Non-adherence to thromboprophylaxis guidelines in atrial fibrillation: A narrative review of the extent and factors for guideline non-adherence

Running heading: Thromboprophylaxis guideline non-adherence in atrial fibrillation

Eyob Alemayehu Gebreyohannes[1*], Sandra Salter[1], Leanne Chalmers[2], Luke Bereznicki[3], Kenneth Lee[1,3]

[1]Division of Pharmacy, School of Allied Health, University of Western Australia, WA, Australia

[2]School of Pharmacy and Biomedical Sciences, Curtin University, WA, Australia

[3]School of Pharmacy and Pharmacology, University of Tasmania, TAS, Australia

[*]Corresponding Author:

Email: eyob.gebreyohannes@research.uwa.edu.au; justeyob@gmail.com

ORCID: 0000-0002-0075-4553

Acknowledgements

Mr. Eyob Alemayehu Gebreyohannes is a Ph.D. student and a recipient of the University of Western Australia International Fee Scholarship and University Postgraduate Award. Mr. Gebreyohannes would like to acknowledge the University of Western Australia for supporting his studies.

Abstract

Atrial fibrillation is the most common arrhythmia. It increases the risk of thromboembolism by up to 5-fold. Guidelines provide evidence-based recommendations to effectively mitigate thromboembolic events using oral anticoagulants (OACs) while minimizing the risk of bleeding. This review focuses on non-adherence to contemporary guidelines and the factors associated with guideline non-adherence. The extent of guideline non-adherence is different based on geographic region, the healthcare setting, and the risk stratification tools used. There has been a gradual improvement in guideline adherence over recent years, but a significant proportion of patients are still not receiving guideline-recommended therapy. Physician-related and patient-related factors (such as patient refusals, bleeding risk, older age, and recurrent falls) also contribute to guideline non-adherence, especially to undertreatment. Quality improvement initiatives that focus on undertreatment especially in the primary healthcare setting may help to improve guideline adherence.

Key points

- A significant proportion of patients with atrial fibrillation across a range of health settings are still receiving guideline non-adherent anticoagulation, the extent of which is highly variable.
- Physician-related (such as a greater emphasis on the risk of bleeding than the risk of stroke) and patient-related (such as patient refusals, bleeding risk, older age, and recurrent falls) factors contribute to guideline non-adherence.
- Guideline non-adherence is primarily because of undertreatment and appears to be higher in high-risk AF patients attending primary healthcare than for patients attending hospitals and cardiology practices. Quality improvement initiatives should focus on addressing undertreatment, especially in the primary healthcare setting.

1. Introduction

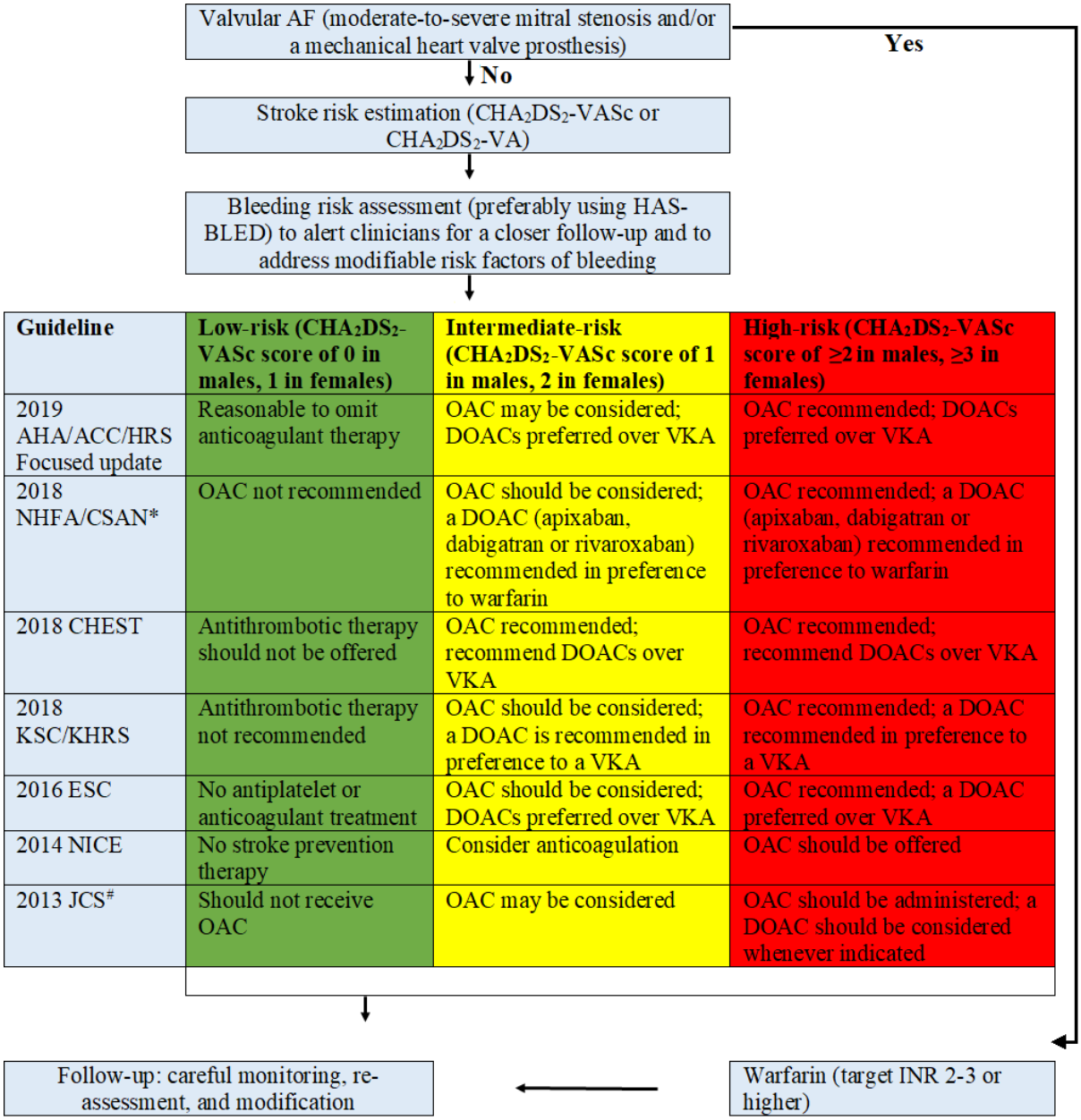
Atrial fibrillation (AF) is the most commonly encountered arrhythmia in clinical practice, affecting 37.5 million people around the world in 2017. [1] AF increases the risk of stroke and systemic embolism by up to 5-fold. [2] It is the primary cause of cardioembolic stroke and results in a more severe type of stroke with a higher mortality rate when compared to strokes in people without AF. [2, 3] The past two decades saw a 33% increase in the prevalence of AF which is expected to continue increasing in the coming three decades. [1] With increasing incidence and prevalence rates, AF poses a substantial burden in terms of the rate of hospitalization, morbidity, and mortality. [4, 5]

Oral anticoagulants (OACs) such as warfarin have proven effectiveness in reducing the incidence of stroke and systemic embolism in patients with AF. [6, 7] As such, they are one of the cornerstones of AF management. [5] In the past decade, the development of direct oral anticoagulants (DOACs) increased anticoagulation options available for use in AF. [8] Their convenience and better safety profile compared to the vitamin K antagonist (VKA), warfarin, has led to a decrease in the utilization of the latter and a rise in the utilization of these newer agents. However, warfarin is still prescribed for many patients with AF. [9]

Since 2013, seven evidence-based guidelines have been recently published by different cardiology expert groups that include sections to guide the utilization of anticoagulants in stroke and systemic embolism prevention in AF. [5, 10-16]

Not all patients with AF have an identical risk of stroke. One of the primary determinants of the risk of stroke is the type of AF. [5, 14] Traditionally, AF has been categorized as either valvular or non-valvular (NVAF). [17] The majority of guidelines define valvular AF as the presence of moderate-to-severe mitral stenosis and/or a mechanical heart valve prosthesis. [5, 10, 13-15] Currently, only VKAs are recommended for the prevention of stroke in patients with valvular AF. [5, 10, 13, 14] The CHEST AF guideline [12] uses the terms "a functional Evaluated Heart valves, Rheumatic or Artificial (EHRA)" type 1 or type 2 in place of valvular AF and NVAF, respectively; although these differences in terminology have no impact on clinical decision-making in these patients [5, 10, 13, 14].

Anticoagulation in patients with NVAF requires estimating the risk of stroke and selecting an appropriate anticoagulant from a number of options. [5, 7, 10-16, 18] Most guidelines [10, 12-14, 16] recommend the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65-74, and female sex category) as a means of stratifying patients' stroke risk (Figure 1). To avoid using different scores in men and women, the Australian AF guideline [5] recommends using the CHA_2DS_2-VA score, i.e. CHA_2DS_2-VASc without the sex category. On the other hand, the 2018 CHEST guideline [12] recommends that the CHA_2DS_2-VASc score be used only to initially identify patients who are at low risk. Anticoagulation should be provided to patients other than those who are at low risk.



*Uses the CHA_2DS_2-VA score (0=low-risk; 1=intermediate risk; ≥2=high-risk); #Preferentially uses the $CHADS_2$ score over the CHA_2DS_2-VASc score; AHA/ACC/HRS: American Heart Association/American College of Cardiology/Heart Rhythm Society; CHA_2DS_2-VASc score: congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65-74, and sex category (female); JCS: Japanese Circulation Society; KSC/KHRS: Korean Society of Cardiology/Korean Heart Rhythm Society; NHFA/CSAN: National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand.

Figure 1: A summary of guideline recommendations on thromboprophylaxis in patients with AF

Similar to the stroke risk, patients' risk of bleeding should also be assessed in patients for whom anticoagulation is being considered. Various bleeding risk assessment tools including HAS-BLED, ATRIA, ORBIT, HEMOR-R_2HAGES, GARFIELD, and the ABC are available. Of these, the HAS-BLED score (hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (>65), drugs/alcohol concomitantly (1 point each)) is recommended by most guidelines. [10, 12, 13, 15, 16] It should be

noted that the risk of bleeding increases with an increasing risk of stroke. [5, 14] Therefore, the purpose of bleeding risk assessment is to identify patients in whom OACs must be used with caution, and to identify and address modifiable risk factors for bleeding, not to withhold anticoagulation in patients who need it. [5, 12-14, 16] The guidelines also stress the need for due attention and adjustment as necessary on each follow up considering the dynamic natures of bleeding and stroke risks. [12, 13]

Guideline non-adherence is associated with an increase in thromboembolic events because of undertreatment or, may increase the risk of bleeding including intracranial bleeding because of overtreatment. [18, 19-22] On the other hand, the benefit of guideline adherence in improving patient outcomes has been supported by the literature. [23] Evidence shows that non-adherence to evidence-based guideline recommendations and risk stratification tools for AF is a common occurrence even with the availability of DOACs. [24-26] Several reviews on thromboprophylaxis guideline non-adherence in patients with AF have been published in recent years. Two studies from 2015 focused only on undertreatment [27] and DOACs [23]. One study included only studies that utilized registry data [23]. A 2018 study reviewed randomized clinical trials and real-life outcomes and focused on DOACs. [28] A further review focused on trends in the prescription of antithrombotic medications, and patient compliance and persistence to OACs. [29] The present review seeks to determine the extent of non-adherence to thromboprophylaxis guidelines in AF and factors associated with guideline non-adherence. To ensure that this review is applicable to contemporary clinical practice, we focused on studies published in the past five years.

2. Methods

This narrative review is based on a key word search conducted in the PubMed and the Cumulative Index of Nursing and Allied Health Literature (CINAHL) Plus databases. The following search string was utilized to retrieve articles published until 5 May 2020: “atrial fibrillation” AND (anticoagul* OR antithrombo* OR anti-coagul* OR anti-thrombo* OR "stroke prophyl*" OR "stroke prevention" OR thromboprophyl*) AND (“guideline adherence”). Studies that assessed non-adherence to one or more thromboprophylaxis guidelines, and studies that reported factors associated with guideline non-adherence were included. Both qualitative and quantitative studies published in English since 2015 were included. We begin our discussion with reported extent of guideline non-adherence by focusing mainly on undertreatment. This will be followed by trends in the extent of guideline non-adherence and studies that compared differences in guideline non-adherence across multiple geographic regions. Then, the extent of guideline non-adherence will be discussed by geographically categorizing studies that used

the CHA_2DS_2-VASc score and were published in the past five years. Lastly factors affecting guideline non-adherence will be discussed.

3. Non-adherence to guidelines

Use of OACs for thromboprophylaxis in patients with AF in adherence to the evidence-based recommendations incorporated into clinical guidelines (i.e. 'guideline adherence') improve patient outcomes; conversely, patients whose therapy is non-adherent to guidelines experience poorer outcomes. [18, 19-22] Therefore, there has been a significant focus in the literature on quantifying guideline adherence in this clinical setting. In this section, the overall extent of guideline non-adherence is described. In addition, changes over time, and differences in guideline non-adherence in different areas of the world and in different healthcare settings are explored.

Reported rates of guideline non-adherence vary widely depending on the type of guideline and/or risk stratification tool used, the region, the study setting, and the specific group of patients included. Undertreatment is typically defined as no OAC treatment in patients at high risk of stroke such as those with valvular AF, or those with NVAF and a CHA_2DS_2-VASc score of ≥2 in males (≥3 in females), or a $CHADS_2$/CHA_2DS_2-VA score of ≥2. [5, 10, 12-16] Overtreatment is defined as the use of antithrombotic agents in patients with AF who have no additional risk factors for thromboembolism and without any other indication. In particular, administration of any antithrombotic agent for thromboprophylaxis in patients with NVAF and a CHA_2DS_2-VASc score of 0 in males (1 in females) or a $CHADS_2$/CHA_2DS_2-VA score of 0 is considered overtreatment, as no contemporary guidelines recommend therapy in these patients. [5, 10, 12-16] The management of NVAF patients with a CHA_2DS_2-VASc score of 1 in males (2 in females) depends on the guideline used.

Non-adherence to guideline recommendations was observed in 4.4% to 95.2% of patients in the studies included in this review. The proportion of patients undertreated ranged from 2.5% [30] to 76.3% [31]. To clearly identify guideline non-adherence, undertreatment in particular, several studies included only patients at high risk for stroke. [32-42] The patients included in these studies either had CHA_2DS_2-VASc or $CHADS_2$ scores ≥2 [33-40] or were aged ≥75 years old [32, 41, 42], all of which made them at high risk. Undertreatment in these high-risk patients ranged from as low as 19.7% [38] to as high as 95.2% [40], with the majority of the studies reporting undertreatment between 40% and 50%. [32, 33, 35-37, 39, 42] Of note, the study by Piccini et al., with 19.7% undertreatment, was part of a quality improvement initiative in hospitalized patients targeting guideline adherence and the extent of undertreatment before hospital admission, and before the intervention, in this study was 40.5%. [38] In the study by Formiga et al., the relatively higher proportion of octogenarians (40%) may have been the

primary contributor to higher undertreatment (95.2%in their study). [40] When it comes to overtreatment, between 0.6% and 79.8% of patients at low risk of stroke who did not need any antithrombotic medication received treatment, which would be considered to be overtreatment. [18, 22, 26, 31, 33, 35, 43-62]

Recent studies that investigated trends in guideline adherence have shown substantial improvements in guideline adherence over time. Cowan et al. [63] reported an increase in the prescription of OACs (by 30.6%) and a decline in the prescription of antiplatelet agents (by 26.8%) over a 10-year period in AF patients at high risk of stroke. Non-prescription of OACs in AF patients at a significant risk of stroke is declining. [33, 37, 64] While the prescription of antithrombotic agents in truly low-risk patients may be decreasing in some areas [64], an increasing trend has been reported in others. For instance, a 2020 Japanese study [65] reported that prescription of OACs in patients with a $CHADS_2$ score of 0 increased from 53% to 66%. However, one should note that the Japanese AF guideline [15] also recommends OACs in patients with a $CHADS_2$ score of 0 but with additional risk factors for thromboembolism such as cardiomyopathy, vascular disease, and age between 65 and 74 years. This may be one potential reason for overtreatment in some of these patients despite their low risk of stroke as per the $CHADS_2$ score. During the same period of time, the prescription of OACs in patients with a $CHADS_2$ score of ≥ 2 also increased from 78% in 2014 to 83% in 2017. [65] Similar findings were reported from Australia, [43] where OAC prescribing increased from the pre-DOAC era to the post-DOAC era both in low-risk patients (from 35.0% to 42.9%, p=0.59) and high-risk patients (from 52.2% to 63.1%). Despite these significant proportions of overtreatment, it must be noted that the actual numbers of low-risk patients in the Japanese and Australian studies were small. [43, 65] Therefore, the primary focus of guideline non-adherence should remain on undertreatment. As shown in Table 1, a significant proportion of patients with AF are still receiving treatment that is not guideline adherent despite gradual improvements over time.

Table 1: Changes in the extent of guideline non-adherence over time in single geographical regions

Study	**Country (setting)**	**Guidelines/ tools**	**Patient population**	**Outcome measures**	**Guideline non-adherence**
Narita et al 2020 [65]	Japan (Health insurance database)	$CHADS_2$	Patients with AF (N=4375)	Prescription of OACs	Undertreatment in $CHADS_2$ score of ≥ 2: -2014 (N=708): 22% -2015 (N=702): 20% -2016 (N=688): 21% -2017 (N=758): 17% Overtreatment in $CHADS_2$ score of 0: -2014 (N=90): 53% -2015 (N=76): 69% -2016 (N=96): 59% -2017 (N=85): 66%

Cowan et al 2018 (The GRASP-AF registry) [63]	England (Hospital)	CHA_2DS_2-VASc	Patients with AF (N=375310)	OAC and AP use in patients with CHA_2DS_2-VASc ≥2 between 2006 and 2016	Undertreatment with non-prescription of OACs: 52.0% (2006) vs 21.4% (2016) Undertreatment with AP: 42.9% (2006) vs 16.1% (2016)
Admassie et al 2017 [43]	Australia (Hospital)	ESC 2012 and AHA 2014/ CHA_2DS_2-VASc and HAS-BLED	Patients with NVAF (N=2118)	OAC prescribing in Pre- (Jan 2011 to Jul 2013) and post-DOAC era (Aug 2013 to Jul 2015)	Undertreatment in high-risk patients: 44.8% (pre-DOAC) vs 36.9% (post-DOAC), p = 0.001. Overtreatment in low-risk patients: 35.0% (pre-DOAC) vs 42.9% (post-DOAC), p = 0.59.
Apenteng et al 2017 [64]	UK (Primary care, internal medicine, cardiology, geriatrics, neurology)	NICE 2014/ CHA_2DS_2-VASc and HAS-BLED	Newly diagnosed NVAF patients	OAC prescribing in high-risk patients (CHA_2DS_2-VASc ≥2) and prescribing no antithrombotic medication in low-risk patients (CHA_2DS_2-VASc=0) between Sep 2011 to Apr 2013 and Jul 2015 to Jun 2016	Undertreatment with non-prescription of OACs in high-risk: - Sep 2011 to Apr 2013: 43.3% - Jul 2015 to Jun 2016: 24.4% Overtreatment with antithrombotic in low-risk: - Sep 2011 to Apr 2013: 78.6% - Jul 2015 to Jun 2016: 64.7%
Lacoin et al 2017 [33]	UK (General practices)	ESC 2012 and NICE 2014/ CHA_2DS_2-VASc	Patients with NVAF eligible for anticoagulation (CHA_2DS_2-VASc ≥2) (N=294786)	Patients who received OACs	Undertreatment: April 2012 (49.8%), April 2013 (46.8%), April 2014 (42.5%), April 2015 (37.1%), and January 2016 (33.1%)
Marzec et al 2017 [37]	U.S. (Ambulatory)	CHA_2DS_2-VASc	Patients with NVAF and high risk for stroke (i.e. CHA_2DS_2-VASc score ≥2) without a documented contraindication for OAC (N=655000)	OAC use	Undertreatment: 2008: 47.6% 2014: 39.3% (p for trend <0.01)
Mochalina et al 2016 [53]	Sweden (Primary and secondary care)	ESC 2012/ CHA_2DS_2-VASc and HAS-BLED	Patients with first episode AF (N=13837)	Guideline adherence; potential undertreatment; and overtreatment, respectively	Guideline non-adherent treatment: 2011: 52.4% 2012: 47.0% 2013: 40.2% 2014: 33.9% Undertreatment: 2011: 51.9% 2012: 46.3% 2013: 39.6% 2014: 33.3%

					Overtreatment: 2011: 0.6% 2012: 0.7% 2013: 0.6% 2014: 0.6%

AF: atrial fibrillation; AHA: American Heart Association; AP: antiplatelet agents; CHA_2DS_2-VASc: congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65-74, and sex category (female); $CHADS_2$: congestive heart failure, hypertension, age ≥ 75 years, diabetes, a history of stroke or transient ischemic attack (doubled); ESC: European Society of Cardiology; GRASP: Guidance on Risk Assessment for Stroke Prevention in AF; HAS-BLED: Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly; NICE: National Institute for Health and Care Excellence; NVAF: non-valvular atrial fibrillation; OAC: oral anticoagulant; U.K.: United Kingdom; U.S.: United States

Studies that included patients from multiple geographical regions demonstrated variations in the extent of guideline non-adherence between regions. Studies from the Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) registry show that undertreatment in terms of not prescribing OACs for patients with a CHA_2DS_2-VASc score of ≥2 is lowest in Europe and highest in Asia. [24, 25] Mazurek et al also reported that undertreatment in Africa/Middle East is lowest second only to Europe. [24] However, with only 32 (of 536) participants from South Africa, it is difficult to generalize this to the entire African population (Table 2).

Table 2: The extent of guideline non-adherence in studies conducted in multiple geographical regions

Study (prospective cohort)	**Country (Setting)**	**Guidelines/ tools**	**Patient population**	**Outcome measures**	**Results**
Miyazawa et al (Fushimi and Darlington AF registries) 2019 [26]	Japan and U.K. (Community-based in-patient and outpatient services; and general practices)	Fushimi: JCS 2013/ $CHADS_2$ Darlington: NICE 2014/ CHA_2DS_2-VASc	Patients with AF or atrial flutter (N=6244)	Guideline non-adherence	Non-adherent (p<0.001): -Fushimi: 41.4% -Darlington: 49.2% Undertreatment (p=0.002): -Fushimi: 40.0% -Darlington: 36.1% Overtreatment (p<0.001): -Fushimi: 1.4% -Darlington: 13.1%
Mazurek et al (The GLORIA-AF Registry, Phase II) 2017 [24]	Asia, Europe, North America, Latin America, Africa/Middle East (inpatient and outpatient)	CHA_2DS_2-VASc	Adult NVAF patients with ≥1 risk factor for stroke as per CHA_2DS_2-VASc (N=12999)	OAC non-prescription in patients with CHA_2DS_2-VASc score of ≥2	Entire population (N=12999): 17.8% Asia (N=2429): 42.4% Europe (N=6310): 8.9% North America (N=2933): 19.2% Latin America (N=791): 13.3% Africa/Middle East* (N=536): 10.8%
Huisman et al (The GLORIA-	Asia, Europe, North America,	CHA_2DS_2-VASc	Adult NVAF patients with ≥1 risk factor	OAC non-prescription in patients with	Entire population (N=10675): 16.7%

AF Registry, Phase II) 2015 [25]	Latin America, Africa/Middle East (inpatient and outpatient)		for stroke as per CHA_2DS_2-VASc (N=10675)	CHA_2DS_2-VASc score of ≥2	Asia (N=1957): 39.3% Europe (N=4703): 8.9% North America (N=3415): 19.3% Latin America (N=476): 13.9% Africa/ Middle East (N=124): not stated

*Africa/Middle East: only 32 patients from South Africa; AF: atrial fibrillation; CHA_2DS_2-VASc: congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65-74, and sex category (female); $CHADS_2$: congestive heart failure, hypertension, age ≥ 75 years, diabetes, a history of stroke or transient ischemic attack (doubled); GLORIA-AF: Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation; JCS: Japanese Circulation Society; NICE: National Institute for Health and Care Excellence; NVAF: non-valvular atrial fibrillation; OAC: oral anticoagulant

Although there are several studies which included participants from multiple countries or regions, few of them compared overall results across the different regions. Table 3 focuses on studies that were published between 2016 and 2020 and that used the CHA_2DS_2-VASc score as a means of stratifying patients' risk of stroke. Significant differences in guideline non-adherence exist across and within different geographic regions (Table 3).

Table 3: The extent of guideline non-adherence in different geographical regions and healthcare settings in the past five years

	Setting (Country)	Patient population	Guideline-adherent treatment	Undertreatment	Overtreatment
Middle East					
Miyazawa et al 2019[&] 2 [66]	Hospital (Gulf countries)	Patients with AF (N=1860)	49%	25.6%	25.4%
Balaghi-Inalou et al 2017[#] [30]	Hospital (Iran)	Patients with NVAF (N=120)	97.5%	-	-
Kezerle et al 2020[λ] [62]	Community and hospital (Israel)	Patients with NVAF (N=58385)	37.1%[2]	62.9%[2]	11.4%[0]
East Asia					
Krittayaphong et al 2018[&] [50]	Hospital (Thailand)	Patients with NVAF (N=3218)	81.6%[2]	18.4%[2]	58.4%[0]
Kim et al 2017[&] [59]	Hospital (South Korea)	Patients with NVAF (N=6275)	82.7%[2]	17.3%[2]	53.4%[0]
Song et al 2019[λ] [67]	Inpatient and outpatient (South Korea)	Patients with NVAF (N=9226)	54.2%[2]	45.8%[2]	-
Lee et al 2017[λ] [34]	Claims database (South Korea)	Patients with NVAF (N=276246)	50.6%[2]	49.4%[2]	-
Australasia					
Wertheimer et al 2020[λ] [57]	Hospital (Australia)	Patients with AF (N=200)	72.8%[2]	27.2%[2]	80%[0]
Admassie et al 2017[λ] [43]	Hospital (Australia)	Patients with NVAF (N=2118)	63.1%[2]	36.9%[2]	42.9%[0]
Bista et al 2017[λ] [68]	Hospital (Australia)	Patients with AF (N=1469)	57%[1c]	43%[1c]	-

Aziz et al 2019[λ] [69]	Remote hospital (Australia)	Patients with AF or atrial flutter (N=59)	83%[2]	17%[2]	-
Frain et al 2018[λ] [70]	Aged care (Australia)	Patients with AF residing in aged care facilities (N=1952)	34.8%[1a]	65.2%[1b]	-
Olivia et al 2020[λ] [71]	Nurse-led clinic (Australia)	Patients with AF (N=136)	91.3%[2]	8.7%[2]	-
Tomlin et al 2017[λ] [18]	General practices (New Zealand)	Patients with AF (N=12712)	60.5%[2]	39.5%[2]	15.6%[0]
Europe					
Kartas et al 2019[#] [49]	Hospital (Greece)	Patients with NVAF (N=768)	83.1% 85.4%[2]	14.6%[2]	67.6%[0]
Jortveit et al 2019[&] [72]	Hospital (Norway)	Patients with acute MI and AF (N=7583)	56.3%[2]	43.7%[2]	-
Cowan et al 2018[λ] [63]	Hospital (England)	Patients with AF (N=375310)	78.6%[2]	21.4%[2]	-
Gundlund et al 2018[λ] [73]	Hospital (Denmark)	Patients with NVAF aged ≥30 years, with moderate to high stroke risk (N=30626)	Pre-stroke population: 36.5%[2] Post-stroke population: 54.2%[2]	Pre-stroke population: 63.5%[2] Post-stroke population: 45.8%[2]	-
Averlant et al 2017[λ] [41]	Hospital (France)	Patients with NVAF aged ≥75 (N=2034)	41.5%	58.5%	-
Başaran et al 2017[λ] [20]	Hospital (Turkey)	Patients with NVAF (N=6273)	71.7%	23.9%	4.4%
Proietti et al 2016[&] [74]	Hospital (Italy and Spain)	Patients with AF aged ≥65 years (N=558)	40.9%	52.3%	6.8%
Lenarczyk et al 2016[&] [51]	Hospital (Poland)	Patients with AF (N=419)	61.1%[2]	38.9%[2]	66.7%[0]
Seelig et al 2020[&] [56]	Hospital, primary care, anticoagulation clinics (Netherlands)	Patients with NVAF (N=1189)	82.6%[1a] to 92.5%[2]	7.5[2] to 17.8%[1a]	71.1%[0]
Cools et al 2018[&] [46]	Hospital cardiology sites, private practice cardiology site, general physician sites (Belgium)	Newly diagnosed NVAF patients with at least one stroke risk factor (N=1713)	84.3%[2]	15.7%[2]	71.4%[0]
Apenteng et al 2017[&] [64]	Primary care, internal medicine, cardiology, geriatrics, neurology (U.K.)	Newly diagnosed NVAF patients (N=3482)	75.6%[2]	24.4%[2]	64.7%
Potpara et al 2016[&] [54]	Multiple settings (Balkan countries)	Patients with AF (N=2663)	74.4%[2]	25.6%[2]	50.38%[0]
Mazurek et al 2017[&] 2 [75]	Primary health care (U.K.)	Patients with AF or atrial flutter (N=2259)	50.8%	36.1%	13.1%

Lacoin et al 2017[#] [33]	General practices (U.K.)	Patients with NVAF eligible for anticoagulation (CHA_2DS_2-VASc≥2) (N=294786)	66.9%[2]	33.1%[2]	-
Mochalina et al 2016[λ] [53]	Primary and secondary care (Sweden)	Patients with first NVAF or atrial flutter (N=13837)	62.8%[2]	37.2%[2]	-
Boriani et al 2018[&] [45]	Cardiology practices (Multicountry)	Patients with AF (N=11096)	78.3-88.8%[2]	11.2-21.7%[2]	73.5%[0]
Navarro-Juan et al 2016[#] [76]	Emergency department (Spain)	Patients with AF (N=144)	33.1%[2]	66.9%[2]	16.7%[0]
Hohnloser et al 2019[λ] [22]	Claims database (Germany)	Patients with NVAF (N=601261)	54.2%[2]	45.8%[2]	29.6%[0]
North America					
Piccini et al 2019[&] [38]	Hospital (U.S.)	Patients with NVAF, CHA_2DS_2-VASc score ≥2, and without a documented contraindication for OAC (N=27270)	80.3%[2]	19.7%[2]	-
Dupree et al 2018[λ] [47]	Hospital (U.S.)	Patients with NVAF without a documented contraindication for OAC (N=246)	83.0%[2]	17.0%[2]	83.3%[0]
McIntyre et al 2018[&] [77]	Hospitals as well as the offices of specialists and primary care providers (U.S. and Canada)	Newly diagnosed patients with AF with a CHA_2DS_2-VASc≥1 in males and ≥2 in females (N=3320)	83%[2]	17%[2]	-
Lubitz et al 2018[&] [36]	Ambulatory (U.S.)	Patients with NVAF and high risk for stroke (i.e. CHA_2DS_2-VASc score ≥2) (N=674841)	57%[2]	43%[2]	-
Marzec et al 2017[&] [37]	Ambulatory (U.S.)	Patients with NVAF and high risk for stroke (CHA_2DS_2-VASc score ≥2) without a documented contraindication for OAC (N=655000)	60.7%[2]	39.3%[2]	-
Thompson et al 2017[&] [39]	Ambulatory (U.S.)	Patients with first NVAF at high stroke risk (CHA_2DS_2-VASc score ≥2) (N=691906)	59.1%[2]	40.9%[2]	-
Barnett et al 2017[λ] [44]	Community-based outpatient practices (U.S.)	Patients with AF (N=9570)	78.9%[2]	21.1%[2]	60%[0]
Africa					

Gebreyohannes et al 2018[λ] [78]	Hospital (Ethiopia)	Patients with AF (N=159)	35.2%	64.8%	-
Latin America					
Jerjes-Sanchez et al 2019[&] [48]	Multiple practices (Argentina, Chile, Brazil, Mexico)	Newly diagnosed NVAF patients with at least one stroke risk factor (N=4162)	49.9%[2]	50.1%[2]	63.5%[0]

[0] Patients who are truly low-risk for stroke (a CHA_2DS_2-VASc scores of 0 in men and 1 in women); [1a] Patients with a CHA_2DS_2-VASc scores of 1 in men and 2 in women; [1b] Patients with a CHA_2DS_2-VASc scores of ≥1 in men and ≥2 in women; [1c] Patients with a CHA_2DS_2-VASc scores of ≥1; [2] Patients at high-risk for stroke; [#]Cross-sectional; [&]Prospective cohort; [λ]Retrospective observational; AF: atrial fibrillation; CHA_2DS_2-VASc: congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65-74, and sex category (female); Balkan countries: Albania, Bosnia-Herzegovina, Bulgaria, Croatia, Montenegro, Romania and Serbia; Gulf countries: Bahrain, Kuwait, Qatar, Oman, The United Arab Emirates, and Yemen; MI: myocardial infarction; NVAF: non-valvular atrial fibrillation; U.K.: the United Kingdom; U.S.: the United States

3.1 Middle East

Three studies from the Middle East reported guideline non-adherence. [30, 62, 66] One study from Iran reported that only 2.5% of patients received guideline non-adherent treatment. [30] Compared to the other two studies [62, 66], this study had a lower sample size. In addition, unlike the other two studies, this study also considered the HAS-BLED score in judging the appropriateness of OAC prescription. This means, individuals that would have been considered receiving undertreatment as per their CHA_2DS_2-VASc score could be classified as receiving guideline-adherent treatment because of their HAS-BLED score. This could have contributed to the very low proportion of patients with guideline non-adherent treatment. On the other hand, a recent hospital-based study conducted in six Gulf countries reported that nearly half of the patients received guideline non-adherent treatment, with patients receiving over- (25.6%) and undertreatment (25.4%) in similar rates. [66] This study did not consider the HAS-BLED score but omission of OACs were considered appropriate in patients at high risk of stroke when contraindications were reported. A study in Israel also reported undertreatment as high as 62.9%. [62] This study assessed the prescription of OACs only in the first three months of AF diagnosis. As such, OACs prescribed after the first three months of treatment would not be considered in assessing guideline adherence. In this study, 11.4% of patients who were truly at low-risk for stroke received prescription of antithrombotic agents. [62] However, the study did not consider the use of antiplatelet agents in low-risk patients as overtreatment. [62]

3.2 East Asia

When considering only patients with a CHA_2DS_2-VASc score of ≥2, undertreatment in East Asia was reported to be as low as 17.3% or as high as 49.4%. [34, 50, 59, 67] Similar rates of undertreatment was reported from two hospital-based studies in Thailand and South Korea. [50, 59] On the other hand, two other studies from South Korea reported that 45.8% to 49.4% of patients received undertreatment. [34, 67] Of note, the reported rates of

undertreatment was much higher in the two retrospective observational studies [34, 67] than in the other two prospective ones [50, 59], indicating that retrospective studies may overestimate guideline non-adherence. When it comes to overtreatment, prescription of antithrombotic agents in patients who were truly at low-risk for stroke ranged from 53.4% to 58.4%. [50, 59] It is difficult to make comparisons between the different healthcare settings as most of the participants were either from the hospital setting or from a claims database. [34, 50, 59, 67]

3.3 Australasia

Undertreatment in Australian patients with a CHA_2DS_2-VASc scores of ≥2 prescribed OACs after hospital attendance range from 17.0% to 36.9%. [43, 57, 69] One study reported that around 40% of patients who are truly low-risk for stroke were overtreated. [43] Another study reported a higher figure of overtreatment (80%), but it included a small number of low-risk patients (N=16). [57] Undertreatment in New Zealand general practices among patients with CHA_2DS_2-VASc scores of ≥2 was around 40% with overtreatment in patients with a CHA_2DS_2-VASc scores of 0 of 15.6%. [18] The lowest extent of undertreatment was reported from a nurse-led clinic in Australia where 8.7% of patients with CHA_2DS_2-VASc scores of ≥2 did not receive OAC prescription. [71] Of note, findings from all of these retrospective studies suggest that studies with lower sample size my underestimate the proportion of patients receiving undertreatment. [18, 43, 57, 69] With the exception of the nurse-led clinic [71], an increasing trend in the proportion of patients receiving undertreatment was observed with increasing sample size. [18, 43, 57, 69]

3.4 Europe

Of all the regions, Europe is the most frequently studied. In all studies that provided data for high-risk patients, undertreatment was considered when OACs were not prescribed in these patients. [22, 33, 41, 45, 46, 49, 51, 53, 54, 56, 63, 64, 72, 73, 76] Similarly, prescription of any antithrombotic agent in patients with a low risk of stroke was considered as overtreatment. [22, 45, 46, 51, 54, 56, 76]

Hospital-based studies in Turkey [20] and Greece [49] reported that 28.3% and 16.9% of patients with NVAF received guideline non-adherent treatments, respectively. Another hospital-based study from France included only elderly patients aged 75 years or older. [41] In this study, where all the patients were high-risk, the proportion of patients receiving undertreatment was 58.5%. Most of the remaining hospital-based studies reported guideline non-adherence based on the patients' risk of stroke. Accordingly, undertreatment in patients at high-risk of stroke ranges from 14.6% in Greece [49] to 59.1% in Italy and Spain [74]. Findings from studies incorporating multiple

practice sites show similar rates of guideline non-adherence in high-risk patients where 15.7%-25.6% of patients received undertreatment. [46, 54, 64] However, the proportion of low-risk patients receiving overtreatment varied considerably. [46, 54, 56, 64] One clear observation is that undertreatment in high-risk patients attending primary healthcare is higher than for patients attending hospitals as 33.1% to 49.2% of patients were receiving undertreatment in primary healthcare. [33, 53, 75] On the other hand, the proportion of low-risk patients receiving overtreatment appears to be lower (0.6% to 13.1%) than their hospital counterparts. [53, 75] The above observations indicate that there may be a tendency towards not prescribing OACs in the primary healthcare setting. One multicenter study that focused on cardiology practices found the proportion of high-risk patients receiving undertreatment ranged from 11.2% to 21.7%%. [45] Close to three-quarters of low-risk patients in this study were receiving overtreatment.

3.5 North America

Guideline non-adherence in the U.S. and Canada also varies depending on the setting. Around 20% of patients with AF attending hospitals and the primary care setting received guideline non-adherent treatment. [38, 44, 47, 77] On the other hand, the proportion of patients receiving guideline non-adherent treatment is much higher among patients attending ambulatory settings. OAC was not provided to 39.3% to 43% patients at high risk of thromboembolism. [36, 37, 39]

3.6 Africa and Latin America

As compared to other parts of the world, literature on the extent of guideline non-adherence from Africa and Latin America is scarce. One single-center hospital-based Ethiopian study reported that 64.8% of patients with AF received guideline non-adherent treatment. [78] A multi-nation study from Latin America that involved multiple practices reported that 50.1% of the patients at high risk of stroke received guideline non-adherent treatment while nearly two-thirds of patients who were at low risk received over treatment. [48]

4. Factors influencing guideline non-adherence

Multiple factors have been associated with non-adherence to guideline recommendations and prescription of OACs. Though they may not always be evident [56, 60, 64], the most common factors can be categorized as (a) patient-related or (b) physician-related.

4.1 Patient-related factors

Patient or family refusal to take anticoagulant therapy is frequently reported by multiple studies. [43, 47, 56, 64] Patient refusals could account for 7.8% to 15% of OAC non-prescribing. [56, 64] Resistance from patients may be because of legitimate or irrational beliefs that are related to patients' knowledge. [79] Patients often feel that they are not receiving adequate information. [80] Therefore, patient resistance may be improved by providing detailed information and education. [81]

Age is one key factor for guideline non-adherence. [32, 35, 43, 61, 70, 73, 74, 82, 83] A statistically significant increase in guideline non-adherence with advancing age, mainly due to undertreatment, has been reported by multiple studies. [35, 74] This is true even after adjusting for the bleeding risk. [32, 35, 43, 70, 73, 83] While the proportion of AF patients who receive OAC decreases with advancing age [32, 35, 43, 70, 73, 74, 82, 83], this may vary depending on the age category. [73] Gundlund et al. reported that, compared to those patients younger than 65 years of age, being 65 to 74 years and ≥75 years, were associated with higher and lower prescriptions of OAC after adjusting for bleeding risk, respectively. [73]

Stroke and bleeding risk or history are important predictors of guideline non-adherence and non-prescription of OACs. As one might expect, risk [36, 43, 76] or history of [58, 83] stroke is directly associated with prescription of OACs, while bleeding risk [58, 70, 76] or previous bleeding [32, 35, 36, 43, 77] has an inverse association. Başaran et al. [20] reported that patients without a history of stroke were 1.4- to 1.9-times more likely to receive guideline non-adherent anticoagulation. As explained below, physicians' preferences contribute to these observations.

Because female sex was considered a risk factor for stroke, it was included in the most commonly recommended stroke risk stratification tool, the CHA_2DS_2-VASc score. However, it is clear that it has been overlooked by most clinicians as sex has emerged as one of the predictors of guideline non-adherence and non-prescription of anticoagulants in different studies, where females have higher chances of undertreatment. [35, 39, 55, 61, 73] However, the female sex category is no longer considered a significant risk for stroke, and as such, has been excluded from the CHA_2DS_2-VASc score by recent AF guidelines. [5] Though there is no clear explanation, one study discussed that prescribers' or females patients' tendencies to decline OACs could be the potential reasons for the higher rates of guideline non-adherence in female patients with AF. [39] The presence of comorbidities such as ischemic heart disease, cancer, chronic kidney disease, chronic obstructive pulmonary disease, dementia, peripheral arterial disease, and heart failure have all been associated with guideline non-adherence, in particular less OAC prescribing. [20, 32, 40, 58, 69, 73, 74] On the other hand, patients with deep venous thrombosis,

hypertension, valvular heart disease, and higher body mass index are more likely to receive OACs. [20, 61, 73, 83] Prescription of antiplatelet agents or non-steroidal anti-inflammatory drugs [36, 41, 56, 64], recurrent falls or history of falls [32, 77], first detected and/or paroxysmal AF [32, 35], alcohol abuse [47, 73], pharmacological (vs electrical) cardioversion [35], rural residence and illiteracy [20], difficult access to monitoring [40] and frailty [84] have all been associated with underprescription of OACs. Most of the above factors that contribute to guideline non-adherence share the common feature of increasing the risk of bleeding and could be the underlying reason for their contribution in guideline non-adherence. One Australian study also reported that indigenous people are less likely to receive guideline-adherent treatment. [31]

4.2 Physician-related factors

Physician preferences make a significant contribution to guideline non-adherence, particularly those related to their beliefs and practice patterns. [64, 68, 85] Prescribers usually focus on the risk of bleeding associated with OACs rather than the risk associated with not prescribing anticoagulants. [20, 35, 54, 58, 70, 76, 80, 85] Reports from qualitative studies indicate that prescribers use formal stroke risk assessment tools but few use formal bleeding assessment tools. [79, 86] Instead, prescribers rely on informal and subjective bleeding risk assessments. These include comorbidities, history of falls and bleeding, and age. [79, 86, 87] However, formal bleeding assessment tools such as HAS-BLED already consider comorbidities, prior history of bleeding, and age. [88] There may be a need to reassure physicians using findings such as that from a European registry-based study that indicated that the risk of stroke increases more than the risk of bleeding with advancing age, [89] and the fact that the risk of falls should not be the sole reason for withholding OACs. [16] According to a mixed-methods European study, the majority of prescribers including primary care or family physicians, cardiologists, and neurologists reported a need for skills improvement in interpreting risk stratification tools such as CHA_2DS_2-VASc and HAS-BLED. [21] Indeed, van Doorn et al. reported that the reason given by a quarter of GPs for overtreatment was that the responsibility of stroke prevention is the cardiologists', not theirs. [60]

5. Conclusion

The extent of guideline non-adherence is highly variable depending on the geographic region, the healthcare setting, the risk stratification used, and other factors. There has been a gradual improvement in guideline adherence over recent years, but non-adherence to guideline recommendations, especially undertreatment, is still a major concern in many areas. Hence, quality improvement initiatives that aim to address guideline non-adherence should be primarily focused on undertreatment. A range of patient- and physician-related factors affect guideline

adherence. Patient-related factors include refusals, bleeding risk and recurrent falls, which are potentially modifiable, as well as non-modifiable factors such as older age, stroke risk and female sex. Clear guidance on thromboprophylaxis among elderly patients seems to be needed. A greater emphasis on the risk of bleeding than the risk of stroke among physicians also significantly contributed to guideline non-adherence. Research into how to best incorporate stroke and bleeding risk assessment tools into the workflow of physicians, improve patient knowledge and understanding of the risks and benefits of OACs, better integrate primary healthcare with higher healthcare settings and increase the involvement of allied health professionals may help minimize guideline non-adherent OAC treatment in patients with AF and thereby improve patient outcomes.

Declarations

Funding: Not applicable.

Conflict of interest: The authors declare no conflicts of interest.

Availability of data and material: All data and material used for synthesis of this review are included in this manuscript.

Code availability: Not applicable.

Ethics approval: Not applicable.

Consent to participate: Not applicable.

Consent for publication: Not applicable.

Author contributions: EAG contributed to the concept and design, and the literature search; wrote the first draft of the manuscript; critically revised the manuscript; and gave final approval of the submitted manuscript. SMS, LC, LB, and KL contributed to the concept and design; critically revised the manuscript; and gave final approval of the submitted manuscript.

References

1. Lippi G, Sanchis-Gomar F, Cervellin G. Global epidemiology of atrial fibrillation: An increasing epidemic and public health challenge. Int J Stroke. 2020:1747493019897870.

2. Pistoia F, Sacco S, Tiseo C, Degan D, Ornello R, Carolei A. The epidemiology of atrial fibrillation and

3. Goralnick E, Bontempo LJ. Atrial Fibrillation. Emerg Med Clin North Am. 2015;33(3):597-612.

4. Ball J, Carrington MJ, McMurray JJ, Stewart S. Atrial fibrillation: profile and burden of an evolving epidemic in the 21st century. Int J Cardiol. 2013;167(5):1807-24.

5. Brieger D, Amerena J, Attia J, Bajorek B, Chan KH, Connell C, et al. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the diagnosis and management of atrial fibrillation 2018. Heart Lung Circ. 2018;27(10):1209-66.

6. Segal JB, McNamara RL, Miller MR, Kim N, Goodman SN, Powe NR, et al. Prevention of thromboembolism in atrial fibrillation: a meta-analysis of trials of anticoagulants and antiplatelet drugs. J Gen Intern Med. 2000;15(1):56-67.

7. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018;39(16):1330-93.

8. Mueck W, Schwers S, Stampfuss J. Rivaroxaban and other novel oral anticoagulants: pharmacokinetics in healthy subjects, specific patient populations and relevance of coagulation monitoring. Thromb J. 2013;11(1):10.

9. Alamneh EA, Chalmers L, Bereznicki LR. The Tasmanian atrial fibrillation study: Transition to direct oral anticoagulants 2011-2015. Cardiovasc Ther. 2017;35(3).

10. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Jr., et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the Heart Rhythm Society in collaboration with the Society of Thoracic Surgeons. Circulation. 2019;140(2):e125-e51.

11. Andrade JG, Verma A, Mitchell LB, Parkash R, Leblanc K, Atzema C, et al. 2018 focused update of the Canadian Cardiovascular Society guidelines for the management of atrial fibrillation. Can J Cardiol. 2018;34(11):1371-92.

12. Lip GYH, Banerjee A, Boriani G, Chiang CE, Fargo R, Freedman B, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. Chest. 2018;154(5):1121-201.

13. Joung B, Lee JM, Lee KH, Kim TH, Choi EK, Lim WH, et al. 2018 Korean guideline of atrial fibrillation management. Korean Circ J. 2018;48(12):1033-80.

14. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37(38):2893-962.

15. Japanese Circulation Society joint working group. Guidelines for pharmacotherapy of atrial fibrillation (JCS 2013). Circulation Journal. 2014:CJ-66.

16. National Institute for Health and Clinical Excellence (NICE). Atrial fibrillation: management 2014 [Available from: www.nice.org.uk/guidance/cg180.

17. Fauchier L, Philippart R, Clementy N, Bourguignon T, Angoulvant D, Ivanes F, et al. How to define valvular atrial fibrillation? Arch Cardiovasc Dis. 2015;108(10):530-9.

18. Tomlin AM, Lloyd HS, Tilyard MW. Atrial fibrillation in New Zealand primary care: Prevalence, risk factors for stroke and the management of thromboembolic risk. Eur J Prev Cardiol. 2017;24(3):311-9.

19. Ancedy Y, Lecoq C, Saint Etienne C, Ivanes F, Angoulvant D, Babuty D, et al. Antithrombotic management in patients with atrial fibrillation undergoing coronary stent implantation: What is the impact of guideline adherence? Int J Cardiol. 2016;203:987-94.

20. Basaran O, Dogan V, Biteker M, Karadeniz FO, Tekkesin AI, Cakilli Y, et al. Guideline-adherent therapy for stroke prevention in atrial fibrillation in different health care settings: Results from RAMSES study. Eur J Intern Med. 2017;40:50-5.

21. Heidbuchel H, Dagres N, Antz M, Kuck KH, Lazure P, Murray S, et al. Major knowledge gaps and system barriers to guideline implementation among European physicians treating patients with atrial fibrillation: a European Society of Cardiology international educational needs assessment. Europace. 2018;20(12):1919-28.

22. Hohnloser SH, Basic E, Nabauer M. Uptake in antithrombotic treatment and its association with stroke incidence in atrial fibrillation: insights from a large German claims database. Clin Res Cardiol. 2019;108(9):1042-52.

23. Camm AJ, Pinto FJ, Hankey GJ, Andreotti F, Hobbs FD. Non-vitamin K antagonist oral anticoagulants and atrial fibrillation guidelines in practice: barriers to and strategies for optimal implementation. Europace. 2015;17(7):1007-17.

24. Mazurek M, Huisman MV, Rothman KJ, Paquette M, Teutsch C, Diener HC, et al. Regional differences in antithrombotic treatment for atrial fibrillation: Insights from the GLORIA-AF phase II registry. Thromb Haemost. 2017;117(12):2376-88.

25. Huisman MV, Rothman KJ, Paquette M, Teutsch C, Diener HC, Dubner SJ, 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.

26. Miyazawa K, Ogawa H, Mazurek M, Shantsila E, Lane DA, Wolff A, et al. Guideline-adherent treatment for stroke and death in atrial fibrillation patients from UK and Japanese AF registries. Circ J. 2019;83(12):2434-42.

27. Vallakati A, Lewis WR. Underuse of anticoagulation in patients with atrial fibrillation. Postgrad Med. 2016;128(2):191-200.

28. Wan D, Healey JS, Simpson CS. The guideline-policy gap in direct-acting oral anticoagulants usage in atrial fibrillation: evidence, practice, and public policy considerations. Can J Cardiol. 2018;34(11):1412-25.

29. Lowres N, Giskes K, Hespe C, Freedman B. Reducing stroke risk in atrial fibrillation: adherence to guidelines has improved, but patient persistence with anticoagulant therapy remains suboptimal. Korean Circulation Journal. 2019;49(10):883-907.

30. Balaghi-Inalou M, Parsa SA, Gachkar L, Andalib S. Anticoagulant Therapy in Atrial Fibrillation for Stroke Prevention: Assessment of Agreement Between Clinicians' Decision and CHA2DS2-VASc and HAS-BLED Scores. High Blood Press Cardiovasc Prev. 2018;25(1):61-4.

31. Wong CX, Lee SW, Gan SW, Mahajan R, Rangnekar G, Pathak RK, et al. Underuse and overuse of anticoagulation for atrial fibrillation: a study in indigenous and non-indigenous Australians. Int J Cardiol. 2015;191:20-4.

32. Bahri O, Roca F, Lechani T, Druesne L, Jouanny P, Serot JM, 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):71-6.

33. Lacoin L, Lumley M, Ridha E, Pereira M, McDonald L, Ramagopalan S, et al. Evolving landscape of stroke prevention in atrial fibrillation within the UK between 2012 and 2016: a cross-sectional analysis study using CPRD. BMJ Open. 2017;7(9):e015363.

34. Lee SR, Choi EK, Han KD, Cha MJ, Oh S, Lip GYH. Temporal trends of antithrombotic therapy for stroke prevention in Korean patients with non-valvular atrial fibrillation in the era of non-vitamin K antagonist oral anticoagulants: A nationwide population-based study. PLoS One. 2017;12(12):e0189495.

35. Lip GY, Laroche C, Popescu MI, Rasmussen LH, Vitali-Serdoz L, Dan GA, 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.

36. Lubitz SA, Khurshid S, Weng LC, Doros G, Keach JW, Gao Q, et al. Predictors of oral anticoagulant non-prescription in patients with atrial fibrillation and elevated stroke risk. Am Heart J. 2018;200:24-31.

37. Marzec LN, Wang J, Shah ND, Chan PS, Ting HH, Gosch KL, et al. Influence of direct oral anticoagulants on rates of oral anticoagulation for atrial fibrillation. J Am Coll Cardiol. 2017;69(20):2475-84.

38. Piccini JP, Xu H, Cox M, Matsouaka RA, Fonarow GC, Butler J, et al. Adherence to guideline-directed stroke prevention therapy for atrial fibrillation is achievable. Circulation. 2019;139(12):1497-506.

39. Thompson LE, Maddox TM, Lei L, Grunwald GK, Bradley SM, Peterson PN, et al. Sex differences in the use of oral anticoagulants for atrial fibrillation: a report from the National Cardiovascular Data Registry (NCDR((R))) PINNACLE Registry. J Am Heart Assoc. 2017;6(7).

40. Formiga F, Polo J, Fernandez de Cabo S, Arumi D. Why are antithrombotic drugs not prescribed to octogenarian patients with atrial fibrillation at risk of stroke? Semergen. 2020.

41. Averlant L, Ficheur G, Ferret L, Boule S, Puisieux F, Luyckx M, et al. Underuse of oral anticoagulants and inappropriate prescription of antiplatelet therapy in older inpatients with atrial fibrillation. Drugs Aging. 2017;34(9):701-10.

42. Pipilis A, Farmakis D, Kaliambakos S, Goudevenos J, Lekakis J. Anticoagulation therapy in elderly patients with atrial fibrillation: results from the Registry of Atrial Fibrillation To Investigate the Implementation of New Guidelines (RAFTING). J Cardiovasc Med (Hagerstown). 2017;18(7):545-9.

43. Admassie E, Chalmers L, Bereznicki LR. Changes in oral anticoagulant prescribing for stroke prevention in patients with atrial fibrillation. Am J Cardiol. 2017;120(7):1133-8.

44. Barnett AS, Kim S, Fonarow GC, Thomas LE, Reiffel JA, Allen LA, et al. Treatment of atrial fibrillation and concordance with the American Heart Association/American College of Cardiology/Heart Rhythm Society Guidelines: Findings from ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation). Circ Arrhythm Electrophysiol. 2017;10(11).

45. Boriani G, Proietti M, Laroche C, Fauchier L, Marin F, Nabauer M, et al. Contemporary stroke prevention strategies in 11 096 European patients with atrial fibrillation: a report from the EURObservational Research Programme on Atrial Fibrillation (EORP-AF) Long-Term General Registry. Europace. 2018;20(5):747-57.

46. Cools F, Wollaert B, Vervoort G, Verstraete S, Voet J, Hermans K, et al. Treatment patterns in anticoagulant therapy in patients with newly diagnosed atrial fibrillation in Belgium: results from the GARFIELD-AF registry. Acta Cardiol. 2019;74(4):309-18.

47. Dupree L, DeLosSantos M, Smotherman C. Evaluation of adherence to guideline-directed antithrombotic therapy for atrial fibrillation at hospital discharge. J Cardiovasc Pharmacol Ther. 2018;23(6):502-8.

48. Jerjes-Sanchez C, Corbalan R, Barretto ACP, Luciardi HL, Allu J, Illingworth L, et al. Stroke prevention in patients from Latin American countries with non-valvular atrial fibrillation: Insights from the GARFIELD-AF registry. Clin Cardiol. 2019;42(5):553-60.

49. Kartas A, Samaras A, Vasdeki D, Dividis G, Fotos G, Paschou E, et al. Flaws in anticoagulation strategies in patients with atrial fibrillation at hospital discharge. J Cardiovasc Pharmacol Ther. 2019;24(3):225-32.

50. Krittayaphong R, Winijkul A, Methavigul K, Wongtheptien W, Wongvipaporn C, Wisaratapong T, et al. Risk profiles and pattern of antithrombotic use in patients with non-valvular atrial fibrillation in Thailand: a multicenter study. BMC Cardiovasc Disord. 2018;18(1):174.

51. Lenarczyk R, Mitręga K, Mazurek M, Janion M, Opolski G, Drożdż J, et al. Polish and European management strategies in patients with atrial fibrillation. Data from the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase (EORP-AF Pilot). Pol Arch Med Wewn. 2016;126(3):138-48.

52. Lip GY, Rushton-Smith SK, Goldhaber SZ, Fitzmaurice DA, Mantovani LG, Goto S, 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 Suppl 1):S12-20.

53. Mochalina N, Joud A, Carlsson M, Sandberg MEC, Sjalander A, Juhlin T, et al. Antithrombotic therapy in patients with non-valvular atrial fibrillation in Southern Sweden: A population-based cohort study. Thromb Res. 2016;140:94-9.

54. Potpara TS, Dan GA, Trendafilova E, Goda A, Kusljugic Z, Manola S, et al. Stroke prevention in atrial fibrillation and 'real world' adherence to guidelines in the Balkan Region: The BALKAN-AF Survey. Sci Rep. 2016;6:20432.

55. Sabouret P, Bricard M, Hermann MA, Cotte FE, Deret-Bixio L, Rushton-Smith S. Discrepancy between guidelines for stroke prevention in atrial fibrillation and practice patterns in primary care. The nationwide French AFIGP survey. Arch Cardiovasc Dis. 2015;108(11):544-53.

56. Seelig J, Verheugt FWA, Hemels MEW, Illingworth L, Lucassen A, Adriaansen H, et al. Changes in anticoagulant prescription in Dutch patients with recent-onset atrial fibrillation: observations from the GARFIELD-AF registry. Thromb J. 2020;18:5.

57. Wertheimer G, Bereznicki LR. Exploring the quality of anticoagulant prescribed for patients with atrial fibrillation at the St John of God Hawkesbury district health centre, New South Wales, Australia. J Cardiovasc Pharmacol Ther. 2019;24(1):46-53.

58. Rathinam I, Anoopkumar-Dukie S, Badrick T, Teasdale T, Bernaitis N. Anticoagulant initiation during hospital admissions for atrial fibrillation in South-East Queensland, Australia. Heart Lung Circ. 2020.

59. Kim H, Kim TH, Cha MJ, Lee JM, Park J, Park JK, et al. A prospective survey of atrial fibrillation management for real-world guideline adherence: COmparison study of Drugs for symptom control and complication prEvention of Atrial Fibrillation (CODE-AF) Registry. Korean Circ J. 2017;47(6):877-87.

60. van Doorn S, Hartman-Weide F, Geersing GJ, Oudega R, Hoes AW, Rutten FH. Reasons for non-adherence to practice guidelines on stroke prevention in patients with atrial fibrillation: A cross-sectional study in primary care. Int J Cardiol. 2015;187:525-6.

61. Hsu JC, Chan PS, Tang F, Maddox TM, Marcus GM. Oral anticoagulant prescription in patients with atrial fibrillation and a low risk of thromboembolism: Insights from the NCDR PINNACLE registry. JAMA Intern Med. 2015;175(6):1062-5.

62. Kezerle L, Tsadok MA, Berliner Senderey A, Hoshen M, Leventer-Roberts M, Reges O, et al. Use of oral anticoagulation therapy in the first 3 months after the diagnosis of atrial fibrillation in Israel: A population-based study. J Cardiovasc Electrophysiol. 2020.

63. Cowan JC, Wu J, Hall M, Orlowski A, West RM, Gale CP. A 10 year study of hospitalized atrial fibrillation-related stroke in England and its association with uptake of oral anticoagulation. Eur Heart J. 2018;39(32):2975-83.

64. Apenteng PN, Gao H, Hobbs FR, Fitzmaurice DA. Temporal trends in antithrombotic treatment of real-world UK patients with newly diagnosed atrial fibrillation: findings from the GARFIELD-AF registry. BMJ Open. 2018;8(1):e018905.

65. Narita N, Okumura K, Kinjo T, Mikami J, Tsushima K, Takahashi R, et al. Trends in prevalence of non-valvular atrial fibrillation and anticoagulation therapy in a Japanese region- analysis using the national health insurance database. Circ J. 2020.

66. Miyazawa K, Li YG, Rashed WA, Al Mahmeed W, Shehab A, Zubaid M, et al. Secondary stroke prevention and guideline adherent antithrombotic treatment in patients with atrial fibrillation: Insights from the Gulf Survey of atrial fibrillation events (Gulf SAFE). Int J Cardiol. 2019;274:126-31.

67. Song HY, Son KB, Shin JY, Bae S. Utilization of oral anticoagulants in Korean nonvalvular atrial fibrillation patients. Int J Clin Pharm. 2019;41(6):1434-41.

68. Bista D, Chalmers L, Peterson GM, Bereznicki LRE. Patient characteristics and antithrombotic prescribing patterns in patients with atrial fibrillation in Tasmania. Clin Appl Thromb Hemost. 2017;23(5):438-44.

69. Aziz H, Mills D, Newbury J. Adherence to antithrombotic therapy guidelines and atrial fibrillation in a rural hospital: a clinical audit. Rural Remote Health. 2019;19(1):4342.

70. Frain B, Castelino R, Bereznicki LR. The utilization of antithrombotic therapy in older patients in aged care facilities with atrial fibrillation. Clin Appl Thromb Hemost. 2018;24(3):519-24.

71. Olivia C, Hastie C, Farshid A. Adherence to guidelines regarding anticoagulation and risk factors for progression of atrial fibrillation in a nurse-led clinic. Intern Med J. 2020.

72. Jortveit J, Pripp AH, Langorgen J, Halvorsen S. Poor adherence to guideline recommendations among patients with atrial fibrillation and acute myocardial infarction. Eur J Prev Cardiol. 2019;26(13):1373-82.

73. Gundlund A, Xian Y, Peterson ED, Butt JH, Gadsboll K, Bjerring Olesen J, et al. Prestroke and poststroke antithrombotic therapy in patients with atrial fibrillation: Results from a nationwide cohort. JAMA Netw Open. 2018;1(1):e180171.

74. Proietti M, Nobili A, Raparelli V, Napoleone L, Mannucci PM, Lip GY. Adherence to antithrombotic therapy guidelines improves mortality among elderly patients with atrial fibrillation: insights from the REPOSI study. Clin Res Cardiol. 2016;105(11):912-20.

75. Mazurek M, Shantsila E, Lane DA, Wolff A, Proietti M, Lip GYH. Guideline-adherent antithrombotic treatment improves outcomes in patients with atrial fibrillation: Insights from the community-based Darlington atrial fibrillation registry. Mayo Clin Proc. 2017;92(8):1203-13.

76. Navarro-Juan M, Carbonell-Torregrosa MA, Palazon-Bru A, Martinez-Diaz AM, Gil-Guillen VF. Nonadherence to guidelines for prescribing antiplatelet/anticoagulant therapy in patients with atrial fibrillation. Fam Pract. 2016;33(3):290-5.

77. McIntyre WF, Conen D, Olshansky B, Halperin JL, Hayek E, Huisman MV, et al. Stroke-prevention strategies in North American patients with atrial fibrillation: The GLORIA-AF registry program. Clin Cardiol. 2018;41(6):744-51.

78. Gebreyohannes EA, Bhagavathula AS, Tegegn HG. Poor outcomes associated with antithrombotic undertreatment in patients with atrial fibrillation attending Gondar University Hospital: a retrospective cohort study. Thromb J. 2018;16:22.

79. Kirley K, GouthamRao VB, Masi C. The role of NOACs in atrial fibrillation management: a qualitative study. Journal of atrial fibrillation. 2016;9(1).

80. Mas Dalmau G, Sant Arderiu E, Enfedaque Montes MB, Sola I, Pequeno Saco S, Alonso Coello P. Patients' and physicians' perceptions and attitudes about oral anticoagulation and atrial fibrillation: a qualitative systematic review. BMC Fam Pract. 2017;18(1):3.

81. Decker C, Garavalia L, Garavalia B, Simon T, Loeb M, Spertus JA, et al. Exploring barriers to optimal anticoagulation for atrial fibrillation: interviews with clinicians. J Multidiscip Healthc. 2012;5:129.

82. Miller RJH, Chew DS, Rezazadeh S, Klassen S, Pournazari P, Lang E, et al. Factors influencing oral anticoagulation prescription for patients presenting to emergency departments with atrial fibrillation and flutter. Can J Cardiol. 2018;34(6):804-7.

83. Pennlert J, Asplund K, Carlberg B, Wiklund PG, Wisten A, Asberg S, et al. Antithrombotic treatment following intracerebral hemorrhage in patients with and without atrial fibrillation. Stroke. 2015;46(8):2094-9.

84. Oqab Z, Pournazari P, Sheldon RS. What is the impact of frailty on prescription of anticoagulation in elderly patients with atrial fibrillation? a systematic review and meta-analysis. J Atr Fibrillation. 2018;10(6):1870.

85. Kea B, Alligood T, Robinson C, Livingston J, Sun BC. Stroke prophylaxis for atrial fibrillation? To prescribe or not to prescribe-a qualitative study on the decision making process of emergency department providers. Ann Emerg Med. 2019;74(6):759-71.

86. Pokorney SD, Bloom D, Granger CB, Thomas KL, Al-Khatib SM, Roettig ML, et al. Exploring patient-provider decision-making for use of anticoagulation for stroke prevention in atrial fibrillation: Results of the INFORM-AF study. Eur J Cardiovasc Nurs. 2019;18(4):280-8.

87. Berti D, Moors E, Moons P, Heidbuchel H. Prevalence and antithrombotic management of atrial fibrillation in hospitalised patients. Heart. 2015;101(11):884-93.

88. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010;138(5):1093-100.

89. Patti G, Lucerna M, Pecen L, Siller-Matula JM, Cavallari I, Kirchhof P, et al. Thromboembolic risk, bleeding outcomes and effect of different antithrombotic strategies in very elderly patients with atrial fibrillation: a sub-analysis from the PREFER in AF (PREvention oF Thromboembolic Events-European Registry in Atrial Fibrillation). J Am Heart Assoc. 2017;6(7).