

Guideline-adherent antithrombotic treatment improves outcomes in patients with atrial fibrillation:

Mazurek, Michal; Shantsila, Eduard; Lane, Deirdre; Wolff, Andreas; Proietti, Marco; Lip, Gregory

DOI:

[10.1016/j.mayocp.2017.05.023](https://doi.org/10.1016/j.mayocp.2017.05.023)

License:

Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

Document Version

Peer reviewed version

Citation for published version (Harvard):

Mazurek, M, Shantsila, E, Lane, D, Wolff, A, Proietti, M & Lip, G 2017, 'Guideline-adherent antithrombotic treatment improves outcomes in patients with atrial fibrillation: Insights from the community-based Darlington atrial fibrillation registry', *Mayo Clinic Proceedings*, vol. 92, no. 8, pp. 1203-1213.
<https://doi.org/10.1016/j.mayocp.2017.05.023>

[Link to publication on Research at Birmingham portal](#)

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Guideline-Adherent Antithrombotic Treatment Improves Outcomes in Patients with Atrial Fibrillation – Insights from the Community-Based Darlington Atrial Fibrillation Registry

Michał Mazurek, PhD,^{1,2} Eduard Shantsila, PhD,¹ Deirdre A Lane, PhD,¹ Andreas Wolff, GP,³ Marco Proietti, MD,¹ Gregory Y H Lip, MD¹

¹ Institute for Cardiovascular Sciences, University of Birmingham, United Kingdom

² Department of Cardiology, Congenital Heart Diseases & Electrotherapy, Silesian Centre for Heart Diseases, Zabrze, Poland

³ Division of Family Practice, Chilliwack General Hospital, Chilliwack, British Columbia, Canada

Financial support: None.

Conflict of interest disclosure:

DAL has received investigator-initiated educational grants from Bayer Healthcare, Bristol Myers Squibb and Boehringer Ingelheim, has been a speaker and consulted for Boehringer Ingelheim, Bayer, and Bristol Myers Squibb/Pfizer. AW has been a clinical advisor to Boehringer Ingelheim, Pfizer, BMS, Sanofi Aventis and Daiichi-Sankyo, also received educational grants and investigator payments from the above. In addition served as speaker for Boehringer Ingelheim, Sanofi and Pfizer. MP has received consultancy fee from Boehringer Ingelheim. GYHL has served as a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo. ES and MM declare no conflicts of interest.

Reprints and correspondence:

Professor GYH Lip

University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Dudley Road, Birmingham B18 7QH, United Kingdom

Tel: +44 121 507 5080; Fax: +44 121 554 4083; E-mail: g.y.h.lip@bham.ac.uk

Word count of the text: 2996

Number of references: 32

Number of tables: 4

Number of figures: 1

Number of supplementary figures: 1

ABSTRACT

Objective: To assess the influence of guideline-adherent versus non-adherent antithrombotic treatment (ATT) on stroke and mortality rates in atrial fibrillation (AF) primary care population.

Patients and Methods: We used Darlington Registry cohort which included 105,000 patients from March 31, 2012, through March 31, 2013. Guideline-adherence in ATT was assessed against 2014 National Institute for Health and Care Excellence (NICE) guidelines, which recommend oral anticoagulation (OAC) for stroke prevention as a default management unless a truly “low-risk” of stroke ($\text{CHA}_2\text{DS}_2\text{-VASc}=0$ in men and 1 in women) is evident.

Results: Overall, 2259 (2.15%) AF patients were identified, of which 36.1% were under-treated, 50.8% guideline-adherent and 13.1% over-treated. OAC was declined by 5.0% and contraindicated at 8.3%. Overall, 67 (3.0%) incident strokes occurred, of which 66 (98.5%) in high-risk patients ($\text{CHA}_2\text{DS}_2\text{-VASc} \geq 2$). For the high-risk cohort, one-year stroke rates were 4.5% (95% CI 3.2-6.3) for under-treatment, 1.9% (95% CI 1.2-2.9) for guideline-adherence, and 7.2% (95% CI 4.4-11.6) for over-treatment; corresponding mortality rates were 16.1% (95% CI 13.6-19.0), 8.0% (95% CI 6.5-9.8), and 8.2% (95% CI 5.2-12.7), respectively.

On multivariable analysis, both under- and over-treatment of high-risk patients were associated with significant increase in stroke rates (OR 2.32, 95% CI 1.30-3.14, $P=.005$ and OR 2.28, 95% CI 1.12-4.63, $P=.02$, respectively). Under-treatment was also associated with a significant increase in all-cause mortality (OR 1.59, 95% CI 1.14-2.21, $P=.006$).

Conclusion: Only half of eligible AF patients are prescribed OAC in accordance with guideline recommendations. Guideline-adherent ATT significantly reduces the risk of stroke and improves survival.

Keywords: atrial fibrillation, oral anticoagulation, guideline adherence, stroke, mortality

Abbreviations and Acronyms:

AF = atrial fibrillation; **CHA₂DS₂-VASc** = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65-74 years, female sex category; **CI** = confidence interval; **EORP-AF** = EuroObservational Research Programme-Atrial Fibrillation; **GRASP-AF** = Guidance on Risk Assessment and Stroke Prevention in Atrial Fibrillation; **NICE** = National Institute for Health and Care Excellence; **NOAC** = non-vitamin K antagonist oral anticoagulant; **OAC** = oral anticoagulant; **OR** = odds ratio; **SD** = standard deviation; **TTR** = time in therapeutic range; **UK** = United Kingdom

Oral anticoagulation (OAC) is the mainstay of effective stroke prevention in atrial fibrillation (AF), as reduces both stroke and mortality in AF.^{1,2} In accordance with current AF guidelines, stroke prevention with OAC should be the default therapy in AF patients, unless truly “low-risk” of stroke, i.e. CHA₂DS₂-VASc=0 in men and 1 in women, is confirmed.^{3,4}

Contemporary registry data show that approximately 5% of AF patients have no risk factors for stroke,^{5,6} which indicates that risk stratification and OAC use should be carefully and repeatedly reviewed in all AF patients as risk factors can develop over time. Nonetheless, approximately one third of AF patients at risk for stroke are not given OAC, but instead are treated with antiplatelet monotherapy or left untreated, while approximately 50% of patients with no risk factors are unnecessarily prescribed OAC.^{6,7}

Absolute OAC prescription rates, commonly reported by AF studies,⁸ may be misleading, as they may not reflect “real-life” eligibility for anticoagulation by failing to take into account the complexity of various clinical and patient-related factors affecting the final decision making on OAC prescription. For example, 1 in 10 AF patients refuse to take OAC,⁹ and the same proportion may have contraindications to anticoagulation.^{10,11} In addition, some AF patients may require temporal combination antithrombotic therapy (OAC + antiplatelets) due to acute vascular disease.^{3,4} The definition of guideline adherence may also vary, depending on applied stroke risk stratification schemes and guideline recommendations.^{12,13} Finally, indication for OAC in individual patients may change over time making comparisons even more complex and difficult to interpret.

Previous reports on guideline adherence on OAC for stroke prevention in AF were based

predominantly¹⁴ or solely^{15–17} on thromboembolic risk assessment and patients were managed by cardiologists, mainly in hospital-based or cardiology outpatient settings, often linked to university centers. Moreover, various combined endpoints and selected patient populations (i.e. only patients at high-risk for stroke) were used to assess the clinical relevance of guideline-recommended antithrombotic therapy.^{14,16,17}

We sought to provide herein a more comprehensive analysis of outcomes related to OAC guideline adherence, taking into account the aforementioned clinical and patient factors, and to assess the impact of guideline-adherent versus non-adherent thromboprophylaxis on “hard” clinical endpoints (stroke and death rates) in an unselected (i.e. consecutive all-comers) contemporary, community-based AF population.

METHODS

The design of the Darlington AF Registry has been described previously.¹⁸ In short, 11 primary care practices, serving the population of 105,000 patients from Darlington, County Durham, United Kingdom (UK) were involved. Consecutive all-comers with established AF or atrial flutter diagnosis and known vital status in March 2013 were eligible for inclusion.

Each primary care practice was equipped with the Guidance on Risk Assessment and Stroke Prevention in Atrial Fibrillation (GRASP-AF) tool.^{10,18} This electronic record interrogation software was designed to support primary care physicians in population-based screening for stroke risk factors and facilitate decision making for OAC prescription. Indeed, GRASP-AF is free and easy to use tool, which interrogates patient clinical data and allows one to display graphically annual stroke risk. This measure helps clinicians identify AF patients who may

have a missing diagnosis code for AF, calculate the risk of stroke in patients with AF, identify patients at high risk of stroke who are not receiving OAC, calculate the number of strokes that a practice can expect in the next twelve months (given current levels of OAC) or help clinicians manage their patients with AF and highlight patients of concern or interest.

As the GRASP-AF tool does not capture outcome events, additional searches of the primary care dataset were performed to identify patients who experienced stroke or died during a 12-month observation period. Incident acute stroke was diagnosed only when there was a concordance between clinical picture of cerebrovascular accident, physical examination and cerebral imaging (computer tomography or magnetic resonance imaging). Cardiovascular death was defined as death resulting from one of the following conditions: cardiac (myocardial infarction, cardiac failure, cardiac arrest, coronary heart disease, ventricular tachycardia, complete heart block), heart failure, stroke, pulmonary embolism or systemic thromboembolism, and intracranial bleeding. Every outcome event was manually reviewed and adjudicated. Read codes were used to capture and identify different types of strokes, comorbidities, medical treatment, contraindications to OAC/antiplatelets and therapy decline.¹⁸

Stroke Risk

The CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65-74 years, female sex category) score was used to assess stroke risk.¹⁹ As per the 2014 National Institute for Health and Care Excellence (NICE) guidelines, “low-risk” were men with CHA₂DS₂-VASc=0 and women with CHA₂DS₂-VASc=1 (1 point for sex category only); “moderate-risk” were men with CHA₂DS₂-VASc=1; and “high-risk” were patients with CHA₂DS₂-VASc score ≥2, regardless of sex.³

Guideline Adherence in Antithrombotic Treatment

Guideline adherence to antithrombotic therapies for stroke prevention was assessed against the 2014 NICE guidelines, including an informed, shared decision making on therapy introduction.³ Lack of guideline adherence was considered as either over-treatment (OAC overuse) or under-treatment (OAC underuse). Thus, our patient categories were defined as follows:

(i) **Guideline adherence** was defined using the following criteria:

- OAC in moderate- and high-risk patients
- combination therapy (OAC + antiplatelets) in patients with acute vascular disease, i.e. recent acute myocardial infarction
- no OAC in low-risk patients
- no OAC in patients with reported contraindications to OAC or therapy decline

(ii) **Under-treatment** was defined using the following criteria:

- no OAC (but antiplatelet or no therapy) in moderate or high-risk patients
- no combination therapy (OAC + antiplatelets) in patients with recent acute myocardial infarction
- no reported contraindications to OAC or therapy decline

(iii) **Over-treatment** was defined as follows:

- OAC in low-risk patients
- OAC + antiplatelet therapy in patients with no evidence of acute vascular disease
- OAC in patients with reported contraindications to anticoagulation therapy
- Antiplatelets in patients with reported contraindications to both OAC and antiplatelet therapy

Statistical Analysis

Categorical variables are reported as absolute frequencies and percentages, and continuous variables as mean and standard deviation (SD). Baseline characteristics, stroke risk and antithrombotic treatment, as well as outcome events were tabulated in relation to the three categories (under-treatment, guideline-adherence and over-treatment). For the outcome events, confidence intervals (CI) were provided for the proportion of one-year incident stroke rates and for the proportion of one-year all-cause mortality rates, respectively.

Multivariable logistic regression analysis was performed to determine the independent predictors for one year stroke rates after adjustment for clinically relevant variables: age, hypertension, previous stroke, heart failure and antithrombotic treatment (under-treatment, guideline-adherence [as reference] and over-treatment). For all-cause death predictors, the multivariable regression analysis was performed after adjustment for the following variables: age, sex, hypertension, diabetes, previous stroke, heart failure, vascular disease and antithrombotic treatment. The multivariable analysis was performed separately for the whole study population and for patients at high-risk for stroke. All statistical analyses were performed using IBM SPSS Statistics (version 21) software (Chicago, Illinois, USA). Statistical significance was set at a two-sided $P < .05$.

RESULTS

Overall, 2259 patients with AF (2.15% of the population) were identified, of which 50.8% received guideline-adherent antithrombotic treatment, 36.1% were under-treated and 13.1% were over-treated. The proportion of women was similar across 3 study groups, at 46.1% on average. Under-treated patients were older (mean age 77.0 years, standard deviation [SD] 11.6) compared to guideline-adherent (75.3, SD 11.9) and over-treated subjects (73.0, SD 14.6), while the proportion of those ≥ 75 years of age was non-significantly different between the under-treated (59.8%) and guideline-adherent (60.4%) groups ($P=.78$) (Table 1).

The highest prevalence of heart failure (26.4%), hypertension (65.6%) and diabetes mellitus (24.0%) was observed in the guideline-adherent group, whereas previous history of stroke (27.4%) was more common in over-treated subjects and least frequent in under-treated patients (13.0%). No significant difference was noted with regard to stable and acute vascular disease (i.e. acute myocardial infarction) amongst all groups (Table 1).

Thromboembolic Risk and Antithrombotic Treatment

Stroke risk, as assessed by CHA₂DS₂-VASc score (mean, SD), was 3.4 (1.6) for under-treatment, 3.6 (1.7) for guideline-adherence and 3.4 (2.3) for over-treatment, respectively (Table 1). In the guideline-adherent cohort, 79.3% patients were prescribed OAC (alone or in combination with antiplatelets), 7.1% antiplatelet therapy and 13.6% were untreated (no antithrombotic therapy). OAC was reported as contraindicated in 5.7% and declined in 9.9%. In the under-treated cohort, 74.1% received antiplatelet therapy and 25.9% were not treated, whereas in the over-treated group 57.5% patients were given OAC (either alone or

in combination with antiplatelets), 42.5% antiplatelets alone, and 41.2% had reported contraindications to OAC (Table 1). Of 1080 patients who received OAC, 1050 (97.2%) were given a vitamin K antagonist (predominantly warfarin) and 30 (2.8%) a non-vitamin K OAC (NOAC). Antithrombotic drug choice in relation to guideline adherence and risk of stroke is summarized in Figure 1.

Clinical Outcomes

At one year, there were 32 incident strokes (3.9%, 95% confidence interval [CI], 2.8-5.5) for the under-treated group, 20 strokes (1.7%, 95% CI, 1.1-2.7) for those guideline-adherent and 15 strokes (5.1%, 95% CI, 3.1-8.2) for those over-treated; corresponding all-cause mortality rates were 14.1% (95% CI, 11.9-16.7), 7.1% (95% CI, 5.7-8.7) and 6.1% (95% CI, 3.9-9.4), respectively. The reasons for cardiovascular deaths were similar across the 3 study groups, except that significantly more fatal strokes were observed among those under-treated (1.1%, n=9) versus guideline-adherent (0.2%, n=2, $P=0.007$). Details of one-year outcomes in relation to guideline adherence (or not) for antithrombotic treatment are summarized in Table 2.

Clinical outcomes by thromboembolic risk profile and applied antithrombotic therapies as per 2014 NICE guidelines³ are shown in Table 3. Of 67 (3.0%) acute strokes, 66 (98.5%) were observed in high-risk patients ($\text{CHA}_2\text{DS}_2\text{-VASc} \geq 2$). For the high-risk cohort, one-year stroke rates were 4.5% (95% CI, 3.2-6.3) for under-treatment, 1.9% (95% CI, 1.2-2.9) for guideline-adherence, and 7.2% (95% CI, 4.4-11.6) for over-treatment; corresponding all-cause, one-year mortality rates were 16.1% (95% CI, 13.6-19.0), 8.0% (95% CI, 6.5-9.8), and 8.2% (95% CI, 5.2-12.7), respectively. One stroke event was noted in a low-risk patient, a man classified

as guideline-adherent (off anticoagulation). No one-year stroke events or deaths were observed in patients at moderate risk of stroke (Table 3).

Antithrombotic Treatment in Patients with Acute Stroke

Antithrombotic drug choice in patients who experienced an acute stroke during 12-month observation is presented in Supplemental Figure 1, separately for the entire study population (Panel A) and the high-risk cohort (Panel B). Of the 32 high-risk patients who were under-treated and had acute stroke, 23 were on antiplatelet therapy and 9 remained untreated. Of the 19 high-risk and guideline-adherent patients who had incident stroke, 18 received OAC alone and 1 OAC in combination with antiplatelets, whereas for the high-risk and over-treated subjects, 10 were on combination therapy (OAC + antiplatelets), 1 received OAC alone and 4 antiplatelet monotherapy (Panel B).

Predictors of Stroke and Death

On multivariable analysis for the entire population, non-guideline adherence to antithrombotic therapy was associated with a significant increase in one-year stroke rate for those under-treated (odds ratio [OR] 2.18, 95% CI, 1.23-3.87, $P=.008$) and over-treated (OR 2.07, 95% CI, 1.03-4.16, $P=.04$). For one-year all-cause mortality, non-guideline adherence was associated with a significant increase in mortality for those under-treated (OR 1.57, 95% CI, 1.13-2.18, $P=.007$).

For high-risk patients, both under- and over-treatment were associated with a significant increase in one-year stroke rates (OR 2.32, 95% CI, 1.30-3.14, $P=.005$ and OR 2.28, 95% CI, 1.12-4.63, $P=.02$, respectively), whereas under-treatment was also associated with

significant increase in one-year all-cause mortality (OR 1.59, 95% CI, 1.14-2.21, $P=.006$) (Table 4).

DISCUSSION

The principal findings of this study are that although nine in ten AF patients managed in general practice are at high risk for acute stroke, only half are prescribed anticoagulation in line with current guideline recommendations. Most importantly, guideline-adherent antithrombotic treatment significantly reduced stroke rates and improved survival.

This study provides important insights into stroke risk profile and stroke prevention strategies in a contemporary, non pre-selected primary care AF population in the United Kingdom. First, at least one non-gender related risk factor for stroke (by CHA₂DS₂-VASc scheme and using GRASP-AF tool) was captured in 92.5% AF all-comers. Contemporary global registry data, confined to new onset AF only, demonstrate a very similar incidence, at 6.8%,⁶ while European registries recruiting AF patients managed by cardiologists indicate even lower prevalence of lone AF, at 3.9%.⁵ These observations highlight the clinical relevance of careful and repeated screening for even a single stroke risk factor in every AF patient, with primary physicians playing a pivotal role, given that stroke risk is not static but changes (increases) over time.^{2,20} Importantly, once the diagnosis of truly low risk has been proven, anticoagulation may be omitted.^{3,4} Indeed, of 170 low-risk patients (CHA₂DS₂-VASc=0 in men and 1 in women) in the present analysis, only a single case of stroke occurred. However, nearly one third of such low-risk patients were unnecessarily prescribed OAC. Similar overuse of stroke prevention therapies among patients with no stroke risk

factors has been noted by previous reports.^{6,8} Importantly, current AF guidelines do not recommend treatment of low-risk patients as there is no evidence of benefit, but there may be increased risk of harm.^{3,4}

Second, none of the 154 men at moderate risk of stroke ($\text{CHA}_2\text{DS}_2\text{-VASc}=1$) in the present study suffered an acute stroke or died during the 12-month observation period. Our study was not powered to analyze whether the use of, or absence of, OAC affects outcomes in patients with only one risk factor for stroke. Annual stroke rates in untreated patients with only 1 risk factor for stroke (beyond sex) do vary amongst studies.²¹⁻²³ A recent Markov decision model suggests that stroke risk $>1.7\%/year$ and $>0.9\%/year$ warrants anticoagulation with warfarin and NOACs, respectively.²⁴ However, this model did not consider quality of anticoagulation control amongst warfarin users; with good quality control, the $1.7\%/year$ treatment threshold may even be lower.²⁵ For example, stroke/systemic thromboembolic events and mortality are high even in patients with only one stroke risk factor and despite OAC use.²⁵ Importantly, these event rates were significantly but inversely associated with time spent in therapeutic range (TTR), ranging from 3.5% in lowest TTR quartile to only 0.7% in the highest TTR quartile. Of note, current AF guidelines already recommend OAC use as a default therapy (whether with an NOAC or warfarin with TTRs as high as possible) in all AF patients unless truly low-risk is shown.²⁻⁴

Third, we show herein that neither underuse nor overuse of antithrombotic therapy is beneficial for high-risk patients ($\text{CHA}_2\text{DS}_2\text{-VASc} \geq 2$). One-year stroke rates were lowest, at 1.9%, for guideline-adherence, whereas the corresponding rates for under- and over-treatment were 4.5% and 7.2%, respectively. Also, all-cause mortality was 2-fold higher in

those non-adherent with recommendations. These findings highlight importance of strict compliance with guideline recommendations (in this case, NICE) in real-life clinical practice.³

Previous studies have also reported that guideline adherence is associated with better outcomes in AF patients.^{14–17} In contrast to our study these patients were managed either by cardiologists,^{14–16} or internal medicine specialists,¹⁷ where the prevalence of in-patients and participating university centers were high, as was the overall OAC uptake (up to 80%).¹⁶ In addition, none of these studies considered contraindications to OAC or therapy decline (8.3% and 5.0%, respectively in our study), and only the EuroObservational Research Programme-Atrial Fibrillation (EORP-AF) Pilot General Registry corrected the definition of guideline adherence for the presence of acute vascular disease.¹⁶ Importantly, definition of clinical outcomes in prior studies did vary considerably. For example, the EORP-AF registry did not show significantly lower rates of stroke alone for guideline-adherence (as shown in the present analysis), but for a combined thromboembolic endpoint that comprised of stroke, transient ischemic attack, acute coronary syndrome, percutaneous coronary intervention, cardiac arrest, peripheral embolism and pulmonary embolism.¹⁶

Moreover, our study supports several important points regarding antithrombotic drug choice. First, aspirin is not effective and should not be used for stroke prevention in AF.^{3,4} One-year stroke rates in high-risk patients were even higher in those under-treated with antiplatelets versus no treatment. This is alarming, given that more than one third of eligible patients in the present analysis were not offered OAC, which not only significantly reduced stroke rates, but was also a life-saving treatment. Importantly, more recent data indicate

that overall mortality reduction with an OAC even exceeds the reduction of stroke-related deaths only.²⁶

Second, one in ten high-risk patients were over-treated, either with an OAC (in combination with antiplatelets or alone) or with antiplatelets (reported contraindications to both OAC and antiplatelet therapy). Importantly, only a few AF patients with recent acute myocardial infarction were guideline-adherent on combination therapy, while the majority received either antiplatelet therapy only (under-treated cohort) or a combination therapy despite reported contraindications (over-treated cohort). Both regimens resulted in an excess in stroke rates, but allocation of many patients with vascular disease to the over-treated cohort creates a bias of their overall increased risk compared to guideline-adherence. Even assuming that contraindications to OAC might have been over-estimated by physicians, and some of these patients could actually be categorized as guideline-adherent, stroke rates of these patients would still remain high.

Limitations and Strengths

The major limitation of this analysis is lack of overall bleeding risk and outcomes. Indeed, the GRASP-AF tool used for data collection in Darlington Registry does not collect data on bleeding risk or events. Consequently, fatal and non-fatal hemorrhages were available only for patients with outcome events (stroke and death). Despite this limitation we think that our findings are of clinical relevance for variety of reasons. First, GRASP-AF tool is part of the cornerstone National Health Service (NHS) quality improvement programs, which was primarily designed and implemented into practice to help primary care physicians tackle the

nation's biggest killer, i.e. stroke. Even more importantly, use of the GRASP-AF tool has been previously described as a means that could help prevent strokes in AF patients.¹⁸

Second, guideline recommendations on stroke prevention in AF highlight that bleeding risk *per se* should not be a reason to preclude or withhold stroke prevention strategies in at risk for stroke AF patients.^{3,4} Indeed, absolute contraindications to OAC are rare and if a patient truly cannot receive any of the available OACs, despite being at high risk for stroke, other options of stroke prevention could be considered (i.e. left atrial appendage exclusion).^{3,4} If contraindications to OAC are not genuine, the priority should be correction of any potentially reversible risk factors for bleeding, but not withholding OAC use simply on a perceived high bleeding risk score.²⁷

Third, stroke and bleeding risk factors commonly overlap.²⁸ Thus, patients at highest risk for bleeding are usually also at highest risk for stroke, but the net clinical benefit of anticoagulation is positive and even greater in patients with both high stroke and bleeding risks,²⁹ i.e. patients with frequent comorbid disease, very elderly and frail,^{11 30} or even those who have already bled (even intracranially).³¹ Indeed, in contrast to stroke rates we did not observe any difference in hemorrhagic strokes or intracranial bleeds amongst all three study groups.

Fourth, patients' views and preferences are also of great importance. Indeed, patients often view a stroke "as a fate worse than death", and may accept 4 major bleeds just to avoid one disabling stroke.⁹ Thus, as the guideline-recommended decision making on OAC prescribing is based on positive net clinical benefit when balancing the risk of stroke against the risk of

bleeding complications (intracranial hemorrhage),²⁴ we do not think that providing the overall bleeding events (in addition to reported non-fatal intracranial bleeds and fatal hemorrhages) would substantially change our conclusions.

Our definition of adherence to guidelines may be inconsistent with previous papers, which reported absolute numbers/percentages of OAC use in AF patients, and thus failed to reflect their “real-life eligibility” for anticoagulation (in particular, including patient’s views and preferences). By doing so, previous reports showed more the impact of OAC use on outcomes rather than the impact of guideline-adherence on outcomes. Indeed, exclusion of contraindications to OAC or therapy decline, assumes that 100% patients must be given OAC (no exceptions), while the real-life data show that 12% of AF patients (so called “medication averse”) refuse anticoagulation, even if the therapy were 100% effective for stroke prevention.⁹

We have assessed the quantity, but not quality of anticoagulation, as neither international normalized ratios nor TTR values were available. Although this registry covered a broad population of over 100,000 patients, it was confined to one UK region only, which may limit the generalizability of the findings. Because patient-specific data were analyzed more in detail only in patients with outcome events, baseline characteristics of the entire study population are limited. However, lack of patient selection allowed for evaluation of antithrombotic treatment patterns and outcomes in low- and moderate-risk cohorts. Unlike other studies, we have also used only “hard” endpoints, which were confirmed by cerebral imaging and adjudicated. Nonetheless, we could not establish the cause of death with certainty in overall 45 patients (21.0% of all deaths), as death certificates could not be

retrieved. Thus, multivariable analysis of cardiovascular mortality predictors was not possible.

We have based our definition of guideline adherence on the 2014 NICE guideline recommendations (which are applicable to our UK-based study),³ which has similarity to the 2012 focused update of European Society of Cardiology guidelines on AF.³² Our study validates the “real world” application of these guidelines and the potential impact on stroke and mortality in AF patients.

CONCLUSION

Despite nine in ten AF patients being at high risk for stroke, only half of eligible patients are prescribed anticoagulation in accordance with current guidelines. Guideline-adherent antithrombotic treatment significantly reduces the risk of stroke and improves survival at one year.

REFERENCES

1. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146(12):857-867. doi:10.7326/0003-4819-146-12-200706190-00007.
2. Freedman B, Potpara TS, Lip GYH. Stroke prevention in atrial fibrillation. *Lancet* 2016;388(10046):806-817. doi:10.1016/S0140-6736(16)31257-0.
3. Atrial Fibrillation: The Management of Atrial Fibrillation - PubMed - NCBI. at <<http://www.ncbi.nlm.nih.gov/pubmed/25340239>>.
4. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation. *Eur Heart J*. August 2016. doi:10.1093/eurheartj/ehw210.
5. Lip GYH, Laroche C, Dan GA, et al. A prospective survey in European Society of Cardiology member countries of atrial fibrillation management: Baseline results of EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry. *Europace*. 2014;16(3):308-319. doi:10.1093/europace/eut373.
6. Lip GYH, Rushton-Smith SK, Goldhaber SZ, et al. Does sex affect anticoagulant use for stroke prevention in nonvalvular atrial fibrillation? The prospective global anticoagulant registry in the FIELD-Atrial Fibrillation. *Circ Cardiovasc Qual Outcomes*. 2015;8(2):S12-S20. doi:10.1161/CIRCOUTCOMES.114.001556.
7. Huisman M V., Rothman KJ, Paquette M, et al. Antithrombotic treatment patterns in patients with newly diagnosed nonvalvular atrial fibrillation: The GLORIA-AF Registry, phase II. *Am J Med*. 2015;128(12):1306-13.e1. doi:

- 10.1016/j.amjmed.2015.07.013doi:10.1016/j.amjmed.2015.07.013.
8. Mazurek M, Huisman M V, Lip GYH. Registries in Atrial Fibrillation: From Trials to Real-Life Clinical Practice. *Am J Med*. October 2016.
doi:10.1016/j.amjmed.2016.09.012.
 9. LaHaye S, Regpala S, Lacombe S, et al. Evaluation of patients' attitudes towards stroke prevention and bleeding risk in atrial fibrillation. *Thromb Haemost*. 2014;111(3):465-73. doi: 10.1160/TH13-05-0424.
 10. Cowan C, Healicon R, Robson I, et al. The use of anticoagulants in the management of atrial fibrillation among general practices in England. *Heart*. 2013;99(16):1166-1172.
doi:10.1136/heartjnl-2012-303472.
 11. Wolff A, Shantsila E, Lip GYH, Lane DA. Impact of advanced age on management and prognosis in atrial fibrillation: Insights from a population-based study in general practice. *Age Ageing*. 2015;44(5):874-8. doi: 10.1093/ageing/afv071.
 12. Camm AJ, Pinto FJ, Hankey GJ, Andreotti F, Hobbs FDR. Non-vitamin K antagonist oral anticoagulants and atrial fibrillation guidelines in practice: barriers to and strategies for optimal implementation. *Europace*. 2015;17(7):1007-1017.
doi:10.1093/europace/euv068.
 13. Chao T-F, Liu C-J, Tuan T-C, et al. Impact on Outcomes of Changing Treatment Guideline Recommendations for Stroke Prevention in Atrial Fibrillation: A Nationwide Cohort Study. *Mayo Clin Proc*. 2016;91(5):567-574. doi:
10.1016/j.mayocp.2016.03.007.

14. Nieuwlaat R, Olsson SB, Lip GYH, et al. Guideline-adherent antithrombotic treatment is associated with improved outcomes compared with undertreatment in high-risk patients with atrial fibrillation. The Euro Heart Survey on Atrial Fibrillation. *Am Heart J.* 2007;153(6):1006-1012. doi:10.1016/j.ahj.2007.03.008.
15. Gorin L, Fauchier L, Nonin E, Charbonnier B, Babuty D, Lip GYH. Prognosis and guideline-adherent antithrombotic treatment in patients with atrial fibrillation and atrial flutter: implications of undertreatment and overtreatment in real-life clinical practice; the Loire Valley Atrial Fibrillation Project. *Chest.* 2011;140(4):911-917. doi:10.1378/chest.10-2436.
16. Lip GYH, Laroche C, Popescu MI, et al. Improved outcomes with European Society of Cardiology guideline-adherent antithrombotic treatment in high-risk patients with atrial fibrillation: A report from the EORP-AF General Pilot Registry. *Europace.* 2015;17(12):1777-86. doi: 10.1093/europace/euv269.
17. Proietti M, Nobili A, Raparelli V, et al. Adherence to antithrombotic therapy guidelines improves mortality among elderly patients with atrial fibrillation: insights from the REPOSI study. *Clin Res Cardiol.* 2016;105(11):912-920. doi:10.1007/s00392-016-0999-4.
18. Shantsila E, Wolff A, Lip GYH, Lane DA. Optimising stroke prevention in patients with atrial fibrillation: application of the GRASP-AF audit tool in a UK general practice cohort. *Br J Gen Pract.* 2015;65(630):e16-23. doi:10.3399/bjgp15X683113.
19. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a

- novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137(2):263-272. doi:10.1378/chest.09-1584.
20. Lip GYH, Lane DA. Stroke prevention in atrial fibrillation: a systematic review. *JAMA*. 2015;313(19):1950-1962. doi:10.1001/jama.2015.4369.
 21. Lip GYH, Skjøth F, Rasmussen LH, Larsen TB. Oral anticoagulation, aspirin, or no therapy in patients with nonvalvular AF with 0 or 1 stroke risk factor based on the CHA2DS2-VASc score. *J Am Coll Cardiol*. 2015;65(14):1385-1394. doi:10.1016/j.jacc.2015.01.044.
 22. Chao T-F, Liu C-J, Wang K-L, et al. Should Atrial Fibrillation Patients With 1 Additional Risk Factor of the CHA2DS2-VASc Score (Beyond Sex) Receive Oral Anticoagulation? *J Am Coll Cardiol*. 2015;65(7):635-642. doi:10.1016/j.jacc.2014.11.046.
 23. Friberg L, Skeppholm M, Terént A. Benefit of anticoagulation unlikely in patients with atrial fibrillation and a CHA2DS2-VASc score of 1. *J Am Coll Cardiol*. 2015;65(3):225-232. doi:10.1016/j.jacc.2014.10.052.
 24. Eckman MH, Singer DE, Rosand J, Greenberg SM. Moving the tipping point the decision to anticoagulate patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2011;4(1):14-21. doi:10.1161/CIRCOUTCOMES.110.958108.
 25. Proietti M, Lip GYH. Major Outcomes in Atrial Fibrillation Patients with One Risk Factor: Impact of Time in Therapeutic Range Observations from the SPORTIF Trials. *Am J Med*. 2016;129(10):1110-1116. doi:10.1016/j.amjmed.2016.03.024.
 26. Bassand J-P, Accetta G, Camm AJ, et al. Two-year outcomes of patients with newly

- diagnosed atrial fibrillation: results from GARFIELD-AF. *Eur Heart J*. 2016.
doi:10.1093/eurheartj/ehw233.
27. Lip GYH, Lane DA. Assessing bleeding risk in atrial fibrillation with the HAS-BLED and ORBIT scores: Clinical application requires focus on the reversible bleeding risk factors. *Eur Heart J*. 2015;36(46):3265-3267. doi:10.1093/eurheartj/ehv415.
 28. Apostolakis S, Lane DA, Buller H, Lip GYH. Comparison of the CHADS₂, CHA₂DS₂-VASc and HAS-BLED scores for the prediction of clinically relevant bleeding in anticoagulated patients with atrial fibrillation: the AMADEUS trial. *Thromb Haemost*. 2013;110(5). doi:10.1160/TH13-07-0552.
 29. Potpara TS, Lip GYH. Oral anticoagulant therapy in atrial fibrillation patients at high stroke and bleeding risk. *Prog Cardiovasc Dis*. 2015;58(2):177-194.
doi:10.1016/j.pcad.2015.07.003.
 30. Bahri O, Roca F, Lechani T, et al. Underuse of Oral Anticoagulation for Individuals with Atrial Fibrillation in a Nursing Home Setting in France: Comparisons of Resident Characteristics and Physician Attitude. *J Am Geriatr Soc*. 2015;63(1):71-76.
doi:10.1111/jgs.13200.
 31. Nielsen PB, Larsen TB, Skjøth F, Gorst-Rasmussen A, Rasmussen LH, Lip GYH. Restarting Anticoagulant Treatment after Intracranial Hemorrhage in Patients with Atrial Fibrillation and the Impact on Recurrent Stroke, Mortality, and Bleeding: A Nationwide Cohort Study. *Circulation*. 2015;132(6):517-525.
doi:10.1161/CIRCULATIONAHA.115.015735.
 32. Camm AJ, Lip GYH, De Caterina R, et al. 2012 focused update of the ESC Guidelines for

the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation--developed with the special contribution of the European Heart Rhythm Association. *Europace*. 2012;14(10):1385-1413.
doi:10.1093/europace/eus305.

FIGURE LEGENDS

Figure 1 Antithrombotic Treatment in Relation to Guideline Adherence and Risk of Stroke

Panel A Low risk ($\text{CHA}_2\text{DS}_2\text{-VASc}=0$ in men and 1 in women)

Panel B Moderate risk ($\text{CHA}_2\text{DS}_2\text{-VASc}=1$ in men)

Panel C High risk ($\text{CHA}_2\text{DS}_2\text{-VASc} \geq 2$)

$\text{CHA}_2\text{DS}_2\text{-VASc}$ = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke/transient ischemic attack (TIA), vascular disease, age 65-74 years, sex category (female); OAC = oral anticoagulant

Supplemental Figure 1 One-Year Stroke Rates in Relation to Antithrombotic Guideline Adherence

Panel A Entire population (unselected study cohort)

Panel B High-risk cohort ($\text{CHA}_2\text{DS}_2\text{-VASc} \geq 2$)

$\text{CHA}_2\text{DS}_2\text{-VASc}$ = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke/transient ischemic attack (TIA), vascular disease, age 65-74 years, sex category (female); OAC = oral anticoagulant.

Some percentages may not sum up to total due to rounding.

Table 1 Baseline Characteristics of the Patient Population

	All	Under-treatment		Guideline-adherence	Over-treatment	
	2259 (100)	816 (36.1)	<i>P</i> value ^a	1147 (50.8)	296 (13.1)	<i>P</i> value ^a
Demographics						
Females	1041 (46.1)	390 (47.8)	.28	520 (45.3)	131 (44.3)	.74
Age, years, mean (SD)	75.6 (12.3)	77.0 (11.6)	.001	75.3 (11.9)	73.0 (14.6)	.006
<65 years	367 (16.2)	100 (12.3)	.05	177 (15.4)	90 (30.4)	<.001
65-74 years	554 (24.5)	228 (27.9)	.06	277 (24.1)	49 (16.6)	.005
≥75 years	1338 (59.2)	488 (59.8)	.78	693 (60.4)	157 (53.0)	.02
Medical history						
Heart failure	514 (22.8)	148 (18.1)	<.001	303 (26.4)	63 (21.3)	.07
Hypertension	1404 (62.2)	494 (60.5)	.02	753 (65.6)	157 (53.0)	<.001
Diabetes	490 (21.7)	150 (18.4)	.003	275 (24.0)	65 (22.0)	.47
Previous stroke	428 (18.9)	106 (13.0)	<.001	241 (21.0)	81 (27.4)	.02
Previous hemorrhagic stroke	17 (0.8)	3 (0.4)	.46	7 (0.6)	7 (2.4)	.006
Vascular disease	389 (17.2)	156 (19.1)	.05	180 (15.7)	53 (17.9)	.36
Acute myocardial infarction	152 (6.7)	53 (6.5)	.97	74 (6.5)	25 (8.4)	.23
Thromboembolic risk by CHA₂DS₂-VASc						
Mean score (SD)	3.5 (1.8)	3.4 (1.6)	<.001	3.6 (1.7)	3.4 (2.3)	.02
Low risk (score=0 in men and 1 in women)	170 (7.5)	0	<.001	86 (7.5)	84 (28.4)	<.001
Moderate risk (score=1 in men)	154 (6.8)	101 (12.4)	<.001	49 (4.3)	4 (1.3)	.02
High risk (score ≥2)	1935 (85.7)	715 (87.6)	.68	1012 (88.2)	208 (70.3)	<.001

Antithrombotic treatment						
None	367 (16.2)	211 (25.9)	<.001	156 (13.6)	0	<.001
Antiplatelets	812 (35.9)	605 (74.1)	<.001	81 (7.1)	126 (42.5)	<.001
OAC	971 (43.0)	0	<.001	906 (79.0)	65 (22.0)	<.001
OAC + antiplatelets	109 (4.8)	0	.09	4 (0.3)	105 (35.5)	<.001
Oral anticoagulation						
Contraindicated	187 (8.3)	0	<.001	65 (5.7)	122 (41.2)	<.001
Declined	113 (5.0)	0	<.001	113 (9.9)	0	<.001

^aversus guideline-adherent group.

Data are presented as n (%) or mean (SD).

CHA₂DS₂-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack (TIA), vascular disease, age 65-74 years, sex category (female); NICE = National Institute for Health and Care Excellence; OAC = oral anticoagulant; SD = standard deviation.

Table 2 One-Year Outcomes in Relation to Antithrombotic Treatment According to the 2014 NICE Guidelines³

Outcome events	All	Under-treatment	<i>P</i> value ^a	Guideline-adherence	Over-treatment	<i>P</i> value ^a
	n (%)	n (%) [95% CI]		n (%) [95% CI]	n (%) [95% CI]	
Stroke	67 (3.0)	32 (3.9) [2.8-5.5]	.003	20 (1.7) [1.1-2.7]	15 (5.1) [3.1-8.2]	<.001
Ischemic	62 (2.7)	30 (3.7) [2.6-5.2]	.003	18 (1.6) [1.0-2.5]	14 (4.7) [2.8-7.8]	.001
Hemorrhagic	5 (0.2)	2 (0.2) [0.1-0.9]	.73	2 (0.2) [0.1-0.6]	1 (0.3) [0.1-1.9]	.58
Death						
All-cause	214 (9.5)	115 (14.1) [11.9-16.7]	<.001	81 (7.1) [5.7-8.7]	18 (6.1) [3.9-9.4]	.55
Cardiovascular						
Cardiac death	14 (0.6)	8 (1.0) [0.5-1.9]	.14	5 (0.4) [0.2-1.0]	1 (0.3) [0.1-1.9]	.82
Heart failure	24 (1.1)	11 (1.3) [0.8-2.4]	.67	13 (1.1) [0.7-1.9]	0	.07
Stroke	11 (0.5)	9 (1.1) [0.6-2.1]	.007	2 (0.2) [0.1-0.6]	0	.47
PE or STE	3 (0.1)	1 (0.1) [0.0-0.7]	.77	2 (0.2) [0.1-0.6]	0	.47
Intracranial bleeding	5 (0.2)	3 (0.4) [0.1-1.1]	.40	2 (0.2) [0.1-0.6]	0	.47
Non-cardiovascular						
Bleeding non-cerebral	3 (0.1)	1 (0.1) [0.0-0.8]	.81	1 (0.1) [0.0-0.5]	1 (0.3) [0.1-1.9]	.30
Cancer	42 (1.9)	15 (1.8) [1.1-3.0]	.65	18 (1.6) [1.0-2.5]	9 (3.0) [1.6-5.7]	.10
Other	67 (3.0)	40 (4.9) [3.6-6.6]	<.001	21 (1.8) [1.2-2.8]	6 (2.0) [0.9-4.4]	.82
Unknown	45 (2.0)	27 (3.3) [2.3-4.8]	.007	17 (1.5) [0.9-2.4]	1 (0.3) [0.1-1.9]	.11

^aversus guideline-adherent group.

All outcome events were confirmed by cranial imaging (CT or MRI, for acute strokes) and adjudicated.

CI = confidence interval; CT = computer tomography; MRI = magnetic resonance imaging; NICE = National Institute for Health and Care Excellence; PE = pulmonary embolism; STE = systemic thromboembolism.

Table 3 One-Year Outcomes in Relation to Stroke Risk and Guideline Adherence in Antithrombotic Treatment

Stroke risk by CHA ₂ DS ₂ -VASc score	Outcomes	All	Under-treatment	<i>P</i> value ^a	Guideline-adherence	Over-treatment	<i>P</i> value ^a
Low risk (score 0 in men and 1 in women)		n=170	n=0		n=86	n=84	
	Stroke	1 (0.6)	-		1 (1.2) [0.2-6.3]	0	
	All-cause death	1 (0.6)	-		0	1 (1.2) [0.2-7.4]	
Moderate risk (score 1 in men)		n=154	n=101		n=49	n=4	
	Stroke	0	0		0	0	
	All-cause death	0	0		0	0	
High risk (score ≥2)		n=1935	n=715		n=1012	n=208	
	Stroke	66 (3.4)	32 (4.5) [3.2-6.3]	.002	19 (1.9) [1.2-2.9]	15 (7.2) [4.4-11.6]	<.001
	All-cause death	213 (11.0)	115 (16.1) [13.6-19.0]	<.001	81 (8.0) [6.5-9.8]	17 (8.2) [5.2-12.7]	.93

^aversus guideline-adherent group.

Data are presented as n (%) [95% CI].

CHA₂DS₂-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack (TIA), vascular disease, age 65-74 years, sex category (female); CI = confidence interval.

Table 4 Multivariable Regression Analysis for One Year Stroke and Death

	Entire population		High-risk cohort ^a	
	OR (95% CI)	P value	OR (95% CI)	P value
Stroke				
Age (per 1 y increase)	1.05 (1.02-1.08)	.001	1.04 (1.01-1.07)	.006
Hypertension	0.92 (0.54-1.58)	.76	0.89 (0.52-1.53)	.67
Previous stroke	5.20 (3.10-8.74)	<.001	4.96 (2.95-8.36)	<.001
Heart failure	1.34 (0.76-2.36)	.32	1.31 (0.74-2.32)	.35
Antithrombotic therapy				
Under-treatment	2.18 (1.23-3.87)	.008	2.32 (1.30-3.14)	.005
Guideline-adherence	1.0 (ref.)		1.0 (ref.)	
Over-treatment	2.07 (1.03-4.16)	.04	2.28 (1.12-4.63)	.02
All-cause death				
Age (per 1 y increase)	1.10 (1.08-1.13)	<.001	1.10 (1.08-1.13)	<.001
Female sex	1.24 (0.89-1.72)	.20	1.18 (0.85-1.64)	.32
Hypertension	0.96 (0.69-1.34)	.81	0.94 (0.67-1.32)	.73
Diabetes	1.51 (1.07-2.14)	.02	1.50 (1.06-2.12)	.02
Previous stroke	0.82 (0.56-1.21)	.32	0.82 (0.55-1.20)	.30
Heart failure	1.96 (1.41-2.72)	<.001	1.93 (1.39-2.69)	<.001
Vascular disease	2.86 (2.10-4.00)	<.001	2.80 (2.00-3.91)	<.001
Antithrombotic therapy				
Under-treatment	1.57 (1.13-2.18)	.007	1.59 (1.14-2.21)	.006
Guideline-adherence	1.0 (ref.)		1.0 (ref.)	
Over-treatment	0.74 (0.43-1.30)	.29	0.71 (0.40-1.25)	.24

^aHigh-risk cohort = CHA₂DS₂-VASc ≥2.

ATT = antithrombotic treatment; CI = confidence interval; OR = odds ratio; ref = reference; y = year.

Figure 1A

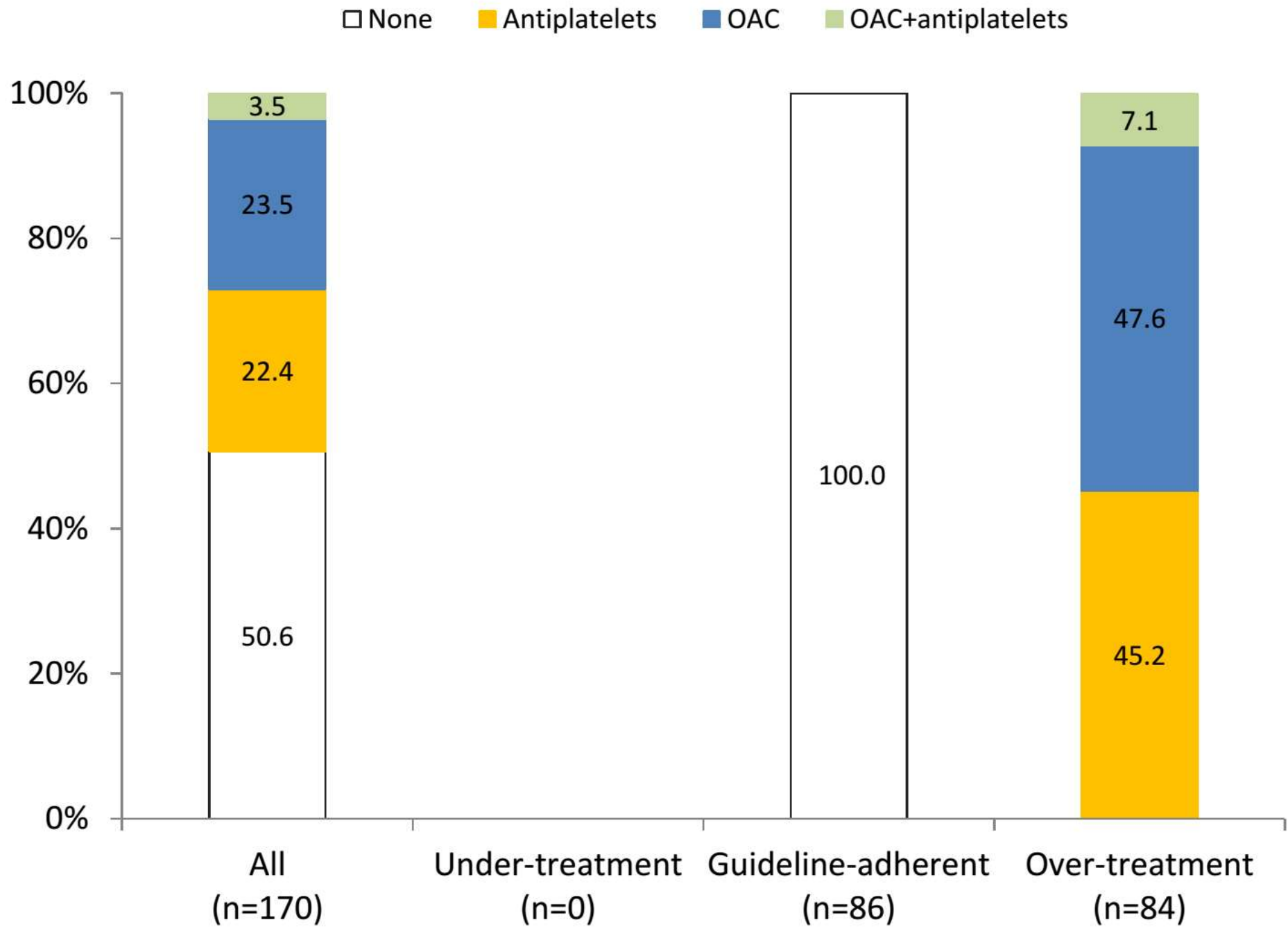


Figure 1B

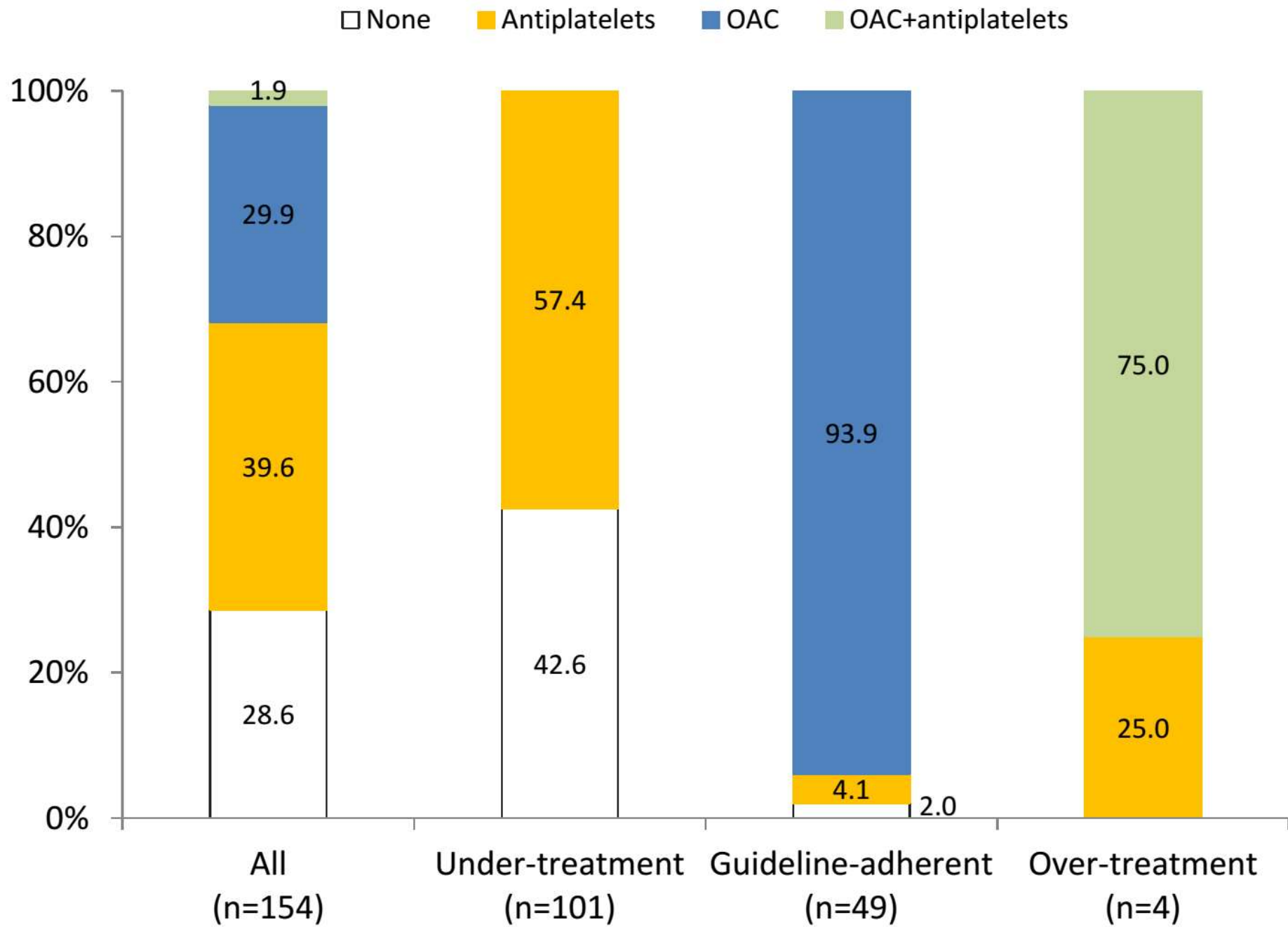


Figure 1C

