone replacement therapy. [60,61,63,64,87-90] In observational studies, however, patients were not randomly assigned to hormone replacement therapy or placebo, so women with healthy behavior probably used postmenopausal hormones more often. A subsequent lower risk of cardiovascular disease in hormone treated women could thus have been caused by selection bias. At present, hormone replacement therapy should not be offered for the prevention of cardiovascular disease, but could be offered to women with menopausal symptoms or osteoporosis.

Combination therapy is already widespread in daily practice whereas conclusive evidence from randomized clinical trials that compare different strategies to reduce mortality and morbidity after myocardial infarction is not available yet. Limited data, however, indicate that the beneficial effects of statins are apparent in the presence of aspirin, beta-blockers, and/or ACE-inhibitors [57] and the other way round, the effects of ACE-inhibitors are apparent in the presence of aspirin, beta-blockers, and/or statins. [79] The combination of oral anticoagulant and aspirin treatment lowered the risk for some combined endpoints but failed to

lower total mortality. Given the increase of bleeding complications, combination therapy seems to provide too little benefits. . Most data on combination therapy come from subgroup analyses. These results have to be interpreted with great care, as patients were randomly assigned to one agent only, whereas treatment with the other agent was not distributed by chance. Treatment with this not randomly assigned agent could be indicative for prognosis after myocardial infarction Awaiting randomized trials on combination therapy, utilization of results from subgroup analyses seems to be the best option, but awareness for bias is required.

Conclusion

Based upon the present evidence, healthcare professionals should do their utmost to incorporate the use of, at least, aspirin or an oral anticoagulant, a beta-blocker or an ACE-inhibitor, along with a statin in treatment routine. Clopidogrel treatment could be an alternative to aspirin as soon as benefits of clopidogrel on lowering mortality have been established in myocardial infarction patients. Addition of a beta-blocker to ACE-inhibitor-treated patients without reduced LVEF can be considered, although the evidence for advantage over monotherapy is limited. The same goes for the addition of an ACE-inhibitor to beta-blocker treated patients with reduced LVEF.

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3

PREVENTIVE DRUG TREATMENT IN THE GENERAL POPULATION

3.1

ORAL ANTITHROMBOTIC USE AMONG MYOCARDIAL INFARCTION PATIENTS

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The Annals of Pharmacotherapy. 2003;37:143-6

Summary

Objective: To examine the use of oral antithrombotics (ie antiplatelet agents and oral anticoagulants) after myocardial infarction in the Netherlands from 1988 till 1998.

Methods: Retrospective follow-up of 3,800 patients with myocardial infarction using data from the PHARMO Record Linkage System.

Results: From 1988 till 1998 oral antithrombotic treatment increased significantly from 54.0 percent to 88.9 percent. In 1998, only 75.8 percent of patients who suffered from a myocardial infarction in the late 1980s received oral antithrombotic treatment compared to 94.4 percent of those who suffered from a recent myocardial infarction.

Conclusions: Oral antithrombotics were considerably underused in patients with a past history of myocardial infarction. Therefore these patients should be reviewed for antithrombotic therapy to assess if their failure to use oral antithrombotics is rightly or wrongly and treatment should be initiated if possible.

Introduction

The benefits of long-term treatment with oral antithrombotics (ie antiplatelet agents and oral anticoagulants) after myocardial infarction have been well established in an overview of antiplatelet trials following myocardial infarction. [1] Therefore all patients with a history of myocardial infarction should receive long-term oral antithrombotic therapy, if tolerated. The ACCP guideline have recommended long-term use of aspirin for all patients without aspirin intolerance since the 1989 issue, while oral anticoagulants (e.g. acenocoumarol, warfarin) after myocardial infarction have been reserved for patients with aspirin intolerance and for patients with a typical indication for oral anticoagulants, like atrial fibrillation and increased risk of embolisation from left ventricular or left atrial clot, since the first issue in 1986. [2 3] The ESC guideline and the ACC/AHA guideline have recommended the same since the first issue in 1994 and 1996, respectively. [4 5] Up to their most recent updates in 1996, 1999 and 2001, the ESC guideline, the ACC/AHA guideline and the ACCP guideline do not recommend concomitant treatment with aspirin and oral anticoagulants. [6-8]

Most studies that evaluated the quality of oral antithrombotic treatment after myocardial infarction were focussed on the use of aspirin at discharge. [9-11] Often the use of oral anticoagulants was beyond the scope of these studies. When the use of aspirin beyond discharge from hospital was assessed, the duration of follow-up was limited to one year.

Hence, we evaluated the use of antiplatelet agents, oral anticoagulants, and the combination of both after myocardial infarction during a long-term follow-up in patients with myocardial infarction between 1988 and 1998.

Methods

We obtained anonymised data from the PHARMO Record Linkage System. [12] In this system, drug-dispensing data from all community pharmacies in eight Dutch cities are linked to morbidity data from the nationwide hospital admission register. Data were gathered on a patient level for all 325,000 residents in the catchment area. The drug name, Anatomical Therapeutic Chemical (ATC) classification [13], the date of delivery, the amount dispensed and the prescribed daily dose were recorded in the database for every prescription. Morbidity data were coded according to the International Classification of Diseases, 9th revision (ICD-9). Both drug dispensing data and morbidity data were available from January 1, 1988 till December 31, 1998.

We selected patients who were admitted due to myocardial infarction (ICD-9 code 410) between January 1, 1988, and December 31, 1998. Exclusion criteria were in-hospital death or movement outside the catchment area and subsequent designation of a pharmacy outside the catchment area. Each patient participated in the study as long as the drug-dispensing data of the patient were available. In case a patient was admitted in hospital for a recurrent myocardial infarction follow-up ended. After discharge from hospital, patients were included once again if the above-mentioned criteria were met.

We estimated the overall use of oral antithrombotics as well as the use of antiplatelet agents, oral anticoagulants and the combination of both. Use was expressed as the number of patients who filled at least one prescription for an antiplatelet agent (ATC-code B01AC) or an oral anticoagulant (ATC-code B01AA) during a particular year, in proportion to the number of patients, identified as having an myocardial infarction since January 1, 1988, still in the database during that year. Annual use was stratified by year of admission. We compared current use in 1998 among patients who suffered from a myocardial infarction in the late 1980s with current use among patients with myocardial infarction in the late 1990s.

In order to be certain that the fill of one prescription a year was indicative for long-term use, we calculated compliance of antiplatelet agents on a patient level. Compliance was expressed as the actual duration of use, based upon the sum of the collected number of tablets and the prescribed daily dose, in proportion to the theoretical duration of use, that is the number of days between first prescription and end of the last prescription. Compliance with oral anticoagulant treatment was not calculated, since dosing regimens of oral anticoagulants were not recorded in pharmacy records. In the Netherlands dosing regimens of oral anticoagulants are adjusted by the thrombosis services.

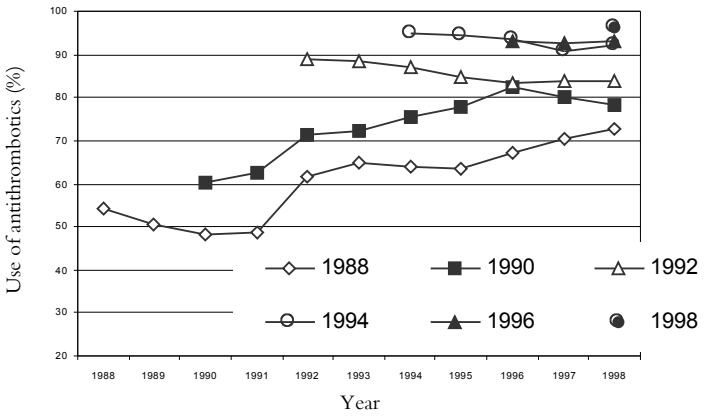
Results

We identified 4,508 admissions due to myocardial infarction from 1988 to 1998, which represents 1.77 percent of all myocardial infarctions in the Netherlands. [14] After exclusion of 456 subjects (10.1%) who died in the hospital and 252 subjects (5.6%) who were no longer living in the catchment area after discharge from hospital, 3,800 (84.3%) admissions remained in the study. Median age 65 was years and 70.8% of the participants were male. In 195 cases, follow-up ended

because of admission for a recurrent myocardial infarction. Median duration of follow-up was 3.2 years. We identified 56,973 prescriptions for oral antithrombotics from 1988 to 1998. Among patients who received antiplatelet therapy, aspirin or its calciumurea salt, carbasalate calcium, was used in 95.5 percent of all cases (59.8 and 35.7% respectively). Dipyridamole and ticlopidine were prescribed to 4.2 and 0.3 percent of all patients who received antiplatelet therapy. Six percent of the oral anticoagulant treated patients received phenprocoumon and 94 percent received acenocoumarol.

The overall use of oral antithrombotics increased from 54.0 percent in 1988 (4.4, 39.2, and 10.4% for antiplatelet agents, oral anticoagulants, and a combination of both, respectively) to 88.9 percent in 1998 (69.5, 13.2, and 6.2%, respectively). Use of oral antithrombotics, stratified by year of admission, is shown in the figure. For reasons of clarity, only the even years of admission are displayed. The level of oral antithrombotic treatment in odd years of admission is between the values of the nearest even years.

Figure 1. *Annual use of oral antithrombotics from 1988 to1998 in patients who suffered from myocardial infarction, stratified by year of admission*



Only 75.8 percent of the patients, who suffered from a myocardial infarction in the late 1980s and were still in the database in 1998, were treated appropriately in 1998. Patients with myocardial infarction in the late 1990s attained a level of oral antithrombotic treatment of 94.4 percent in 1998.

One prescription for an oral antithrombotic agent in a particular year was indicative for the use of oral antithrombotics during the entire year, since overall 84.7 percent of the patients who filled at least one prescription for an antiplatelet agent collected enough tablets to be more than 70 percent compliant during their follow-up period.

Discussion

Although antithrombotic treatment after myocardial infarction increased during an 11-year period, current use of oral antithrombotics was lower among patients who suffered from a myocardial infarction in the late 1980s than among patients with myocardial infarction in recent years. We recommend reviewing patients who do not receive oral antithrombotics to asses whether the alleged undertreatment is rightly due to, for instance, intolerance or wrongly and treatment should still be initiated.

In comparison to our results, previous studies reported somewhat different levels of antiplatelet therapy. [9-11] Martinez et al. reported aspirin use at discharge of 28 percent in 1986-88, but 75 and 71 percent in 1989-91 and 1994 respectively. [9] Rogers et al. reported aspirin use at discharge of about 80 percent in 1998. [10] Both studies did not collect data on oral anticoagulants prescribed at discharge. The slightly higher levels of aspirin use in 1986-1988 reported by Martinez and in 1998 reported by Rogers were probably due to the limitation to the evaluation of discharge medication only. [9 10] We can rule out that non-prescription aspirin have biased our results for two reasons. First, in the Netherlands a prescription is required for low-dose aspirin. Second, use of non-prescription aspirin of higher doses is negligibly low as non-prescription aspirin is not reimbursed by the health insurance, whereas prescription aspirin is fully reimbursed. In the Netherlands, 98.6 percent of all inhabitants have a health insurance policy covering the costs for prescription drugs. [15] Brotons et al. reported aspirin use of 70.7 and 67.2 percent and oral anticoagulant use of 8.9 and 9.9 percent, at discharge and one year after discharge respectively, in patients admitted due to myocardial infarction in 1995. [11] These results were in accordance with our own findings.

Although the overall use of oral antithrombotics seemed to be on a satisfying level, as previously reported [16], our stratification by year of admission revealed that patients with myocardial infarction in former years are disadvantaged when

compared with patients with myocardial infarction in recent years. Furthermore, use of oral antithrombotics in patients with myocardial infarction in recent years gradually decreases. So not only should patients be reviewed for oral antithrombotic treatment, but once oral antithrombotic treatment is initiated, patients should be closely monitored to prevent an untimely ending of oral antithrombotic treatment.

We tried to estimate the projected number of myocardial infarction that might have occurred due to undertreatment. We assumed that the population in our study resembles the population in randomized clinical trials (RCTs) and therefore the number needed to treat calculated from the RCTs is applicable in our calculation. In our database were 2859 untreated personyears from 1988 to 1998. Based upon the assumption mentioned above and a number needed to treat for two years of 56 [17], 26 new AMI's might have occurred due to undertreatment. Applied to a national level, optimal aspirin treatment in patients with myocardial infarction from 1988 to 1998 would have prevented 1469 non-fatal re-infarctions in the Netherlands.

Our study has several limitations. First, we can not rule out that our results have been biased by difference in duration of follow-up. Due to large variations in duration of follow-up, the period that patients were at risk to suffer from an adverse reaction that would contraindicate oral antithrombotic treatment varies widely among patients. So, intolerance can account for the low use of oral antithrombotics in patients with a past myocardial infarction to a certain extent. However, we do not believe that the 24.8 percent of patients who did not receive any oral antithrombotic is entirely due to ineligibility. As shown in our figure, the yearly increase of the antithrombotics showed has not leveled off yet in patients with a past history of myocardial infarction. Therefore we assume that there are still patients in the database who are eligible for oral antithrombotic treatment. Besides, several surveys in primary care among patients who had been discharged after myocardial infarction over a one to five year lasting period reported rates of aspirin intolerance that ranged from 8.5 to 13 percent, which is substantially below 24.8 percent. [11 18 19] Results from a multipractice audit showed that aspirin use among patients, who had had a myocardial infarction during the past five years, rose from 75.7 percent to 84.1 percent despite a rise in aspirin intolerance of 10.0 to 13.0 percent. [18]

We could not reveal the possible reasons for the low use of antithrombotics among patients with a history of myocardial infarction. As our database is

anonymised, we did not have the opportunity to question patients about their reluctance in getting a prescription filled or to question doctors about their deliberations upon prescribing oral antithrombotics or not. Therefore further research needs to be done to elucidate the reasons for not taking oral antithrombotics and before future intervention strategies can be applied to the right persons.

In interpreting our results, one should consider that no direct evidence is available about the benefits of oral antithrombotic therapy started long after myocardial infarction. However, just as continuation of oral antithrombotic treatment after the end of follow-up is supposed to be beneficial [1], initiation of oral antithrombotic therapy in patients who have been untreated for the duration of follow-up should be beneficial as well.

Lastly, our results can be extrapolated to a general population of patients after myocardial infarction but not to patients living in nursing homes, since those patients are not included in the PHARMO system.

Conclusion

Summarized, our results suggest that, once oral antithrombotics are not prescribed at discharge, the post myocardial infarction status of a patient falls into the background and many patients stay deprived of oral antithrombotic treatment. Thus, if cardiologists, general practitioners, and pharmacists want to improve secondary prevention after myocardial infarction they should focus their attention on patients who do not receive oral antithrombotic treatment, mainly those who have had myocardial infarction in former years, and initiate this treatment of which benefits have been clearly established.

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3.2

PREVENTIVE DRUG USE IN PATIENTS WITH A HISTORY OF NON-FATAL MYOCARDIAL INFARCTION DURING12-YEAR FOLLOW-UP IN THE NETHERLANDS: A RETROSPECTIVE ANALYSIS

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Clinical Therapeutics. 2005; 27: 1806-1814.

Summary

Background: Myocardial infarction (MI) is a common cause of death in developed countries. Long-term preventive pharmacotherapy has been shown to decrease mortality and morbidity after MI. Based on a literature search studies of these therapies to date have estimated the use of monotherapy, whereas many patients are prescribed combination therapy. Thus, assessment of long-term combination drug use after MI is timely.

Objective: The aim of this study was to assess the use of oral antithrombotics, beta-blockers, angiotensin converting enzyme (ACE) inhibitors, hydroxy-methylglutaryl coenzyme A reducatase inhibitors ("statins"), and their combinations after MI at discharge and during 12-year follow-up.

Methods: This community-based, retrospective data analysis was conducted at Utrecht University, Utrecht, The Netherlands. Data from patients aged 18 years at hospital admission who experienced non-fatal acute MI between 1991 and 2000 and had a duration of follow-up ~30 days were included in the analysis. Data were retrieved from the PHARMO Record Linkage System database, which links pharmacies' dispensation records to hospitals' discharge records on an individual patient level, allowing the investigator to observe individual patients' medication use over time. Primary outcome measures were the use of preventive medicines (oral antithrombotics, beta-blockers, ACE inhibitors, and statins) at discharge, overall use, and persistence during 12-year follow-up.

Results: Of 330,000 patients in the database, 4,007 were included in the analysis (2,828 men, 1,179 women; mean [SD] age, 63.5 [12.5] years). Use at discharge and overall use of oral antithrombotics and statins increased significantly between 1991 and 2000, whereas use of beta-blockers and ACE inhibitors increased mainly in patients discharged in the latter years of the follow-up period. Therapy with any combination of drugs increased strikingly from 1991 to 2000, from 47% to 90%. At one year after discharge, 32% of patients had discontinued their first-prescribed combination treatments. At five year after discharge, this rate increased to 57%, suggesting low rate of persistence.

Conclusion: Based on the results of this retrospective data analysis, the use of MI-preventive drug treatment at and after discharge increased significantly in this population in The Netherlands during the 1990s. Combination therapy increased strikingly. However, persistence with combination therapy was low.

Introduction

Myocardial infarction (MI) is one of the most prevalent causes of death in developed countries. [1-3] Several randomized clinical trials [4-8] have shown that preventive pharmacotherapy decreased mortality and morbidity after MI. In particular, the long-term use of oral antithrombotics (antiplatelet agents and oral anticoagulants), beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and hydroxymethylglutaryl coenzyme A reductase inhibitors ("statins") have shown clinical benefit. [4-8]

Guidelines from the European Society of Cardiology and the American Heart Association recommend continuing treatment with these drugs after MI. [9] Several observational studies have examined the use of drugs after MI. [10-15] Analysis of prescription patterns revealed increased use of aspirin, beta-blockers, and ACE inhibitors at discharge during the past decade. [10-12] Some surveys have estimated the use of preventive drug treatment in primary care within two years after hospital discharge. [13-15] AII surveys have shown that drug use in primary care had decreased within one or two years compared with use at discharge, despite that in randomized clinical trials benefits appeared only after two to five years and that continuing treatment is emphasized in the guidelines. [4-9]

Based on a Medline search (key terms: myocardial infarction, secondary prevention, aspirin, antiplatelet, beta-blocker, ACE inhibitor, anticoagulant, and statin; years: 1966-2004), to date, no studies have reported on long-term (>= five years after discharge) drug treatment in patients with MI in clinical practice. A study in The Netherlands of discontinuation of prescribed long-term treatment with different classes of drugs showed that 50% to 70% of patients discontinued therapy too early for the treatment to have been effective. [16] Although patients with a history of MI use a variety of drug combinations, based on the literature search, all studies to date have estimated the use of mono therapy, disregarding this widespread use of multiple drugs. Therefore, an assessment of long-term combination drug use after MI is timely.

The purpose of this study was to assess the use of oral antithrombotics, beta-blockers, ACE inhibitors, statins, and their combinations at and after discharge in patients with a history of MI during long-term (12-year) follow-up.

Methods

Setting

This community-based, retrospective data analysis was conducted at Utrecht University, Utrecht, The Netherlands. Data were retrieved from the PHARMO Record Linkage System (PHARMO-RLS) database, [17] which links pharmacies' dispensation records to hospitals' discharge records on an individual patient level, allowing the observation of medication use by individual patients over time. The database includes records from 8 medium-sized cities in The Netherlands (n = 330,000 inhabitants), from 1985 onward. [18] Each registered patient is identified with a unique, anonymous number. The information per prescribed medicine includes the drug name, anatomic therapeutic chemical (ATC) classification, dispensation date, prescribed daily dose, and amount dispensed. Patient characteristics include gender and year of birth. Due to a strong patient-pharmacy commitment in The Netherlands and sophisticated pharmacy software, the medication records for each patient are virtually complete. [19] The hospital discharge records provide discharge diagnosis (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM [20] code) and admission and discharge dates. The database does not provide information concerning drug indications or laboratory or diagnostic data, such as cholesterol level or left ventricular ejection fraction.

Patients

Data from patients aged > 18 years at hospital admission who were admitted for non-fatal acute MI (ICD-9 code 410) between January 1, 1991, and December31, 2000; had a follow-up of at least 30 days' duration; and had at least 1 prescription filled at any day after discharge were included. Data from patients who died in hospital were excluded. We also excluded data from patients who were transferred to another hospital or discharged to a long-term care facility (LTCF) because after transfer, patients' medications are no longer supplied and recorded on a patient level by community pharmacies participating in the Pharmo-RLS database. Patient data were included in the study for the duration that drug-dispensation records were available. Data collected during hospital stays for recurrent MI were excluded; data after discharge following a recurrent MI

were included if the previously mentioned criteria were met Waivers of consent were not needed.

Definitions of drug exposure

We retrieved all data concerning prescriptions dispensed between January 1, 1991, and December 31, 2002, using ATC codes (codes: antiplatelet agents, B01AC; oral anticoagulants, B01AA; beta-blockers, C07; ACE inhibitors, C09A; and statins, C10AA). We constructed episodes of drug use by "pasting" subsequent prescriptions, as previously described. [21] If the dispensation date of the next prescription fell before the theoretic end date of the previous prescription, the dispensation date was adjusted. In cases in which the dose and dosing regimen were identical for subsequent prescriptions, the dispensation date of the next prescription was artificially reset to the theoretic end date of the previous prescription. If, after pasting, the time span between 2 subsequent periods of drug use was <30 days, the patient was considered to have used medication during the entire period.

Analysis

Patients were considered to have used medication at discharge if an episode of drug use covered (part of) the first 30 days after discharge. P values were calculated using the chi square test. To estimate drug use during the period 1991-2002, we estimated point prevalences on May 25 and November 25 of each year Van Eijk et al. [22] validated the estimation of prevalence with randomly chosen dates.

P values were estimated using multi-level logistic regression analysis.

The time to discontinuation of treatment initiated at discharge was estimated using Kaplan-Meier survival analysis. Monotherapy use was considered to be discontinued in cases in which the time span between 2 consecutive prescriptions was >2-fold the duration of the previous prescription, with a minimum of 90 days. In estimating the time to discontinuation of combination treatment, the addition of drugs or switching between drugs in the same drug class was allowed. Use of a combination of drugs was considered to have been discontinued when one of the components prescribed at discharge had a time span between 2 consecutive prescriptions of >2-fold the duration of the previous prescription, with a minimum of 90 days. Statistical analysis of the effect of

demographic and baseline clinical characteristics on time to discontinuation was performed using Cox regression analysis. Analyses were performed using SPSS version 10.0 (SPSS Inc., Chicago, Illinois). Multilevel logistic regression was performed with a generalized linear mixed-effects model using S-Plus version 6.0 (Insightful Corporation, Seattle, Washington).

Results

Of 330,000 patients in the database, we identified 4,924 admissions for MI (ICD-9 code 410) between January 1, 1991, and December 31, 2000. After the exclusion of 854 admissions due to a follow-up of < 30 days (523 died in-hospital, 86 were transferred to another hospital, 8 were transferred to an LTCF, and 237 for unknown reasons) and the exclusion of 63 additional subjects who did not fill at least 1 prescription at any time after discharge from the hospital (44 died at home, 19 for unknown reasons), data from 4,007 admissions were included in the analysis (2,828 men, 1,179 women; mean [SD] age, 63.5 [12.5] years). General characteristics of the patients are shown in table 1.

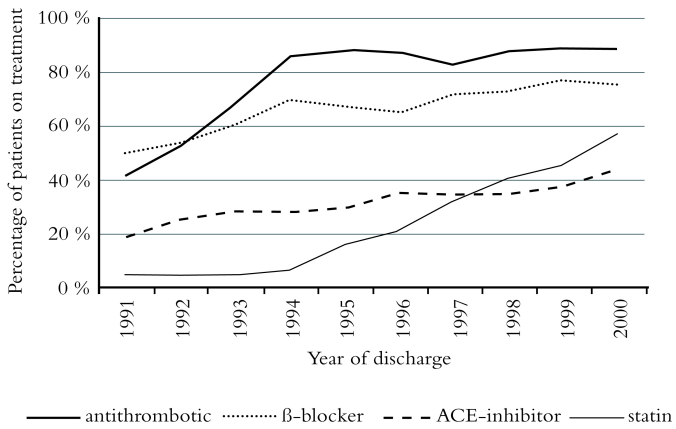
Table 1. *General characteristics of patients included.*

		N	(%)
Sex	male	2828	(70.6%)
	female	1179	(29.4%)
Age on admission (yr, mean ± SD)		63.5	± 12.5
Duration of hospital stay (days, mean ± SD)		11	± 6.7
Duration of follow-up (yr, mean ± SD)		4.9	± 3.0
Location of MI	anterior wall	1023	(25.5%)
	inferior wall	1208	(30.2%)
	other site	594	(14.8%)
	unspecified site	1182	(29.5%)
Number of MI	first	3527	(88.0%)
	recurrent	480	(12.0%)

Discharge medication

The use of oral antithrombotics, beta-blockers, ACE inhibitors, and statins increased significantly from 1991 to 2000 (by 42%-88%, 49%-76%, 19%-44%, and 5%-58%, respectively) (all $P < 0.001$) (Figure 1). Closer exploration of discharge medication use by patients who received 1 or more prescriptions at discharge revealed that in 1991, 87% received a beta-blocker and/or ACE inhibitor; 11 % received an oral antithrombotic only, and 6% of patients received a combination of an oral antithrombotic plus a beta-blocker In 2000, 48% received an oral antithrombotic plus a beta-blocker and/or ACE inhibitor plus a statin, and 36% received at least a beta-blocker and an ACE inhibitor (Figure 2). The types of combinations prescribed at discharge changed gradually from 1991 to 2000 (any combination, 47%-90%). During the entire study period, women received monotherapy with beta-blockers significantly more of ten than combination therapy compared with men ($P = 0.002$). In the late 1990s, men were significantly more likely to receive a combination that included a statin compared with women ($P = 0.03$).

Figure 1. *Discharge medication from 1991 to 2000.*

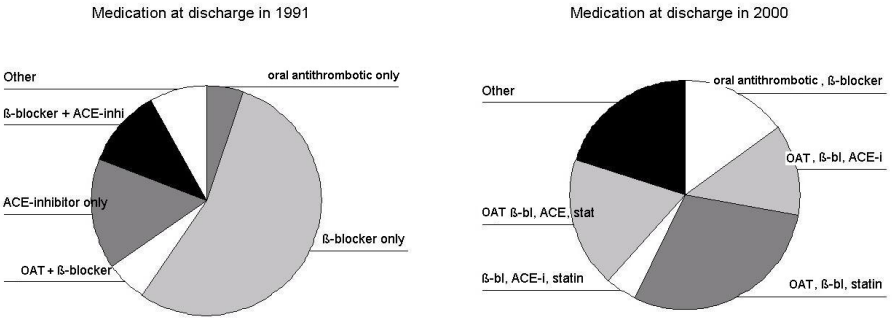


Annual use

Figure 3 shows annual use of secondary preventive drug treatment after MI for all patients. Data from all patients at discharge and during postdischarge follow-up were included in the analysis. The proportion of patients receiving oral antithrombotic treatment increased gradually, from 38% to 76% ($P < 0.001$).

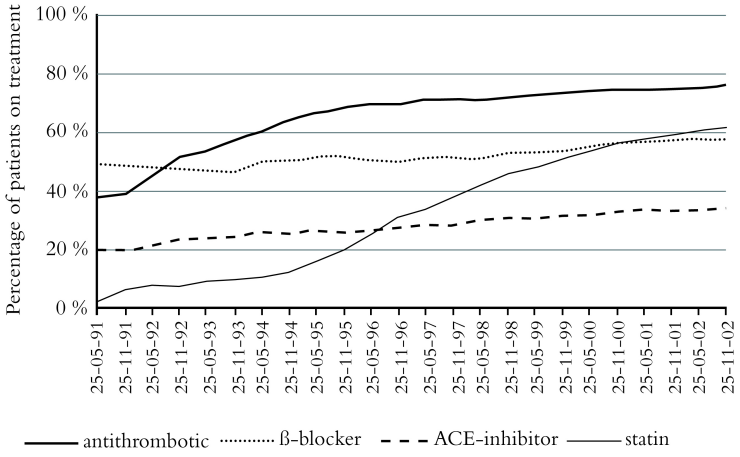
The use of beta-blockers and ACE inhibitors, on the contrary, increased only moderately (beta-blockers, from 48% to 57%; ACE inhibitors, from 20% to 35% [both, P < 0.001]). In 1994, the use of statins started to increase significantly (3% in 1991, to 10% in 1994, to 62% in 2002; P < 0.001).

Figure 2. *Combination treatment at discharge in 1991 and 2000*



OAT=oral antithrombotic, ß-bl = beta-blocker, ACE-I = ACE-inhibitor, stat = statin

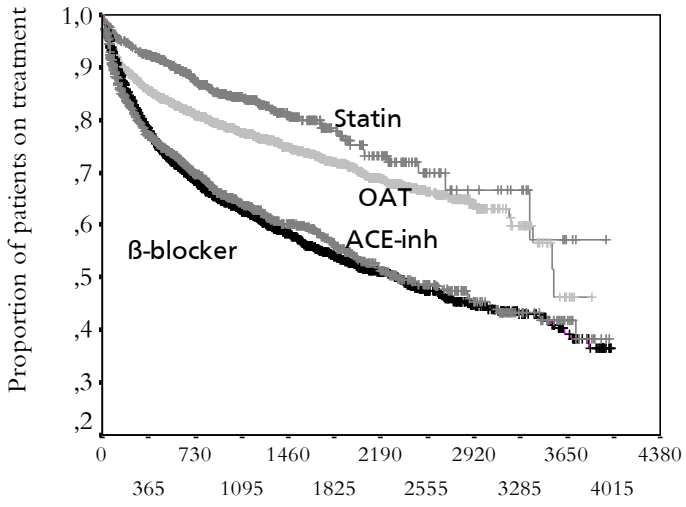
Figure 3. *Annual use of preventive drug treatment after myocardial infarction, estimated at May 25th and November 25th , from 1991 to 2002.*



Persistence with therapy

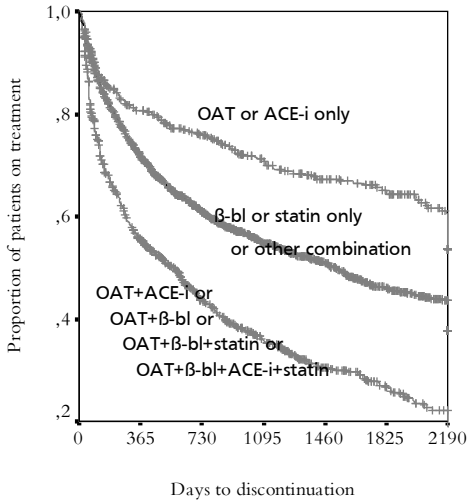
Time to discontinuation of individual drugs (both as monotherapy and as part of combination therapy) and combination therapy prescribed at discharge are shown in Figure 4. Persistence appeared to be best with statins: 20% of patients discontinued treatment within four years after discharge. Persistence with oral antithrombotics was reasonable (27% discontinued within four years). However, persistence with beta-blockers and ACE inhibitors was much lower: at four years after discharge, 40% and 43%, respectively, had discontinued treatment Persistence with combination treatment was even worse: at one year after discharge, 32% of the patients had discontinued combination treatment. At four years after discharge, 52% of patients had discontinued combination treatment. Cox proportional hazard analysis revealed that the odds ratio (OR) for discontinuation was 2.3 (95% CI, 1.9-2.8) for beta-blocker treatment and 2.2 (95% a, 1.8-2.7) for ACE inhibitor treatment compared with statin treatment Patients discharged in the early 1990s were slightly more likely to discontinue compared with their peers in the late 1990s (OR, 1.4; 95% CI, 1.3-1.6). Sex and age were not independent predictors of time to discontinuation.

Figure 4. *Time course to discontinuation in patients discharged on oral antithrombotics (OAT), beta-blocker, ACE-inhibitor, statin (combined with other drugs or monotherapy) or combination therapy.*



Times to discontinuation of all possible treatments (four monotherapies and 11 combination therapies) prescribed at discharge are shown in Figure 5. For clarity, different treatments are shown grouped by their persistence rates. Persistence with oral antithrombotic monotherapy and ACE inhibitor monotherapy was moderate (6-year rate, 58%). Persistence with combination treatment with an oral antithrombotic plus an ACE inhibitor, oral antithrombotic plus a beta-blocker, oral antithrombotic plus a beta-blocker plus a statin, or oral antithrombotic plus a beta-blocker plus an ACE inhibitor plus a statin was poorest (persistence rate at six years, 25%). Persistence with beta-blocker or statin monotherapy or any combination was in between (6-year rate, 43%).

Figure 5. *Time course to discontinuation of several different combinations.*



Discussion

In patients with a history of MI, the use of oral antithrombotics, beta-blockers, ACE inhibitors, and statins increased significantly during the 1990s in The Netherlands. This increase included both the use of discharge medication and the use of medication in the period after discharge. However, persistence with prescribed medications was low to moderate, and due to our yielding definition of discontinuation, actual day-to-day persistence probably was poor.

Combination treatment increasingly is used for secondary prevention after MI. However, in the present study, the proportion of patients who succeeded in adhering to the combinations over several years was low (range, 25%–43%).

The use of oral antithrombotics and statins increased strikingly in our study population in the early 1990s. Although publications concerning the benefits of oral antithrombotic therapy appeared as early as 1980, [23-27] the subsequent publication of a meta-analysis in 1988 [28] may have contributed to the increased use of aspirin in the early to mid-1990s. The pattern of statin use strongly reflects the introduction of those drugs and the publication of landmark studies, such as the Scandinavian Simvastatin Survival Study (4S) [29] and the West of Scotland Coronary Prevention (WOSCOP) trial [30] in the early 1990s. Moreover, marketing efforts of the statin industry after these landmark studies likely contributed to the increased use of statins. The use of beta-blockers and ACE inhibitors increased steadily, mainly in patients who had been discharged recently. Benefits of beta-blocker treatment were widely accepted as early as the 1980s, [31] and the publication of a review in the 1990s did not seem to influence practice. It is likely that ACE inhibitor treatment did not increase, as did that of statins due to the inconclusive evidence that became apparent in the 1990s. [7]

The low persistence with beta-blocker treatment may have been the result of adverse events or contraindications: it is well known that the initial side effects of (beta-blockers (eg, dizziness, fatigue) can be bothersome. [32] Although ACE inhibitors are believed to be associated with fewer drug-related adverse effects, our results did not agree with that: persistence with ACE inhibitors was as low as with (beta-blockers. It is possible that patients with a history of MI are more prone to the side effects of ACE inhibitors.

Our findings of the increased use of evidence-based pharmacotherapy at discharge in 2000 compared with 1991 are comparable with those from previous studies. [10-12] Previous studies with shorter follow-up periods have shown that persistence with beta-blockers and ACE inhibitors decreased rapidly after discharge in patients with congestive heart failure. [33] However, the adherence to statins in our study population was not consistent with the adherence of other patient populations that have been studied.[34] Patients in our study adhered better to statin therapy. It is likely that the patients in our study (ie, patients with a history of MI) were more persistent compared with the patients in the study by

Benner et al, [34] which included hypercholesterolemic patients both with and without cardiovascular complications. Conversely, our definition of discontinuation may have overestimated the persistence of treatment We defined discontinuation as having a gap between two prescriptions of at least 2-fold the duration of the first prescription, with a minimum of 90 days, and the median duration of a prescription for chronically intended treatment is almost 90 days. For example, patients who restarted treatment after five months were considered to be continuous users. The cut-off point was not arbitrary; larger gaps did not result in less variable adherence rates (personal communication, B. van Wijk, Utrecht University, 2004). However, narrowing the gap would likely have led to even lower persistence rates.

Unlike other studies, our study expanded the category "low-dose aspirin" to "oral antithrombotics" by including oral anticoagulants in this group. We did so because oral anticoagulants are used more frequently in The Netherlands compared with other countries because The Netherlands has a network of anticoagulant clinics, and patients living in The Netherlands regularly switch between low-dose aspirin and oral anticoagulants. Leaving out the oral anticoagulants and limiting this group to low-dose aspirin would have led to an underestimation of the use of antithrombotics for secondary prevention.

In general, persistence with the different drug categories seems to be slightly better than those reported in previous studies (67%-71 % for aspirin, 34%-72% for beta-blockers, 26%-69% for ACE inhibitors, and 25%-80% for lipid-lowering drugs). [13-15] This finding could be related to the prescription-reimbursement system in The Netherlands, where 99% of all inhabitants have a health insurance policy covering me costs for prescription drugs, including the drugs we studied, and a prescription is compulsory for all drugs included in this study.

Because our data were anonymised, we cannot reveal the possible patient characteristics that might have been reasons why these patients with a history of MI did not receive or adhere to preventive treatment. Therefore, further research needs to be performed to elucidate the reasons for not initiating or continuing treatment before future intervention strategies can be applied to the appropriate persons.

The Pharmo-RLS database does not provide data concerning all cardiovascular risk factors. For example, data concerning smoking status, body mass index, and

hypertension are not registered. Although knowledge about risk factors is important for me clinical prognosis of patients over time, the authors believe that the lack of knowledge of other cardiovascular risk factors does not affect the validity of the results of the present study. Considering that the aim of the present study was to assess long-term drug use after MI, and
that long-term drug use is recommended for all patients after :MI regardless of additional risk factors by guidelines from the European Society of Cardiology and the American Heart Association, [9] the presence of risk factors is of less importance compared with long-term drug use. In fact, all patients with a history of MI should receive preventive treatment regardless of risk. More attention should be given to finding strategies to help patients adhere to these regimens.
Drug use in this study was deduced from pharmacy dispensation records, which does not imply that patients actually used the medication. However, computed pharmacy records have proved to be a reliable source of drug exposure. [35]

Conclusions

The findings of this retrospective analysis show that, although secondary prevention after MI has improved strongly since 1991 in patients admitted to the hospital for MI, especially recurrent MI, there remains room for improvement. The majority of patients from whom data were collected did not adhere to combination therapies in the long term.

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4

NON-PERSISTENCE IN DAILY PRACTICE

4.1

REASONS FOR NON-PERSISTENCE WITH STATIN TREATMENT ACCORDING TO BOTH PATIENTS AND GENERAL PRACTITIONERS

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Submitted

Summary

Background: Non-persistence with statins seems to prevent optimal reduction of re-infarction and mortality in patients with a history of myocardial infarction. Understanding of the reason for non-persistence from a patient's and GP's point of view is needed to determine if discontinuation matches criteria for evidence based treatment, and to determine which patients are eligible to enrol in programs to improve statin treatment.

Objective: To assess the 3-year persistence with statin treatment, to reveal the reason for discontinuation and to describe predictors for untimely discontinuation of statin treatment.

Method: Retrospective follow-up study in nine community pharmacies in the Netherlands. Patients and their GPs received a questionnaire. Outcomes were the rate of discontinuation, the reason for discontinuation of statin treatment, and predictors of discontinuation.

Results: Out of 425 patients, 104 patients (24%) discontinued statin treatment during 3-year follow-up. Major reason for discontinuation according to the GP was the patient's own initiative, while patients reported side effects to be the main reason for non-adherence. 56% of the non-persistent patients discontinued treatment without a reason that meets criteria for evidence based treatment. Low compliance with treatment (PDC < 80%) was associated with discontinuation of statin treatment.

Conclusion: Three out of four patients were still on statin treatment after three years of follow-up. Low compliance with treatment was associated with discontinuation of statin treatment. Half of the patients who discontinued treatment seem to do so without a reason that meets criteria for evidence based treatment, but reasons according to patients and GPs mismatch.

Introduction

In randomized clinical trials, HMG-co-A-reductase inhibitors (statins) have proven to reduce coronary heart disease by 25-40% in both primary [1, 2] and secondary prevention [3-5]. Mortality during the five to six year follow-up was reduced by 22-30 % in randomized trails. [1, 3, 4] Nowadays statins are prescribed to large numbers of patients assuming that the results achieved in randomized clinical trials can definitely be extrapolated to daily practice. However, there are indications that the results from randomized controlled trails are not readily applicable to daily practice. Patients included in trials were closely monitored and underwent treatment for on average 5 years. Several studies have shown that the use of statins is discontinued more often in daily practice than in controlled trials. [6-10] Untimely discontinuation of statins could result in preventable morbidity and mortality among patients with cardiovascular disease. So based upon the best available evidence, patients who start statin treatment should be treated long-term.

Investigators have expressed the costs for pharmaceuticals for patients that discontinue treatment within a year as economic loss. This economic loss has been estimated to be 16-31% of the total costs spent annually on statin treatment (i.e. € 166-302 million/$ 209-381 million) in the Netherlands only. [9] Though, by expressing premature discontinuation as damage one assumes that all untimely discontinuation is undesirable. However, to determine if non-persistence with statin treatment is undesirable, understanding of the reasons for discontinuation is wanted.

Many studies tried to reveal predictors for medication refill adherence of cardiovascular therapy. [11-14] Those studies focused on prognostic factors and determinants for non-adherence, but omitted the patient's reason for discontinuation. Adherence has been associated with age, sex, marital status, educational level, race, medical history, treating physician, medication class, dosing regimen, and concomitant use of medication. [11-15] However data are not conclusive as paradoxically other studies showed no associations on many of these determinants. Few studies on discontinuation of treatment questioned patients. They either assessed the belief about medication but did not ask the reason for discontinuation [16, 17] or they assessed reasons for discontinuation of non-cardiovascular drugs. [18-20] We think understanding of the reason for non-persistence with statin treatment from a patient's point of view is highly

important; both to determine if discontinuation is evidence based and to determine which patients would benefit from programs that improve persistence.

Objective

Our objective was to assess the 3-year persistence with statin treatment, to reveal the reason for discontinuation, and to assess if the reason for discontinuation meets criteria for evidence based treatment. Furthermore, we wanted to describe predictors for untimely discontinuation of statin treatment.

Method

Study population

We performed a retrospective follow-up study in nine community pharmacies in the Netherlands. We selected all patients who initiated statin treatment between January 1, 1998, and December 31, 1998 and were still alive at the end of the 3-year follow-up period. All 425 patients were sent the patients' questionnaire and to the general practitioners (GPs) of those patients we sent the GP's questionnaire.

Questionnaires

We designed two questionnaires, one questionnaire for patients and one for the patients' GPs. Different questionnaires were constructed to deal with recall bias of patients and the ability of GPs to look up information in patients records. In the patient's questionnaire, we asked for the indication, satisfaction with the prescribed statin, cholesterol level, expected duration of use, and wish for education about hypercholesterolemia and treatment. In patients who discontinued treatment or switched to another statin, we asked the patient for the main reason of this change of treatment. With the GP's questionnaire, we verified the indication, cholesterol level and main reason for discontinuation or switching. Furthermore we asked the GP for co-morbidity. Comprehensibility of the questionnaires was pre-tested in a patient and a pharmacist technician of each participating pharmacy. The language used in this paper is professional and differs from the language used in the patients' questionnaire.

Pharmacy data

From the pharmacy computer system, age, gender, type of statin, first prescriber, compliance, drug switching, discontinuation, and co-medication were extracted. Compliance was expressed as percentage of days covered (PDC) and was calculated by dividing the amount of tablets dispensed by the theoretical duration of use.

Main outcome measures

We assessed the discontinuation rate of statin treatment, the main reason for discontinuation of statin treatment, the proportion of patients with a reason for discontinuation that meets criteria for evidence based treatment, and the predictors of discontinuation. Discontinuation was defined as having no active prescription at three years after initiation of treatment. To avoid misclassification due to non-compliance, treatment gaps of at most 30 days were allowed. The 30-day period was chosen as most chronically intended medication is dispensed for a 90-day period in the Netherlands. A 30-day period therefore may account for a non-compliance rate of 25%. This method of estimation of prevalence of drug use have been described in full by Mantel-Teeuwisse *et al.* [21] Discontinuation without a reason that seems to meet evidence based criteria was considered to be of special interest as these patients might be eligible for re-initiation of treatment. From a patients' point of view, side effects and the doctor's decision to discontinue treatment were considered to be evidence based. From he GPs point of view, side effects, specialists' instigation and guideline adherence were considered to be evidence based. Possible predictors of discontinuation were sex, age, co-medication, compliance with statin treatment (PDC > 80%), type of statin, and first prescriber of statin treatment.

Statistics

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression. Age, gender and factors that were independently associated with non-persistence ($p<0.1$) were put in the model, and ORs were adjusted for all variables included in the model. Survival function describing the persistence with statin treatment was calculated using Kaplan-Meier survival analysis. All statistical analyses were performed using SPSS 10.0 (SPSS Inc., Chicago, Illinois).

Results

We selected 425 patients who initiated statin treatment in 1998. Baseline characteristics are shown in table 1. During the 3-year follow-up, 104 patients (24%) discontinued statin treatment. A Kaplan-Meier plot displays the proportion of patients on treatment during follow-up (figure 1).

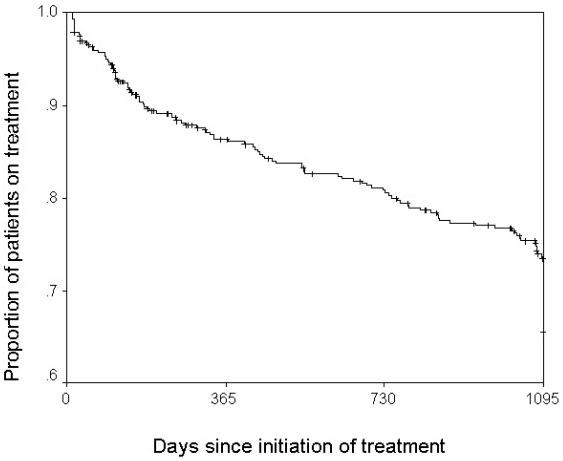
Table 1. *Baseline characteristics of patients included in the study.*

Variable		N = 425	(%)
Sex	male	260	(61)
	female	165	(39)
Age	< 55	130	(31)
	55-70	203	(48)
	>70	92	(22)
Statin	simvastatin	176	(41)
	pravastatin	48	(11)
	fluvastatin	43	(10)
	atorvastatin	149	(35)
	cerivastatin	9	(2)
First prescriber	GP	217	(51)
	specialist physician	156	(37)
	unknown	52	(12)
Comedication	aspirin / oral anticoagulant	222	(52)
	beta-blocking agents	172	(41)
	ACE-inhibitors / angiotensin II antagonists	132	(31)
	nitrates	124	(29)
	anxiolytics and sedatives	117	(28)
	calcium channel blockers	111	(26)
	diuretics	88	(21)
	antidiabetics	52	(12)
	antidepressants	24	(6)
	cardiac glycosides	9	(2)
	anti-arrhythmics	5	(1)

Closer exploration of the patients who were non-persistent with treatment after the 3-year follow-up period, revealed that 77 out of 104 patients (74%) who discontinued treatment did so without switching to another statin. Furthermore, only 25 patients (24%) had a PDC of at least 80%. On the contrary, the 321 patients who stayed on treatment were much more compliant; 270 patients

(84%) had a PDC of at least 80%. The most compliant patients were those who did not switch to another statin; 309 out of 336 patients who did not switch to another statin (92%) had a PDC over 80%. Frequently, drug-switches were associated with treatment gaps. In 89 patients who switched to another statin, only 40 patients (45%) started immediately with the new statin, whereas 29 patients (32%) had a treatment gap of more than one month.

Figure 1. *Proportion of patients on treatment*



Comparison of patients who discontinued treatment during the 3 year follow-up with patients who remained on treatment, revealed that patients with a PDC > 80% were less likely to discontinue statin treatment (OR 0.12 95% CI 0.07-0.19) and patients treated with anti-depressants were more likely to discontinue statin use (OR 2.34 95% CI 1.02-5.36). Furthermore, women and elderly seem to be more likely to discontinue treatment (see table 2). First prescriber, type of insurance, and switching to another statin were not associated with discontinuation of treatment.

Reasons for discontinuation as cited by patients and GPs are shown in table 3.

Table 2. *Crude and adjusted Odds Ratios (OR) and 95% Confidence Intervals (95% CI)*

		Continued N=321		Discontinued N=104		Crude OR (95% CI)	Adjusted * OR (95% CI)
		N	%	N	%		
Sex	Male	201	(63)	59	(57)	ref	ref
	Female	120	(37)	45	(43)	1.30 (0.86-1.98)	1.17 (0.72-1.89)
Age category	< 55	99	(31)	31	(30)	ref	ref
	55-70	156	(49)	47	(45)	0.98 (0.61-1.58)	1.29 (0.74-2.24)
	> 70	66	(20)	26	(25)	1.31 (0.74-2.30)	1.40 (0.73-2.68)
Compliance	< 80%	50	(16)	79	(76)	ref	ref
	> 80%	271	(84)	25	(24)	0.12 (0.07-0.19)	0.12 (0.07-0.19)
Co medication	anti-depressants	15	(5)	9	(9)	2.34 (1.02-5.36)	2.54 (0.98-6.56)

* *Adjusted for sex, age and all variables with p<0.1 in univariate analysis (compliance and use of anti-depressants)*

Table 3. *Reason for discontinuation and drug-switching*

GP's questionnaire	N=23	(%)	Patients questionnaire	N = 32	(%)
Reason for discontinuation			Reason for discontinuation		
patient's initiative	7	(30)	side effects	15	(47)
specialist's instigation	5	(22)	drug-switch *	6	(19)
withdrawal from market **	4	(17)	doctor's advice	4	(13)
side effects	3	(13)	completing treatment period	4	(13)
implementation of guideline	2	(9)	other	3	(9)
other	2	(9)			
Reason for switch of statin	N=26	%			
specialist's instigation	10	(38)			
side effects	8	(31)			
continuing medical education	4	(15)			
withdrawal from market	3	(12)			
information from industry	1	(4)			

* *Patients ultimately did discontinue statin treatment, even though preceded by drug switch*

** *Four out of seven responders who used cerivastatin before market withdrawal completely stopped statin treatment*

Reasons for non-persistence varied and relying on the GP's opinion, 57% of the patients seem to discontinue treatment for a reason that does not meet criteria for evidence based treatment. However, the majority of the patients themselves (72%) did believe to have a reason that, from a professional point of view, would be considered to be evidence based.

The response rate for the patient's questionnaire was 68% and 52% for the GP's questionnaire The questionnaires of 425 patients were sent to 62 GPs. Women, patients who discontinued treatment, patients who had a PDC < 80%, and patients who used benzodiazepines, were more often non-responders (OR 2.32 95% CI 1.48-3.64, OR 1.96 95% CI 1.24-3.10, OR 2.21 95% CI 1.44-3.41, OR 2.06 95% CI 1.32-3.21 respectively). GP questionnaire were more likely to be returned for patients who did receive one or more preventive drugs besides statin treatment (i.e. antithrombotics, beta-blockers, angiotensin-converting-enzyme inhibitors) and for patients who received the first statin prescription from a specialist physician (OR 1.77 95% CI 1.19-2.64 and OR 1.77 95% CI 1.02-2.36 respectively). Results from the questionnaires are shown in table 4.

Table 4. *Results from patient's and GP's questionnaires.*

Patient's questionnaire	N = 290	(%)	GP's questionnaire	N=222	(%)
Indication			Indication		
hypercholesteremia	145	(50)	primary prevention	77	(35)
myocardial infarction	69	(24)	secondary prevention	100	(45)
familial hypercholesterolemia	37	(13)	familial hypercholesterolemia	20	(9)
other	29	(10)	other	2	(1)
unknown	10	(3)	unknown	22	(10)
Known cholesterol level	143	(49)	Known cholesterol level	172	(78)
Satisfied with treatment	234	(81)	Comorbidity		
Known period of treatment	86	(30)	any	181	(82)
Need for further info	75	(26)	diabetes mellitus	33	(15)
			CVA / TIA	17	(8)
			hypertension	59	(27)
			angina pectoris	66	(30)
			myocardial infarction	55	(25)
			peripheral vascular disease	18	(8)

The vast majority of patients was able to mention the indication for statin treatment (97%), but knowledge about cholesterol level and the expected

duration of use was less (49% and 30% respectively). Analysis of the 290 patients of whom the patient's questionnaire was available and analysis of the 222 patients of whom the GP's questionnaire was available did not reveal other predictors of discontinuation of statin treatment. We did not compare patients who stayed on treatment with patients who seemed to have discontinued treatment without an evidence based reason, as numbers of the last-mentioned group were to small.

Discussion

The results of our study show that 76% of the patients who initiated statin treatment were still on treatment after three years of follow-up. Both low compliance with treatment (PDC < 80%) and use of anti-depressants were associated with discontinuation of statin treatment. The majority of patients who discontinued treatment seem to do so without a reason that meets criteria for evidence based treatment.

Although items from the questionnaire were not associated with discontinuation of treatment, the questionnaires did reveal some incongruities. GPs were unable to report the cholesterol level in one fifth of their patients. For only 45% of the patients with known cholesterol level achievement of the treatment goal was recorded (i.e. total cholesterol below 5.0 mmol/L). Although part of the failure to report cholesterol levels by GPs might be explained by the fact that part of the patients is treated by specialist physicians, the proportion of specialist's prescriptions did not explain all unrecorded cholesterol levels in the GP practices. Besides, all patients should achieve treatment goals disregarding whoever is treating the patient. Although 51% of the patients was unaware of their cholesterol level and 68% of the patients were unaware of the expected duration of use, only 26% of the patients said to be in need for further information on those issues.

The reasons for discontinuation of treatment as cited by patients did not match the reasons reported by GPs. Data from both the patient's questionnaire and the GP's questionnaire on the same patient was rarely available in patients who discontinued treatment. Therefore we could not compare the reasons as cited by patients and the reasons reported by GPs directly. However, the difference in reported reasons at least raises the question which point of view is most reliable. Anyhow, the mismatch between both questionnaires implies that

communication between GP and patients and probably between specialist physician and GP may be improved.

While the strength of our study was the assessment of a basic reason for non-adherence instead of constructing a deduction of patient characteristics, our study has several limitations too. First, we classified the different reasons for discontinuation as meeting criteria for evidence based treatment or not. We did so because we wanted to focus on patients who might benefit from re-initiation of treatment. Therefore, we needed to exclude patients who were no longer eligible for statin treatment. We relied on the professional skills of doctors, so we considered a doctor's decision to discontinue treatment to be evidence based and side effects reported by GPs as a conclusive reason to discontinue treatment. We considered the patient's own initiative and withdrawal of a statin from the market as reasons that do not meet criteria for evidence based treatment. Although we recognize the arbitrariness of such a classification, from a practical perspective as community pharmacists, we wanted to define a group of patients that would be identifiable and eligible for pharmaceutical care programs to improve persistence with statin treatment. Weakness of this classification is the disregard of factors that are related to the patient such as quality of life (QOL) and satisfaction. Due to small sample size and some non-response, the number of patients without an evidence based reason for discontinuation was to small to compare with patients who stayed on treatment. Particularly predictors for non-evidence-based discontinuation would have been interesting as in practice these patients are considered to be highly eligible for re-initiation of treatment.

Second, we reported higher persistence rates than other studies on this issue (2-year persistence of 25-47%). [8-10] This may be due to our definition of discontinuation, which allowed patients to have treatment gaps between consecutive prescriptions. We did so to avoid misclassification; smaller treatment gaps might have classified patients as non-persistent while re-initiating treatment during follow-up.

Third, non-response might have biased our results as 32% of the patients' questionnaires and 48% of the GPs' questionnaires was not returned. Patients who discontinued treatment, who had a low compliance, and who used benzodiazepines did return the questionnaire less often. This might indicate that especially the less conscientious patients are under-represented in our sample and therefore the proportion of patients who discontinue without an evidence based reason might be even larger then the 56% we established. GPs did return

questionnaires concerning patients who were treated with preventive drugs besides statins and concerning patients whose statin treatment was initiated by specialists physicians more often. This might indicate that patients with a poor condition are over-represented among respondents.
Lastly, the sample of patients who discontinued treatment and answered the questionnaire was relatively small. Therefore, our results may be encouraging, but need to be confirmed in a larger study.
But besides some limitations, our results show that it is too simplistic to state that all discontinuation of statin treatment in untimely, as there surely seem to be sufficient reasons for non-adherence that meet criteria for evidence based treatment. However, it seems that there are other reasons for non-adherence as well. Therefore, healthcare professionals must be aware of the diversity of reasons for non-adherence and judge those reasons on a patient level. In consultation with the patient a doctor could reconsider the possibilities for statin treatment and by that the feasibility of prevention of morbidity and postponement of mortality.

Conclusions

Our findings show that persistence with statin treatment had declined by 24% over a 3-year period. Major reason for discontinuation according to the GP was the patient's own initiative, while patients reported side effects to be the main reason for non-adherence. The majority of the patients seem to discontinue treatment without a reason that meets criteria for evidence based medicine. As QOL might play an important role in non-adherence too, further research needs to be done to unravel the reasons for non-adherence more thoroughly. Then health care professionals could indicate which patient might be eligible for re-initiation of treatment and health care professionals could develop pharmaceutical care programs dedicated to these patients.

Acknowledgements

We thank S.F. Cheung PharmD, C.G. Colijn PharmD, W.P. Goemans PharmD, R.J. Gores PharmD, P.E. Hougée PharmD, P.D.M. Janssen PharmD, J. Klok Pharm, M. Verwegen PharmD, and T.I.C van der Wal PharmD for their contribution to the design and the execution of this study.

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4.2

DISCONTINUATION OF BETA-BLOCKER TREATMENT AND REASONS AS REPORTED BY PATIENTS

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Submitted

Summary

Background: Several studies estimated that persistence with chronically intended medication, like beta-blockers, in daily practice is poor. Many studies tried to reveal predictors for the failure of medication refill adherence but disregarded the patient's opinion on this matter.

Objective: Our aim was to clarify the reason for discontinuation of beta-blocker treatment in patients with cardiovascular disease and to establish the proportion of patients that might be eligible for reconsideration of treatment.

Method: We administered a telephone questionnaire to patients who discontinued beta-blocker treatment. Main reasons for discontinuation and switch to another cardiovascular drug were assessed.

Results: 72% of 29 patients reported to have discontinued drug treatment in consultation with their physician. Adverse effects were most frequently cited to have prompted discontinuation. Eleven patients persisted with pharmacological treatment by switching to another drug. Considering switching rates and reasons for discontinuation, 52% of the patients should be reviewed for possible re-initiation of treatment with a cardiovascular agent.

Conclusion: Many patients discontinued beta-blocker treatment for unclear or questionable reasons from an evidence-based point of view. 55% of the patients was eligible for re-evaluation of their treatment status. As the majority of patients discontinued treatment in consultation with their doctor, future interventions should be directed towards prescribing physicians in particular.

Introduction

The use of beta-blockers is an important evidence-based strategy to prevent cardiovascular disease. Both patients with established cardiovascular disease, like myocardial infarction, [1] and patients who are at increased risk for developing cardiovascular complications, like hypertensive patients, [2] can benefit from beta-blocker treatment. In general beta-blockers, as cardiovascular disease prevention, are intended for long-term treatment. [1 2] Several studies estimated persistence with chronically intended medication in daily practice. [3-6] Persistence was defined as the accumulation of time from initiation to discontinuation of therapy. These studies revealed that persistence with drugs intended for long-term use is poor and therefore treatment is not evidence-based. Persistence with beta-blocker might be especially poor, since beta-blockers frequently have bothersome side effects. [7] Many studies tried to reveal predictors for the failure of medication refill adherence. [6 8-10] Almost all studies focused on socio-economic, demographic and prescriber related determinants. Some studies approached the patient more directly. [11-13] However, they assessed the patient's believe about medication [11] , were limited to patients with chronic heart failure [12] or were restricted to non-adherence. [13] When establishing predictors of non-persistence, most studies assume that non-persistence is undesirable and therefore patients should be encouraged to re-initiate treatment. However, it might be questionable if this applies for all patients. Legitimacy of deviation from general guidelines should always be judged considering individual patients needs. Hence we think it is important to reveal the underlying reason for discontinuation of treatment before establishing the number of patients that could benefit from re-initiation of treatment. Therefore our aim was to clarify the reason for discontinuation of beta-blocker treatment in patients with cardiovascular disease and to establish the proportion of patients that might be eligible for consideration of restart of treatment.

Method

Study population

We aimed to study a sample of patients with cardiovascular disease. Therefore we selected patients who filled prescriptions for both low-dose aspirin and beta-blockers between March 1, 2003 and August 31, 2003, but did not fill any prescription for a beta-blocker from September 1, 2003 to February 28, 2004 in 5 community pharmacies in the Netherlands.

Survey
We designed a telephone questionnaire and participating pharmacist interviewed their patients. Patients were questioned about the indication for beta-blocker treatment, the reason for discontinuation, and switch to another drug.

Pharmacy data
Patient characteristics (age, gender) and prescription characteristics (beta-blocker, duration of use, prescriber) were retrieved from the pharmacy computer system.

Main outcome measure
Main outcome was the reason for discontinuation as reported by the patient, subsequent switching to other drug treatment after discontinuation of beta-blocker treatment and eligibility for reassessment of need for treatment.

Results

We selected 32 patients who discontinued beta-blocker treatment according to the drug dispensing records kept in the pharmacy. All 32 patients were contacted by telephone. One patient had never discontinued treatment but only had reduced the daily dose. As a consequence, the telephone questionnaire was administered to 31 patients. Baseline characteristics are shown in table 1. Most patients were male (58%) and median age (±SD) was 73 (±11). Thirteen patients (42%) had discontinued beta-blocker treatment within 3 months after initiation, whereas 23% of the patients had been on beta-blocker treatment for more than two years. Two patients had never started treatment. Metoprolol was the most frequently prescribed drug followed by bisoprolol and atenolol.
The reasons for discontinuation and the doctors involved in the conclusion for discontinuation as cited by patients are shown in table 2. Cardiologists were most frequently cited to have been consulted prior to discontinuation of beta-blocker treatment (15 patients or 48%). Five patients reported that adverse effects prompted the cardiologist to recommend discontinuation of treatment (one case of hypotension, one case of tiredness with reduced ability to exercise and three unspecified adverse drug reactions). In three cases the cardiologist advised to discontinue treatment because of convalescence of the patient (one patient

Table 1. *Baseline characteristics of patients*

		N	(%)
Sex	Male	18	(58)
	Female	13	(42)
Median age (±SD)		73	(±11)
Beta-blocker	atenolol	5	(16)
	bisoprolol	6	(19)
	celiprolol	1	(3)
	metoprolol	18	(58)
	propranolol	1	(3)
First prescriber	cardiologist	20	(65)
	GP	7	(23)
	unknown	4	(13)
Duration of treatment	never started	2	(6)
	less than 3 months	13	(42)
	3 months to 2 years	9	(29)
	more than 2 years	7	(23)
Indication	myocardial infarction	2	(6)
	angina pectoris	4	(13)
	hypertension	8	(26)
	CABG/PTCA	2	(6)
	arrhythmia	1	(3)
	unknown	13	(42)

appeared to have a better prognosis after myocardial infarction than initially estimated, another patient was free of complaints after a PTCA procedure and the third patient had no angina pectoris symptoms anymore). Furthermore, one suspected myocardial infarction appeared to be misdiagnosed. Six patients were unable to clarify the rationale of the decision of the cardiologist.

Six patients (19%) had discontinued beta-blocker treatment in consultation with the general practitioner (GP). Out of them, one patient reported side effects (tiredness with reduced ability to exercise) and one patient cited lack of effect to be the main reason for discontinuation, and four patients did not know the rationale of the GP's instruction to discontinue treatment.

Table 2. *Reasons for discontinuation of beta-blocker treatment, stratified by involvement of physicians.*

Involvement of doctor and reason	N =31	Switch to other drug	Eligible for reassessment of medical necessity
In consultation with the cardiologist	15		
Adverse effects	5	4	1
Return to health	3	1	0
Misdiagnosis	1	0	0
Not specified	6	3	3
In consultation with the GP	6		
Adverse effects	1	1	0
Lack of effect	1	1	0
Not specified	4	1	3
Without consulting any doctor	4		
Misunderstood	1	0	1
Adverse effects	1	0	1
Never started due to anxiety for side effects	1	0	1
Never started due to miscommunication	1	0	1
Could not remember	6	0	6
			17

Four patients were not on treatment without having consulted a doctor. Two patients had never started treatment, one patient because of anxiety for treatment and the other patient due to miscommunication with the cardiologist. Two other patients had discontinued treatment because of unspecified side effects and due to miscommunication between patient and cardiologist.

Six patients (19%) could not remember both the reason for non-persistence and if any physician was involved in the decision to discontinue treatment.

Overall, 16 patients (52%) were not able to mention the reason for discontinuation and 9 patients (29%) reported a reason that possibly does not meet criteria for evidence based treatment.

Eleven patients switched to another drug for treatment of their original complaint. Linking the reasons for discontinuation with switching to a different cardiovascular agent resulted in potential eligibility for reassessment of therapy (table 2). We considered return to health and misdiagnosis as medically valid reasons to discontinue treatment and therefore consistent with evidence based medicine. Therefore, 17 patients (55%) could be reviewed for re-initiation of

beta-blocker treatment or initiation of a different cardiovascular agent as those patients were not able to cite a reason that agrees with evidence based prescribing.

Discussion

Our results show that many patients (52%) discontinued beta-blocker treatment for unclear reasons and another 29% may have questionable reasons from an evidence-based point of view. After exclusion of patients who switched to other drug treatment, 55% of the patients were eligible for re-evaluation of their treatment status by the doctor in attendance based upon evaluation of reasons for discontinuation in relation to evidence based prescribing. However, the majority of patients (68%) discontinued treatment in consultation with their doctor. Therefore future interventions should be directed towards prescribing physicians in particular.

Our study gives an impression of the kind of reasons for non-persistence. Part of the patients switched to another drug treatment and part of the patients seemed to have no need for substitution, as their condition did not require treatment anymore. In consequence of this, the rates of non-persistence as observed in daily practice must be interpreted cautiously and rates of non-persistence cannot be equated with rates for possible re-initiation of treatment. However, the majority of the patients may be considered for re-initiation of treatment. Therefore monitoring of patients who discontinued treatment should be done more often. Especially patients who discontinued treatment under supervision of a GP seem to be eligible for closer monitoring as they got substitute drug treatment less often than patients who saw a cardiologist.

We selected patients who used both low-dose aspirin and beta-blockers to select a group of patients with cardiovascular disease. Given the widespread use of low-dose aspirin in cardiovascular disease (e.g. secondary prevention of myocardial infarctions and TIAs, angina pectoris, after CABG), the combination of low-dose aspirin with a beta-blocker seemed to be a feasible marker for cardiovascular disease.

Our results were not in accordance with the results from the study of Parameswaran et al. that reported failure to restart beta-blockers after hospitalisation to be the main reason for non-persistence. [12] However, Parameswaran studied a secondary care population with heart failure, whereas we studied an unselected population of both secondary and primary care

patients, especially as far as hospitalisations are concerned, the conflicting results are not surprisingly. The reasons for non-persistence we reported did agree with the reasons for non-adherence reported by Svensson et al. [13] Despite the temporarily nature of non-adherence and the permanent nature of non-persistence, side effects and return to health were most often cited by the patients in both studies.

Our study has some limitations. First, due to some recall bias we were not able to establish the main reasons for discontinuation of all patients. But since answers from patients were very detailed, we don't think that recall bias influenced the nature of the reasons in patients who were able to answer our questions. Second, the number of patients included was small. Therefore the external validity of the results might be limited. But given our results that indicate that although the majority of patients discontinued beta-blocker treatment in agreement with their doctor, half of the patients should be reviewed for possible re-initiation of treatment with a cardiovascular agent, further research in a larger sample of patients seems warranted.

Acknowledgements

We thank C. van Gompel PharmD, L. Macic PharmD, E. Otten PharmD and B. van de Steeg PharmD for their contribution to the design and the execution of this study.

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5

EFFECT OF DRUG TREATMENT ON MYOCARDIAL INFARCTION

5.1

EFFECTS OF DRUG COMBINATIONS ON RECURRENT MYOCARDIAL INFARCTION

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Submitted

Summary

Objective: To determine the effect of the number of different drugs with a compliance of at least 70% on recurrent admission for myocardial infarction in patients with a history of myocardial infarction.

Design: Nested case control study in an open prospective cohort.

Setting: The PHARMO record linkage database that contains pharmacy dispensing records and hospital discharge records on 350,000 Dutch citizens.

Subjects: All patients hospitalised for first myocardial infarction (ICD-9 410) between January 1, 1991 and December 31, 2000 with at least a 30-day survival after their first myocardial infarction. Cases were admitted for recurrent myocardial infarction and were matched for age, sex, and year of admission to controls that did not have a recurrent myocardial infarction during follow-up.

Main outcome measure(s): Odds ratio with 95% confidence interval for admission for recurrent myocardial infarction. Exposure was the number of preventive drugs (low-dose aspirin, statins and beta-blockers or ACE inhibitors) used for at least 70% of the time between first myocardial infarction and index date.

Results: 4,451 patients with myocardial infarction were identified. 389 cases were matched to 2,344 controls. The use of one drug was associated with a 7% odds reduction (95% confidence interval 31% reduction to 26% increase) for admission for recurrent myocardial infarction. The use of two or three drugs was associated with reductions of 24 and 38% (45% reduction to 6% increase and 3% to 61% reduction respectively). Addition of one drug caused a 14% reduction (2% to 25%).

Conclusions: Multiple drug treatment decreases admissions for recurrent myocardial infarction in patients with a history of myocardial infarction. Every addition of a drug, regardless of drug class, reduces the risk even further. These results support the treatment strategies as applied in daily practice.

Introduction

Randomised clinical trials have shown that preventive pharmacotherapy lowers mortality and morbidity after myocardial infarction, one of the most prevalent causes of death in developed countries. [1-3] In particular, the long-term use of oral antithrombotics (i.e. antiplatelet agents and oral anticoagulants), beta-blockers, angiotensin converting enzyme inhibitors (ACE inhibitors) and statins proved to be beneficial in randomised clinical trials. [4-8] Nearly all the clinical trials have estimated the benefits of single drugs, even though in daily practice most patients use a large variety of drug-combinations. Only the combined effect of aspirin and oral anticoagulants was assessed in clinical trials. [8] The effects of other drug combinations can only be estimated using subgroup analyses of trials that investigated a single drug. These subgroup analyses indicate that beta-blockers and statins may be beneficial regardless of concomitant drug treatment. [5 9-13] Results from studies on ACE inhibitors were not conclusive. Some studies reported benefits regardless of concomitantly used medication [14 15], while negative interaction between ACE inhibitors and aspirin was mentioned too. [16] International guideline committees assumed additive effects of drug combinations and recommend continuing combination treatment after myocardial infarction. [17 18] Wald and Law have proposed to combine multiple drug treatment in a 'polypill'. Their estimate of the effect of the polypill strategy on ischemic heart disease and stroke assumed additive effects of the different single drugs too. By multiplying the relative risks of each single drug an 80% risk reduction was obtained. [19] Recently, Hippisley-Cox et al. studied the effect of combinations of drugs in the secondary prevention of all cause mortality in a nested case-control study. [20] Current use of combinations of aspirin, statins and beta-blockers improved survival in high-risk patients, whereas the addition of ACE inhibitors did not offer additional benefits. The duration of drug use and compliance with prescribed medication were not covered by the definition of current use. However, most randomised clinical trials showed beneficial effects of preventive treatment after long-term use in relatively compliant patients, due to close monitoring of patients in randomised clinical trials. It seems therefore appropriate to study the extent of exposure over a longer period of time on the effectiveness of secondary prophylaxis after myocardial infarction in daily clinical practice.

Our aim was to determine the effect of the number of different drugs with a compliance of at least 70% on recurrent admission for myocardial infarction in patients with a history of myocardial infarction.

Methods

We performed nested case-control study in an open cohort using the PHARMO record linkage system. PHARMO includes pharmacy-dispensing records from community pharmacies linked to hospital discharge records of all 350,000 community-dwelling residents of 8 population-defined areas in the Netherlands from 1985 onwards. [21] Since virtually all patients in the Netherlands are registered with a single community pharmacy, independent of prescriber, pharmacy records are virtually complete with regard to prescription drugs. The computerised drug dispensing histories contain information concerning the dispensed drug, dispensing date, the prescriber, amount dispensed, prescribed dosage regimen, and the estimated duration of use. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification. The hospital discharge records are obtained from Prismant, an institute that collates nationwide all hospital discharge records in the Netherlands since the 1960s into a standardised format. [22] These records include detailed information concerning the primary and secondary discharge diagnoses, diagnostic, surgical and treatment procedures, type and frequency of consultations with medical specialists and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases, 9th edition (ICD-9-CM).

Participants

We identified all patients in the PHARMO database hospitalised for first myocardial infarction (ICD-9 410) between January 1, 1991 and December 31, 2000 with at least a 30-day survival after their first myocardial infarction. Cases were patients with a history of myocardial infarction who had a recurrent myocardial infarction during follow-up. Follow-up continued until the last date of registration in the database but not later than December 31, 2003. Registration could end due to death or movement outside the catchment area. Index date was the date of admission for recurrent myocardial infarction. Controls were patients with a history of myocardial infarction but without a recurrent myocardial infarction during follow-up and had to be in the database at

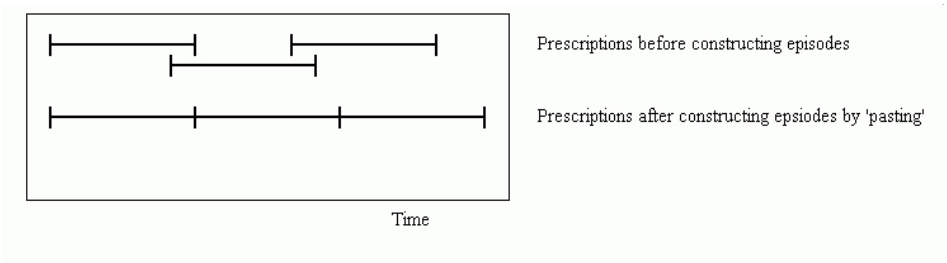
the index date of the matching case. Cases were matched to up to 10 controls on age (5-year band), sex, and year of admission for first myocardial infarction. Patients with myocardial infarction before January 1, 1991 were excluded. Other reasons for exclusion were admission for congestive heart failure (CHF), coronary artery bypass grafting (CABG), and percutaneous transluminal coronary angioplasty (PTCA), prior to the first myocardial infarction.

Exposure

We determined the exposure to four classes of drugs: low-dose aspirin, beta-blockers, ACE-inhibitors and statins. Patients were considered to be 'exposed' in case they took medication for at least 70% of the time. The four drug classes were combined into three categories; low-dose aspirin, statins, and beta-blockers and/or ACE-inhibitors. Beta-blockers and ACE-inhibitors were taken together as results from clinical trials and restricted applicability due to contra-indications and adverse effects in daily practice should result in the use of at least a beta-blocker or an ACE-inhibitor. [7] Assuming additive effects of similar magnitude of the different drugs a 'treatment score' was calculated. For each patient we counted the number of drugs with a percentage of days covered (PDC) of at least 70% between first myocardial infarction and index date. This resulted in a score that ranged from zero to three.

We calculated the percentage of days patients were exposed to aspirin, statins and beta-blockers and/or ACE-inhibitors between first myocardial infarction and index date. This PDC was calculated after construction of episodes of drug use to correct for irregular dispensing patterns. Episodes were constructed by 'pasting' subsequent prescriptions. If the dispensing date of the next prescription fell before the theoretical end date of the previous prescription, the dispensing date was adjusted (see Figure 1). Dispensing dates were shifted at most 30 days to avoid disproportionate accumulation. This way of construction of episodes and estimation of drug use has been described in full by Mantel et al. [23] The PDC was calculated by dividing the summed up duration of the episodes by the time between first myocardial infarction and index date.

Figure 1. *Construction of episodes of drug use by pasting subsequent prescriptions*



Analysis

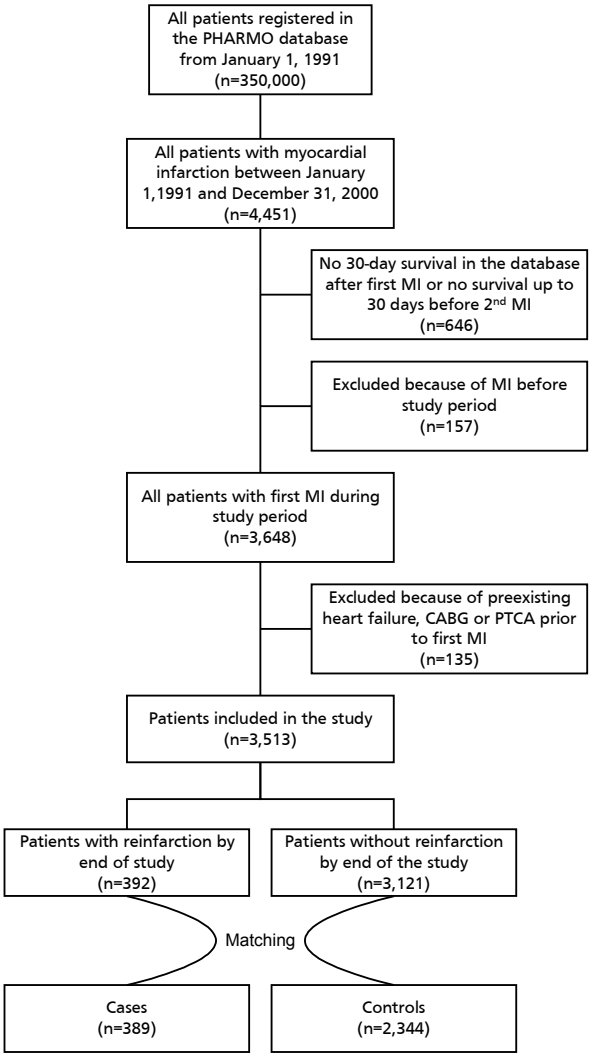
We used conditional logistic regression to calculate odds ratios and 95% confidence intervals. Patients who did not have a PDC of at least 70% for any of the three drug classes served as a reference group. Odds ratios were adjusted for several potential confounders; diabetes mellitus, angina pectoris, use of calcium channel blockers, antiarrhythmics, digoxin and oral anticoagulants, admission for CHF, PTCA, and CABG after first myocardial infarction. The fill of at least one prescription for an anti-diabetic between first myocardial infarction and index date was considered to be a proxy for diabetes mellitus. [24] The fill of at least two nitrate prescriptions between first myocardial infarction and index date was considered to be a proxy for angina pectoris. [25] Use of medication was defined as having filled at least one prescription between first myocardial infarction and index date. All analyses were performed using SPSS 12.0 (SPSS Inc., Chicago, IL, USA).

Results

Overall, 350,000 patients were registered within the PHARMO database. We identified 4,451 patients with myocardial infarction between January 1, 1991 and December 31, 2000. Overall incidence of myocardial infarction was 15.3 per 10,000 person years (all ages and both sexes). Out of the 4,451 patients, 646 were not eligible for study entry because they did not have a 30-day survival in the PHARMO database after the first admission for myocardial infraction. Furthermore 157 patients were excluded due to admission for myocardial infarction before January 1, 1991 and 135 patients were excluded because of admission for CHF, PTCA or CABG prior to the admission for first myocardial infarction. Therefore, 3,513 patients were eligible for participation in the study.

By the end of the study period 392 patients had a re-current myocardial infarction and 3,121 patients did not have had a recurrent myocardial infarction at the end of the study (Figure 2).

Figure 2. *Selection of cases and controls*



Case control analysis

Of the 392 possible cases with recurrent myocardial infarction during the study period 389 cases could be matched by age, gender and year of admission for first myocardial infarction to 2,344 controls. Cases and controls were well matched at baseline (Table 1). Median duration between first myocardial infarction and index date was 32.6 months for cases and 30.7 months for controls. Cases were less often treated with aspirin and statins for at least 70% of the time between first myocardial infarction and index date. Cases had a higher prevalence of angina pectoris and tend to have diabetes mellitus more often. Use of different combinations of aspirin, beta-blockers, ACE-inhibitors and statins is shown in tale 2. Aspirin plus a beta-blocker was the most frequently used drug treatment with a PDC of at least 70%.

Table 1. *Baseline characteristics of cases and controls. Values are numbers (percentages) unless otherwise noted.*

	Cases	n=389	Controls	n=2,344	p value
Mean age at index date (± SD)	66.8	(11.7)	66.0	(11.3)	0.216
Mean no of months between first myocardial infarction and index date (± SD)	32.6	(34.8)	30.7	(32.6)	0.32
Men	283	(72.8)	1719	(73.3)	0.809
Women	106	(27.2)	625	(26.7)	
Drugs used (PDC > 70%) *					
aspirin	197	(50.6)	1314	(56.1)	0.047
beta-blocker	216	(55.5)	1199	(51.2)	0.110
ACE inhibitor	88	(22.6)	557	(23.8)	0.624
statin	51	(13.1)	547	(23.3)	< 0.001
beta-blocker and/or ACE inhibitor	253	(65.0)	1491	(63.6)	0.587
Co morbidity or co medication					
admission for CHF	15	(3.9)	67	(2.9)	0.285
PTCA or CABG procedure	24	(6.2)	190	(8.1)	0.188
Diabetes mellitus	75	(19.3)	361	(15.4)	0.053
Angina pectoris	267	(68.6)	1386	(59.1)	0.000
use of anti-arrhythmics	12	(3.1)	102	(4.4)	0.247
use of calcium channel blockers	182	(46.8)	951	(40.6)	0.021
use of oral anticoagulants	136	(35.0)	865	(36.9)	0.462
use of digoxin	43	(11.1)	233	(9.9)	0.500

* *percentage of days covered (PDC) of at least 70% between first myocardial infarction and index date*

The adjusted and unadjusted odds ratio for the different number of compliantly used drugs is shown in table 3. Odds ratios were adjusted for diabetes mellitus, angina pectoris, use of calcium channel blockers, antiarrhythmics, digoxin and oral anticoagulants, admission for CHF, PTCA, and CABG after first myocardial infarction. After adjustment the use of one drug with a PDC of at least 70% was associated with a 7% reduction (95% confidence interval (95% CI) 31% reduction to 26% increase) in odds for admission for recurrent myocardial infarction, whereas the use of two or three drugs with a PDC of at least 70% was associated with an odds reduction of 24 and 38% (95% CI of 45% reduction to 6% increase and 3% to 61% respectively). Addition of one drug caused a 14% reduction in the odds for recurrent myocardial infarction (95% CI of 2% to 25%).

Table 2. *Frequency distribution according to combination of drugs used for at least 70% of the time. Values are numbers (percentages).*

	Case	n=389	Cont	n=2,344
none	90	(23.1)	491	(20.9)
aspirin alone	43	(11.1)	261	(11.1)
beta-blocker alone	52	(13.4)	216	(9.2)
ACE-inhibitor alone	17	(4.4)	116	(4.9)
statin alone	3	(0.8)	29	(1.2)
aspirin and beta-blocker	82	(21.1)	428	(18.3)
aspirin and ACE-inhibitor	13	(3.3)	86	(3.7)
aspirin and statin	4	(1.0)	107	(4.6)
beta-blocker and ACE-inhibitor	23	(5.9)	84	(3.6)
beta-blocker and statin	2	(0.5)	40	(1.7)
ACE-inhibitor and statin	2	(0.5)	24	(1.0)
aspirin, beta-blocker and ACE-inhibitor	18	(4.6)	115	(4.9)
aspirin, beta-blocker and statin	25	(6.4)	215	(9.2)
aspirin, ACE-inhibitor and statin	1	(0.3)	31	(1.3)
beta-blocker, ACE-inhibitor and statin	3	(0.8)	30	(1.3)
aspirin, beta-blocker, ACE-inhibitor and statin	11	(2.8)	71	(3.0)

Table 3. *Unadjusted and adjusted odds ratio for admission for recurrent myocardial infarction according to number of drugs used for at least 70% of the time. Values are numbers (percentages).*

Treatment score (0-3)	Case n=389		Control n=2,344		OR	(95% CI)	OR*	(95% CI)
0 drugs with PDC > 70%	89	(22.9)	480	(20.5)	ref		ref	
1 drug with PDC > 70%	136	(35.0)	701	(29.9)	1.02	(0.75-1.37)	0.94	(0.70-1.28)
2 drugs with PDC > 70%	127	(32.6)	838	(35.8)	0.84	(0.61-1.15)	0.74	(0.53-1.03)
3 drugs with PDC > 70%	37	(9.5)	325	(13.9)	0.66	(0.42-1.04)	0.59	(0.37-0.94)
addition of 1 drug					0.88	(0.77-1.01)	0.84	(0.74-0.96)

* *adjusted for DM, AP, use of oral anticoagulants, digoxin and calcium channel blockers, admission for CHF and PTCA or CABG procedure between first myocardial infarction and index date.*

Discussion

Multiple drug treatment decreases admissions for recurrent myocardial infarction in patients with a history of myocardial infarction. Regardless of drug class, addition of any drug known to prevent recurrent myocardial infarction causes a risk reduction.

The results from our study support the treatment strategies as applied in daily practice. Although randomised clinical trials established the benefits of individual drugs, evidence for additive effects of different drug classes was absent up to the present. [7] Besides new evidence for multiple drug treatment, our study supplies data on patients who were seldom included in randomised clinical trials as we included elderly, patients with co-morbidities or recent myocardial infarction. Furthermore we included more women than studied in randomised clinical.

The study does have some limitations. First, case-control studies are susceptible to confounding by indication. Although we adjusted for several potential confounders, we could not adjust for smoking status, BMI and socio-economic background. Further residual confounding might be present due to unmeasured variables. However there are no clues to expect that these confounders will be disproportionally distributed among cases and controls. Although results from observational studies might be less valued than results from randomised clinical trials, given the absence of data from randomised clinical trials on the combined effect of different drugs on recurrent myocardial infarction results from

observational studies may be very useful. Second, in case control studies odds ratios may be misleading when interpreted as relative risks. However, the overstatement of the effect size when using ORs can be calculated. [26 27] Given the incidence of recurrent myocardial infarction in the non-exposed the OR of 0.54 we reported for the use of 3 drugs with PDC > 70% the corresponding relative risk would be 0.58. Therefore we can state that odds reductions we found closely approximate risk ratios. Moreover the odds reduction in this study of adding one drug (14%; 95% CI 2-25%) is of the same magnitude as the risk reduction established in randomised clinical trials (30% for low-dose aspirin, 25% for beta-blockers, 10-25% for ACE-inhibitors and 10-40% for statins). [7] Third we assumed that the preventive effects the different drug classes are similar, both concerning the duration of treatment and the effect size. However, the different drug classes have very different pharmacodynamic effects. The platelet inhibitory effects of aspirin for example persist for 4-6 days, while the lipid lowering effects and antiatherogenic action of statins take weeks to months. Therefore one could state that current treatment is suitable for aspirin use, while the duration of exposure matters for statins. Nonetheless randomised clinical trials showed benefits after treatment periods that ranged from two to five years and risk reductions of aspirin, beta-blockers, ACE inhibitors and statins appeared to be comparable. Therefore we think it is appropriate to use one definition of exposure for different drug classes and to incorporate the duration of exposure in its definition. Furthermore, subdivision into 15 different combinations out of the four earlier mentioned drug classes (aspirin, beta-blockers, ACE-inhibitors and statins) and incorporation of the degree of compliance led to the frequency distribution shown in table 2. As the number of observations for numerous combinations is low results would be difficult to interpret, assuming that statistical significance could be reached at all.

Both outcome and exposure were not subject to recall bias, as the diagnosis of the hospital admission is recorded at discharge and exposure was derived from prescriptions recorded in the pharmacy at dispensing. Misclassification of exposure to beta-blockers, ACE inhibitors and statins seems to be unlikely too as drug dispensing records on a patient are virtually complete due to a strong patient-pharmacy liaison in the Netherlands and these drugs are not available over the counter. Although aspirin is available over the counter, we can rule out that non-prescription aspirin has biased our results, for two reasons. First, in the Netherlands a prescription is required for low-dose aspirin. Second, use of non-

prescription aspirin of higher doses is negligibly low, as over the counter aspirin is not reimbursed by the health insurance, whereas prescription aspirin is fully reimbursed. In the Netherlands, 98.6% of all inhabitants have a health insurance policy covering the costs for prescription drugs.[3]

Summarizing this study shows that multiple drug treatment lowers the number of admissions for recurrent myocardial infarction in patients with a history of myocardial infarction. Furthermore a higher number of drugs used concomitantly, increases the size of the risk reduction. As only 13% of patients with a hospitalisation for myocardial infarction received at least 3 drugs and was adequately compliant, there seems to be a potential for the improvement of secondary prevention of ischemic heart disease.

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5.2

ACUTE EFFECTS OF DISCONTINUATION OF STATIN TREATMENT ON THE OCCURRENCE OF A FIRST ACUTE MYOCARDIAL INFARCTION

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Summary

Background: Randomised clinical trials have shown that statin treatment lowers mortality and cardiovascular morbidity. In patients with acute coronary syndromes, discontinuation of statins tended to increase event rates. It is unknown whether discontinuation of statin treatment will have similar effects in patients without previous myocardial infarction.

Objective: To determine the effect of discontinuation of statin treatment on first acute myocardial infarction within 30 days after discontinuation in a general population.

Methods: A nested case-control study was performed in the PHARMO database that comprises pharmacy-dispensing records from community pharmacies linked to hospital discharge records. Cases were patients who were admitted for a first myocardial infarction while being on statin treatment at 30-days before the admission for myocardial infarction. Cases were matched to controls on age and sex. Controls were patients who were on statin treatment at 30-days before the assigned index date, but who had no admission for myocardial infarction prior to the index date. Recent discontinuation was defined as having discontinued statin treatment in the 30-day period prior to the index date. Conditional logistic regression was used to adjust for potential confounders.

Results: 450 cases could be matched to 2413 controls. A total of 277 subjects discontinued statin treatment. Overall, recent discontinuation was not associated with an immediately increased risk of first MI (adjusted OR 0.96; 95% CI 0.64-1.43). In patients without any prior cardiovascular disease an essentially similar effect was observed (adjusted OR 1.59; 95% CI 0.49-5.21). In patients with prior CHD a more profound though non-significant effect of discontinuation of statin therapy on the occurrence of a first MI was observed (adjusted OR 2.21; 95% CI 0.90-5.41).

Conclusion: Patients without prior myocardial infarction who discontinue statin treatment do not seem to be at increased risk of myocardial infarction within 30 days after discontinuation. In patients with previous CHD, a non-significant 2-fold increase in the risk of first myocardial infarction in patients who recently discontinued their statin treatment was observed, but the 95% confidence interval was very wide. Whether there is a true association between recent discontinuation of statin treatment and acute myocardial infarction remains therefore inconclusive in patients with prior CHD.

Introduction

Randomised clinical trials have shown that preventive pharmacotherapy lowers mortality and morbidity both in patients with and without cardiovascular disease. [1-3] In secondary prevention, the use of antiplatelet agents, oral anticoagulants, beta-blockers, angiotensin converting enzyme inhibitors (ACE inhibitors) and statins proved to be beneficial in randomised clinical trials when used for at least several years. [1 3-7] In primary prevention especially antihypertensives and lipid lowering drugs proved to be beneficial. [2 3] In daily practice long-term persistence with preventive treatment is poor. [8 9]

Untimely discontinuation of preventive treatment withholds long-term benefits concerning cardiovascular morbidity and mortality from patients who were eligible for treatment at first. Furthermore, discontinuation of preventive treatment might have unfavourable short-term effects. Recent discontinuation of beta-blockers has been associated with a fourfold increased risk of cardiovascular disease in patients without prior coronary heart disease. [10] Ferrari et al. suggested that discontinuation of low dose aspirin might increase the risk of acute coronary syndromes. [11] In the Sixty-plus reinfarction study, discontinuation of long-term oral anticoagulant treatment increased the risk of recurrent myocardial infarction when compared with patients still on treatment. [12]

Although historically the effects of statins were believed to need long-term therapy, an increasing number of studies report acute onset of the beneficial effects of statins. [13 14] These acute effects of statins might have a different mechanism of action apart from the cholesterol lowering properties. Studies showed favourable 'pleiotropic' effects of statins on platelet aggregation, smooth muscle cell proliferation, inflammation, and endothelial cell function. [15] These beneficial effects may especially play an important role in acute coronary syndromes. As several studies have shown these acute beneficial effects, hypothetically that acute unfavourable effects could occur after withdrawal of statins.

In patients with acute coronary syndromes, discontinuation of statins tended to increase the event rates due to the impairment of vascular function independent of cholesterol levels. [16-18] In patients with coronary artery disease and chest pain in the previous 24 hours, discontinuation of statin treatment tended to double the risk for cardiac events during a follow-up period of 30 days when compared with patients who continued to receive statins, but differences were non-significant. [16 17] Spencer et al showed that early withdrawal of statin treatment in

the first 24 hours after hospitalisation for non-ST-segment elevation myocardial infarction was associated with increased hospital mortality and morbidity. [18] The unfavourable effects of statin withdrawal were observed in patients who were hospitalised for acute coronary events. Limited evidence is available that discontinuation of statins in stable cardiac patients does not lead to clinically important increase in risk of acute coronary symptoms. [19] It is however still unknown whether discontinuation of statin treatment will have acute effects in patients without previous myocardial infarction.

Objective

Our objective was to determine the effect of discontinuation of statin treatment on first acute myocardial infarction within 30 days after discontinuation in a general population.

Methods

Study setting

We used the PHARMO record linkage system as data source for this study. PHARMO includes pharmacy-dispensing records from community pharmacies linked to hospital discharge records of all 950,000 community-dwelling residents of 25 population-defined areas in the Netherlands. [16] Since virtually all patients in the Netherlands are registered with a single community pharmacy, independent of prescriber, pharmacy records are virtually complete with regard to prescription drugs. The computerised drug dispensing histories contain information concerning the dispensed drug, dispensing date, the prescriber, amount dispensed, prescribed dosage regimen, and the estimated duration of use. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification. The hospital discharge records are obtained from Prismant, an institute that collates nationwide all hospital discharge records in the Netherlands since the 1960s into a standardised format. [17] These records include detailed information concerning the primary and secondary discharge diagnoses, diagnostic, surgical and treatment procedures, type and frequency of consultations with medical specialists and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases, 9th edition (ICD-9-CM).

Study subjects and design

We identified all patients in the PHARMO database with at least one prescription for a statin between January 1, 1991 and December 31, 2002. Patients were eligible for inclusion in the cohort if they had at least one year of registration in the PHARMO database.

In this cohort a nested case-control study was performed. Cases were patients who were admitted for a first myocardial infarction while being on statin treatment at 30-days before the admission for myocardial infarction and with a PHARMO registration of at least one year prior to this admission. Each case was matched to up to 20 controls on sex and age (three-year band width). An index date was assigned to both cases and controls. For cases the index date was the day of admission for myocardial infarction, for controls the index date was the day of admission for myocardial infarction of the matching case.

Controls were patients who were on statin treatment at 30-days before the assigned index date and with a PHARMO registration of at least one year prior to this date, but who had no admission for myocardial infarction prior to the index date.

Discontinuation of statin treatment

We assessed the discontinuation of statin treatment within 30 days before the index date. Patients were considered to have discontinued statin treatment in the 30-day period prior to the index date in case their last prescription before the index date theoretically ended within the 30-day period before the index date (based on the dispensing date plus the calculated duration of use) and no new prescription for any statin was filled within this 30-day period.

Potential confounders

The association between discontinuation of statin treatment and acute myocardial infarction might be confounded by secondary factors. Therefore we evaluated the influence of current, past or no use of other cardiovascular drugs (antiplatelets including low dose aspirin, diuretics, beta-blockers, drugs acting on the renin-angiotensin system (RAS), calcium-channel blockers, other antihypertensives, nitrates, antiarrhythmics, and non-statin lipid lowering drugs). Current use of medication was defined as being on treatment at the index date. Past use was defined as having filled at least one prescription in the year prior to the index date, but not being on treatment at the index date. No use of

medication was defined as having filled no prescription in the year prior to the index date. For anticoagulants and nitrates used as rescue medication use in the year prior to the index date was only assessed dichotomously (yes/no) due to their special dosing regimens. Also, we evaluated the influence of simultaneous discontinuation of other cardiovascular drugs. Simultaneous discontinuation of other preventive medication was defined similar to discontinuation of statin treatment, i.e. the last prescription ended within the 30-day period before the index date and no prescription was filled within this 30-day period.

Furthermore, we evaluated the influence of type of statin, dosage, compliance with statin therapy, the total duration of statin therapy, diabetes mellitus, admission for percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) prior to the index date, admission for coronary heart disease (CHD) prior to the index date (composite of angina pectoris (ICD-9 413), other acute and sub acute forms of ischemic heart disease (ICD-9 411), and other forms of chronic ischemic heart disease (ICD-9 414)), and admission for cerebrovascular events (ICD-9 codes 430-438) prior to the index date. To compare dosing of different statins we expressed the prescribed daily dose as the number of defined daily doses (DDDs). This unit corresponds to the average daily dose of a drug for its main indication in adults, and is recommended by the World Health Organization for drug utilization studies. Compliance with statin therapy was assessed in the year prior to the index date. A cut-off point for good compliance was set at 70% compliance. Compliance was calculated by dividing the summed up duration of the statin prescriptions dispensed in the year prior to the index date by 365 days. Total duration of statin use before the index date was established and three mutually exclusive categories were defined (less than 181 days of statin therapy, 181-365 days of statin use, and use > 1 year). The fill of at least one prescription for an antidiabetic drug prior to the index date was considered to be a proxy for diabetes mellitus. [22]

Analysis

We compared cases with controls using conditional logistic regression and calculated odds ratios and 95% confidence intervals for the association between recent discontinuation of statin treatment and admission for acute myocardial infarction. No potential confounder changed the estimated crude odds ratio by more than 10%. The inclusion of the use of nitrates and the inclusion of

simultaneous discontinuation of beta-blockers or calcium-channel blockers led to a change by 5% or more. We chose to include these three confounders in our final model in addition with potential confounders that showed a strong relationship with the occurrence of a first MI in the present study. In the final model, odds ratios were therefore adjusted for age, compliance, duration of statin use, prior hospitalisation for PTCA or CHD, diabetes mellitus, the use of beta-blockers, calcium-channel blockers, nitrates, nitrates used as rescue medication and anticoagulants, and the simultaneous discontinuation of beta-blockers, calcium-channel blockers or antiarrhythmics.

Results were also stratified by gender. To determine the stability of the overall risk estimate, we performed a sensitivity analysis by varying our definition of discontinuation. Discontinuation was also defined as the ending of the last prescription 1-15 days prior to the index date and as the ending of the last prescription 16-30 days prior to the index date.

In addition, a pre specified subgroup analysis was performed in patients without any cardiovascular disease prior to the index date except for hypercholesterolemia. For this analysis, all patients using cardiovascular co-medication except lipid-lowering drugs or having been hospitalised for any cardiovascular event (ICD-9 codes 411, 413, 414, 430-438, and PTCA or CABG) before the index date were excluded. We intended to include the same potential confounders in the model as mentioned above, but due to exclusion of cardiovascular co-medication and prior cardiovascular events, only age, compliance, duration of statin use and diabetes mellitus remained in the model.

Similarly, a subgroup analysis was performed in patients with known coronary heart disease, defined as a previous hospitalisation for ischemic heart disease (ICD-9 codes 411, 413 and 414) or use of nitrates in the year prior to the index date. Potential confounders that changed the crude OR by 5% or more or had a strong relationship with the occurrence of a first MI in this population included age, compliance, prior hospitalisation for CABG, the use of beta-blockers, calcium-channel blockers, nitrates, nitrates used as rescue medication, antiplatelets, and RAS drugs, and the simultaneous discontinuation of antiplatelets or RAS drugs.

All analyses were performed using SPSS 12.0 (SPSS Inc., Chicago, IL, USA).

Results

In the PHARMO database, we identified 450 subjects with a first MI who were users of any statin 30 days prior to hospitalisation for this event (cases). These cases were matched to a total of 2413 controls. Most cases (96.1%) were matched to three or more controls, 53 cases (2.2%) were matched to two controls and 41 cases (1.7%) were matched to only one control.

Baseline characteristics of cases and controls are shown in table 1. Due to matching, the mean age was similar in cases and controls (65.3 and 63.1 years, respectively). However, as more controls were available for women than for men, the sex distribution was different in cases and controls (men 64.2% and 53.2% in cases and controls, respectively). Simvastatin was the most frequently used statin (almost 60% in both cases and controls), followed by atorvastatin and pravastatin. Cases had a shorter duration of statin treatment prior to the index date and were less non-compliant with statin treatment than controls. Furthermore, cases had a history of hospitalisation for coronary heart disease more often than controls (28.4% and 18.2%, respectively) and used cardiovascular co-medication more frequently. A well-known cardiovascular risk factor such as diabetes was also more prevalent in cases than in controls.

Table 1. *Characteristics of cases and control. Values are numbers (percentages) unless otherwise noted.*

		Cases (n=450)		Controls (n=2413)	
Mean age (±SD)		65.3	(10.9)	63.1	(10.4)
Sex	Female	161	(35.8%)	1129	(46.8%)
	Male	289	(64.2%)	1284	(53.2%)
Statin used 30 days prior	Simvastatin	258	(57.3%)	1407	(58.3%)
to index date	Pravastatin	82	(18.2%)	412	(17.1%)
	Fluvastatin	31	(6.9%)	158	(6.5%)
	Atorvastatin	72	(16.0%)	433	(17.9%)
	Cerivastatin	7	(1.6%)	3	(0.1%)
Dosage in DDD eq.	=< 2 DDD	414	(92.0%)	2155	(89.3%)
	> 2 DDD	36	(8.0%)	258	(10.7%)
Statin discontinued at index date		42	(9.3%)	235	(9.7%)
Duration of statin use	<= 180 days	51	(11.3%)	128	(5.3%)
	181-365 days	47	(10.4%)	189	(7.8%)
	> 365 days	352	(78.2%)	2096	(86.9%)
Compliance with statin	<70%	32	(7.1%)	110	(4.6%)
Prior CVA/TIA		29	(6.4%)	129	(5.3%)

Table 1 (continued) *Characteristics of cases and controls.*

		Cases (n=450)		Controls (n=2413)	
Prior CABG		22	(4.9%)	140	(5.8%)
Prior PTCA		40	(8.9%)	120	(5.0%)
Prior CHD		128	(28.4%)	438	(18.2%)
Diabetes Mellitus		102	(22.7%)	415	(17.2%)
Use of other antilipaemics	no	428	(95.1%)	2312	(95.8%)
	past	10	(2.2%)	27	(1.1%)
	current	12	(2.7%)	74	(3.1%)
Simultaneous stop of other antilipaemics		1	(0.2%)	5	(0.2%)
Use of antiplatelets	no	219	(48.7%)	1368	(56.7%)
	past	33	(7.3%)	147	(6.1%)
	current	198	(44.0%)	898	(37.2%)
Simultaneous stop of antiplatelets		17	(3.8%)	90	(3.7%)
Use of antiarrhythmics	no	417	(92.7%)	2324	(96.3%)
	past	8	(1.8%)	16	(0.7%)
	current	25	(5.6%)	73	(3.0%)
Simultaneous stop of antiarrhythmics		4	(0.9%)	2	(0.1%)
Use of organic nitrates	no	325	(72.2%)	2162	(89.6%)
	past	22	(4.9%)	74	(3.1%)
	current	103	(22.9%)	177	(7.3%)
Simultaneous stop of organic nitrates		9	(2.0%)	22	(0.9%)
Use of rescue organic nitrates		145	(32.2%)	263	(10.9%)
Use of diuretics	no	351	(78.0%	1927	(79.9%)
	past	29	(6.4%)	123	(5.1%)
	current	70	(15.6%)	363	(15.0%)
Simultaneous stop of diuretic		13	(2.9%)	36	(1.5%)
Use of beta-blockers	no	245	(54.4%)	1490	(61.7%)
	past	41	(9.1%)	155	(6.4%)
	current	164	(36.4%)	768	(31.8%)
Simultaneous stop of beta-blockers		18	(4.0%)	63	(2.6%)
Use of RAS drugs	no	295	(65.6%)	1752	(72.6%)
	past	24	(5.3%)	83	(3.4%)
	current	131	(29.1%)	578	(24.0%)
Simultaneous stop of RAS drugs		12	(2.7%)	46	(1.9%)
Use of calcium-ch. blockers	no	278	(61.8%)	1892	(78.4%)
	past	37	(8.2%)	88	(3.6%)
	current	135	(30.0%)	433	(17.9%)
Simultaneous stop of calcium-channel blockers		16	(3.6%)	36	(1.5%)
Use of other antihypertensives	no	437	(97.1%)	2376	(98.9%)
	past	3	(0.7%)	9	(0.4%)
	current	10	(2.2%)	28	(1.2%)
Simultaneous stop of other antihypertensives		2	(0.4%)	3	(0.1%)

A total of 277 subjects discontinued their statin treatment according to our definition. In table 2 the association between recent discontinuation of statin treatment and admission for myocardial infarction is shown. Overall, the discontinuation of statin treatment did not lead to an immediately increased risk of first MI (adjusted OR 0.96; 95% CI 0.64-1.43). No difference in effect was found between men and women or when the definition of discontinuation was varied. In patients without any prior cardiovascular disease a slightly larger but essentially similar effect of discontinuation on the risk of first MI was observed (adjusted OR 1.59; 95% CI 0.49-5.21). Due to the small numbers in this subgroup analysis the95% confidence interval was wide. In patients with prior CHD we also observed a non-significant effect of discontinuation of statin therapy on the occurrence of a first MI (adjusted OR 2.21; 95% CI 0.90-5.41). A further analysis restricted to patients with a hospitalization for coronary heart disease in the year prior to the index date only was not feasible because of too small numbers.

Table 2. *Discontinuation of statin treatment and the risk of first myocardial infarction.*

	Cases	Controls	OR crude (95%CI)	OR adjusted* (95% CI)
All subjects (n=2863)	42 (9.3%)	235 (9.7%)	0.98 (0.68-1.40)	0.96 (0.64-1.43)
Male subjects (n=1573)	24 (8.3%)	130 (10.1%)	0.87 (0.54-1.40)	0.91 (0.54-1.51)
Female subjects (n=1290)	18 (11.2%)	105 (9.3%)	1.16 (0.67-2.01)	1.00 (0.51-1.96)
No prior CVD (n=170)	6 (13.3%)	16 (12.8%)	1.42 (0.48-4.21)	1.59 (0.49-5.21)**
Prior CHD (n=512)	19 (10.9%)	25 (7.4%)	1.65 (0.87-3.11)	2.21 (0.90-5.41)***
Stop 1-15 days prior to index date	29 (6.4%)	166 (6.9%)	0.99 (0.65-1.51)	1.00 (0.63-1.60)
Stop 16-30 days prior to index date	13 (2.9%)	69 (2.9%)	0.95 (0.51-1.78)	0.86 (0.43-1.71)

* *adjusted for age, compliance, duration of statin use, prior hospitalisation for PTCA or CHD, diabetes mellitus, the use of beta-blockers, calcium-channel blockers, nitrates, nitrates used as rescue medication and anticoagulants, and simultaneous discontinuation of beta-blockers, calcium-channel blockers or antiarrhythmics*

** *adjusted for age, compliance, duration of statin use and diabetes mellitus*

*** *adjusted for age, compliance, prior hospitalisation for CABG, the use of beta-blockers, calcium-channel blockers, nitrates, nitrates used as rescue medication, antiplatelets, and RAS drugs, and the simultaneous discontinuation of antiplatelets or RAS drugs*

Discussion

The results from our study indicate that patients without prior myocardial infarction who discontinue statin treatment are not at increased risk of myocardial infarction within 30 days after discontinuation. Pre-specified subgroup analysis in patients without prior cardiovascular disease neither revealed an association between discontinuation of statin treatment and acute myocardial infarction. In patients with previous CHD, we observed a non-significant 2-fold increase in the risk of first myocardial infarction in patients who recently discontinued their statin treatment.

Two studies focused on the association between statin withdrawal and the occurrence of acute events. [13–15] Both studies were conducted in a hospital setting including patients hospitalized for acute coronary events (acute coronary syndrome or non-ST-segment elevation myocardial infarction). Statin withdrawal was defined as discontinuation of statin use during hospital admission in patients who were on statin treatment prior to hospitalisation. Event rates were compared between these patients and patients who continued statin therapy during hospitalisation. The decision to discontinue statin treatment in a hospital setting may be essentially different from discontinuation treatment in daily medical practice. Physician reasons for early discontinuation of statins in patients with acute coronary syndromes are unknown. Main reasons for discontinuation of lipid-lowering therapy in daily medical practice are the occurrence of adverse events, therapeutic ineffectiveness, noncompliance, a patient's lack of desire to continue medication use, and concomitant serious illness. [19]

Many studies showed favourable 'pleiotropic' effects of statins on platelet aggregation, smooth muscle cell proliferation, inflammation, and endothelial cell function. [15] These beneficial effects may especially play an important role in acute coronary syndromes. It could be hypothesised that these effects of statins would be less pronounced in our population with prior CHD, due to differences in definition of CHD, and that these effects play a minor role in patients on long-term statin treatment in our general population. As could be expected from this hypothesis, we did not observe an increased risk in the general population. Despite probable differences in reasons for discontinuation and severity of CHD at the time of the withdrawal of statin treatment, we observed a similar non-significant two-fold increased risk of myocardial infarction in our patients with previous CHD, as did Heeschen et al. [16 17] Since results from most of the limited number of studies including the present study were non-significant, it remains

questionable whether there is a true association between the withdrawal of statins and the risk of an acute myocardial infarction in patients with prior CHD.

Our study has several limitations. First, our results might have been biased by misclassification. We considered patients to have discontinued treatment if their last prescription before the index date theoretically ended within the 30-day period before the index date. Due to disregard of non-compliance patients actually might have been on treatment, while they were classified as having discontinued treatment. As discontinuation was assessed similarly in both cases and controls, misclassification would have been non-differential. Non-differential misclassification will bias the true odds ratio towards 1. [21] However, although we reported odds ratios around 1 for all patients and for several subgroups of patients, it seems unlikely that misclassification has completely determined our results. In case the true risk for myocardial infarction was high, we would have detected at least a slightly increased risk as we do in patients with prior CHD. Prescriptions dispensed after hospital admission were left out of the consideration as we could not determine if these were prolonged prescriptions meaning patients did not actually discontinued taking medication or if patients restarted treatment due to the hospital admission and the associated reconsideration of pharmacotherapy.

Our results might have been biased by the absence of data on other potential confounders like cholesterol level, smoking, and blood pressure. Although our study suffers from some limitations, we do not feel that the absence of an association between discontinuation and myocardial infarction could completely be explained by these limitations. In case of a true strong association, we should have observed at least a small effect or trend towards increased risk.

Second, we assessed the association between discontinuation of statin treatment and the occurrence of myocardial infarction in a sample of patients without prior myocardial infarction. Therefore, these patients had a lower risk for myocardial infarction than patients with a history of myocardial infarction. A sample of patients with prior myocardial infarction would have resulted in more cases and probably our study would have had more power.

From a clinical point of view it is reassuring that discontinuation of statin treatment is not associated with an increased risk of acute myocardial infarction in the general population. Long-term persistence with statin treatment is known to be poor [9 22 23] In the Netherlands, persistence decreased to 46.5% after two

years in patients who newly started statin therapy. [9] Persistence was even worse in patients who restarted statin therapy and in patients who used statins for primary prevention. Furthermore, in several countries statins have become available as over-the-counter (OTC) drugs. The use of OTC statins without medical supervision leaves us with fewer opportunities to detect incorrect use of statins, so concerns on safety need to be addressed.

In conclusion, patients without prior myocardial infarction who discontinue statin treatment are not at increased risk of myocardial infarction within 30 days after discontinuation. Given the small number of subjects and the wide confidence interval, it remains inconclusive whether there is a true association between recent discontinuation of statin treatment and acute myocardial infarction in patients with prior CHD. In all cases, continuation of statin treatment is important to gain full long-term benefit of these drugs.

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6

INTERVENTIONS TO IMPROVE DRUG TREATMENT

6.1

IMPROVING PHARMACOTHERAPY AFTER MYOCARDIAL INFARCTION BY GROUP ACADEMIC DETAILING USING FEEDBACK DATA ON A PATIENT LEVEL

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Pharmacotherapy (In press)

Summary

Objective: To develop and evaluate a peer review group (PRG) meeting using feedback data on a patient level to improve the quality of drug therapy for prevention of recurrent myocardial infarction.

Methods: A prospective follow-up study with an external control group was performed in patients who suffered from myocardial infarction. The intervention was based on the principles of group academic detailing and consisted of: scoring the current cardiovascular treatment on separate forms for each patient, a presentation and discussion of an overview of evidence based medicine after myocardial infarction, defining the target population, formulating a binding consensus and marking patients who were eligible for improvement of pharmacotherapy. Drug use and adherence to the newly formulated consensus was assessed at baseline and at one year after the intervention.

Results: Forty percent of the patients who were subject to the intervention and who were not treated according the PRG consensus at baseline did receive treatment according to the consensus at twelve months after the PRG meeting. In the external control group this percentage was 9.5 percent (prevalence ratio 4.2; CI 95% 1.8-9.7).

Conclusions: PRG meetings can be a valuable tool to improve pharmacotherapy after myocardial infarction.

Introduction

Group academic detailing has been demonstrated to be an effective way to improve the quality of pharmacotherapy. [1 2] In the Netherlands, the principles of group academic detailing can be applied to peer review groups. The expression "peer review group" (PRG) is used for regular meetings of groups of general practitioners (GPs) and community pharmacists to discuss and improve pharmacotherapy. [3] The establishment of peer review groups was encouraged by the Dutch government from the assumption that the exchange of knowledge about existing and new therapies would improve the quality of treatment of individual patients. Transmural PRGs include specialist physicians too, but these PRGs are rare. Most of the 7,500 Dutch GPs and 2,600 community pharmacists are organized in 840 PRGs that meet approximately four times a year. PRG meetings offer GPs and pharmacists the opportunity to exchange knowledge about new therapies, to discuss both new and existing treatment strategies, and to discuss the quality of treatment of individual patients. Part of the PRGs commit themselves to evidenced based prescribing, and check the commitments afterwards by using prescription data. Approximately 64 percent of the PRGs are limited to the exchange of information only. About 36 percent of the PRGs reach consensus. Although approximately 80 percent of the PRGs uses feedback data, only 8 percent uses feedback data to evaluate the implementation of local guidelines. [4] These feedback data are not presented on a patient level, but concern aggregated prescription data. Aggregated prescription data for example concerns an overall percentage of patients on treatment while data on a patient level concerns marks of being on treatment for each patient individually.

Pharmacists do not have access to patients' medical records kept by GPs, but they do have a virtually complete overview of both GP and specialists prescriptions due to a strong pharmacy-patient liaison. [5] Therefore, most of the PRGs that work with prescription figures and feedback select topics based on drug use or diseases and conditions that can be identified by drug use. Some conditions are not easily identifiable using prescription data and therefore are less likely to be discussed. Among others, myocardial infarction is such a condition. Myocardial infarction is a major cause of death in the Netherlands and throughout all other developed countries. [6 7] Therefore, prevention of future cardiovascular events in patients who experienced myocardial infarction should receive proper attention. Previous surveys concerning the prevention of recurrent myocardial infarction in primary care report that the dissemination of

evidence-based treatments to routine clinical practice remains low. [8-10] Treatment with beta-blockers and ACE-inhibitors in particular remains disappointingly low. [11-14]

In the Netherlands, the PRG meeting is a widely used instrument to improve the quality of pharmacotherapy. Although Van Eijk et al. proved that PRG meetings did affect prescribing of anticholinergic antidepressant use [1] , little is known about the effectiveness of PRG meetings in daily practice. Besides, practically all PRGs use aggregated feedback data and no prescription data on a patient level. Therefore, we aimed to develop and evaluate a PRG meeting using feedback data on a patient level to improve the quality of drug therapy for prevention of recurrent myocardial infarction.

Methods

Study design

The study was a prospective follow-up study, conducted in December 2000. The study group consisted of patients who suffered from myocardial infarction. As a control group we used patients with myocardial infarction who were not subject to the intervention.

Setting and participants

The GPs and pharmacists from one PRG in the city of Leiden, the Netherlands, were invited to take part in a PRG on myocardial infarction, all of them accepted. This PRG consisted of six GPs and four pharmacists. Patients with established myocardial infarction (ICPC code K75) were identified from the GP's computerized patient records. Patients who were also treated by a cardiologist were excluded from the intervention, as GPs did not want to interfere with the specialist's treatment.

Controls were selected from the PHARMO record linkage system. [5] Controls were patients with established myocardial infarction (ICD-9 code 410) and were matched to cases on calendar time and type of physician (i.e. GP).

Intervention

The intervention, based on the principles of academic detailing [15], consisted of:

- Scoring the current cardiovascular treatment on separate forms for each patient using the complete medication history of each patient from 6 months

prior till the week before of the PRG meeting. Cardiovascular treatment included low-dose acetylsalicylic acid (aspirin), oral anticoagulants, ACE-inhibitors, angiotensin II receptor antagonists, antiarrhythmics, beta-blockers, calcium channel blockers, diuretics, nitrates, and statins.

- The presentation and discussion of an overview of evidence based medicine after myocardial infarction. Results from randomized trials were shown. In randomized clinical trials low-dose acetylsalicylic acid (75–150 mg/d), high-intensity oral anticoagulant treatment (INR 2.8– 4.8), beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and statins proved to be effective in lowering the risk of mortality and re-infarction after MI. [16] ACE-inhibitors are effective especially in patients with reduced left ventricular ejection fraction, while the benefits of statins were mainly established in patients with elevated cholesterol. Randomized clinical trials using calcium-channel blockers, antiarrhythmics, and hormone replacement therapy did not show benefits in patients with prior MI. Effects of the combined use of acetylsalicylic acid or oral anticoagulants with beta-blockers or ACE-inhibitors plus statins must be derived from subgroup analysis of trials, but seemed to be beneficial. 16
- Definition of the target population.
- Formulating a binding consensus:
    - ✓ All patients should receive at least either acetylsalicylic acid or an oral anticoagulant.
    - ✓ In hypertensive patients, treatment with beta-blockers or ACE-inhibitors should be preferred to calcium channel blockers or angiotensin-II receptor antagonists.
    - ✓ Calcium channel blockers may be indicated in patients who suffer from angina pectoris but should not be given for reasons of secondary prevention or hypertension.
    - ✓ Statin treatment was considered to be indicated in case of elevated cholesterol levels (i.e. > 190 mg/dL) only. This opinion was consistent with the Dutch guidelines concerning hypercholesterolemia which were in effect at that time. [17 18] As we did not have access to patient's cholesterol levels and statin treatment was considered to be indicated in case of elevated cholesterol levels only, we were not able to evaluate the effect of the intervention on

statin treatment. Therefore, we excluded statin treatment from all further analyses.

- Marking of patients who were eligible for improvement of pharmacotherapy based on the new formulated consensus. GPs got separate sheets that displayed the current status of their patients' cardiovascular drug treatment.
- Decision to adjust treatment within 3 months.

Study outcome

Outcomes of the study were the adherence to the new formulated consensus one year after the PRG meeting and the use of drugs known to lower mortality and reinfarction after myocardial infarction. To assess adherence to the consensus and drug use, we used the drug dispensing records. For patients in the intervention group drug dispensing records from the pharmacies computer system were used, while the PHARMO drug dispensing records were used for the control group. Drug use at baseline was defined as having filled a prescription between one and five months prior to the PRG meeting. Current use at one year after the PRG meeting was defined as having filled a prescription between eight and 12 months after the PRG meeting. The four month time window was chosen as in the Netherlands chronically used drugs are dispensed for a three month period and accounting for non-compliance of 30 percent lead to a four month period. Quality of secondary prevention was valued based on the consensus formulated during the PRG meeting.

Data-analysis

Patients were stratified according to adherence to the consensus at baseline. As our intervention was directed to patients who were eligible for improvement (i.e. patients who did not meet the consensus criteria at baseline), we included only the stratum of patients who did not meet the consensus criteria at baseline in our analysis. Prevalence ratio and 95% CI for treatment according to the consensus at 12 months after the intervention was calculated using Statcalc (EpiInfo, Centers for Disease Control and Prevention, Atlanta, GA, USA)

Results

Patient population

GPs identified 94 patients with a history of myocardial infarction. Forty patients were treated by their GP solely and 54 patients were also treated by cardiologists or other specialists. As specialists did not participate in this PRG, the intervention was restricted to the 40 GP treated patients.

We identified 1,030 controls with a history of myocardial infarction, who were treated by GPs solely and who were in the database during the study period.

Patient characteristics and drug treatment at baseline are shown in table 1.

At baseline, 754 patients were already treated according to the PRG consensus, while 316 patients were not (10 patients in the intervention group and 306 controls). Our analysis was restricted to those 316 patients who were eligible for improvement and therefore subject to the intervention.

Table 1. *Patient characteristics and drug treatment at baseline.*

	Index group (N=40)		Control group (N=1030)	
	N	(%)	N	(%)
Age, mean (SD)	64	(13)	66	(12)
Male sex	28	(70)	720	(70)
Treatment matches the PRG consensus	30	(75)	724	(70.3)
Antiplatelet agent	28	(70)	756	(73.4)
Oral anticoagulant	5	(13)	97	(9.4)
Antiplatelet and/or oral anticoagulant	33	(82.5)	848	(82.3)
Beta-blocker	19	(48)	506	(49.1)
ACE-inhibitor	16	(40)	258	(25.0)
Calcium channel blocker	8	(20)	215	(20.9)
Calcium channel blocker without treatment for angina pectoris (i.e. nitrate use)	2	(5)	137	(13.3)
Angiotensin-II receptor antagonist without beta-blocker or ACE-inhibitor treatment	1	(2.5)	17	(1.7)

Quality of treatment

Out of the 10 patients in the intervention group who were not treated according to the PRG consensus at baseline, 40 percent was treated according to the PRG consensus at twelve months after the PRG. Out of the 306 patients in the control group who were not treated according to the PRG consensus at baseline,

9.5 percent received treatment according to the PRG consensus at twelve months after the PRG meeting. Patients who were subject to the intervention were more likely to adhere to the PRG consensus at twelve months after the PRG meeting than controls (prevalence ratio 4.22; 95% CI 1.83-9.72). Age and sex did not confound the association between the intervention and adherence to the PRG consensus at twelve months after the meeting.
Prevalence ratio for the stratum of patients who were already treated according to the PRG consensus at baseline was 1.03 (95% CI 0.96-1.10) when intervention patients were compared with controls.

Discussion

This study shows that PRG meetings can be a valuable tool to improve pharmacotherapy after myocardial infarction. When assessed patient by patient, the PRG consensus criteria were met more often in patients in the intervention group. Comparison with a sample of similar patients with known myocardial infarction indicates that the increase in quality of treatment probably is not attributed to a general rise in the use of preventive medication.
Although treatment of some patients improved, several other patients did not benefit from the intervention. Closer examination of the results revealed that GPs who managed to improve their patients quality of pharmacotherapy, did so within the first three months after the PRG meeting. Strikingly, some GPs changed the treatment of almost all their eligible patients, while other GPs changed treatment of hardly any of their patients. To reveal possible reasons for not following the consensus, a subgroup analysis could have been suitable. However, our sample size was too small to perform a subgroup analysis. So, future studies should include more patients to have enough power to establish the reasons for not following the consensus.
We compared the intervention group to an external control group to rule out that observed changes were just natural course. Our study did not evaluate the effectiveness of a PRG meeting beyond one year of follow-up. Previous studies have shown that repeated interventions are needed to maintain achieved benefits. [1] So a successful PRG meeting should be part of a larger and enduring intervention. Our results were consistent with results from previous studies on group detailing. [2 19-22]

Data on drug use might indicate that the quality of treatment in our intervention group was already better at baseline than in the control group, but differences were not statistically significant. This might be because this PRG was already familiar with working towards consensuses before they participated in the study and therefore patients might have been treated better at baseline. Nevertheless, in this population with a good quality of treatment, we were able to establish the benefits of a PRG meeting. Possibly, the advantages would be even more pronounced in populations with a lower baseline level.

The results of our study apply to GP treated patients only. The limitation of the target population to GP-treated patients can be explained by the different role of a GP and a specialist physician (e.g. a cardiologist) in the Dutch healthcare system. GPs function as gatekeepers to secondary care services, since patients need a referral from their GP to consult a specialist physician for the first time. Patients are referred to specialist physicians in case of complicated or severe disorders. The specialist examines the patient and initiates pharmacotherapy if necessary. The findings and treatment are communicated to the GP. Ideally, specialist physicians refer patients back to their GP once the patients' condition is stable. In general, as long as a specialist physician treats a patient, GPs plan not to interfere with the specialist's treatment. Given the Dutch health care system, future studies on intervention by academic detailing should also aim at transmural PRGs. Only then, the effects on specialist treated patients can be determined.

Finally, although our study concerns only one PRG, the number of patients is small and the baseline data in our study population indicated that quality of treatment might have been already better than in controls, we were able to establish that PRG consensus criteria are met more often after group academic detailing.

Conclusion

An intervention through group academic detailing, in which patients were discussed one by one, improves the quality of treatment, although ACE-inhibitors and beta-blockers, in particular, may still be underused. More research into the reasons why GPs did not adhere to the consensus and the development of even more effective strategies in academic detailing on this topic are warranted.

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6.2

A PHARMACEUTICAL CARE PROGRAM TO IMPROVE COMPLIANCE WITH STATIN TREATMENT

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Summary

Objective: To present the design of a pharmacist-led pharmaceutical care program for dyslipidemic patients who started statin treatment and to show some preliminary results.

Design of the trial: The pharmacist-led pharmaceutical care program is a randomised multi-centre trial performed in 26 community pharmacies in the Netherlands. New users of statins are enrolled in the study, and randomised to a pharmaceutical care program or usual care. The pharmaceutical care program consists of five consecutive visits during which patients receive education on statin treatment from their pharmacist, starting at first dispensing of the statin prescription. At 3, 6, and 12 months, cholesterol levels are measured, compliance is calculated and the relation between cholesterol level and compliance is discussed. At baseline, 6 and 12 months patients from both groups receive questionnaires on background (at baseline), lifestyle, health status and satisfaction with intervention program (at 12 months).

Main outcome measures of the trial: Primary outcome of the study is one-year persistence of statin treatment. Secondary outcomes are compliance, cholesterol level, life style, and side effects of statin treatment. Expecting an increase in persistence from 67 to 76%, with a statistical power of 80% and a type I error alpha = 0.05 (two-sided) the required sample size is 394 patients in both arms. Given these calculations and considering 20% loss of patients during the study we aim at including a conservative number of 1,000 patients in the study.

Results: So far 810 patients have been included in the study. Data on self-perceived health and lifestyle modifications were available for 285 patients. Perceived health and lifestyle modifications did not differ between intervention group and usual care group at baseline and at 6 months. For 105 patients in the intervention arm, reports on compliance and cholesterol levels were available. Compliance was high (97%) but only 47% of the patients had reached target cholesterol level.

Conclusions: We developed a pharmacist-led pharmaceutical care program that comprises counselling on compliance and cholesterol level. Up to now this study is the first multi-centre trial in the Netherlands that evaluates the effect of a pharmaceutical care program on persistence and compliance with lipid lowering drug therapy. This pharmaceutical care program reflects the present shift from prescription-orientated pharmacy towards patient-orientated pharmacy.

Introduction

Inappropriate drug use is a considerable problem in health care. In the Netherlands it has been estimated that 33-87% of the patients use drugs too short to be effective. [1] Inappropriate drug use withholds patients from the benefits of drug treatment as established in randomised clinical trials. The estimated investment loss due to early discontinuation of statins in 1998 in the Netherlands has been estimated at € 10-34 million, which equals 5-17% of the total sales of statins in 1998 (€ 202 million). [1] One-year persistence with lipid-lowering drugs has been estimated at 61-67% in the Netherlands.[1 2] Given the increasing use of lipid-lowering treatment and its associated costs, [3] and the governmental measures to control health care expenses, [4 5] reducing inappropriate use of lipid lowering drugs probably will become even more important in the future. To decrease inappropriate drug use and improve clinical outcomes pharmaceutical care programs for hyperlipidemic patients have been developed. Formal integrated pharmaceutical care plans during a 1-year period showed to lower the total cholesterol and LDL-cholesterol levels. [6 7] In the IMPROVE study, managed pharmaceutical care resulted in better control of total and LDL-cholesterol levels for lower costs. [8] Bozovich et al. showed that both compliance and LDL-cholesterol levels improved due to the launch of pharmacist-managed lipid clinics. [9] So far, no randomised pharmaceutical care trials that measured cholesterol level or another clinical parameter have been evaluated in the Netherlands.

In the Netherlands, the management of hypercholesterolemia is addressed in two national guidelines; the CBO Guideline from the Dutch Institute for Health Care Improvement (CBO), and the NHG Guideline from the Dutch College of General Practitioners (NHG). [10 11] The NHG Guideline recommends simvastatin 20mg daily or pravastatin 40mg daily in patients eligible for lipid lowering treatment. The recommended target level for total cholesterol is below 5 mmol/L (190 mg/dL). Once treatment has been initiated, measurement of cholesterol level at three months after start of treatment to evaluate whether prescribed statin and dose are appropriate is recommended. When the target level has not been reached yet, daily dose may be doubled once and after that, periodical monitoring of cholesterol level is not recommended. [11] However, the Dutch general population seems to appreciate feedback on cholesterol level as became visible after the success of a 'National Cholesterol Test' that was organized by the Netherlands Heart Foundation.

Given the non-persistence with statin treatment, the favourable outcomes in foreign pharmaceutical care programs, the absence of evaluated pharmaceutical care programs on statin therapy in the Netherlands, and the lack of periodical feedback of cholesterol level to patients on statin treatment, we developed a pharmaceutical care program for hyperlipidemic patients that focussed on improving compliance through education and feedback on achieved cholesterol levels. In this chapter we present the design of a pharmacist-led pharmaceutical care program for dyslipidemic patients who started statin treatment and show some preliminary results.

Objective and design of the pharmaceutical care program

The Statin Intervention Program (STIPT) is a pharmacy-based open-label randomised clinical trial in approximately 1,000 new users of statins to determine the benefits of a pharmaceutical care program when compared to "usual care".

Aim of the study

Our aim was to assess the effects of a pharmacist-led pharmaceutical care program for dyslipidemic patients who started statin treatment on persistence and compliance with lipid-lowering drug therapy.

Anticipated sample size

Persistence rate in the Netherlands was derived from the PHARMO report on chronic pharmacotherapy and persistence that reported one-year persistence of 67%. [1] Expecting an increase in persistence from 67 to 76%, with a statistical power of 80% and a type I error alpha = 0.05 (two-sided) the required sample size to test the primary hypothesis of the study was 394 patients in both arms. Expecting a loss to follow up of 20% we aimed at including 1,000 patients in the study. The incidence rate of new users of statins was assumed to be one patient per week for an average community pharmacy. Expecting 20 participating pharmacies, inclusion would take approximately one year.

Recruitment of pharmacies

We invited all 400 community pharmacies working with Pharmacom® software and an electronic patient care system in the Netherlands to participate in the

study. These pharmacies were expected to be accustomed to keeping patient records on pharmaceutical care.

Inclusion of patients

Participating pharmacies invited new users of statins to participate in the trial. After obtaining informed consent patients were randomly assigned to the intervention group or the usual care group. Inclusion was planned to take one year or less in case 1,000 participants are included. Patients had to be aged 18 or older and capable of understanding the purpose and risks of the study. Patients who filled a prescription for statins in the preceding six months were not considered to be new users of statins and therefore were excluded. The study was reviewed by the Medical Committee of Ethics and approved by the board of directors of the University Medical Centre Utrecht (protocol number 04/007-E).

Intervention program

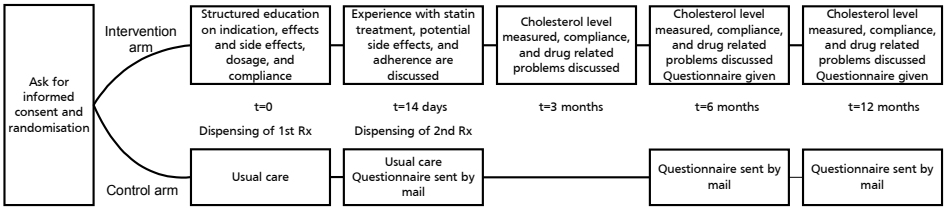
Patients in the intervention group were invited to attend the pharmacy for five counselling visits that take approximately 15 minutes each. Participants got individual counselling by their pharmacist at first prescription, second prescription (after 15 days) and at three, six and 12 months after start of treatment. Counselling at first prescription comprised structured education on indication, effects and side effects of statin treatment, dosage, and the importance of compliance. Additionally a drug information letter that summarizes the verbal information was given. At second prescription, the patients were asked about their experience with statin treatment, potential side effects and use and again adherence to the dosing regimen was emphasized. At three, six and 12 months, compliance was calculated, and cholesterol levels (total, LDL, HDL and triglycerides) were measured. Measured cholesterol levels and treatment goals were recorded on a wallet card that was kept by all patients to monitor their progress in lowering cholesterol levels. The association between compliance and cholesterol level was discussed to encourage patients to adhere to the prescribed dosing regimen. Compliance was calculated using dispensing records from the pharmacy (including date, amount dispensed, daily dosage) and the number of tablets the patients had in stock. Furthermore drug-related problems and experience with cholesterol lowering treatment were discussed. At second prescription (after 15 days), and at six and 12 months after start of treatment

questionnaires were given. The first questionnaire was administered at second prescription as patients had 14 days to consider whether or not to participate in the study.

Usual care

The elaboration of usual care varied among the participating pharmacies, but on no account cholesterol levels were measured and counselling sessions were offered. At first dispensing patients received verbal and written drug information as was common in the concerned pharmacy. Some pharmacies offered information at second dispensing too. No further counselling was offered at three, six and 12 months. Of course, request from patients for more information or education were granted. Controls received questionnaires by mail at second prescription (after 15 days), and at six and 12 months after start of treatment. The flow of the patients through the trial is shown in figure 1.

Figure 1. *Diagram showing the flow of participants through the trial.*



Referral to physicians

When patients had a cholesterol level above 5.5 mmol/L despite a compliance of at least 80%, the pharmacist refers the patient back to the prescribing physician to consider dose adjustment or switch to a more potent statin.

Outcome and analysis of the pharmaceutical care program

Primary outcome of the study was one-year persistence of statin treatment. Secondary outcomes were mean compliance, relative reduction of cholesterol level, number of lifestyle changes and proportion of patients with side effects of statin treatment.

Data collection

Reports of the individual patient counselling (including cholesterol level and compliance) of patients in the intervention group were recorded in the pharmacy computer system. Patients in both the intervention and the usual care group received questionnaires at second prescription (after 15 days) and at six and 12 months. All questionnaires comprised questions on lifestyle and self perceived health (single-item measure that ranged from poor to excellent). Furthermore the questionnaire at second prescription assessed cardiovascular diseases, co-morbidity, smoking habits, alcohol consumption, diet, marital status, education, and ethnicity. Satisfaction with the pharmaceutical care program was assessed in the intervention group at 12 months. At the end of the study, both for patients in the intervention arm and patients in the usual care arm, cholesterol levels as measured by the prescribing physician and the drug dispensing records from one year prior to study entry until end of the study is collected.

The cholesterol level in the pharmaceutical care program was measured using Cholestech LDX Analyzers. Total and HDL cholesterol were measured with an enzymatic reaction based upon the method of Allain et al. [12] and Roeschlau [13]. Total cholesterol/HDL cholesterol (TC/HDL) ratio was calculated.

Analysis

Statistical analysis will be done on the intent-to-treat basis. Persistence will be compared between intervention and usual care arm with Cox proportional hazard model and adjusted for possible confounders. Dichotomised data on compliance will be compared between intervention and usual care arm using logistic regression and adjusted for possible confounders. Categorical data will be compared using Chi square when sample sizes support the approximation. Continuous variables will be compared by Student T test if assumptions of normality and homogeneity of variances appeared to be reasonable. Paired proportions will be compared with McNemar test. A p-value <0.05 will be considered statistically significant.

Preliminary analysis

We compared self-perceived health and lifestyle between the intervention arm and the usual care arm and between six months and three months. We compared 6-month mean compliance and cholesterol levels with 3-month mean

compliance and cholesterol levels in patients subject to the pharmaceutical care program. Mean compliance and cholesterol level were compared between men and women. The proportion of patients that reached target cholesterol level and the proportion of patients that reported side effect at six months was compared to three-month values.

Preliminary results

Out of the 400 invited community pharmacies, 86 pharmacies were interested to participate in the study at first. Most of the pharmacies that refrained from participating in the study were relatively small, had no experience with pharmacy practice research or were not able to find enough time to carry out the pharmaceutical care program. Eventually 26 out of the 86 pharmacies were actually willing to participate in the study. Pharmacies were geographically equally distributed over the Netherlands. Pharmacies started inclusion in fall 2004 and at September 30, 2005, 810 patients were included in the study with a follow-up period that ranged from some days to almost one year.

Patients

The sex ratio (male to female) was approximately 1:1 as 402 (49.6%) were male and 408 (50.4%) were female. Mean age (± SD) at study entry was 60 (± 11.6). 400 patients were allocated to the intervention arm and 410 patients were allocated to the usual care arm. Response rate to the questionnaire at baseline was 78.6% and therefore baseline characteristics of 637 patients are shown in table 1.

At baseline no differences in characteristics between patients in the intervention group and the usual care group were observed.

Self-perceived health and lifestyle adjustments

Both baseline and six-month questionnaire were available for 285 patients. For those patients, self-reported health (single-item measure that ranged from poor to excellent) and self-reported lifestyle modifications are shown in table 2. No statistically significant differences were observed between intervention arm and controls.

Table 1. *Baseline characteristics of index patients and controls. Values are numbers (percentages) unless otherwise noted.*

		Intervention arm (n=305)		Usual care arm (n=332)	
Age (mean ± SD)		60	(±12)	60	(±11)
Male sex		136	(44.6)	172	(51.8)
Dutch origin		275	(90.2)	305	(91.9)
Marital status	married/living together	219	(72.8)	270	(81.8)
	widowed/divorced/single	62	(20.6)	47	(14.2)
	unknown	20	(6.6)	13	(3.9)
Education	primary school	49	(16.1)	41	(12.3)
	high school	199	(65.2)	222	(66.9)
	university	35	(11.5)	54	(16.3)
	unknown	22	(7.2)	15	(4.5)
Smoking	current	77	(25.2)	68	(20.5)
	past	134	(43.9)	162	(48.8)
	never	92	(30.2)	101	(30.4)
	unknown	2	(0.7)	1	(0.3)
Alcohol use	never	156	(51.1)	166	(50.0)
	less than once a week	74	(24.3)	98	(29.5)
	once a week or more	55	(18.0)	56	(16.9)
	unknown	20	(6.6)	12	(3.6)
Applying cholesterol lowering strategies beyond medication					
	healthy food plan	152	(45.2)	162	(49.7)
	more physical exercise	115	(12.5)	129	(17.5)
	weight loss	89	(5.9)	85	(8.1)
	quit / decrease cigarette smoking	43	(4.3)	34	(5.1)
	less alcohol consumption	43	(4.9)	40	(8.1)
Hypercholesterolemic relative(s)					
	first-degree relatives	85	(27.9)	98	(29.5)
	second-degree relatives	51	(16.7)	52	(15.7)
	other relatives	20	(6.6)	33	(9.9)
Cardiovascular	hypertension	138	(45.2)	165	(49.7)
disease	angina pectoris	38	(12.5)	58	(17.5)
	arrhythmia	18	(5.9)	27	(8.1)
	myocardial infarction	13	(4.3)	17	(5.1)
	CABG/PCTA	15	(4.9)	27	(8.1)
	heart valve disorders	8	(2.6)	7	(2.1)
	TIA/CVA	5	(1.6)	3	(0.9)
Other chronic	diabetes mellitus	88	(28.9)	90	(27.1)
morbidity	asthma	22	(7.2)	29	(8.7)

Table 2. *Health and lifestyle at baseline and six months in intervention (n=140) and usual care (n=145) arm. Values are numbers (percentages).*

	Baseline				Six months			
	Intervention		Usual care		Intervention		Usual care	
Self-perceived health								
excellent	2	(1.4)	3	(2.1)	0	(0.0)	2	(1.4)
very good	14	(10.0)	12	(8.3)	20	(14.3)	13	(9.0)
good	90	(64.3)	89	(61.4)	96	(68.6)	101	(69.7)
moderate/poor	34	(24.3)	38	(26.2)	24	(17.1)	26	(17.9)
bad	0	(0.0)	3	(2.1)	0	(0.0)	3	(2.1)
Lifestyle								
healthy food plan	61	(43.6)	74	(51.0)	88	(62.9)	87	(60.0)
more physical exercise	49	(35.0)	53	(36.6)	59	(42.1)	65	(44.8)
weight loss	36	(25.7)	33	(22.8)	47	(33.6)	47	(32.4)
quit / decrease cigarette smoking	14	(10.0)	14	(9.7)	19	(13.6)	19	(13.1)
less alcohol consumption	18	(12.9)	16	(11.0)	20	(14.3)	29	(20.0)
none	56	(40.0)	53	(36.6)	20	(14.3)	24	(16.6)

No statistical significant differences between intervention arm and usual care arm, but significant difference between six months and baseline.

Persistence and cholesterol level

At August 31, 2005, 133 patients in the intervention arm had a follow-up of at least 6 months. Two patients were lost to follow-up due to movement to another pharmacy and decease. 27 patients did discontinue statin treatment within 6 months after initiation. Therefore the six-month persistence rate was 80%. For 105 patients in the intervention arm, reports of individual patient counselling at three and six months of follow-up were available. Mean age (± SD) was 59.9 (± 11.6) and 49.5% was male. Atorvastatin, pravastatin, rosuvastatin, and simvastatin were used by 40.0%, 15.2%, 10.5%, and 34.3% of the patients respectively. Compliance and cholesterol levels are shown in table 3. Compliance was high (97%) but only 47% of the patients had reached target cholesterol level. Compliance rates did neither differ between the sexes, nor among the four different statins. HDL cholesterol level was lower in men compared to women at 3 and 6 months ($p<0.05$). TC/HDL ratio was higher in men compared to women at 3 months ($p<0.001$) but did not differ at 6 months. Total cholesterol level appeared to be lower in patients using more potent statins (i.e. atorvastatin, rosuvastatin) compared to other statins (i.e. pravastatin, simvastatin) but differences were not significant.

Table 3. *Compliance and cholesterol levels at 3 and 6 months.*

	At 3 months		At 6 months		
Mean compliance, % (±SD)	96.6	(±9.6)	96.8	(±12.8)	ns
Mean total cholesterol level, mmol/dL (±SD)	5.17	(±1.04)	5.19	(±1.06)	ns
Mean HDL cholesterol level, mmol/dL (±SD)	1.28	(±0.59)	1.36	(±0.44)	ns
Mean ratio TC/HDL (±SD)	4.52	(±1.54)	4.04	(±1.38)	p<0.005
Total cholesterol < 5 mmol/L, N (%)	43	(41.0)	49	(46.7)	ns
Ratio TC/HDL< 4, N (%)	34	(32.4)	62	(59)	p<0.001
Side effects reported, N (%)	21	(20)	15	(14.3)	ns

Discussion

We developed a pharmacist-led pharmaceutical care program that comprises counselling on compliance and feedback on achieved cholesterol levels. Up to now this study is the first multi-centre trial in the Netherlands that evaluates the effect of a pharmaceutical care program on persistence and compliance with lipid lowering drug therapy. Furthermore this is the first multi-centre pharmaceutical care program that incorporated measurement of cholesterol levels in the Netherlands. Therefore, our study joins the present shift from prescription-orientated towards patient-orientated pharmacy services and from medication-orientated towards health care outcome orientated pharmacy services.

In our study, women are included more often than in the landmark trials on statins. Furthermore we did not exclude elderly and patients with severe diseases and consequently limited life expectancy. At present the inclusion rate of patients is as expected. Therefore we expect that we will have enough power to address our primary hypothesis.

We designed a study without measurement of the cholesterol level in patients in the usual care group during the study period in which the cholesterol level of patients in the intervention arm is measured three times. Although this is a limitation of our study, measurement in the usual care group probably would cause unwanted influencing of patients in the usual care group and thereby dilute the effect of the intervention. Therefore we choose to restrict the attention paid to the usual care group to sending questionnaires. To compare cholesterol level of patients in the intervention group with usual care group, we collect all cholesterol level measurements performed by the prescribing physicians. Thereby we obviate the absence of measured cholesterol levels in controls as far as possible.

At present, six-month persistence with statin treatment was 80% and compliance of patients still on treatment was 97%. Mean total cholesterol level appears to be slightly above the treatment goal and less than half the patients had reached target cholesterol level. The six-month persistence rate could not be compared with controls, but comparison with a previous study in the Dutch general population revealed that persistence in our study was slightly better (75% vs. 80%). [2]

Our preliminary results should be interpreted with caution due to a limited follow-up and the small sample size.

As the mean total cholesterol level is slightly above target level and the majority of patients did not achieve treatment goal, the cut off limit when pharmacists refer patients back to the prescribing physician (5.5 mmol/L) might be debatable. Increasing the cut off limit might result in achievement of treatment goal more often. However the NHG Guideline that is in effect in the Netherlands does not recommend further dose adjustment or switching to a more potent statin in case the initial statin dose is doubled due to evaluation at three months after initiation of treatment. [11] Furthermore, in daily practice the reduction of cholesterol level will be related to the initial cholesterol level. Therefore we think the cut off point of 5.5mmol/L for referring patients back to the prescribing physician is appropriate.

In conclusion we demonstrated the feasibility and implementation of a pharmaceutical care program in patients who start treatment with statins. The results of this trial will help to assess the potential beneficial effects of this program on persistence and compliance with statin treatment.

Acknowledgements

PharmaPartners is gratefully acknowledged for the adaptation of the Pharmacom software. The study is performed in collaboration with DM Steinmeijer, Alkemade Pharmacy, Roelofarendsveen; LCGM Bakker, Delfgauw Pharmacy, Delfgauw; AJE Zaagman, Elderveld Pharmacy, Arnhem; JFG Trooster-Bosse, Goorse Pharmacy, Goor; JCM Kruik-Smits, Groenewoud Pharmacy, Tilburg; PMJM Cornips, Hoge Vucht Pharmacy, Breda; WG Doppenberg, Holtenbroek Pharmacy, Zwolle; LG Biesma, Kruyt Pharmacy, Delft; SJ Komen, Laarhoeve Pharmacy, Aarle-Rixtel; EPM Claushuis, Langstraat Pharmacy, Wassenaar; M van der Meer, Loosduinse Apotheek Pharmacy, The Hague; T Vlaar, Molentocht Pharmacy, Purmerend; B Kruissel, Monnickendam Pharmacy, Monnickendam; MF Gilissen, Plesman Pharmacy, Amsterdam; JAJ van Gent, Pluymaekers Pharmacy, Utrecht; M van den Berg-de Witte, Ridderveld Pharmacy, Alphen a/d Rijn; J Schijf, Sassenheim Pharmacy, Sassenheim; CHM van Uem, Schul Pharmacy, Roosendaal;

JA Kiestra, Themmen Pharmacy, Assen; EG Lipperts, Tolberg Pharmacy, Roosendaal; A Polman, Toolenburg Pharmacy, Hoofddorp; R Fransens, Van der Sluis Pharmacy, Sneek; MH Oosterveld, Waldeck Apotheek Pharmacy, The Hague; RWMM Langenhoff, Wassenaarse Apotheek Pharmacy, Wassenaar; WM Verhoeven, Wippolder Pharmacy, Delft; A Sellier, Zuiderpark Pharmacy, The Hague.

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7

GENERAL DISCUSSION

In the past decades cardiovascular disease has been the leading cause of death in the Netherlands and other developed countries. Although cancer is believed to surpass cardiovascular disease as the main cause of death in the next decades, cardiovascular disease will continue to contribute to mortality considerably. [1] Therefore, prevention of cardiovascular disease and its most prevalent manifestation, myocardial infarction, will remain an important public health issue. The prevention of cardiovascular disorders is a 'ménage à trois':

- Primary prevention through a vigorous treatment of risk factors such as diabetes mellitus, hyperlipidemia, hypertension, obesity and smoking habits;
- Improving the acute management of cardiovascular disorders;
- Secondary prevention and intensified treatment of risk factors in patients with prior cardiovascular disease.

Important progress has been made in the management of acute myocardial infarction during in hospital stay and thereby the outlook of patients has markedly improved compared to some decades ago. However as primary- and secondary prevention are about pharmacological and behavioural treatments that have to be sustained for prolonged periods, preventive treatment is susceptible to non-adherence to guidelines by health care professionals and to non-compliance by patients.

This thesis deals with prevention of cardiovascular disease, with a special focus on secondary prevention. To lower the risk for mortality and morbidity after myocardial infarction further, more attention should be paid to appropriate long-term treatment of drugs with proven therapeutic benefits. Our ambition was to complete an entire cycle on quality improvement of treatment for the prevention of cardiovascular disease. Repeatedly our focus was myocardial infarction. The cycle started at preparing an evidence-based overview of drug treatment for long-term secondary prevention of myocardial infarction. Then the quality of secondary prevention after myocardial infarction in the Netherlands was assessed. Next, the problems that lead to non-persistence with preventive treatment were uncovered and effects of both wanted and unwanted patterns of drug use were estimated. Finally interventions that might improve the quality of preventive drug treatment in patients with cardiovascular disease were tested.

Evidence based secondary prevention after myocardial infarction

Attempts to establish the beneficial effects of long-term drug treatment after myocardial infarction have been undertaken since the early 1960s. The first randomised trials on secondary prevention concerned oral anticoagulants, anti-arrhythmics, beta-blockers, and antiplatelet agents, followed by calcium channel blockers (since 1980s), angiotensin converting enzyme (ACE) inhibitors (since early 1990s), statins (mid 1990s), and hormone replacement therapy (late 1990s).[2-11] Although the preventive effects of antiplatelet agents have been studied since the 1960s, only after the publication of a meta-analysis by the Antiplatelet Trialists' Collaboration in 1988 the benefits of antiplatelet agents became clearly established.[6] Similarly, the benefits of beta-blockers became apparent with the meta-analysis of Yusuf et al. in 1985.[4] Ultimately next to antiplatelet agents and beta-blockers, oral anticoagulants, ACE-inhibitors and statins proved to lower mortality and re-infarction rates when used long-term after myocardial infarction. The reduction in all cause mortality of the different drug categories varies from 10 to 25% while re-infarction rates declined by 20-30%.[2 4 5 7 10 12-26] Anti-arrhythmics, calcium channel blockers, and hormone replacement did not lower all cause mortality after myocardial infarction[3 8 27-38] Beneficial effects of antiplatelets, oral anticoagulants, beta-blockers, ACE-inhibitors and statins are obtained by different pharmacological actions. Antiplatelet agents inhibit platelet activation by inhibition of prostaglandin production or blocking ADP-induced aggregation, while anticoagulants inhibit the synthesis of coagulation factors. Beta-blockers seem to be protective after myocardial infarction by their heart rhythm and blood pressure lowering properties, whereas ACE-inhibitors seem to contribute by lowering blood pressure and attenuation of ventricular remodelling after myocardial infarction. Statins act by lowering cholesterol levels and by pleiotropic effects like improvement of endothelial function and inhibition of inflammatory responses. Although different time is needed to give optimal protection due to underlying pharmacological mechanisms, all drugs have to be used long-term to maintain optimal protection. Main omission in results from randomised clinical trials on secondary prevention is the absence of evidence on the combined effect of different drugs. Although assumptions can be made upon results from observational studies and subgroup analyses these may be subject to

bias, confounding and chance. [39] Furthermore, a posteriori subgroup analysis may suffer from statistical problems due to limited study power. Therefore the conduct of a randomised clinical trial to assess the preventive effect of drug combinations would be greatly appreciated. But since the return on investments of large multicentre trials is probably low, as most drugs used for secondary prevention are no longer protected by patent, the conduction of such studies is very unlikely. Given the present evidence from randomised clinical trials, use of at least a combination of low dose aspirin, a beta-blocker and a statin seems to be appropriate. Additional ACE-inhibitor treatment in indicated in patients with reduced LVEF. In case of beta-blocker intolerance, ACE-inhibitor treatment can be considered although evidence for benefits of ACE-inhibitor treatment in patients with normal LVEF is limited.

Recently the Dutch Association of General Practitioners (NHG) published a guideline on the Management of patients with myocardial infarction. [40] Subsequently a National Transmural Agreement between cardiologist physicians and GPs on the management of patients after myocardial infarction was issued. [41] This latter agreement coordinates the referral between GPs and cardiologists. The Dutch Association of Cardiologists issued a guideline for cardiologist consultants in 2001 that was mainly based on the American Heart Association (AHA)/ American College of Cardiology (ACC) guideline and the European Society of Cardiology (ESC) guideline on management of patients with myocardial infarction. [42 43] Similar to the overview of pharmacological strategies for secondary prevention after myocardial infarction in Chapter 2, life long use of low-dose aspirin, a beta-blocker, an ACE-inhibitor and a statin are recommended. Surprisingly angiotensin type II receptor blockers (ARBs) were alleged to be substitutes for ACE-inhibitors in case of ACE-inhibitor intolerance. To our knowledge no studies on the benefits of ARBs compared to ACE-inhibitors in patients with a history of myocardial infarction have been published. Although a recent study showed that ARBs lower the risk of non-fatal myocardial infarction in patients with heart failure [44], data from the OPTIMAAL trial showed a non-significant increase of all cause mortality in patients with a history of myocardial infarction who received losartan compared to patients taking captopril. [45] Therefore we think ACE-inhibitor should be preferred above ARBs and ACE-inhibitor intolerance should be diagnosed thoroughly. Furthermore calcium channel blockers were likewise mentioned as a substitute for beta-blockers in case of intolerance. Although calcium channel

blockers proved to be effective in the symptomatic treatment of angina pectoris [46], no such benefits were observed in trials on the prevention of myocardial infarction. Therefore we think the section on calcium channel blockers should be changed to emphasise that calcium channel blockers are not indicated for the prevention of recurrent myocardial infarction. Calcium channel blockers should only be used in patients with symptoms of angina pectoris that do not tolerate beta-blockers.

Based upon results from randomised clinical trials, we evaluated the quality of pharmacotherapy after myocardial infarction in the Netherlands. Previous studies in other countries showed that preventive treatment at discharge from hospital was sub-optimal and persistence with prescribed medication was worrisome. Detailed data concerning long-term treatment in the Netherlands were absent, but data from the EUROASPIRE studies indicated that the use of antiplatelets, beta-blockers and ACE-inhibitors in Dutch patients with a history of cardiovascular disease was lower than in other European patients with cardiovascular disease. [47] We assessed the use of preventive medication in Dutch patients in the PHARMO record linkage system between 1988 and 2002 in Chapter 3. In particular the use of oral antithrombotics and statins at discharge increased markedly, whereas the use of beta-blockers and ACE-inhibitors at discharge increased moderately. A similar pattern was noted when establishing the prevalence of preventive drug treatment during the entire follow-up. Although the increased use of drugs with proven effectiveness in lowering mortality and morbidity is remarkable, a substantial number of patients does not seem to benefit from this overall increased prevalence. Closer exploration revealed that the observed increase is a composite of two opposite developments. On the one hand, the use of preventive drugs increased in patients recently discharged from hospital, while on the other hand the use of preventive treatment decreased after discharge due to non-persistence with prescribed medication. As far as beta-blockers and ACE-inhibitors are concerned, these two opposite developments seem to balance each other. For low dose aspirin and statins, the rise in new users outweighs the downward shift caused by non-persistence. Especially statin treatment was initiated in both new users and patients with a history of myocardial infarction. Probably the publication of landmark trials like the 4S study in 1994, [10] the WOSCOP study in 1995, [48] the CARE study in 1996, [14] and the LIPID study in 1998 [12] have caused a non-stop

attention to cholesterol lowering in high risk patients. Furthermore marketing campaigns by pharmaceutical companies presumably did amplify the attention. Landmark trials concerning oral antithrombotics and beta-blockers have not been published during our study period, whereas results from ACE-inhibitor trials sometimes contradicted each other. Moreover patents of beta-blockers and antithrombotics had already expired before the study period and patents on the most frequently used ACE-inhibitors (captopril, enalapril and lisinopril) expired during the study period.

In general, we observed the same patterns of drug use as observed in foreign studies; despite increasing use of aspirin, beta-blockers, ACE-inhibitors and statins, the use of preventive medication at discharge from hospital remains sub-optimal and the estimated persistence with prescribed medication during follow-up was poor. [47 49-53] However, a 12 year follow-up period has never been studied before; most studies were limited to the first one or two years after discharge. The observed pattern seems not to be unique for secondary prevention after myocardial infarction only. In the Netherlands a similar pattern of sub-optimal treatment was noted in patients with other cardiovascular diseases or cardiovascular risk factors like heart failure and hypercholesterolemia. [54-56] Furthermore, under-treatment was observed in hypertensive patients [57 58] and persistence with chronically intended medication has been shown to be poor in unselected patients. [59]

The observed patterns of drug use suggest two opportunities to improve the quality of preventive drug treatment: interventions towards physicians with the objective to initiate treatment in patients who have been untreated so far and interventions towards both patients and health care professionals to improve long-term persistence with treatment that is already initiated.

Non-persistence in daily practice

Before we developed and evaluated strategies to improve persistence with preventive drug treatment, Chapter 3 focused on mapping non-persistence in daily practice.

In literature, the terms adherence, compliance and persistence are used to describe the extent to what actual patterns of drug use match the originally intended treatment plans. In pharmacotherapy, compliance is the extent to

which patients follow dosing regimens prescribed to them by physicians. Compliance is an obedience-based approach – assuming that the prescriber knows what is best – and in general non-compliance is considered as erroneous patient behaviour. Persistence is a measure of whether a patient is continuing to use the prescribed medication. A patient may be persistent but non-compliant. That is, the patient may continue taking the medication but irregular or in another way than intended. Persistence is a dichotomous outcome whereas compliance is a continuous outcome. Adherence combines compliance and persistence. Different from compliance, adherence is considered to be a collaborative process in which the prescriber may be an expert in pharmacotherapy, but the patients are experts on the factors in daily living that enable or disable them to carry out a treatment plan. Success and failure of pharmacotherapy is shared between prescribers and patients. [60]

Concordance is a new way to define the process of successful prescribing and medicine taking, based on partnership. Concordance refers to the creation of an agreement about whether, when, and how medicines are to be taken, that respects the beliefs and wishes of the patient. [61] Concordance is the description of a process, unlike adherence, compliance, and persistence concordance cannot be expressed as a dichotomous or continuous measure of medication use.

In Chapter 4 we focused on reasons for non-persistence as our studies in Chapter 3 had shown that long-term persistence with preventive medication was poor. Initially we alleged that non-persistence is unwanted, just as many other studies that examined persistence of preventive medication did. Our opinion was based upon the aspiration that patients in every day life could benefit from preventive treatment similar to patients in randomised clinical trials, if only they were as adherent with prescribed medication as patients in randomised clinical trials are. However, this reasoning assumes that patients who once were considered to be eligible for preventive treatment will be eligible for treatment until further notice. Considered at a population level this might be reasonable, however at a patient level "indefinite eligibility for treatment" may be questionable. In daily practice patients possibly discontinue treatment for reasons that are beyond the scope of the guidelines that recommend long-term treatment with preventive medication. Therefore knowing the rationale behind non-persistence could be helpful. Previous studies had estimated predictors for adherence with chronically intended therapy. Adherence has been associated with age, sex, marital status,

educational level, race, medical history, treating physician, medication class, dosing regimen, and concomitant use of medication. [62-66] However data are not conclusive as paradoxically other studies showed no associations on many of these determinants. [67] Although predictors may be useful to specify patient groups that are at increased risk of non-adherence, predictors do not clarify if patients are still eligible for treatment. Therefore reviewing the reasons for non-persistence could contribute to the verification of eligibility for re-initiation of treatment. We examined reasons for discontinuation of cardiovascular drug treatment in two different populations. First we assessed the reason for discontinuation of statin treatment in a cohort of patients that initiated statin treatment in Chapter 4.1. We performed a cohort study as we had a multiple aim. We wanted to assess the reasons for discontinuation of statin treatment (reported by both patients and general practitioners (GPs)), the 3-year persistence, and the proportion of patients that remained on treatment from day to day. Therefore a cohort study with a three-year follow-up appeared to be suitable. Due to the design of our study, the time between discontinuation and questioning could have been up to three years. This might have accounted for substantial non-response that did not strengthen the results of the study. Therefore we chose a different design for our second study on non-persistence. In Chapter 4.2 we described the reasons for non-persistence with beta-blocker use. Patients were questioned within one year after they discontinued treatment, to avoid as much as possible non-response and recall bias due to long time between discontinuation and questioning.

In both studies, communication between patient and physician seemed to be sub-optimal, as knowledge of indication and duration of treatment was often lacking. Furthermore, the ranking of the main reason for discontinuation of statin treatment by patients and GPs was different, but data on individuals both from the GP and patient were too rare to draw definite conclusions on this discrepancy. A substantial proportion of patients seemed to be eligible to be considered for re-initiation of treatment. These results agree with a recent study that showed that 50-60% of patients on four evidence based treatments after discharge for acute coronary syndrome (ACS) reported to have discontinued treatment in consultation with their prescriber. [68] These results do give cause to some confusion. As patients with acute coronary syndromes are certainly in need of antithrombotics, antihyperlipidemics and at least a beta-blocker or ACE-inhibitor, it seems unsupported by clinical evidence to discontinue these drugs.

This raises the question whether the original diagnosis of ACS might have been erroneous or whether the patient has misinterpreted the physician's advice. Taking the results from Chapter 4.1 and 4.2 into account, non-persistence requires a collaborative approach in which patients, pharmacists, and physicians are involved. Given the proportion of patients that may be considered for re-evaluation of eligibility of treatment, quality of preventive treatment might be improved by addressing non-persistence. In fact, the issue of non-persistence should be managed according to the philosophy of concordance; the process of successful prescribing and medicine taking is based on partnership. Pharmacists should monitor persistence and, in case of non-persistence, discuss non-persistence with both the patient and the physician. Then, an agreement about whether, when and how medicines are to be taken may be concluded with respect for the beliefs and wishes of the patient. By considering both the expert opinion on pharmacotherapy and the factors in a patient's daily living that affect the success of a treatment plan optimal preventive pharmacotherapy can be attained.

Effects of drug treatment on cardiovascular outcomes

After reviewing the optimal pharmacotherapy after myocardial infarction in Chapter 2 and studying the actual use and non-persistence with preventive drug use in daily practice in Chapter 3 and 4, we aimed to establish the effects of drug use in daily practice on clinical outcomes in Chapter 5. Two case control studies were performed with (re)admission for myocardial infarction as the unfavourable outcome. In Chapter 5.1 the effect of combination treatment on admission for recurrent myocardial infarction was studied. We felt a study on this topic was timely, given the lack of results from randomised clinical trials on this matter, the media attention for multiple drug treatment combined in a 'polypill' [69] and the recent publication of a case-control study that reported a very large risk reduction of mortality in patients on combination treatment. [70] The 'polypill' (formulation; a statin, thiazide diuretic, beta-blocker, ACE-inhibitor, folic acid, and low dose aspirin) was estimated to lower the risk for ischemic heart disease and stroke by 80%. [69] Hippisley-Cox et al. reported a 70-80% risk reduction of mortality in patients who used low-dose aspirin, statins and either a beta-blockers

or ACE-inhibitors concomitantly. The addition of an ACE inhibitor to a regimen of aspirin, statin and beta-blocker conferred no additional benefit. [70] Given the risk reduction in all cause mortality we showed in Chapter 2, the 80% risk reduction could be an overestimation; especially as the risk reduction of some single drugs was demonstrated in populations that used other preventive medication too. [71] The results from our nested case control study showed that concomitant use of low dose aspirin, a statin and a beta-blocker or an ACE-inhibitor could reduce the risk for recurrent myocardial infarction with 38% in patients with a history of myocardial infarction. We think our results do match the extrapolations from randomised clinical trials quite well, in case risk reductions are multiplicative instead of additive. Furthermore our results show that deprivation of combination treatment leads to preventable cardiovascular morbidity.

In Chapter 5.2 we described the acute effect of discontinuation of statin treatment on the occurrence of first myocardial infarction. This nested case control study was performed in a cohort of patients without prior myocardial infarction to determine the immediate harmful effects of discontinuation of statin treatment. Previous studies indicated that discontinuation of statin treatment may increase the risk for cardiac events when compared with patients who continued to receive statins. [72-74] We found no association between recent discontinuation and occurrence of myocardial infarction in the general population. The association between recent discontinuation of statin treatment and occurrence of acute myocardial infarction in patients with prior CHD remains inconclusive.

As the results from Chapter 5.1 still stands, compliance with preventive treatment is associated with a considerable risk reduction in myocardial infarction. Discontinuation therefore withholds long-term benefits concerning cardiovascular morbidity and mortality from patients but in the case of statins, does not seem to cause additional harm in the short term in the general population. This does not yet preclude that acute effects of discontinuation are also absent in selected high-risk populations (e.g. patients with previous myocardial infarctions). Both studies described in Chapter 5 may suffer from limitations that go with case-control design like confounding, no possibility to establish a causal relationship between exposure and outcome, and selection and recall bias. However, at present data from randomised clinical trials are lacking. Considering the probable low return on investments of a randomised clinical trial on a 'polypill' and the fact that discontinuation of statin treatment would be

unethical given the established benefits of statin treatment, this lack of data will probably continue. Therefore results from observational studies are the best available evidence.

Role of the pharmacist

In Chapter 6 we explored the possible role of pharmacists in improving the quality of pharmacotherapy in patients with cardiovascular disease or cardiovascular risk factors. As previous Chapters have shown that physicians, pharmacists and patients might be responsible for suboptimal treatment, we designed two pharmacist-lead interventions; one directed towards GPs and another intervention directly aimed at patients.

In Chapter 6.1 we developed and evaluated a peer review group (PRG) meeting using feedback data on a patient level to improve the quality of drug therapy for prevention of recurrent myocardial infarction. We showed that pharmacists can improve the quality of pharmacotherapy after myocardial infarction through PRG meetings. Although this intervention was performed in one PRG only and the number of patients was small, the results are promising and confirmation in a larger trial would be worthwhile. Besides, both the conduct of the PRG itself and the outcomes on a patient level give rise to a closer examination of the role of GPs and pharmacists and further development of the collaboration between GPs and pharmacists. When preparing the intervention, our first obstacle was the absence of knowledge of chronic conditions by the pharmacist. In the Netherlands, information from medical records is not shared with pharmacists. Community pharmacists do deduce conditions from the dispensed medication. However, deduction is only reliable in case the relation between medication and condition is univocal. The use of anti-diabetics obviously indicates diabetes mellitus and in the majority of patients the use of organic nitrates indicates the presence of angina pectoris. However the indication of medication used for secondary prevention after myocardial infarction is more difficult to discover. Low dose aspirin may be prescribed after CABG or TIA or in patients with angina pectoris, beta-blockers and ACE-inhibitors may be indicated in patients with hypertension or heart failure and statins may be used both for primary and secondary prevention. Though, especially when the aim is to assess the quality of pharmacotherapy, deduction can be uncertain. Myocardial infarction could only

be deduced from medication use when patients are treated appropriate. Therefore chronic conditions deduced from pharmacy records are not a reliable source to assess sub-optimal treatment in patients with a history of myocardial infarction. To assess the quality of secondary prevention after myocardial infarction independently from physicians, community pharmacists should have access to the conditions or diseases as recorded by physicians. The second hurdle in improving the quality of secondary prevention through a PRG meeting was the limitation to GP-treated patients only. GPs stated that they did not want to interfere with pharmacotherapy that was initiated by cardiology consultants. Consequently all patients treated by cardiology consultants could not benefit from the intervention. Although studies have shown that the quality of preventive pharmacotherapy in patients treated by cardiologist is higher, there remains room for improvement. [75] Therefore we think that future interventions should be directed towards cardiology consultants too, especially since the peer review group (PRG) meeting did improve the quality of pharmacotherapy after myocardial infarction. Previously, Van Eijk et al. also showed that PRG meetings can be used to improve prescribing. [76] Recently, Muijrers et al. stated that PRG meetings do not improve the quality of pharmacotherapy. [77] Muijrers et al. supposed that the high level of permissiveness in which responsibilities were not clearly assigned might have caused no association between PRG meetings and prescribing according to national guidelines. However, Muijrers et al. did not assess the effectiveness of PRGs through interventions, but performed an observational study using data from questionnaires administered among GPs and pharmacists. Consequently the PRGs could not be judged on adherence to local guidelines or PRG agreements. Therefore we think that our results, obtained in an intervention study in daily practice, still stands and PRG meetings can be a valuable tool to improve pharmacotherapy.

The ongoing Statin Intervention Project as described in Chapter 6.2 was inspired by both successful experiences with pharmacist-led interventions to promote compliance with statin treatment from abroad [78-81] and observations from community pharmacists that patients indicated to be in want of recurring cholesterol level measurements to give them feedback on the efforts to lower their cholesterol level. We chose to perform a multicentre randomised trial to avoid demerits of observational studies and to increase its external validity. By the multicentre design, variety in the performance of the intervention would be assured. Possibly diversity may dilute the results and might cause lack of effect in

the trial. However, as diversity is common in pharmaceutical practice, implementation of the intervention in daily practice, assuming the research would reveal positive results, would also introduce diversity in the performance. Therefore obtaining results in a trial that resembles daily practice as much as possible is important for its external validity. We aimed to stick to the experimental design as much as possible in this practice trial in community pharmacies. Inherent to the nature of the intervention the trial could not be blinded. Randomisation was ascertained by sophisticated pharmacy software that assigned the patient to the intervention or control group at the processing of the first statin prescription. When considering both the desirable contrast between the intervention arm and the control arm and the collection of data to obtain complete information on controls similar to intervention patients, several choices were made. First we do not measure cholesterol levels in controls during the conduct of the study. Therefore we collect cholesterol levels measured by GPs at initiation of treatment and during follow-up to compare cholesterol levels between intervention and control patients. Consequently reporting on the achievement of treatment goals at one year is uncertain. However, measuring cholesterol levels in the control group would have blurred the contrast between intervention and control arm too much as feedback on cholesterol level measurements plays such an important role in the counselling visits in the control arm. Furthermore, the questionnaires for controls are sent by post while they are handed over to patients in the intervention group. Questionnaires were send to controls by post to minimise the attention and contact that are beyond the usual care. Possibly the different manner of distribution will affect the response rates. However, at present the response rates in the control arm seem to be slightly higher that the rates in the intervention arm, which indicates that the differential method of distribution does not affect the response rates.

During the past decade 'usual care' in community pharmacies transformed from brief information on request through structured communication at dispensing of first and second prescription to entire pharmaceutical care programs. The Statin Intervention Project is such a pharmaceutical care program and offers a new approach by measuring the cholesterol level to motivate patients to adhere to their treatment regimen. In the Netherlands the efficacy of pharmaceutical care strategies has rarely been evaluated in randomised trials, although pharmaceutical care has been evaluated in patients with heart failure and in pulmonary patients.

[82] [83] We think critical evaluation of strategies to improve treatment in daily practice is essential. As the results of the pharmaceutical care program we developed are awaited and unfavourable outcomes are not precluded, introduction of the Statin Intervention Project has to wait for the final results. On balance, efforts to improve patient outcomes may better be put into strategies that proved to be effective than in strategies that are believed to be effective.

Final considerations

In this thesis, we have utilised several data sources to obtain information on quality improvement of pharmacological cardiovascular disease prevention. Best clinical evidence was gathered through a review of the medical literature. Pharmacy records have given a profound insight in the quality of pharmacological treatment of patients with myocardial infarction in the Netherlands and were useful to complete omissions in data from randomised clinical trials on the benefits of combination treatment in patients with a history of myocardial infarction. Contacts with patients and physicians have revealed some interesting details on patterns of drug use in daily practice. Finally, interventions in daily practice gained insight in the possible role of pharmacists in improving the quality of pharmacotherapy for cardiovascular prevention. These different data sources gave us the opportunity to complete a cycle on quality improvement of treatment for the prevention of cardiovascular disease. Therefore, now we can state that, based upon best clinical evidence, patients with a history of myocardial infarction should receive appropriate treatment with antiplatelet agents, beta-blockers, ACE-inhibitors and statins. Although it was demonstrated that the quality of long-term secondary prevention after myocardial infarction had improved over the last decade, many patients were treated sub-optimally. Sub-optimal treatment appeared to involve both undertreatment of patients discharged from hospital several years ago and decreased use of preventive treatment due to non-persistence with medication prescribed at discharge from hospital. Assessment of reasons for non-persistence revealed that re-evaluation of pharmacotherapeutic needs is warranted in many patients. Considerable efforts of health care professionals and patients are required to obtain full benefits of the available preventive medication. Given the

complexity of prevention of cardiovascular disease and the involvement of patients, general practitioners, consultant cardiologists as well as pharmacists, a multi-disciplinary approach like advocated in the concept of concordance seem to be timely. Given the experience of pharmacists with systematic and critical reappraisal of patients' drug use, pharmacists should take the initiative in starting a multi-specialty team to improve drug treatment for cardiovascular disease. The research presented in this thesis has shown that pharmacists-led interventions can be a valuable tool to improve the quality of preventive pharmacotherapy. Healthcare professionals should put the interest of patients first and share data needed to provide appropriate pharmaceutical care. Furthermore, pharmacy software should get applications that identify patients who discontinue possibly chronically intended treatment. Supported by appropriate software, pharmacists could identify patients who might be eligible for re-initiation of treatment at an early stage. In consultation with both physicians and patients, re-initiation of treatment may be considered. This way of incorporation of concordance in daily practice could make sure that no patients stay deprived from the benefits from preventive treatment unnecessarily, unless explicitly chosen for grounded reasons.

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8

SUMMARY

The aim of the research presented was to describe an entire cycle on quality improvement of preventive drug treatment. This cycle comprises an overview of evidence-based preventive drug treatment, quality assessment of secondary prevention after myocardial infarction in the Netherlands, evaluation of reasons for non-persistence with preventive treatment, estimation of the effects of both sub-optimal and optimal secondary prevention on myocardial infarction in daily practice. Finally examples of pharmaceutical care interventions that might improve the quality of preventive drug treatment in patients with cardiovascular disease were presented.

Strategies to reduce mortality and cardiovascular morbidity in patients with myocardial infarction have been studied extensively and have been translated into guidelines for the management of acute myocardial infarction. However, guidelines for secondary prevention after myocardial infarction remain inconclusive concerning combination therapy. Given the importance of long-term secondary prevention of myocardial infarction, the lack of clear recommendations concerning combination therapy in guidelines, and the wide spread practice of it we provided an overview of evidence-based medicine after myocardial infarction in **Chapter 2**. Searches of Medline and the Cochrane Controlled Trial Register revealed trials and meta-analyses that fulfilled our criteria considering randomisation, methods, myocardial infarctions, duration of follow-up, and outcome definition. In randomised clinical trials, low-dose aspirin, high intensity oral anticoagulants, beta-blockers, ACE-inhibitors and statins decreased the risk of mortality and reinfarction after myocardial infarction. Randomised clinical trials on calcium channel blockers, anti-arrhythmics, and hormone replacement therapy did not show benefits in patients with prior myocardial infarction. Effects of the combined use of aspirin or oral anticoagulants with beta-blockers or ACE-inhibitors along with statins have to be derived from subgroup analysis of trials, but seem to be beneficial. Therefore the use of, at least, aspirin or an oral anticoagulant, a beta-blocker or an ACE-inhibitor, along with a statin should be incorporated in treatment routine. Clopidogrel treatment might be an alternative to aspirin. Standard addition of a beta-blocker to ACE-inhibitor-treated patients without reduced LVEF seems to be untimely.

As the overview presented in Chapter 2 revealed that several drugs lowers mortality and morbidity after myocardial infarction, we studied the use of that preventive medication in the Netherlands using the PHARMO Record Linkage

System in **Chapter 3**. In **Chapter 3.1** we focussed on the use of oral antithrombotics (i.e. antiplatelet agents and oral anticoagulants) after myocardial infarction. Retrospective follow-up of 3,800 patients with myocardial infarction showed that from 1988 till 1998 oral antithrombotic treatment increased significantly from 54.0 percent to 88.9 percent. However, treatment was not equally distributed among patients with a recent admission for myocardial infarction and patients with a past history of myocardial infarction. In 1998, only 75.8 percent of patients who suffered from a myocardial infarction in the late 1980s received oral antithrombotic treatment compared to 94.4 percent of those who suffered from a recent myocardial infarction. Part of the patients may not have been treated because of aspirin intolerance. However, we do not believe that one quarter of the patients were aspirin intolerant given surveys in primary care that reported rates of aspirin intolerance that ranged from 8.5 to 13 percent, which is substantially below 24.2 percent.

Estimation of the projected number of myocardial infarction that may have occurred on a national level due to under-treatment (assuming a number needed to treat for two years of 56), revealed that optimal oral antithrombotic treatment in patients with myocardial infarction from 1988 to 1998 would have prevented 1469 non-fatal re-infarctions in the Netherlands. Therefore patients with a past history of myocardial infarction who are currently not treated with oral antithrombotics should be reviewed for antithrombotic therapy.

Putting preventive medication after myocardial infarction in a wider perspective, we examined the use of oral antithrombotics, beta-blockers, ACE-inhibitors, statins, and their combinations after myocardial infarction both at discharge from hospital and during a 12-year follow-up (**Chapter 3.2**). Retrospective follow-up of 4,007 patients revealed that both the overall use and the use at discharge of antiplatelets and statins increased markedly between 1991 and 2000 (42 percent to 88 percent and 5 percent to 58 percent respectively at discharge), whereas the use of beta-blockers and ACE-inhibitors increased mainly in recently discharged patients (49 percent to 76 percent and 19 percent to 44 percent respectively during the 30 day period after discharge). Combination therapy increased strikingly; in 1991, 47 percent of the treated patients received any kind of combination therapy at discharge. In 2000, 90 percent received any combination. At one year after discharge 32 percent of the patients already had discontinued the original combination treatment. At five year after discharge, 57 percent of the patients had not discontinued original combination treatment.

The results from Chapter 3 show that secondary prevention after myocardial infarction is still sub-optimal. The observed patterns of drug use suggest that the quality of preventive treatment might be improved by initiating treatment in patients who have been untreated so far and by improving long-term persistence with treatment that is already initiated.

As non-persistence appeared to be one of the reasons accounting for sub-optimal preventive drug use, we aimed to reveal the reasons for discontinuation of statin treatment and beta-blocker treatment in **Chapter 4**.Untimely discontinuation of preventive medication could result in preventable morbidity and mortality among patients with cardiovascular disease. Based upon the best available evidence, patients who start preventive treatment should be treated long-term. At times, the costs for pharmaceuticals for patients that discontinue treatment were expressed as economic loss. Though, by expressing premature discontinuation as damage one assumes that all untimely discontinuation is undesirable. Understanding of the reason for non-persistence is needed to determine if discontinuation matches criteria for evidence based treatment, and to determine if patients are eligible for (re)initiation of treatment.
In **Chapter 4.1** the 3-year persistence with statin treatment, the reason for discontinuation, and the predictors for untimely discontinuation of statin treatment were assessed. Nine community pharmacies in the Netherlands questioned patients and GPs. Out of 425 patients, 104 patients (24%) discontinued statin treatment during 3-year follow-up. Major reason for discontinuation according to the GP was the patient's own initiative, while patients reported side effects to be the main reason for non-adherence. 56% of the non-persistent patients discontinued treatment without a reason that meets criteria for evidence based treatment. Low compliance with treatment (PDC < 80%) was associated with discontinuation of statin treatment. Half of the patients who discontinued treatment seem to do so without a reason that meets criteria for evidence based treatment, but reasons according to patients and GPs mismatch.
Reasons for non-persistence with beta-blocker treatment in patients with cardiovascular disease the proportion of patients that might be eligible for reconsideration of beta-blocker treatment was investigated in **Chapter 4.2**. The administration of a telephone questionnaire to patients who discontinued beta-blocker treatment revealed that 72% of 29 patients had discontinued drug treatment in consultation with their physician. Adverse effects were most frequently cited to have prompted discontinuation. Considering switching rates

and reasons for discontinuation, 52% of the patients should be reviewed for possible re-initiation of treatment with a cardiovascular agent.

After the establishment of evidence-based medicine after myocardial infarction and the sub-optimal drug use in the general population, we aimed to determine the effects of prescription patterns as observed in daily practice in **Chapter 5**.

Given the inconclusive evidence from randomised clinical trials on combination therapy after myocardial infarction, the widespread use of it, and the implausible large risk reductions ascribed to combination treatment reported in other studies, we aimed to determine the effect of the number of different drugs with a compliance of at least 70% on recurrent admission for myocardial infarction in patients with a history of myocardial infarction in a nested case control study in the PHARMO Record Linkage System (**Chapter 5.1**). Analysis of 389 cases who were matched to 2,344 controls during or study period from January 1, 1991 till December 31, 2000 revealed that the use of one drug was associated with a 7% odds reduction for admission for recurrent myocardial infarction. The use of two or three drugs was associated with reductions of 24 and 38% respectively. Addition of each single drug caused a 14% reduction. This odds reduction of adding one drug seems to be of the same magnitude as the risk reduction established in randomised clinical trials (10-40%, dependent on the specific agent). So multiple drug treatment decreases admissions for recurrent myocardial infarction in patients with a history of myocardial infarction and every addition of a drug, regardless of drug class, reduces the risk even further. These results support the treatment strategies as applied in daily practice.

Results from Chapter 3 and Chapter 4 showed that non-persistence with preventive treatment is cannot be swept away. Untimely discontinuation of preventive treatment may withhold long-term benefits concerning cardiovascular morbidity and mortality from patients who were eligible for treatment at first. However, it is still unknown whether discontinuation of statin treatment will have acute effects in patients without previous myocardial infarction. Therefore, we determined the effect of discontinuation of statin treatment on first acute myocardial infarction within 30 days after discontinuation in a general population **Chapter 5.2**. In a nested case-control study in the PHARMO database analysis of 450 cases and matched 2413 controls recent discontinuation was not associated with an immediately increased risk of first MI (adjusted OR 0.96). In patients without any prior cardiovascular disease an essentially similar effect was observed (adjusted OR 1.59). In patients with prior CHD a more profound though non-significant effect of discontinuation of statin therapy on

the occurrence of a first MI was observed (adjusted OR 2.21). These results indicate that patients without prior myocardial infarction who discontinue statin treatment do not seem to be at increased risk of myocardial infarction within 30 days after discontinuation. In patients with previous CHD, the presence of an association between recent discontinuation of statin treatment and acute myocardial infarction remains inconclusive.

In **Chapter 6** we developed two interventions to improve the quality of preventive pharmacotherapy. The patterns of drug use as observed in Chapter 3 suggested two opportunities to improve the quality of preventive drug treatment: interventions towards physicians with the objective to initiate treatment in patients who have been untreated so far and interventions towards both patients and health care professionals to improve long term persistence with treatment that is already initiated.

In **Chapter 6.1** we developed and evaluated a peer review group (PRG) meeting using feedback data on a patient level to improve the quality of drug therapy for prevention of recurrent myocardial infarction. The intervention was based on the principles of group academic detailing. This PRG meeting consisted of: scoring the current cardiovascular treatment on separate forms for each patient, a presentation and discussion of an overview of evidence based medicine after myocardial infarction, defining the target population, formulating a binding consensus and marking patients who were eligible for improvement of pharmacotherapy. Drug use and adherence to the newly formulated consensus was assessed at baseline and at one year after the intervention. At twelve months after the PRG meeting, 40% of the patients who were subject to the intervention and who were not treated according the PRG consensus at baseline did receive treatment according to the consensus. Comparison with an external control group using logistic regression revealed a prevalence ratio of 4.2. Although a previous observational study stated that PRG meetings do not improve the quality of pharmacotherapy, we believe that our results, obtained in an intervention study in daily practice, still stands and PRG meetings can be a valuable tool to improve pharmacotherapy.

Secondly, we developed an intervention to improve long-term persistence with treatment that was directed towards patients (**Chapter 6.2**). A pharmacist-led pharmaceutical care program for dyslipidemic patients who started statin treatment was designed and 26 community pharmacies in the Netherlands participate in this randomised multi-centre trial. New users of statins are enrolled in the study, and randomised to a pharmaceutical care program or usual care.

The pharmaceutical care program consists of five consecutive visits during which patients receive education on statin treatment from their pharmacist, starting at first dispensing of the statin prescription. At 3, 6, and 12 months, cholesterol levels will be measured, compliance calculated and the relation between cholesterol level and compliance discussed. At baseline, 6 months and 12 months patients from both groups will receive questionnaires on background (at baseline), lifestyle, health status and satisfaction with intervention program (at 12 months). Finally, one-year persistence of statin treatment will be determined. Secondary outcomes will be compliance, cholesterol level, life style, and side effects of statin treatment. As we expected an increase in persistence from 67 to 76% and the statistical power and a type I error alpha were set at 80% and 0.05 (two-sided) respectively, the required sample size is 394 patients in both arms. Given these calculations and considering 20% loss of patients during the study we aim at including a conservative number of 1,000 patients in the study.
So far 810 patients have been included in the study. Data on self-perceived health and lifestyle modifications were available for 285 patients. Perceived health and lifestyle modifications did not differ between intervention group and usual care group at baseline and at 6 months. For 105 patients in the intervention arm, reports on compliance and cholesterol levels were available. Compliance was high (97%) but only 47% of the patients had reached target cholesterol level.
Awaiting definite results, this study is the first multi-centre trial in the Netherlands that evaluates the effect of a pharmaceutical care program on persistence and compliance with lipid lowering drug therapy. This pharmaceutical care program reflects the present shift from prescription-orientated pharmacy towards patient-orientated pharmacy.

Finally, in **Chapter 7**, the main findings of the research presented in this thesis are discussed. The different studies are put into perspective of each other and related to literature. Finally the current role of the pharmacist in the field of prevention of cardiovascular diseases and the future role of the pharmacist are outlined. Given the complexity of prevention of cardiovascular disease and the involvement of patients, general practitioners, consultant cardiologists as well as pharmacists, a multi-disciplinary approach like advocated in the concept of concordance seem to be timely. As pharmacists are familiar with systematic and critical reappraisal of patients' drug use, pharmacists should take the initiative in starting a multi-specialty team to improve drug treatment for cardiovascular disease. The research presented in this thesis has shown that pharmacists-led

interventions can be a valuable tool to improve the quality of preventive pharmacotherapy. Successful incorporation of concordance in daily practice could make sure that no patients stay deprived from the benefits from preventive treatment unnecessarily, unless explicitly chosen for grounded reasons.

9

SAMENVATTING

Het doel van het in dit proefschrift beschreven onderzoek was het schetsen van een volledige cyclus ten einde de kwaliteit van farmacotherapie ter voorkoming van hart- en vaatziekten te verbeteren. Deze cyclus omvat een overzicht van evidence-based secundaire preventie van het hartinfarct, het in kaart brengen van de kwaliteit van de behandeling van patiënten met een doorgemaakt hartinfarct in Nederland, het achterhalen van de redenen waarom preventieve medicatie niet langdurig wordt gebruikt en het bepalen van de gevolgen van (sub)optimaal gebruik van medicatie ter voorkoming van hart- en vaatziekten. Uiteindelijk worden enkele voorbeelden van farmaceutische patiëntenzorg interventies gegeven die de kwaliteit van de behandeling van patiënten met hart- en vaatziekten kunnen verbeteren.

Er is veel onderzoek gedaan naar de mogelijkheden om mortaliteit en morbiditeit van patienten met een doorgemaakt hartinfarct te verlagen, wat heeft geleid tot richtlijnen voor de behandeling hiervan. Deze richtlijnen zijn echter niet erg uitgesproken over het gebruik van combinaties van verschillende geneesmiddelen. In het licht van het belang van secundaire preventie van hart- en vaatziekten, het gebrek aan duidelijke aanbevelingen betreffende combinatie therapie en de wijdverbreide toepassing van combinatie therapie in de dagelijkse praktijk was een actueel overzicht van de literatuur op dit gebied gewenst. Dit overzicht wordt beschreven in **Hoofdstuk 2**. Relevante literatuur werd gezocht in Medline en de Cochrane Library. Gerandomiseerde onderzoeken en meta-analyses werden opgenomen in ons overzicht indien zij voldeden aan criteria betreffende de randomisatie procedure, beschrijving van de gebruikte methoden, hartinfarcten, duur van het onderzoek en gemeten uitkomsten. Uit de gerandomiseerde onderzoeken en meta-analyses kwam naar voren dat thrombocytenaggregatieremmers, orale anticoagulantia (in toereikende dosering), ACE-remmers en statines de kans op mortaliteit en een nieuw hartinfarct na een eerder hartinfarct verlagen. Calciumantagonisten, anti-arrhythmica en hormoonsuppletie hebben deze gunstige effecten niet.
De effecten van het gecombineerde gebruik van thrombocyten-aggregatieremmers of orale anticoagulantia met betablokkers of ACE-remmers kunnen alleen geschat worden op basis van subgroep analyses en lijken dan gunstig. Op basis van de beschikbare literatuur kan dan ook gesteld worden dat gecombineerd gebruik van een thrombocytenaggregatieremmer of een oraal anticoagulans met een betablokker of een ACE-remmer samen met een statine de standaardbehandeling zou moeten zijn na een doorgemaakt hartinfarct. Behandeling met clopidogrel zou een alternatief voor een thrombocyten-

aggregatieremmer kunnen zijn indien deze niet wordt verdragen. Routinematig toevoegen van een betablokker aan een ACE-remmer bij patiënten met hartfalen lijkt voorbarig.

In **Hoofdstuk 3** wordt het gebruik van de middelen die in Hoofdstuk 2 een gunstig effect op het verlagen van mortaliteit en morbiditeit na een doorgemaakt hartinfarct hadden in kaart gebracht voor de Nederlandse situatie. Hiervoor werden gegevens uit de PHARMO database gebruikt. In **Hoofdstuk 3.1** is het gebruik van orale antithrombotica (dit zijn thrombocyten-aggregatieremmers en orale anticoagulantia samen) beschreven. Retrospectieve analyse van apotheekaflevergegevens van 3800 patiënten tussen 1988 en 1998 laat een toename in het gebruik van orale antithrombotica zien van 54.0 procent tot 88.9 procent. Niet alle patienten hebben echter in gelijke mate van deze toename geprofiteerd; in 1998 wordt 75.8 procent van de patiënten die eind jaren '80 een hartinfarct heeft gehad adequaat behandeld terwijl 94.4 procent van de patiënten die in de tweede helft van de jaren '90 een hartinfarct kreeg adequaat behandeld wordt. Deels zal het niet behandeld worden verklaard worden doordat sommige patiënten de medicatie niet verdragen. Waneer echter de mate waarin intolerantie voor thrombocytenaggregatieremmers voorkomt (8.5 tot 13 procent van de patiënten) wordt afgezet tegen het deel van de patiënten dat bijvoorbeeld eind jaren '80 een hartinfarct heeft gehad en in 1998 niet wordt behandeld (24.2 procent) blijkt dat intolerantie voor geneesmiddelen iet de enige verklaring kan zijn voor het niet optimaal behandeld worden. Nu de mate van onderbehandeling is gekwantificeerd kan hieruit berekend worden hoeveel nieuwe hartinfarcten voorkomen hadden kunnen worden wanneer alle patiënten na een hartinfarct wel behandeld zouden zijn met orale antithrombotica. Uitgaande van een 'number-needed-to-treat' van 56 hadden in heel Nederland 1469 niet-fatale hartinfarcten voorkomen kunnen worden tussen 1998 en 1998 wanneer alle patiënten met een doorgemaakt hartinfarct behandeld waren met orale antithrombotica. Dit op zich zou al voldoende reden moeten zijn om na te gaan of alle patiënten met een doorgemaakt hartinfarct wel behandeld worden met orale antithrombotica.
In **Hoofdstuk 3.2** is de horizon verbreed en naast orale antithrombotica ook het gebruik van betablokkers, ACE-remmers, statines en combinaties van deze middelen in kaart gebracht. Wederom werd de PHARMO database gebruikt voor de bestudering van zowel ontslagmedicatie als het gebruik van medicatie na ontslag uit het ziekenhuis gedurende een periode van 12 jaar. Gegevens waren

beschikbaar voor 4007 patiënten die een hartinfarct hadden tussen 1991 en 2000. Het gebruik van thrombocytenaggregatieremmers en statines direct na ontslag uit het ziekenhuis nam in deze periode toe van respectievelijk 42 en 5 procent tot 88 en 58 procent. Ook nam het gebruik van deze middelen toe bij patiënten die langer geleden een hartinfarct hadden gehad. Het gebruik van betablokkers en ACE-remmers nam voornamelijk toe bij patiënten die kort geleden uit het ziekenhuis waren ontslagen (respectievelijk van 49 tot 76 procent en van 19 tot 44 procent). Het gecombineerd gebruik van de verschillende geneesmiddelen nam explosief toe; in 1991 kreeg 47 procent van de patiënten enige combinatie bij ontslag uit het ziekenhuis, terwijl in 2000 90 procent van de patiënten het ziekenhuis verliet met ene combinatie van geneesmiddelen. Echter, één jaar na ontslag gebruikte 32 procent van de patiënten de hen voorgeschreven combinatie van geneesmiddelen niet meer, terwijl dit percentage was opgelopen tot 57 procent vijf jaar na ontslag.
De resultaten in Hoofdstuk 3 laten zien dat de secundaire preventie na een doorgemaakt hartinfarct in Nederland niet optimaal is. Nadere bestudering van de gegevens suggereert dat de behandeling verbeterd zou kunnen worden door enerzijds de behandeling te starten bij patiënten die tot op heden nog niet behandeld werden en anderzijds de patiënten die al wel behandeld worden te stimuleren om deze behandeling niet voortijdig te staken.

Aangezien het voortijdig staken van de behandeling een van de oorzaken leek te zijn voor de suboptimale behandeling na een hartinfarct, is in **Hoofdstuk 4** getracht de redenen voor dit voortijdige staken te achterhalen. Uitgaande van de beschikbare literatuur en richtlijnen zouden patiënten gedurende lange tijd behandeld moeten worden. Voortijdig stoppen van geneesmiddelen kan dan dus resulteren in te vermijden morbiditeit en mortaliteit. Voortijdig stoppen met chronisch bedoelde medicatie kan ook bekeken worden vanuit een economisch perspectief. Hiertoe worden de kosten gemoeid met chronische medicatie die voortijdig gestopt is uitgedrukt als economisch verlies. Deze zienswijze gaat er dan echter vanuit dat elk geval waarin chronische medicatie voortijd gestopt wordt ongewenst is. Dit is echter nog maar de vraag. Waneer de reden waarom een patiënt gestopt is met de voorgeschreven medicatie bekend is, zou kunnen worden bepaald of het stoppen inderdaad ongewenst is en kan vervolgens bekeken kunnen worden of de patiënt in aanmerking komt om de gestopte medicatie of vervangende medicatie te (her)starten.
In **Hoofdstuk 4.1** worden de 3-jaars persistentie van statine gebruik, de redenen voor stoppen van statine gebruik en voorspellende factoren van dit

stoppen beschreven. In negen openbare apotheken in Nederland werden patiënten en hun huisartsen benaderd. Van de 425 geselecteerde patiënten waren er drie jaar na het eerste statine recept 104 patiënten (24%) gestopt. Volgens de huisartsen hadden de meeste patiënten het statine gebruik op eigen initiatief gestaakt, terwijl de patiënten bijwerkingen meldden als voornaamste reden om het statine gebruik te staken. 56% van de patiënten die de behandeling met een statine hadden gestaakt konden geen reden melden die paste in een behandeling die evidence-based was. Verminderde therapietrouw (< 80%) was geassocieerd met het staken van de voorgeschreven statine.
In **Hoofdstuk 4.2** werden de redenen om te stoppen met betablokkers achterhaald en werd in kaart gebracht in welke mate patiënten die gestopt waren in aanmerking kwamen voor heroverwegen van de behandeling met betablokkers. Uit telefonisch afgenomen interviews bleek dat 72% van de 29 geïnterviewde patiënten het gebruik van betablokkers had gestaakt in overleg met de arts. Bijwerkingen waren de voornaamste reden om de behandeling te staken. Wanneer de reden voor stoppen en eventuele vervanging door andere geneesmiddelen in overweging werden genomen, zou 52% van de patiënten die gestopt waren met de voorgeschreven betablokker in aanmerking komen om behandeling met cardiovasculaire medicatie te hervatten.

Nadat in Hoofdstuk 2 beschreven was hoe patiënten na een doorgemaakt hartinfarct zouden moeten worden behandeld en in de Hoofdstukken 3 en 4 naar voren kwam dat de behandeling in de dagelijkse praktijk niet optimaal is, zijn in **Hoofdstuk 5** de gevolgen van de behandeling zoals die in de dagelijkse praktijk onderzocht.
In **Hoofdstuk 5.1** is het effect van verschillende combinaties van geneesmiddelen die ten minste met 70% therapietrouw werden gebruikt onderzocht op het optreden van een nieuw hartinfarct bij patiënten die eerder een hartinfarct hadden doorgemaakt. Deze vraag was relevant gezien het gebrek aan duidelijke resultaten uit gerandomiseerde onderzoeken betreffende gecombineerd gebruik van verschillende middelen, de wijdverbreide toepassing van combinatie therapie en de onwaarschijnlijk grote effecten van combinatietherapie die uit een eerder gepubliceerd observationeel onderzoek naar voren kwamen.
Uit analyse van 389 cases en 2344 daarmee gematchte controles tijdens de studie periode van 1 januari 1991 tot 31 december 2000 kwam naar voren dat het gebruik van één preventief middel met een therapietrouw van ten minste 70%

de kans op een nieuw hartinfarct met 7% verlaagde (odds reductie). Het gebruik van twee of drie middelen verlaagde de kans met respectievelijk 24 en 38%. Elke toevoeging van één middel zorgde voor een afname van de kans op een nieuw hartinfarct van 14%. Deze afname lijkt in dezelfde orde van grootte te liggen als de afname die gerapporteerd is in gerandomiseerde onderzoeken (10-40%, afhankelijk van het betreffende middel). Op basis van het hier uitgevoerde onderzoek kan gesteld worden dat combinatie therapie de kans op ene nieuw hartinfarct verlaagt in patiënten die eerder een hartinfarct hebben doorgemaakt. Elke toevoeging van een preventief middel dat als monotherapie bewezen effectief is verlaagt de kans op een hartinfarct nog verder, onafhankelijk van het soort middel.
Uit Hoofdstuk 3 en 4 bleek al dat stoppen met preventieve medicatie frequent voorkomt. Op basis van eerder onderzoek kan dan gesteld worden dat voortijdig staken van chronisch bedoelde therapie nadelig kan zijn voor patiënten omdat zij hierdoor niet profiteren van de gunstige effecten van de medicatie op lange termijn. Of het staken van bijvoorbeeld statines ook een ongunstig effect heeft op de korte termijn is tot op heden niet duidelijk. In **Hoofdstuk 5.2** is een geneste case-control onderzoek beschreven naar de acute effecten van het stoppen van behandeling met statines. Bestudering van 450 cases en 2413 daarmee gematchte controles in de PHARMO database laten zien dat de kans op en hartinfarct niet geassocieerd is met het recent staken van statine gebruik (odds ratio 0.96). Ook in subgroepen van patiënten zonder hart- en vaatziekten in hun voorgeschiedenis en in patiënten die wel coronaire hartziekten in hun voorgeschiedenis hadden was er geen statistisch significant verband tussen staken van statine gebruik en het optreden van hartinfarcten (odds ratio's respectievelijk 1.59 en 2.21). Deze resultaten lijken erop te wijzen dat patiënten zonder doorgemaakt hartinfarct geen verhoogd risico lopen op het krijgen van een hartinfarct vlak na het stoppen met een statine. Over patiënten met coronaire hartziekten in hun voorgeschiedenis kunnen op basis van dit onderzoek geen definitieve uitspraken gedaan worden.

In **Hoofdstuk 6** worden twee interventies beschreven die als doel hebben de kwaliteit van farmacotherapie ter voorkoming van hart- en vaatziekten te verhogen. Uit Hoofdstuk 3 was naar voren gekomen dat er ruwweg twee routes waren om de kwaliteit te verbeteren. Enerzijds interventies gericht op voorschrijvers met als doel de niet adequaat behandelde patiënten op te sporen ten einde preventieve medicatie bij deze patiënten te (her)starten. Anderzijds

kunnen interventies gericht zijn op patiënten om zo het langdurig gebruik van medicatie te promoten en voortijdig staken te voorkomen.
In **Hoofdstuk 6.1** wordt een interventie beschreven in de vorm van een farmacotherapeutisch overleg (FTO) waarin door terugkoppeling van prescriptiecijfers op individueel patiëntniveau is getracht de kwaliteit van de behandeling van patiënten met een doorgemaakt hartinfarct te verbeteren. Het programma van de FTO bijeenkomst bestond uit het per patiënt in kaart brengen van de huidige behandeling van patiënten met een doorgemaakt hartinfarct, een presentatie over evidence-based behandelen na een hartinfarct, bediscussiëren van deze materie, bepalen van de doelgroep, formuleren van een bindende consensus hoe deze patiënten te behandelen en het markeren van patiënten die voor verbetering van de behandeling in aanmerking kwamen. Evaluatie vond plaats 12 maanden na de FTO bijeenkomt. Van de besproken patiënten die voorheen niet conform de vastgestelde consensus werden behandeld werd na 12 maanden 40% wel volgens de consensus behandeld. Hiermee lag de prevalentie ratio op 4.2 wanneer deze groep vergeleken werd met een externe controle groep met behulp van logistische regressie. Hoewel eerder op grond van observationeel onderzoek werd gesteld dat FTO bijeenkomsten niet bijdragen aan het verbeteren van de kwaliteit van farmacotherapie, kan op grond van onze onderzoeksresultaten gesteld worden dat FTO bijeenkomsten wel degelijk bijdragen aan de verbetering van farmacotherapie.
Vervolgens wordt in **Hoofdstuk 6.2** een interventie gericht op startende statine gebruikers beschreven dat als doel heeft de persistentie van het statinegebruik te bevorderen. Er werd een farmaceutisch patiëntenzorg programma ontwikkeld waarbij startende statine gebruikers intensief worden begeleid door hun apotheker. Dit gerandomiseerde onderzoek wordt uitgevoerd in 26 Nederlandse openbare apotheken. Startende statine gebruikers worden gerandomiseerd over twee groepen; een groep die deelneemt aan het farmaceutisch patiëntenzorg programma en een groep die de gebruikelijke zorg krijgt. Het programma bestaat uit vijf contactmomenten tussen de patiënt en de apotheker met als eerste moment de eerste uitgifte van de statine. Na 3, 6 en 12 maanden meet de apotheker het cholesterolgehalte, berekent de therapietrouw en bespreekt het verband tussen therapietrouw en cholesterolwaarden met de patiënt. Bijwerkingen en eventuele problemen worden besproken tijdens alle afspraken. Bij aanvang van het onderzoek en na 6 en 12 maanden ontvangen beide groepen patiënten vragenlijsten met vragen over hun achtergrond (bij aanvang van het

onderzoek), leefgewoonten, gezondheid en mening over het onderzoek (na 12 maanden). Uiteindelijk wordt het effect van het programma op de 1-jaars persistentie bepaald. Tevens worden uitkomstmaten als therapietrouw, cholesterolwaarden, veranderingen in leefgewoonten en bijwerkingen meegenomen. Om een verandering in 1-jaars persistentie van 67 naar 76% aan te kunnen tonen uitgaande van een statistische power van 80% en een type I fout van alfa = 0,05 (twee-zijdig) dienen er 394 patiënten in elke arm ingesloten te worden. Wanneer vervolgens rekening gehouden wordt met een uitval van ten hoogste 20% moeten er 1000 patiënten worden geïncludeerd.
Tot op heden nemen er 810 patiënten deel aan het onderzoek. Gegevens over zelf gerapporteerde gezondheid en veranderingen in leefgewoonten zijn beschikbaar voor 285 patiënten. Gerapporteerde gezondheid en veranderingen in leefgewoonten verschillen niet tussen beide groepen. Van 105 patiënten die het farmaceutisch patiëntenzorg programma aangeboden hebben gekregen zijn cholesterolwaarden en therapietrouw bekend. De therapietrouw was hoog (97%) maar slechts 47 procent van de patiënten had een totaal cholesterol onder de streefwaarde van 5,0 mmol/L.
In afwachting van definitieve resultaten is dit onderzoek vooralsnog het eerste Nederlandse gerandomiseerde multi-center onderzoek waarbij de effecten van een farmaceutisch patiëntenzorg programma op persistentie en therapietrouw van statine gebruik worden gemeten. Dit programma is een voorbeeld van de huidige verandering van de recept gestuurde apotheek praktijk naar de situatie waarin de patiënt centraal staat.

Tot slot worden in **Hoofdstuk 7** de belangrijkste resultaten van het onderzoek beschreven in dit proefschrift besproken. De verschillende onderzoeken worden gerelateerd aan elkaar en aan ander gepubliceerd onderzoek. Ook wordt de rol die de apotheker zowel nu als in de toekomst kan spelen op het gebied van preventie van hart- en vaatziekten geschetst. Gezien de complexiteit van farmacotherapie ter preventie van hart- en vaatziekten en de betrokkenheid van patiënten, huisartsen, specialisten en apothekers leent deze materie zich uitermate goed voor het in praktijk brengen van het begrip 'concordance'. Aangezien apothekers al gewend zijn om te werken met prescriptiecijfers en projectmatig het gebruik van medicatie door groepen patiënten met een bepaalde aandoening te beoordelen, zouden zij het voortouw moeten nemen in het opzetten van een multidisciplinair overleg ten einde de kwaliteit van farmacotherapie ter preventie van hart- en vaatziekten te verhogen. Het onderzoek beschreven in dit proefschrift laat zien dat door de apotheker geïnitieerde interventies waardevolle

initiatieven kunnen zijn waarmee de behandeling van patiënten verbeterd wordt. Het met succes handen en voeten geven aan 'concordance' in de dagelijkse praktijk kan ervoor zorgen dat patiënten niet verstoken blijven van de gunstige effecten van preventieve farmacotherapie, tenzij daar op basis van zorgvuldige afwegingen expliciet voor gekozen is.