# Large Left Ventricular Thrombus as a Cause of Recurrent Cardioembolic Stroke While on Dabigatran



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## INTRODUCTION

Cardioembolic stroke (CES) is responsible for an increasing number of ischemic strokes. Half of the cases are often secondary to nonvalvular atrial fibrillation, while another 10% are due to mural thrombus in the atrium or ventricle.[1] In comparison with other subtypes of ischemic stroke, studies have shown that CES cause more severe devastating effects because of the increased likelihood of compromise of a larger area of the brain.[1] Thrombus formation can develop in the atrium secondary to atrial fibrillation, while clot formation in the left ventricle occurs mostly following myocardial infarction (MI) of the anterior wall because of blood stasis from a dysfunctional left ventricle.[2] In patients who have had ischemic stroke with left ventricular (LV) thrombus as an identifiable cause, guidelines issued by the American College of Cardiology recommend the use of oral vitamin K antagonists (VKAs) as primary anticoagulant therapy.[3] Although there has been some evidence for the use of direct oral anticoagulants (DOACs) for LV thrombus in case reports, there have been no randomized studies to demonstrate its role in large clot burden, appropriate therapeutic dosing, and effective duration. We report a case of a young man with a history of a significant LV thrombus burden who had recurrent large cardioembolic ischemic stroke while on dabigatran.

## CASE PRESENTATION

A 39-year-old African American man presented with a syncopal event and subsequently developed myoclonic activity concerning for seizure, for which he was loaded with fosphenytoin and treated with lorazepam. Head computed tomography demonstrated an acute right parietal cerebrovascular accident with progressive cerebral edema. Due to increased somnolence, he required intubation.

His medical history was significant for type 2 diabetes mellitus, hypertension, anterior MI with stent placement to the left anterior descending coronary artery in 2006, and chronic total occlusion of the left anterior descending coronary artery in 2015. He also had a previous left middle cerebral artery ischemic stroke in 2011 with residual moderate to severe expressive aphasia and right-sided weakness, for which he was on anticoagulation with dabigatran. The etiology of his first stroke was considered to be cardioembolic, for which warfarin was initiated, but because of noncompliance, the patient was switched to dabigatran.

He was admitted to the medical intensive care unit because of initial concerns of seizure-like activity in the setting of a new acute ischemic stroke. Cardiovascular examination was negative for murmurs, rubs, or gallops. No peripheral edema was noted. Laboratory data showed normal platelet count, white blood cell count, hemoglobin, and hematocrit. Hypercoagulable studies including factor II, factor V, protein C, protein S, lupus anticoagulant, anti–deoxyribonucleic acid antibody (Ab), ribonucleic protein Ab, anti-SSA/SSB Ab, and anti-Smith Ab were all negative. Hemoglobin electrophoresis performed showed an elevation of hemoglobin $A_2$ suggestive of β-thalassemia minor. Transthoracic echocardiography revealed LV ejection fraction of 25% and segmental wall motion abnormalities in LAD distribution. A large, pedunculated mobile elongated hyperechoic mass measuring 5.6 cm in length and 3.4 cm in width was visualized attached to the LV apex with a narrow stalk (Figure 1, Videos 1-7). Given its of size and mobility, there was concern for thrombus dislodgement and embolization. He was placed on a heparin drip, and both cardiology and cardiothoracic surgery were consulted given the likely ischemic nature of his cardiomyopathy and large LV thrombus. Left heart catheterization and coronary angiography showed total occlusion of the proximal portion of the LAD (Figure 2). Following stabilization of neurologic status, the patient underwent excision of the LV mass. Intraoperative findings included heavy calcification of the LV apex, distal septum, and distal anterior wall. Pathology confirmed a nonmalignant mass and findings consistent with a thrombus.

Due to concern for medication noncompliance and social issues, he was not considered an ideal candidate for warfarin. He was discharged home on DOAC therapy. Follow-up echocardiography 1 month and 2 years after thrombectomy showed no evidence of LV thrombus (Figure 3) on DOAC therapy. He declined the recommendation of an implantable cardioverter-defibrillator for persistent LV dysfunction despite optimal medical therapy. He continues to be followed as an outpatient in the cardiology clinic.

## DISCUSSION

LV mural thrombi account for up to 10% of CES and are most often seen in patients who have had extensive anterior MIs. Regional wall motion abnormality resulting in blood stasis, endocardial injury with associated inflammatory changes, and hypercoagulable state all contribute to thrombus formation in the setting of acute MI. In addition to anterior MI, other risk factors for the development of LV thrombus include large infarct size, severe apical asynergy (i.e.,

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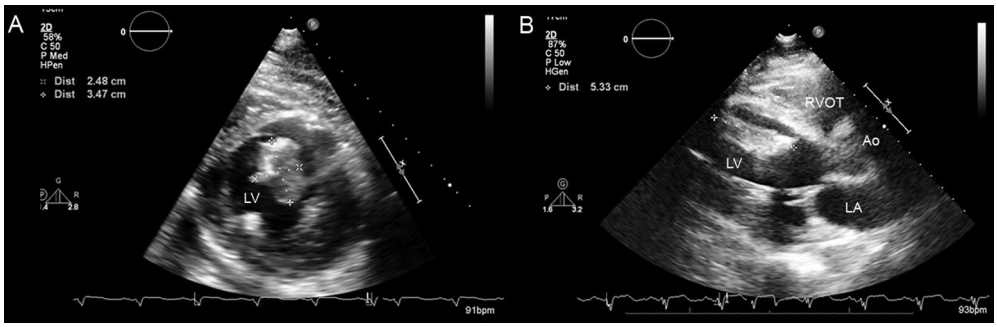


**Figure 1** Transthoracic echocardiogram demonstrating left ventricular thrombus observed in the parasternal **(A)** short- and **(B)** long-axis views. Thrombus dimensions seen in both views are measured as 2.48 x 3.47 x 5.33 cm. *Ao*, Aorta; *LA*, left atrium; *LV*, left ventricle; *RVOT*, right ventricular outflow tract.

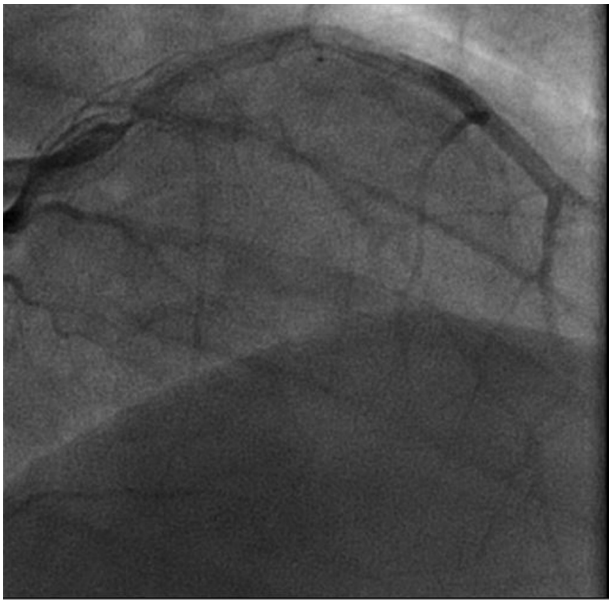

**Figure 2** Left heart catheterization and coronary angiogram demonstrating total occlusion of the proximal portion of the LAD with trace antegrade filling.

akinesis or dyskinesis), and LV aneurysm.[4] The timeline for development of a thrombus after MI varies between 24 hours and 2 weeks, with an increased risk in patients with worsening LV function.[2] In the absence of anticoagulation, 3-month embolism risk with an LV thrombus is as high as 10%–20%, with the highest risk during the first 1–2 weeks.[3,5] Risk for embolization diminishes after 3 months because of organized fibrotic clot adhering to the endocardium. With therapy, patients with apical akinesia seem to have more rapid resolution compared with those with apical aneurysm or dyskinesia.[5]

The current American College of Cardiology guidelines recommend oral VKA for 3 months in patients with asymptomatic LV thrombus (class IIa). The main goal of anticoagulation is to prevent systemic embolization and stroke. In patients who require concurrent dual-antiplatelet therapy, such as those who undergo percutaneous coronary intervention with stent placement, a lower international normalized ratio goal of 2.0–2.5 is recommended because of the increased risk for bleeding (class IIb).[2,3] In comparison, the European Society of Cardiology recommends treatment with a VKA for up to 6 months, guided by repeat echocardiography, and consideration for concomitant DAPT and bleeding risk.[6]

Dabigatran is a direct competitive inhibitor of thrombin. There are no studies comparing the effectiveness of dabigatran versus warfarin in patients with LV thrombus, but there have been studies evaluating hemorrhagic risk. In the Randomized Evaluation of Long-Term Anticoagulation Therapy trial,[7] rates of hemorrhagic stroke were found to be significantly reduced in the group receiving dabigatran (150 mg) than in those receiving warfarin (0.10% vs 0.38%, respectively; relative risk, 0.26; 95% CI, 0.14–0.49; $P < .001$). Despite these findings, the utility of DOAC therapy for the treatment of LV thrombus has not been fully elucidated. The majority of the evidence that support use of DOAC therapy originate from case reports,[8-11] but there are no randomized studies or case reports involving large and mobile clots. The use of apixaban,[8] rivaroxaban,[9] and dabigatran[10] has been cited in a few case reports of LV thrombus resolution, but notably, the majority of the clot burden was <2 cm in size.

Our patient did have a history of nonadherence to therapy and reported missing <1 week of his medication. Although it is possible for mural thrombus to develop within this time frame, it is questionable that a massive thrombus of the size observed could develop within a short span of time. It is likely that he had pre-existing thrombus burden that increased rapidly following interruption of therapy rather than de novo thrombus formation. Studies both in vitro and in vivo have shown that in contrast to factor Xa inhibitors, direct thrombin inhibitors such as dabigatran in lower doses tend to have a potential paradoxical effect by increasing thrombin generation via suppression of the negative feedback system.[11] Mechanical prosthetic valve thrombosis on dabigatran therapy has been reported in the literature, and it has been proposed that local generation of thrombin via intrinsic pathway in mechanical heart valves tends to overwhelm conventional doses of dabigatran.[12] This brings into question the efficacy of DOACs in management of existing thrombus burden. In addition, Vene *et al.*,[13] on the basis of registry data, showed that interruption of DOAC therapy increased short-term thromboembolic risk by >20-fold, typically in the first month. In a recent case report by Bachvarova *et al.*,[14] disruption of dabigatran in addition to inadequate dosing was shown to have potentially contributed to the development of two large thrombi in the left atrium. We believe that a combination of factors unique to direct thrombin inhibitors described above, such as paradoxical thrombus generation, possible decreased efficacy in the setting of existing thrombus burden, and rebound hypercoagulability following discontinuation, all likely contributed to the massive thrombus rather than nonadherence to therapy alone given the brief period of interruption. Although many potential explanations exist as to the mechanism of massive mural thrombus in our patient, it raises several important questions not only with respect to the role of DOAC therapy in management of existing LV mural thrombus but also appropriate dosing and bridging

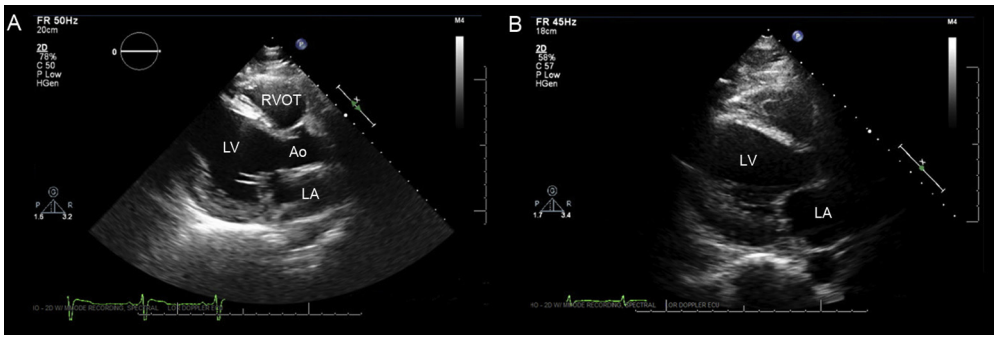


**Figure 3** Transthoracic echocardiogram parasternal long-axis views **(A)** one month and **(B)** two years after thrombectomy with no evidence of thrombus. *Ao*, Aorta; *LA*, left atrium; *LV*, left ventricle; *RVOT*, right ventricular outflow tract.

strategy if interruption is necessitated for elective procedures. Future studies targeted to answer these specific issues are crucial.

There are currently no statements outlining the appropriateness of anticoagulation in large thrombus burden. A study measuring the long-term outcomes of anticoagulation versus surgical resection of LV thrombi was conducted, and the risk for systemic thromboembolism was higher in the former at 17.7% compared with 0% in the latter.[15] In another meta-analysis by Vaitkus and Barnathan,[3] there was a reduction in incidence of LV thrombus if thrombolytic therapy was used, but this did not achieve statistical significance. In our patient, who had significant LV thrombus burden and a history of noncompliance, surgical thrombectomy as first-line therapy followed by a DOAC may have produced a better outcome. As such, for future consideration, the utility of DOAC therapy in LV thrombus may be recommended for LV thrombus size of <2 cm. Additional studies of its use in large LV thrombi are further warranted.

## CONCLUSION

LV mural thrombi have significant morbidity and potential mortality because of risk for systemic embolization and ischemic stroke. Anticoagulation with oral VKA therapy for a duration of 3 months is the recommended treatment of choice in patients with LV mural thrombus. DOAC therapy is considered second-line and is reserved for patients who are intolerant to VKA therapy, as there are no large-scale randomized studies to date demonstrating long-term outcomes. The majority of current use of DOAC therapy in LV thrombus originates from observational case reports, with no data to support use for large thrombus size. Our report of a patient with a large LV thrombus and recurrent stroke while on dabigatran highlights the important question of the utility of DOAC therapy in patients with large LV thrombi and need for further studies.

## SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.case.2018.04.008.

## REFERENCES

1. Kamel H, Healey JS. Cardioembolic stroke. Circ Res 2017;120:514-26.
2. Delewi R, Zijlstra F, Piek JJ. Left ventricular thrombus formation after acute myocardial infarction. Heart 2012;98:1743-9.
3. Vaitkus PT, Barnathan ES. Embolic potential, prevention and management of mural thrombus complicating anterior myocardial infarction: a meta-analysis. J Am Coll Cardiol 1993;22:1004-9.
4. Shacham Y, Leshem-Rubinow E, Ben Assa E, Rogowski O, Topilsky Y, Roth A, et al. Frequency and correlates of early left ventricular thrombus formation following anterior wall acute myocardial infarction treated with primary percutaneous coronary intervention. Am J Cardiol 2013;111:667-70.
5. Keren A, Goldberg S, Gottlieb S, Klein J, Schuger C, Medina A, et al. Natural history of left ventricular thrombi: their appearance and resolution in the posthospitalization period of acute myocardial infarction. J Am Coll Cardiol 1990;15:790-800.
6. Steg G, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, Borger MA, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology (ESC). Eur Heart J 2012;33:2569-619.
7. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom JW, Oldgren J, Parekh A, et al. RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51.
8. Yildirim E, Kalkan K, Ipek E, Demirelli S, Ermis E. Successful resolution of left ventricular thrombus with apixaban treatment. Int J Cardiovasc Acad 2016;2:57-8.
9. Makrides C. Resolution of left ventricular postinfarction thrombi in patients undergoing percutaneous coronary intervention using rivaroxaban in addition to dual antiplatelet therapy. BMJ Case Rep 2016;2016. bcr2016217843.
10. Chung K, Paek YM, Lee HJ, Hong KS. Dabigatran effect on left ventricular thrombus in a patient with acute ischemic stroke. J Stroke 2015;17:366-8.
11. Perzborn E, Heitmer S, Buetehorn U, Laux V. Direct thrombin inhibitors, but not the direct factor Xa inhibitor rivaroxaban, increase tissue factor-induced hypercoagulability in vitro and in vivo. J Thromb Haemost 2014;12:1054-65.
12. Jaffer IH, Stafford AR, Fredenbrugh JC, Whitlock RP, Chan NC, Weitz JI. Dabigatran is less effective than warfarin at attenuating mechanical heart valve-induced thrombin generation. JAMA 2015;4:e002322.
13. Vene N, Mavri A, Gubensek M, Tratar G, Vizintin Cuderman T, Perme MP, et al. Risk of thromboembolic events in patients with non-valvular atrial fibrillation after dabigatran or rivaroxaban discontinuation—data from the Ljubljana registry. PLoS One 2016;11:e0156943.
14. Bachvarova V, Bucci C, Ho N, Yazdan-Ashoori Morgan C. Massive left atrial thrombi during dabigatran therapy for nonvalvular atrial fibrillation. CASE 2017;1:198-201.
15. Lee JM, Park JJ, Jung HW, Cho YS, Oh IY, Yoon CH, et al. Left ventricular thrombus and subsequent thromboembolism, comparison of anticoagulation, surgical removal, and antiplatelet agents. J Atheroscler Thromb 2013;20:73-93.