Gastroenterología y Hepatología 46 (2023) 621–627

Gastroenterología y Hepatología

www.elsevier.es/gastroenterologia

ORIGINAL ARTICLE

Impact of left atrial appendage closure in patients on anticoagulation for atrial fibrillation and recurrent or chronic gastrointestinal bleeding

Laura Gonzalez-Gonzalez[a], Anna Calm[a], Míriam Mañosa[a,d], Víctor Bazán[b,c], Andrea Borrellas[b,c], Xavier Carrillo[b,c], Felipe Bisbal[b,c], Nuria Vallejo[b,c], Fiorella Cañete[a,d], Margalida Calafat[a,d], Eugeni Domènech[a,d,e,*]

[a] *Gastroenterology Department, Hospital Universitari Germans Trias i Pujol, Badalona, Catalonia, Spain*
[b] *Cardiology Department, Hospital Universitari Germans Trias i Pujol, Badalona, Catalonia, Spain*
[c] *Centro de Investivación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain*
[d] *Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain*
[e] *Departament de Medicina, Universitat Autònoma de Barcelona, Barcelona, Spain*

Received 14 October 2022; accepted 8 February 2023

KEYWORDS
Left atrial appendage closure;
Atrial fibrillation;
Anticoagulation;
Chronic gastrointestinal bleeding

Abstract
Background: Oral anticoagulation in non-valvular atrial fibrillation is associated with an increased risk of bleeding, particularly gastrointestinal bleeding, leading to treatment withdrawal in up to 50% of patients and putting them at risk of embolic events. Left atrial appendage closure (LAAC) can be an alternative to chronic anticoagulation. We aim to describe the impact of LAAC in patients with gastrointestinal bleeding (GIB) or chronic iron deficiency anaemia (CIDA) on healthcare resources consumption.
Methods: Observational retrospective study of patients who underwent LAAC for GIB or CIDA at a single centre.
Results: Nineteen patients with a median age of 74 years and a median Charlson score of six points were included in the study. Angiodysplasias were the most frequent cause of GIB or CIDA. The procedural success rate of LAAC was 100% with a median anticoagulant and antiplatelet treatment duration of 92 days. One year after the LAAC, we found a significant improvement in the lowest haemoglobin concentration and a reduction in the number of red blood cells transfusion, hospital admissions due to GIB and CIDA and the number of endoscopic examinations. One patient died due to a pulmonary thromboembolism. No deaths related to GIB were observed.
Conclusions: LAAC seems to be a safe and effective alternative to anticoagulation in patients with GIB or CIDA.

* Corresponding author.
E-mail address: eugenidomenech@gmail.com (E. Domènech).

PALABRAS CLAVE
Cierre de la orejuela izquierda;
Fibrilación auricular;
Anticoagulación;
Sangrado gastrointestinal crónico

Impacto del cierre de la orejuela izquierda en pacientes anticoagulados por fibrilación auricular y con sangrado gastrointestinal recurrente o crónico

Resumen
Introducción: La anticoagulación oral en la fibrilación auricular no valvular se asocia a un incremento del riesgo de sangrado, especialmente gastrointestinal, lo que conlleva la retirada del tratamiento hasta en el 50% de los pacientes e implica un mayor riesgo de padecer un evento embólico. El cierre de la orejuela izquierda (COI) puede ser una alternativa a la anticoagulación crónica. Nuestro objetivo es describir el impacto del COI en pacientes con sangrado gastrointestinal (SGI) o anemia crónica ferropénica (ACF) en el consumo de recursos sanitarios.
Métodos: Estudio observacional retrospectivo de pacientes sometidos a COI por SGI o ACF.
Resultados: Diecinueve pacientes con una mediana de edad de 74 años y una mediana del índice de Charlson de 6 puntos fueron incluidos en el estudio. Las angiodisplasias fueron la causa más frecuente de SGI o ACF. La tasa de éxito técnico del COI fue del 100%, con una duración mediana del tratamiento anticoagulante y antiagregante de 92 días. Tras un año del COI, se observó una mejoría significativa del valor mínimo de hemoglobina, así como una reducción en el número de transfusiones de concentrados de hematíes, en la necesidad de hospitalización por SGI o ACF y en el número de endoscopias. Un paciente falleció debido a un tromboembolismo pulmonar. Ningún paciente falleció por SGI.
Conclusiones: El COI parece una alternativa segura y efectiva a la anticoagulación en pacientes con SGI o ACF.

Introduction

Nonvalvular atrial fibrillation (AF) is the most common arrhythmia[1,2] with an estimated worldwide prevalence of 33 million people.[3] Moreover, as a consequence of the ageing population, it is expected to double in the next two decades,[4] since its incidence increases with age. AF is associated with high mortality and morbidity rates due to the increased risk of congestive heart failure, systemic thromboembolism and, particularly, cardioembolic stroke, which is increased 5-fold as compared to the background population.[4–6] Oral anticoagulation with vitamin K antagonists (VKA) or nonvitamin K dependent oral anticoagulants (NOAC) is efficient for preventing strokes and embolic complications in patients with AF. However, oral anticoagulation is also associated with an increased risk of bleeding, which is mainly gastrointestinal, intracranial or from other locations.[4,7]

In order to improve the efficacy of anticoagulation and minimise the risk of bleeding, two clinical scores are routinely used in daily clinical practice for oral anticoagulation decision-making. The CHA_2DS2-VASc index was developed to assess the risk of cardioembolic events, reflecting a significant risk when it is over two points in men and three in women, these thresholds being the proper indication for anticoagulation.[5,8] On the other hand, the HAS-BLED index, which was developed to assess the risk of anticoagulation-related bleeding events, considers there to be a high risk of bleeding when it is greater than two. Higher scores do not contraindicate anticoagulation but warrant caution, particularly when additional risk factors for bleeding are present (i.e., concomitant antiaggregation or the use of non-steroidal anti-inflammatory drugs).[5]

Since both indexes share a number of variables, it is not unusual for patients with high CHA_2DS2-VASc to also have high HAS-BLED scores. In fact, up to 50% of the patients with AF are not on anticoagulation in spite of having an established indication according to guidelines, mainly due to bleeding complications that force treatment discontinuation.[9] Nonetheless, these patients remain at risk of suffering a preventable cardioembolic event[10] and therapeutic alternatives for these patients are needed. Since most thrombi leading to embolic events are originated in the left atrial appendage (LAA),[11] the devices used for left atrial appendage closure (LAAC) may serve as an alternative to chronic anticoagulant treatment in patients with a high risk or a past history of bleeding complications. Two randomised, controlled, non-inferiority studies, the PROTECT-AF[12–14] and the PREVAIL[15] trials, demonstrated that LAAC and warfarin are equivalent in terms of preventing stroke, systemic embolism, and mortality due to cardiovascular disease or any other cause. LAAC was licensed for the first time in March 2015 by the Food and Drug Administration for the prevention of cardioembolic stroke in patients with AF and a CHA_2DS_2-VASc score ε 3.

Since then, some long-term studies confirmed the reduction in thromboembolic and major bleeding complications after LAAC implantation. In the prospective, 2-year follow-up study from the Iberian Registry,[16] the observed complications were compared to the expected as for the CHA_2DS_2-VASc and HASBLED scores. Moreover, the reduction in the bleeding risk was even more significant after the second year after LAAC implantation, probably due to the discontinuation of antithrombotic therapies. This was also observed in the prospective, 4-year follow-up of the PRAGUE-17 randomised, non-inferiority trial[17]

that compared LAAC vs. NOAC (almost exclusively Apixaban). A significant reduction of major bleeding events in the LAAC group was noticed, particularly those related to non-procedural bleeding and after completing the antithrombotic strategy regimen.

Although growing experience in the clinical impact of LAAC is available, there is scarce data specifically evaluating the clinical impact of LAAC in patients who are not good candidates for anticoagulation and with recurrent gastrointestinal bleeding (GIB) or chronic iron deficiency anaemia.

We aim to describe the clinical characteristics of patients undergoing LAAC due to chronic or recurrent GIB and its impact on transfusion requirements, hospital admissions, endoscopic, radiological or surgical rescue treatments and mortality, as well as procedure-related complications.

Methods

This is an observational, descriptive and retrospective study based on a cohort of patients who underwent LAAC for GIB or chronic iron deficiency anaemia at the Hospital Universitari Germans Trias i Pujol between April 2015 and October 2021. The study was approved by the local Ethics Committee.

Study population

Patients were identified from the local LAAC registry. The inclusion criteria were as follows: (1) LAAC indicated because of recurrent macroscopically GIB (melena, hematochezia, or rectal bleeding) or chronic iron deficiency anaemia (defined as a haemoglobin (Hb) < 13 g/dL in men and <12 g/dL in women) of >6 months with or without macroscopically GIB and no other known aetiology for the anaemia; and (2) follow-up (as defined by the last blood cell count) of at least 12 months or until death if it occurred before. A careful review of all medical records was carried out, excluding those patients undergoing LAAC for reasons other than GIB or iron deficiency anaemia and those patients who were lost to follow-up.

The following variables were registered: demographic, main comorbidities (severe chronic diseases and vascular risk factors), CHA_2DS_2-VASc, HAS-BLED and Charlson scores, type and duration of anticoagulant and antiplatelet treatment, GIB-related features, technical-related complications of LAAC, post-LAAC anticoagulant and antiplatelet therapeutic strategy and duration of the treatment, and thromboembolic complications. In order to assess changes in healthcare resources use after LAAC, we collected the number of blood transfusions, the need for intravenous iron, treatment with somatostatin analogues, and hospital admissions due to GIB and GIB-related complications, within one year before and after the LAAC procedure, as well as death and its aetiology.

Left atrial appendage closure procedure

After an initial positive evaluation for LAAC by a multidisciplinary committee including cardiologists, gastroenterologists, neurologists, haematologists and nephrologists, patients underwent a transoesophageal echocardiography or cardiac computed tomography to determine atrium and left atrial appendage size, as well as to rule out the presence of intracavitary thrombus. Subsequently, the LAAC procedure was performed using the AMPLATZER™ Amulet™ device (St. Jude Medical, Inc., USA).

After left atrial appendage closure, the multidisciplinary committee decided the anticoagulation and antiplatelet strategy. Since the first LAAC was performed at our centre in 2015, an increasing body of literature regarding treatment strategies after this procedure has been published. The treatment decision was made following clinical guidelines and taking into account comorbidities and the aetiology of GIB. Two different strategies were usually followed: either a dual antiplatelet regimen with acetylsalicylic acid (AAS) 100 mg/day plus clopidogrel 75 mg/day for six weeks followed by monotherapy with clopidogrel 75 mg/day for six months or anticoagulation with a NOAC alone or in combination with one antiplatelet drug for three months.

Statistical analysis

Continuous variables are described by mean and standard deviation or median and interquartile range, as needed. For categorical variables, frequencies and confidence intervals were calculated. Categorical variables were compared using the Chi-square test and continuous variables using the Student's *t*-test.

Results

During the study period, 102 patients were evaluated by the local Committee of LAAC. Among them, LAAC was proposed due to recurrent GIB or CIDA while on oral anticoagulation for 47 patients in whom LAAC was finally performed in 21. Two patients were lost to follow-up early after the procedure (Fig. 1).

Characteristics of the cohort

The main characteristics of the cohort are summarised in Table 1. As expected, our cohort mainly featured elderly males with a high median Charlson score (greater than eight points in 75% of the patients), with a predominance of cardiovascular comorbidities. All patients had a history of nonvalvular AF, which was permanent in 80% of cases. The median CHA_2Ds_2-VASc score was of four points (range, 2–7) which reflected the indication for anticoagulation; however, the median HAS-BLED index was also high (median of four points, range 2–6).

All patients had previously been treated with VKA (acenocumarol or warfarin) for AF, which was switched to a NOAC in 84% of cases in an attempt to improve the clinical course of GIB or CIDA. The most frequently used NOAC were apixaban in 42% and dabigatran in 26% of cases. Anticoagulant therapy was switched at least twice in 21% of patients, using more than one NOAC. However, up to 53% of patients discontinued the anticoagulant treatment immediately before the LAAC due to GIB or CIDA. Moreover, in agreement with the high rate of cardiovascular comorbidities, 58% of the patients also used antiplatelet therapy,

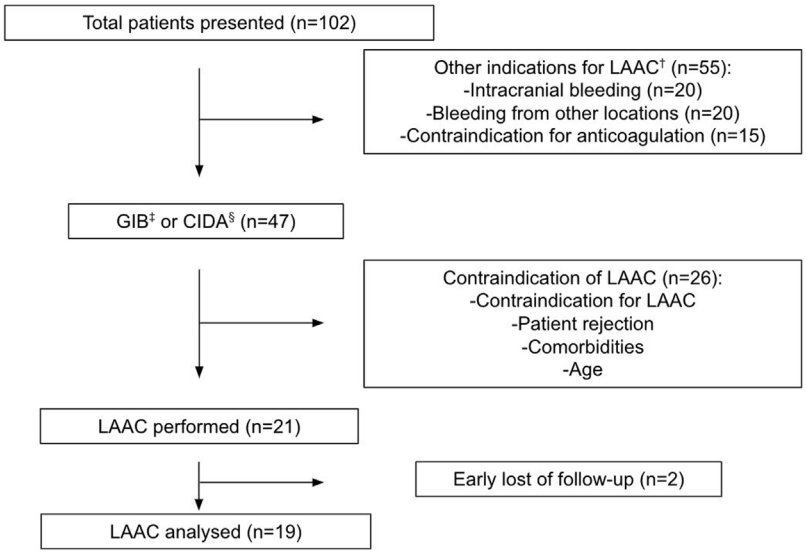

Figure 1 Study flowchart.

Table 1 Clinical and demographic characteristics of the patients ($n = 19$). Results are expressed in absolute numbers (frequencies) and median (range).

Age (years)	74 (65–86)
Male gender	13 (68)
Arterial hypertension	16 (84)
Diabetes mellitus	11 (58)
Chronic obstructive pulmonary disease	11 (58)
Ischaemic heart disease	14 (74)
Cerebral stroke	5 (26)
Peripheral vasculopathy	4 (21)
Previous pulmonary embolism	3 (16)
Embolism in other locations[a]	1 (5)
Charlson score	6 (3–13)

[a] Retinal artery embolism.

Table 2 Aetiology of gastrointestinal bleeding ($n = 19$). Results expressed in absolute numbers (frequencies).

Small bowel angiodysplasia	4 (21)
Gastric angiodysplasia	1 (5)
Colonic angiodysplasia	1 (5)
Angiodysplasia of multiple location	4 (21)
Obscure gastrointestinal bleeding	4 (21)
Chronic iron deficiency anaemia	1 (5)
Diverticular bleeding	1 (5)
Hemorrhoidal bleeding	1 (5)
Gastric *Dieulafoy*	1 (5)
Anastomotic ulcer[a]	1 (5)

[a] Chronic anastomotic colonic ulcer in a patient with Chagas disease.

which was discontinued in 91% of cases before LAAC. None of the patients were on dual antiplatelet therapy.

Characteristics of the gastrointestinal bleeding before left atrial appendage closure

The causes of GIB and CIDA in our cohort are listed in Table 2. Of note, gastrointestinal angiodysplasia was the most frequent cause (53% of patients), and was usually multiple or located at the small bowel. Five of these patients with angiodysplasias had been undergoing treatment with somatostatin analogues before the LAAC and four of them continued the treatment after the procedure (50% of those potentially candidates to this treatment). The bleeding source could not be identified after a complete study with upper and lower gastrointestinal endoscopy, capsule endoscopy and CT-scan in 21% of cases (obscure gastrointestinal bleeding).

All the patients had a past history of multiple red blood cell transfusions due to GIB/CIDA. Moreover, 79% also needed intravenous iron therapy. All the patients underwent at least one endoscopic examination before the LAAC (a median of two gastroscopies [range, 0–4], two colonoscopies [range, 0–7] and one endoscopic capsule [range, 0–2]). The main clinical outcomes and need for healthcare resources within one year prior to LAAC are summarised in Table 3.

Clinical outcomes and use of healthcare resources after left atrial appendage closure

No deaths related to the procedure were registered and there were only two early complications related to the LAAC procedure: a mild pericardial effusion that did not require any specific intervention and an acute urinary retention that resolved after a temporary bladder catheterization. NOAC as monotherapy for three months was the most frequent treatment schedule after LAAC (eight patients), followed by dual antiplatelet treatment for six weeks and clopidogrel for six months (five patients). All the regimens used to prevent thromboembolic events after LAAC are summarised in Table 4. Median anticoagulant and antiplatelet treatment duration after LAAC was 92 days (range, 2–183). Antiplatelet treatment was not discontinued in two patients

Table 3 Clinical outcomes and use of healthcare resources before and after left atrial appendage closure.

	12 months prior to LAAC[a]	12 months following LAAC[a]	*P*-value
Lowest haemoglobin concentration (g/dL)	6.6 (4.0–9.0)	10.8 (6.9–16.2)	$P < 0.0001$
Red blood cell transfusion	8 (0–27)	2 (0–13)	$P = 0.005$
Patients not needing transfusions	4	8	$P = 0.018$
Need of intravenous iron treatment	15	7	$P = 0.086$
Number of hospital admissions related to GIB[b]/CIDA[c] complications	3 (2–12)	0 (0–3)	$P = 0.002$
Number of endoscopic examinations	2 (0–9)	0 (0–4)	$P = 0.003$

[a] Left atrial appendage closure.
[b] Gastrointestinal bleeding.
[c] Chronic iron deficiency anaemia.

Table 4 Summary of post-LAAC antiplatelet and anticoagulation strategies followed in our study. Results expressed in absolute numbers (frequencies) and percentages (%).

AAS[a] + Clopidogrel	5 (26)
NOAC	8 (42)
NOAC[b] (Apixaban) + Clopidogrel	2 (11)
Clopidogrel alone	2 (11)
LMWH[c]	1 (5)
LMWH + AAS	1 (5)

[a] Acetylsalicylic acid.
[b] Non-vitamin K dependant oral anticoagulants.
[c] Low molecular weight heparin.

due to severe peripheral vasculopathy. All patients who did not die followed ultrasonographic device monitoring within 3–12 months after the procedure. No clinically relevant thrombosis related to the device was noticed.

Seven patients (37%) required early withdrawal of post-procedural treatment due to recurrent GIB or worsening of anaemia during follow up (four on anticoagulation and three on antiplatelet treatment). The median time to bleeding recurrence that required withdrawal of the anticoagulant/antiplatelet treatment was 26 days (range 2–183 days). No differences were observed in bleeding recurrence rates between patients on antiplatelet or anticoagulant treatment (two vs. three patients; $p = 0.1$).

Median time of follow-up was 10 months (range, 1–77). Regarding clinical outcomes and the need for healthcare resources in the year following the LAAC, there was a significant improvement in the lowest haemoglobin concentration ($p < 0.0001$), the number of transfusions of red blood cells ($p = 0.005$), the number of hospital admissions due to GIB or anaemia-related complications ($p = 0.002$) and the number of endoscopic examinations ($p = 0.003$). There were eight patients in whom no red blood cell transfusions were required within the year following the LAAC (Table 3). No patients required surgical or radiologic intervention due to bleeding during the follow-up.

During follow-up, only one thromboembolic event occurred (pulmonary thromboembolism) nine months after LAAC. This was a 74-year-old female with paroxysmal AF and a CHA_2DS_2-VASc score of four and a HAS-BLED score of three who discontinued antiplatelet treatment earlier than expected due to GIB. Four months later she presented with a pulmonary thromboembolism and died due to congestive heart failure.

Seven patients (37%) died during follow-up, five of them within the first year after the LAAC procedure. In addition to the above-mentioned case of pulmonary thromboembolism, there were four deaths secondary to cardiac arrest in patients with previous structural cardiopathy (after two, nine and 77 months of follow-up), one due to severe cardiac effusion and cardiac tamponade (two months after the LAAC) one due to a septic shock (six months after the procedure) and one of unknown cause (20 months from the procedure).

Discussion

The management of recurrent GIB or chronic iron-deficiency anaemia in patients on anticoagulation therapy due to non-valvular AF poses a medical challenge since the balance between bleeding and thrombotic risks is complex. Since the GIB recurrence rate has been reported to be up to 40% within one year after the previous GIB event,[18] anti-thrombotic alternatives to anticoagulation therapy are needed.

Many studies have shown that LAAC can be an alternative to anticoagulation in patients suffering from GIB.[13,15,19,20] However, most of these studies were performed by cardiologists and only include patients with ''major gastrointestinal bleeding'', which is a vague definition, and their results cannot usually be extrapolated to gastroenterologists' clinical practice. Therefore, there exists the need to assess the usefulness of LAAC in patients who are anticoagulated and have persistent or recurrent GI bleeding or CIDA.

In line with the results of the Iberian Registry in 2014,[16] our study also shows that LAAC with the Amplatzer Amulet® device can reduce bleeding complications and use of healthcare resources due to GIB. In comparison to this study, we observed a higher rebleeding rate during the first year after LAAC (37% vs. 9.5%). These differences may be explained by our small sample size, the heterogeneity in post-LAAC antithrombotic therapy in our study and the fact that we only included those patients with a previous history of GI bleeding, which justifies a greater tendency to rebleeding. On the other hand, regarding ischaemic or thromboembolic

complications, the difference between both studies was less (5% vs. 3.9%).

Faroux et al.,[21] reported the results of an observational, multicentre study in which patients with a previous major episode of GIB underwent LAAC to discontinue anticoagulation. Unfortunately, the study did not provide the aetiology of GIB but only its anatomic location (upper, lower, upper and lower, or unknown). The authors found that global GIB recurrence was 55.8% and identified lower gastrointestinal source of GIB and chronic renal disease as risk factors for GIB recurrence. Interestingly, they observed a lower risk of recurrence of GIB as compared to other studies among patients with GIB in whom LAAC was not performed and anticoagulant treatment was maintained after the first GIB episode. Our results are close to those of Faroux et al., regarding GIB recurrence. Nevertheless, it must be taken into account that some of our patients were not treated with anticoagulants immediately before LAAC and this may bias our results as all these patients were put on anticoagulation or antiplatelet therapy after the procedure, increasing the risk of GIB for some months as compared to immediately before LAAC. In line with the above-mentioned study, we did not observe differences in GIB recurrence regarding the post-LAAC anti-thrombotic schedule. However, the small sample size in our study does not allow us to reach robust conclusions and the adequate post-LAAC anti-thrombotic regimen requires further evaluation. In this sense, some studies suggest that simple antiplatelet therapy may be associated with a lower rate of GIB recurrence without increasing the risk of thrombosis of the device.[22]

Although some authors have proposed that LAAC may decrease the severity of GIB due to the possibility of discontinuing anticoagulation without increasing thromboembolic risk,[13,15] our study is the first to assess the impact of LAAC on healthcare resources related to acute, recurrent and chronic GIB or CIDA. Interestingly, we observed a significant decrease in transfusion requirements, the need for hospital admission and endoscopic treatment, and an improvement in the haemoglobin concentration after the LAAC procedure. Of note, these are well-established and robust endpoints to assess the clinical impact of the procedure in this population. The high mid-term mortality in our population may question the futility of performing such an invasive procedure in a so fragile population. This should highlight the need for a multidisciplinary committee to be in charge of decision-making for LAAC indication, which is also a strength of our study. On the other hand, our study has several limitations related mainly to its retrospective design and small sample size. In addition, during the study period, different anticoagulation/antiaggregation regimens were used and this might influence the GIB recurrence rate. Moreover, although angiodysplasias were the cause of GIB in most of our patients, we included all GIB regardless of their aetiology, leading to a very heterogeneous population as every cause of GIB behaves differently. Finally, in spite of our robust endpoints, blood transfusion or hospital admission decision-making may have been biassed by the clinical judgement of the treating physician.

In summary, we observed that LAAC can be an efficient alternative to anticoagulation in patients with AF and chronic or recurrent GIB or CIDA. Prospective, controlled studies with pre-defined antiplatelet/anticoagulant post-LAAC schedules are warranted to confirm our results before establishing this clinical scenario as an indication for LAAC.

Funding

This research has not received specific aid from public sector agencies, the commercial sector, or non-profit entities.

Conflicts of interest

None.

Acknowledgments

We thank the Gastroenterology and Cardiology departments for their contribution in the elaboration of this paper.

References

1. De Backer O, Loupis AM, Ihlemann N, Vejlstrup NG, Søndergaard L, Franzen OW. Percutaneous left atrial appendage closure for stroke prevention. Dan Med J. 2014;61:A4879. PMID: 25162439.
2. Black-Maier E, Piccini JP, Granger CB. Left atrial appendage closure: a therapy uniquely suited for specific populations of patients with atrial fibrillation. J Cardiovasc Electrophysiol. 2019;30:2968–76, http://dx.doi.org/10.1111/jce.14182. PMID: 31520437.
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, http://dx.doi.org/10.1161/circulationaha.113.005119. PMID: 24345399.
4. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 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 Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014;64:e1–76, http://dx.doi.org/10.1016/j.jacc.2014.03.022. Epub 2014 March 28. Erratum in: J Am Coll Cardiol. 2014;64:2305–7. PMID: 24685669.
5. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. ESC Committee for Practice Guidelines (CPG). 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J. 2012;33:2719–47, http://dx.doi.org/10.1093/eurheartj/ehs253. Epub 2012 August 24. Erratum in: Eur Heart J. 2013 Mar;34(10):790. Erratum in: Eur Heart J. 2013;34(36):2850–1. PMID: 22922413.
6. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991;22:983–8, http://dx.doi.org/10.1161/01.str.22.8.983. PMID: 1866765.
7. Marini C, De Santis F, Sacco S, Russo T, Olivieri L, Totaro R, et al. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. Stroke. 2005;36:1115–9, http://dx.doi.org/10.1161/01.STR.0000166053.83476.4a. PMID: 15879330.
8. 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:e125–51, http://dx.doi.org/10.1161/CIR.0000000000000665. Epub 2019 January 28. Erratum in: Circulation. 2019 Aug 6;140(6):e285. PMID: 30686041.

9. Kachroo S, Hamilton M, Liu X, Pan X, Brixner D, Marrouche N, et al. Oral anticoagulant discontinuation in patients with nonvalvular atrial fibrillation. Am J Manag Care. 2016;22:e1–8. PMID: 26799200.
10. Dar T, Yarlagadda B, Vacek J, Dawn B, Lakkireddy D. Management of Stroke risk in atrial fibrillation patients with bleeding on oral anticoagulation therapy-role of left atrial appendage closure, octreotide and more. J Atr Fibrillation. 2017;10:1729, http://dx.doi.org/10.4022/jafib.1729. PMID: 29487685.
11. Wintgens LIS, Vorselaars VMM, Klaver MN, Swaans MJ, Alipour A, Rensing BJWM, et al. Left atrial appendage closure in atrial fibrillation patients with prior major bleeding or ineligible for oral anticoagulation. Neth Heart J. 2019;27:613–20, http://dx.doi.org/10.1007/s12471-019-1295-5. PMID: 31187455.
12. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, et al., PROTECT AF Investigators. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. Lancet. 2009;374:534–42, http://dx.doi.org/10.1016/S0140-6736(09)61343-X. Erratum in: Lancet. 2009 November 7;374(9701):1596. PMID: 19683639.
13. Reddy VY, Sievert H, Halperin J, Doshi SK, Buchbinder M, Neuzil P, et al., PROTECT AF Steering Committee and Investigators. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. JAMA. 2014;312:1988–98, http://dx.doi.org/10.1001/jama.2014.15192. Erratum in: JAMA.2015 March 10;313(10):1061. PMID: 25399274.
14. Reddy VY, Doshi SK, Sievert H, Buchbinder M, Neuzil P, Huber K, et al., PROTECT AF Investigators. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-year follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) Trial. Circulation. 2013;127:720–9, http://dx.doi.org/10.1161/circulationaha.112.114389. PMID: 23325525.
15. Holmes DR Jr, Kar S, Price MJ, Whisenant B, Sievert H, Doshi SK, et al. Prospective randomized evaluation of the Watchman left atrial appendage closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. J Am Coll Cardiol. 2014;64:1–12, http://dx.doi.org/10.1016/j.jacc.2014.04.029. Erratum in: J Am Coll Cardiol. 2014 Sep 16;64(11):1186. PMID: 24998121.
16. López Mínguez JR, Asensio JM, Gragera JE, Costa M, González IC, de Carlos FG, et al. Two-year clinical outcome from the Iberian registry patients after left atrial appendage closure. Heart. 2015;101:877–83, http://dx.doi.org/10.1136/heartjnl-2014-306332. Epub 2015 January 8. PMID: 25573984.
17. Osmancik P, Herman D, Neuzil P, Hala P, Taborsky M, Kala P, et al., PRAGUE-17 Trial Investigators. 4-Year outcomes after left atrial appendage closure versus nonwarfarin oral anticoagulation for atrial fibrillation. J Am Coll Cardiol. 2022;79:1–14, http://dx.doi.org/10.1016/j.jacc.2021.10.023. Epub 2021 November 5. PMID: 34748929.
18. Lai KC, Lam SK, Chu KM, Hui WM, Kwok KF, Wong BC, et al. Lansoprazole reduces ulcer relapse after eradication of Helicobacter pylori in nonsteroidal anti-inflammatory drug users – a randomized trial. Aliment Pharmacol Ther. 2003;18:829–36, http://dx.doi.org/10.1046/j.1365-2036.2003.01762.x.
19. Wintgens LIS, Vorselaars VMM, Klaver MN, Swaans MJ, Alipour A, Rensing BJWM, et al. Left atrial appendage closure in atrial fibrillation patients with prior major bleeding or ineligible for oral anticoagulation. Neth Heart J. 2019;27:613–20, http://dx.doi.org/10.1007/s12471-019-1295-5. PMID: 31187455.
20. Lempereur M, Aminian A, Freixa X, Gafoor S, Shakir S, Omran H, et al. Left atrial appendage occlusion in patients with atrial fibrillation and previous major gastrointestinal bleeding (from the Amplatzer Cardiac Plug Multicenter Registry). Am J Cardiol. 2017;120:414–20, http://dx.doi.org/10.1016/j.amjcard.2017.04.046. PMID: 28595859.
21. Faroux L, Cruz-González I, Arzamendi D, Freixa X, Nombela-Franco L, Peral V, et al. Incidence, predictors, and clinical impact of bleeding recurrence in patients with prior gastrointestinal bleeding undergoing LAAC. Pacing Clin Electrophysiol. 2021;44:1216–23, http://dx.doi.org/10.1111/pace.14293. Epub 2021 June 24. PMID: 34110038.
22. Korsholm K, Nielsen KM, Jensen JM, Jensen HK, Andersen G, Nielsen-Kudsk JE. Transcatheter left atrial appendage occlusion in patients with atrial fibrillation and a high bleeding risk using aspirin alone for post-implant antithrombotic therapy. EuroIntervention. 2017;12:2075–82, http://dx.doi.org/10.4244/EIJ-D-16-00726. PMID: 27973336.