



Antithrombotic agents used by older people: prevalence and associated factors

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Abstract

Objective: To analyze the types and prevalence of use of antithrombotic drugs by older people and associated factors. **Method:** A cross-sectional study of community-dwelling older people was carried out in the city of Goiânia, Midwest Brazil. The pharmacological classification of antithrombotic drugs was performed according to the Anatomical Therapeutic Chemical (ATC) classification. Bivariate and multivariate analyses were performed with a significance level of 5%. **Results:** 212 older people participated in the study and the prevalence of antithrombotic drug use was 27.8%. The most used types were acetylsalicylic acid (ASA) (n= 49; 83%), Clopidogrel (n=6; 10.1%) and Cilostazol (n=4; 6.7%). Associated factors were the 70-79 years age group (p<0.001) and polypharmacy (p<0.001). **Conclusion:** The proportion of antithrombotic use by the participants was high and the most used drugs posed a risk of complications and drug-drug interactions. Attention should be heightened in individuals aged >70 years and in use of polypharmacy and efforts must be made to clinically monitor these users of antithrombotic drugs therapy.

Keywords: Anticoagulants.
Venous thromboembolism.
Cardiovascular nursing.
Polypharmacy. Aged.

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INTRODUCTION

Cardiovascular Disease (CVD) is one of the leading causes of morbimortality globally, with a prevalence rising from 271 million in 1990 to 523 million in 2019. Due to the growth in the older population, estimated to number 1.5 billion by 2050, CVDs are expected increase in the years ahead^{1,2}. Of the different CVDs, thromboembolic diseases (involving formation of anomalous thrombus in the vascular system) are important, being classified into arterial and venous thrombosis³. Acute Coronary Syndrome (ACS) and stroke are two of the main cardiovascular outcomes of arterial thrombosis^{2,4}, while Deep Vein Thrombosis (DVT) and Pulmonary Thromboembolism (PTE) are consequences of venous thrombosis⁵.

The use of antithrombotic agents is a pillar of thromboembolic disease management and involves the use of the antiplatelet, anticoagulant class drugs, substances which can prevent thrombus progression, recurrence and embolism⁶.

The literature reports high use of medications in older people to treat the multiple diseases affecting this population^{7,8}. Estimates in Iran suggest that 55.1% of older individuals with chronic diseases use antithrombotic agents compared with 23.8% in community-dwelling older Brazilians¹⁰. Another Brazilian study found that up to 5% self-medicated with antithrombotic drugs¹¹. Moreover, mortality from adverse events arising from the use of anticoagulants in older users totaled 632 deaths during 2008-2016¹². However, there is a lack of recent studies specifically addressing the antithrombotic agent class of drugs and factors associated with their use in older people.

Depending on the class of antithrombotic agents used, their use can pose greater risk of complications, such as hemorrhaging, renal issues and drug-drug interactions⁸. In older patients, drug treatment should balance the risk of bleeding against the benefits of antithrombotic therapy, since greater age is associated with a higher chance of bleeding associated with anticoagulation¹³. The use of antithrombotic medications in older people warrants greater research attention, since few

studies have investigated antithrombotics use in oldest-old, who typically exhibit multimorbidity, frailty and polypharmacy¹³.

In addition, antithrombotic therapy, particularly when prescribed to reduce disease recurrence after a first thromboembolic episode, sometimes requires outpatient follow-up and regular laboratory tests, besides health treatments for hemorrhagic complications which, ultimately, increase total health costs¹⁴.

The projected growth in the older population, together with the incidence of thromboembolic diseases and antithrombotic use, make understanding the use of antithrombotic therapy in older people a priority. This knowledge can serve to inform health actions with specific approaches aimed at reducing health risks, as well as help relieve the burden on health systems^{3,8,14}.

Therefore, the primary objective of the present study is to report the types of antithrombotic agents used by older people. The secondary objective of the investigation is to analyze the prevalence of antithrombotic drugs use and its associated factors.

METHOD

A cross-sectional study, nested within a cohort study called "Life, health and frailty status and body composition of older adults: a cohort of the Older Adult/Goiânia project" was conducted. The current research project commenced in 2009 in Goiânia city, Goiás state, when the baseline stage of the study was performed, followed in 2018/2019 by the second wave of the cohort study. Details of the sampling procedure have been reported elsewhere^{15,16}.

The present study included the population of the second wave of the cohort, carried out between July 2018 and March 2019. The sample included 221 subjects who were older adults aged >70 years, survivors since the baseline study 10 years earlier, residing within the catchment area of Primary Care units, and located by the researchers.

Given this study was part of a larger research project, the sample size was defined based on the

outcome of interest with lower prevalence. Thus, to check whether the present study sample had statistical power to identify statistically significant differences, the sample size was calculated *a posteriori*. The following parameters were applied: outcome of interest (antithrombotics use) prevalence of 23.8%¹¹; confidence interval of 95% ($\alpha < 0.05$); statistical power of 80%; exposed:non-exposed ratio of 2:1; and prevalence ratio (PR) of 2. Employing these parameters yielded an estimated final sample size of 210 people. Therefore, the sample for this stage of the project (221 participants) met the objectives of the present study.

The study participants had sufficient cognitive capacity to answer the questionnaire, as determined by applying the Mini-Mental State Exam (MMSE). In cases of cognitive deficit of the respondent, a guardian answered the objective questions on health.

Individuals not found at the home after 3 tries, whose address was not found during the visit, or who had moved to another city, were excluded.

At the time of data collection, after presenting and explaining of the study aims, the standardized questionnaire was applied, gathering information on demographic conditions, general health status and medication use.

The main variable of interest was use of direct oral anticoagulants. Thus, the respondents were first probed about use of medications via the question: "Are you taking any medications?". When the response was affirmative, the respondent was then asked to provide the prescription and/or packaging, if available, allowing the main active ingredient and posology to be recorded. All of the medications were then classified according to the Anatomical Therapeutic Chemical Classification System (ATC)¹⁷, as per the anatomical classification.

For direct oral anticoagulants, ATC code B (Blood and blood forming organs) was referenced, the B01A antithrombotics therapeutic subgroup, and the drug groups, namely: B01AA - Vitamin K antagonists; B01AB - Heparin groups; B01AC - Platelet aggregation inhibitors; B01AD - Enzymes; B01AE - Direct thrombin inhibitors; B01AF -

Direct factor Xa inhibitors; and B01AX - other antithrombotic agents¹⁷.

The sociodemographic exposure variables were sex, age group, marital status, education, and economic class (A/B, C and D/E)¹⁸. The health-related variables were number of morbidities reported, polypharmacy, hospitalization in past year, self-rated health, nutritional status, hypertension, diabetes mellitus, current smoking and sedentarism¹⁹⁻²³.

Number of diseases was obtained by asking the question: "What diseases has your physician said you have?"; self-rated health: "How would you rate your health status in the past month?"; and for hospitalization: "Have you been hospitalized in the past year?". Presence of polypharmacy was determined as the use of 5 or more medications, based on the medical prescription and/or packaging provided²⁰. Estimated body mass index (BMI) was calculated using the formula: (kg)/ height² (m), where weight was measured by electronic scales (Tanita model, capacity 200 kg; accuracy nearest 100 g), and height by a wall-mounted stadiometer (accurate to nearest 0.1cm). BMI value was classified as underweight ($\leq 22 \text{ kg/m}^2$), normal weight ($22-26.9 \text{ kg/m}^2$) or excess weight ($\geq 27 \text{ kg/m}^2$)¹⁹⁻²¹.

All statistical analyses were performed using the STATA software package, version 12.0 (StataCorp, College Station, USA). All variables were analyzed descriptively and expressed as mean, median, standard deviation, and absolute and relative frequency. The prevalence of antithrombotics use was estimated for all variables assessed in the study. The measure of association employed was Prevalence Ratio (PR) together with the respective 95% confidence interval (95%CI) obtained using simple Poisson regression for a 5% level of significance ($p < 0.05$). Variables with a p-value < 0.20 were entered in the multiple regression model using the stepwise forward approach. Variables with a p-value < 0.05 were retained in the model.

The study was approved by the Research Ethics Committee of the Clínicas Hospital of the Federal University of Goiás (UFG) (permit no. 2.500.441). Before completing the questionnaire, the Free and Informed Consent Form was read and explained to all respondents, who subsequently signed or fingerprinted the document. The study posed low risk to patients given the observational nature of the research.

RESULTS

In this study, a total of 221 older participants were interviewed, of which 212 (95.9%) were in use of some type of medication (95%CI.92.4–98.1). With regard to general characteristics, 66.0% were women, 58.5% aged 70-79 years, and 25.1% economic class D/E. Regarding level of education, 84.4% were illiterate.

Of the 212 users of medication, 27.8% (95%CI 21.9–34.4) (n=59) used drugs for antithrombotic

therapy, where the most used were acetylsalicylic acid (ASA)(n= 43; 72.8%), Clopidogrel (n=6; 10.1%) and Cilostazol (n=4; 6.7%), classified as antiplatelet drugs (Table 1).

The use of antithrombotic drugs was more frequent in participants who were female (29.2%), aged 70-79 years (36.3%), with economic class C (26.8%) and educational level of ≥ 9 years (50.0%). However, a statistically significant difference was only evident for age (PR 2.28, $p < 0.001$, 95%CI 1.33-3.89) (Table 2).

Table 1. Antithrombotic agents used by older participants, based on ATC classification (N=59). Goiânia, Goiás state, 2018-2019.

Antithrombotic agents	n(%) ¹
Antiplatelet drugs	49 (83.0)
Acetylsalicylic acid (ASA)	43 (72.8)
Clopidogrel	6 (10.1)
Cilostazol	4 (6.7)
Clonidine	2 (3.3)
Direct factor Xa inhibitors (xabans)	5 (8.3)
Rivaroxaban	3 (5.0)
Apixaban	2 (3.3)
Vitamin K antagonists (VKAs)	3 (5.2)
Vitamin K	3 (5.2)
Heparin group	2 (3.5)
Heparin	2 (3.5)
Total	59 (100.0)

¹Respondents can be in use of more than 1 antithrombotic drug concomitantly.

Table 2. Occurrence and association of antithrombotics use by older participants, according to sociodemographic characteristics. Goiânia, Goiás state, 2018-2019.

Variables	Sample n(%)	Antithrombotics use (n= 59)	PR (95%CI)	p-value
Sex				
Female	140 (66.0)	21 (29.2)	1.09 (0.69-1.72)	0.756
Male	72 (34.0)	38 (27.1)	1.00	
Age group (years)				
70-79	124 (58.5)	45 (36.3)	2.28 (1.33-3.89)	<0.001
≥ 80	88 (41.5)	14 (15.9)	1.00	
Economic class				
A/B	32 (15.0)	12 (37.5)	1.09 (0.62-1.89)	0.757
C	127 (60.0)	34 (26.8)	1.52 (0.79-2.93)	0.202
D/E	53 (25.0)	13 (24.5)	1.00	
Education (years)				
Illiterate	178 (84.4)	48 (27.0)	1.00	
1-4	19 (9.0)	8 (42.1)	1.56 (0.87-2.79)	0.133
5-8	10 (4.7)	1 (10.0)	0.37 (0.06-2.42)	0.301
≥ 9	4 (1.9)	2 (50.0)	1.85 (0.67-5.09)	0.232

Analysis of antithrombotic use according to health status revealed that use was greater in participants with good/fair health (29.1%), hypertensive (28.7%), diabetic (32.9%), presenting ≥ 3 diseases (28.8%), presence of polypharmacy (35.0%), and overweight/obesity (31.0%). The presence of polypharmacy was statistically

significant (PR=8.56, $p < 0.001$, 95%CI 2.16-33.9) (Table 3).

On the multivariate analysis, the factors associated with use of antithrombotic agents were the 70-79 years age group (PR_{adj} 2.20, 95%CI 1.31-3.69) and presence of polypharmacy (PR_{adj} 8.30, 95%CI 2.12-32.46) (Table 4).

Table 3. Occurrence and association of antithrombotics use by older participants, according to health status. Goiânia, Goiás state, 2018-2019.

Variables	Sample n(%)	Antithrombotics use (n= 59)	PR (95%CI)	p-value
Self-rated health				
Very good/Good/Fair	165 (78.6)	48 (29.1)	1,30 (0,72-2,37)	0,361
Poor/Very poor	45 (21.4)	10 (22.2)	1,00	
Arterial hypertension				
Yes	150 (71.1)	43 (28.7)	1,09 (0,67-1,78)	0,721
No	61 (28.9)	16 (26.2)	1,00	
Diabetes mellitus				
Yes	82 (38.6)	27 (32.9)	1,31 (0,84-2,03)	0,188
No	130 (61.3)	32 (24.6)	1,00	
Multimorbidities				
0-2	66 (31.1)	17 (25.7)	1,00	
≥ 3	146 (68.9)	42 (28.8)	1,12 (0,69-1,81)	0,651
Polypharmacy				
≥ 5	163 (76.9)	57 (35.0)	8,56 (2,16-33,9)	<0,001
0-4	49 (23.1)	2 (4,08)	1,00	
Body Mass Index				
Underweight	31 (16.7)	7 (22.6)	1,00	
Normal weight	55 (29.6)	15 (27.3)	1,20 (0,55-2,64)	0,637
Overweight / Obese	100 (53.8)	31 (31.0)	1,37 (0,67-2,81)	0,386
Smoking				
Yes	15 (7.1)	4 (26.7)	0,92 (0,38-2,26)	0,872
No	108 (51.0)	31 (28.7)	1,00	
Ex-smoker	89 (42.0)	24 (27.0)	0,93 (0,59-1,47)	0,788
Alcohol use				
No	180 (84.9)	51 (28.3)	1,00	
Yes	32 (15.1)	8 (25.0)	0,88 (0,46-1,68)	0,698
Hospitalization in past year				
Yes	50 (23.6)	16 (32.0)	1,20 (0,74-1,94)	0,452
No	162 (76.4)	43 (26.5)	1,00	

Table 4. Association with antithrombotics use by older participants according to sociodemographic variables and health status. Goiânia, Goiás state, 2018-2019.

Variables	PR _{cru} (95%CI)	PR _{adi} (95%CI)	p-value
Age group (years)			
70 – 79	1.00	1.00	
≥80	2.28 (1.33-3.89)	2.20 (1.31-3.69)	0.003
Polypharmacy			
0-4	1.00	1.00	
≥5	8.56 (2.16-33.9)	8.30 (2.12-32.46)	0.002

PR_{cru} (crude Prevalence Ratio); PR_{adi} (adjusted Prevalence Ratio); adjusted for sex, age and polypharmacy, R²=0.0962

DISCUSSION

This study assessed the use of antithrombotic agents in older users (>70 years) of Primary Care services. In addition, factors associated with this use, such as age 70-79 years and polypharmacy, were identified. The findings underscore the need for health professionals to monitor and intervene in cases of antithrombotic drugs use toward improving the safety of drug-based treatment by lowering the health risks. This is the first study in the region of older users of Primary Care services assessing the use of these medications and their associated factors.

The rate of antithrombotic use (27.8%) identified was similar to that detected by an earlier study in Brazil, which showed that 23.8% of older individuals used antithrombotic agents¹⁰, but higher than the rates found among people aged >40 in the UK (15.9%), Denmark (18.1%), Italy (16.6%) and Spain (13.6%)²⁴. In older people, changes induced by the aging process, such as hemostatic imbalance, increased coagulation factors, platelet activation and decreased fibrinolysis, can favor both the occurrence of thrombus and thrombotic complications. These entities, together with other common conditions in older individuals, such as immobility and frailty, can lead to the prescribing of these medications^{13,25}. Thus, these complications can be prevented with the use of antithrombotic agents, arresting the progression of thrombus and preventing recurrence of thrombotic diseases¹³.

In a recent study on new drugs registered by the Brazilian Health Surveillance Agency (ANVISA) between 2003 and 2013, many new antithrombotic

agents were incorporated²⁶. The present analysis revealed that ASA (83%) and Clopidogrel (10.1%) remained the most used agents, higher rates than those reported in previous studies of 60.5% and 2.2%, respectively.^{27,28}. Notably, both of these antiplatelet drugs are widely used globally, prescribed alone or combined in cases of Acute Coronary Syndrome (ACS) or patients undergoing percutaneous coronary interventions (PCI)²⁵. In Brazil, these medications are dispensed free on the national health system (SUS) and feature in the National List of Essential Medications (RENAME) which, in part, explains the high prevalence of use²⁹.

However, is it important to point out that the use of ASA in older patients should be restricted to cases of secondary prevention of ischemic events, such as stroke and acute myocardial infarction. Use of ASA in individuals aged over 70 for primary prevention of vascular complications is inadvisable, since the risks of hemorrhagic events appear to be greater than the benefits derived from the treatment²⁵. According to the Beers criteria, the risk of bleeding with chronic use of ASA in older patients is well established³⁰.

Further, a recent study found that 30.4% of older patients admitted to hospital after sustaining falls were in use of antithrombotic medications and that 35.9% of this group had intracranial hemorrhaging, a higher rate than in the group not taking antithrombotics (25.0%)³¹.

In this context, a study assessing total costs of health treatment for 3 consecutive years in individuals diagnosed with thromboembolic diseases found that the presence of major hemorrhage complications

secondary to the use of antithrombotic agents, such as intracranial and gastrointestinal bleeding, with resultant hemodynamic imbalance and need for hospitalization, further increased total healthcare and societal costs¹⁴.

Clopidogrel, besides presenting risk of bleeding, is an antiplatelet agent with a variable response, risk of platelet reactivity, and propensity for drug-drug interactions, in competing for the same binding site as other drug classes, such as proton pump inhibitors and calcium channel blockers which, when used concomitantly, can reduce their effect^{25,32}.

In the present study, only 5 (8.3%) participants were using factor Xa inhibitors, a recent class of drugs in the direct oral anticoagulant group which, compared to conventional drugs, have a more rapid onset of action, lower interaction with other drugs and foods, and appear to require less laboratory monitoring for dose adjustments³³. The new anticoagulants are designed to reduce undesirable effects in an effort to improve quality of life and treatment adherence by users^{25,33}. However, these drugs have not been fully incorporated by the SUS³⁰. According to the list of potentially inappropriate medications (PIM) for older adults, use of Rivaroxaban by individuals aged >75 years is not recommended because of increased risk of gastrointestinal bleeding. Likewise, Apixaban should not be used by older adults, where both these drugs lack robust evidence of efficacy and safety³⁰.

With regard to associated factors, the use of antithrombotic agents was greater in the 70-79 age group than those aged ≥ 80 years. The oldest-old may be underdiagnosed where a study involving older patients with venous thromboembolism (VTE) showed that signs and symptoms may be weak and non-specific, hampering diagnosis in this population. In addition, diagnostic techniques are less sensitive and more limited in this age group, while there are few specific recommendations for administering drugs treatment in oldest-old individuals, leading to lower use of these medications in people age 80 or older^{10,34}.

Polypharmacy was also shown to be associated with an increased likelihood of antithrombotics use. Polypharmacy correlates with number of diseases which, in turn, increases the use of medications. Given

the high prevalence of cardiovascular diseases in this group, the use of antithrombotic drugs is expected to be greater in polymedicated older individuals. Importantly, there is an increased risk of adverse events with the presence of polypharmacy, as well as low treatment acceptance and inappropriate use³⁴.

Given the complexity of use of multiple medications, and aging-related changes, it is important to monitor older individuals in use of antithrombotic agents and establish protocols for the use and maintenance of these drugs and for line of care in patients that present adverse events³⁵.

A limitation of the present study is the method of collection of data on the medications used which, although gathered from medical prescriptions or packaging, failed to assess the clinical conditions for which antithrombotic agents were prescribed. Also, this study adopted the use of a sole means of classification, namely anatomical.

CONCLUSION

Taken together, the results revealed a high rate of use of antithrombotic agents in the older people assessed, with antiplatelet drugs proving the most commonly used. The association found for participants aged 70-79 years and for presence of polypharmacy points to the need for greater care over use of these drugs in this age group. Pharmacoepidemiology studies such as the present investigation are important for identifying the profile of antithrombotic agents used and helping promote strategies for pharmacotherapy monitoring and attention in older people. Despite the development of new agents for controlling thromboembolic conditions with lower risks of bleeding and complication, the use of these drugs is complex with advancing age. Future studies exploring actions which improve patient safety and quality of life of this older group through the use of antithrombotic agents are warranted.

AUTHORSHIP

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- First Draft, Writing – Review and Editing, Investigation, Methodology, and Securing of Funding.
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