ACUTE CORONARY SYNDROMES

Effect of drug combinations on admission for recurrent myocardial infarction

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Objective: To determine the effect of the number of different drugs with adherence to medication of at least 70% on recurrent admission for myocardial infarction (MI) in patients with a history of MI.
Design: Nested case–control study in a dynamic cohort.
Setting: PHARMO database that contains pharmacy dispensing records and hospital discharge records of 350 000 Dutch citizens.
Subjects: All patients admitted to hospital for first MI (ICD-9 410) from 1991 to 2000 with at least a 30-day survival after admission. Cases were admitted for recurrent MI and were matched for age, sex, and year of admission with controls who did not have a recurrent MI.
Main outcome measure(s): Odds ratio with 95% CI for admission for recurrent MI. Exposure was the number of preventive drugs (antiplatelet agents, statins and β blockers or ACE inhibitors) used for at least 70% of the time.
Results: 389 cases were matched with 2344 controls. The use of one drug was associated with a 6% odds reduction (95% CI 30% reduction to 28% increase) for admission for recurrent MI. The use of two or three drugs was associated with reductions of 26% and 41% (47% reduction to 3% increase and 6% to 63% reduction, respectively). Addition of one drug caused a 16% reduction (4% to 26%).
Conclusions: Multiple drug treatment decreases admissions for recurrent MI in patients with a history of MI. 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.

Randomised clinical trials have shown that preventive pharmacotherapy lowers mortality and morbidity after myocardial infarction (MI), one of the most prevalent causes of death in developed countries.[1–3] In particular, the long-term use of oral antithrombotic agents (ie, antiplatelet agents and oral anticoagulants), β blockers, angiotensin converting enzyme inhibitors (ACE inhibitors) and statins proved to be beneficial in randomised clinical trials.[4–8] Nearly all 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 antiplatelet agents 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 β 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] but negative interaction between ACE inhibitors and antiplatelet agents was also mentioned.[16]

International guideline committees assumed additive effects of drug combinations and recommend continuing combination treatment after MI.[17 18] Wald and Law have proposed combining multiple drug treatment in a ''polypill''. Their estimate of the effect of the polypill strategy on ischaemic 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 and Coupland studied the effect of combinations of drugs on the secondary prevention of all-cause mortality in a nested case–control study.[20] Current use of combinations of antiplatelet agents, statins and β blockers improved survival in high-risk patients, whereas the addition of ACE inhibitors did not offer additional benefits. The duration of drug use and medication adherence 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, owing to the close monitoring of patients in such trials. It seems therefore appropriate to study the extent of exposure, over a longer period of time, on the effectiveness of secondary prophylaxis after MI in daily clinical practice.

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

METHODS

We performed a 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 eight 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 for prescription drugs are virtually complete. The computerised drug-dispensing histories contain information about 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 Classification. The hospital discharge records are obtained from Prismant, an institute that collates nation wide all hospital discharge records in the Netherlands since the 1960s into a standardised format.[22] These records include detailed information concerning the primary and

Abbreviations: CABG, coronary artery bypass grafting; CHF, chronic heart failure; MI, myocardial infarction; OR, odds ratio; PDC, percentage of days covered; PTCA, percutaneous transluminal coronary angioplasty

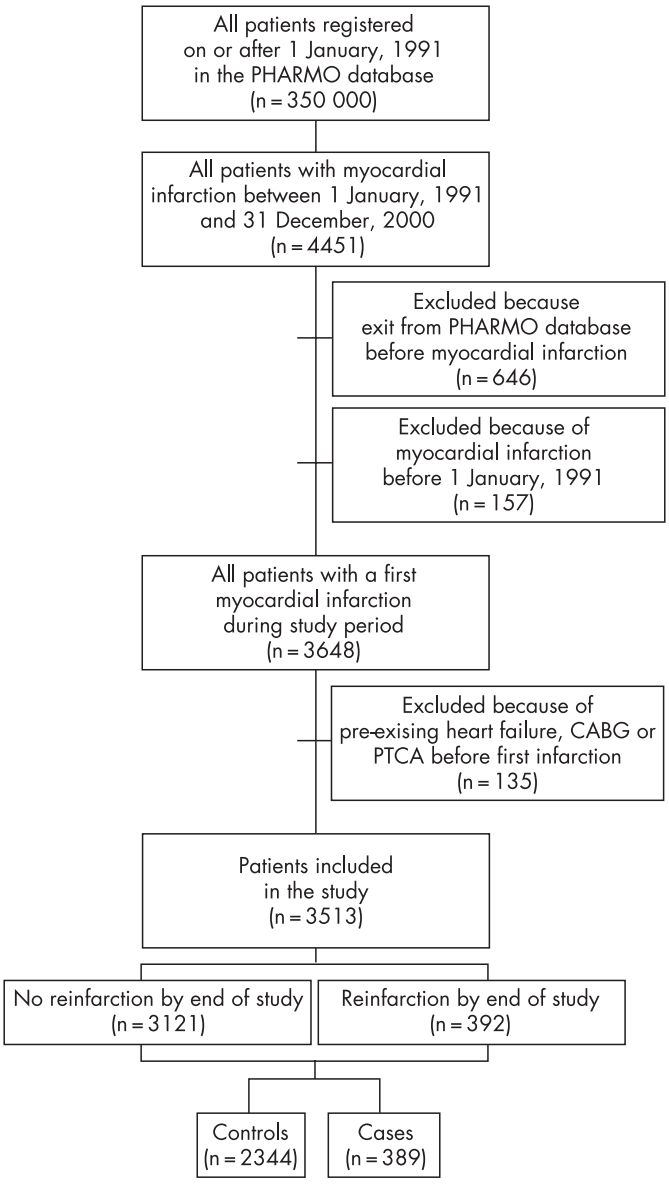

Figure 1 Selection of patients.

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 in the hospital according to the International Classification of Diseases, 9th edition (ICD-9-CM).

Participants

We identified all patients in the PHARMO database admitted to hospital for first MI (ICD-9 410) between 1 January 1991 and 31 December 2000. Patients with an MI before 1 January 1991 and patients with less than 30-days' survival after their first MI were excluded. Moreover patients with pre-existing congestive heart failure (CHF), percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) before their first MI were excluded (fig 1).

Definition of cases and controls

We defined cases as patients with a history of MI who had a recurrent MI during follow-up. Follow-up continued until the last date of registration in the database but no later than 31 December 2003. Registration could end owing to death or movement outside the catchment area. Index date was the date of admission for recurrent MI.

We defined controls as patients with a history of MI but without a recurrent MI during follow-up who were in the database at the index date of the matching case.

Cases were matched with up to 10 controls by age (5-year band), sex and year of admission for first MI.

Exposure

We determined the exposure to four classes of drugs: antiplatelet agents, β blockers, ACE inhibitors and statins. Patients were considered to be "exposed" if they received medication for at least 70% of the time. The four drug classes were combined into three categories: antiplatelet agents, statins, and β blockers and/or ACE-inhibitors. β Blockers and ACE inhibitors were considered together as results from clinical trials and restricted applicability due to contraindications and adverse effects in daily practice should result in the use of at least a β blockers or an ACE inhibitor.[7] Assuming additive effects of similar magnitude for 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 the first MI and the index date. This resulted in a score that ranged from 0 to 3.

We calculated the percentage of days patients were exposed to antiplatelet agents, statins and β blockers and/or ACE inhibitors between the first MI and the 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 of the next prescription was shifted to the theoretical end date of the previous prescription (fig 2). Dispensing dates were shifted at most by 30 days to avoid disproportionate accumulation. This way of construction of episodes and estimation of drug use has been described in full by Mantel-Teeuwisse *et al*.[23] The PDC was calculated by dividing the summed duration of the episodes in the time between the first MI and the index date.

Analysis

We used conditional logistic regression to calculate odds ratios for admission for recurrent MI and 95% confidence intervals.

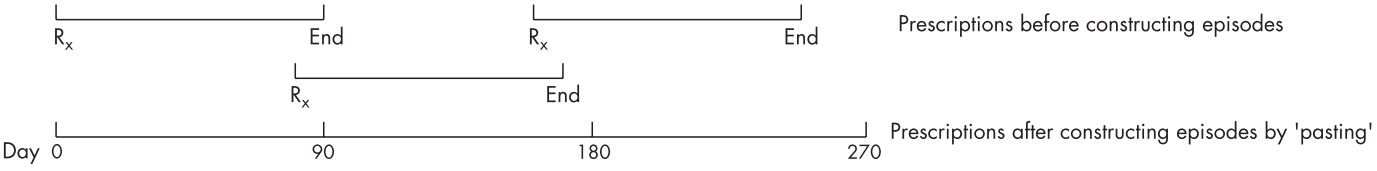

Figure 2 Construction of episodes of drug use by "pasting" subsequent prescriptions. Patient receives three consecutive prescriptions with 90 days' drug supply on days 0, 80 and 160. Each new prescription is dispensed before the end of the expected duration of use of the previous prescription. It is presumed that these new prescriptions are started at the time the previous prescription should be finished.

Table 1 Baseline characteristics of cases and controls

Characteristics	Cases (n = 389)	Controls (n = 2344)	p Value
Age at index date, mean (SD)	66.8 (11.7)	66.0 (11.3)	0.216
Number of months between first MI and index date, mean (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 between first MI and index date (PDC >70%)			
Antiplatelet agent	197 (50.6)	1314 (56.1)	0.047
β 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
β Blocker and/or ACE inhibitor	253 (65.0)	1491 (63.6)	0.587
Comorbidity or comedication			
Admission for CHF after first MI	15 (3.9)	67 (2.9)	0.285
PTCA or CABG procedure after first MI	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 antiarrhythmic drugs	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

Results are shown as number (%) unless otherwise stated.
CABG, coronary artery bypass grafting; CHF, chronic heart failure; MI, myocardial infarction; PDC, percentage of days covered; PTCA, percutaneous transluminal coronary angioplasty.

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 by conditional logistic regression for the following potential confounders: diabetes mellitus, angina pectoris, use of calcium channel blockers, antiarrhythmic drugs, digoxin and oral anticoagulants, admission for CHF, PTCA, and CABG after first MI. At least one prescription for an antidiabetic drug between the first MI and the index date was considered to be an indicator for diabetes mellitus.[24] At least two nitrate prescriptions between the first MI and the index date were considered to be an indicator for angina pectoris.[25] Use of calcium channel blockers, antiarrhythmic drugs, digoxin and oral anticoagulants was defined as having obtained at least one prescription between the first MI and the 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 4451 patients with MI between 1 January 1991 and 31 December 2000. Overall incidence of MI was 15.3 per 10 000 person-years (all ages and both sexes). Of the 4451 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 MI. Furthermore 157 patients were excluded due to admission for MI before 1 January 1991 and 135 patients were excluded because of admission for CHF, PTCA or CABG before the admission for first MI. Therefore, 3513 patients were eligible for participation in the study. By the end of the study period 392 patients had a re-current MI and 3121 patients did not have had a recurrent MI at the end of the study (fig 1).

Table 2 Distribution of drug combinations used for at least 70% of the time

Drugs	Case (n = 389)	Controls (n = 2344)
None	90 (23.1)	491 (20.9)
Antiplatelet agent alone	43 (11.1)	261 (11.1)
β 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)
Antiplatelet agent and β blocker	82 (21.1)	428 (18.3)
Antiplatelet agent and ACE inhibitor	13 (3.3)	86 (3.7)
Antiplatelet agent and statin	4 (1.0)	107 (4.6)
β Blocker and ACE inhibitor	23 (5.9)	84 (3.6)
β Blocker and statin	2 (0.5)	40 (1.7)
ACE inhibitor and statin	2 (0.5)	24 (1.0)
Antiplatelet agent, β blocker and ACE inhibitor	18 (4.6)	115 (4.9)
Antiplatelet agent, β blocker and statin	25 (6.4)	215 (9.2)
Antiplatelet agent, ACE inhibitor and statin	1 (0.3)	31 (1.3)
β Blocker, ACE inhibitor and statin	3 (0.8)	30 (1.3)
Antiplatelet agent, β blocker, ACE inhibitor and statin	11 (2.8)	71 (3.0)

Values are numbers (%).

Case–control analysis

Of the 392 possible cases with recurrent MI during the study period, 389 cases could be matched by age, gender and year of admission for first MI with 2344 controls. Cases and controls were well matched at baseline (table 1). Mean duration between the first MI and the index date was 32.6 months for cases and 30.7 months for controls. Cases were less often treated with antiplatelet agents and statins for at least 70% of the time between the first MI and the index date. Cases had a higher prevalence of angina pectoris and tended to have diabetes mellitus more often. Table 2 shows the use of different combinations of antiplatelet agents, β blockers, ACE inhibitors and statins. An antiplatelet agent plus a β blocker was the most commonly used drug treatment, with a PDC of at least 70%.

Table 3 shows the adjusted and unadjusted odds ratio for the different number drugs used compliantly. Odds ratios were adjusted for diabetes mellitus, angina pectoris, use of calcium channel blockers, antiarrhythmic drugs, digoxin and oral anticoagulants, admission for CHF, PTCA and CABG after first MI. After adjustment, the use of one drug was associated with a 6% odds reduction (95% confidence interval (95% CI) 30% reduction to 28% increase) in odds for admission for recurrent MI, whereas the use of two or three drugs with a PDC of at least 70% was associated with an odds reduction of 26% and 41% (95% CI of 47% reduction to 3% increase and 6% to 63% reduction, respectively). Addition of one drug caused a 16% reduction in the odds for recurrent MI (95% CI of 4% to 26%).

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.

Treatment score (range 0–3)	Case (n = 389)	Control (n = 2344)	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 to 1.37	0.94	0.70 to 1.28
2 Drugs with PDC >70%	127 (32.6)	838 (35.8)	0.84	0.61 to 1.15	0.74	0.53 to 1.03
3 Drugs with PDC >70%	37 (9.5)	325 (13.9)	0.66	0.42 to 1.04	0.59	0.37 to 0.94
Addition of 1 drug with PDC>70%			0.88	0.77 to 1.01	0.84	0.74 to 0.96

Values are numbers (%).
OR, odds ratio; PDC, percentage of days covered.
*Adjusted for diabetes mellitus, angina pectoris, use of oral anticoagulants, antiarrhythmic drugs, digoxin and calcium channel blockers, admission for chronic heart failure and percutaneous transluminal coronary angioplasty or coronary artery bypass grafting procedure between first MI and index date.

DISCUSSION

Multiple drug treatment decreases admissions for recurrent MI in patients with a history of MI. Regardless of drug class, an additional drug known to prevent recurrent MI leads to an additional 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 the additive effects of different drug classes has been 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 comorbidities or recent MI. Furthermore, we included more women than were studied in randomised clinical trials.

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 other potential confounders such as the severity of the original MI, hypertension, dyslipidaemia, smoking status, body mass index and socioeconomic background. Further residual confounding due to unmeasured variables might be present. However, there is no indication that these confounders will be disproportionately distributed among cases and controls. This is an observational study and therefore provides less evidence than results from randomised clinical trials. However, given the lack of data from randomised clinical trials on the combined effect of different drugs on recurrent MI, results from observational studies may be very useful.

Second, in case–control studies odds ratios (ORs) 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 MI in the non-exposed, and the OR of 0.59 we reported for the use of three drugs with PDC >70%, the corresponding relative risk would be 0.64. Therefore we can state that the odds reductions we found closely approximate the risk ratios. Moreover the odds reduction in this study of adding one drug (16%; 95% CI 4 to 26%) is of the same magnitude as the risk reduction established in randomised clinical trials (30% for antiplatelet agents, 25% for β blockers, 10–25% for ACE inhibitors and 10–40% for statins).[7]

Third, we assumed that the preventive effects of the different drug classes are similar, both for the duration of treatment and the effect size. However, the different drug classes have very different pharmacodynamic effects. The platelet inhibitory effects of antiplatelet agents, for example, persist for 4–6 days, whereas the lipid-lowering effects and antiatherogenic action of statins take weeks to months. Therefore one might state that current treatment is suitable for use of antiplatelet agents, but the duration of exposure matters for statins. Nonetheless, randomised clinical trials showed benefits after treatment periods that ranged from 2 to 5 years and risk reductions of antiplatelet agents, β blockers, ACE inhibitors and statins seemed 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 from the four earlier mentioned drug classes (antiplatelet agents, β blockers, ACE inhibitors and statins) and incorporation of the degree of medication adherence 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 dispensed in the pharmacy. Although pharmacy dispensing does not imply that the patient always took the drug, there is no reason to suspect systematic bias between cases and controls in adherence to medication. Misclassification of exposure to β blockers, ACE inhibitors and statins seems to be unlikely too as drug-dispensing records on a patient are virtually complete owing to a strong patient–pharmacy liaison in the Netherlands, and these drugs are not available over the counter. Although antiplatelet agents are available over the counter, we can rule out the possibility that non-prescription antiplatelet agents have biased our results, for two reasons. First, in the Netherlands a prescription is required for these agents. Second, use of non-prescription acetylsalicylic acid of higher doses is negligibly low, as over the counter acetylsalicylic acid is not reimbursed by health insurance, whereas prescription antiplatelet agents are fully reimbursed. In the Netherlands, 98.6% of all inhabitants have a health insurance policy covering the costs for prescription drugs.[3]

In summary, this study shows that multiple drug treatment lowers the number of admissions for recurrent MI in patients with a history of MI. Furthermore, the magnitude of the risk reduction increases as the number of drugs used concomitantly increases. As only 13% of patients admitted to hospital for MI received at least three drugs and were adequately compliant, there seems to be a potential for the improvement of secondary prevention of ischaemic heart disease.

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