**Antithrombotic therapy for stroke prevention in patients with atrial fibrillation who survive an intracerebral haemorrhage: results of an EHRA survey**

Elena Ivany\*1

Deirdre A. Lane\*1,2

Gheorge-Andrei Dan3

Wolfram Doehner4,5

Michal M. Farkowski6

Konstantinos Iliodromitis7

Radoslaw Lenarczyk8

Tatjana S. Potpara9

1Liverpool Centre for Cardiovascular Science, University of Liverpool, United Kingdom

2Aalborg Thrombosis Research Unit, Department of Clinical Medicine

Aalborg University, Aalborg, Denmark

3 “Carol Davila” University of Medicine, Colentina University Hospital, Bucharest, Romania

4Berlin Institute of Health Center for Regenerative Therapies, and Department of Cardiology (Virchow Klinikum), Charité- Universitätsmedizin Berlin, and German Centre for Cardiovascular Research (DZHK), Partner Site Berlin, Germany

5Center for Stroke Research Berlin, Charité Universitätsmedizin Berlin, Germany

6II Department of Heart Arrhythmia, National Institute of Cardiology, Warsaw, Poland

7Clinic for Cardiology and Electrophysiology, Evangelisches Krankenhaus Hagen-Haspe, Germany

8Department of Cardiology, Congenital Heart Defects and Electrotherapy, Medical University of Silesia, Silesian Center of Heart Disease, Zabrze, Poland

9Serbia School of Medicine, University of Belgrade, Belgrade, Serbia; and Cardiology Clinic, Clinical Centre of Serbia, Belgrade, Serbia

**\***Joint first authors

**Corresponding Author**

Dr Deirdre A Lane

Liverpool Centre for Cardiovascular Science, University of Liverpool, Liverpool, L7 8TX, United Kingdom

E-mail: [deirdre.lane@liverpool.ac.uk](mailto:deirdre.lane@liverpool.ac.uk)

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**Running head** Antithrombotic management in AF patients with ICH patients **Abstract**

**Background:** The aim of this survey is to provide a snapshot of current practice regarding antithrombotic therapy (ATT) in patients with atrial fibrillation (AF) comorbid with intracerebral haemorrhage (ICH).

**Methods:** An online survey was distributed to members of the European Heart Rhythm Association.

**Results:** A total of 163 clinicians responded, mostly cardiologists or electrophysiologists (87.7%), predominantly working in University hospitals (61.3%). Most respondents (47.2%) had seen 1-5 patients with AF comorbid with ICH in the last 12-months. Among patients sustaining an ICH on oral anticoagulation (OAC), 84.3% respondents would consider some form of ATT post-ICH, with 73.2% preferring to switch from a vitamin-K antagonist (VKA) to a non-VKA oral anticoagulant (NOAC) and 37.2% preferring to switch from one NOAC to another. Most (36.6%) would restart OAC >30 days post-ICH. Among patients considered unable to take OAC, left atrial appendage occlusion procedure was the therapy of choice in 73.3% respondents. When deciding on ATT, respondents considered patient’s CHA2DS2-VASc score, ICH type, demographics, risk factors, and patient adherence. The main reason for not restarting or commencing ATT was concern about recurrent ICH (80.8%). National or international clinical guidelines would be advantageous to support decision-making (84.3%). Other helpful resources reported were multidisciplinary team involvement (46.9%) and patient education (82%).

**Conclusions:** Most survey respondents would prescribe OAC therapy for patients with AF who have sustained an ICH on OAC. Most would restart OAC >30 days post-ICH. The main reason for not prescribing any ATT post-event is the risk of recurrent ICH.

**Introduction**

Atrial fibrillation (AF) is associated with a five-fold increased risk of ischaemic stroke (1) and as a result, long-term oral anticoagulation (OAC) is the cornerstone of AF treatment for the majority of patients (2). However, OAC treatment is associated with an increased risk of bleeding, where intracerebral haemorrhage (ICH) is the most feared haemorrhagic complication due to its’ increased risk of death (36% at one month) and significant morbidity (3). Over 10% of ICH is OAC-related (4), although it may also be the case that OAC acts as a catalyst for the ICH process rather than as a direct cause. It is estimated that up to 30% of patients with ICH also have AF (5). All types of antithrombotic therapy (ATT) are associated with increased bleeding risk, although non vitamin-K antagonist oral anticoagulants (NOAC) are associated with a reduced risk of intracranial haemorrhage in AF patients compared to warfarin [RR 0.49 (95% 0.38-0.64, p < 0.0001)] (6).

A dilemma for clinicians and patients is the initiation of ATT for ischaemic stroke prevention in patients who have AF and have also sustained an ICH. Patients with ICH were excluded from seminal trials on NOAC but data from observational studies seems to suggest that restarting OAC post-ICH in patients with known AF reduces the risk of ischaemic stroke without significantly increasing the risk of repeat ICH (7-9). However, there are currently no definitive data from randomised controlled trials (RCT) that address OAC treatment in the AF and ICH patient population, although several trials are ongoing (NCT02565693, NCT03907046, NCT03996772, NCT02998905, NCT03186729, NCT03186729).

The aim of this European Heart Rhythm Association (EHRA) survey was to assess current practice regarding ATT in patients who have AF and who have also sustained an ICH. This survey explored how physicians decide on ATT for this patient population by addressing issues such as timing of restarting or initiating ATT, first choice of ATT, and clinical factors that influence physicians’ decision-making on ATT post-ICH.

**Methods and Results**

The EHRA network was utilised to distribute an on-line questionnaire of 18 questions and five scenario-based questions (Box 1), between 18 August and 17 September 2020. A total of 163 physicians responded to the survey. Most respondents were based in Western Europe, although 73/163 (45%) clinicians from Asia Pacific, the Middle East, Africa, and the Americas also participated. Most respondents were cardiologists (88/163, 54%) or electrophysiologists (55/163, 33.7%) and worked at a University hospital (100/163, 61.3%) and in hospitals with a stroke unit (118/163, 72.4%).

Most respondents had encountered 1-5 patients with AF and ICH in the last 12 months (77/163, 47.2%), although 11/163 (6.7%) respondents had encountered >20 patients with AF and ICH in the last 12 months.

*Factors considered when restarting or commencing antithrombotic therapy in patients with AF and an ICH*

Patient’s CHA2DS2-VASc score was the main consideration (143/149, 96%) in ATT decision-making (Figure 1), followed by ICH aetiology (traumatic vs. spontaneous, 140/146, 95.9%), ICH severity (139/150, 92.7%), ICH type (124/141, 88%), and ICH volume/size (120/142, 84.5%). Risk of bleeding (HAS-BLED score) was selected as a consideration when deciding whether to restart or commence ATT by 127/151 (84.1%) respondents. Patient demographics and medical history were also important considerations for most participants. Patient age was a consideration for 119/141 (84.4%) participants, along with severity of uncontrolled hypertension (124/140, 88.6%), patient’s functional (119/136, 87.5%) and neurological status (116/137, 84.7%), and alcohol intake (106/138, 76.8%). Nearly all respondents (140/146, 95.9%) stated that patient adherence to medication was a consideration when deciding whether to commence or restart ATT. Type of AF (52/132, 39.4%) and severity of AF symptoms (21/123, 17.1%) were of much less importance when making ATT treatment decisions.

**Insert Figure 1 here**

Multidisciplinary team input (133/142, 93.7%) and patient preference (120/138, 87%) were considered more important in the decision-making process than individual clinician preference (85/131, 64.9%).

Respondents also had the option of adding their own individual considerations; three would consider the possibility of a left atrial appendage occlusion (LAAO) procedure. Echocardiography data was considered by two respondents, with drug cost, patient’s lifestyle, and patient proximity to the hospital, considered by one respondent each.

*Factors influencing physicians’ decision to restart or commence ATT in patients with AF who sustained an ICH while on OAC*

The type of OAC prescribed to the patient pre-ICH was the most influential factor (125/146, 85.6%) in the decision to restart or commence ATT post-ICH sustained on OAC (Figure 2), followed by patient-related factors, such as adherence (113/146, 77.4%), age (111/146, 76%), and history of falls (78/146, 53.4%). Individual stroke (CHA2DS2-VASc score, 110/146, 75.3%) and bleeding risk (HAS-BLED score, 108/146, 74%) was selected by about three-quarters of respondents as important factors in ATT decision-making. More than half of participants took into consideration previous quality of VKA control (such as time in therapeutic range, 96/146, 65.7%).

**Insert Figure 2 here**

Additional factors influencing whether or not to prescribe ATT for a patient with AF who sustained an ICH while on OAC reported in free-text responses were patient’s lifestyle (n=1), high cardioembolic risk and high cerebral haemorrhagic risk, such as cerebral amyloid angiopathy (CAA) (n=1), and feasibility of an LAAO procedure (n=1).

*Choice of OAC therapy to restart post-ICH*

The first-choice ATT among patients who had an ICH on OAC differed slightly depending on whether the patient was previously receiving a VKA or a NOAC (Figure 3). Overall, the preferred OAC was apixaban. A minority of respondents (15/153, 9.8%) said that they would restart the patient’s previous OAC (Figure 4). If the patient sustained an ICH while on NOAC, 57/153 (37.2%) of respondents said that they would switch the patient from one type of NOAC to another NOAC. A decision not to restart any type of OAC was only chosen by 24/153 (15.7%) respondents.

**Insert Figure 3 here**

**Insert Figure 4 here**

If the patient sustained an ICH while on NOAC, 57/153 (37.2%) respondents would switch the patient from one NOAC to another NOAC. For those who experienced an ICH on a NOAC, the preferred NOAC when restarting was apixaban (72/153, 47.1%), followed by dabigatran (20/153, 13.1%), rivaroxaban (12/153, 7.8%), and edoxaban (10/153, 6.5%). VKA were selected by 10/153 respondents, with 8/153 (5.2%) choosing VKA with international normalised ratio (INR) 2.0 to 2.5 and 2/153 (1.3%) choosing VKA with INR 2.0 to 3.0. Antiplatelets were not a popular choice amongst respondents; only 4/153 (2.6%) respondents selected clopidogrel over other types of ATT, 3/153 (2%) chose aspirin, 2/153 (1.3%) chose aspirin plus clopidogrel, while one respondent (0.6%) chose aspirin plus ticagrelor. For this patient group, 19/153 (12.4%) respondents would not consider restarting any form of ATT.

For patients with AF who had an ICH while on VKA, the preferred choice of ATT post-ICH was apixaban (88/153, 57.5%), followed by one of the other NOACs, dabigatran (22/153, 14.4%), rivaroxaban (17/153, 11.1%), and edoxaban (8/153, 5.2%). Restarting VKA with a lower INR range of 2.0 to 2.5 was the preferred option for 5/153 (3.3%) respondents, while restarting VKA with a traditional target INR range of 2.0 to 3.0 was the preferred option for only 2/153 (1.3%) respondents. No respondents chose to start antiplatelet therapy for patients who sustained an ICH while on VKA.

*Reasons for not restarting or commencing OAC*

Concern for recurrent ICH was the main reason for not restarting or commencing OAC in patients with AF post-ICH (118/146, 80.8%) (Figure 5), in addition to other types of bleeding, such as a history of major bleeding (82/146, 56.2%) and multiple micro-bleeds (67/146, 45.9%). Half (74/146, 50.7%) of the respondents selected suspected CAA as a reason not to prescribe OAC post-ICH. Only 39% (57/146) would not commence or restart OAC in patients with a high risk of bleeding (HAS-BLED score ≥3). Other common reasons for not restarting or commencing OAC post-ICH were poor patient adherence with medication or follow-up appointments (88/146, 60.3%), reduced life expectancy (84/146, 57.5%), and severe multi-morbidity (76/146, 52.1%). Dementia and increased risk of falls were reasons for not restarting OAC for 54/146 (37%) and 66/146 (45.2%) of participants, respectively. Very few respondents considered type of AF (8/146, 5.5%) or symptomatic AF in older patients (>75 years) (13/146, 8.9%) among their reasons for not restarting or commencing OAC in ICH-survivors with AF.

**Insert Figure 5 here**

*Timing of restarting or commencing OAC*

When considering the timing of restarting or commencing OAC in patients with AF and ICH, the responses were highly variable (Figure 6). Most (56/153, 36.6%) respondents would consider restarting some type of OAC >30 days post ICH onset, 37/153 (24.2%) between day 15 and 30 post-event, and 25/153 (16.3%) within the first 10-14 days post-ICH. Fewer than 5% of respondents (7/153, 4.6%) would consider restarting or commencing OAC prior to hospital discharge, while 15/153 (9.8%) would not consider restarting OAC.

**Insert Figure 6 here**

*Alternatives to OAC for stroke prevention in patients with AF post-ICH*

In patients who were unable or unwilling to take OAC, 107/146 (73.3%) respondents preferred LAAO as their first-choice stroke prevention strategy. Single antiplatelet therapy was favoured as first choice by only 14/146 (9.6%) and dual antiplatelet therapy by 11/146 (7.5%) respondents. Around 10% of respondents would opt for no stroke prevention therapy among patients unable or unwilling to take OAC.

*Barriers to restarting or commencing OAC*

For the overwhelming majority of respondents (135/145, 93%), recurrent ICH was the main barrier to prescribing OAC to patients with AF who had survived an ICH (Figure 7), followed by concerns about major bleeding (91/145, 63%), risk of falls (70/145, 48%), concerns about patient adherence to medication or follow-up appointments (63/145, 43%), and patients’ understanding of medication choice (40/145, 28%). Lack of clinical guidelines and paucity of clinical evidence were also cited as barriers to prescribing OAC to patients with AF and ICH (30/145 (21%) and 40/145 (28%), respectively).

**Insert Figure 7 here**

*Factors that could improve or support physicians’ decision-making*

International or national clinical guidelines were reported as the most important tool for making decisions about ATT for patients with AF post-ICH (123/145 (84.8%) (Figure S1, Supplementary materials), with nearly half of respondents (72/145, 49.7%) desiring more robust clinical evidence. A similar percentage of respondents (68/145, 46.9%) reported that greater multidisciplinary input would aid them in their decision-making process.

Education, both patient and physician, was identified as a tool to aid physicians’ decision-making regarding ATT for patients with AF and ICH. Improved patient education about their condition and risk factors for recurrent bleeding (65/145, 44.8%) and treatment options (54/145 (37.2%) were cited as beneficial and almost one third of respondents (43/145, 29.7%) said that improved physician education about treatment options would be advantageous.

*Patient education tools utilised by physicians*

Most respondents (120/145, 82.8%) reported providing informal education at the bedside or during clinic appointment (101/145, 69.7%), with written information utilised by only one-third (48/145, 33%) of respondents. Some respondents referred patients to a specialist support group (30/145, 20.7%), signposted them to online sources of information (24/145, 16.5%), or engaged a specialist nurse to provide patients with information (25/145, 17.2%).

**Scenario-based questions**

Five scenario-based questions were presented (Box 1) and respondents were asked to state their first choice of ATT or alternative stroke prevention strategy. For all scenarios, NOAC were preferred to VKA and apixaban was the most popular NOAC. In scenario 4, which referred to a patient with reduced renal function (CrCl of 47ml/min), most respondents (47/138, 34.1%) chose the reduced dose of apixaban 2.5mg bid, although 19/138 (13.8%) respondents chose the standard dose of apixaban 5mg bid.

**Insert Box 1 here**

Dabigatran was the second most popular NOAC, especially in scenario 2, which referred to a 57-year old female patient; with 18/138 (13%) participants choosing dabigatran 150mg bid and 6/138 (4.3%) choosing dabigatran 110mg bid. Edoxaban was the least popular choice amongst all the NOACs. Antiplatelet therapy was not a popular choice for any of the scenarios.

LAAO procedure was the preferred stroke prevention therapy for a patient who sustained an ICH due to CAA (scenario 3), with 69/134 (59.5%) participants selecting this option. LAAO procedure was also a popular treatment choice for scenario 5, (57-year old female patient with HAS-BLED = 4), chosen by 49/138 (29.7%) participants.

No stroke prevention therapy was chosen by 17/134 (12.7%) respondents for patients who sustain an ICH due to CAA (scenario 3). For all other scenarios, no stroke prevention therapy was not a popular choice, with less than 4% choosing this option.

**Discussion**

Respondents were more likely to prescribe NOAC rather VKA for stroke prevention for patients with AF comorbid with ICH. Antiplatelet therapy was not a popular choice for stroke prevention amongst survey participants, in-line with current clinical guidelines (10). LAAO procedure was the stroke prevention of choice for patients in who sustain an ICH due to CAA.

NOACs are recommenced as first-line OAC treatment by the European Society of Cardiology (ESC) and the American Heart Association (AHA) guidelines for the treatment of AF (11, 12). Aspirin therapy is less effective in preventing stroke in patients with AF as compared to OAC (13), nor does aspirin reduce the risk of bleeding as compared to VKA (14). Clinical guidelines suggest that OAC rather than antiplatelet therapy should be the stroke prevention treatment of choice for patients with AF (10).

LAAO procedure was a popular choice, especially in patients with increased bleeding risk or patients who survived an ICH while on OAC or among patients with CAA who are at risk of repeat ICH and ischaemic stroke (15). Most participants in this survey were cardiologists and electrophysiologists, which may help explain the popularity of LAAO procedure. Nonetheless, concerns about the safety and efficacy of LAAO procedures remain (16) and patients still require antiplatelet therapy post LAAO procedure (16, 17).

Recurrent ICH and risk of bleeding were the major barriers to commencing or restarting OAC. These concerns mirror those expressed by neuro-specialists who reported that the risk of recurrent ICH was the main contraindication to restarting OAC therapy (18). The results of the present survey reflected this, as respondents predominantly considered the severity, type, and aetiology of the patient’s ICH, and the patient’s CHA2DS2-VASc score when deciding on post-ICH ATT.

The survey also showed that patients’ age, history of falls, and functional status were important considerations in post-ICH ATT decisions. Patients with AF who are older, have reduced functional status or dementia are less likely to receive OAC therapy (19-21). Prescribers report being concerned about bleeding due to falls and about patients’ ability to adhere to medication (22). However, a patient would have to fall nearly 300 times before the risk of a major bleed on warfarin would outweigh the benefits (23).

*Decision-making in ATT in patients with AF and ICH*

Respondents felt that the lack of international or national clinical guidelines and paucity of RCTs data on post-ICH antithrombotic therapy management affected decision-making. Nonetheless, several RCTs addressing ATT in this patient group are ongoing. These include APACHE-AF (NCT02565693), ASPIRE (NCT03907046), PRESTIGE-AF (NCT03996772), NASPAF-ICH (NCT02998905); STATICH (NCT03186729), and SoSTAR (NCT 03186729).

Multidisciplinary working was also recognised as helpful by almost half of the survey participants, which is in-line with current European clinical guidelines (11). Integrated care of patients with AF has been shown to reduce all-cause mortality and cardiovascular hospitalisations (24). Use of the Atrial Fibrillation Better Care (ABC) Pathway, which promotes a streamlined approach to AF care, has been shown to reduce all-cause mortality when used in patients with AF who have a high frailty risk and to reduce healthcare costs associated with cardiovascular events in patients with AF (25, 26).

*Patient involvement in decision-making*

Almost 90% of respondents considered patient preference when deciding whether to restart or commence ATT. However, respondents also felt that better patient knowledge of their conditions and treatment options would aid decision-making. Patients with AF often lack knowledge about their condition (27, 28), as do patients with stroke (29, 30). Almost all survey respondents stated that they provide some form of informal education to their patients. However, patients with AF who participated in an enhanced education programme showed better understanding of their condition versus usual care (31). Anticoagulation control and uptake of OAC also improved post structured education interventions (32, 33).

*Limitations*

The response rate was low, with only 163 participants overall. Participation also varied by question, meaning that not every participant answered every question. The low response rate limits the ability of the survey to provide a comprehensive snapshot of current practice regarding ATT for patients with AF and ICH and limits generalisability. The survey responses came mainly from cardiologists and electrophysiologists, which reflects the membership of EHRA. However, patients with AF who survive an ICH receive input from multiple other specialties and treatment patterns may differ by specialty and timing in the treatment pathway (acute vs. longer-term).

**Conclusions**

This EHRA survey provides a snapshot of current practice regarding ATT for patients with AF post-ICH. NOACs are the treatment of choice, including for patients who experienced an ICH while on OAC; apixaban was the most popular NOAC. LAAO procedure was a popular choice in patients with increased bleeding risk, particularly CAA. Decision-making is complicated by concerns about major bleeding, patient’s functional status, falls risk, and medication adherence. Concern for recurrent ICH was the main reason for not prescribing OAC. Ongoing RCTs will hopefully provide definitive evidence on safety and efficacy of ATT in AF patients post-ICH to inform clinical decision-making.

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**Conflicts of interest**

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**Figure Legends**

Figure 1: Factors considered when deciding on antithrombotic therapy

(AF: atrial fibrillation; HTN: hypertension; ICH: intracerebral haemorrhage)

Figure 2: Factors influencing choice of antithrombotic therapy for a patient with AF who sustained an ICH on OAC

(AF: atrial fibrillation; ICH: intracerebral haemorrhage; OAC: oral anticoagulant; VKA: vitamin K antagonist)

Figure 3: First choice of antithrombotic therapy for a patient with AF who sustained an ICH on VKA or NOAC

(ATT: antithrombotic therapy; INR: international normalised ratio; NOAC: non-vitamin K antagonist oral anticoagulant; VKA: vitamin-K antagonist)

Figure 4: What would you do if a patient sustained an ICH while on OAC?

(NOAC: non-vitamin-K antagonist oral anticoagulants; OAC: oral anticoagulant; VKA: vitamin K antagonist)

Figure 5: Reasons for not restarting/commencing OAC

(AF: atrial fibrillation; ICH: intracerebral haemorrhage; OAC: oral anticoagulant)

Figure 6: When would you consider restarting/commencing OAC?

(ICH: intracerebral haemorrhage; OAC: oral anticoagulant)

Figure 7: Main barriers to restarting/commencing OAC

(ICH: intracerebral haemorrhage; INR: international normalised ratio)

**Box 1:** Scenario-based questions utilised in the on-line survey\*

|  |  |
| --- | --- |
| **Scenario 1** | 80-year male patient with AF who has sustained an ICH (CHA2DS2-VASc = 4, HAS-BLED = 2, BMI = 27, normal renal function) |
| **Scenario 2** | 57-year female patient with AF who has sustained an ICH (CHA2DS2-VASc = 3, HAS-BLED = 2, BMI = 27, normal renal function) |
| **Scenario 3** | A patient with AF who has sustained an ICH due to cerebral amyloid angiopathy |
| **Scenario 4** | 80-year male patient with AF who has sustained an ICH (CHA2DS2-VASc = 4, HAS-BLED = 3, BMI = 27, CrCl 47ml/min) |
| **Scenario 5** | 57-year female patient with AF who has sustained an ICH (CHA2DS2-VASc = 3, a HAS-BLED = 4, BMI = 27, normal renal function) |

\*Results available in Supplementary Table 1

AF: atrial fibrillation; BMI: body mass index; CrCl: creatinine clearance; ICH: intracerebral haemorrhage

**Figure 1**

**Figure 2**

**Figure 3**

**Figure 4**

**Figure 5**

**Figure 6**

**Figure 7**

**Supplementary materials**

**Table S1:** First-choice antithrombotic treatment for the case-based scenarios

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Case 1:** 80-year male patient with AF who has sustained an ICH (CHA2DS2-VASc = 4, HAS-BLED = 2, BMI = 27, normal renal function) | **Case 2:** 57-year female patient with AF who has sustained an ICH (CHA2DS2-VASc = 3, HAS-BLED = 2, BMI = 27, normal renal function) | **Case 3:** A patient with AF who has sustained an ICH due to cerebral amyloid angiopathy | **Case 4:** 80-year male patient with AF who has sustained an ICH (CHA2DS2-VASc = 4, HAS-BLED = 3, BMI = 27, CrCl 47ml/min) | **Case 5:** 57-year female patient with AF who has sustained an ICH (CHA2DS2-VASc = 3, a HAS-BLED = 4, BMI = 27, normal renal function) |
| VKA (INR 2.0-2.5) | 4 | 4 | 13 | 4 | 5 |
| VKA (INR 2.0-3.0) | 2 | 1 | 2 | 3 | 2 |
| Apixaban 5mg bid | 45 | 64 | 12 | 19 | 42 |
| Apixaban 2.5mg bid | 31 | 2 | 5 | 47 | 10 |
| Dabigatran 150mg bid | 0 | 18 | 2 | 2 | 6 |
| Dabigatran 110mg bid | 19 | 6 | 1 | 9 | 9 |
| Edoxaban 60mg od | 5 | 3 | 1 | 1 | 4 |
| Edoxaban 30mg od | 2 | 2 | 1 | 10 | 1 |
| Rivaroxaban 20mg od | 7 | 15 | 2 | 0 | 7 |
| Rivaroxaban 15mg od | 8 | 3 | 1 | 13 | 3 |
| Aspirin 75-150mg od | 2 | 0 | 3 | 4 | 0 |
| Aspirin 300mg od | 0 | 0 | 0 | 0 | 0 |
| Clopidogrel 75mg od | 0 | 0 | 2 | 2 | 2 |
| Ticagrelor 90mg bid | 0 | 0 | 0 | 0 | 0 |
| Prasugrel 5-10mg od | 0 | 0 | 0 | 0 | 0 |
| Aspirin + clopidogrel | 0 | 0 | 2 | 1 | 1 |
| Aspirin + ticagrelor | 0 | 0 | 1 | 0 | 0 |
| Aspirin + prasugrel | 0 | 0 | 0 | 0 | 0 |
| Left atrial appendage occlusion | 11 | 16 | 69 | 19 | 41 |
| No stroke prevention therapy | 3 | 4 | 17 | 4 | 5 |
| Total | 139 | 138 | 134 | 138 | 138 |

**Figure S1:** Tools that could aid clinical decision-making