

PHARMACOEPIDEMOLOGY

Patterns of antiplatelet drug use after a first myocardial infarction during a 10-year period

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AIMS

The aims of the present study were to assess antiplatelet drug use patterns after a first myocardial infarction (MI) and to evaluate the determinants of antiplatelet nonpersistence.

METHODS

The present study was conducted in 4690 patients from the Utrecht Cardiovascular Pharmacogenetics cohort with a first MI between 1986 and 2010, who were followed for a maximum of 10 years. Medication use and event diagnosis were obtained from the Dutch PHARMO Record Linkage System. Antiplatelet drug users were classified as persistent users (gap between prescriptions ≤ 90 days), nonpersistent users (>90 -day gap and no refills), and restarters (a new prescription after a >90 -day gap). The association between potential determinants and antiplatelet nonpersistence was analysed using Cox regression.

RESULTS

The proportions of persistent users decreased from 84.0% at the 1-year follow-up to 32.8% at 10 years for any antiplatelet drug, and 77.3% to 27.5% for aspirin; and 39.0% to 6.4% for clopidogrel at 6 years. Most nonpersistent users restarted antiplatelet drugs later, leading to 89.3% overall antiplatelet drug users at 10 years after MI. Diabetes (hazard ratio [HR] 0.44; 0.32–0.60), hypertension (HR 0.77; 0.60–0.99), hypercholesterolaemia (HR 0.49; 0.39–0.62) and more recent MI diagnosis period (2003–2007: HR 0.69, 0.61–0.79; 2008–2010: HR 0.38, 0.19–0.77, compared to ≤ 2002 period) lowered the risk of antiplatelet nonpersistence, while vitamin K antagonist (VKA) comedication (HR 18.97; 16.91–21.28) increased this risk.

CONCLUSIONS

A large proportion of patients with a first MI still used antiplatelet drugs after 10 years. The frequent discontinuations during this time frame are expected to reduce the effectiveness of antiplatelet drugs as secondary prevention of cardiovascular diseases. Diabetes, hypertension, hypercholesterolaemia, VKA comedication and MI diagnosis period were determinants of antiplatelet nonpersistence.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Antiplatelet drugs should be used life-long to prevent recurrent cardiovascular events after myocardial infarction (MI).
- Patterns of antiplatelet drug use after myocardial infarction have been studied only for short-term periods.

WHAT THIS STUDY ADDS

- This long-term drug persistence study showed a dynamic pattern of antiplatelet drug use after the first MI, with many discontinuations and restarts during follow-up.
- Diabetes, hypertension, hypercholesterolaemia, vitamin K antagonist comedication and calendar period of MI diagnosis were determinants of antiplatelet nonpersistence.
- Increased attention to the persistent use of antiplatelet drugs is important for lowering the risk of recurrent cardiovascular events.

Tables of Links

TARGETS
Enzymes [2]
COX-1
COX-2
G protein-coupled receptors [3]
P2Y ₁₂ receptor

LIGANDS
Aspirin
Clopidogrel

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2, 3].

Introduction

Coronary heart diseases (CHD), particularly myocardial infarction (MI), is responsible for almost 1.8 million deaths annually in Europe. This mortality rate has decreased during the last three decades, owing to improvements in the acute treatment and secondary prevention of cardiovascular diseases (CVD). Nevertheless, death from CHD still constitutes 20% of all-cause mortality [4].

Antiplatelet drugs are given as acute treatment for acute coronary syndrome (ACS) and as secondary prevention for thrombotic events. Before 2002, only aspirin was used for secondary prevention. Since the publication of the European Society of Cardiology (ESC) guideline on the management of MI in 2002, aspirin in combination with a P2Y₁₂-inhibiting drug is recommended for secondary prevention. Aspirin should be used indefinitely, while the P2Y₁₂-inhibiting drug should be used for up to 1 year after an MI [5]. In the Netherlands, since 2006, the cost of prescriptions of the P2Y₁₂-inhibiting drug clopidogrel has been reimbursed by the public health-care system for 1 year after MI.

Several studies have been carried out on the use of antiplatelet drugs. The EuroAspire III survey on lifestyle, risk factors and drug use in patients with CHD was conducted in selected areas in 22 countries, and the results showed a relatively wide range of proportions (73.6–98.4%) of patients who used antiplatelet drugs at 6 months after the index CHD [6]. The Antiplatelet Therapy Observational Registry (APTOR) study in ACS patients who underwent percutaneous

coronary intervention (PCI) in several hospitals in 14 European countries reported 32–94% dual antiplatelet drug users at 1 year [7].

Studies on antiplatelet drugs have seldom evaluated the persistence of drug use. The proportions of users reported have usually been based on antiplatelet drug use at a certain point in time, without providing information on the continuous use until that time point. Early discontinuation of antiplatelet drugs after CHD and PCI has been associated with an increased risk of stent thrombosis, recurrent MI, ischaemic stroke and cardiac death [8]. Therefore, persistence with antiplatelet treatment is critical in terms of the clinical outcome of these patients. Furthermore, none of the previous studies have followed the patients for a long period. In the present study, we took episodes of discontinuation into account, followed the patients for much longer (i.e. for a maximum of 10 years) and specifically studied MI patients, in whom the adverse effects of antiplatelet drug discontinuation might be more severe. Information on antiplatelet drug persistence after hospital discharge may be used to improve the secondary prevention of MI, and eventually will improve the outcome of MI patients.

The present study aimed to assess the patterns of antiplatelet drug use in MI patients by describing the proportions of persistent users, nonpersistent users and restarters over time. The changes in antiplatelet drug use before and after a recurrent ACS event following the first MI were also reported. As a secondary aim, the study evaluated determinants of nonpersistence with antiplatelet drugs after the first MI.

Methods

Data source and study population

The study cohort for the present retrospective study was recruited from the participants of the Utrecht Cardiovascular Pharmacogenetics (UCP) studies, who were enrolled from the Dutch population-based Pharmaco-Morbidity Record Linkage System (PHARMO) database. The PHARMO database links drug dispensing history from a representative sample of Dutch community pharmacies to the national registry of hospital discharge diagnoses. In the UCP studies, patients who had been dispensed an antihypertensive drug (low-ceiling diuretic, beta-blocker, angiotensin-converting enzyme inhibitor, calcium antagonist, angiotensin II type 1 receptor blocker, miscellaneous antihypertensive or combination of antihypertensive agents) and/or had hypercholesterolaemia (dispensed a cholesterol-lowering drug, or had a total cholesterol level of >5.0 mmol l⁻¹ or self-reported hypercholesterolaemia) were selected from the PHARMO database. Detailed descriptions on the designs of the UCP studies have been reported previously [9, 10]. The UCP studies received ethics approval from the Medical Ethics Committee of the University Medical Center Utrecht, the Netherlands.

The present study included UCP patients who had had their first hospitalization for an MI [International Classification of Diseases, Ninth Revision (ICD-9) code 410] during 1986–2009, been registered in the PHARMO database for at least 1 year before the index MI and were 18 years of age or older. Patients were followed from their hospital discharge for their first MI up to a maximum follow-up of 10 years, or until the patients left the database, or until 30 July 2010, whichever occurred first.

Data collection

Data on antiplatelet drug use were obtained from the PHARMO database. This database contains the name of the dispensed drug, Anatomical Therapeutic Chemical (ATC) code, dispensing date, code of the prescriber, amount of drug dispensed and daily dose. The duration of use of each dispensed drug can be calculated by dividing the number of dispensed drugs by the daily dose. The theoretical end date will be the dispensing date plus the estimated duration of use. Antiplatelet drug episodes were constructed based on the dispensed date and the theoretical end date. When an overlap between two episodes of an antiplatelet drug occurred, the number of overlapping days was added to the duration of the second episode.

Persistence and adherence to antiplatelet drug use

An MI patient was considered as an antiplatelet drug initiator if the drug was dispensed within 90 days after hospitalization for the first MI. Aspirin (ATC code B01AC06) and clopidogrel (ATC code B01AC04) were considered in the study. We did not include prasugrel or ticagrelor because the former had rarely been used and the latter was not yet commercially available during the study period.

The patterns of antiplatelet drug use after the first MI were assessed by classifying the antiplatelet drug initiators into persistent users, nonpersistent users and restarters. An antiplatelet drug initiator was considered a persistent user when the gap between consecutive antiplatelet drug episodes was ≤ 90 days. Otherwise, the patient was considered a nonpersistent user. An antiplatelet initiator who had a new antiplatelet drug episode after discontinuation of an antiplatelet drug for >90 days was considered a restarter. Patients who restarted an antiplatelet drug could have one or more antiplatelet drug episode(s) after the restart date. These patterns were evaluated for the use of any antiplatelet drug (ATC code B01AC), individual drugs (aspirin or clopidogrel) and dual antiplatelet therapy (DAPT) (the combination of aspirin and clopidogrel), at 6 months, 1 year and each additional year up to 10 years, or up to 6 years for clopidogrel and DAPT because of the shorter follow-up associated with these drugs. The pattern of use of clopidogrel was assessed in MI patients who had been discharged since 1998 because the marketing authorization of clopidogrel was issued on 15 July 1998 [11]. The pattern of DAPT use was assessed in MI patients who had been discharged since 2002 as the combination was indicated for ACS patients in the 2002 ESC guideline [5].

Adherence was calculated by dividing the sum of the durations of drug episodes by the elapsed time between the start date of the first drug episode and the end date of follow-up.

Determinants of antiplatelet drug nonpersistence

Potential determinants that might be associated with antiplatelet drug nonpersistence were evaluated. The factors considered were age, gender, diabetes, hypertension, hypercholesterolaemia, vitamin K antagonist (VKA) comedication, bleeding diagnosis during hospitalization, calendar period of MI diagnosis, and history of CAD, heart failure, atrial fibrillation and transient ischaemic attack/ischaemic stroke.

Pattern of antiplatelet drug use before and after recurrent ACS

Antiplatelet drug use before and after a recurrent ACS event following the first MI was also evaluated. The first recurrence of ACS event was defined as the occurrence of a recurrent MI (ICD-9 code 410) or unstable angina (ICD-9 code 411.1) in the year following the first MI; the second recurrence of ACS event was defined as the occurrence of a recurrent MI or unstable angina in the year following the first recurrence of ACS event, and so on. We only looked at the recurrent ACS events in the year following the previous event as CV events mostly occur within this period [8]. The dispensing of antiplatelet prescription in the 90 days before and 90 days after the first MI, and the first, second and third recurrence of ACS events was compared.

Statistical analysis

The proportions of persistent users, nonpersistent users and restarters were calculated by dividing the number of users and restarters at a certain time point by the number of initiators. These proportions were assessed for the use of any antiplatelet drug, individual antiplatelet drugs and DAPT. Kaplan–Meier curves were used to illustrate the distribution

of nonpersistence and restart since the time of discontinuation. A stratified analysis of nonpersistence with any antiplatelet drug, aspirin and clopidogrel was conducted, based on calendar periods of the first MI diagnosis. The periods were ≤2002, 2003–2007 and 2008–2010. These periods were categorized based on the year when the ESC guidelines for MI [5, 12–14] were published. Adherence to antiplatelet drugs was reported as the average percentage, and the mean differences were analysed using the independent *t*-test. A stratified analysis of adherence was conducted based on age. Cox regression analysis was used to analyse the association between potential determinants and antiplatelet drug nonpersistence. VKA comedication and a bleeding diagnosis during hospitalization were included as time-varying variables.

The proportions of antiplatelet drug use in the 90 days before and 90 days after an event (the first MI or the recurrent ACS events) were calculated by dividing the number of antiplatelet drug users in that time period by the number of patients who had the event. The differences between the proportions of antiplatelet drug users before and after an event were analysed using McNemar’s chi-square test. The analyses in the present study were conducted using SPSS Statistics 20 (IBM, New York, USA) and R 3.1.3 (the R Foundation for Statistical Computing, Vienna, Austria) statistical software. A *P*-value less than 0.05 was considered significant.

Results

A total of 4690 MI patients were included in the study, with a median follow-up of 5.6 (interquartile range [IQR] 3.3–7.7) years. The baseline characteristics of the patients are shown in Table 1. The MI patients had an average age of 67.3 ± 11.6 years, most were men (63.7%) and a considerable proportion had a history of hypertension (72.7%) or hypercholesterolaemia (29.6%). 80.7% of patients started on any antiplatelet drug in the 90 days after discharge from hospital but less than a third started on DAPT (i.e. the combination of aspirin and clopidogrel). 11.1% patients had a first recurrence of ACS event over the following year, 20.0% of whom had a second recurrence of ACS event. Later, 28.2% of MI patients who had a second recurrence of ACS event experienced a third recurrence of ACS event.

Persistence with antiplatelet drug use

Figure 1 shows the proportion of antiplatelet drug users during follow-up. At the end of the first year, there were still 84.0% persistent users. The proportion of persistent users decreased over time, to 56.2% at 5 years and 32.8% at 10 years. Some of the nonpersistent users restarted antiplatelet drugs some time during the follow-up, resulting in 89.3% of antiplatelet drug users (combination of persistent users and restarters) at 10 years (Figure 1A). When the individual antiplatelet drugs were assessed, aspirin showed a similar pattern, starting with 82.6% of persistent users at 6 months, which decreased to 77.3% at 1 year, and the number was reduced further to 27.5% at 10 years. Some of the nonpersistent users restarted aspirin use, and there were 77.1% aspirin users at 10 years (Figure 1B).

Table 1

Baseline characteristics of patients at their first myocardial infarction

Characteristics	<i>n</i> (% of 4690 patients)
Age, mean (standard deviation)	67.3 (11.6)
Gender (male)	2987 (63.7)
Antiplatelet drug users starting this treatment within 90 days after hospitalization (initiators)	
Any antiplatelet drug	3787 (80.7)
Aspirin	2321 (49.5)
Clopidogrel^a	1257 (33.4)
Aspirin monotherapy	1489 (31.7)
Clopidogrel monotherapy^a	595 (15.8)
Aspirin + clopidogrel^b	641 (27.5)
Disease history	
Diabetes	215 (4.6)
Hypertension	3408 (72.7)
Hypercholesterolaemia	1386 (29.6)
Coronary artery diseases	716 (15.3)
Heart failure	143 (3.0)
Atrial fibrillation	150 (3.2)
Transient ischaemic attack/ischaemic stroke	108 (2.3)
Bleeding	107 (2.3)

^aOnly for myocardial infarction patients who were discharged after 1998 (*n* = 3761)

^bOnly for myocardial infarction patients who were discharged after 2002 (*n* = 2327)

In contrast with aspirin, clopidogrel showed a different pattern. At 6 months, 37.0% of patients discontinued clopidogrel use, and the proportion of persistent users was reduced steeply, to 39.0% at 1 year. Only a small proportion of patients continued using clopidogrel beyond 1 year. At 6 years after MI, 19.6% patients had restarted clopidogrel use, leading to 26.0% overall clopidogrel users (Figure 1C).

DAPT use followed the same pattern as clopidogrel (Figure 1D). The proportion of DAPT persistent users declined rapidly, from 56.8% at 6 months to 31.5% at 1 year. The DAPT nonpersistent users mostly continued their antiplatelet treatment with aspirin only (the cumulative proportion in 6 years was 23.7%), and a small proportion continued with clopidogrel only (the cumulative proportion in 6 years was 9.6%). The proportion of restarters for DAPT showed a small increase after 5 years.

Discontinuations and restarts of antiplatelet drugs after the first MI are also shown as Kaplan–Meier curves (Figure S1). The number of antiplatelet persistent users declined gradually over the years, but around 60% of those who discontinued had restarted again within 1 year after the discontinuation date. Aspirin users showed a similar gradual declining persistence pattern but with a slower increase in restarting after the discontinuation date. The percentage of clopidogrel persistent users declined more rapidly, to 39.0%

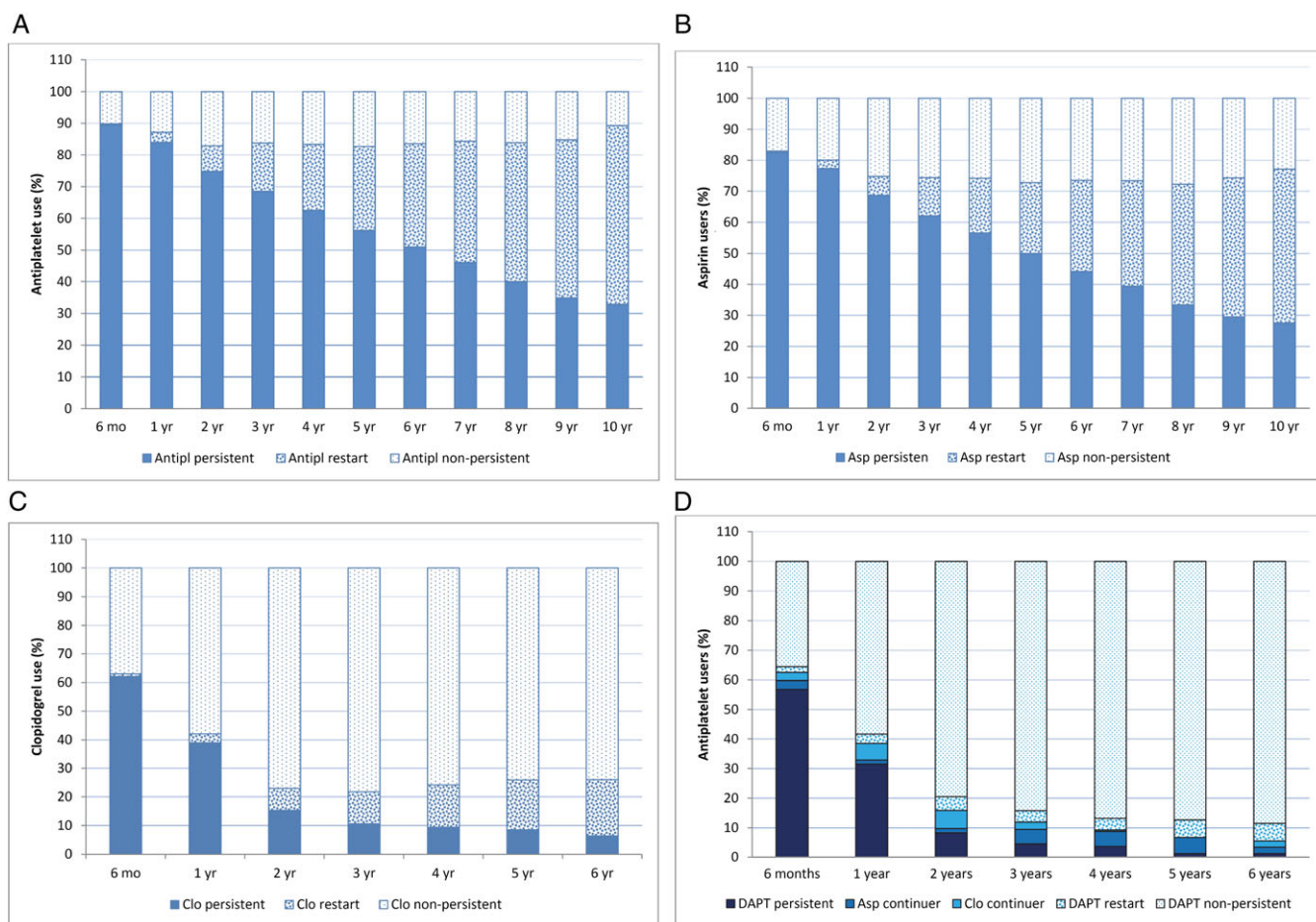


Figure 1

The percentages of antiplatelet drug users in myocardial infarction (MI) patients after hospital discharge, stratified as persistent users, nonpersistent users and restarters. The x-axis shows the time elapsed since the first MI. (A) Any antiplatelet drug; (B) aspirin; (C) clopidogrel; (D) DAPT. antipl, antiplatelet; asp, aspirin; clo, clopidogrel; DAPT, dual antiplatelet therapy; mo, month; yr, year

at 1 year, and less than 40% restarted gradually after the discontinuation date. Around 48% of these restarters had an ACS or PCI in the 90 days before the restart date (data not shown). As expected, DAPT persistent users showed a similar pattern to clopidogrel, with a small proportion restarting after discontinuation.

In those who became nonpersistent users within 6 months, 30% experienced a recurrent ACS event within 6 months after the discontinuation date. The median time interval between the discontinuation date and the first recurrence of ACS event in this group was 80 (IQR 34–150) days. In all patients who discontinued antiplatelet drugs, 15.8% of them experienced a first recurrence of ACS during the entire follow-up, and the median time interval between discontinuation date and the first recurrence of ACS event was 1101 (IQR 163–2236) days.

Determinants of antiplatelet drug nonpersistence

Stratification of persistent users by the calendar periods of MI diagnosis showed that the probability of antiplatelet

discontinuation was significantly different between calendar periods ($P < 0.05$). There was an increase in antiplatelet persistence in patients whose MI diagnosis followed the publication of the updated ESC guidelines on MI in 2002–2003 and 2007–2008 (Figure 2). In Table 2, the corresponding HRs of the calendar periods are presented. VKA comedication (HR values ranged from 2.20 for clopidogrel to 18.97 for any antiplatelet drug) was associated with a higher risk of nonpersistence with any antiplatelet drug, aspirin, clopidogrel and DAPT. By contrast, diabetes (HR ranged from 0.44 to 0.52) and hypercholesterolaemia (HR ranged from 0.45 to 0.49) were both associated with a lower risk of nonpersistence with any antiplatelet drug and aspirin. Nonpersistence with clopidogrel was also associated with age [HR for every 10-year increase: 0.92; 95% confidence interval (CI) 0.87, 0.98], diabetes (HR 1.74; 95% CI 1.11, 2.73), hypercholesterolaemia (HR 1.43; 95% CI 1.12, 1.83) and previous CAD (HR 0.83; 95% CI 0.69, 0.98).

Adherence to antiplatelet drug use

The average adherence to antiplatelet drugs during the follow-up is shown in Figure S2. Average adherence to any

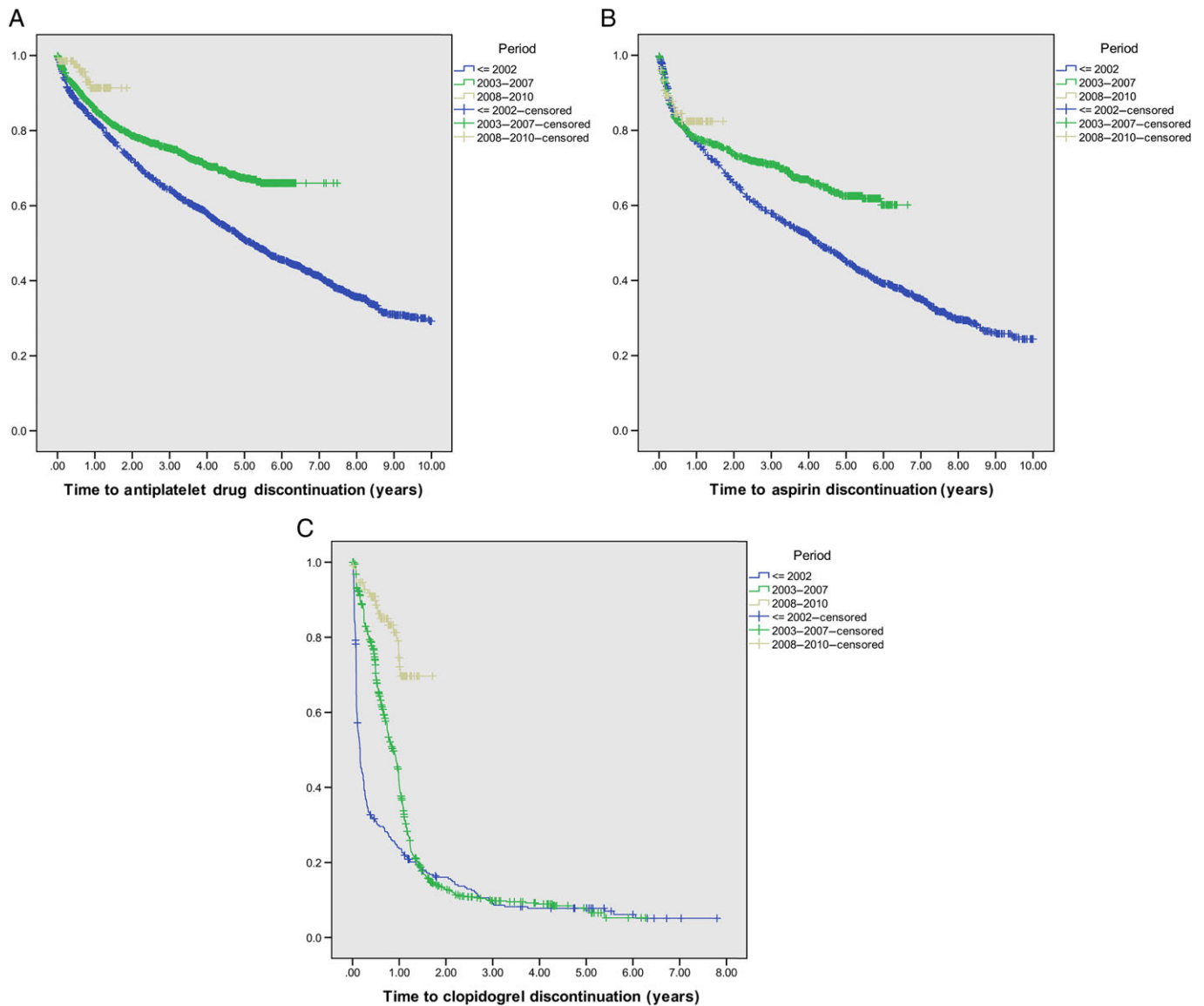


Figure 2

Kaplan–Meier curves for the discontinuation of antiplatelet drugs, stratified by calendar period of myocardial infarction diagnosis. (A) Any antiplatelet drug; (B) aspirin; (C) clopidogrel

antiplatelet drug was high ($86.3 \pm 23.9\%$). Aspirin adherence was almost as high ($79.0 \pm 30.6\%$), while the adherence to clopidogrel was lower ($38.6 \pm 36.1\%$). The difference between the average adherence to aspirin and to clopidogrel was significant ($P < 0.01$). Patients who were 65 years of age or younger had an average adherence to antiplatelet drug of 89.2%, while those who were older than 65 years had an average of 84.3% (Figure S3).

Antiplatelet drug use before and after the first MI and recurrent ACS events

In general, there was an increase in antiplatelet drug use in the 90 days after an event compared with the use in the 90 days before the event, with the largest difference for the first MI (Figure 3). As expected, the increase in

clopidogrel use for recurrent ACS events was larger than that for aspirin.

Discussion

Persistence of the use of any antiplatelet drug after hospitalization for the first MI was relatively high in the Netherlands at 1 year. The proportion of persistent users decreased with each additional year following MI after the first year. At 10 years, the proportion of antiplatelet drug users was still fairly high (89.3%), due to a large proportion of restarters. A similar pattern was observed for aspirin. Clopidogrel persistence decreased rapidly in the first year, and the overall proportion of clopidogrel users was 26.0%

Table 2

Determinants of nonpersistence with antiplatelet drugs

Covariate	Hazard ratio (95% confidence interval) ^a			
	Any antiplatelet drug ^b	Aspirin ^b	Clopidogrel ^b	DAPT ^c
Age (10-year increase)	1.02 (0.98–1.08)	1.00 (0.94–1.06)	0.92 (0.87–0.98)	0.96 (0.80–1.14)
Gender (male)	0.94 (0.85–1.05)	1.03 (0.90–1.18)	0.89 (0.77–1.03)	0.78 (0.52–1.17)
Diabetes	0.44 (0.32–0.60)	0.52 (0.37–0.72)	1.74 (1.11–2.73)	0.69 (0.20–2.39)
Hypertension	0.77 (0.60–0.99)	0.69 (0.52–0.93)	1.07 (0.84–1.36)	0.88 (0.44–1.76)
Hypercholesterolaemia	0.49 (0.39–0.62)	0.45 (0.33–0.60)	1.43 (1.12–1.83)	1.20 (0.60–2.42)
Previous coronary artery disease	1.09 (0.95–1.25)	1.05 (0.88–1.24)	0.83 (0.69–0.98)	1.70 (1.11–2.59)
Previous heart failure	0.98 (0.69–1.39)	0.73 (0.46–1.19)	1.55 (0.80–3.02)	–
Previous atrial fibrillation	0.77 (0.58–1.01)	0.91 (0.59–1.41)	0.79 (0.53–1.17)	0.76 (0.26–2.21)
Previous TIA/ischaemic stroke	0.83 (0.58–1.18)	0.98 (0.64–1.50)	1.03 (0.68–1.56)	1.94 (0.83–4.52)
Time-varying bleeding	1.33 (0.63–2.81)	2.46 (1.09–5.54)	0.32 (0.08–1.31)	–
Time-varying use of VKAs	18.97 (16.91–21.28)	11.48 (9.89–13.33)	2.20 (1.79–2.70)	10.19 (6.21–16.72)
Calendar period of MI diagnosis				
≤2002	1.00	1.00	1.00	1.00
2003–2007	0.69 (0.61–0.79)	0.82 (0.69–0.96)	0.60 (0.51–0.70)	0.51 (0.32–0.81)
2008–2010	0.38 (0.19–0.77)	0.85 (0.44–1.66)	0.16 (0.10–0.26)	0.14 (0.04–0.47)

DAPT, dual antiplatelet therapy; MI, myocardial infarction; TIA, transient ischaemic attack; VKA, vitamin K antagonist

^aSignificant estimates ($P < 0.05$) are shown in bold

^bIncluded in the model: age, gender, diabetes, hypertension, hypercholesterolaemia, previous coronary artery disease, heart failure, atrial fibrillation and ischemic stroke/transient ischaemic attack, calendar period of MI diagnosis, time-varying bleeding and time-varying VKA use

^cIncluded in the model: age, gender, diabetes, hypertension, hypercholesterolaemia, previous coronary artery disease, atrial fibrillation and ischaemic stroke/transient ischemic attack, calendar period of MI diagnosis and time-varying VKA use

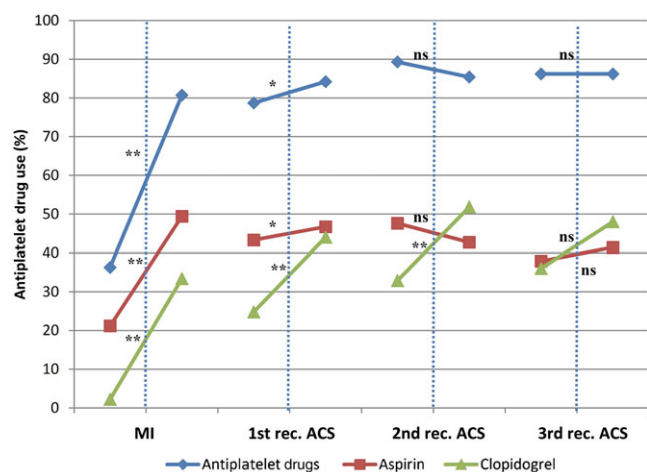


Figure 3

The percentages of antiplatelet drug use in the 90 days before and 90 days after the first myocardial infarction (MI), and the 90 days before and 90 days after the first, second and third recurrence of acute coronary syndrome (rec. ACS). ns, non-significant. * $P < 0.05$, ** $P < 0.01$

at 6 years. DAPT and clopidogrel use patterns were similar. Several predictors for nonpersistence with antiplatelet drugs were identified.

While the proportion of MI patients who persistently used antiplatelet drugs was relatively high in the first year, it was not optimal. A discontinuation of antiplatelet drugs early after CHD and PCI might lead to a recurrent ACS event [8]. In the present study, the nonpersistent user proportion at 1 year was driven mostly by early discontinuation within 6 months. Indeed, the present study showed that in 30% of the patients who discontinued antiplatelet drugs within 6 months after the first MI, a recurrent ACS occurred within 6 months after the discontinuation date. Early antiplatelet discontinuation might be caused by drug intolerance, major bleeding, invasive procedures, comedications and patient-related factors [8, 15]. The reasons for discontinuation of antiplatelet drugs were not recorded in the present study.

The proportion of antiplatelet drug users at 6 months found in the present study was similar to that found in the EuroAspire III survey in the Netherlands [6]. However, the proportion of antiplatelet drug users at 1 year in the present study was higher than that found in the Netherlands Heart Foundation (NHF) study, which reported 58–65% antiplatelet drug use at 1 year after MI hospitalization [16]. This might be caused by differences in the methods used to calculate the number of users. The NHF study reported a point prevalence based on the dispensing of a prescription which period including 1 October each year.

Compared with the studies on antiplatelet drug use in other countries, the proportion of persistent antiplatelet drug

users in the Netherlands was lower. In a primary care study in the UK, 85% patients were still using aspirin at 1 year after an acute coronary event [17], as opposed to 77.3% in the Netherlands. Another study in the UK reported a higher proportion of clopidogrel persistent users (53.0–54.0%) at 1 year after MI [18] compared with that in the Netherlands. However, a study in the USA showed a lower proportion of clopidogrel persistent users, with only 31.5% of patients remaining on clopidogrel at 1 year after acute MI or coronary stenting [19].

The high nonpersistence of clopidogrel and DAPT is in line with the results of the clinical trials and long-term observational studies leading to ESC guideline recommendations on the use of antiplatelet drugs after coronary stenting for ACS [20–23]. DAPT should be used for at least 1 month after a bare metal stent (BMS) implantation, for at least 6 months after a drug-eluting stent (DES) implantation and up to a maximum of 1 year, or longer in patients with a high cardiovascular and low bleeding risk, after which monotherapy with aspirin should be continued indefinitely [23]. A previous study in Japan, conducted in patients who underwent coronary revascularization between 2005 and 2007, showed that the percentage of patients using DAPT was 67.3% in those receiving DES vs. 33.4% in those receiving BMS at 1 year, and 48.7% vs. 24.3% at 5 years, respectively [24]. However, there is no information available on the type of stent used in the present study.

Stratification of calendar periods corresponding with the publication dates of revised guidelines for MI demonstrated that nonpersistence with antiplatelet drugs improved during 2000–2010. The calendar period of MI diagnosis was also shown to be an independent determinant of antiplatelet nonpersistence. Concomitant VKA use was strongly associated with a higher risk of nonpersistence with antiplatelet drugs. This finding was in line with that of a previous study by Rossini *et al.*, who showed that the use of an oral anticoagulant was a predictor of discontinuation of aspirin, clopidogrel and DAPT [8]. As the concomitant use of an antiplatelet drug and an oral anticoagulant is associated with bleeding [25], this combination should be avoided. However, there are indications, such as for those with atrial fibrillation undergoing coronary stenting, in whom the combination is indicated [14]. In any antiplatelet drug users and in aspirin users, diabetes and hypercholesterolaemia were significantly associated with a lower risk of nonpersistence. This was expected as these conditions are associated with a higher risk of recurrent cardiovascular events. In clopidogrel users, diabetes and hypercholesterolaemia were associated with a higher risk of antiplatelet drug nonpersistence. Although this was unexpected, it might be partly explained by the concern of a pharmacokinetic interaction between atorvastatin and clopidogrel in patients with hypercholesterolaemia [26], and diabetes was reported as a predictor of insufficient antiplatelet response to clopidogrel [27]. Patients with previous CAD, who also have a higher risk for recurrent cardiovascular events, had a lower risk of clopidogrel nonpersistence but a higher risk of DAPT nonpersistence. The latter might have been confounded by bleeding events (major and minor) as we did not include the time-varying bleeding event variable in the analysis of DAPT use. We did not have information on minor bleeding events, while more

severe bleeding events that needed hospitalization were rare, occurring in 1% of patients.

The average adherence to any antiplatelet drug and aspirin was relatively high, while clopidogrel adherence was low. A study by Tuppin *et al.* [28], in France, showed an approximately similar proportion (81.7%) of adherent users of antiplatelet drugs (aspirin and clopidogrel) to that in our study (78.9%). Another study, in Italy, showed a lower proportion of adherent antiplatelet drug users (58.7%) [29]. The population of MI patients in our study were, on average, younger than that in the Italian study. Younger patients tend to be more adherent to treatment than older patients [28], as also shown in the present study. However, even the older patients in the present study showed a high adherence to antiplatelet drugs.

When considering the results of the present study, some limitations should be taken into account. We included patients who had previous conditions that might have affected the use of antiplatelet drugs – e.g. those with hypertension, hypercholesterolaemia, atrial fibrillation, stroke/transient ischaemic attack and bleeding. We do not have information on the reasons for antiplatelet discontinuation, or whether the discontinuation was physician- or patient initiated. The persistence of DAPT might be affected by the type of stent used; however, the stent type is not available in the database. Furthermore, the in-hospital use of drugs dispensed by the hospital pharmacy was not recorded in our database, which might have led to immeasurable time bias. However, as patients were defined as persistent users when the gap between consecutive drug episodes was ≤ 90 days, it is unlikely that a misclassification of persistent users as nonpersistent users occurred as the length of stay in hospital was rarely more than 90 days.

The strengths of the present study were that it had a longer follow-up compared with the previous studies in this field, and that it considered the proportions of persistent users and restarters as opposed to point prevalence proportions. The data source, the PHARMO dispensing database, contained complete outpatient medication use data for patients still registered in the database. The use of a dispensing database, rather than patient/physician interview or recall, in the study ensured a more reliable source of antiplatelet exposure information. Furthermore, in contrast to other countries, in the Netherlands low-dose aspirin for CVD secondary prevention is available only on prescription and is reimbursed, so the misclassification of aspirin exposure due to over-the-counter dispensing was not an issue in the present study. The choice of a 90-day gap as the definition of nonpersistence has been used before. This gap is equivalent to the length of a single chronic prescription period in the Netherlands.

We showed that there is a need to improve persistence in the use of antiplatelet drugs following MI. There should be more attention to unjustified discontinuation of antiplatelet drugs, particularly if it is initiated by patients. Future research should be directed at monitoring antiplatelet drug use and elucidating the reasons for antiplatelet drug discontinuation, so that interventions can be developed to improve the persistence with antiplatelet drugs.

In conclusion, there was a relatively high persistence with any antiplatelet drug early after MI in this long-term follow-

up study in the Netherlands but this decreased in the years following the MI. Many patients restarted antiplatelet drugs during follow-up. However, in spite of the restart, it is important to be aware that the gap between discontinuation and restart is a critical period for the occurrence of recurrent CV events. Diabetes, hypertension, hypercholesterolaemia, VKA comedication and calendar period of MI diagnosis were important determinants of antiplatelet nonpersistence. Improvement is still needed in the secondary prevention of MI in the Netherlands.

Competing Interests

All authors have completed the Unified Competing Interest form and declared no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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Contributors

A.Y., A.d.B. and O.H.K. designed this study, P.C.S. obtained and cleaned the data from the Dutch PHARMO Record Linkage System, and A.Y. conducted the statistical analysis and wrote the first draft of the manuscript. A.Y., A.d.B., O.H.K., V.H.M.D. and P.C.S. critically evaluated and approved the final manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

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Figure S1 Kaplan–Meier curves for the discontinuation and restart of the following antiplatelet drugs: (A) any antiplatelet drug; (B) aspirin; (C) clopidogrel; and (D) DAPT aspirin and clopidogrel

Figure S2 Average adherence to antiplatelet drugs

Figure S3 Average adherence to antiplatelet drugs, stratified by age