Oral Antithrombotic Use Among Myocardial Infarction Patients

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OBJECTIVE: To examine the use of oral antithrombotics (i.e., antiplatelet agents, oral anticoagulants) after myocardial infarction (MI) in the Netherlands from 1988 to 1998.

METHODS: Retrospective follow-up of 3800 patients with MI, using data from the PHARMO Record Linkage System.

RESULTS: From 1988 to 1998, oral antithrombotic treatment increased significantly from 54.0% to 88.9%. In 1998, only 75.8% of patients who experienced a MI in the late 1980s received oral antithrombotic treatment compared with 94.4% of those who experienced a recent MI.

CONCLUSIONS: Oral antithrombotics were considerably underused in patients with a past history of MI. Therefore, these patients should be reviewed for antithrombotic therapy to assess whether their failure to use oral antithrombotics was right or wrong, and whether treatment should be initiated if possible.

KEY WORDS: myocardial infarction, Netherlands, oral anticoagulants.

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The benefits of long-term treatment with oral antithrombotics (i.e., antiplatelet agents, oral anticoagulants) after myocardial infarction (MI) have been well established in an overview[1] of antiplatelet trials following MI. Therefore, all patients with a history of MI should receive long-term oral antithrombotic therapy, if it can be tolerated. The American College of Chest Physicians' (ACCP) guidelines[2,3] have recommended since 1989 the long-term use of aspirin for all patients without aspirin intolerance, while oral anticoagulants (e.g., acenocoumarol, warfarin) after MI have been reserved since 1986 for patients with aspirin intolerance and for patients with a typical indication for oral anticoagulants, such as atrial fibrillation and increased risk of embolization from left ventricular or left atrial clot. The European Society of Cardiology (ESC) guidelines[4] and the American College of Cardiology/American Heart Association (ACC/AHA) guidelines[5] have recommended the same since the first issue in 1994 and 1996, respectively. Up to their most recent updates in 1996, 1999, and 2001, respectively, the ESC guidelines,[6] the ACC/AHA guidelines,[7] and the ACCP guidelines[8] do not recommend concomitant treatment with aspirin and oral anticoagulants.

Most studies that evaluated the quality of oral antithrombotic treatment after MI focused 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 the hospital was assessed, the duration of follow-up was limited to 1 year.

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

Methods

We obtained anonymous data from the PHARMO Record Linkage System.[12] In this system, drug-dispensing data from all community pharmacies in 8 Dutch cities are linked to morbidity data from the nationwide

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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] date of delivery, amount dispensed, and prescribed daily dose were recorded in the database for every prescription. Morbidity data were coded according to ICD-9. Both drug-dispensing data and morbidity data were available from January 1, 1988, to December 31, 1998.

We selected patients who were admitted due to MI (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. If a patient was admitted for a recurrent MI, follow-up ended. After discharge from the 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 1 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 MI since January 1, 1988, who were still in the database during that year. Annual use was stratified by year of admission. We compared current use in 1998 among patients who experienced an MI in the late 1980s with current use among patients with MI in the late 1990s.

To be certain that the filling of 1 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 on 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 thrombosis services.

Results

We identified 4508 admissions due to MI from 1988 to 1998, which represents 1.77% of all MIs 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 the hospital, 3800 (84.3%) admissions remained in the study. Median age was 65 years, and 70.8% of the participants were male. In 195 cases, follow-up ended because of admission for a recurrent MI. 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 calcium urea salt, carbasalate calcium, was used in 95.5% of all cases (59.8% and 35.7%, respectively). Dipyridamole and ticlopidine were prescribed to 4.2% and 0.3% of all patients who received antiplatelet therapy. Six percent of the oral anticoagulant–treated patients received phenprocoumon and 94% received acenocoumarol.

The overall use of oral antithrombotics increased from 54.0% in 1988 (4.4%, 39.2%, and 10.4% for antiplatelet agents, oral anticoagulants, and a combination of both, respectively) to 88.9% in 1998 (69.5%, 13.2%, and 6.2%, respectively). Use of oral antithrombotics, stratified by year of admission, is shown in Figure 1. 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. Only 75.8% of the patients who experienced an MI in the late 1980s and were still in the database in 1998 were treated appropriately in 1998. Patients with MI in the late 1990s attained a level of oral antithrombotic treatment of 94.4% 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% of the patients who filled at least 1 prescription for an antiplatelet agent collected enough tablets to be more than 70% compliant during their follow-up period.

Discussion

Although antithrombotic treatment after MI increased during an 11-year period, current use of oral antithrombotics was lower among patients who experienced an MI in the late 1980s than among patients with MI in recent years. We recommend reviewing patients who do not receive oral antithrombotics to assess whether the alleged undertreatment is appropriate due to, for instance, intolerance, or inappropriate, in which case treatment should still be initiated.

In comparison to our results, previous studies[9-11] reported somewhat different levels of antiplatelet therapy. Martinez et al.[9] reported aspirin use at discharge of 28% in 1986–1988, but 75% and 71% in 1989–1991 and 1994, respectively. Rogers et al.[10] reported aspirin use at discharge of about 80% in 1998. 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 of evaluating only discharge medication.[9,10] We can rule out that nonprescription aspirin has biased our results, for two reasons. First, in the Netherlands a prescription is required for low-dose aspirin. Sec-

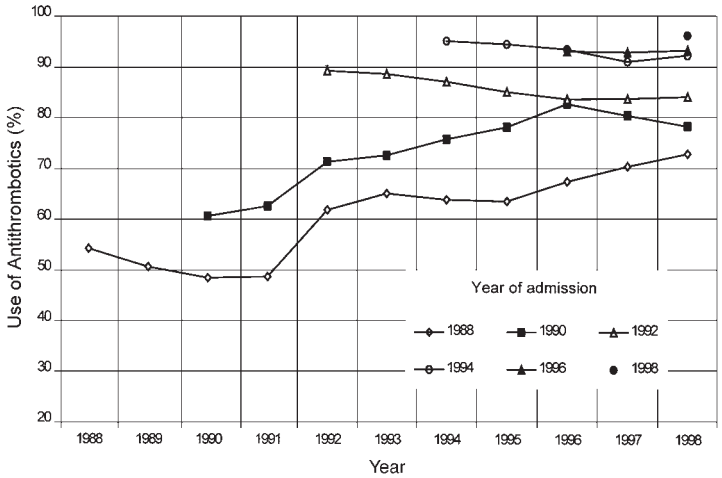

Figure 1. Annual use of oral antithrombotics from 1988 to 1998 in patients who experienced myocardial infarction, stratified by year of admission.

ond, use of nonprescription aspirin of higher doses is negligibly low, as nonprescription 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.[15] Brotons et al.[11] reported aspirin use of 70.7% and 67.2% and oral anticoagulant use of 8.9% and 9.9% at discharge and 1 year after discharge, respectively, in patients admitted due to MI in 1995. 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 MI in former years are disadvantaged when compared with patients who experienced MI in recent years. Furthermore, use of oral antithrombotics in patients with MI in recent years gradually decreases. So not only should patients be reviewed for oral antithrombotic treatment, but they should be closely monitored once oral antithrombotic treatment is initiated to prevent an untimely ending of oral antithrombotic treatment.

We tried to estimate the projected number of MIs that might have occurred due to undertreatment. We assumed that the population in our study resembles the population in randomized clinical trials and, therefore, the number needed to treat calculated from the randomized clinical trials is applicable in our calculation. Our database included 2859 untreated personyears from 1988 to 1998. Based on the assumption mentioned above and a number needed to treat for 2 years of 56,[17] 26 new acute MIs might have occurred due to undertreatment. Applied to a national level, optimal aspirin treatment in patients with MI from 1988 to 1998 would have prevented 1469 nonfatal reinfarctions in the Netherlands.

Our study has several limitations. First, we cannot rule out that our results have been biased by the difference in duration of follow-up. Due to large variations in duration of follow-up, the period that patients were at risk of an adverse reaction that would contraindicate oral antithrombotic treatment varies widely among patients. Intolerance can account for the low use of oral antithrombotics in patients with a past MI to a certain extent; however, we do not believe that the 24.8% of patients who did not receive any oral antithrombotic is entirely due to ineligibility. As shown in Figure 1, the yearly increase of antithrombotics use has not leveled off yet in patients with a past history of MI. 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 MI over a 1- to 5-year period reported rates of aspirin intolerance that ranged from 8.5% to 13%, which is substantially below 24.8%.[11,18,19] Results from a multipractice audit showed that aspirin use among patients who had experienced an MI during the past 5 years rose from 75.7% to 84.1% despite a rise in aspirin intolerance from 10.0–13.0%.[18]

We could not reveal the possible reasons for the low use of antithrombotics among patients with a history of MI. As our database is anonymized, we did not have the opportunity to question patients about their reluctance in filling a prescription or to question doctors about their deliberations upon prescribing oral antithrombotics. Therefore, further research needs to be performed to elucidate the reasons for not taking oral antithrombotics before future intervention strategies can be applied to the appropriate persons.

In interpreting our results, one should consider that no direct evidence is available about the benefits of oral antithrombotic therapy started long after MI. However, just as continuation of oral antithrombotic treatment after the end of follow-up is believed 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 MI but not to patients living in nursing homes, since those patients are not included in the PHARMO system.

Summary

Our results suggest that, once oral antithrombotics are not prescribed at discharge, the post-MI 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 MI, they should focus their attention on patients who do not receive oral antithrombotic treatment, mainly those who have had MI in former years, and initiate this treatment, as its benefits have been clearly established.

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References

1. Mehta RH, Eagle KA. Secondary prevention in acute myocardial infarction. BMJ 1998;316:838-42.
2. Resnekov L, Chediak J, Hirsh J, Lewis D. Antithrombotic agents in coronary artery disease. Chest 1986;89(2 suppl):54S-67S.
3. Resnekov L, Chediak J, Hirsh J, Lewis HD Jr. Antithrombotic agents in coronary artery disease. Chest 1989;95(2 suppl):52S-72S.
4. Pyorala K, De Backer G, Graham I, Poole-Wilson P, Wood D. Prevention of coronary heart disease in clinical practice. Recommendations of

the Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension. Eur Heart J 1994;15:1300-31.
5. Ryan TJ, Anderson JL, Antman EM, Braniff BA, Brooks NH, Califf RM, et al. ACC/AHA guidelines for the management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). J Am Coll Cardiol 1996;28:1328-428.
6. Acute myocardial infarction: pre-hospital and in-hospital management. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J 1996;17:43-63.
7. Spinler SA, Hilleman DE, Cheng JWM, Howard PA, Mauro VF, Lopez LM, et al. New recommendations from the 1999 American College of Cardiology/American Heart Association acute myocardial infarction guidelines. Ann Pharmacother 2001;35:589-617.
8. Cairns JA, Theroux P, Lewis HD Jr, Ezekowitz M, Meade TW. Antithrombotic agents in coronary artery disease. Chest 2001;119(1 suppl):228S-52S.
9. Martinez M, Agusti A, Arnau JM, Vidal X, Laporte JR. Trends of prescribing patterns for the secondary prevention of myocardial infarction over a 13-year period. Eur J Clin Pharmacol 1998;54:203-8.
10. Rogers WJ, Canto JG, Lambrew CT, Tiefenbrunn AJ, Kinkaid B, Shoultz DA, et al. Temporal trends in the treatment of over 1.5 million patients with myocardial infarction in the US from 1990 through 1999: the National Registry of Myocardial Infarction 1, 2 and 3. J Am Coll Cardiol 2000;36:2056-63.
11. Brotons C, Calvo F, Cascant P, Ribera A, Moral I, Permanyer-Miralda G. Is prophylactic treatment after myocardial infarction evidence-based? Fam Pract 1998;15:457-61.
12. Herings RMC. PHARMO: a record linkage system for postmarketing surveillance of prescription drugs in the Netherlands [dissertation]. Utrecht University, 1993.
13. ATC Classification and DDD assignment. 1st ed. Oslo: WHO Collaborating Center for Drug Statistics Methodology, 1996.
14. Clinical admissions with diagnosis code 410 — acute myocardial infarction. In: Jebbink M, ed. Utrecht, Netherlands: Prismant, 2002.
15. Statline. Population, monthly and yearly data. Voorburg/Heerlen, Netherlands: Statistics Netherlands, 2002.
16. Wood DA. Clinical reality of coronary prevention guidelines: a comparison of EUROASPIRE I and II in nine countries. Lancet 2001;357:995-1001.
17. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71-86.
18. Khunti K, Sorrie R, Jennings S, Farooqi A. Improving aspirin prophylaxis after myocardial infarction in primary care: collaboration in multipractice audit between primary care audit group and health authority. BMJ 1999;319:297.
19. Eccles M, Bradshaw C. Use of secondary prophylaxis against myocardial infarction in the north of England. BMJ 1991;302:91-2.

EXTRACTO

OBJETIVO: Evaluar la utilización de los agentes antitrombóticos orales (agente antiplaquetario y anticoagulante) posterior a un infarto del miocardio (IM) en Netherlands durante el período de 1988 hasta 1998.

MÉTODOS: Se hizo una revisión retrospectiva de 3800 pacientes con IM usando datos de PHARMO Record Linkage System.

RESULTADOS: Desde 1988 hasta 1998, la utilización de antitrombótico oral aumentó significativamente de 54% a 88.9%. En 1998, solo un 75.8% de los pacientes que tuvieron un IM a finales de los años 80 recibieron tratamiento antitrombótico oral comparado con un 94.4% en los cuales tuvieron un IM reciente.

CONCLUSIONES: Los antitrombóticos orales tuvieron una considerable baja utilización en pacientes con historial de IM. Por tanto, estos pacientes deben ser evaluados sobre la terapia de antitrombóticos para determinar sin en ellos; el fallo a usar este tratamiento es correcto o incorrecto y el tratamiento debe ser iniciado si es possible.

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RÉSUMÉ

OBJECTIF: Revoir l'utilisation d'agents antithrombotiques par voie orale (c'est-à-dire les agents antiplaquettaires et les anticoagulants oraux) après un infarctus du myocarde (IM) entre 1988 et 1998 aux Pays-Bas.

MÉTHODOLOGIE: Un suivi rétrospectif de 3800 patients ayant subi un IM en utilisant les données du PHARMO Record Linkage System.

RÉSULTATS: Entre 1988 et 1998, l'utilisation d'agents antithrombotiques par voie orale a augmenté de façon significative de 54.0 % à 88.9%. En 1998, on a évalué que seulement 75.8% des patients ayant présenté un IM vers la fin des années 1980 recevaient une thérapie antithrombotique par voie orale comparé à 94.4% de ceux ayant présenté un IM récemment.

CONCLUSIONS: Les agents antithrombotiques par voie orale ont été considérablement sous utilisés chez les patients ayant un antécédent lointain IM. Dès lors, ces patients devraient être revus pour évaluer si la non utilisation d'agents antithrombotiques par voie orale est justifiée ou non et pour débuter un traitement si possible.

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