Direct Oral Anticoagulants and Prosthetic Heart Valves: A Systematic Review of Case Reports

Tyler Richie, Steven Carter Jr, MS, Jayden Lee, PharmD, BCACP, CACP
Philadelphia College of Osteopathic Medicine – Georgia Campus

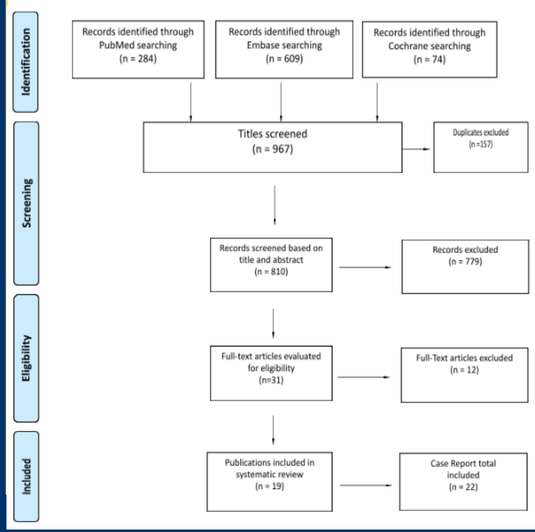
Introduction

- Direct oral anticoagulants (DOACs) are indicated to treat and prevent venous thromboembolism and to prevent stroke or systemic embolism in patients with non-valvular atrial fibrillation.
- The introduction of DOACs has provided an alternative to warfarin for patients in need of oral anticoagulation. It is, however, unclear whether DOACs are safe and effective in patients with heart valve replacement.
- The RE-ALIGN trial published in 2013 did not support the use of dabigatran in patients with mechanical valve replacements; however, there are ongoing studies, such as the PROACT Xa trial and the ATLANTIS trial, investigating the use of other DOACs in patients with heart valve replacements.
- This purpose of this study is to evaluate and describe a potential risk of thrombosis in patients with heart valve replacement and treated with a DOAC.

Methods

- Following the PRISMA guidelines, a systematic literature search was performed on June 24th, 2020 using three electronic databases (Pubmed, Embase, Cochrane Library) with the following key terms: (apixaban OR rivaroxaban OR edoxaban OR dabigatran OR direct oral anticoagulant OR factor Xa inhibitor OR direct thrombin inhibitor OR target specific oral anticoagulant) and (valve replacement OR valve implantation).
- Two authors independently screened the search result using Rayyan QCRI (a systematic review web app). Different decisions were resolved through consensus between the two authors with the input of the third author.

FIGURE 1 – PRISMA flow diagram



Summary of Case Reports

Author (year)	Age	DOAC (Time on DOAC)	Type of valve replacement (Time since replacement)	Past Medical History	Thrombotic Event	Interventions	Outcome
Akgülü (2012)	41	dabigatran 110 mg BID (9 days)	Bioprosthetic mitral valve (3 weeks)	Prior ischemic stroke, previous mechanical mitral thrombosis, recent bacterial endocarditis	Valve thrombosis and ischemic stroke	Continuous Heparin Infusion	Complete valve thrombosis resolution
Atar (2013)	72	dabigatran 110 mg BID (5 months)	Mechanical mitral valve (8 years)	AF, prior stroke	Valve thrombosis	Valve replacement with bioprosthetic valve	Patient died 3 days after surgery
Atar (2013)	73	dabigatran 150 mg BID (2 months)	Mechanical mitral valve (12 years)	Paroxysmal AF, GI bleeding	Valve thrombosis	Valve replacement with bioprosthetic valve	Patient died hours after surgery
Chu (2012)	78	dabigatran 150 mg BID (3 months)	Mechanical aortic valve (15 years)	CABG, hyperlipidemia, hypertension, and type 2 diabetes mellitus	Valve thrombosis	Heparin, surgical excision of thrombus	Full recovery, pt restarted on warfarin
Coulter (2013)	80	dabigatran 150 mg BID (7 weeks, 4 days)	Mechanical mitral valve (N/A)	Subdural Hematoma	Valve thrombosis	Valve replacement with bioprosthetic valve	Pt had a succesful valve replacement
Kuwauchi (2013)	57	dabigatran 150 mg BID (10 days)	Mechanical mitral Valve (18 years)	Paroxysmal AF, congenitally corrected transposition of the great arteries	Right Axillary Artery Thrombus	Thromboembolectomy	Discharged on Warfarin
Molinier (2014) (Abstract)	65	dabigatran 150 mg BID (2 months)	Mechanical mitral valve (9 years)	N/A	Valve thrombosis and ischemic stroke	Pt given Heparin	Favorable after Tx with heparin
Price (2012)	51	dabigatran 150 mg BID (2 months)	Mechanical aortic Valve (8 years)	Unremarkable	Valve thrombosis	Valve replacement	Postoperative course was uneventful with complete recovery
Price (2012)	59	dabigatran 150 mg BID (3 months)	Mechanical mitral valve (N/A)	Rheumatic mitral disease	Valve thrombosis	Replacement of mitral valve and repair of tricuspid	Complete recovery
Stewart (2012)	62	dabigatran 150 mg BID (9 months)	Mechanical aortic valve (2 years)	AF	Valve thrombosis and ischemis stroke	Tx with phenindione and ASA 100 mg daily	No recurrence of thrombus
Apostilidou (2019	57	rivaroxaban, unknown dose (14 days)	Bioprosthetic mitral valve (3 years)	IVDU, prior valve thrombosis, bacterial endocarditis	Valve thrombosis	TPA, valve replacement	Discharged home on warfarin
Bamford (2019)	74	rivaroxaban 20 mg daily (N/A)	Bioprosthetic aortic valve (6 years)	DVT, Renal Transplant, Multiple Strokes	Valve thrombosis	Heparin, Warfarin, low dose ASA	Improvement of valve thrombosis
Carvalho (2019)	67	rivaroxaban 20 mg daily (6 months)	Mechanic mitral valve (10 years)	AF, dyslipidemia, former smoking, epilepsy, and rheumatic fever in childhood	Valve thrombosis	Diuretics and Heparin, Valve replacement with mechanical valve	Discharged on warfarin
Franzeck (2017) (Abstract)	73	rivaroxaban 20 mg daily (11 months)	TMVR (11 months)	Prior mitral annuloplasty, CHF, pulmonary HTN	Valve thrombosis	Rivaroxaban switched to phenprocoumon	Complete resolution of thrombus
Kumar (2017)	54	rivaroxaban, unknown dose (N/A)	Mechanical aortic Valve (N/A)	MI, RA, obesity, HTN, diabetes, and hyperlipidemia	Valve thrombosis	Alteplase and heparin infusion	No clinical improvement
Leatherby (2018)	82	rivaroxaban, unknown dose (2 years)	Bioprosthetic aortic valve (2 years)	Paroxysmal AF	Valve thrombosis	Valve replacement with new bioprosthetic valve	Pt discharged on warfarin
Strozzi (2019)	33	rivaroxaban 20 mg daily (33 months)	Bioprosthetic pulmonary valve (3 years)	Paroxysmal AF, VSD, congenital TOF repair	Valve thrombosis	Implantation of new pulmonary valve bioprosthesis	Good post-op recovery, placed on warfarin.
Bamford (2019)	79	apixaban 5 mg BID (N/A)	Bioprosthetic aortic valve (7 years)	AF, sleep apnea, COPD	Valve thrombosis	Heparin, Antibiotics, and valve replacement	Discharged home on Warfarin
Buchanan (2017)	87	apixaban 2.5 mg BID (4.5 months)	TAVR (5 months)	AF, heart block, hyperlipidemia, obstructive sleep apnea, non-obstructive CAD, and **lung cancer**	Valve thrombosis	Apixaban discontinued and warfarin started	Leaflet thrombosis progressed despite warfarin treatment
Fusco (2020) (Abstract)	47	apixaban, unknown dose (N/A)	Pulmonary valve replacement, uknown type (3 years)	AF, Tetralogy of Fallot, congenital absence of L pulmonary branch, **Metastatic CA**	Valve thrombosis	N/A	Patient died suddenly before treatment
O'Callaghan (2018)	63	apixaban 5mg BID (N/A)	Bioprosthetic aortic and mitral valves (4 years)	Paroxysmal AF, coronary artery disease with stent, HTN, HLD, 45 PPY smoking Hx	Valve thrombi (mitral and aortic)	IV heparin, ASA 81mg/d, replacement of both mitral and aortic valves with new bioprosthetic valves	Pt discharged after 7 days on warfarin
Perrin (2018) (Abstract)	80	apixaban, unknown dose (12 months)	TAVR (18 months)	Persistent AF, **polycythemia vera**, chronic total occlusion of the left circumflex coronary artery	Valve thrombosis	Warfarin, ASA 100mg BID	Clinical improvment

Table 1 – Characteristics of individual case reports
AF=Atrial Fibrillation; CABG=Coronary Artery Bypass Graft; RA=Rheumatoid Arthritis; CA=Cancer; CAD=Coronary Artery Disease; DVT=Deep Vein Thrombosis; IVDU=Intravenous Drug Use; CHF=Congestive Heart Failure; MI=Myocardial Infarction; HTN=Hypertension; COPD=Chronic Obstructive Pulmonary Disease; TOF=Tetralogy of Fallot; HLD=Hyperlipidemia; TAVR=Transcatheter Aortic Valve Replacement; TMVR=Transcatheter Mitral Valve Replacement; ASA=Aspirin; TPA=Tissue Plasminogen Activator; VSD=Ventricular Septal Defect; Tx=Treatment

Results

- Among 967 citations, 19 case reports involving 22 patients were identified and assessed in this study.
- 45.5%, 31.8%, and 22.7% of the patients were taking dabigatran, rivaroxaban, and apixaban, respectively.
- 11 patients (50%) had mechanical valves, and 11 patients (50%) had bioprosthetic valves.
- The average age of the patients was 65.2 years (SD±14.3) with 54.5% female. 59.1% of the patients had another indication for anticoagulation other than heart valve replacement.
- Of the patients with another indication for anticoagulation, 92.3% had atrial fibrillation, and 7.7% had deep vein thrombosis.
- 13.6% of the cases reported concurrent aspirin use
- 3 patients (13.6%) had cancer as a comorbid condition, and 1 patient (4.5%) had a valve-in-valve replacement.
- 95.5% of the 21 cases reported an intervention with 13 patients (61.9%) receiving surgery (11 valve replacements, 2 thrombectomies) and 8 patients (38.1%) receiving medical management.
- 4.5% of the cases reported death prior to intervention.
- The time reported from onset of DOAC therapy to onset of thrombotic event ranged from 9 days to 33 months.

Discussion

- It is still uncertain whether DOACs are safe or effective in preventing valve thrombosis for different types of valve replacements.
- The use of DOACs in patients with valve replacement should be limited to those with no other alternative.
- Further research is needed to determine the effectiveness and safety of DOAC use in patients with prior valve replacements.

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Disclosures

- All authors are affiliated with the Philadelphia College of Osteopathic medicine. All authors have nothing to disclose.