JAFIB
Case Report
Journal of Atrial Fibrillation
www. jafib.com

Left Atrial Appendage Thrombus Resolution with Reduced Dose Apixaban

Beatriz Vaquerizo, MD, PhD, Magdi Sami, MB, BCh

Division of Cardiology, McGill University Health Centre, Montreal, Quebec, Canada.

Abstract

A 63 year old woman with a history of persistent atrial fibrillation and CHADSVASC score of 2, suffered a massive stroke with a hemorrhagic transformation, 2 days following an appendectomy and reversal of warfarin anticoagulation with vitamin K. A left atrial appendage occlusive device (LAAOD) was considered for stroke prevention given the risk of recurrent cerebral hemorrhage. A transesophageal echocardiography (TEE) however, revealed left atrial appendage (LAA) clots which precluded the use of a LAAOD. A computed tomography revealed only partial resolution of the right hemispheric hematoma. Apixaban 2.5 mg twice daily was successful in resolving the LAA clots within 2 months without aggravating her cerebral hematoma which continued to resolve. This is the first case, to our knowledge showing reduced-dose Apixaban to completely resolve left atrial thrombus. Our case also addresses the issue of bridging following reversal of warfarin anticoagulation with vitamin K.

Introduction

Unless patients have a mechanical heart valve then there is a knowledge gap related to the appropriate management of heparin bridging.[1] Although, vitamin K antagonists (VKAs) are very well characterized, they have important limitations such as slow onset of action, narrow therapeutic window and unpredictable anticoagulant effect that make their use problematic.[2] The new oral anticoagulants have a rapid onset of action, low potential for food and drug interactions, predictable anticoagulant effect and short plasma half-life making them an attractive alternative to use around surgical interventions.[3] We describe a case where Apixaban 2.5 mg twice daily was successful in resolving a left atrial appendage (LAA) clot within 2 months without increasing the risk of brain hemorrhage in a patient who had developed a peri-infarct hematoma following her right hemispheric stroke.

Case Report

This is a case of a 63 year-old female with a past medical history of hypertension, persistent atrial fibrillation (AF), in rhythm control and a dual chamber pacemaker. She had a CHADS2 score of I, CHADSVASC2 score of 2 and thus was receiving warfarin for stroke prevention as well as a beta-blocker for hypertension and rhythm control. Three months prior to her admission, routine clinical follow-up was uneventful with pacemaker rhythm (DDD) at 80/min and no evidence of AF in the preceding 6 months.

She was admitted to our center with acute appendicitis and was scheduled to undergo urgent surgery. INR at arrival was 2.9. Warfarin was reversed with vitamin K. INR prior to surgery 12 hours later, was 1.3. She underwent an appendectomy and was discharged on day 2 post-op on warfarin, but with an INR still only at 1.4. On day 3 she was admitted with a massive right hemispheric stroke. She received thrombolytic therapy, which did not reduce the extent of the stroke but did cause early hemorrhagic transformation (Figure 1A). Anticoagulation was stopped and 6 days later the patient was re-admitted to our institution with deep vein thrombosis in the paralyzed lower limb. She received a retrievable inferior vena cava filter.

Stroke prevention remained a concern at that point and a left atrial appendage occlusive device (LAAOD) was considered, in view of her recent brain hemorrhage. LAAOD, however, cannot be implanted before making sure she has no LAA clot. A transesophageal echocardiography (TEE) was performed. The TEE revealed 2 small thrombi (one of 10 x 7.3 mm and another of 9.6 x 7.4 mm) in the LAA (Figure 2A-C, and Video I A-C in the Data Supplement). These findings contraindicated LAA closure device implantation. A multi slice computed tomography (MSCT) was then performed to assess the status of her peri-infarct hematoma. It showed a dense infarct with reduced hemorrhagic transformation area at the border (Figure 1B). Low dose heparin IV for a few days did not appear to aggravate

Disclosures:
Dr. Sami is a member of the National Advisory Board of Bristol-Myers Squibb (BMS) and Pfizer Alliance for Apixaban. He has also received educational grants for travel from various pharmaceutical companies including BMS/Pfizer Alliance.

Corresponding Author:
Dr. Magdi Sami, MB; BCh
Division of Cardiology, Suite M476
McGill University Health Centre
687, Avenue des Pins Ouest
Montreal (Québec) Canada H3A 1A1.

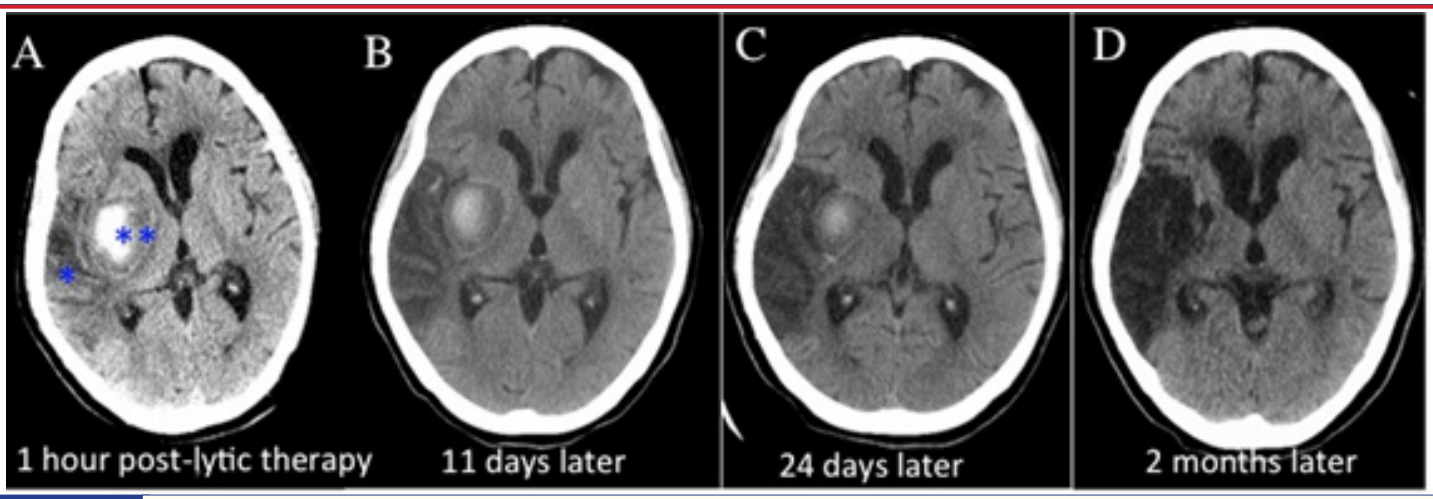

Figure 1: **Sequential axial unenhanced cranial MSCT demonstrating area of low attenuation in the right middle cerebral artery territory infarct (*) with parenchyma hemorrhage in the border of the wedge-shaped area of infarction (**), consistent with hemorrhagic transformation. Mass effect on the right lateral ventricle with midline shift (A). MSCT images 11 and 24 days later, showed a large intense hypodensity (dense infarct), with reduced haemorrhagic area at the border (B, C) with complete hematoma resorption on MSCT 2 months later (D).**

the peri-infarct hematoma or cause any new bleeding. In consultation with a neurologist the patient was treated with a reduced dose of Apixaban 2.5 mg bd and followed closely with imaging techniques to monitor the status of the intracranial hematoma. A repeat TEE 2 months later showed complete thrombus resolution (Figure 2 C-E and video I C-D in the Data Supplement) with progressive hematoma resorption on serial MSCT (Figure 1C, D). The patient is currently followed-up in our institution and the dose of Apixaban was increased to the standard dose of 5 mg bd as per guidelines, 2 months after initiating the treatment and when there was no more evidence of a hematoma in the MSCT. During a follow up period of approximately 6 months, the patient has gradually improved with only a mild residual left-sided hemiparesis. She displayed no side effects from her anticoagulant therapy. An interesting additional fact is that pacemaker interrogation did not show evidence of AF episodes at any time in the 6 months preceding the stroke or since.

Discussion

Peri-procedural Management of Long-term vitamin K Antagonist (VKA) Discontinuation: Rationale and Current Evidence of Heparin Bridging Therapy

We show an example of a patient with a moderate stroke risk and low-risk of bleeding, in which the lack of bridging anticoagulation, following surgery, was clearly related to an early massive stroke. Except for patients with a mechanical heart valve there is no universal strategy for peri-procedural anticoagulation for those on chronic warfarin therapy. Due to warfarin's slow onset of action, in general, bridging anticoagulation may well be appropriate in patients who have a high or moderate thromboembolic risk, especially following reversal of their anti-coagulant with vitamin K. Recent evidence, however, suggests that heparin bridging (for oral VKA or new anticoagulants), did not affect the rates of cardiovascular events but significantly increased the risk for any bleeding or major bleeding complication.[4,5] This variation in the individual management of heparin bridging may reflect the persisting lack of evidence and the need for a good randomized trial.[1]

Left Atrial Thrombus (LA) in the Presence of Sinus Rhythm

Left atrial (LA) is usually detected in association with recent or existing AF. It is remarkable that in our patient pacemaker interrogation did not show evidence of AF episodes at any time in the 6 months preceding the stroke. It has been reported that the combination of LA and SR was detected in about 0.1% of more than 20,000 TEE examinations performed over an 11-year period.[6] Several structural and functional cardiac abnormalities are associated with significant LA stasis, which may lead to LA formation even in the presence of SR.[7] In the absence of valve disease or significant left ventricular dysfunction, as it was the case for our patient, previous AF is a high-risk marker for recurrent AF. Transient paroxysms of AF may result in atrial dysfunction during the arrhythmia and after conversion to SR (the phenomenon of atrial stunning), thus predisposing to LA formation. The time course resolution of LAA stunning is variable and dependent on several factors, including LA function as assessed by TEE.[6] However, in our patient LA function at the time of TEE study was preserved (Video I A-C in the Data

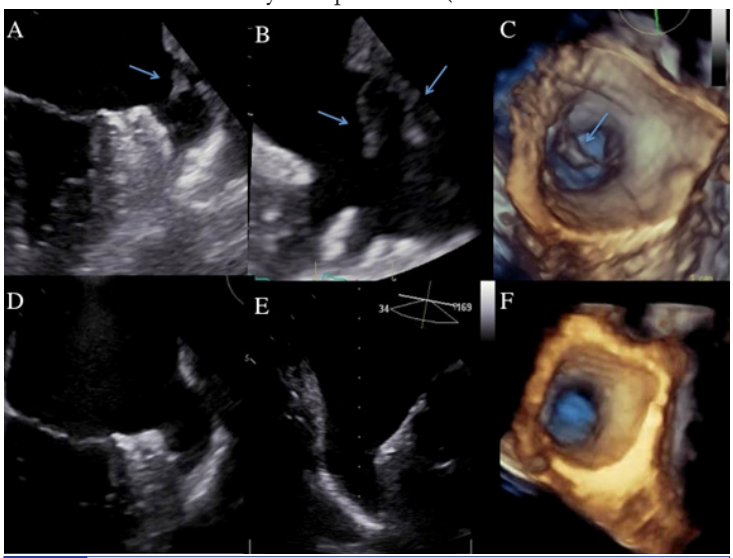

Figure 2: **2 and 3-Dimension Transesophageal echocardiography (TEE) . Formation of two thrombi (arrow) in the left atrial appendage (LAA) on day 11 post-stroke - the largest one near the ostium and the smaller one in the superior anterior lobule (A- C). Thrombus resolution after 2 months of anticoagulant therapy with Apixaban at 2.5 mg bd (D - F).**

Supplement), thus we could suggest as a hypothesis that the treatment with vitamin K and the re-introduction of VKA without bridging, seemed to have exerted a "pro-thrombotic" effect as evidenced by the early post-operative stroke, thrombus formation in the LAA and deep vein thrombosis.

VKAs have a slow onset of action and a narrow therapeutic window. They also have an unpredictable anticoagulant effect that results from multiple factors such as age, body-weight, gender, and drug interactions. Disease conditions and variable dietary intake of vitamin K can also contribute to variations in INR2.

Left Atrial Thrombus (LA) Resolution with New Anticoagulants (NOAC)

Reduced Dose Of Apixaban, 2.5 mg Bd May Be Sufficient In Some Patients To Dissolve Thrombus Formation In The LA

In our patient, successful thrombus resolution was obtained after 2 months of reduced dose of Apixaban, 2.5 mg bd, without any bleeding complication. There are some other case studies showing that Apixaban can dissolve left atria thrombi. In one case a reduced dose of Apixaban partially dissolved a large thrombus in the LA from (48 × 22 mm) to (15 x 6mm) in 11 weeks.[8] In another case study, a standard dose of Apixaban was used to resolve completely a smaller thrombus (11 x 10mm) in the LAA, in 16 days.[9] LA resolution has been reported with other new anticoagulants such as dabigatran and rivaroxaban. In these case studies, standard dose of the drugs were used to resolve the thrombi.[10]

Reduced Dose Of Apixaban Can Be Used In A Patient With High-Risk Of Bleeding

To our knowledge this is the first-documented case using a reduced dose of Apixaban therapy for stroke prevention, in a patient with a massive stroke and hemorrhagic transformation. Although the hemorrhage had stopped by the time Apixaban was started, the hematoma was not completely resolved.

Can Apixaban 2.5 mg bd still protect AF patients from stroke? In a sub-group analysis from the ARISTOTLE trial, 831 patients with higher risk of bleeding, (age ≥80 years, body weight ≤60 kg, or creatinine ≥133 mmol/L), dose reduction to 2.5 mg bd was associated with a similar reduction in stroke and major bleeding as the normal dose of 5 mg twice daily3. Furthermore our case report added to others, suggest that this dose might be appropriate in specific circumstances, when the risk of bleeding is high.

Conclusion

The above case history is remarkable and highlights some key issues related to stroke prevention in non valvular AF. First, there is a knowledge gap related to the appropriate management of heparin bridging. Our case suggests that bridging VKA with heparin could be a good option in such cases. However, in this controversial issue we await the results of randomised trials, in the meantime careful weighing of the risk/benefit of bridging must be individualised. Second, LAA can form during sinus rhythm in patients with previous AF. We theorizes that in our case, without obvious risk factor for such an occurrence, maybe the combination of vitamin K and the re-introduction of VKA, may have contributed to facilitate thrombus formation in the LAA. This reflects the evidence that although VKAs are very well characterized, they have important limitations such as slow onset of action, narrow therapeutic window and unpredictable anticoagulant effect that make their use problematic. Finally, the new oral anticoagulants have a rapid onset of action, low potential for food and drug interactions, predictable anticoagulant effect and short plasma half-life making them an attractive alternative to use around surgical interventions. In our case Apixaban 2.5 mg bid was also successful in resolving a LAA clot within 2 months without increasing the risk of brain hemorrhage in a patient who had developed a peri-infarct hematoma following her right hemispheric stroke.

References

1. BRIDGE Study Investigators. Bridging anticoagulation: is it needed when warfarin is interrupted around the time of a surgery or procedure? Circulation. 2012; 125:e496-8.
2. Scaglione F. New oral anticoagulants: comparative pharmacology with vitamin K antagonists. Clin Pharmacokinet. 2013; 52:69-82.
3. Halvorsen S, Atar D, Yang H, De Caterina R, Erol C, Garcia D, Granger CB, Hanna M, Held C, Husted S, Hylek EM, Jansky P, Lopes RD, Ruzyllo W, Thomas L, Wallentin L. Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial. Eur Heart J. 2014; 35:1864-72.
4. Siegal D1, Yudin J, Kaatz S, Douketis JD, Lim W, Spyropoulos AC. Periprocedural heparin bridging in patients receiving vitamin K antagonists: systematic review and meta-analysis of bleeding and thromboembolic rates. Circulation. 2012; 126:1630-9.
5. Beyer-Westendorf J, Gelbricht V, Förster K, Ebertz F, Röllig D, Schreier T, Tittl L, Thieme C, Hänsel U, Köhler C, Werth S, Kuhlisch E, Stange T, Röder I, Weiss N. Safety of switching from Vitamin-K antagonists to dabigatran or rivaroxaban in daily care - results from the Dresden NOAC registry. Br J Clin Pharmacol. 2014; 78(4):908-17.
6. Agmon Y, Khandheria BK, Gentile F, Seward JB. Clinical and echocardiographic characteristics of patients with left atrial thrombus and sinus rhythm: experience in 20 643 consecutive transesophageal echocardiographic examinations. Circulation. 2002; 105:27-31
7. Agmon Y, Khandheria BK, Gentile F, Seward JB. Echocardiographic assessment of the left atrial appendage. J Am Coll Cardiol. 1999; 34:1867-77.
8. Dobashi S, Fujino T, Ikeda T. Use of apixaban for an elderly patient with left atrial thrombus. BMJ Case Rep. 2014 Jun 24; 2014.
9. Kawakami T, Kobayakawa H, Ohno H, Tanaka N, Ishihara H. Resolution of left atrial appendage thrombus with apixaban. Thromb J. 2013; 11:26-8.
10. Hammerstingl C, Pötzsch B, Nickenig G. Resolution of giant left atrial appendage with rivaroxaban. Thromb Haemost. 2013; 8:583-4.