CASE REPORT

Reduced dose apixaban resolving dual cardiac chamber thrombi in a patient with ischaemic cardiomyopathy in sinus rhythm

Hossam Abubakar,¹ Mohamed Shokr,² Ahmed Subahi,¹ Ahmed Rashed³

¹Department of Internal Medicine, Wayne State University, Detroit, Michigan, USA

²Department of Internal Medicine, DMC/Wayne state university, Detroit, Michigan, USA

³Department of Cardiovascular Diseases, DMC/Wayne State University, Detroit, Michigan, USA

Correspondence to
Dr Hossam Abubakar,
hossamelhadi@gmail.com

Accepted 20 July 2017

SUMMARY

Left atrial (LA) thrombus is a known sequela of atrial fibrillation (AF) but it is less frequently encountered in patients in sinus rhythm. Left ventricular (LV) dysfunction may predispose patients without evidence of atrial tachyarrhythmias to atrial thrombosis. Warfarin is the standard treatment for cardiac chamber thrombosis and prevention of the associated thromboembolic complications. Despite that apixaban was found to be superior to warfarin in prevention of stroke and systemic embolism in patients with AF, evidence for its use in treatment of cardiac chamber thrombi is scarce and is limited to case reports. We report a case of simultaneously occurring LV and LA thrombi successfully treated with reduced dose apixaban in a patient with ischaemic cardiomyopathy and in sinus rhythm. Although apixaban maybe a potential effective treatment for intracardiac thrombi, further studies are needed to demonstrate efficacy and safety of this agent in larger patient populations.

BACKGROUND

Left atrial (LA) thrombus is a known complication in cases of atrial fibrillation (AF); however, it is less frequently encountered in patients in sinus rhythm.¹ Left ventricular (LV) dysfunction may predispose this subset of patients without evidence of atrial tachyarrhythmias to atrial thrombus.² Warfarin is the standard treatment for cardiac chamber thrombosis and prevention of the associated thromboembolic complications.³ Despite that apixaban was found to be superior to warfarin in prevention of stroke and systemic embolism in patients with AF,⁴ evidence for its use in treatment of cardiac chamber thrombi is scarce and is limited to case reports. We report a case of simultaneously occurring LV and LA thrombi successfully treated with apixaban in a patient with ischaemic cardiomyopathy and in sinus rhythm.

CASE PRESENTATION

A 68-year-old man with a history of ischaemic cardiomyopathy and chronic kidney disease presented to our emergency department with complaints of chest pain. ECG showed normal sinus rhythm with T wave inversions in leads V1-V3. The first and second troponin I levels were elevated at 0.897 and 0.722 ng/mL, respectively. N-terminal pro B-type natriuretic peptide was significantly elevated at 32 619 pg/mL and

chest X-ray showed cardiomegaly and pulmonary vascular congestion. Serum chemistry panel showed a creatinine level of 1.56 mg/dL and remaining labs were within reference range. Patient was transferred to the coronary care unit with a diagnosis of non-ST segment elevation myocardial infarction (NSTEMI) and acute congestive heart failure exacerbation. The patient received aspirin, clopidogrel and intravenous unfractionated heparin in addition to intravenous diuresis. Transthoracic echocardiography (TTE) showed a left ventricular ejection fraction (LVEF) of 25%, LA area of 27 square cm and a 10×11 mm mobile echodensity was visualised at the mouth of the LA appendage suggestive of a left atrial thrombus (figure 1). Furthermore, images obtained following intravenous administration of ultrasound contrast showed an 8×10 mm spherical filling defect at the apex consistent with an LV apical thrombus (figure 2). The patient then underwent coronary angiography that revealed mild coronary artery disease with no significant flow limiting lesions. Oral anticoagulation with warfarin was offered to the patient given the newly diagnosed LV and LA thrombi, however, the patient expressed concerns regarding the frequent international normalisation ratio (INR) monitoring and the dietary restrictions associated with warfarin therapy. After discussing alternative therapies with the patient, a decision was made to use apixaban for oral anticoagulation. He was discharged on dual antiplatelet therapy and appropriate cardioprotective medication in addition to apixaban 2.5 mg twice daily. Follow-up TTEs 2 and 6 months later revealed resolution of the LA and LV thrombi, respectively (figure 3, figure 4). During the follow-up period, there was no evidence of neurological deficits, systemic embolism or bleeding complications.

OUTCOME AND FOLLOW-UP

Follow-up TTEs 2 and 6 months later revealed resolution of the LA and LV thrombi, respectively (figures 3 and 4). During the follow-up period, there was no evidence of neurological deficits, systemic embolism or bleeding complications.

DISCUSSION

Our case demonstrates two important clinical issues. First, the development of atrial thrombosis in a

CrossMark

To cite: Abubakar H, Shokr M, Subahi A, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-220922

Figure 1 Transthoracic echocardiogram showing a 10×11 mm echodensity at the mouth of the left atrial appendage suggestive of a left atrial thrombus.

patient in sinus rhythm with no previous history of atrial fibrillation. Atrial thrombus formation is commonly associated with atrial tachyarrhythmias mainly AF. This is attributed to atrial stasis secondary to abnormal contractility associated with AF. In addition, atrial stunning (transient mechanical dysfunction of the atrium and atrial appendage) following spontaneous, pharmacological or electrical cardioversion to sinus rhythm further predisposes to thrombus formation through atrial stasis.⁵ Although atrial thrombi in patients in sinus rhythm are a relatively uncommon occurrence,¹ certain risk factors have been identified to predispose this subset of patients to thromboembolic complications. Mitral stenosis, severe aortic regurgitation and mitral prosthesis have been associated with LA stasis and increased risk of thrombus formation.⁶ Furthermore, LV dysfunction is also a well-recognised cause of atrial thrombosis in patients with sinus rhythm. LV failure is associated with elevation of LA pressure, which in turn compromises the left atrial emptying velocity causing atrial stasis and thrombus formation.² Our presented patient had no valvular disease identified through TTE but had an LVEF of 25% that may have contributed to left atrial thrombus formation. Furthermore, although he was in sinus rhythm with no previous documented history of AF, it is difficult to ascertain that the patient did not have undocumented paroxysms of abnormal atrial rhythm that were not detected during his previous clinical encounters. However, unrecognised episodes of AF in patients without previously documented AF has been demonstrated to be an exceedingly rare cause of LA thrombus formation.¹

Figure 2 Transthoracic echocardiographic image following intravenous administration of ultrasound contrast showing an 8×10 mm spherical filling defect at the left ventricular apex consistent with a left ventricular apical thrombus.

Figure 3 Follow-up transthoracic echocardiogram after 2 months showing complete resolution of the left atrial appendage thrombus.

Second, the use of reduced dose apixaban for treatment of simultaneously occurring left atrial appendage and left ventricular thrombi. Apixaban has been demonstrated to be superior to warfarin with regards to prevention of systemic embolism, stroke and major bleeding in patients with atrial fibrillation.⁴ Evidence regarding its use for treatment of cardiac chamber thrombi is limited to case reports with no randomised trials to date. We searched two literature databases (PubMed and Embase) to identify evidence reporting the use of apixaban to treat cardiac chamber thrombosis (results in table 1). To the best of our knowledge, our case is the first to report the use of reduced dose apixaban to treat simultaneously occurring LA and LV thrombi. The dosage used in the majority of reported cases was 5 mg twice daily which is consistent with recommendations based on evidence from the "Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation" trial.⁴ Reduced dose apixaban (2.5 mg twice daily) was used in a relatively small subset of patients with two or more of the following criteria: age ≥80 years, body weight ≤60 kg and/or serum creatinine ≥1.5 mg/dL. The reduced dose appeared to be non-inferior to warfarin in preventing stroke and systemic embolism; however, the sample size was relatively small.⁴ In two of the reported cases that involved patients with increased risk of bleeding,^{7,8} a reduced dose of 2.5 mg twice daily was used and resulted in successful thrombus resolution. Our patient had a serum creatinine of 1.56 mg/dL but did not fulfil a second criterion to justify using the reduced dosage. However, it is important to note that he was simultaneously started on dual antiplatelet therapy for treatment of NSTEMI. The "Apixaban for Prevention of Acute Ischemic Events-2" trial reported a significantly increased risk of bleeding with use of full-dose apixaban (5 mg twice daily) simultaneously with dual antiplatelet therapy when compared with dual antiplatelet

Figure 4 Image following intravenous administration of ultrasound contrast showing complete resolution of left ventricular apical thrombus (6 months follow-up transthoracic echocardiogram).

Table 1 Reported cases of intracardiac thrombi treated with apixaban

Author	Age	Gender	Location of thrombus	Size (mm)	Aetiology	Previous anticoagulant treatment	Apixaban dose	Duration of therapy	Outcome
Case presented	68	M	LV apex LAA	LV: 8×10 LAA: 10×11	ICMP	UFH for 2 days	2.5 mg Twice daily	LAA: 8 weeks LV: 6 months	Thrombus resolution
Dobashi <i>et al</i> ⁷	86	M	Left atrium	48×22	NV-AF	None	2.5 mg Twice daily	15 weeks	Thrombus resolution
Freixa <i>et al</i> ¹⁵	61	M	LAA occluding device thrombosis	25×23×13	NV-AF with left atrial appendage occluding device	None	5 mg Twice daily	6 months	Thrombus resolution
Jacob <i>et al</i> ¹⁶	75	F	LAA	Not reported	NV-AF	Apixaban 2.5 mg twice daily (duration not reported)	5 mg twice daily	6 weeks	Thrombus resolution
Kawakami <i>et al</i> ¹⁷	72	M	LAA	11×10	NV-AF	None	5 mg twice daily	2 weeks	Thrombus resolution
Lee ¹⁸	78	F	LAA	12×16	NV-AF	Warfarin and UFH for 12 days	5 mg twice daily	6 weeks	Thrombus resolution
Lee ¹⁸	79	F	LAA	six×5	NV-AF	None	5 mg twice daily	5 weeks	Thrombus Resolution
Miwa <i>et al</i> ¹⁹	63	M	LAA	Not reported	NV-AF	Warfarin for 1 year and dabigatran for 5 months	5 mg twice daily	5 months	Thrombus resolution
Sugawara <i>et al</i> ²⁰	74	F	Left Atrium	38×31	NV-AF breast cancer	Warfarin (duration not reported)	5 mg twice daily	8 weeks	Thrombus resolution
Valero <i>et al</i> ²¹	69	F	LAA	Not reported	NV-AF	Warfarin for 4 years	5 mg twice daily	3 weeks	Thrombus resolution
Vaquero ²²	63	F	LAA	10×7.3×9.6×7.4	NV-AF	Warfarin (duration not specified)	2.5 mg twice daily	8 weeks	Thrombus resolution
Ohyagi <i>et al</i> ¹²	55	M	LAA	25×9	NV-AF	None	5 mg twice daily	8 days	Embololic stroke.
Eftekhari <i>et al</i> ¹³	63	M	LAA	Not reported	NV-AF	None	5 mg twice daily	5 days	Embololic stroke.
Koyama <i>et al</i> ²³	78	M	LAA	16×26	NV-AF	Dabigatran for 1 year	5 mg twice daily	8 weeks	Thrombus resolution
Bolayir <i>et al</i> ²⁴	70	M	LV	40×30	NICMP	None	5 mg twice daily	4 weeks	Thrombus resolution
Yildirim <i>et al</i> ²⁵	68	M	LV anterior septum	13×6	ICMP	None	5 mg twice daily	4 weeks	Thrombus resolution
Kaya <i>et al</i> ²⁶	60	F	LV chordal apparatus of the mitral valve	30×20	HCM	None	5 mg twice daily	4 weeks	Thrombus resolution
Mano <i>et al</i> ²⁷	62	M	LV apex	40×15	STEMI	None	5 mg twice daily	6 weeks	Thrombus resolution
Yanikoglu <i>et al</i> ²⁸	55	M	LV apex	Not reported	Anti-MI	None	5 mg twice daily	4 weeks	Thrombus resolution

BID, twice daily; F, female; HCM, hypertrophic cardiomyopathy; ICMP, ischaemic cardiomyopathy; LAA, left atrial appendage; LV, left ventricle; M, male; Mg, milligrams; MI, myocardial infarction; NICMP, non-ischaemic cardiomyopathy; NV-AF, non-valvular atrial fibrillation; STEMI, ST segment elevation myocardial infarction; UFH, unfractionated heparin.

therapy alone in patients with acute coronary syndromes.⁹ This reported increased risk of bleeding along with our patient's elevated creatinine raised concerns with regards to the use of the full dose (5 mg twice daily) of the drug. Consequently, a decision was made to initiate therapy with the reduced dose of 2.5 mg twice daily that resulted in successful resolution of the thrombi. Our case is one of a few that demonstrated the efficacy of this reduced dosage with regards to resolution of intracardiac thrombi.

The mechanism underlying clot resolution is only partially understood. Apixaban inhibits factor X that is an essential clotting factor in both the intrinsic and extrinsic coagulation pathways. In addition, it inhibits prothrombinase (an enzyme that catalyses conversion of prothrombin to thrombin) and platelet aggregation both of which are essential components in clot development.¹⁰ It is also suggested that the decreased thrombin level associated with inhibition of factor X may modify whole blood clot structure to a more penetrable organisation.¹¹ This structural transformation enhances entry of the crucial endogenous fibrinolytic factors mainly plasminogen and tissue plasminogen activator into the clot, increasing plasmin production and fibrinolysis.¹¹

Cardiac chamber thrombi are effectively treated with warfarin that is currently the standard of practice.³ However, this agent is associated with known limitations including its narrow therapeutic window, the need for continuous INR monitoring, high incidence of food and drug interaction and lastly its slow onset of action that requires bridging with parenteral anticoagulants that may lead to occasional prolongation of hospital stay. Apixaban maybe a reasonable alternative given its potential efficacy demonstrated by the available evidence and its ability to be prescribed without outpatient monitoring. Although most reports point towards the efficacy of this agent, there are some reported cases of treatment failure evidenced by the occurrence of embolic strokes while on the appropriate dose of apixaban for treatment of intracardiac thrombi.^{12–14} Further randomised studies are thus needed to demonstrate efficacy and safety of this agent in larger patient populations.

Learning points

- ▶ Atrial thrombus formation is an uncommon occurrence in patients with no history of atrial tachyarrhythmias.
- ▶ Left ventricular systolic dysfunction is a risk factor for both atrial and ventricular thrombus formation in patients in sinus rhythm.
- ▶ Apixaban may be an alternative anticoagulant for the treatment of intracardiac thrombi and the prevention of their associated thromboembolic complications. Randomised trials are needed to study its efficacy and safety for this indication.

Contributors HA: literature review, construction of discussion. MS: identification of case, proofreading of prefinal draft, contribution to discussion. AS: case presentation write up. AR: acquisition of images, editing of final draft content/grammar and spelling.

Competing interests Consultancy for Pfizer.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 Agmon Y, Khandheria BK, Gentile F, *et al.* 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.
- 2 Tabata T, Oki T, Fukuda N, *et al.* Influence of left atrial pressure on left atrial appendage flow velocity patterns in patients in sinus rhythm. *J Am Soc Echocardiogr* 1996;9:857–64.
- 3 January CT, Wann LS, Alpert JS, *et al.* 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation: Executive Summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation* 2014;130:2071–104;130:2071–104.
- 4 Granger CB, Alexander JH, McMurray JJ, *et al.* Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981–92.
- 5 Shively BK, Gelgand EA, Crawford MH, *et al.* Regional left atrial stasis during atrial fibrillation and flutter: determinants and relation to stroke. *J Am Coll Cardiol* 1996;27:1722–9.
- 6 Chiang CW, Lo SK, Ko YS, *et al.* Predictors of systemic embolism in patients with mitral stenosis. A prospective study. *Ann Intern Med* 1998;128:885–9.
- 7 Dobashi S, Fujino T, Ikeda T, *et al.* Use of apixaban for an elderly patient with left atrial thrombus. *BMJ Case Rep* 2014;2014:bcr2014203870.
- 8 Vaquerizo B, Sami M. Left atrial appendage thrombus resolution with reduced dose apixaban. *J Atr Fibrillation* 2015;8:28–30.
- 9 Alexander JH, Lopes RD, James S, *et al.* Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med* 2011;365:699–708.
- 10 Mandernach MW, Beyth RJ, Rajasekhar A, *et al.* Apixaban for the prophylaxis and treatment of deep vein thrombosis and pulmonary embolism: an evidence-based review. *Ther Clin Risk Manag* 2015;11:1273–82.
- 11 Varin R, Mirshahi S, Mirshahi P, *et al.* Whole blood clots are more resistant to lysis than plasma clots—greater efficacy of rivaroxaban. *Thromb Res* 2013;131:e100–e109.
- 12 Ohayagi M, Nakamura K, Watanabe M, *et al.* Embolic stroke during apixaban therapy for left atrial appendage thrombus. *J Stroke Cerebrovasc Dis* 2015;24:e101–e102.
- 13 Eftekhari A, Damgaard D, Grove EL, *et al.* Fatal stroke following treatment with apixaban in a patient with atrial fibrillation and left atrial appendage thrombus. *Int J Cardiol* 2016;214:131–2.
- 14 Kawakami T, Tanaka N, Ishihara H, *et al.* The role of soluble fibrin during anticoagulant therapy: a case report. *Thromb J* 2015;13.
- 15 Freixa X, Scalone G, Martín-Yuste V, *et al.* Large protruding thrombus over left atrial appendage occlusion device successfully treated with apixaban. *Eur Heart J* 2015;36:1427.
- 16 Jacobs B, Willems R, Garweg C, *et al.* Why it is important to use the correct dose of the non-vitamin K oral anticoagulants. *Eur Heart J Cardiovasc Imaging* 2015;16:461.
- 17 Kawakami T, Kobayakawa H, Ohno H, *et al.* Resolution of left atrial appendage thrombus with apixaban. *Thromb J* 2013;11:26.
- 18 Lee SH, Han S. Series with complete resolution of left atrial appendage thrombi with apixaban in elderly patients. *Korean J Intern Med* 2016;31:396–8.
- 19 Miwa Y, Minamishima T, Sato T, *et al.* Resolution of a warfarin and dabigatran-resistant left atrial appendage thrombus with apixaban. *J Arrhythm* 2016;32:233–5.
- 20 Sugawara Y, Okamura R, Taniguchi S, *et al.* Left atrium mass in a patient with breast Cancer: a case report. *J Med Case Rep* 2016;10:285.
- 21 Valero E, Santos E, Núñez J, *et al.* Thrombolytic action of apixaban on intra-atrial thrombus developed after previous treatment with warfarin: a case report. *Med Princ Pract* 2016;25:491–3.
- 22 Vaquerizo B, Sami M. Left atrial appendage thrombus resolution with reduced dose apixaban. *J Atr Fibrillation* 2015;8:1182.
- 23 Koyama T, Otsuka Y, Kawahara M, *et al.* A left atrial appendage thrombus that developed during prophylactic low-dose dabigatran treatment resolved after switching to apixaban. *Clin Case Rep* 2017;5:711–3.
- 24 Bolayır HA, Güneş H, Şahin Ömer, *et al.* Complete resolution of huge left ventricular thrombus with apixaban treatment. *International Journal of the Cardiovascular Academy* 2016;2:160–1.
- 25 Yıldırım E, Kalkan K, Ipek E, *et al.* Successful resolution of left ventricular thrombus with apixaban treatment. *International Journal of the Cardiovascular Academy* 2016;2:57–8.
- 26 Kaya A, Hayroğlu Mİ, Keskin M, *et al.* Resolution of left ventricular thrombus with apixaban in a patient with hypertrophic cardiomyopathy. *Türk Kardiyol Dern Ars* 2016;44:335–7.
- 27 Mano Y, Koide K, Sukegawa H, *et al.* Successful resolution of a left ventricular thrombus with apixaban treatment following acute myocardial infarction. *Heart Vessels* 2016;31:118–23.
- 28 Yanıkoğlu A, Altıntaş MS, Ekinözü İ, *et al.* Dissolution of an apical thrombus by apixaban in a patient with old anteroseptal myocardial infarction. *Anatol J Cardiol* 2015;15:671–2.

Copyright 2017 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow