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PHARMACOEPIDEMIOLOGY

Appropriateness of antiplatelet therapy for primary and secondary cardio- and cerebrovascular prevention in acutely hospitalized older people

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Keywords antiplatelet therapy, appropriateness, cardio- and cerebrovascular prevention, internal medicine and geriatric wards, older people

AIMS

Antiplatelet therapy is recommended for the secondary prevention of cardio- and cerebrovascular disease, but for primary prevention it is advised only in patients at very high risk. With this background, this study aims to assess the appropriateness of antiplatelet therapy in acutely hospitalized older people according to their risk profile.

METHODS

Data were obtained from the REPOSI register held in Italian and Spanish internal medicine and geriatric wards in 2012 and 2014. Hospitalized patients aged ≥65 assessable at discharge were selected. Appropriateness of the antiplatelet therapy was evaluated according to their primary or secondary cardiovascular prevention profiles.

RESULTS

Of 2535 enrolled patients, 2199 were assessable at discharge. Overall 959 (43.6%, 95% CI 41.5–45.7) were prescribed an antiplatelet drug, aspirin being the most frequently chosen. Among patients prescribed for primary prevention, just over half were inappropriately prescribed (52.1%), being mainly overprescribed (155/209 patients, 74.2%). On the other hand, there was also a high rate of inappropriate underprescription in the context of secondary prevention (222/726 patients, 30.6%, 95% CI 27.3–34.0%).

CONCLUSIONS

This study carried out in acutely hospitalized older people shows a high degree of inappropriate prescription among patients prescribed with antiplatelets for primary prevention, mainly due to overprescription. Further, a large proportion of patients who had had overt cardio- or cerebrovascular disease were underprescribed, in spite of the established benefits of antiplatelet drugs in the context of secondary prevention.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Antiplatelet drugs are recommended for secondary prevention of cardio- and cerebrovascular disease.
- For primary prevention these drugs are advised only in patients at very high risk but are not mandatory because the balance between risk and benefit is still unsettled.
- In older people, the age-related risk of bleeding demands a careful risk/benefit evaluation before prescribing antiplatelet drugs, both in primary and secondary cardiovascular prevention.

WHAT THIS STUDY ADDS

- A relatively large number of patients were inappropriately treated for primary and secondary prevention of cardiovascular disease.
- A large rate of underprescription with antiplatelet drugs was found among patients in secondary prevention, while among patients prescribed for primary prevention many were inappropriately overprescribed.
- The inappropriate drug ticlopidine was still largely prescribed in Italian patients, both for primary and secondary prevention.

Introduction

In spite of the fact that mortality rates are declining worldwide, cardiovascular diseases remain the greatest cause of mortality in Europe, responsible for over 4 million deaths per year [1]. The incidence of stroke and myocardial infarction increases dramatically with age, which is the strongest risk factor for cardio- and cerebrovascular disease [2]. The consequences of cardiovascular events are particularly dramatic in older people, increasing their disability and impairing quality of life [3]. Therefore, the implementation of strategies aimed to decrease this risk is mandatory. On the other hand, pharmacological treatments in older people are always challenging, because this population is affected by multiple chronic diseases, takes multiple drugs and undergoes physiological changes of pharmacodynamics and pharmacokinetics that expose patients to drug-related adverse events [4–8]. Moreover, ageing is associated *per se* with a higher risk of bleeding [9], so that any antithrombotic therapy for cardio- and cerebrovascular disease prevention is further amplifying the age-related risk of bleeding [10].

The drugs most widely used to prevent cardiovascular diseases are antiplatelet agents, **acetylsalicylic acid** (ASA) being the most popular due to the longstanding evidence that supports its use [11]. Other oral antiplatelet drugs are recommended in people with contraindications to ASA or in addition to it (e.g., **clopidogrel**, **ticagrelor**, **prasugrel**, **dipyridamole**) [12]. Despite underrepresentation of multimorbid older people in clinical trials, there is solid evidence for the benefit of antiplatelet drugs for secondary prevention of atherothrombotic disease (after myocardial infarction, ischemic stroke, unstable or stable angina or transient ischemic attacks) [13], so that the Screening Tool to Alert Doctors to the Right Treatment (START) criteria prompt their use in older people [14]. On the other hand, there is little evidence favouring their use for primary prevention, because several studies have shown fewer benefits than risks [2, 13–17]. In particular, Beers and colleagues suggest to avoid the use of **ticlopidine** and dypiridamole [18]. Thus a careful risk–benefit appraisal is warranted for the optimal prescription of antiplatelet drugs in older people, employing as a basis for choice the guidelines of scientific societies and working groups that provide recommendations for prevention of cardiovascular disease (for instance, the European Society of Cardiology [ESC] guidelines) [19, 20]. With this background, the aim of this study was to assess the appropriateness of antiplatelet therapy at hospital discharge according to the ESC guidelines in a large cohort of older people acutely hospitalized in Italian and Spanish internal medicine and geriatric wards participating in the REPOSI register.

Methods

Setting

This study was conducted in internal medicine and geriatric wards participating in the REPOSI (REgistro POliterapie SIMI) register, an independent register of the Italian Society of Internal Medicine (SIMI), IRCCS Fondazione Cà Granda Policlinico Hospital, and the IRCCS – Istituto di Ricerche Farmacologiche Mario Negri [6, 21]. REPOSI is a multicentre prospective register designed to collect information on drug prescription in patients aged ≥65 years who are consecutively admitted to internal medicine or geriatric wards of Italian hospitals during four index weeks (one for each season). The collection of data occurred every 2 years in 2008, 2010, 2012 and 2014, and since 2015/2016 data collection has become yearly [22]. Starting in 2014 also a small number of Spanish hospital wards participated in data collection. The principal data collected included socio-demographic factors, clinical data and pharmacological therapies. After discharge, additional follow-up data were obtained via telephone calls after 3 months. Participation was voluntary and all patients provided signed informed consent. REPOSI was approved by the Ethics Committee of the Cà Granda Maggiore Policlinico Hospital Foundation and then by the local ethical committees of the participating centres. The study was conducted according to Good Clinical Practice and the Declaration of Helsinki.

Data collection

For the purpose of this study, data collected in 2012 and 2014 were analysed. Patients assessable at discharge were scrutinized in order to establish whether or not they were

prescribed with at least one antiplatelet drug (Anatomical Therapeutic Chemical classification system (ATC) codes: B01AC*, N02BA01–N02BA51). Because lysine salicylate has the same therapeutic indications of ASA, the two drugs have been lumped together and hereafter are called aspirin.

A careful evaluation of the clinical history of each patient was performed by a hospital physician and a pharmacist on the basis of comorbidity data collected according to the Cumulative Illness Rating Scale (CIRS) [23], with the goal to categorize patients in the frame of primary or secondary prevention.

Criteria for prescription appropriateness

The prescribed drug was considered appropriate or not in the frame of primary or secondary cardio- and cerebrovascular prevention according to the ESC 2007 guidelines [24] for patients enrolled in REPOSI 2012 and to the ESC 2012 guidelines (Paragraph 4.10) [19] for those in REPOSI 2014. Beers criteria were also considered [18]. Antiplatelet drug appropriateness was also defined looking at the type and dose of the drug chosen.

Primary prevention. ESC guidelines do not recommend the use of antiplatelets [19, 24] in patients who previously experienced no major cardio- or cerebrovascular event due to the high risk of bleeding. However, they encourage the use of the Systematic Coronary Risk Evaluation Project (SCORE) in order to assess the degree of cardiovascular risk [19, 24, 25]. SCORE estimates the 10-year risk of a first fatal cardiovascular event taking into account age, sex, smoking, systolic blood pressure and total cholesterol [25]. Indeed, in the frame of primary prevention, aspirin (75–150 mg up to 320 mg) or clopidogrel (75 mg) as second line choice should be considered appropriate only in patients with an increased cardiovascular risk [19, 24]. Since older people, especially men, are at increased cardiovascular risk regardless of the other risk factors and considering that the adverse effects of drugs could outweigh the benefits, a SCORE risk of 10% or higher was deemed to be more appropriate for treatment with antiplatelet drugs in the frame of primary prevention in our older population [13, 26–28]. The use of antiplatelet agents was considered appropriate also for patients with cerebral arterial occlusion and stenosis without infarction (International Classification Disease-9 codes [ICD-9]: 433.x0, 434.x0) and acute coronary occlusion without myocardial infarction (ICD-9: 411.8). When it was impossible to assess the SCORE risk due to missing data (mainly regarding smoke and total cholesterol), age and gender being the main determinants of the SCORE, a favourable scenario (no smoking and/or low to normal cholesterol level) and an unfavourable one (smoking and/or high cholesterol level) were simulated. If both scenarios produced a SCORE risk ≥10%, patients were reclassified as being at very high risk. On the opposite side, if both scenarios produced a medium to high risk profile (<10%), the missing data for the risk SCORE were filled according to the unfavourable scenario. In the remaining situations, data were classified as missing and the corresponding patients were considered 'Not assessable'.

With this background, in the frame of primary prevention patients with SCORE risk <10% and prescribed with an antiplatelet agent were considered 'Not appropriate – Overprescribed'.

Patients with atrial fibrillation prescribed with antiplatelets. Among patients prescribed with antiplatelets, those with the indication for atrial fibrillation (AF), without any cardiovascular comorbidities, were separately considered, given that specific guidelines have been proposed [29]. For the purpose of the present study they have been considered 'Not appropriate – Patients with atrial fibrillation'. Indeed in these patients, oral anticoagulants (OAC) are recommended as first line treatment [29]. Aspirin should be considered appropriate only when OAC is contraindicated or refused. To assess possible contraindication to OAC treatment due to the risk of bleeding, we used a low platelet count (<100 000 mm^{-3}) as proxy [31]. The co-prescription of an antiplatelet drug and OAC was always considered inappropriate for older patients already at higher risk of bleeding. The OAC ATC codes assessed were B01A* excluding B01AC*.

Secondary prevention. According to the ESC guidelines, the first line antiplatelet drugs recommended for secondary prevention are low dose aspirin (75–150 mg) or alternatively clopidogrel (75 mg). A patient was considered in secondary prevention if he/she had already experienced a previous cardiovascular or cerebrovascular atherothrombotic event, such as stroke (ICD-9: 436), transient ischaemic attack (ICD-9: 435), angina pectoris (ICD-9: 413), myocardial infarction (ICD-9: 410, 411, 412), peripheral artery disease (ICD-9: 443.9), coronary revasculation or another arterial revasculation procedures (by-pass and stenting) and chronic ischaemic heart disease (CIHD) (ICD-9: 414). The previous occurrence of these events was assessed both at admission and during hospital stay. In the acute phase and for the following 12 months from the cardio-cerebrovascular event, dual antiplatelet therapy with aspirin and clopidogrel or ticagrerol or prasugrel was considered appropriate. When it was impossible to assess whether or not a cardio-cerebrovascular event had occurred, the dual antiplatelet therapy was considered 'Not Assessable'. With this background, patients who had already experienced a previous cardiovascular or cerebrovascular atherothrombotic event and had been prescribed with an antiplatelet drug were considered 'Appropriate'.

Patients inappropriately prescribed with a wrong medication. Both in primary and secondary prevention, patients prescribed with ticlopidine, according to Beers criteria [18], or dual antiplatelet therapy for more than 12 months were considered 'Not appropriate'.

Criteria for appropriateness of non-prescription

Patients not prescribed with antiplatelets were considered appropriate or not according to their cardiovascular risk profile.

Primary prevention. As stated above, ESC guidelines advise antiplatelet therapy for patients with SCORE risk ≥10%, but

treatment is not mandatory, and a careful consideration of the risk of bleeding and of the risk–benefit ratio of antiplatelets is warranted. Accordingly, it was not advisable to consider them inappropriately underprescribed. Because there is no validated score for the assessment of the risk of bleeding in the general older population, the diagnoses of major bleeding reported in the CIRS and platelet counts lower than 100 000 mm^{-3} [31] were used as proxies for this risk. With this background, in the frame of primary prevention patients not prescribed with an antiplatelet drug although they have a SCORE risk ≥10% were considered 'Appropriate – Not prescribed'. We considered these patients as a separate group in order to distinguish them from patients with SCORE ≥ 10% and appropriately prescribed with antiplatelets.

Secondary prevention. In the frame of secondary prevention, patients with evidence of previous cardio- or cerebrovascular events not on treatment with any antiplatelet drug were always considered not appropriate and thereafter called 'Not appropriate – Underprescribed', because there is evidence that the benefits from this treatment outweigh the risks [2]. Also in this case, the diagnoses of major bleeding reported in the CIRS and low platelet counts were used as proxies for the risk of bleeding.

Co-prescription of antiplatelet and OAC in patients with AF or CIHD was also analysed in the frame of secondary prevention.

Statistical analysis

Data were summarized as frequencies (%), means and standard deviations or medians and interquartile ranges, as appropriate. To ascertain the degree of uncertainty, the 95% confidence intervals (CI) were provided when pertinent. The analysis was performed using the SAS/STAT software Version 9.2 (SAS Institute Inc., Cary, NC, USA).

Nomenclature of targets and ligands

Key ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [31].

Results

Among the 2535 patients enrolled in 2012 and 2014 in 98 internal medicine and geriatric wards of the REPOSI register, 2199 were assessable at discharge. The participating wards were distributed throughout Italy (48 in the north, 16 in the centre and 21 in the south of the country) and 13 in Spain. Among patients included in the analysis, 959 (43.6%, 95% CI 41.5–45.7) were prescribed with at least one antiplatelet drug at discharge, while 1240 were not (Figure 1). Table 1 reports the main characteristics of prescribed and non-prescribed patients according to primary and secondary prevention assignment.

Appropriateness of antiplatelet therapy prescription

Out of 959 patients prescribed with an antiplatelet drug, 455 (47.4%, 95% CI 44.3–50.6) were prescribed in the frame of primary prevention and 504 (52.6%, 95% CI 49.4–55.7) in secondary prevention. Women were more often prescribed in primary prevention (246/458 patients) than men (209/501).

Primary prevention. Table 2 shows the antiplatelet drugs prescribed for primary prevention. Overall, aspirin was the most prescribed (76.3%), followed by ticlopidine (11.2%) and clopidogrel (8%). Table 3 reports the profiles of appropriateness of antiplatelet therapy in primary prevention. Of 455 patients in primary prevention, 201 (44.2%, 95% CI 39.7–48.8) were appropriately prescribed (group 1) and 237 (52.1%, 95% CI 47.4–56.7) were inappropriately prescribed (group 2). Among patients taking aspirin, 52.4% (182/347), and those taking clopidogrel, 37.2% (19/51), were appropriately prescribed due to their high risk profile (Table 2 and 3).

Among patients inappropriately prescribed, we distinguished those overprescribed and those with AF without any other cardiovascular comorbidity (Table 3 – group 2a and 2b). In group 2a, 155/209 (74.2%) were overprescribed, because they had little or no cardiovascular risk factor (SCORE < 10%), nor any previous cardiovascular disease. Among these overprescribed patients, 10 (6.5%) were from Spain, leading to a 33.3% rate of inappropriate overprescription among Spanish patients prescribed in primary prevention.

In group 2b, 28 (6.2%) patients with AF were inappropriately prescribed. Among those, 7 (25.0%) were prescribed both antiplatelet drugs and OACs. Of the remainder, 20 (71.4%) showed no contraindication for OAC according to the platelet count.

For 114 patients it was not possible to assess the SCORE for the cardiovascular risk due to missing values. As explained in the Methods section, it was, however, possible to impute it for 88 of them, but for the other 26 it was not possible to fill the missing data. For 17 of them there was no other risk factor and so that they remained 'Not assessable' (Table 3 – group 3).

Secondary prevention. Antiplatelet therapy was appropriately prescribed in 418 patients (82.9%, 95% CI 79.4–86.0), both aspirin and clopidogrel being considered appropriate for secondary prevention according to the ESC guidelines (Table 3 – group 1a). The most frequently prescribed drug was aspirin (73.7%), followed by clopidogrel (18.4%) and the combination of both (6.0%). In terms of dose prescribed both in the frame of primary and secondary prevention, the use of aspirin was mostly appropriate, but for 85 patients the dose was not assessable, because in the REPOSI database the type of package dispensed and/or the related doses was missing. Clopidrogrel was prescribed in almost all cases at the appropriate dosages.

All in all, 77 (15.3%, 95% CI 12.4–18.7) patients were inappropriately treated, due to the use of inappropriate drug or to an unduly prolonged dual antiplatelet prescription (Table 3 – group 2a).

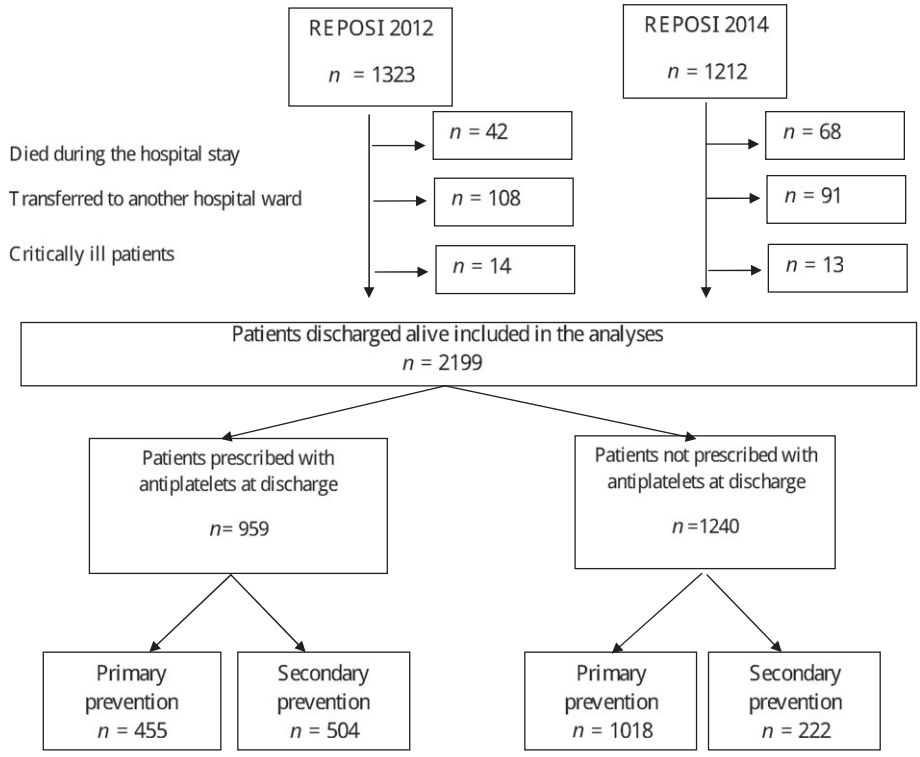

Figure 1
Flow chart of the study

Among 284 patients with CIHD, 21 (7.4%) were inappropriately prescribed both with antiplatelet agents and OACs and among 108 with AF, 21 (19.4%) were inappropriately prescribed with both.

Patients inappropriately prescribed with a wrong medication. Table 2 shows that 100 patients were inappropriately prescribed with ticlopidine. Among those, 53 were in primary prevention and 47 in secondary prevention. Among patients in primary prevention, 19 were classified as overprescribed owing to the lack of any CV risk factor, and 34 patients were classified as inappropriately prescribed as they were given ticlopidine (Table 3 – group 2a). All the patients prescribed with ticlopidine were from Italian hospital wards.

Patients prescribed with ticlopidine at hospital admission numbered 133, 82 of whom (61.7%) were still on the drug at discharge, while for 23 patients (17.3%) hospital clinicians changed it with a more appropriate antiplatelet drug. However, 18 patients were newly prescribed ticlopidine at discharge by hospital clinicians.

Appropriateness of non-prescription

Primary prevention. Of 1018 patients not prescribed with an antiplatelet drug in primary prevention, 970 (95.3% 95% CI 93.7–96.5) were appropriately not prescribed. Among these, 370 (38.2%) were not prescribed in spite of their high SCORE risk (Table 3 – group 1b). Of them, 92 (24.9%) were prescribed with an OAC. In these patients the antiplatelet therapy is recommended by the ESC guidelines, but it is not mandatory depending on their risk of bleeding. Among them, about 6% of patients had diagnoses of previous bleeding and 10% had a platelet count lower than 100 000 mm^{-3}. Finally, for 48 patients the SCORE was not assessable (Table 3 – group 3).

Secondary prevention. Patients not prescribed in secondary prevention were always considered 'Not appropriate'.

Among 726 patients in secondary prevention, 222 (30.6%, 95% CI 27.3–34.0) were not prescribed with an antiplatelet drug, thus being inappropriately underprescribed (Table 3 – group 2a). Among those, 15/31 patients (48.4%) were Spanish. Among patients inappropriately underprescribed, 74 were prescribed with OACs. Among them, 8% had diagnoses of previous bleeding and 8% had a platelet count lower than 100 000 mm^{-3}.

Discussion

This study evaluated the appropriateness of antiplatelet therapy for primary and secondary prevention of cardiovascular disease in hospitalized older people acutely admitted to internal medicine and geriatric wards. Among patients prescribed, in the frame of primary prevention half were inappropriately prescribed, being mainly overprescribed. On the other hand, we found a high proportion of patients underprescribed in the frame of secondary prevention.

While a number of clinical trials and meta-analyses showed that in the frame of secondary prevention there was a lower rate of recurrent atherothrombotic cardio-

Table 1

Characteristics of patients prescribed and not prescribed with antiplatelet agents in the frame of primary and secondary prevention of cardiovascular disease

Patient characteristics	Patients prescribed		Patients not prescribed		Missing, *n*
	Primary prevention,*n* (%)	Secondary prevention,*n* (%)	Primary prevention,*n* (%)	Secondary prevention,*n* (%)	
Overall	455	504	1018	222	
Year					
2012	259 (56.9)	265 (52.6)	526 (51.7)	109 (49.1)	
2014	196 (43.1)	239 (47.4)	492 (48.3)	113 (50.9)	
Country					
Italy	425 (93.4)	488 (96.8)	933 (91.7)	207 (93.3)	
Spain	30 (6.6)	16 (3.2)	85 (8.3)	15 (6.8)	
Age (mean, SD)	79.5 (7.7)	79.1 (7.5)	77.9 (7.3)	79.7 (7.0)	
Gender					
Males	209 (45.8)	292 (58.0)	553 (54.3)	100 (45.0)	
Females	246 (54.2)	212 (42.0)	465 (45.7)	122 (55.0)	
Smoking					73
Yes	185 (42.1)	262 (54.1)	601 (60.8)	112 (52.3)	
No	254 (57.9)	222 (45.9)	388 (39.2)	102 (47.7)	
Total cholesterol (mean, SD), mg dl^{-1}	165 (41.5)	159.9 (44.9)	159.2 (44.1)	151.0 (45.3)	491
Systolic blood pressure (mean, SD)	129 (16)	126.9 (16.3)	124.6 (15.2)	124.4 (16.3)	13
Body mass index – BMI (mean, SD)	26.2 (4.9)	26.1 (5.3)	25.8 (5.2)	26.0 (4.7)	279
Diagnosis				83 (37.4)	
Diabetes mellitus	132 (29.0)	205 (40.8)	249 (24.5)		
Atrial fibrillation	98 (21.5)	108 (21.5)	280 (27.5)	103 (46.4)	
Arterial occlusion and stenosis with/without infarction	43 (9.4)	81 (16.1)	22 (2.4)	46 (20.7)	
Stroke	0	1 (0.2)	0	3 (1.4)	
Transient ischemic attack	0	61 (12.1)	0	22 (9.9)	
Acute myocardial infarction	0	74 (14.7)	0	26 (11.7)	
Angina	0	15 (3)	0	6 (2.7)	
Revascularization procedures (by-pass and stenting)	0	20 (4)	0	10 (4.5)	
Thrombotic arterial events	0	5 (1)	0	11(5.0)	
Chronic ischemic heart disease	0	284 (56.3)	0	141 (63.5)	
Cardiovascular risk:					96
Medium (<5)	81 (18.9)		231 (24.3)		
High [5–10)	130 (30.3)		360 (38.0)		
Very high (≥10)	218 (50.8)		357 (37.7)		

SD, standard deviation

cerebrovascular events and a lower mortality in patients taking aspirin (alone or with clopidogrel) [2, 11, 32], aspirin fails to demonstrate clear benefits in primary prevention, except in people at very high cardiovascular risk [17], because in this setting the harms outweigh the benefits [2, 11]. The long-term use of aspirin even at low doses increases the risk of gastrointestinal haemorrhage [33]. This risk is amplified in older people who usually take multiple drugs, are highly susceptible to adverse drug reactions and are at a high risk of bleeding due to their advanced age [9]. This concern could

Table 2

Antiplatelet drugs prescribed for primary and secondary prevention of cardiovascular disease

Active substances	Primary prevention *n* (%)	Secondary prevention *n* (%)
Overall	**455**	**504**
Aspirin	347 (76.3)	308 (61.1)
Ticlopidine	51 (11.2)	44 (8.7)
Clopidrogrel	36 (8.0)	77 (15.3)
Clopidrogrel + aspirin	12 (2.6)	63 (12.5)
Indobufene	3 (0.7)	2 (0.4)
Ticlopidine + aspirin	2 (0.4)	3 (0.6)
Ticagrelor + aspirin		5 (1.0)
Pasugrel + clopidogrel		1 (0.2)
Aspirin + picotamide		1(0.2)
Others	4 (0.8)	

explain why in the context of our study a proportion of patients (370/1473, 25.1%, 95% CI 22.9–27.4) were undertreated in spite of their very high risk profile, even if the percentage of patients at risk of bleeding was low. Notwithstanding the evidence against the use of aspirin for primary prophylaxis, this study showed a high prevalence of its use even in the absence of cardiovascular risk factors, confirming previous data on overprescription [34, 35]. The high rate of inappropriate use of aspirin was somewhat more pronounced in women, notwithstanding the fact that women are usually at lower risk of cardiovascular events than men, but at higher risk of bleeding. This result confirmed the previous findings of Manes *et al.* [35], who showed that female sex was among the factors more likely associated with the inappropriate prescription of aspirin. It is unlikely that the unduly high rate of aspirin prescription in the frame of primary prevention is due to the recent findings that the prolonged intake of aspirin may reduce the risk of cancer [36].

In the frame of secondary prevention, this study pointed out a large underprescription of antiplatelets in older people. This finding is consistent with other studies [37–39] and may reflect concerns about the risk of bleeding. However, even if older people may be at high risk of adverse drug events, their

Table 3

Profiles of appropriateness of antiplatelet drug prescription in prescribed and non-prescribed patients according to primary and secondary prevention of cardiovascular disease

Groups	Patients prescribed (*n* = 959)		Patients not prescribed (*n* = 1240)	
	Primary prevention	Secondary prevention	Primary prevention	Secondary prevention
	455	***504***	***1018***	***222***
1) Appropriate	**201 (44.2)**	**418 (82.9)**	**970 (95.3)**	
a) Overall	***201 (100)***	***418 (100)***	***600 (61.8)***	
Aspirin	182 (90.5)	308 (73.7)		
Clopidogrel	19 (9.5)	77 (18.4)		
Dual antiplatelet therapy		25 (6.0)		
Other associations		8 (1.9)		
Not prescribed (SCORE < 10)			600 (100)	
b) Overall			***370 (38.2)***	
Not prescribed (SCORE ≥ 10)			370 (100)	
2) Not appropriate	**237 (52.1)**	**77 (15.3)**		**222 (100)**
a) Overall	***209 (88.2)***	***77 (100)***		***222 (100)***
Ticlopidine Use	34 (16.3)	44 (57.1)		
Dual antiplatelet therapy	18 (8.6)	31 (40.3)		
Other drugs	2 (0.9)	2 (2.6)		
Overprescribed (SCORE < 10)	155 (74.2)			
Underprescribed				222 (100)
b) Overall	***28 (11.8)***			
Patients with atrial fibrillation (AF)	28 (100)			
3) Not assessable	**17 (3.7)**	**9 (1.8)**	**48 (4.7)**	

risk for the adverse consequences of no treatment are likely to be substantially higher [2]. However, in our population only a small proportion of patients showed a possible risk of bleeding. On the opposite side, we identified a number of patients unduly treated for secondary prevention with both antiplatelets and OACs, a double antithrombotic therapy which carries a very high risk of bleeding.

Further, we were surprised to find that an inappropriate antiplatelet agent such as ticlopidine was still largely prescribed in Italy, both in primary and secondary prevention, notwithstanding the high risk of haematological adverse events associated with its use (such as aplastic anaemia, agranulocytosis and thrombotic trombocytopenic purpura) and hepatic toxicity, particularly in older people [40–43]. This undue prescription behaviour did not occur in the small group of Spanish patients, but it has been seen recently in other European countries such as Poland [44]. Furthermore, not only did a number of hospital clinicians in Italy fail to deprescribe ticlopidine during hospitalization, but they even prescribed this inappropriate drug afresh.

The main strength of the study based upon data from a large register of hospitalized older people is to provide a broad view on the adherence or lack of adherence of older people to current European guidelines on antiplatelet therapy, both in the frame of primary and secondary cardiovascular prevention. Although the hospital-based case series may be seen as a limitation, in our population 92.6% of patients (n = 2027) were discharged at home (data not shown), thus not impairing the generalizability of results. On the other hand, a possible poor accuracy of the compilation of CIRS may have caused a lower identification of patients treated in the frame of secondary prevention, even though the severity of some events are unlikely to be underreported in a hospital-based register aimed at monitoring multimorbidity and polypharmacy. The lack of a bleeding score validated for older patients in the general population makes it difficult to evaluate the risk of bleeding in this cohort. Furthermore, it was not always possible to identify the dose prescribed. Finally, we were unable to evaluate the effects of the inappropriate prescription of antiplatelet drugs on such important outcomes as mortality and re-hospitalization, because even though clinical data were collected again at 3 months after discharge, the insufficient number of actual events makes the results unreliable.

In conclusion, this study showed a high degree of inappropriateness among hospitalized older patients prescribed with antiplatelets for primary prevention and a widespread underprescription for secondary prevention. Ticlopidine still remains largely prescribed in Italy, despite its documented risk of serious adverse events. Pharmacoepidemiological studies like this should be useful to stir clinicians to update their pharmacological knowledge and to highlight the need to review their therapies, in order to save resources and decrease the risk of adverse drug reactions in older patients.

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.

Appendix

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