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INTRACARDIAC CLOTS: IS RIVAROXABAN THE FUTURE?

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ABSTRACT

Intracardiac clots, including Left atrial (LA) clots and Left ventricular (LV) clots can be potentially life threatening for the patient and challenging for the physician. The traditionally used Vitamin-K antagonists although to a certain extent effective in treatment, do have some disadvantages that limit their use. New treatment options have to be explored to ensure more effective and efficient therapy.

The advent of new oral anticoagulants (NOACs), which are currently not approved for treatment of intracardiac clots, might add to the armory against them. One such NOAC, Rivaroxaban is the first to be approved for treatment of DVT and PE, and for the secondary prevention of VTE. Here, we review the cases reported and the possible use of Rivaroxaban for treatment of intra cardiac clots.

Keywords: Anticoagulants; Rivaroxaban; Thrombosis; Thrombin; Prothrombin; Hemostasis; Platelet Activation; Vitamin K.

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INTRODUCTION

Factor Xa: a target for novel oral anticoagulants

Factor Xa and factor Va are vital components of the coagulation system which regulate thrombin production.[1,2] Factor Xa by activating effect on factor V, regulates the assembly of the Prothrombinase complex.[3] The critical role of factor Xa in the coagulation cascade makes it an important target in achieving anti-coagulation. Recently much work has been in the development of synthetic direct and specific factor Xa inhibitors which has led to the development of new oral anticoagulants as a substitute for vitamin K antagonists. One such New Oral Anti-coagulant (NOAC) is Rivaroxiban, which was the first oral direct factor Xa inhibitor with clinical approval in 2008.[2]

Pharmacology of Rivaroxaban

Rivaroxaban has high oral bioavailability and very high affinity for factor Xa inhibiting the generation of thrombin from Prothrombin (Figure 1). Rivaroxaban achieves peak plasma concentrations in about 3–4 hours after oral intake. It is eliminated by liver as well as unchanged by kidney and has a half-life of 7-11 hours.[4]

As per standards established by the International Society of Thrombosis and Hemostasis, the bleeding profile of Rivaroxaban was slightly better as compared to warfarin. The rates of fatal bleeding, bleeding at critical areas and intracranial bleeding were higher with warfarin while

gastrointestinal bleeds were higher with Rivaroxaban.[5]

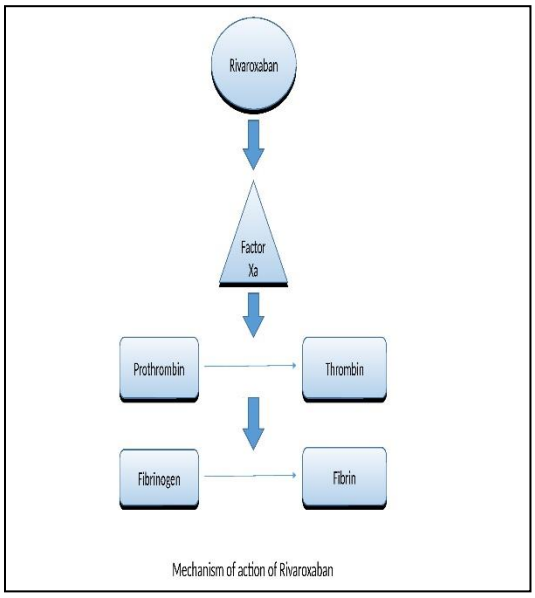

Figure 1: Mechanism of action of Rivaroxaban.

Approved use of Rivaroxaban

Low-molecular-weight heparin combined with a vitamin K antagonist (VKA) forms the standard therapy for venous thromboembolism (VTE) including Deep vein thrombosis (DVT) and Pulmonary embolism (PE).[6-8] Recently a number of direct oral anticoagulants have been used and analyzed for the acute and extended treatment of symptomatic VTE.[9-14] EINSTEIN-DVT and EINSTEIN-PE are two studies which evaluated a single-drug approach using Rivaroxaban with standard-therapy consisting of initial enoxaparin followed by a VKA for the treatment of DVT and/or PE.[8,9] Results from these studies demonstrated similar efficacy accompanied by a lower incidence of major bleeding with Rivaroxaban. On the basis of these trials, Rivaroxaban has been approved for acute and extended treatment of DVT and/or PE.[8,9] Rivaroxaban has yielded particularly encouraging results in elderly, frail patients as well as patients who have renal impairment and cancer. Moreover, there was significant reduction in major bleeding with Rivaroxaban in all these patients.[6,15]

Comparison of the various NOACs available have been done in some landmark trials such as EINSTEIN-I, EINSTEIN-II, RECOVER-I, RECOVER-II, AMPLIFY and Hokusai-V. Some of the results have been summarized in Table 1. With the exception of bleeding profile no significant difference was observed regarding recurrent VTE and death with the use of various NOACs.[9,12,13,15,16]

Table 1: Comparison of relative risk of various outcomes for NOACs

Outcome	Rivaroxaban vs Edoxaban		Rivaroxaban vs Dabigatran		Apixaban vs Rivaroxaban	
	RR	p	RR	p	RR	p
Death	0.85	0.40	0.89	0.65	0.88	0.63
Recurrent VTE[a]	1.00	0.99	0.82	0.40	0.94	0.80
CRNB[b]	1.15	0.16	1.50	0.001	0.47	0.61
Major bleeding	0.64	0.10	0.74	0.30	0.64	0.10

[a] **Venous thromboembolism**
[b] **Clinically relevant non major bleeding**

The ROCKET AF trial [20] studied Rivaroxaban (20 mg/day; 15 mg/day) in comparison with warfarin (international normalized ratio 2-3) in patients with AF and previous history of stroke or its risk factors. The results of ROCKET AF trial showed non inferiority of Rivaroxaban compared with warfarin for the prevention of stroke and systemic embolism. The rate of

major bleeding was similar while Rivaroxiban showed markedly reduced intracranial bleeds.

Left ventricular clots

Left ventricular thrombus (LVT) is a well-recognized complication of congestive heart failure (CHF) and acute myocardial infarction (AMI). The risk of LVT in patients with anterior wall myocardial infarction (AMI) has been reported to be around 30-40% while in dilated cardiomyopathy and heart failure the incidence is between 10-30%.[18-21] Diagnosis and treatment of this condition is essential because of the potential risk of systemic embolization.

Pathogenesis of Left Ventricular Thrombus

Thrombus formation in dependent on Virchow's triad which includes endothelial injury due to ischemia, blood stasis due to regional wall akinesia and hypercoagulability (Figure 2).[25] This triad can result in the formation of LV thrombus composed of platelets, fibrin and red

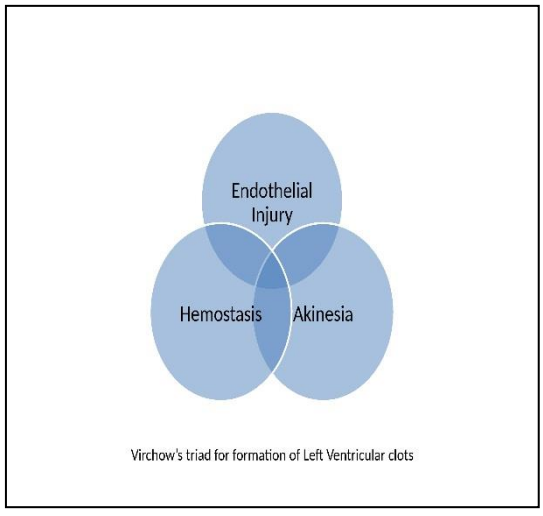

Figure 2: Virchow's triad for Left Ventricular clot formation.

blood cells.[23,24] Although considered a complication of infarction, thrombus formation is also speculated to reinforce the underlying myocardial scar, limits infarct expansion, and partially restores the thickness of the myocardial wall resulting in reduced bulging and a more effective myocardial contraction.[13,25] Data from multiple studies comprising a total of 390 patients analyzed the incidence of Left ventricular (LV) thrombus formation in those patients treated with thrombolysis and without thrombolytic therapy. It demonstrated only a trend in favor of thrombolysis with no significant difference in the incidence of LV thrombus formation.[26]

Vitamin K antagonists

There are no large trials that have evaluated the efficacy of long term anticoagulation in prevention of embolization in patients with LV thrombus hence rendering the effect of long term anticoagulants on the risk of embolization debatable.[13] Some unanswered questions are what dose and for how long to give an anticoagulant.

Significant thrombus burden may accompany STEMI.[27,28] During PCI for acute myocardial infarction a LV thrombus can be managed by aspiration thrombectomy.[29] In a study a patient of coronary artery disease (CAD) presented with an estimated LVEF of about 35% with possible apical intramural thrombus. The patient was given aspirin 75 mg, Clopidogrel 75 mg, Carvedilol 3.125 mg twice a day, and atorvastatin 80 mg as well as Spironolactone 12.5 mg. For LV thrombus anticoagulation, Rivaroxaban 20 mg a day was prescribed because of difficulty in monitoring INR and as well as because of complex dosing regimen associated with warfarin.[30] Five weeks later the patient was reassessed and no evidence of LV clots was found.

In case of tachycardia-induced heart failure, a thrombus mass was noted in the left ventricle (LV) on echocardiography.[31] There was also evidence of systemic embolism in the spleen, kidneys, brain, and limbs. Limb thrombectomy was done and the patient was placed on

Rivaroxaban for seven days. Transthoracic echocardiography was then repeated, which showed the disappearance of the LV thrombus hence providing evidence of fibrinolytic effects of Rivaroxaban on thrombi in Left ventricle.[31]

In another case report,[32] a patient with AF, heart failure and LV thrombus was successfully treated with 4 weeks treatment of Rivaroxaban. So, Rivaroxaban not only helps to prevent thrombosis but also resolves established thrombi.[31,33] It also has also been shown to reduce platelet activation by through modulation of ADP-induced platelet aggregation.[34]

Left atrial clots

Till recently, the mainstay anticoagulant left atrial appendage (LAA) thrombus has been warfarin.[35] Presence of thrombus in the Left atrium poses a significant risk for subsequent thromboembolism.[36-39] Although the data for the use of novel oral anticoagulants (NOACs) in left atrial thrombi is currently limited, it's use has been increasing and cases have been reported of its use for LAA thrombus as well. NOACs might become the choice of drug in left atrium thrombus due to the diverse range of advantages that they offer including better relative efficacy, safety, convenience and as well as their faster onset of action.[40,41]

In a study[42] three patients with LAA thrombus were treated with Rivaroxaban for 6 weeks. It resulted in complete resolution without any embolic events as shown by transesophageal echocardiography. Moreover, Takasugi et al[43] also described a set of 3 cases, which showed similar results with 8 to 33 days of Rivaroxaban treatment. Such case reports are encouraging and clinical trials such X-TRA and CLOT-AF[1] will provide the much needed insight as well as evidence for the use of Rivaroxaban in left atrial clots.

Intracoronary clots

Intra coronary thrombi and clots are generally managed with antiplatelet drugs such as aspirin and Clopidogrel. Although quiet effective, lack of response to such treatment is present which can frustrate physicians. It has been shown that 5-11% of the population are non-responders while 9-26% are semi-responders in the case of Clopidogrel.[44] Similarly, another study showed that 6% of the population are non-responders to dual antiplatelet therapy including aspirin and Clopidogrel.[45]

In acute myocardial infraction patients, thrombi can be managed during percutaneous coronary intervention (PCI) by aspiration thrombectomy, however it has not shown any clinical benefit.[46] Another option would include intracoronary thrombolysis after exclusion of any contraindication. In one case report, a medical regimen including aspirin, Clopidogrel and Rivaroxaban resulted in the resolution of the massive intracoronary thrombus and left ventricular apical intramural thrombus which has also been previously reported.[27,47] In this case Rivaroxaban was used due to lack of reliable and satisfactory results with other anticoagulants. So, although triple anti-coagulant therapy was used, the role of Rivaroxaban cannot be overlooked. Further studies are needed to confirm such a role for Rivaroxaban.

Future implications

In a setup where availability of health system, early recognition, financial resources, time restraints and lack of follow up are major issues, NOACs definitely can come up as a very soothing alternative, both for physicians and patients. The latest recognition of antidote for Rivoroxaban (Andexanet Alfa: ANNEXA-R)[48] and the fact that it has a much shorter half-life, also relieves the prescriber for potential bleeding risk, especially in a setting

where a patient is already on dual antiplatelet therapy after acute coronary syndrome.

Although a far-fetched idea, but in future one may consider trial of patients with prosthetic valves. This might not be possible as in-human trial, but there is definitely a scope for animal trials with NOACS in prosthetic valve cases. One cannot imagine the relief on health system if that's feasible, with scrapping up of all the warfarin clinics with no extra burden on health system for regular INR monitoring.

CONCLUSION

Due to the vast number of advantages that Rivaroxaban has to offer along with its convenience for the patients and physicians as well as its better economics, it is fast becoming a dominant alternative to the conventional Vitamin K antagonists in AF and DVT. As far as intracardiac clots are concerned, further studies and trials are needed to test the limits of its use in left ventricular, left atrial and coronary thrombi, its efficacy as well as its potential serious and undesirable effects such as bleeding and stroke.

REFERENCES

1. Ahrens I, Bode C. Clinical utility of Rivaroxaban in stroke prevention associated with nonvalvular atrial fibrillation- patient considerations. J Blood Med. 2014 Feb;5:25-30.
2. Ahrens I, Lip GY, Peter K. New oral anticoagulant drugs in cardiovascular disease. Thromb Haemost. 2010 Jul;104(1):49-60.
3. Hara T, Yokoyama A, Ishihara H, Yokoyama Y, Nagahara T, Iwamoto M. DX-9065a, a new synthetic, potent anticoagulant and selective inhibitor for factor Xa. Thromb Haemost. 1994 Mar;71(3):314-19.
4. Perzborn E, Roehrig S, Straub A, Kubitza D, Misselwitz F. The discovery and development of Rivaroxaban, an oral, direct factor Xa inhibitor. Nat Rev Drug Discov. 2011 Jan;10(1):61-75.
5. Hirsh J, Fuster V, Ansell J, Halperin JL. American Heart Association/American College of Cardiology Foundation Guide to Warfarin Therapy. Circulation. 2003 April 1;107(12):1692–1711.
6. Prins MH, Lensing AWA, Bauersachs R, van Bellen B, Bounameaux H, Brighton TA, et al. Oral Rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. Thrombosis Journal. 2013 Sep;11(1):21-9.
7. Prandoni P, Lensing AW, Buller HR, Carta M, Cogo A, Vigo M, et al. Comparison of subcutaneous low-molecular-weight heparin with intravenous standard heparin in proximal deep-vein thrombosis. Lancet. 1992 Feb 22;339(8791):441-5.
8. The Columbus Investigators. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. N Engl J Med. 1997 Sep 4;337(10):657-62.
9. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H; the RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009 Dec 10; 361(24):2342-52.
10. Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D; RE-MEDY Trial Investigators; RE-SONATE Trial Investigators. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med. 2013 Feb 21;368(8):709-18.
11. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M; AMPLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. N Engl J Med. 2013 Feb 21;368(8):699-708.
12. The EINSTEIN Investigators. Oral Rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010 Dec 23;363(26):2499-2510.
13. The EINSTEIN-PE Investigators. Oral Rivaroxaban for the treatment of symptomatic

pulmonary embolism. N Engl J Med. 2012 Apr 5;366(14):1287-97.

14. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012 Feb 14;141(2 Suppl):e419S-e494S.
15. Hokusai-VTE Investigators; Buller HR, Decousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013 Oct 10;369(15):1406-15.
16. Schulman S, Kakkar AK, Goldhaber SZ, Schellong S, Eriksson H, Mismetti P; RE-COVER II Trial Investigators. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation. 2014 Feb 18;129(7):764-72.
17. Paikin JS, Manolakos JJ, Eikelboom JW. Rivaroxaban for stroke prevention in atrial fibrillation: a critical review of the ROCKET AF trial. Expert Rev Cardiovasc Ther. 2012 Aug;10(8):965-72.
18. Billingsley IM, Leong-poi H. Left ventricular thrombus: diagnosis, prevention and management. Cardiology Rounds. 2005;10(7):1-6.
19. Asinger RW, Mikell FL, Elsperger J, Hodges M. Incidence of left-ventricular thrombosis after acute transmural myocardial infarction. Serial evaluation by two-dimensional echocardiography. N Engl J Med. 1981 Aug 6;305(6):297-302.
20. Ciaccheri M, Castelli G, Cecchi F, Nannini M, Santoro G, Troiani V, et al. Lack of correlation between intracavitary thrombosis detected by cross sectional echocardiography and systemic emboli in patients with dilated cardiomyopathy. Br Heart J. 1989 Jul;62(1):26-9.
21. Gottdiener JS, Gay JA, VanVoorhees L, DiBianco R, Fletcher RD. Frequency and embolic potential of left ventricular thrombus in dilated cardiomyopathy: assessment by 2-dimensional echocardiography. Am J Cardiol. 1983 Dec 1;52(10):1281-5.
22. Delewi R, Zijlstra F, Piek JJ. Left ventricular thrombus formation after acute myocardial infarction. Heart. 2012 Dec;98(23):1743-9.
23. Moutzouris JP, Ng AC, Chow V, Chung T, Curnow J, Kritharides L. Acute pulmonary embolism during warfarin therapy and long-term risk of recurrent fatal pulmonary embolism. Thromb Haemost. 2013 Sep;110(3):523-33.
24. Gallus AS, Baker RI, Chong BH, Ockelford PA, Street AM. Consensus guidelines for warfarin therapy. Recommendations from the Australasian Society of Thrombosis and Haemostasis. Med J Aust. 2000 Jun 19;172(12): 600-5.
25. Morris L, Stevermer JJ. PURLs: An alternative to warfarin for patients with PE (Comment). J Fam Pract. 2012 Dec 6;61(12):751-2.
26. Fiessinger JN, Huisman MV, Davidson BL, Bounameaux H, Francis CW, Eriksson H, et al. Ximelagatran vs low-molecular weight heparin and warfarin for the treatment of deep vein thrombosis: a randomized trial. JAMA. 2005 Feb 9;293(6):681-9.
27. Jamal N, Bapumia M. Dual antiplatelet agents and Rivaroxaban for massive intracoronary thrombus in STEMI. Clinical Case Reports. 2015 Nov;3(11):927-31.
28. American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. J Am Coll Cardiol. 2013 Jan 29;61(4):485-510.
29. Sianos G, Papafaklis MI, Serruys PW. Angiographic thrombus burden classification in patients with ST- segment elevation myocardial infarction treated with percutaneous coronary intervention. J Invasive Cardiol. 2010 Oct;22(10 Suppl B):6B-14B.
30. Jacobsen A. Is there a role for warfarin anymore? Hematology Am Soc Hematol Educ Program. 2012;2012:541-6.

31. Nakasuka K, Ito S, Noda T, Hasuo T, Sekimoto S, Ohmori H, et al. Resolution of left ventricular thrombus secondary to tachycardia-induced heart failure with Rivaroxaban. Case Rep Med. 2014;2014:814524.
32. Padilla Pérez M, Salas Bravo D, Garcelán Trigo JA, Vazquez Ruiz de Castroviejo E, Torres Llergo J, Lozano Cabezas C, et al. Resolution of left ventricular thrombus by Rivaroxaban. Future Cardiol. 2014 May;10(3):333-6.
33. Yeh CH, Fredenburgh JC, Weitz JI. Oral direct factor Xa inhibitors. Circulation Research. 2012 Sep 28;111(8):1069-78.
34. Flierl U, Fraccarollo D, Micka J, Bauersachs J, Schäfer A. The direct factor Xa inhibitor Rivaroxaban reduces platelet activation in congestive heart failure. Pharmacological Research. 2013 Aug;74:49-55.
35. Marino B, Kim J, Spinelli M. Persistent Left Atrial Appendage Thrombus with Use of Rivaroxaban. Eplabdigest.com [Webpage] 2015 Mar;15(3). Available from: https://www.eplabdigest.com/articles/Persistent-Left-Atrial-Appendage-Thrombus-Use-Rivaroxaban.
36. Lip GY, Hammerstingl C, Marin F, Cappato R, Meng IL, Kirsch B, et al. Rationale and design of a study exploring the efficacy of once-daily oral Rivaroxaban (X-TRA) on the outcome of left atrial/left atrial appendage thrombus in nonvalvular atrial fibrillation or atrial flutter and a retrospective observational registry providing baseline data (CLOT-AF). Am Heart J. 2015 Apr;169(4):464-71.
37. Corrado G, Tadeo G, Beretta S, Tagliagambe LM, Manzillo GF, Spata M, et al. Atrial thrombi resolution after prolonged anticoagulation in patients with atrial fibrillation. Chest. 1999 Jan;115(1):140-3.
38. Nagarakanti R, Ezekowitz MD, Oldgren J, Yang S, Chernick M, Aikens TH, et al. Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. Circulation. 2011 Jan 18;123(2):131-6.
39. The Stroke Prevention in Atrial Fibrillation Investigators Committee on Echocardiography. Transesophageal echocardiographic correlates of thromboembolism in high-risk patients with nonvalvular atrial fibrillation. Ann Intern Med. 1998 Apr 15:128(8):639-47.
40. De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, et al. General mechanisms of coagulation and targets of anticoagulants (section I). Position paper of the ESC Working Group on Thrombosis–Task Force on Anticoagulants in Heart Disease. Thromb Haemost. 2013 Apr;109(4):569-79.
41. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, et al. 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 Nov;33(21):2719-47.
42. Hammerstingl C, Pötzsch B, Nickenig G. Resolution of giant left atrial appendage thrombus with Rivaroxaban. Thromb Haemost. 2013 Apr;109(4):583-4.
43. Takasugi J, Yamagami H, Okata T, Toyoda K, Ngatsuka K. Dissolution of the left atrial appendage thrombus with Rivaroxaban therapy. Cerebrovasc Dis. 2013 Oct;36(4):322-3.
44. Müller I, Besta F, Schulz C, Massberg S, Schönig A, Gawaz M. Prevalence of clopidogrel non-responders among patients with stable angina pectoris scheduled for elective coronary stent placement. Thromb Haemost. 2003 May;89(5):783-7.
45. Gori AM, Marcucci R, Migliorini A, Valenti R, Moschi G, Paniccia R, et al. Incidence and clinical impact of dual nonresponsiveness to Aspirin and Clopidogrel in patients with drug-eluting stents. J Am Coll Cardiol. 2008 Aug;52(9):734-9.
46. American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions, O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: a report of the American

College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013 Jan 29;61(4):e78-140.

47. Nakasuka K, Noda SIT, Hasuo T, Sekimoto S, Ohmori H, Inomata M, et al. Resolution of left ventricular thrombus secondary to tachycardia-induced heart failure with Rivaroxaban. Case Rep Med. 2014;2014:814524.
48. Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. N Engl J Med 2015 Dec 17;373:2413-24.