


Safety of Antiplatelet Agents: Analysis of ‘Real-World’ Data from the Italian National Pharmacovigilance Network

Lucia Gozzo^{1,2} · Andrea Navarra¹ · Giuseppe Benfatto³ · Laura Longo³ · Silvana Mansueto³ · Laura Sottosanti⁴ · Luca Pani⁴ · Salvatore Salomone¹ · Filippo Drago^{1,3} 

Published online: 30 August 2017

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Abstract

Introduction According to the Italian National Report on drug use, thienopyridines (ticlopidine, clopidogrel and prasugrel) and ticagrelor represent the most prescribed antiplatelet agents, beside aspirin. The aim of this study was to analyse the safety profile of these drugs using data from spontaneous reporting of suspected adverse reactions (ADRs).

Methods Suspected ADRs for ticlopidine, clopidogrel, prasugrel and ticagrelor, reported on the Italian National Pharmacovigilance Network between January 2009 and December 2016, were included in the analysis. All suspected ADRs were classified by frequency, seriousness, outcome, age and system organ class.

Results Clopidogrel showed the highest absolute number of suspected ADRs, followed by ticlopidine. However, these data need to be contextualized in view of the differences in marketing authorization dates, prescription

rates and a characterization of the relative seriousness of ADRs per each drug. After the correction for prescription rate, ticagrelor showed the highest reporting trend and ticlopidine the lowest. Most ADRs occurred in the elderly, in particular for ticlopidine. Bleeding represents one of the most reported events (ticlopidine 40%, clopidogrel 26%, prasugrel 42%, ticagrelor 30%) and aspirin was the most frequently associated suspected drug. The majority of ADRs had complete recovery and were non-serious, except for ticlopidine (serious ADRs 53%). Prasugrel showed the highest percentage of ‘life-threatening’ events and ‘death’.

Conclusions Based on the analysis conducted on spontaneous ADRs reporting system in Italy, the safety profile of antiplatelet drugs seems favourable. However, the overall risk-benefit ratio of these drugs needs to be reassessed taking into account the appropriateness of use in particular populations at risk, such as the elderly. Based on this information, we believe that more attention from clinicians and/or an implementation of regulatory measures could be useful for clinical practice.

✉ Filippo Drago
f.drago@unict.it

¹ Department of Biomedical and Biotechnological Sciences, Section of Pharmacology, University of Catania, Via S. Sofia 97, Catania, Italy

² UNIFARM Research Centre, Catania, Italy

³ Regional Pharmacovigilance Centre of Catania, A.O.U. Policlinico-Vittorio Emanuele, Catania, Italy

⁴ Italian Medicines Agency, Rome, Italy

Key Points

Suspected adverse drug reactions (ADRs) represent a validated and reliable source of information about the ‘real-world’ safety of drugs prescribed in clinical practice. This study aimed to analyse data from the Italian National Pharmacovigilance Network collecting spontaneously reported ADRs, in order to evaluate the safety profile of antiplatelet agents beside aspirin (ticlopidine, clopidogrel, prasugrel and ticagrelor).

We found a higher absolute total number of suspected ADRs for clopidogrel, followed by ticlopidine, ticagrelor and prasugrel. These data need to be contextualized in view of the differences in marketing authorization, prescription rates and the relative seriousness of ADRs per each drug. In particular, ticagrelor and prasugrel were licensed more recently in Italy and clopidogrel and ticlopidine have a higher prescription rate. According to our results, the safety profile of these medications seems favourable, considering that reported ADRs were generally non-serious and/or completely recovering.

Further studies are needed to better define their overall risk-benefit ratio and place in therapy, ensuring an appropriate and safe use for patients. Moreover, considering that most of the suspected ADRs observed with ticlopidine come from its use in the elderly, representing an example of misuse according to Beers list, an evaluation of prescription appropriateness could be useful for clinical practice.

1 Introduction

Antiplatelet agents interfere with platelet activation and are commonly prescribed for the primary and secondary prevention of serious vascular events, such as non-fatal myocardial infarction (MI), non-fatal stroke or vascular death [1]. According to the annual Italian National Report on drug use, thienopyridines (ticlopidine, clopidogrel and prasugrel) and ticagrelor represent the most prescribed antiplatelet agents, beside aspirin [2]. These medications are commonly used in patients with unstable angina, patients with acute coronary syndromes (ACSs) and/or patients undergoing percutaneous coronary intervention

(PCI) [3]. In this population, these drugs reduce the restenosis rate, risk of thrombosis and major adverse cardiac events [4]. Moreover, the use of thienopyridines has been demonstrated to be safe and effective in the prevention of transient ischaemic attack (TIA) or ischaemic stroke in patients at high risk [5].

Over the last decade, several studies in this field produced evidence about the association of ticlopidine with a number of serious adverse drug reactions (ADRs), including aplastic anaemia, thrombotic thrombocytopenic purpura, agranulocytosis and pancytopenia [6]. Based on these findings, the use of ticlopidine has been reduced accordingly, and it has been substituted mainly by the second-generation thienopyridine derivative clopidogrel [7]. Recently, international clinical guidelines and clinical trials also support the use of prasugrel and ticagrelor instead of ticlopidine and clopidogrel in several clinical conditions, including interventional cardiology and non-ST elevation MI [8, 9].

The Italian National Pharmacovigilance Network is an electronic spontaneous reporting database that collects reports of all suspected ADRs from the Italian National territory [10]. Once observed by healthcare professionals (or patients), reports of suspected ADRs are submitted electronically to the Network by the qualified person responsible for pharmacovigilance and become visible to the professionals of regional pharmacovigilance centres. Although these reports are based on the hypothetical suspicion of an ADR, rather than a clear causal association between an event and a specific treatment, they represent a validated and reliable source of information about the ‘real-world’ safety of drugs prescribed in clinical practice.

The aim of this study was to analyse data from the Italian National Pharmacovigilance Network collecting spontaneously reported ADRs, in order to produce evidence about the ‘real-world’ safety profile of ticlopidine, clopidogrel, prasugrel and ticagrelor.

2 Methods

We accessed the Italian National Pharmacovigilance Network, searching for all suspected ADRs related to any prescription of medicinal products containing ticlopidine, clopidogrel, prasugrel and ticagrelor, reported during the period between January 2009 and December 2016. All suspected ADRs were classified by frequency, seriousness, outcome, sex, age and according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology [11]. MedDRA is a clinically validated international medical

terminology used by regulatory authorities and the biopharmaceutical industry in order to standardize data and manage their processing for regulatory communications (registration, documentation and safety monitoring of medical products in both pre- and post-marketing phases).

MedDRA hierarchy is made up of the following five terminology levels:

- System organ classes (SOCs);
- High level group terms (HLGTs);
- High level terms (HLT);
- Preferred terms (PT);
- Lowest level terms (LLTs).

The highest level, represented by SOC, groups symptoms, signs, disease diagnosis, identified by a PT, according to aetiology (e.g. infections and infestations), manifestation site (e.g. gastrointestinal disorders) or purpose (e.g. surgical and medical procedures).

Considering that a single patient could present more than one clinical manifestation/symptom within the same ADR, we calculated the rate for each of the observed conditions classified by SOC over the total number of clinical manifestations, rather than over the total number of ADRs as for the other parameters considered.

The classification by seriousness was based on the distinction between non-serious, undefined and serious ADRs. Serious suspected ADRs include ‘death’, ‘life-threatening’, ‘persistent or significant disability’, ‘hospitalization/prolongation of existing hospitalization’, ‘other clinically meaningful condition’ and ‘congenital anomalies/birth defects’ [12].

Information about the cause of the events (‘therapeutic error’, ‘abuse’, ‘misuse’, ‘overdose’, ‘interaction’, ‘off-label use’, ‘occupational exposure’) was available only for a small percentage of ADRs (almost 5%), therefore we did not take into account these data.

In order to adjust results taking into account the exposed population, we estimated the number of patients treated with each drug using the following formula:

$$X = \text{DDD} \times \text{reference population}/1000$$

with X representing the number of patients treated per day, DDD representing the Daily Defined Dose (DDD)/1000 inhabitants per day, and the reference population being the one used for the calculation of the DDD. DDD and reference population were those reported in the annual OSMED Reports published by the Italian Medicine Agency (Agenzia Italiana del Farmaco–AIFA) [2, 13–18] between 2009 and 2015 (data for 2016 are not available yet).

Assuming that the number of subjects treated can be considered constant over a year, the number of patients treated per day obtained with the formula above has been used to calculate the ADRs/patient treated ratio for each drug.

3 Results

3.1 Absolute Number of Suspected Adverse Drug Reactions (ADRs) and ADRs/Patients Treated Ratio

Figure 1a shows the absolute number of suspected ADRs per medication. Clopidogrel resulted in the highest absolute number of suspected ADRs (3298), followed by ticlopidine (1169), ticagrelor (471) and prasugrel (126). Non-serious ADRs were the most represented type of events, except for ticlopidine, which showed a higher percentage of serious ADRs (53.0%, Fig. 1b). Table 1 shows in detail ADRs per year per drug.

Table 2 shows the number of prescriptions for ticlopidine, clopidogrel, prasugrel and ticagrelor. Data are presented as DDD/1000 inhabitants per day. Prescription rates were significantly higher for ticlopidine until 2013, but clopidogrel has shown an increasing consumption rate over the recent years. Overall, ticlopidine and clopidogrel had a comparable prescription rate, which was more than 25-fold higher than for ticagrelor and prasugrel. Table 3 shows the number of patient treated per day (extrapolated from DDD value) for ticlopidine, clopidogrel, prasugrel and ticagrelor in the period between 2007 and 2015. Reference population per year were 38 million for 2007, 37 million for 2008, 40 million for 2009, 38 million for 2010, 44 million for 2011, 59.4 million for 2012, 59.7 million for 2013, 60.8 million for 2014 and 60.8 million for 2015. Analysing the ADRs/patients treated ratios (Table 4), the drugs with the highest and the lowest ADRs reported were ticagrelor and ticlopidine, respectively.

3.2 Seriousness of ADRs

The most frequent serious conditions were those that resulted in ‘hospitalization/extended hospitalization’, followed by ‘other clinically relevant condition’ for each of the evaluated drugs, with the exception of prasugrel, which showed a higher percentage of life-threatening conditions: 11% over total serious ADRs compared to ticagrelor (9%), clopidogrel (6%) and ticlopidine (4%) (Fig. 2). Furthermore, prasugrel also showed the highest relative percentage of reports with fatal outcome (9% over total serious ADRs, related to fatal bleeding), followed by ticagrelor (3%, related to fatal bleeding and in one case related to bone marrow aplasia), ticlopidine (2.5%, almost half related to fatal bleeding and the other half to bone marrow aplasia) and clopidogrel (2.0%, related to fatal bleeding or lack of effectiveness, one case related to pancreatitis, one case to liver failure and one to bone marrow aplasia). No congenital anomalies/birth defects have been observed.

Fig. 1 a Absolute number of suspected adverse drug reactions (ADRs) per drug; **b** percentage of ADRs per seriousness

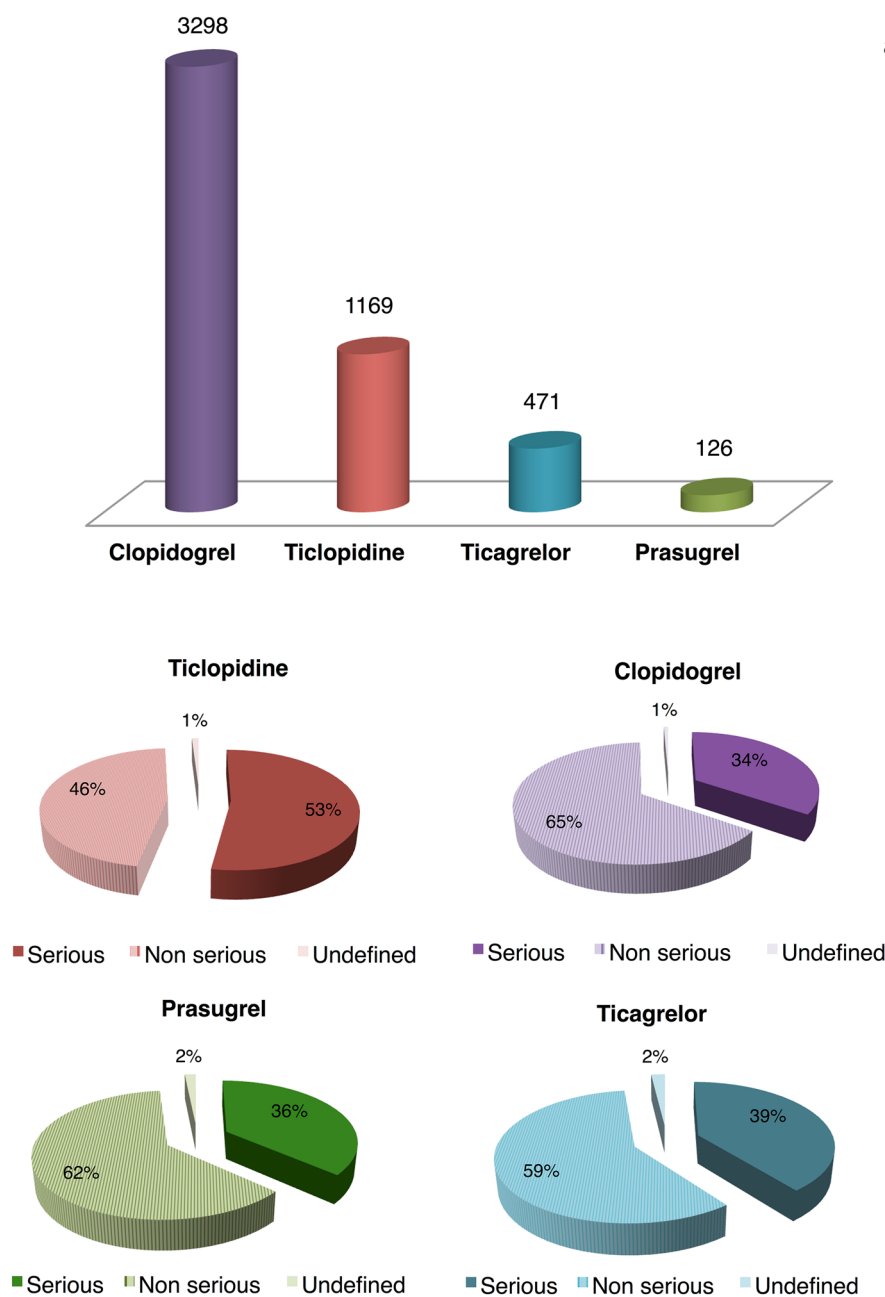


Table 1 Number of adverse drug reactions (ADRs) per year from 2009 to 2016 for ticlopidine, clopidogrel, prasugrel and ticagrelor

Drug	2009	2010	2011	2012	2013	2014	2015	2016	Total
Ticlopidine	111	150	117	144	212	166	164	105	1169
Clopidogrel	83	112	186	312	482	787	656	680	3298
Ticagrelor	–	–	–	22	74	98	142	135	471
Prasugrel	–	5	10	13	26	26	24	22	126

3.3 Outcome of ADRs

Figure 3 shows suspected ADRs listed by outcome, with the most frequent condition represented by ‘complete recovery’ or ‘improvement’, all together accounting for

more than half of the reported outcomes (77.0% for ticlopidine, 76.2% for prasugrel, 74.3% for clopidogrel, 70.0% for ticagrelor). When considering ‘death’ as the final outcome of any type of reaction, the drug associated with the highest percentage of events with fatal outcome was

Table 2 Number of prescriptions (daily defined dose/1000 inhabitants per day) for ticlopidine, clopidogrel, prasugrel and ticagrelor in the period between 2007 and 2015 (data for 2016 were not yet available)

Drug	2009	2010	2011	2012	2013	2014	2015
Ticlopidine	6.8	6.6	6.7	6.2	5.5	4.7	4.0
Clopidogrel	0.9	0.9	3.5	4.7	5.9	7.1	8.1
Ticagrelor	–	–	–	0.1	0.3	0.5	0.6
Prasugrel	–	–	0.1	0.2	0.3	0.3	0.3

Adapted from: Agenzia Italiana del Farmaco—L'uso dei Farmaci in Italia. Rapporto OSMED 2015. June 2016 [2]

prasugrel (4.8%, compared to 2.7% for ticlopidine, 1.3% for ticagrelor and 1.1% for clopidogrel). Additional information about outcome, such as spontaneous recovery, use of active intervention/treatment, discontinuation of suspected drug prior to recovery (positive dechallenge), was not available.

3.4 Correlation of ADRs with Age and Sex

Figure 4a shows that 85.5% of all suspected ADRs for ticlopidine occurred in patients ≥ 65 year old, 77% for clopidogrel, 60% for ticagrelor and 45% for prasugrel. Figure 4b shows the number of ADRs per decade of age. The rate of ADRs in the elderly was homogeneous over the years (Table 5).

Figure 5 presents stratification per sex of all suspected ADRs, showing a relatively higher frequency of ADRs in men, except for ticlopidine. Missing data about sex (0.9%

for clopidogrel, 0.4% for ticlopidine and 1.7% for ticagrelor) have been considered negligible.

3.5 Suspected ADRs by System Organ Class (SOC) and Association with Other Drugs

3.5.1 Ticlopidine

Out of 1765 total clinical conditions, the most frequently reported events for ticlopidine were gastrointestinal disorders (26.9%), blood and lymphatic system disorders (15.2%), respiratory, thoracic and mediastinal disorders (14.3%), and skin and subcutaneous tissue disorders (10.9%, Table 6). Ten events (0.6%) were related to lack of effectiveness (ischaemic stroke, MI, thrombosis). Almost 40% of the events (713/1765) were represented by bleedings.

Out of 1169 total suspected ADRs, 284 (24.3%) were associated with concomitant use of other suspected drugs (Table 7). Aspirin represented the most frequently associated suspected drug (26%) and bleeding was the most frequently reported event with this association (90%). About 19.6% of the total number of bleedings were associated with concomitant use of other antiplatelet and/or anticoagulant drugs (data not shown).

3.5.2 Clopidogrel

Out of 5605 total clinical conditions, the most frequently reported events for clopidogrel were gastrointestinal disorders (27.3%), skin and subcutaneous tissue disorders (24.5%), respiratory, thoracic and mediastinal disorders

Table 3 Patients-treated-per-day extrapolated from daily defined dose values for ticlopidine, clopidogrel, prasugrel and ticagrelor in the period between 2009 and 2015 (data related to year 2016 were not yet available)

Drug	2009	2010	2011	2012	2013	2014	2015
Ticlopidine	272,000	250,800	294,800	368,280	328,350	285,760	243,200
Clopidogrel	36,000	34,200	154,000	279,180	352,230	431,680	492,480
Ticagrelor	–	–	–	5940	17,910	30,400	36,480
Prasugrel	–	–	4400	11,880	17,910	18,240	18,240

Data from: Agenzia Italiana del Farmaco—L'uso dei Farmaci in Italia. Rapporto OSMED 2009 [13], Rapporto OSMED 2010 [14], Rapporto OSMED 2011 [15], Rapporto OSMED 2012 [16], Rapporto OSMED 2013 [17], Rapporto OSMED 2014 [18], Rapporto OSMED 2015 [2]

Table 4 Rate of adverse drug reactions per number of patients treated

Drug	2009 (%)	2010 (%)	2011 (%)	2012 (%)	2013 (%)	2014 (%)	2015 (%)
Ticlopidine	0.04	0.06	0.04	0.04	0.06	0.06	0.07
Clopidogrel	0.23	0.33	0.12	0.11	0.14	0.18	0.13
Ticagrelor	–	–	–	0.37	0.41	0.32	0.39
Prasugrel	–	–	0.23	0.11	0.15	0.14	0.13

Fig. 2 Percentage of different type of serious adverse drug reactions (ADRs)

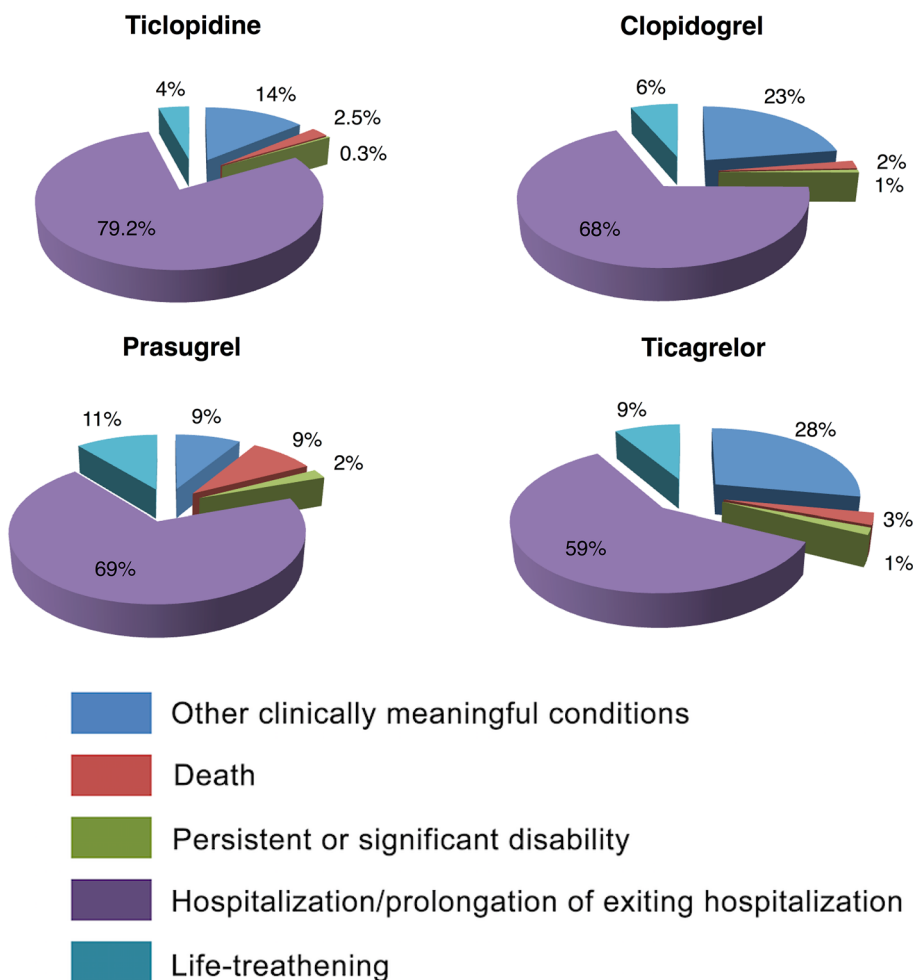
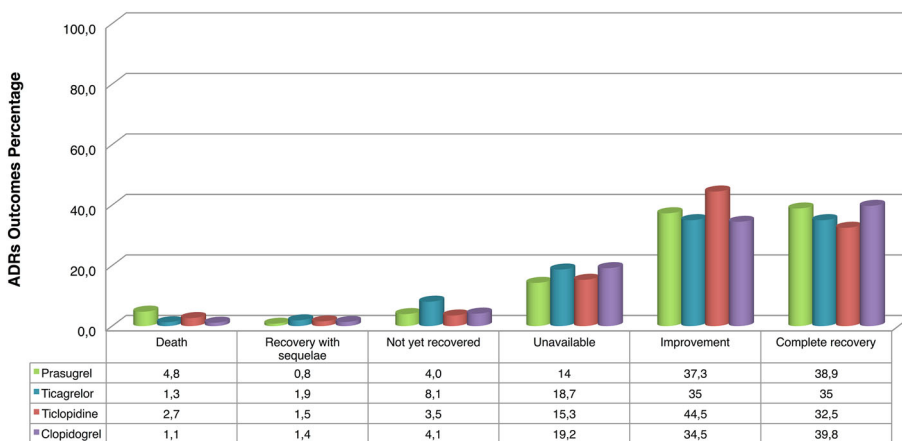


Fig. 3 Suspected adverse drug reactions (ADRs) listed by outcome



(11.5%), and general disorders and administration site conditions (6.2%, Table 8).

Few events (80/5605; 1.4%) were related to lack of effectiveness (ischaemic stroke, MI, stent thrombosis, intermittent claudication). Almost 26% of the events (1496/5605) were represented by bleedings.

Out of 3298 total suspected ADRs, 1129 (34.2%) were associated with the concomitant use of other suspected drugs (Table 7). Aspirin represented the most frequently associated suspected drug (56.8%) and bleeding was the most frequent reported event with this association (86.9%). About 64.8% of the total number of bleedings was

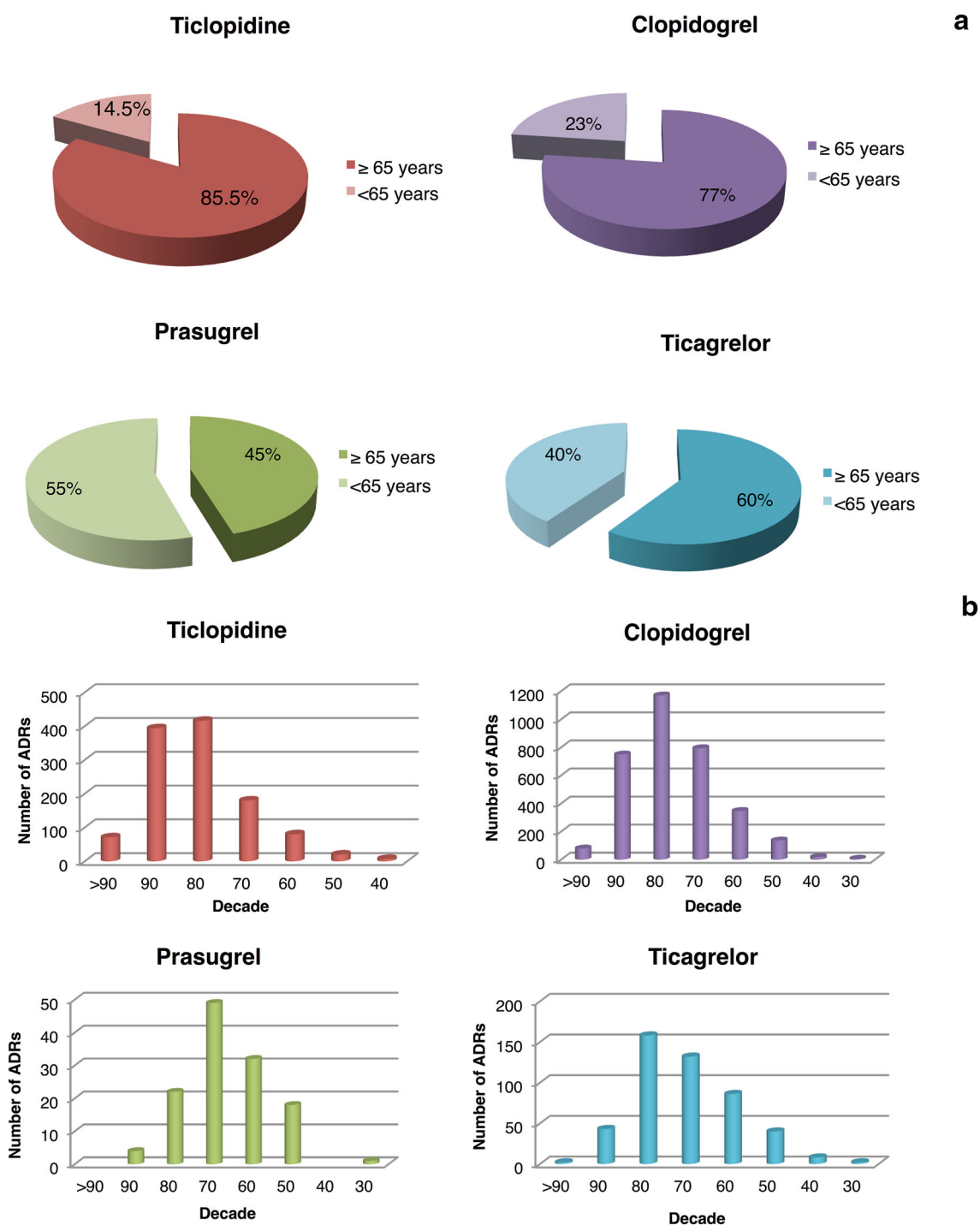


Fig. 4 **a** Data stratified by age of presentation (≥ 65 or < 65 years); **b** adverse drug reactions (ADRs) per decade of presentation

associated with concomitant use of other antiplatelet and/or anticoagulant drugs (data not shown).

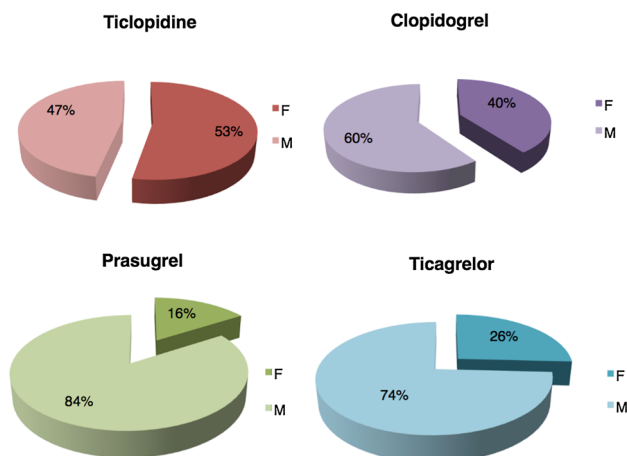
3.5.3 Prasugrel

Out of 186 total clinical conditions, the most frequently reported events with prasugrel were respiratory, thoracic

and mediastinal disorders (24.7%), skin and subcutaneous tissue disorders (23.1%), gastrointestinal disorders (15.6%) and neurological disorders (8.6%, Table 9). Two events (1.1%) were related to lack of effectiveness (thrombosis and coronary thrombosis). Almost 42% of the events (78/186) were represented by bleedings.

Table 5 Percentage of adverse drug reactions per year for ticlopidine reported by age

Age (years)	2009	2010	2011	2012	2013	2014	2015	2016	Total
<65	22 (19.8%)	23 (15.3%)	22 (18.8%)	23 (16%)	29 (13.7%)	18 (11.4%)	21 (12.8%)	12 (11.4%)	170 (14.5%)
≥65	89 (80.2%)	127 (84.7%)	95 (81.2%)	121 (84%)	183 (86.3%)	148 (88.6%)	143 (87.2%)	93 (88.6%)	999 (85.5%)
Total	111 (100%)	150 (100%)	117 (100%)	144 (100%)	212 (100%)	166 (100%)	164 (100%)	105 (100%)	1169 (100%)

**Fig. 5** Stratification per sex. F female, M male

Out of 126 total suspected ADRs, 73 (57.9%) were associated with concomitant use of other suspected drugs (Table 7). Aspirin represented the most frequently associated suspected drug (63.3%), and bleeding was the most frequently reported event with this association (92.7%). About 77% of the total number of bleedings were associated with the concomitant use of other antiplatelet and/or anticoagulant drugs (data not shown).

3.5.4 Ticagrelor

Out of 694 total clinical conditions, the most frequently reported events with ticagrelor were respiratory, thoracic and mediastinal disorders (32.4%), gastrointestinal disorders (16.1%), skin and subcutaneous tissue disorders (13.4%), and cardiac disorders (6.3%, Table 10). Few events (7/694; 1.0%) were related to lack of effectiveness (MI, thrombosis). Almost 30% of the events (212/694) were represented by bleedings.

Out of 471 total suspected ADRs, 187 (39.7%) were associated with concomitant use of other suspected drugs (Table 7). Aspirin represented the most frequently associated suspected drug (68.1%) and bleeding was the most frequent reported event with this association (88.3%). About 70% of the total number of bleedings was associated

with the concomitant use of other antiplatelet and/or anti-coagulant drugs (data not shown).

4 Discussion

Treatment-related medical conditions represent an important issue in clinical practice, considering both their potential poor outcome and the costs for their management and follow-up. Recent studies in the field pointed out that up to 20% of the ADRs that occur in clinical practice are preventable, as long as the use is in compliance with the requirements of current labels and the international consensus clinical guidelines [19]. Given the existing gap between clinical trials and 'real-world' clinical practice, a relatively unpredictable efficacy and safety profile is often observed at a post-marketing level, especially for special populations that are normally excluded from evaluation at the pre-registration stage such as children and the elderly [20]. Most of the evidence about the safety profile of antiplatelet drugs collected up to now comes from data published in clinical trials and individual case reports, while 'real-world' data have not been, so far, extensively investigated. The spontaneous reporting system for suspected ADRs represents the basis of a pharmacovigilance system, as it allows a rapid detection of potential alarm signals and appropriate follow-up actions. However, it shows several limitations, mainly related to under-/over-reporting [21].

We found a higher absolute total number of suspected ADRs for clopidogrel (3298), followed by ticlopidine (1169), ticagrelor (471) and prasugrel (126). At first sight, these data would suggest that clopidogrel and ticlopidine have a lower safety profile, compared to prasugrel and ticagrelor. However, these data need to be contextualized in view of the differences in marketing authorization dates, prescription rates and a characterization of the relative seriousness of ADRs per each drug. In particular, ticagrelor and prasugrel were licensed more recently in Italy compared to clopidogrel and ticlopidine. Given the lack of access to detailed information about prescriptions, we used data reported in the official OSMED National Reports on drug use in Italy, which provides an estimate value for

Table 6 Clinical conditions associated with ticlopidine per system organ classes (SOCs). Most frequent preferred terms (PTs) (with at least five reports) are listed for each drug. Percentage of each PT was calculated on the total of the corresponding SOC

Clinical conditions	Number	%
Ticlopidine		
Gastrointestinal disorders	474	26.9
Rectal haemorrhage	81	17.1
Diarrhoea	61	12.9
Melaena	60	12.7
Abdominal pain upper	31	6.5
Haematemesis	26	5.5
Gastrointestinal haemorrhage	26	5.5
Nausea	16	3.4
Abdominal pain	14	3.0
Dyspepsia	11	2.3
Gastric ulcer haemorrhage	10	2.1
Others	138	29.1
Blood and lymphatic system disorders	267	15.1
Anaemia	104	39
Leukopenia	37	13.9
Neutropenia	31	11.6
Thrombocytopenia	18	6.7
Agranulocytosis	18	6.7
Pancytopenia	11	4.1
Febrile neutropenia	7	2.6
Bone marrow failure	6	2.2
Thrombotic thrombocytopenic purpura	6	2.2
Others	33	10.9
Respiratory, thoracic and mediastinal disorders	252	14.3
Epistaxis	221	87.7
Haemoptysis	12	4.8
Dyspnoea	6	2.4
Others	13	5.2
Skin and subcutaneous tissue disorders	193	10.9
Urticaria	40	20.7
Pruritus	32	16.6
Erythema	21	10.9
Angioedema	9	4.7
Ecchymosis	8	4.1
Rash	8	4.1
Pruritus generalised	7	3.6
Hyperhidrosis	6	3.1
Others	62	32.1
Others (nervous system disorders, injury, poisoning and procedural complications, etc.)	578	32.7
Total	1765	100

prescription rates of antiplatelet agents. More specifically, the OSMED National Report–2015 [2] shows that ticlopidine was the most prescribed antiplatelet agent until 2013, though later clopidogrel reached ticlopidine's DDD/1000 inhabitants per day. However, these data should be considered as reflecting the actual consumption since 2011

only, because in this year the OSMED Report calculation started to include both the 'direct channel of distribution' (through hospitals or local public pharmacies) and the 'indirect channel' (including private pharmacies distribution on behalf of the National Health System). Within the prescription values for 2015, clopidogrel and ticlopidine

Table 7 Associations between ticlopidine, clopidogrel, prasugrel and ticagrelor and other suspected drugs

Drugs' associations	Number	%
Ticlopidine		
Ticlopidine + aspirin	101	26.0
Ticlopidine + vitamin K antagonists	31	8.0
Ticlopidine + heparins	29	7.5
Clopidogrel + statins	17	4.4
Ticlopidine + other antiplatelet agents (beside aspirin)	12	3.1
Ticlopidine + Others	199	51.2
Ticlopidine associations	389	100
Clopidogrel		
Clopidogrel + aspirin	839	56.8
Clopidogrel + vitamin K antagonists	179	12.1
Clopidogrel + heparins	58	3.9
Clopidogrel + statins	53	3.6
Clopidogrel + proton pump inhibitors	24	1.6
Clopidogrel + Others	324	21.9
Clopidogrel associations	1477	100
Prasugrel		
Prasugrel + aspirin	57	63.3
Prasugrel + other antiplatelet agents (beside aspirin)	8	8.9
Prasugrel + heparins	4	4.4
Prasugrel + Others	21	23.3
Prasugrel associations	90	100
Ticagrelor		
Ticagrelor + aspirin	154	68.1
Ticagrelor + statins	16	7.1
Ticagrelor + heparins	5	2.2
Ticagrelor + Others	51	22.6
Ticagrelor associations	226	100

Vitamin K antagonists: acenocumarol, warfarin; *heparins*: dalteparin, enoxaparin, heparin, nadroparin, parnaparin; *statins*: atorvastatin, pravastatin, rosuvastatin, simvastatin; *proton pump inhibitors*: lansoprazole, omeprazole, pantoprazole; *other antiplatelet agents (beside aspirin)*: abciximab, clopidogrel, dipyridamole, eptifibatide, ticagrelor, ticlopidine, tirofiban

were the most prescribed antiplatelet agents, not considering aspirin (respectively 8.1 DDD/1000 inhabitants per day for clopidogrel, and 4.0 DDD/1000 inhabitants per day for ticlopidine), while prasugrel and ticagrelor had a significantly lower rate of prescription (0.3 DDD/1000 inhabitants per day for prasugrel and 0.6 DDD/1000 inhabitants per day for ticagrelor) [2]. These data may explain, at least in part, the higher absolute number of suspected ADRs associated with clopidogrel and ticlopidine compared to ticagrelor and prasugrel. In fact, analysing the ADRs/patients treated ratios (Table 4), the drug with the highest ADRs reported was ticagrelor, whereas the drug with the lowest ADRs reported was ticlopidine. However, a formal comparison is still not possible due to other biases related to the spontaneous reporting system. In particular, under-reporting is a common phenomenon, but it is difficult to quantify and to correct. In general, it

involves mainly less severe and better-known ADRs and it seems to be lower for drugs recently marketed. This fact should be taken into account when comparing ADR profiles of different drugs, and could explain the relatively lower rate of reporting for the oldest drugs clopidogrel and ticlopidine. Moreover, spontaneous reporting could be influenced by safety alerts (notoriety bias), leading to over-reporting of specific ADRs for a given drug. This bias cannot be solved by compensating for prescription rates and must be taken into account in order to avoid incorrect conclusions.

Non-serious ADRs were the most represented conditions, except for ticlopidine, which showed a higher rate of serious ADRs (53%, most of which related to 'hospitalization/prolongation of existing hospitalization') compared to ticagrelor (39%), prasugrel (36%) and clopidogrel (34%). Considering that more than 85% of ticlopidine

Table 8 Clinical conditions associated with clopidogrel per system organ classes (SOCs). Most frequent preferred terms (PTs) (with at least five reports) are listed for each drug. Percentage of each PT was calculated on the total of the corresponding SOC

Clinical conditions	Number	%
Clopidogrel		
Gastrointestinal disorders	1530	27.3
Abdominal pain upper	197	12.9
Diarrhoea	170	11.1
Rectal haemorrhage	150	9.8
Nausea	128	8.4
Melaena	117	7.6
Abdominal pain	110	7.2
Vomit	92	6.0
Dyspepsia	63	4.1
Gastrointestinal haemorrhage	48	3.1
Gingival bleeding	43	2.8
Others	374	24.4
Skin and subcutaneous tissue disorders	1371	24.5
Pruritus	282	20.6
Urticaria	257	18.7
Erythema	210	15.3
Rash	133	9.7
Pruritus generalised	111	8.1
Ecchymosis	43	3.1
Dermatitis	40	2.9
Rash generalised	32	2.3
Petechiae	22	1.6
Dermatitis allergic	20	1.5
Others	221	16.1
Respiratory, thoracic and mediastal disorders	644	11.5
Epistaxis	485	75.3
Dyspnoea	52	8.1
Haemoptysis	32	5.0
Cough	19	3.0
Bronchospasm	9	1.4
Suffocation feeling	6	0.9
Dyspnoea exertional	5	0.8
Throat irritation	5	0.8
Others	31	4.8
General disorders and administration site conditions	348	6.2
Asthenia	69	19.8
Malaise	43	12.4
Drug interaction	37	10.6
Oedema peripheral	17	4.9
Drug ineffective	17	4.9
Chest pain	13	3.7
Pyrexia	13	3.7
Feeling hot	13	3.7
Drug intolerance	12	3.4
Face oedema	10	2.9
Others	104	29.9
Others (nervous system disorders, cardiac disorders, etc.)	1712	30.5
Total	5605	100

Table 9 Clinical conditions associated with prasugrel per system organ classes (SOCs). Most frequent preferred terms (PTs) (with at least five reports) are listed for each drug. Percentage of each PT was calculated on the total of the corresponding SOC

Clinical conditions	Number	%
Prasugrel		
Respiratory, thoracic and mediastinal disorders	46	24.7
Epistaxis	32	69.6
Dyspnoea	6	13.0
Others	8	17.4
Skin and subcutaneous tissue disorders	43	23.1
Erythema	12	27.9
Pruritus	9	20.9
Rash	6	14.0
Others	16	37.2
Gastrointestinal disorders	29	15.6
Melaena	5	17.2
Others	24	82.8
Nervous system disorders	16	8.6
Central nervous system haemorrhage	8	50
Others	8	50
Others (blood and lymphatic system disorders, vascular disorders, etc.)	52	28.0
Total	186	100

ADRs have been reported in the elderly, a population at high-risk and more subject to hospitalization, these data could support the high rate of serious ADRs reported for this drug. When stratifying the suspected ADRs, we found that, among serious suspected ADRs, the most frequently reported condition was represented by ‘hospitalization/extended hospitalization’, followed by ‘other clinically relevant condition’ and ‘life-threatening’, with the exception of prasugrel, which showed a higher percentage of ‘life-threatening’ events: 11% out of total serious ADRs compared to ticagrelor (9%), clopidogrel (6%) and ticlopidine (4%). Even the highest percentage of the event ‘death’ was observed in association with prasugrel (3.2% out of total ADRs and 9% out of total serious ADRs), followed by ticagrelor (1.1% out of total ADRs; 3% out of serious ADRs), ticlopidine (1.3% out of total ADRs; 2.5% out of serious ADRs) and clopidogrel (0.7% out of total ADRs; 2.0% out of serious ADRs). The higher percentage of serious ADRs reported for prasugrel and ticagrelor might be explained by their specific drug indication in association with aspirin.

For further stratification we considered the outcome of the cumulative ADRs for the four medications; the most frequent outcomes were ‘complete recovery’ or ‘clinical improvement’ for all of them. Such a high percentage of complete recovery/improvement is consistent with the higher percentage of non-serious ADRs.

When analysing these data by the parameter ‘age of reaction onset’, an interesting finding was that the majority of the suspected ADRs were reported in the elderly, especially for ticlopidine and clopidogrel. This could be at

least partly explained by the specific indications of ticlopidine and clopidogrel for pathologies (such as TIA) with a higher incidence after 65 years of age, hence suggesting possible greater use in a much older population. However, Beers Criteria for potential inappropriate use of medications in older adults already reported in 2002 that ‘Safer, more effective alternatives exist’ for ticlopidine [22] and a clear strong recommendation to avoid its use in all adults aged 65 years and older was provided from 2012 [23], and confirmed in the most updated version [24, 25]. The reporting of such a high percentage (85.5%) of ADRs in the elderly in the Italian database demonstrates that ticlopidine use in this population has continued despite these recommendations. Data from our study suggest that most of the suspected ADRs observed with ticlopidine come from its use in the elderly, representing an example of misuse; therefore, an evaluation of prescription appropriateness could be useful for clinical practice. The Beers list does not mention clopidogrel, and considers the use of prasugrel as inappropriate only in patients older than 75 years.

Interestingly, suspected ADRs were more frequently observed in men than in women for the medications analysed, except for ticlopidine. This finding could be related to a difference in terms of prescription rate of antiplatelet agents according to gender, but we have no information about this specific issue in Italy. In contrast, some studies suggested gender-specific effects on clinical outcomes with antiplatelet agents, reporting a higher risk of bleeding in women than in men [26–28]. However, to date, no conclusive data have been produced concerning the correlation of efficacy and/or safety with gender.

Table 10 Clinical conditions associated with ticagrelor per system organ classes (SOCs). Most frequent preferred terms (PTs) (with at least five reports) are listed for each drug. Percentage of each PT was calculated on the total of the corresponding SOC

Clinical conditions	Number	%
Ticagrelor		
Respiratory, thoracic and mediastinal disorders	225	32.4
Dyspnoea	134	59.6
Epistaxis	55	24.4
Dyspnoea at rest	8	3.6
Haemoptysis	5	2.2
Others	23	10.2
Gastrointestinal disorders	112	16.1
Rectal haemorrhage	21	18.8
Melaena	18	16.1
Haemorrhage	7	6.3
Gingival bleeding	7	6.3
Abdominal pain upper	6	5.4
Haematemesis	6	5.4
Diarrhoea	5	4.5
Haemorrhage	5	4.5
Nausea	5	4.5
Others	32	28.6
Skin and subcutaneous tissue disorders	93	13.4
Erythema	19	20.4
Urticaria	14	15.1
Rash	11	11.8
Pruritus	11	11.8
Ecchymosis	10	10.8
Pruritus generalised	5	5.4
Others	23	24.7
Cardiac disorders	44	6.3
Sinus arrest	9	20.5
Bradycardia	9	20.5
Others	26	59.1
Others (nervous system disorders, blood and lymphatic system disorders, etc.)	220	31.7
Total	694	100

According to SOCs, the most frequent events reported with ticlopidine and clopidogrel were rectal haemorrhage, diarrhoea and melaena with ticlopidine and 'gastrointestinal disorders', in particular abdominal pain, diarrhoea and rectal haemorrhage with clopidogrel (Tables 6, 8). For both drugs, the most frequent PT observed was epistaxis (485 events, corresponding to 8.6% of the total ADRs and 32% of bleedings, and 221 events, corresponding to 12.5% of the total ADRs and 31% of bleedings, respectively, for clopidogrel and ticlopidine). Haematological disorders known to be associated with the use of ticlopidine, such as leukopenia, thrombocytopenia, pancytopenia and others, accounted for almost 13.5% of all the ADRs associated with the drug. It is noteworthy that almost 82% of these events were serious and 6.7% were fatal (data not shown). Therefore, although this association is well known, this risk

should not be underestimated and patients have to be carefully monitored.

'Respiratory, thoracic and mediastinal disorders' were the most frequent events reported with ticagrelor and prasugrel, in particular dyspnoea (134 events, corresponding to 19.3% of the total ADRs) for the first one (Table 10) and epistaxis for the latter one (32 events, corresponding to 11.2% of the total ADRs and 41% of bleedings; Table 9). Heart rate and cardiac conduction abnormalities known to be associated with the use of ticagrelor, such as sinus arrest, bradycardia and atrioventricular block, accounted for almost 4% of all the ADRs associated with the drug and almost 62% of these events were serious (almost all with complete recovery, but one case with sequelae; data not shown). Even in this case, probably there is the need for more attention, in particular in identifying patients with

major risk factors. Bleeding is reported for all four drugs, and this is expected due to their pharmacological action. Furthermore, excluding the case of ticlopidine, a very high rate of bleeding was related to the association of antiplatelet agents or antiplatelet agents plus anticoagulants, suggesting that more attention should be paid to the prescription of these drugs in combination.

Limitations of this study are represented by the possible phenomenon of the under-/over-reporting characteristic of pharmacovigilance databases and by the lack of a reliable denominator, such as accurate prescription data.

5 Conclusions

This study presents an evaluation of safety data regarding the use of the most prescribed antiplatelet agents (beside aspirin) in the Italian population, through the analysis of the Italian National Pharmacovigilance Network. The safety profile of antiplatelet drugs seems favourable, as supported by the fact that the majority of detected ADRs were generally non-serious and/or completely recovered. However, the overall risk-benefit ratio of these drugs in the 'real-world' should be reassessed, based on the appropriateness of use in particular in specific high-risk populations, such as the elderly. The risk-benefit profile of ticlopidine could be reconsidered in view of its non-appropriate use according to the available International Guidelines and scientific reports from clinical practice, since the medication still represents a treatment option for specific groups of patients. Based on this information, we believe that more attention from clinicians and/or an implementation of regulatory measures by Competent Authorities, could be useful for clinical practice.

A better definition of the overall risk-benefit ratio of these drugs requires further studies that will also ensure both prescription appropriateness and safety for patients.

Compliance with Ethical Standards

Funding No funding was received for the production of this paper.

Conflict of interest Authors declare that they have no conflicts of interest.

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