Bosphorus Medical Journal
Boğaziçi Tıp Dergisi

Original Article

DOI: 10.14744/bmj.2024.12599

Bosphorus Med J 2024;11(1):1–6

Retrospective Analysis of the Potential Effects of CHA_2DS_2-VASc and HAS-BLED Scores on Treatment Choices for Atrial Fibrillation Patients in a Stroke Center

Bir İnme Merkezinde Atrial Fibrilasyon Hastalarının Tedavi Seçimlerinde CHA_2DS_2-VASc ve HAS-BLED Skorlarının Potansiyel Etkilerinin Geriye Dönük Analizi

Işıl Kalyoncu Aslan, Ceren Erkalaycı, Leyla Ramazanoğlu, Kadriye Güleda Keskin

Department of Neurology, Fatih Sultan Mehmet Training and Research Hospital, University of Health Sciences Istanbul, Türkiye

Cite this article as:
Kalyoncu Aslan I, Erkalaycı C, Ramazanoğlu L, Keskin KG. Retrospective Analysis of the Potential Effects of CHA_2DS_2-VASc and HAS-BLED Scores on Treatment Choices for Atrial Fibrillation Patients in a Stroke Center. Bosphorus Med J 2024;11(1):1–6.

Received: 26.09.2023
Revision: 13.02.2024
Accepted: 21.02.2024

Correspondence:
Dr. Ceren Erkalaycı. Department of Neurology, Fatih Sultan Mehmet Training and Research Hospital, University of Health Sciences Istanbul, Türkiye

Phone:
+90 506 697 08 97

e-mail:
cerkalayci@gmail.com

ABSTRACT

Objectives: Current information lacks an algorithm that directs us to a specific anticoagulation treatment option for patients with atrial fibrillation (AF), except in certain situations. Our aim was to evaluate the potential relationship between different oral anticoagulant choices and the CHA_2DS_2-VASc (congestive heart failure, hypertension, age, diabetes mellitus, stroke, vascular disease, age, sex category) and HAS-BLED (hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio (INR), elderly, drugs or alcohol) scores of patients, and their treatment compliance.

Methods: We retrospectively documented the patients' age, gender, CHA_2DS_2-VASc, and HAS-BLED scores to assess our preference for oral anticoagulants in AF patients. Two hundred patients with AF were divided into two main groups: those with newly diagnosed AF and those with an established diagnosis of AF. The treatment compliance of patients with AF was documented, and the treatment choices at discharge for patients in both groups were compared based on age, gender, and the two scores. Scores were divided into three main groups for easy comparison. The level of statistical significance was accepted as $p<0.05$.

Results: Ninety-nine of the two hundred patients had a stroke and were diagnosed with AF, while 101 patients had an already established diagnosis of AF and experienced a stroke while using OAC or NOAC on a regular or irregular basis. Warfarin sodium (59.6%) was most often preferred at the discharge of patients, and apixaban (22.2%) was the most preferred NOAC. The daily dosage number of NOACs doesn't make any difference in terms of compliance. The irregular usage of warfarin sodium constituted the vast majority in the irregular group. No statistically significant difference was found between the two scoring system groups and the treatment choices in both groups.

Conclusion: Patients should be evaluated individually when choosing an oral anticoagulant, with the intention to prioritize education aimed at the correct use of the drug rather than the selection of an appropriate drug.

Keywords: Atrial fibrillation; CHA_2DS_2-VASc; HAS-BLED; new oral anticoagulant.

ÖZET

Amaç: Mevcut bilgilere göre, atriyal fibrilasyon (AF) hastalarında hangi antikoagülasyon tedavi seçeneğinin başlanması gerektiğini gösteren net bir algoritma, belirli durumlar dışında henüz bulunmamaktadır. Amacımız, farklı oral antikoagülan seçimleri ile AF hastalarının CHA_2DS_2-VASc (konjestif kalp yetmezliği, hipertansiyon, yaş, diyabet, inme, vasküler hastalık, yaş, cinsiyet kategorisi) ve HAS-BLED (hipertansiyon, anormal böbrek ve karaciğer fonksiyonu, inme, kanama, labil uluslararası normalleştirilmiş oran (INR), yaşlılık, ilaçlar, ilaçlar veya alkol) skorları arasındaki olası ilişkiyi ve farklı antikoagülan seçimlerinin tedaviye uyumunu değerlendirmektir.

Yöntem: İnme merkezimizde takip edilen AF hastalarında oral antikoagülan tercihimizle ilgili olarak hastaların yaş, cinsiyet, CHA_2DS_2-VASc ve HAS-BLED skorlarını retrospektif olarak taradık. İki yüz AF hastası, yeni tanı konulan AF'li hastalar ve tanısı zaten konmuş AF'li hastalar olmak üzere iki ana gruba ayrıldı. AF tanılı hastaların tedavi uyumları dökümante edildi ve her iki gruptaki hastaların taburculuk sırasındaki tedavi tercihleri yaş, cinsiyet, iki skor açısından karşılaştırıldı. Bu skorlar, tedavi tercihleriyle kolay karşılaştırma yapılabilmesi için üç ana gruba ayrıldı. İstatistiksel anlamlılık düzeyi $p<0,05$ olarak kabul edildi.

Bulgular: İki yüz hastadan doksan dokuzu hastanemize inme ile prezente olup yeni AF tanısı aldı, diğer yüz bir hasta ise AF tanısı almış ve düzenli veya düzensiz olarak OAK veya NOAK kullanırken inme geçirmişti. İskemik inme ve AF tanısı konmuş hastalara en çok warfarin sodyum (%59.6) reçetelemeyi tercih ettiğimizi belgeledik ve apiksaban (%22.2) ise en çok tercih ettiğimiz NOAK oldu. Bulgularımıza göre, NOAK'ların günlük kullanım doz sayısı ilaç uyumuna herhangi bir fark yaratmıyor. Warfarin sodyumunun düzensiz kullanımı, düzensiz tedavi grubunun büyük bir kısmını oluşturuyor. Yeni tanı konmuş ve zaten bilinen AF'li hastalarda CHA_2DS_2-VASc ve HAS-BLED skorlama sistemleri grupları ile yaptığımız tedavi seçimleri arasında istatistiksel olarak anlamlı bir fark saptamadık.

Sonuç: Oral antikoagülan seçerken hastalar bireysel olarak değerlendirilmeli ve hastaların ilaçları doğru kullanımına teşvik etmeyi, uygun ilaç seçiminden daha önce amaçlamalıyız.

Anahtar sözcükler: Atrial fibrilasyon; CHA_2DS_2-VASc; HAS-BLED; yeni oral antikoagülan.

According to the definition of the World Health Organization (WHO), stroke is a syndrome characterized by the emergence of signs and symptoms of focal cerebral function loss lasting longer than 24 hours due to impaired cerebral blood flow as a result of only vascular morbidities.[1] Worldwide, 28 million people suffer a stroke attack each year, and stroke is among the 2nd most frequent causes of death and long-term disability. Ischemic strokes constitute 87% of strokes in the world. The causes of ischemic stroke include cerebral circulation atherosclerosis, occlusion in small cerebral vessels (lacunar syndromes), and cardiac embolisms.[2] Major causes of cardio-embolism, accounting for approximately 20% of strokes, include atrial fibrillation (AF), systolic heart failure, recently experienced myocardial infarction (MI), patent foramen ovale (PFO), aortic arch atheroma, prosthetic heart valve, and infective endocarditis. AF, the leading cause of cardio-embolism, is a cardiac rhythm disorder affecting 33 million people worldwide and is associated with a 3-5-fold increased risk of ischemic stroke.[3] According to the 2021 updated guideline of the American Heart Association (AHA), anticoagulant therapy is recommended as a secondary stroke prophylaxis in the presence of persistent or paroxysmal AF in ischemic stroke patients unless any contraindication to this treatment exists. In patients who have suffered from a transient ischemic attack (TIA), it is appropriate to start treatment immediately after the event. In ischemic stroke patients, it is recommended to start anticoagulation between 2 and 14 days after the stroke, depending on the size of the infarct. In anticoagulation treatment, preference is made between oral anticoagulant (OAC) and new/novel oral anticoagulant (NOAC) treatments, except in cases where only OAC should be used. Despite clinical guidelines that continue to be updated in light of studies, there is no clear consensus regarding the choice of OAC or NOAC in ischemic stroke patients (except in certain conditions) with non-valvular atrial fibrillation (NVAF). Clinicians make their choices based on the patient's comorbidity status, and their clinical experience as well as considering the validated CHA_2DS_2-VASC (congestive heart failure, hypertension, age ≥75, diabetes mellitus, stroke, vascular disease, age 65-74, sex category) and HAS-BLED (hypertension, abnormal renal and liver function, stroke, bleeding, labile INR, elderly, drugs, drugs or alcohol) scoring systems.[4,5] The treatment is started by evaluating the advantages and disadvantages of using OAC or NOAC on a patient-by-patient basis. Real-life data collection is needed to facilitate the selection of appropriate treatments in the long term. For this purpose, we statistically compared the treatment choices of 99 newly diagnosed AF patients and 101 patients with an established diagnosis of AF we followed up in our stroke center in Türkiye in terms of age, gender, CHA_2DS_2-VASC, and HAS-BLED scores, and the possible relationships between them. We also documented the treatment compliance of 101 patients with an established diagnosis of AF.

Methods

In our hospital, which has been actively working as a stroke center since 2016, every stroke case has been recorded in the database since 2017. Our population-based retrospective cohort study included 200 NVAF patients who had an ischemic cerebrovascular accident (CVA) between January 2018 and December 2021 in Istanbul, Ataşehir region. The data of our patients were obtained through the database. The Ethics Committee's approval of the study was received by the University of Health Sciences Fatih Sultan Mehmet

Training and Research Hospital Clinical Research Ethics Committee on February 25, 2021, with application file no. 26 of FSMEAH-KAEK. The study was conducted in accordance with the Declaration of Helsinki. Two hundred patients with AF that we retrospectively screened were divided into two main groups; patients with newly diagnosed AF and those with an established diagnosis of AF. Treatment choices at discharge of the patients in both groups were compared in terms of age, gender, CHA_2DS_2-VASC, and HAS-BLED scores, and treatment compliance was evaluated. These scores were divided into three main groups for easy comparison with the treatment choices. For CHA_2DS_2-VASC; the low-risk group was 0-1, the moderate-risk group was 2-3, and the highest-risk group was 4-5-6. For HAS-BLED; the low-risk group was 0-1, the high-risk group was 3-4-5, and the highest-risk group was 6-7-8. Number (n) and percentage (%) values were used to show demographic characteristics. Mean ± standard deviation values were used in descriptive statistics. Cross tables were created for the comparison of categorical variables according to the CHA_2DS_2-VASC and HAS-BLED scoring systems, and test statistics of number (n), percentage (%), and chi-square (χ^2) were given. IBM SPSS Statistics 21.0 (IBM Corp., released 2012; IBM SPSS Statistics for Windows, Version 21.0; Armonk, NY, USA) and MS-Excel 2007 programs were used for statistical analyses and calculations. The level of statistical significance was accepted as $p<0.05$.

Results

Two hundred AF patients were retrospectively included in the study. Ninety-nine patients had a stroke and were newly diagnosed with AF in our hospital, while 101 patients had already received the diagnosis of AF and had a stroke while using OAC or NOAC on a regular or irregular basis. The mean age of the individuals participating in the study was 76.98 years. More than half (60.5%, n=121) of the participants were female, and 39.5% (n=79) of them were male. Newly diagnosed AF patients' discharge treatments are summarised in Table 1.

We have most often preferred to prescribe OAC (59.6%) at the discharge of patients diagnosed with ischemic stroke and AF, and apixaban (22.2%) was the most preferred type of NOAC. The distribution percentage of the recently diagnosed 101 AF patients who used their anticoagulant drugs irregularly or skipped their drug doses was as follows: 22.7% warfarin sodium use lacking any effect on international normalized ratio (INR) values; 10.9% irregular use of rivaroxaban; 8.9% apixaban; 2% dabigatran; 1% edoxaban; and the remaining 55 patients had an ischemic stroke while regularly using NOACs (rivaroxaban, apixaban, edoxaban, and dabigatran) or warfarin sodium that maintained an effective range of INR levels (Table 2).

Table 1. Distribution of the anticoagulant drugs given to the patients with newly diagnosed atrial fibrillation

	n (%)
Anticoagulant drugs given	
Deceased	5 (5.1)
Warfarin sodium	59 (59.6)
Apixaban	22 (22.2)
Rivaroxaban	9 (9.1)
Edoxaban	4 (4.0)

Mostly NOACs were preferably prescribed at the discharge of both patients with the diagnosis of AF who had used their medications irregularly and had an ischemic stroke, and also warfarin sodium users with an ineffective range of INR (Table 3). For the vast majority of patients who had ischemic stroke under irregular use of any NOAC, as a second chance, the same NOAC was prescribed at their discharge. According to our findings, while the vast majority of irregular treatment users are on warfarin sodium, which requires strict blood screening and diet regulation, the other major group of regular treatment users is on one of the NOACs, which is rivaroxaban. The same drug was preferably prescribed at discharge for the respective percentages of patients who irregularly used rivaroxaban (80%), apixaban (100%), edoxaban (100%), and dabigatran (50%), but we didn't prefer warfarin sodium as a second chance in the irregular usage of warfarin sodium group. We mostly prefer apixaban as a second drug after irregular usage of warfarin sodium, like the newly diagnosed AF group's discharge treatment.

Evaluation of the possible relationship between anticoagulant choices and scoring systems; we analyzed the discharge treatment options of our patients with prior or newly diagnosed AF using CHA_2DS_2-VASC and HAS-BLED scores for possible statistical significance.

We divided the patients based on CHA_2DS_2-VASC scores to facilitate the statistical analysis into low (0-1), moderate (2–3), and high-risk (4-5–6) stroke groups. Similar to CHA_2DS_2-VASc classification, for HAS-BLED comparison to facilitate statistical analyses, the patients were divided into low (1-2), high (3-5), and very-high-risk (6-8) groups according to the HAS-BLED scoring system.

Table 2. Distribution of the anticoagulant drugs regularly and irregularly used by the patients with the diagnosis of atrial fibrillation

Anticoagulant drugs used	Regular drug users or patients with effective INR, n (%)	Irregular drug users or patients with ineffective INR, n (%)
Warfarin	10 (9.9)	23 (22.7)
Rivaroxaban	21 (20.8)	11 (10.9)
Apixaban	12 (11.9)	9 (8.9)
Edoxaban	3 (3)	1 (1)
Dabigatran	9 (8.9)	2 (2)
Total	55	46

Tablo 3. Discharge treatment of patients who were using warfarin with ineffective INR at admission

Anticoagulant drugs used	Patients (n)
Warfarin	2
Apixaban	9
Rivaroxaban	6
Edoxaban	3
Dabigatran	1
Deceased	2
Total	23

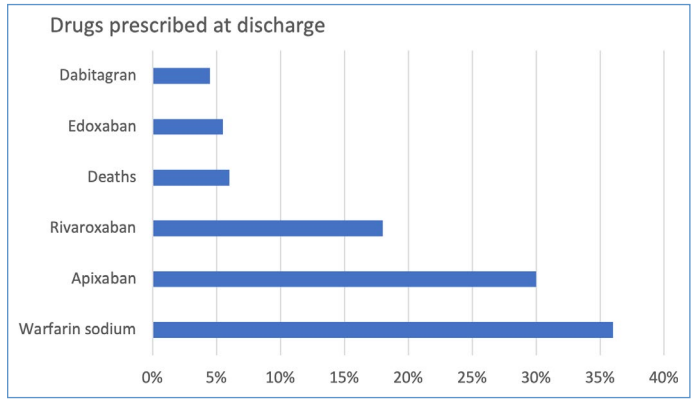

Figure 1. Anticoagulant drug treatments prescribed for all AF patients at discharge.

Among the newly diagnosed AF patients categorized according to the CHA_2DS_2-VASc risk stratification, 4 (50%) patients in the moderate risk group preferably received initial treatment with warfarin sodium and apixaban, while in the high-risk group, warfarin sodium (60.4%: n=55), apixaban (19.8%: n=18), rivaroxaban (9.9%: n=9), and edoxaban (4.4%: n=4). According to the CHA_2DS_2-VASc risk stratification, no statistically significant difference was found in terms of being in the high or moderate-risk group or the distribution of the drugs used in both groups. Similarly, there is no statistically significant difference between the CHA_2DS_2-VASc risk stratification grouping and the discharge treatment options of patients with irregular oral anticoagulant usage. According to HAS-BLED risk stratification, 101 individuals diagnosed with AF were included in low (8.9%: n=9), high (87.1%: n=88), and very high (4.0%: n=4) risk groups. Similar to the previous scoring system, according to the retrospective comparing method, there is no statistically significant difference in terms of the distribution of anticoagulants prescribed at discharge for newly diagnosed AF patients by grouping made according to the HAS-BLED classification. When the relationship between the distribution groups of 200 AF patients according to the CHA_2DS_2-VASc classification and their treatment options at discharge (summarized in Fig. 1) was examined, apixaban (43.8%: n=7), warfarin (31.3%: n=5), rivaroxaban (12.5%: n=2), and dabigatran (6.2%: n=1) were prescribed for the respective numbers of patients in the moderate risk group, and warfarin (36.4%: n=67), apixaban (28.8%: n=53), rivaroxaban (18.5%: n=34), and dabigatran (4.3%: n=8).

No statistically significant difference was found in the distribution of the anticoagulant drugs given to the patients at discharge in the risk groups determined based on the CHA_2DS_2-VASc classification. When the relationship between the distribution groups determined according to the HAS-BLED classification and the anticoagulant treatment options of 200 AF patients at discharge was examined, in the low-risk group, the indicated percentages of patients received warfarin sodium (50.0%: n=28), apixaban (28.6%: n=16), rivaroxaban (12.5%: n=7), and edoxaban (3.5%: n=2), while in the high-risk group, apixaban (30.9%: n=43), warfarin sodium (29.5%: n=41), rivaroxaban (20.9%: n=29), dabigatran (6.5%: n=9), and edoxaban (5.7%: n=8) were used. In the very high-risk group, the patients received warfarin (60.0%: n=3), apixaban, and edoxaban (20.0%: n=1 each). According to the HAS-BLED classification, no statistically significant difference was found in terms of the distribution of anticoagulant drugs given to all individuals at discharge.

Discussion

Vitamin K-dependent OAC, i.e., warfarin, with a history dating back to 1954, was used as the sole anticoagulant for a long time. While this treatment provides optimal anticoagulation and cardioembolism risk management, it is challenging for patients as it requires strict INR and treatment monitoring due to its interactions with nutrients or other drugs. A new group of anticoagulant therapies, which act through different mechanisms, entered the market as a result of comparative studies performed between 2008 and 2010. These drugs show activity through factor Xa inhibition (edoxaban, rivaroxaban, and apixaban) or direct thrombin inhibition (dabigatran). These drugs have advantages such as ease of use, unnecessary routine INR control, lesser drug-nutrient interactions, and a wider therapeutic range.[6,7] The disadvantages of these treatments are that they are more expensive and that there are insufficient studies on agents to be used to reverse their anticoagulant effects in cases of surgery or severe bleeding. While there is an antidote to reverse the effect of standard OACs, this is limited for NOACs. In addition, in our country, it is difficult to access these antidotes. Except for certain situations like mitral stenosis or valve changes, NOACs are recommended as the first step of anticoagulation.[8] In the presence of ischemic stroke or TIA (transient ischemic attack) with cardioembolic etiology, one of the NOAC treatments can be preferred instead of OAC, on a patient basis and considering the profit/loss ratio.[8] Additionally, switching to NOAC therapy may be considered in patients who cannot maintain the therapeutic INR level with OAC therapy, which is the most preferable treatment method rather than being a first-step treatment because of its cost-effectiveness as in our results.

Many comparative studies have been published since the introduction of NOAC treatment into our lives. In the RELY (2010) study, the benefit of dabigatran in ischemic stroke in AF patients was proven, and it was shown to be superior to warfarin in preventing the risk of stroke or systemic embolism. Compared to warfarin, dabigatran causes intracranial bleeding complications in patients at a lower rate, while the rate of gastrointestinal bleeding complications is higher, without any significant differences in the comparison of major bleeding rates caused by these two agents.[9] Rivaroxaban was approved after dabigatran in many countries, including ours. The efficacy of rivaroxaban was proven by the ROCKET-AF study performed in 2011. In this study, no significant difference was found between rivaroxaban and warfarin in terms of the prevention rate of stroke or systemic embolism, but as shown, rivaroxaban may lead to fewer intracranial bleeding complications.[10] A comparative study performed between apixaban and warfarin has shown that apixaban both prevents ischemic stroke and systemic embolism risk and causes fewer bleeding complications in AF patients, resulting in lower mortality rates.[11] Edoxaban was approved in 2015, and although its efficacy has been proven by studies, no significant difference was found compared to warfarin in terms of the prevention of ischemic stroke, systemic embolism, or bleeding risk.[12]

As far as we know, there is no definite information regarding the superiority of one NOAC treatment over another. Although there is no clear treatment algorithm, NOACs are preferred in clinical practice based on the individual characteristics of the patients. For example, dabigatran at a dose of 110 mg and apixaban are more frequently preferred in patients with higher HAS-BLED scores, while rivaroxaban is preferred more often in the elderly under multidrug therapy. As also supported by the AHA guidelines, apixaban is considered in the foreground in patients with renal dysfunction, and dabigatran at twice-daily doses of 150mg seems to be the best option in patients with higher stroke risk.[6]

Many risk-scoring systems have been developed for clinicians that can guide their treatment choices in clinical practice. Today, the CHA_2DS_2-VASc scoring system, whose validity has been proven by studies and also recommended by international guidelines, can define the risk of thromboembolic events in an individual, but any study cited in the literature used the risk categories of this scoring system to guide the selection of OAC or NOAC. HAS-BLED scoring is also one of the accepted scoring systems to predict the risk of bleeding when starting anticoagulant therapy in patients with AF. This scoring system is more often recommended for comparing the relative risk of stroke versus major bleeding. When we compiled the retrospective data of our patients, the vast majority of AF patients were women, which is different from the literature; also, our patients' mean ages are older than the literature.[3] Warfarin sodium (59.6%) was the most preferred drug treatment used at the time of discharge for newly diagnosed AF patients presenting with ischemic stroke, while apixaban (22.2%) was the most preferred anticoagulant drug among NOACs. While NOAC group drugs were preferred mostly as the discharge treatment of both patients with an established diagnosis of AF who experienced an ischemic stroke and warfarin sodium users with an ineffective INR range, the NOAC drug irregularly used by the

majority of patients who had an ischemic stroke has been prescribed again at discharge. In the presence of ischemic events despite regular anticoagulant drug use, perhaps due to familiarity with the drug, the anticoagulant drug was prescribed again at discharge. When we retrospectively analyzed the possible relationship between the oral anticoagulant options we prefer for our patients and the risk categories of the CHA_2DS_2-VASC and HAS-BLED scoring systems, we could not detect any significant correlation between HAS-BLED and CHA_2DS_2-VASc scores in terms of the retrospectively screened treatment options of 200 AF patients administered at discharge. Also, it was seen that the use of the drug in 1 or 2 dosages per day in the irregular use of our patients did not provide a significant difference in terms of irregular usage. The conduct of multicenter and prospective studies is needed to reveal whether the available scoring systems play a role in the decision-making process, intending to select the best treatment alternative for the patient.

Conclusion

The patients should be evaluated individually when choosing an oral anticoagulant to prioritize education aimed at the correct use of that drug rather than the selection of an appropriate drug.

Disclosures

Ethics Committee Approval: The Ethics Committee's approval of the study was received by the Health Sciences University Fatih Sultan Mehmet Training and Research Hospital Clinical Research Ethics Committee on February 25, 2021, with application file no. 26 of FSMEAH-KAEK. The study was conducted in accordance with the Declaration of Helsinki.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Use of AI for Writing Assistance: Not declared.

Authorship Contributions: Concept – I.K.A.; Design – C.E.; Supervision – I.K.A.; Materials – K.G.K., C.E.; Data collection &/or processing – I.K.A., L.R.; Analysis and/or interpretation – C.E., K.G.K.; Literature search – C.E.; Writing – I.K.A., C.E.; Critical review – I.K.A., L.R.

References

1. Coupland AP, Thapar A, Qureshi MI, Jenkins H, Davies AH. The definition of stroke. J R Soc Med 2017;110:9–12.
2. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35–41.
3. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: A global burden of disease 2010 study. Circulation 2014;129:837–47.
4. Gažová A, Leddy JJ, Rexová M, Hlivák P, Hatala R, Kyselovič J. Predictive value of CHA_2DS_2-VASc scores regarding the risk of stroke and all-cause mortality in patients with atrial fibrillation (CONSORT compliant). Medicine (Baltimore) 2019;98:e16560.
5. 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;138:1093–100.
6. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, et al. 2021 guideline for the prevention of stroke in patients with stroke and transient ıschemic attack: A guideline from the American Heart Association/American Stroke Association. Stroke 2021;52:e364–e467.
7. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: A meta-analysis of randomised trials. Lancet 2014;383:955–62.
8. Cheung CC, Nattel S, Macle L, Andrade JG. Management of atrial fibrillation in 2021: An updated comparison of the current CCS/CHRS, ESC, and AHA/ACC/HRS guidelines. Can J Cardiol 2021;37:1607–18.
9. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–51.
10. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883–91.
11. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981–92.
12. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093–104.