Inappropriate combined antiplatelet and anticoagulant therapy in older patients with atrial fibrillation: trend over time (2009-2018)

Running heading: Inappropriate antiplatelet plus anticoagulant therapy in AF

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Abstract.

Background and objectives. Antiplatelet therapy, when prescribed in combination with anticoagulant therapy to older patients with atrial fibrillation and no recent cardiovascular event, is inappropriate and a reversible risk factor of major bleeding. We aimed to assess the trend over time of the prevalence of inappropriate combined antiplatelet and anticoagulant therapy (ICAAT) and to determine its associated factors during the direct oral anticoagulants (DOAC) era.

Methods. Study of consecutive older patients (≥ 75 years) with atrial fibrillation, anticoagulant therapy upon admission, and a comprehensive geriatric assessment during their first admission in a Belgian teaching hospital between 2009 and 2018. Antiplatelet therapy was considered inappropriate in the absence of a recent cardiovascular event. We studied the ICAAT's prevalence by two-year periods and assessed its associated factors since the year 2013.

Results. ICAAT was identified in 21 % of the 654 patients (median age 84 years, 51% women), with a prevalence decreasing ($p \leq 0.01$) from 25% (2009-2010) to 14.8% (2017-2018). Among the 469 patients recruited during the DOAC era, ICAAT (19%) was associated in multivariable analysis with history of stroke/transient ischemic attack (OR 1.11, $p=0.007$), anticoagulation with low-molecular-weight heparin (OR 1.25, $p=0.006$), and history of vascular disease (OR 1.31, $p<0.001$).

Conclusions. While ICAAT has declined over the last decade, there is still room for improvement. Antiplatelet deprescribing should be considered in all patients with ICAAT, including those with vascular disease and no recent cardiovascular event.

Key points

- The prevalence of inappropriate combined antiplatelet and anticoagulant therapy (ICAAT) decreased from 25 to 15% over a decade, especially since 2012.
- During the DOAC era (after 2013), the main risk factor for ICAAT was a history of vascular disease, as expected, although 34.4% of the patients on ICAAT had no such history.
- Since antiplatelet therapy is a reversible risk factor of major bleeding among older patients on anticoagulation for atrial fibrillation, its inappropriateness should be assessed, and - when present - lead to its deprescribing.

1. Introduction

Since 2012, guidelines from the European Society of Cardiology (ESC) and from the French society of geriatrics and gerontology and the French society of cardiology for the management of atrial fibrillation (AF)[1, 2, 3] have recommended avoiding antiplatelet therapy in patients on anticoagulant for AF with no recent cardiovascular event (no acute coronary syndrome [ACS] or percutaneous coronary intervention in the last 12 months). Those recommendations were based on observational studies as there was until 2019 no RCT on the subject [4]. However, there is ample evidence that adding antiplatelet therapy to anticoagulant therapy significantly increases bleeding risk [5] without reducing the risk of recurrent coronary events or thromboembolism [6, 7].

Despite those recommendations, overprescription of antiplatelets in older patients on anticoagulation for AF is a well-documented problem [8, 9], especially those with vascular disease. AF patients often have concomitant coronary or peripheral artery disease, with a prevalence of 17% to 46% for the former [10]. The potential of combined antiplatelet and anticoagulant for harm makes it an important issue to address.

Over the past decade, the arrival of direct oral anticoagulants (DOACs) on the market, offering several benefits over the previously dominant vitamin K antagonists[11], has resulted in a significant change in prescription habits and a higher rate of AF patients on anticoagulant [12]. As the DOAC's promotion has been accompanied by the diffusion of guidelines on AF management since 2012, we made the hypothesis that the prevalence of inappropriate combined antiplatelet therapy (ICAAT) has decreased from 2009 to 2018.

The main aim of the present study was to assess the 10 year-trend of the prevalence of ICAAT in patients over 75 years old with AF. A secondary aim was to assess patients' characteristics associated with ICAAT during the 2013-2018 period, i.e., after the 2012 ESC guidelines and the introduction of the first DOAC in 2012 in Belgium.

2. Materials and methods

2.1.Study design and patient population

We conducted a retrospective study of consecutive inpatients aged 75 years or over evaluated by the inpatient geriatric consultation team, with documented AF prior to hospital admission, at significant stroke risk ($CHADS_2$ score ≥ 2) and on anticoagulant therapy prior to their admission at the Cliniques Universitaires Saint Luc, a teaching

hospital in Brussels, Belgium. Patients evaluated by the inpatient geriatric consultation team between January 2009 and December 2018 were included. For patients with multiple evaluations during the study period, only the first evaluation was considered, in order to avoid bias by hospital recommendation to deprescribe inappropriate antiplatelet therapy. In our hospital, we use the ISAR score[13] (Identification of Senior At Risk) for patients over 75 years old to evaluate the need for a geriatric evaluation (if the ISAR score is ≥2). Nurses and physicians from other wards also call the inpatient geriatric consultation team for multiple other reasons (agitation, falls, suspicion of caregiver exhaustion, request for help for medication reconciliation…).

Patients with a recent (less than 12 months) cardiovascular event (ACS, angioplasty, stenting or other vascular prosthesis, carotid endarterectomy) were excluded from the analysis, as antiplatelet therapy is appropriate in such cases.

Patients with a metallic valve or recent deep vein thrombosis or pulmonary embolism were not included in the database.

2.2.Data collection

Data were systematically collected during the patient's stay at the hospital by the inpatient geriatric consultation team (by accessing the patient's medical records available in our hospital and on the national health network, by interviewing the patient, their family and occasionally their general practitioner) as part of their CGA, then retrospectively added to the database used in this study. Data collected included socio-demographic data (age, sex, residency); recent (< 12 months) cardiovascular events (ACS, angioplasty, stenting or other vascular prosthesis, carotid endarterectomy); the patient's antithrombotic regimen upon hospital admission (type of anticoagulant therapy, type of antiplatelet therapy and when available the order in which they were prescribed); the presence of vascular disease (history of myocardial infarction, peripheral artery disease or aortic plaque); data pertaining to the $CHADS_2$ and $HEMORR_2HAGES$ scores.

We also collected data to identify the risk of functional decline (ISAR score); and the presence of major geriatric syndromes, i.e. malnutrition (assessed on the basis of a nutritionist evaluation and/or a body mass index of < 21 kg/m2 and/or a mid-arm circumference < 23 cm and/or albumin <3 g/dL), multiple falls in the previous year, elevated risk of falls (history of falls, dementia, Parkinson's disease, or evidence according to the team's physiotherapist), cognitive disorder (clinical diagnosis or Mini

Mental State Examination < 24/30), functional dependence in the activities of daily living (Katz ≥ 10/24 two weeks before admission). Congestive heart failure was considered significant if the patient was hospitalised at least once for acute heart failure during the last year or had a left ventricle ejection fraction <40%. A patient was considered to have hepatic or renal dysfunction if he had a known history of cirrhosis or an eGFR at discharge under 30ml/min. All definitions chosen for the variables studied are detailed in the supplementary materials.

2.3.Endpoints

The main study endpoint was the time trend over 10 years of the prevalence of inappropriate combined antiplatelet and anticoagulant therapy (ICAAT). ICAAT was defined (according to the 2012 ESC Guidelines[1]) as an antiplatelet therapy in the absence of a recent cardiovascular event (ACS, angioplasty, stenting or other vascular prosthesis, or carotid endarterectomy in the last 12 months) in a patient with AF on anticoagulation, i.e. DOAC, vitamin K antagonist (VKA) or therapeutic dose of low-molecular-weight heparin (LMWH).

To assess the trend over time of the prevalence of ICAAT, we compared five consecutive two-year periods (2009-2010, 2011-2012, 2013-2014, 2015-2016 and 2017-2018).

To assess the factors associated with ICAAT, we selected the patients included from 2013 onwards as it was the year following the publication of the first Guidelines recommending against ICAAT [1] and the introduction of the DOACs in Belgium (2012).

We chose to limit the analysis of the factors associated with ICAAT to the period after 2012 for several reasons. Firstly, the association of antiplatelet agents and AVKs is not strictly comparable to the association of antiplatelet agents and DOACs, which could have led to different prescription habits after the introduction of DOACs. Secondly, the communication surrounding their promotion helped introduce the 2012 ESC guidelines and might have been a driving force for a change in practice. As our study included patients over a ten-year period, the reasons why physicians prescribe an ICAAT might have changed between the beginning and the end of the study. We focused on patients from 2013 onwards since the prescription habits during this period are closest to our current prescription habits, and thus those we need to understand to further reduce the prevalence of ICAAT.

We also compared the patients before 2013 with the patients from 2013 onwards.

2.4.Risks of cardio-embolism and major bleeding

To assess the risk of AF-related cardio-embolism, we used the $CHADS_2$ score: 1 point for each of Congestive heart failure, history of Hypertension, Age ≥ 75 years, Diabetes mellitus; and 2 points for a history of Stroke/Transient ischemic attack (TIA). According to Maes et al. [14], we chose the $CHADS_2$ score rather than the CHA_2DS_2-VASc score because this score was developed in an older population (mean age 81 years) and it correlates with the risk of stroke in a linear, precise, and valid manner (C-statistics : 0.82).

To assess the patient's bleeding risk, we used the $HEMORR_2HAGES$ score: 1 point each for Hepatic or renal disease (cirrhosis or estimated Glomerular Filtration Rate [eGFR] <30 ml/min at discharge), Ethanol abuse, Malignancy likely to bleed, Old age (≥ 75 years), Reduced platelet count or function (count <150,000/μ^3 or antiplatelet therapy), uncontrolled Hypertension (160/90mmHg more than twice during the hospitalisation), Anaemia (haemoglobin < 10g/L), Genetic factors, Excessive fall risk (history of falls, dementia, Parkinson, psychiatric history [depression excluded], walking disorders [Tinetti score < 24]), history of Stroke; and 2 points for Rebleeding risk (history of significant bleeding in the last 3 years). We chose the $HEMORR_2HAGES$ score rather than the HAS-BLED score because the former was developed in an older population (mean age 81 years, the same as the population of the $CHADS_2$ score, i.e. the NRAF cohort) and includes additional factors quite prevalent in a geriatric population (Malignancy, Anaemia and Excessive fall risk,). Moreover, it does not include the INR value, as HAS-BLED does, which became much less relevant with the constant rise in DOAC use rather than the previously used VKA. The expert consensus of the French society of geriatrics and gerontology and the French society of cardiology on the management of AF in elderly people [2] also deemed the $HEMORR_2HAGES$ score the most appropriate score to assess bleeding risk in patients aged 75 years and over.

Finally, we defined uncontrolled hypertension using measures taken during the patient's hospitalisation, although they may not be representative of their usual arterial tension (due, for example, to pain or anxiety).

We calculated a corrected $HEMORR_2HAGES$ score [14], removing 1 point to patients on antiplatelet therapy with a normal platelet count, in order to simulate their bleeding risk in the absence of the inappropriate antiplatelet therapy.

2.5.Statistical analysis

Continuous variables are presented as medians [P_{25}; P_{75}] and were compared between groups using a Wilcoxon-Mann-Whitney test. Categorical variables are presented as numbers and proportions and were compared between groups using Pearson's chi^2 test, Pearson's Chi squared test with Yates' continuity correction, or Fisher-Freeman-Halton test depending on the condition of validity of each test.

Trends in proportion of patients with ICAAT over time were assessed using a Chi-squared test for trend.

Variables associated with an ICAAT during the DOAC era (from 2013 onwards) were first assessed using a binary logistic regression. All variables associated with this outcome in univariate analysis with a p-value <0.15 were candidate for the multivariable model. A stepwise selection based on the Akaike Information Criterion was then applied to select the final multivariable model. The goodness-of-fit of the final multivariable model was assessed using the Hosmer and Lemeshow test. All analyses were performed using R software version 3.3.1. A p-value<0.05 was considered statistically significant.

3. **Results**

3.1. Patients' selection and characteristics

We included 690 patients admitted to our hospital during a 10-year period, between the 1st of January 2009 and the 31st of December 2018, meeting the inclusion criteria. The 36 patients with a recent cardiovascular event (ACS or coronary artery stenting, n=26; lower limbs artery angioplasty or stenting, n=7; other vascular prostheses, n=2; carotid endarterectomy, n=1) were excluded (Figure 1) as their antiplatelet therapy was appropriate. The characteristics of the 654 included patients (median age 84 years; 50.8% female) are shown in table 1. The prevalence of geriatric syndromes was as follows: malnutrition (27%), cognitive disorder (30%), dependency in the basic activities of daily living (35%) and multiple falls in the past year (45%). Overall, the median $CHADS_2$ score was 3 [2-4], based on the score's items, i.e. congestive heart failure (34.4%), hypertension (80.1%), age ≥ 75 years (100%), diabetes mellitus (23.1%) and stroke/TIA (29.8%). the median $HEMORR_2HAGES$ score was also at 3 [2-4], based on the score's items, namely hepatic/renal failure (14.2%), ethanol abuse (4.6%), active malignancy (11%), reduced platelets or function (33.9%), rebleeding risk (8.3%), uncontrolled hypertension (20.5%), anaemia (12.5%), excess fall risk (67.4%) and history of stroke/TIA 529.8%). By design,

all patients were on anticoagulant therapy. Upon hospital admission, VKA was the most prescribed anticoagulant (58.6%), followed by DOAC (35%) and LMWH at therapeutic dosage (6.4%). These proportions changed over time towards more DOAC and less VKA (Table 1).

Table 1 compares the 185 patients included before 2013 and the 469 included from 2013 onwards. These two groups were comparable for most variables. There was no difference in $CHADS_2$ score nor in $HEMORR_2HAGES$ score. As compared to the patients included before 2013, those included since 2013 were slightly older (83 vs. 85 years) and had a lower prevalence of hepatic/renal failure (18.9% vs. 12.4%) and stroke/TIA (36.2% vs. 27.3%).

3.2.Inappropriate combined antiplatelet and anticoagulant therapy (ICAAT)

Of the 654 patients, 140 (21.4%) were on inappropriate combined antiplatelet and anticoagulant therapy (ICAAT). Among the 140 patients with ICAAT, 54 (38.6%) had no history of vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque), 34 (24.3%) neither a history of vascular disease nor stroke and 23 (16.4%) had neither a history of vascular disease, stroke nor diabetes mellitus. Most patients with ICAAT were on a single antiplatelet drug (95.7%) and prescribed aspirin (94.3%). The timing of the initiation of both the antiplatelet therapy and the anticoagulant therapy could be identified in 123 patients of the 140, of whom 76 (61.8%) were prescribed the antiplatelet therapy before the anticoagulant therapy.

ICAAT was more frequent before 2013 than since 2013 (antiplatelet use: 27.0% vs. 19.2%, p=0.028) (Table 1). The Figure 2 shows that ICAAT progressively decreased from 25% in 2009-2010 to 15% in 2017-2018 (p=0.01). This decrease occurred after the year 2012. For the sake of comparison, the proportion of patients with vascular disease (about 33%) has remained stable over time from 2009 to 2018 (Figure 2, circles).

3.3.The DOAC era (2013-2018)

Table 2 compares, among the 469 patients included from 2013 onwards, the 90 patients (19%) on ICAAT to the 379 patients (81%) on anticoagulation monotherapy. Patients on ICAAT were slightly younger (median age 83 vs. 85 years), had more frequently a history of vascular disease (65.6% vs. 27.7%, p<0.001) and stroke/TIA (36.7% vs 25.1%, p=0.026). They were more often on LMWH upon hospital admission (11.1% vs 3.4%,

p=0.010). When corrected for the use of antiplatelet agent (one point removed to the patients on antiplatelet therapy with a normal platelet count, see methods), the bleeding risk was similar in the two groups (median corrected HEMORR$_2$HAGES score 3 [2-4] vs. 3 [2-4], *p*=0.289).

Table 3 shows the factors associated with ICAAT during the DOAC era. In multivariable analysis, ICAAT was associated with a history of vascular disease (OR [95%CI] = 1.31 [1.22;1.40]; p<0.001), of stroke or TIA (OR [95%CI] = 1.11[1.03;1.20]; p=0.007), as well as with a prescription of LMWH as compared to DOAC (OR [95%CI] = 1.25[1.07;1.47]; p=0.006), but not with a VKA.

4. Discussion

4.1.Main finding

The main finding is that the prevalence of ICAAT (21%) in the very old patients (median age 84 years) with atrial fibrillation seen in our academic hospital has gradually decreased from 25% in 2009 to 15% in 2018.

4.2.ICAAT prevalence

Literature shows that the use of inappropriate antiplatelet and anticoagulant combination therapy varies in patients with atrial fibrillation from 6% up to 45% [8, 9, 15, 16]. Two European prospective cohort studies showed a low ICAAT prevalence (11.9% and 6.1%) [8, 9]. In the first one (2012-2013), most patients were male (60%), patients had less frequent history of stroke and while they reported separately coronary heart disease and peripheral artery disease, they seem to have a lower prevalence of vascular disease (around 27% if we addition those comorbidities). The second one (2013-2017), which included patients (76±9 years) initiating DOAC, excluded patients with recent stroke (<1 year). This probably excluded a number of patients with a history of vascular disease (as the added prevalence of coronary heart disease and peripheral artery disease in this study was only around 16%). On the other hand, the two US studies reported a high ICAAT prevalence (37.5% and 45.3%) [15, 16] that might be partly explained by the aspirin over-the-counter availability in this country, as well as by a lower mean age (66±15 and 71±12 years). This latter difference may have led to a different prescriber perspective, less afraid of bleeding complication in a younger population. Of interest, the former study included patients followed at anticoagulation clinics for AF or venous thromboembolism [15], while de latter one included patients seen in a primary care network [16]. The first US study excluded patients with a recent cardiovascular event with a cut-off of 6 months, so they might have labelled antiplatelet therapy as inappropriate in cases where we deemed it appropriate (they estimate this concerns 5% of their patients). In the second US study, the higher prevalence of ICAAT might be explained by a higher prevalence of vascular disease (46%) and diabetes mellitus (33%). While these four studies had a relatively old study population (averaging 72 to 74 years of age), none reported on geriatric syndromes such as cognitive disorder, recurrent falls, malnutrition and functional dependency. This information makes our study particularly interesting as old frail patients are more at risk of bleeding event [17] and thus are likely to benefit from appropriate prescription.

4.3.Trend-over time of ICAAT

In our study, the 10-year trend analysis of the ICAAT prevalence showed a decrease from 25% to 15% from 2009 to 2018. The study by Apenteng and al. evaluated the trend over five years (2011-2016) of the number of patients on combination therapy among those with newly diagnosed AF in primary care, without determining its appropriateness nor its risk factors, and showed a variable proportion ranging from 14% to 12% between 2011 and 2016 despite a stable proportion (12.5% – 14.7%) of vascular patients [18].
Several hypotheses can be made as to why the overuse of antiplatelets has been decreasing in our study. We do not have enough information to know exactly how many patients were on antiplatelet as primary prevention. However, 34.4% were not vascular and still had ICAAT. In primary prevention of atherosclerotic events, there could be a reduction in antiplatelet prescribing following recent studies showing little benefit of aspirin in this indication [19, 20]. On the other hand, two-thirds of the patients with ICAAT had vascular atherosclerotic disease. In this population, there could have been a change in prescription habits following several firm recommendations not to continue a combined antiplatelet and anticoagulant therapy in patients with stable coronary heart disease (ESC guidelines 2010 [21], ESC guidelines focused update 2012 [1], Expert consensus of the French Society of Geriatrics and Gerontology and the French Society of Cardiology 2013 [2], ESC guidelines 2016 [3]).

4.4.Risk factors of ICAAT

A history of vascular disease was the main predictor of ICAAT in our study, an expected finding which was consistent with other studies [8, 9, 16]. Another factor associated with ICAAT on admission was receiving LMWH as anticoagulant therapy rather than DOAC in multivariable analysis. Use of LMWH is a complex variable to interpret. It was more often used when there was more need for VKA bridging. The patients on LMWH might have had their anticoagulation therapy prescribed earlier, before DOACs became available. Our data confirms there were more patients on LMWH before 2012 (table 1). Barring the case of active cancer, it is unusual to prescribe LMWH as a long-term anticoagulant in older patients. Looking into their medical records, we observed that most patients on LMWH were prescribed this medication for perioperative bridging or as a temporary treatment pending instauration of a VKA by their general practitioner.

Surprisingly, our study showed no relation between geriatric syndromes and the absence of ICAAT. We had expected to observe a lower ICAAT in patients with falls, malnutrition, cognitive disorder, as these syndromes are associated with an increased bleeding risk. Falls in the last year or risk of falls (71.1% from patients with ICAAT vs 68.6% of patient without ICAAT) could have prevented physicians from prescribing ICAAT [22] as intracranial bleedings are a common complication of falls even without antiplatelet or anticoagulant [23]. We also could have thought that ICAAT would be less prevalent in malnourished patients as it can be associated with a higher bleeding risk, for example in patients on VKA [24, 25].

The persistence of ICAAT in patients with stable vascular disease could be explained by the fact that there is a persistent belief that the prevention of arterial thrombosis should include antiplatelet therapy, despite this paradigm changing [26, 27].

Other hypotheses could explain why there are still some patients receiving ICAAT. The haemorrhagic risk related to the prescription of antiplatelets could be underestimated because of a lingering idea that antiplatelets cause less bleeding than anticoagulants, despite a recent meta-analysis confirming the risk is similar [28]. As far as antiplatelet therapy is concerned, physicians seem to be more fearful of recurring atherosclerotic events compared to bleeding events. In our study, there was no difference in prevalence of history of major bleeding or high HEMORR$_2$HAGES score after correcting for the use of antiplatelet therapy between patients on ICAAT and patients on anticoagulant monotherapy.

In our study, a majority of the patients (61.8%) were on antiplatelet therapy before introduction of the anticoagulant therapy, a finding consistent with previous publications [15, 16]. The hypothesis is that antiplatelet was not discontinued at that time. In some cases, physicians might not want or dare to stop antiplatelets when they start anticoagulants out of a reluctance to question the prescriptions initiated by another specialist. In other cases, concerning patients who have taken their antiplatelets for a long time, physicians might tend to forget that the patient they see now is no longer the patient they prescribed this drug decades ago. They might forget that time has passed and that the 85-year-old patient with several comorbidities they now have in front of them does not have the same risk-benefit balance than twenty years ago. Some patients may also be reluctant to stop a medication they were once told was a “life-long prescription”.

4.5.Bleeding risk

Our results showed that in those on ICAAT, the additional bleeding risk was predominantly due to the antiplatelet overuse or misuse (similar HEMORR$_2$HAGES scores after correcting for antiplatelet use). Numerous studies have shown that, even for patients with CAD or vascular disease, additional antiplatelet therapy in patients on anticoagulation for atrial fibrillation increases bleeding without significant benefit in reduction of thrombotic events [4, 6, 7, 29, 30, 31, 32, 33, 34, 35]. Therefore, it is generally recommended that in the context of stable cardiovascular disease, antiplatelets should not be prescribed to anticoagulated patients with AF [1, 2, 3, 21]. As frail older people are more at risk of bleeding [17], avoiding these antiplatelets over- and misuse is even more crucial since bleeding events could precipitate hospitalizations and other associated outcomes like functional decline, which can have a significant impact on their quality of life. It is therefore concerning that geriatric syndromes do not seem to influence antiplatelet prescription.

4.6.Strengths and limitations

This single-centered study of older patients (≥ 75 years) with atrial fibrillation may not be representative of this population but it included over 600 consecutive patients seen by the inpatient geriatric consultation team during ten years, before and after the years 2012-2013 (when recommendations were released to limit the prescription of an antiplatelet therapy in those patients without a recent cardiovascular event), with an antithrombotic regimen prescribed in a real-world setting. In particular, having a mix of people living in long-term care/nursing homes and in the community mean our findings can be relevant in both settings. This study lacked information on patient preferences and on physicians' beliefs regarding antiplatelet therapy, which have influenced the antiplatelet prescribing, but no other studies have included geriatric syndromes in their analysis, while we had the benefit of a detailed chart review, including a CGA. Our inclusion process via the inpatient geriatric consultation team might result in a selection bias (more frail patients than in the general population), but this was a conscious decision in order to include geriatric syndromes in our analysis.

Several people collected the data included in this study. To ensure reproducibility, explicit criteria were chosen to define each variable. To control the adherence to these criteria, one of the authors verified a sample of 20 patients in each subset of patients.

4.7.Perspective for research

Because there is still room for progress to limit ICAAT prevalence, it could be interesting to explore other factors which could influence inappropriate antiplatelet prescription. In particular, bringing to light prescriber-related factors (age, medical specialty, beliefs concerning older patients) and patient-related factors (beliefs and fears, context-related, etc.) could help us better understand the mechanisms underlying the prescribing of ICAAT. It could help understand how to raise awareness of these factors to convince prescribers and patients that combined antiplatelet and anticoagulant therapy should be avoided, with a few exceptions, in older patients anticoagulated for AF, thus enabling better adherence to guidelines and reduction of iatrogenic major bleeding events.

5. Conclusions

Although the ICAAT prevalence showed a 40% relative decrease during the last decade in very old patients with atrial fibrillation, inappropriate antiplatelet therapy is still frequent (15%). It is important to further reduce the inappropriate antiplatelet prescribing as older and frailer geriatric patients with AF are at high risk of severe iatrogenic bleeding. Antiplatelet deprescribing should be considered in all patients with ICAAT, including those with vascular disease and no recent cardiovascular event, and research should be done concerning patient-related factors and prescriber-related factor to optimize antiplatelet deprescribing.

Declarations

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Conflicts of interests

Emilie Philippe Séverine Henrard, Benoit Boland, and Sophie Marien have no potential conflicts of interest that might be relevant to this work.

Ethics approval

The study protocol was approved by the Comité d'Ethique Hospitalo-Facultaire, Cliniques univeritaires Saint-Luc, UCLouvain (reference 2018/14FEV/063, registration number B403).

Consent to participate

Considering the signification proportion of deceased patients included in this study, related to its retrospective nature and the age and frailty of the cohort included, we elected not to ask for informed consent, so as not to cause undue distress to deceased patients' families.

Consent for publication

Not applicable.

Availability of data and material

The datasets that support the findings of this study are available from the corresponding author on reasonable request.

Code availability

Not applicable.

Authors' contribution

All authors have made significant contributions to the study. EP, SH and SM conceptualized and designed the study. EP, BB and SM worked on literature review and data collection. EP performed the initial analysis and interpretation of data while SH performed the formal statistical analysis. EP and SM drafted the manuscript and all authors contributed to critically revising it. All the authors read and approved the final manuscript.

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Delivery Research - Researcher Led Board member. NJW, JS, and SD report NIHR and Medical Research Council grants during the conduct of the study, outside the present work. Other authors have no potential conflicts of interest to declare.

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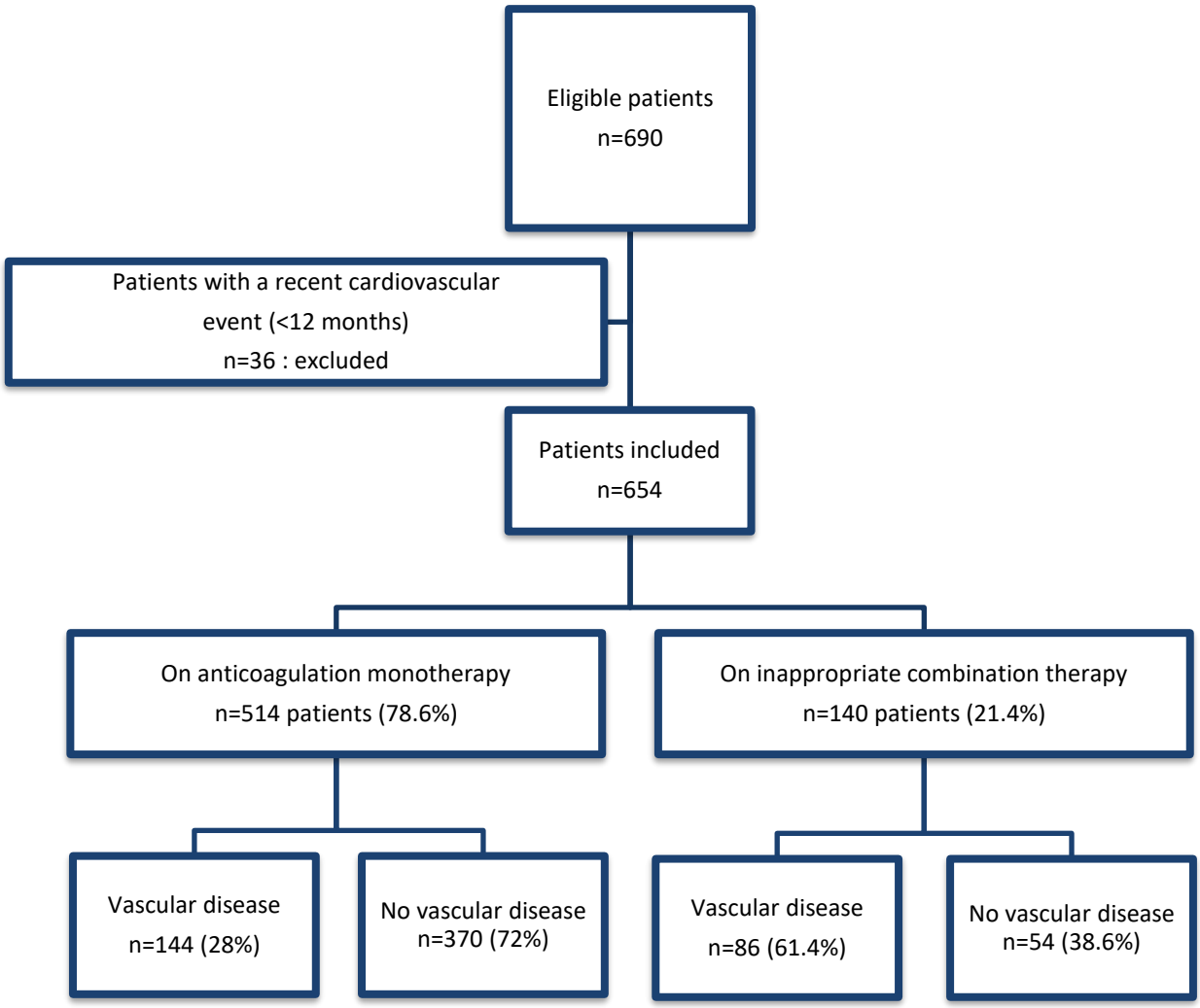
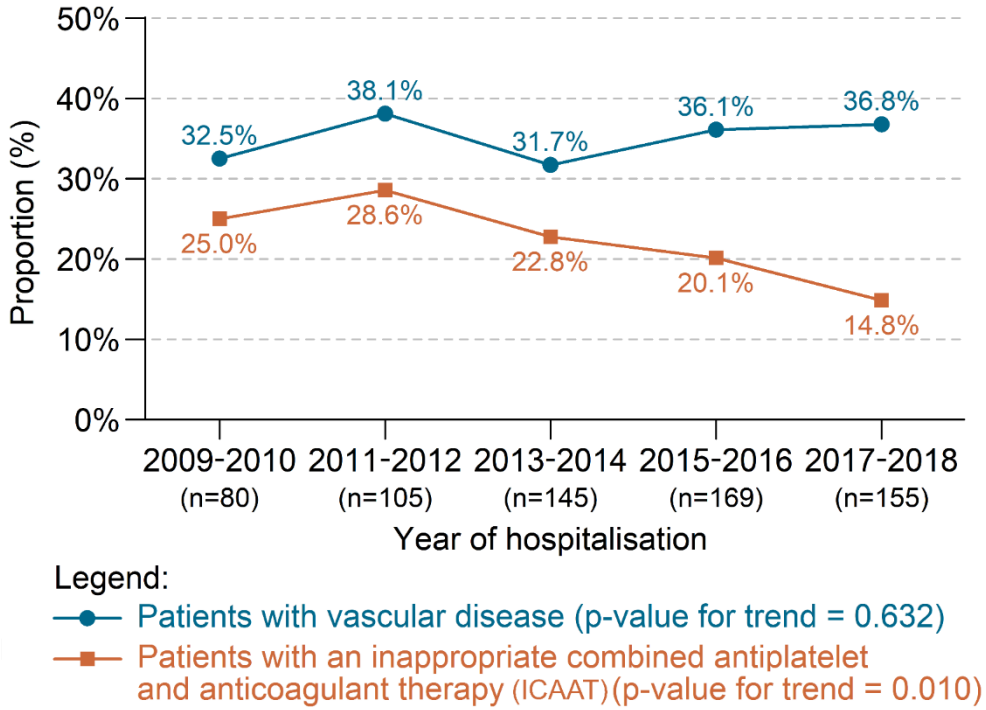
Figures:

Figure 1. Flowchart of patient selection and anti-thrombotic regimen



Vascular disease; history of myocardial infarction, peripheral artery disease or aortic plaque.

Figure 2. Trend over time of the prevalence of ICAAT and of vascular disease (N=654)



Tables

Table 1. Patient's characteristics according to the period of inclusion: before 2013 and since 2013

	All patients n=654 n (%) or Median (P_{25}; P_{75})	Before 2013 n=185 n (%) or Median (P_{25}; P_{75})	Since 2013 n=469 n (%) or Median (P_{25}; P_{75})	*p*-value
Socio-demographic				
Age, in years	84 (81 ; 88)	83 (79 ; 87)	85 (81 ; 88)	0.002
Female sex	332 (50.8)	104 (56.2)	228 (48.6)	0.080
Living in a nursing home	110 (16.8)	25 (13.5)	85 (18.1)	0.156
Geriatric syndromes				
Malnutrition **	176 (27.0)	54 (29.2)	122 (26.1)	0.427
Cognitive disorder ***	198 (30.4)	51 (27.6)	147 (31.5)	0.320
Falls in the past year **	293 (44.9)	84 (45.4)	209 (44.8)	0.880
ADL dependency ‡[a]	227 (35.5)	65 (35.1)	162 (35.6)	0.910
High risk of decline †[b]	522 (80.4)	146 (78.9)	376 (81.0)	0.540
Comorbidities				
Vascular disease	230 (35.2)	66 (35.7)	164 (35.0)	0.864
Congestive heart failure	225 (34.4)	65 (35.1)	160 (34.1)	0.805
Hypertension	524 (80.1)	145 (78.4)	379 (80.8)	0.483
Diabetes	151 (23.1)	49 (26.5)	102 (21.7)	0.195
Stroke or TIA	195 (29.8)	67 (36.2)	128 (27.3)	0.025
Hepatic or renal failure *	93 (14.2)	35 (18.9)	58 (12.4)	0.032
Ethylism	30 (4.6)	4 (2.2)	26 (5.5)	0.063
Malignancy	72 (11.0)	23 (12.4)	49 (10.4)	0.465
Low platelet count	97 (14.9)	24 (13.0)	73 (15.6)	0.409
Rebleeding risk	54 (8.3)	11 (5.9)	43 (9.2)	0.177
Hypertension, uncontrolled *	134 (20.5)	47 (25.4)	87 (18.6)	0.052
Anemia (Hb < 10 g/dL)	82 (12.5)	18 (9.7)	64 (13.6)	0.173
Excess fall risk	441 (67.4)	117 (63.2)	324 (69.1)	0.151
Anthrombotic regimen				
Anticoagulant				<0.001
DOAC	229 (35.0)	3 (1.6)	226 (48.2)	
VKA	383 (58.6)	163 (88.1)	220 (46.9)	
LMWH	42 (6.4)	19 (10.3)	23 (4.9)	
Antiplatelet	140 (21.4)	50 (27.0)	90 (19.2)	0.028
$CHADS_2$				0.205
score 2	281 (43.0)	71 (38.4)	210 (44.8)	
score 3	184 (28.1)	52 (28.1)	132 (28.1)	
score 4 to 6	189 (28.9)	62 (33.5)	127 (27.1)	
$HEMORR_2HAGES$				
score	3 (2; 4)	3 (2; 4)	3 (2; 4)	0.211
corrected score (see methods)	3 (2; 4)	3 (2; 4)	3 (2; 4)	0.537

* 1 missing value (0.2%); ** 2 missing values (0.3%); *** 3 missing values (0.5%); †5 missing values (0.8%); ‡14 missing values (2.1%)

bADL basic activities of daily living, *DOAC* direct oral anticoagulants, *Hb* hemoglobin, *LMWH* low molecular weight heparin, *TIA* transient ischemic attack, *VKA* vitamin K antagonist.

[a] Dependency in bADL : Katz score ≥ 10/24

[b] High risk of decline: ISAR score ≥ 3/6

Table 2. Patient's characteristics according to the presence or absence of inappropriate combined antiplatelet and anticoagulant therapy (ICAAT) during the DOAC era

	All patients n=469 n (%) or Median (P_{25}; P_{75})	ICAAT present n=90 n (%) or Median (P_{25}; P_{75})	ICAAT absent n=379 n (%) or Median (P_{25}; P_{75})	*p*-value
Socio-demographic				
Age, in years	85 (81; 88)	83 (80; 87)	85 (81; 88)	0.049
Female sex	228 (48.6)	39 (43.3)	189 (49.9)	0.265
Living in a nursing home	85 (18.1)	16 (17.8)	69 (18.2)	0.925
Geriatric syndromes				
Malnutrition	122 (26.1)	25 (27.8)	97 (25.7)	0.691
Cognitive disorder***	147 (31.5)	24 (26.7)	123 (32.7)	0.268
Falls in the last year**	209 (44.8)	37 (41.1)	172 (45.6)	0.439
Dependency in bADL‡[a]	162 (35.6)	36 (41.4)	126 (34.2)	0.211
High risk of decline†[b]	376 (81.0)	78 (86.7)	298 (79.7)	0.129
Comorbidities				
Congestive heart failure	160 (34.1)	26 (28.9)	134 (35.4)	0.245
Vascular disease	164 (35.0)	59 (65.6)	105 (27.7)	<0.001
Hypertension	379 (80.8)	69 (76.7)	310 (81.8)	0.267
Uncontrolled hypertension	87 (18.6)	15 (16.7)	72 (19.0)	0.602
Diabetes	102 (21.7)	25 (27.8)	77 (20.3)	0.123
History of stroke or TIA	128 (27.3)	33 (36.7)	95 (25.1)	0.026
Hepatic or renal failure	58 (12.4)	11 (12.2)	47 (12.4)	0.963
Ethylism	26 (5.5)	5 (5.6)	21 (5.5)	0.996
Malignancy	49 (10.5)	9 (10.0)	40 (10.6)	0.877
Low platelet count*	73 (15.6)	11 (12.2)	62 (16.4)	0.326
Rebleeding risk	43 (9.2)	10 (11.1)	33 (8.7)	0.477
Anemia (Hb< 10g/dL)	64 (13.6)	16 (17.8)	48 (12.7)	0.204
Excess fall risk	324 (69.1)	64 (71.1)	260 (68.6)	0.643
Anticoagulant therapy				0.010
DOAC	226 (48.2)	40 (44.4)	186 (49.1)	
VKA	220 (46.9)	40 (44.4)	180 (47.5)	
LMWH	23 (4.9)	10 (11.1)	13 (3.4)	
$CHADS_2$ score				0.241
2	210 (44.8)	34 (37.8)	176 (46.4)	
3	132 (28.1)	26 (28.9)	106 (28.0)	
4 to 6	127 (27.1)	30 (33.3)	97 (25.6)	
$HEMORR_2HAGES$ score	3 (2; 4)	4 (3; 5)	3 (2; 4)	<0.001
Corrected $HEMORR_2HAGES$ score	3 (2; 4)	3 (2; 4)	3 (2; 4)	0.233

* 1 missing value (0.2%); ** 2 missing values (0.4%); *** 3 missing values (0.6%); †5 missing values (1.1%); ‡14 missing values (3.0 %)

bADL basic activities of daily living, *DOAC* direct oral anticoagulants, *Hb* hemoglobin, *LMWH* low molecular weight heparin, *TIA* transient ischemic attack, *VKA* vitamin K antagonist.

a Dependency in bADL : Katz score ≥ 10/24

b High risk of decline: ISAR score ≥ 3/6

Table 3. Factors associated with inappropriate combined antiplatelet and anticoagulant therapy (ICAAT) since 2013 (N=469)

	Univariate analysis		**Multivariate full model**		**Multivariate stepwise model**	
Variable	OR (95%CI]	p-value	OR (95%CI]	p-value	OR (95%CI]	p-value
Socio-demographics						
Age, per 10 years	0.60 [0.37; 0.97]	0.035	0.63 [0.37; 1.07]	0.089	Not kept	
Type of anticoagulant						
DOAC	1.00		1.00		1.00	
VKA	1.03 [0.64; 1.68]	0.894	1.18 [0.70; 1.98]	0.539	1.12 [0.67; 1.87]	0.664
LMWH	3.58 [1.47; 8.73]	0.005	3.29 [1.20; 9.00]	0.021	3.44 [1.28; 9.26]	0.015
Comorbidities						
Vascular disease	4.97 [3.04; 8.10]	<0.001	5.53 [3.30; 9.28]	<0.001	5.68 [3.40; 9.49]	<0.001
History of stroke / TIA	1.73 [1.06; 2.82]	0.026	2.17 [1.25; 3.76]	0.006	2.13 [1.24; 3.67]	0.007
Diabetes	1.51 [0.89; 2.55]	0.123	1.22 [0.68; 2.18]	0.511	Not kept	

95%CI 95% confidence interval, *DOAC* direct oral anticoagulants; *LMWH* low molecular weight heparin, *OR* odds ratio, *TIA* transient ischemic attack, *VKA* vitamin K antagonist

Hosmer and Lemeshow goodness-of-fit test for the multivariate full model: p-value=0.9812 and for the multivariate stepwise model: p-value=0.8483Vascular disease; history of myocardial infarction, peripheral artery disease or aortic plaque