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REVIEW ARTICLE

Stroke and atrial fibrillation: An update

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Abstract

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice. AF is associated with an increased risk of cardiovascular disease, heart failure, stroke, cognitive impairment and dementia, and mortality. Individuals with AF have a 5-fold risk of ischemic stroke, and AF-related strokes are associated with greater disability and mortality compared with strokes from other causes. Moreover, the burden of AF and AF-related stroke on patients, their caregivers, health-care systems, and society is significant and projected to increase in the coming decades due to the rapid growth of the ageing population. The care and management of patients with AF and AF-related stroke are challenging, often involving complex decision-making to weigh the risks and benefits of various treatment and prevention strategies. This topical review focuses on the latest science and advances in AF and AF-related stroke and identifies knowledge gaps and future directions of continued research.

Keywords: *Ischemic stroke. Hemorrhagic stroke. Atrial fibrillation. Prevention. Cerebrovascular disease. Anticoagulation.*

Actualización en ictus y fibrilación auricular

Resumen

La Fibrilación Auricular (FA) es la arritmia sostenida mas común en la practica clínica. La FA se asocia a un riego incrementado de enfermedad cardiovascular, falla cardiaca, enfermedad cerebrovascular, deterioro cognitivo y demencia. Los individuos con FA tienen un riesgo cinco veces mayor de ictus, y los infartos isquémicos asociados a la FA causan mayor discapacidad y mortalidad comparado con otras causas de ictus isquémico. Se estima que las consecuencias y la carga de la FA y el ictus ocasionado por la FA en pacientes, sus familias, la sociedad y el sistema de salud, se incrementara de manera importante en las próximas décadas dado el incremento de la población añosa, la cual tiene un riesgo aumentado de FA. El manejo de los pacientes con ictus y FA es complejo dado el riesgo de hemorragia en pacientes con enfermedad cerebrovascular, particularmente en las etapas tempranas después del ictus. Esta revisión temática se enfoca en avances recientes en la terapéutica del ictus asociado a FA e identifica direcciones futuras de investigación.

Palabras clave: *Ictus cerebral. Derrame cerebral. Fibrilación auricular. Prevención. Anticoagulación.*

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Introduction

Atrial fibrillation (AF) is common, affecting an estimated 37.6 million individuals globally in 2017[1], an increase from 33.5 million individuals in 2010[2]. The prevalence of AF increases with age, nearly doubling every decade after age 60 years[3]. As people are living longer and the ageing population continues to grow rapidly, the prevalence of AF is projected to nearly triple by the year 2050[4]. Similarly, the burden of AF posed by the increased risk of cardiovascular disease, heart failure, stroke, cognitive impairment and dementia, and mortality is also expected to increase in parallel over the ensuing decades[4].

The treatment of patients with AF and AF-related stroke is complex, and the burden on patients, caregivers, health-care systems, and society is high. Although there have been significant scientific advances in the area of AF and cardioembolic stroke recently, many key knowledge gaps remain. In this topical review, an overview of AF and AF-related stroke will be discussed, with an emphasis on treatment, prevention, screening, special considerations, and future research directions.

Risk factors for AF and stroke

Increased age and male sex are the strongest non-modifiable risk factors for AF. Male sex is associated with a 1.5-fold risk of developing AF and 2-fold higher incidence compared with female sex[5,6]. Although the overall incidence, prevalence, and age-adjusted lifetime risk of AF is higher in men, there are more women than men with AF due to differences in Regarding other non-modifiable risk factors, the literature suggests that white men have a higher incidence of AF; however, black patients have a higher risk of death related to AF and a higher risk of AF-related stroke[7].

Common modifiable risk factors for AF include hypertension, diabetes, obesity, cardiovascular disease, smoking, and alcohol use. Similarly, these same risk factors increase the risk of stroke in patients with AF. Women with AF tend to be older and have more hypertension, hyperlipidemia, and obesity, while men with AF tend to have more coronary artery disease, left ventricular dysfunction, and chronic obstructive pulmonary disease[5].

AF is associated with a 5-fold risk of ischemic stroke[8], one of the most feared and debilitating sequelae of the arrhythmia. AF accounts for approximately 20-25% of all ischemic strokes, though the frequency of AF increases to approximately 40% in ischemic stroke patients ≥ 80 years old[9]. Risk factors for stroke in the setting of AF include increased age, female sex, hypertension, heart failure, diabetes, and history of cardiovascular or cerebrovascular ischemic events. Women with AF have a higher risk of stroke compared with men, which is thought to be mediated by increased age and vascular risk factors[10-14]. Moreover, AF-related stroke tends to be more severe in women, and more women than men die or are disabled from AF-related stroke every year[15].

Risk stratification schemes, such as the CHA_2DS_2-VASc score, assist in assessing the risk of stroke and systemic embolism in AF patients, giving weight to common risk factors (Table 1). The American Heart Association and American Stroke Association guidelines recommend using the CHA_2DS_2-VASc score for risk stratification to guide the use of anticoagulants for the prevention of stroke and systemic embolism[16].

Mechanisms and clinical presentation of stroke in AF

AF is characterized by irregular atrial activity, resulting in abnormal and irregular atrial contractions. Several factors, such as enlarged atrial size, atrial fibrosis, chronic inflammation, and upregulation of ion channel subunits, contribute to the development and maintenance of AF. Irregularities in atrial contraction associated with AF increase the risk of stasis of blood flow and thrombus formation, thereby predisposing to stroke and systemic embolism. Over 90% of thrombi secondary to AF arise from the left atrial appendage[17]. There is emerging evidence suggesting that atrial cardiopathy, characterized by structural, contractile, architectural, or electrophysiological changes within the atria, may contribute to stroke through thrombus formation even in the absence of AF[18,19]. The lack of temporal association between implantable device-detected AF and stroke events supports the notion that the thrombi may arise from the dysfunctional atria and atrial appendage rather than from the AF itself[20,21]. In some cases, the stroke itself may contribute to the development of AF, and AF detected after stroke may have a different risk profile for recurrent thromboembolic events[19,22].

AF can be paroxysmal or sustained; however, the risk of stroke is similar regardless of AF type. Although generally considered a “silent” condition, up to 60% of individuals report symptoms such as fatigue, dizziness, palpitations, dyspnea, chest pain, generalized weakness, and other less common symptoms[23]. Women tend to be more symptomatic compared with men and they report higher burden of symptoms and lower quality of

Table 1. The CHA2DS2-VASc score components and estimated yearly risk of stroke and systemic embolism

CHA_2DS_2-VASc Risk Factor	Points	CHA_2DS_2-VASc score	Yearly risk of ischemic stroke (%)	Yearly risk of stroke/TIA and systemic embolism (%)
Congestive heart failure	+ 1	0	0.2	0.3
Hypertension	+ 1	1	0.6	0.9
Age < 65 years	0	2	2.2	2.9
Age 65-74 years	+ 1	3	3.2	4.6
Age ≥ 75 years	+ 2	4	4.8	6.7
Diabetes	+ 1	5	7.2	10.0
Vascular disease	+ 1	6	9.7	13.6
Male sex	0	7	11.2	15.7
Female sex	+ 1	8	10.8	15.2
Stroke/TIA/thromboembolism	+ 2	9	12.2	17.4

Adapted from Friberg et al. 2012[11]. TIA signifies transient ischemic attack.

life compared with men. Accordingly, women are more likely than men to seek care for AF[5]. Given the relatively silent and potentially paroxysmal nature of AF, it can be challenging to detect. It is estimated that approximately 13% of individuals with AF have undetected AF[24].

In up to 37% of cases, stroke is the first sign of AF[25]. The symptoms of stroke secondary to AF are characterized by the sudden onset of neurological deficits that are typically maximal at onset. The course of symptoms is less likely to be progressive or stuttering as is sometimes the case in strokes due to small or large vessel disease. Patients with AF-related stroke present with greater severity and higher frequency of large vessel occlusion strokes compared to strokes from other causes.

Infarct patterns in AF-related stroke include large territory wedge-shaped infarcts and/or smaller multifocal infarcts in multiple arterial territories (Fig. 1). In addition, patients with AF tend to have a higher burden of white matter hyperintensities and evidence of cerebral small vessel disease, including microhemorrhages[26]. Vessel imaging in the acute stroke setting may show large vessel occlusion. Hemorrhagic transformation of the infarcted tissue is more common in cardioembolic strokes, likely due to larger infarct size and increased patient age.

Treatment and outcomes of AF-related stroke

Population-based studies in the US and Canada suggest that ischemic stroke admissions with comorbid AF have been steadily increasing over the past decade[9,27]. Thrombolytic therapy and endovascular therapy remain the hallmark of acute ischemic stroke treatment for eligible patients, regardless of the presence of AF. One caveat is that patients with known AF who are on anticoagulation for stroke prevention may not be eligible for intravenous thrombolysis, thus endovascular therapy may be the only acute treatment option. In addition, blood pressure management, heart rate and rhythm control, and management of post-stroke complications are crucial to in-hospital treatment of AF-related stroke. Several studies have shown that rate control is not inferior to rhythm control regarding cardiovascular outcomes and mortality for the treatment of AF[28,29], and the focus of this section will be the use of anticoagulants for stroke prevention.

Oral anticoagulants (OACs) for secondary stroke prevention

Initiation of anticoagulation therapy in patients with AF-related stroke is paramount for secondary stroke prevention. Decision-making in this setting is challenging, given the risk of hemorrhage in the immediate post-stroke period, weighed against the risk of recurrent ischemic stroke, or other ischemic events. The estimated risk of a recurrent ischemic stroke is 1.5% per day in the first 2 weeks after an acute stroke[30], while the risk of any radiographic hemorrhagic

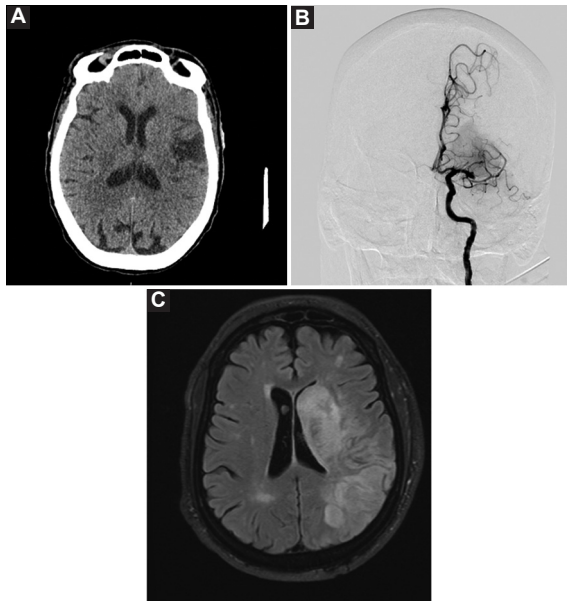

Figure 1. Imaging patterns in AF-related stroke. **A:** A non-contrast head CT in a 85-year-old woman presenting with aphasia and right-sided weakness, demonstrating a wedge-shaped infarct in the left middle cerebral artery distribution. **B:** The digital subtraction angiogram for the same patient demonstrating an acute left middle cerebral artery occlusion. **C:** A T2 FLAIR MRI in a 58-year-old man with new onset AF and a large left hemispheric acute infarct, as well as evidence of hyperintensities in bilateral hemispheres suggestive of small vessel disease.

transformation ranges from 3.2% to 44% in the first 5 days depending on the use of thrombolytic therapy[31].

Vitamin K antagonists (VKAs) and direct OACs (DOACs) are the mainstay of stroke prevention in patients with AF, each with their unique set of advantages and risks (Table 2)[32-36]. Although VKAs, such as warfarin, have been used for decades and are associated with a two-thirds relative risk reduction of stroke and systemic embolism compared with aspirin, the need for constant serum level monitoring and multiple food and drug interactions makes warfarin difficult to use. Patients with AF on warfarin tend to have suboptimal time in the therapeutic range[37], and women tend to be more at risk of stroke than men while on warfarin due to differences in metabolism[5].

DOACs, such as dabigatran, rivaroxaban, apixaban, and edoxaban, have emerged into clinical practice in the past decade. DOACs are as effective, if not more effective, than warfarin for stroke and systemic embolism prevention[33-36]. In addition, DOACs have a more favorable safety profile and do not require constant blood level monitoring, making them easier to use. In 2019, the American College of Cardiology and American Heart Association published updated guidelines recommending DOACs as first line for eligible patients with AF[23]. The main contraindication to DOACs includes patients with mechanical heart valves and moderate-to-severe mitral valve stenosis[23].

Timing of initiation of OACs

The timing of initiation of OACs for secondary stroke prevention after acute stroke depends on many factors, mainly the size of the infarct and the presence of hemorrhage on brain imaging. One decision-making algorithm is illustrated in figure 2. As patients with recent ischemic stroke were excluded from the clinical trials on anticoagulation, much of the evidence is based on observational studies and robust evidence is lacking in this patient population. The AHA/ASA guidelines suggest initiation of OACs immediately after TIA and 14 days after acute ischemic stroke event in most cases, apart from very large infarcts (defined as either NIHSS > 15 or an infarct involving the complete territory of a vessel) with severe hemorrhagic transformation in which delaying OAC initiation beyond 2 weeks is reasonable. European guidelines from the pre-DOAC era suggest a more granular approach to initiating OACs depending on stroke severity, recommending initiation of OACs 1 day after a transient ischemic attack, 3 days after minor stroke (NIHSS < 8), 6 days in mild stroke (NIHSS 8-15), and 12 days after severe stroke (NIHSS > 15)[38].

Data from observational studies suggest that in clinical practice, DOACs are started on average 4-11 days after ischemic stroke. Early start of DOACs in these studies was associated with an average risk of intracerebral hemorrhage (ICH) of 2.2% per year, which was 3-fold lower than the risk of ischemic stroke events over the same time[39].

Despite current guidelines, an estimated 50% of patients with acute stroke and AF are discharged from the hospital without OAC, with evidence of sex and race/ethnic differences in OAC utilization[40]. Risk of bleeding, risk for falls, and goals of care (comfort measures/hospice care) are commonly cited reasons for not starting OACs at stroke hospital discharge, and the rate of OAC use may increase over time after hospital discharge.

At present, there are several randomized controlled trials underway evaluating various OAC initiation

Table 2. Oral anticoagulants recommended for stroke prevention in AF

Anticoagulant	Benefits	Disadvantages
Vitamin K antagonists – Warfarin	67% relative risk reduction versus aspirin 26% reduction in mortality versus aspirin Can be used in patients with mechanical valves and mod-severe mitral stenosis Point of care confirmation of anticoagulation Reversible	Significant food and drug interactions Need for blood level monitoring Suboptimal time in therapeutic range Low patient adherence
Direct oral anticoagulants (DOACs) Direct thrombin inhibitors – Dabigatran Factor Xa inhibitors – Apixaban – Rivaroxaban – Edoxaban	About 19% relative risk reduction compared with warfarin 10% reduction in mortality compared with warfarin Easy to use, less food/drug interactions Lower rates of hemorrhage Reversible	Contraindicated in mechanical valves and moderate-to-severe mitral stenosis Reversal agents less readily available, costly Caution in renal and hepatic impairment

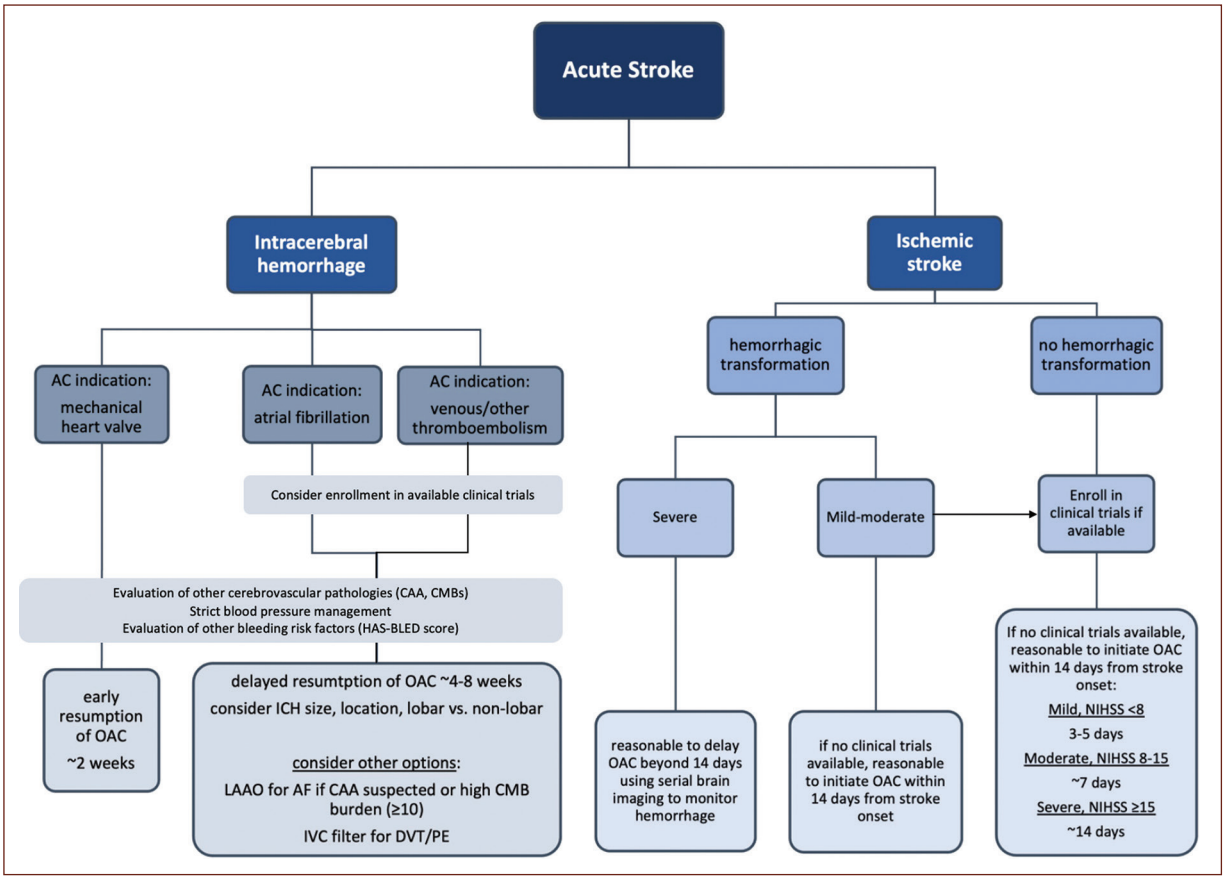

Figure 2. One evaluation and management algorithm for decision-making in patients with acute stroke with indications for anticoagulation. AC: anticoagulation; OAC: oral anticoagulation; CAA: cerebral amyloid angiopathy; CMB: cerebral microbleed; HAS-BLED: Hypertension, abnormal liver/renal function, stroke history, bleeding history or predisposition, labile INR, elderly, and drug/alcohol usage; ICH: intracerebral hemorrhage; IVC: inferior vena cava; DVT: deep venous thrombosis; PE: pulmonary embolism; NIHSS: National Institutes of Health Stroke Scale.

protocols after acute ischemic stroke for patients with AF (ELAN, [Switzerland/International NCT03148457]; TIMING [Sweden, NCT02961348]; OPTIMAS [United Kingdom, EduraCT 2018-003859-38]; START [United States, NCT03021928]; and AREST [United States, NCT02283294]).

Left atrial appendage occlusion (LAAO)

Since approximately 90% of thrombi in AF arise from the left atrial appendage, LAAO is an attractive approach to secondary prevention in patients with AF in which long-term anticoagulation is contraindicated. The PROTECT AF trial showed non-inferiority of LAAO with the WATCHMAN device compared with warfarin for the endpoint of stroke, systemic embolism, and cardiovascular death[41]. Similarly, the PREVAIL trial showed significantly lower complication rates (2.2%), and non-inferiority of the WATCHMAN device for LAAO versus warfarin for stroke and systemic embolism > 7 days post-randomization. Although there is an upfront risk of periprocedural complications (such as cardiac tamponade) and a long-term risk of ischemic stroke with LAAO, the overall risk seems to be offset by significantly lower rates of hemorrhage in the long-term[39]. In patients with AF undergoing cardiac surgery for other reasons, surgical LAAO has also been shown to reduce the risk of stroke and systemic embolism compared to those randomized not to have LAAO, though the majority of these patients also remained on anticoagulation during follow-up[42]. The updated American and European guidelines indicate LAAO as a Class IIb indication for stroke prevention in AF patients undergoing cardiac surgery or with a contraindication to long-term anticoagulation[23,43]. It remains challenging to identify those patients at such a high risk of stroke in whom LAAO is preferred to anticoagulation. For example, recent data suggest that even patients with AF and falls[44], dementia[45], or microhemorrhages[46] have a relatively low risk of subsequent ICH and a greater risk of recurrent ischemic stroke.

ICH and anticoagulants in AF

The management of ICH in patients with AF who require anticoagulation is another challenging scenario, specifically if and when to resume anticoagulants. Observational data suggest that resumption of OAC after ICH is associated with reduced ischemic events and mortality, without a significant increase in hemorrhagic events[47]. Moreover, observational studies suggest that the optimal timing of resumption of OAC after ICH is within 4-8 weeks, depending on individual patient characteristics, the size, and location of the ICH (Fig. 2). However, the SoSTART randomized trial of 203 participants in the UK was unable to show non-inferiority for resumption versus avoidance of OAC after ICH (median time 115 days post-ICH): although there was no significant difference in ICH recurrence, the mortality in the start-OAC group was twice that in the avoid-OAC group[48]. Several randomized clinical trials are currently underway and expected to provide more robust data on outcomes after resumption of OAC initiation and LAAO versus best medical care after ICH: ASPIRE (NCT03968393); PRESTIGE-AF (NCT03996772); STATICH (NCT03186729); A3ICH (NCT03243175); and ENRICH-AF (NCT03950076); STROKECLOSE (NCT02830152).

Screening for AF

Current US Preventive Services Task Force recommendations state that there is an insufficient evidence to support widespread screening given the low frequency of AF in the general unselected population and in individuals over age 50 years[49-51]. Nevertheless, significant technological advances over the past decade have yielded newer devices which are easy to use, commercially available and have high sensitivity and specificity for detecting AF[52].

Given that the risk factors for stroke and AF are similar, the role of screening for AF in high-risk populations (increased age and high-risk CHA2DS2-VASc score) has become a recent research focus, especially in post-stroke patients with various stroke subtypes. The CRYSTAL-AF study of cryptogenic stroke patients (mean age 62 years) showed an AF detection rate of 12% at 1 year with implantable loop recorders versus 2% with standard of care[53]. In the EMBRACE trial, also in patients with cryptogenic stroke with a mean age of 73 years, the AF detection rate with a 30-day external monitor was 16% versus 3% in the control group[54]. More recently, the STROKE-AF and PER DIEM studies have shown significantly higher AF detection rates with the use of implantable loop recorders in post-stroke patients with various non-AF stroke etiologies, compared with the standard of care or 30-day external loop recorder monitoring, respectively[55,56]. Several studies have also shown favorable results in screening high-risk patients for AF in the absence of recent stroke with various protocols, from intermittent electrocardiogram screening to implantable loop recorders[50,51]. One question that remains to be answered, however, is the amount or burden of device-detected AF that would warrant initiation of anticoagulation. In other words, is the risk-benefit balance the same for a patient with a 30-s episode of AF compared with a patient with > 24 h of AF detected during screening?

Future directions

Significant scientific advances have been made in the past few decades regarding the screening, prevention, and treatment of patients with AF and AF-related stroke. Nevertheless, the prevalence of both AF and AF-related stroke, and the burden associated with each, are steadily increasing with the rapid growth of the ageing population. Several questions remain unanswered and are the focus of ongoing and future clinical trials. First, is screening for AF in high-risk populations for the primary prevention of stroke effective and cost-efficient? Second, what is the minimum burden of device-detected AF necessary to warrant anticoagulation? Third, should all non-AF post-stroke patients be screened for AF with implantable loop recorders, regardless of stroke subtype? Fourth, when is the optimal time to initiate oral anticoagulation in patients with recent AF-related stroke (both ischemic and hemorrhagic stroke)? Finally, the association between AF, stroke, and the development of cognitive impairment and dementia has been well established in observational studies, and the underlying pathophysiological mechanisms, and strategies for prevention, are also the focus of ongoing research.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the Relevant Clinical Research Ethics Committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective and observational study.

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