HSPI The Open Access Publisher

JCCM JOURNAL OF CARDIOLOGY AND CARDIOVASCULAR MEDICINE
ISSN 2575-0143

Case Study

Morbidity and Mortality with Pericardial Effusion Associated with Direct Oral Anticoagulants and P-glycoprotein Inhibitors

Jessica Song[1], Jered Arquiette[2], Jack Vo[1], Benjamin Dang[1], Susie Bae[1] and Sun Yong Lee[3]*

[1]Thomas J. Long School of Pharmacy, University of the Pacific, Stockton, California, USA
[2]Pharmacy Department, San Joaquin General Hospital, French Camp, California, USA
[3]Internal Medicine Department/Primary Medicine Clinic, San Joaquin Health Centers/San Joaquin General Hospital, French Camp, California, USA

Abstract

Pericardial effusion is a rare but potentially fatal adverse effect reported with apixaban, dabigatran, edoxaban, and rivaroxaban (direct oral anticoagulants). We report three cases of pericardial effusion that occurred at a single institution with two patients requiring urgent pericardiocentesis. All patients took a direct oral anticoagulant with a p-glycoprotein inhibitor or a combined p-glycoprotein and CYP3A4 inhibitor. Our patients had underlying conditions predisposing them to developing pericardial effusion.

More Information

***Address for correspondence:** Sun Yong Lee, MD, Attending Physician, Internal Medicine Department/Primary Medicine Clinic, San Joaquin Health Centers/San Joaquin General Hospital, French Camp, California, USA,
Email: sunyong.lee55@gmail.com

Submitted: June 13, 2025
Approved: June 18, 2025
Published: June 19, 2025

How to cite this article: Song J, Arquiette J, Vo J, Dang B, Bae1 S, Lee SY. Morbidity and Mortality with Pericardial Effusion Associated with Direct Oral Anticoagulants and P-glycoprotein Inhibitors. J Cardiol Cardiovasc Med. 2025; 10(3): 098-103. Available from: https://dx.doi.org/10.29328/journal.jccm.1001215

Keywords: Direct oral anticoagulants; Pericardial effusion; Hemopericardium; Pericardiocentesis; Drug interactions

Introduction

Direct Oral Anticoagulants (DOACs) are recommended as first-line drugs for stroke prevention in patients with non-valvular atrial fibrillation [1]. Similarly, the American College of Chest Physicians recommends DOACs over warfarin for patients with venous thromboembolism [2]. Unlike warfarin, DOACs have a lower propensity for drug interactions and offer the convenience of fixed dosing with less frequent laboratory monitoring. Apixaban, dabigatran, edoxaban, and rivaroxaban are the four DOACs marketed in the United States [3-6]. However, the manufacturers of apixaban, dabigatran, edoxaban, and rivaroxaban caution prescribers about the potential risk of increased exposure when taken concurrently with p-glycoprotein inhibitors (with or without strong CYP3A4 inhibitors).

Hemorrhagic pericardial effusion is classified as a major bleeding event and is characterized by blood accumulation in the pericardial space, potentially resulting in cardiac tamponade [7]. Pharmaceutical companies have not included pericardial effusion cases when summarizing major bleeding events in the DOAC package inserts. However, there are published reports of hemorrhagic pericardial effusion associated with the four marketed DOACs [8-24]. In most cases, patients had a predisposing factor such as acute/chronic kidney disease, malignancy, or drug interaction. Also, given the rarity of pericardial effusion associated with DOACs, the incidence of this adverse effect has not been established.

We report here our experience with three patients who were hospitalized with pericardial effusion associated with a DOAC. This report intends to heighten awareness about the occurrence of pericardial effusion in patients taking DOACs in conjunction with interacting drugs.

Presentation of cases

We initially conducted a single-center retrospective cohort study of patients with or without DOAC therapy who experienced pericardial effusion between February 2018 and March 2024. Demographic, laboratory, clinical characteristics, treatment interventions, and outcomes were retrieved from the medical records. The San Joaquin General Hospital Institutional Review Board Committee approved the study.

Patients 18 years and older with pericardial effusion were eligible for study inclusion. Exclusion criteria included acute or chronic aortic dissection, cardiac valve replacement or coronary artery bypass graft surgery within 30 days,

myocardial infarction, or traumatic injury to the chest within 30 days of pericardial effusion.

The DOAC registry at San Joaquin General Hospital showed 2,117 apixaban, 1,073 rivaroxaban, and 220 dabigatran recipients from February 2018 to March 2024. Our review of the echocardiography database revealed 105 pericardial effusion cases. After screening for exclusion criteria, we identified 74 patients with pericardial effusion (10 patients on DOAC and 64 patients not on DOAC). Of the ten patients on DOAC, seven were on apixaban, two on rivaroxaban, and one on dabigatran. Three of the 10 patients died shortly after their diagnosis of pericardial effusion, and two patients (one of the deaths) required urgent pericardiocentesis. Our review identified three cases of pericardial effusion resulting in hospitalizations with two deaths that could have been attributed to DOAC therapy. Table 1 includes details of the three patients' anticoagulation history, treatment indication, stroke risk for atrial fibrillation (if applicable), bleeding risk, and p-glycoprotein inhibitor drug interactions.

Case 1

A 63-year-old Caucasian male with past medical histories significant for atrial fibrillation, myocardial infarction status post automatic implantable cardioverter-defibrillator (AICD), heart failure with reduced ejection fraction (HFrEF), chronic obstructive pulmonary disease/asthma, hypertension, and hyperlipidemia was brought in by ambulance after being found at home wedged between his bed and wall for more than 4 hours. When found by emergency medical services, the patient lost his pulse and went into cardiac arrest, requiring cardiopulmonary resuscitation (CPR). En route, he had CPR for an unknown duration. He received two doses of intraosseous epinephrine, 1 mg. Upon arrival at the Emergency Department (ED), his Glasgow Coma Score was at 3 requiring intubation, and he was in pulseless electrical activity (PEA). He received four rounds of Advanced Cardiac Life Support (ACLS) with a Return of Spontaneous Circulation (ROSC).

The patient's vital signs were as follows: heart rate 93 beats per minute, respiratory rate 13 breaths per minute, blood pressure 102/66 mm Hg, SpO2 97% on ventilator. His temperature was at 36 degrees Celsius and his body mass index was at 45.71 kg/m^2.

He was on dabigatran for atrial fibrillation and his other home medications included albuterol inhaler, carvedilol, ciclesonide inhaler, digoxin, furosemide, hydralazine, ipratropium inhalation solution, isosorbide mononitrate, lisinopril, montelukast, nicotine transdermal supplements, potassium chloride extended-release, simvastatin, and tiotropium bromide. Laboratory results showed an elevated WBC count of 32.9 x 10^9/L and neutrophilia (91.0%). He was anemic with a hemoglobin of 10.6 g/dL. His chemistry showed acute renal impairment, with a serum creatinine of 2.23 mg/dL, estimated glomerular filtration rate (eGFR) of 26 mL/minute/1.73 m^2, and creatine clearance of 37 mL/min. The patient showed evidence of coagulopathy, with an international normalized ratio (INR) of 5.2. BNP was at 173 but troponins were negative.

Computed tomography (CT) of the chest/abdomen/pelvis with contrast revealed a pericardial effusion measuring 1.8 cm in thickness, indicating a potential hemopericardium. The bedside cardiac ultrasound showed a large pericardial effusion, prompting the decision to proceed with a pericardiocentesis. The pericardial fluid analysis revealed a red blood cell count of 4,927,765 and red/turbid fluid. After the removal of about 1,000 mL of sanguineous fluid from the pericardium, the patient was noted to have improved cardiac activity with organized rhythm and palpable pulses. The pericardial drain was left in place. However, he was still hypotensive therefore, norepinephrine was started. The patient's AICD was interrogated which showed low voltage and end of service. The post-pericardiocentesis echocardiogram showed a mildly dilated left ventricle with a biplane ejection fraction of 37%. A small and loculated pericardial effusion was present.

The patient was admitted to the Medical Intensive Care Unit for status post-cardiac arrest. After a discussion of the goal of care with the patient's family, the care plan proceeded to focus on providing comfort and symptom management rather than life-prolonging treatment. The patient died six hours later. The patient's cause of death was considered as cardiopulmonary collapse related to PEA, from cardiac tamponade with hemopericardial effusion with underlying acute exacerbation of congestive heart failure. Other contributing causes of death included supratherapeutic INR due to the use of dabigatran for atrial fibrillation, renal failure, and aspiration pneumonia.

Table 1: Patient Characteristics.

Case	Age (Y)	Gender	DOAC History	Indication	CHA2DS2VASc HAS-BLED Assessment	P-glycoprotein Inhibitor Drug Interactions [25-29]
1	63	Male	D 150 mg BID x 14 days	AF	3, 1	Carvedilol, simvastatin (a)
2	77	Female	R 2.5 mg Qday (unknown duration - started in Mexico)	DVT (lower extremity)	Not applicable	Atorvastatin, carvedilol (b)
3	70	Male	A 5 mg BID x 400 days	AF	2, 2	Atorvastatin, diltiazem (c)

A = apixaban; AF = atrial fibrillation; BID = twice daily; CHA2DS2-VASc = congestive heart failure, hypertension, age ≥ 75 (doubled), prior stroke or transient ischemic attack (doubled), vascular disease, age 65-74, female; D = Dabigatran; DVT = Deep Vein Thrombosis; HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history/predisposition, labile INR, elderly, drugs/alcohol; Qday = Once Daily; R = Rivaroxaban.

a. Unknown when the drugs were started.

b. The patient was on atorvastatin and carvedilol for at least 60 days before hospital admission.

c. The patient was on atorvastatin when apixaban was initiated. Diltiazem was started 259 days before the pericardiocentesis. It is a combined p-glycoprotein and moderate CYP3A4 inhibitor.

Case 2

A 77-year-old Hispanic female with past medical histories significant for lower extremity deep vein thrombosis (DVT), chronic kidney disease, heart failure with preserved ejection fraction (HFpEF), hypertension, hyperlipidemia, hypothyroidism, liver cirrhosis, type 2 diabetes mellitus (DM), and cerebrovascular accident who presented to the geriatric clinic as somnolent, not very responsive, with bilateral wheezing and lower extremity edema. The geriatric clinic sent her to the ED due to concern for abnormal labs and a fluid overload state. The patient presented with mild labored breathing, with exams notable for bilateral crackles and 2+ pitting edema on bilateral lower extremities.

She was on rivaroxaban 2.5 mg daily for the history of DVT and her other home medications included amlodipine, aspirin, atorvastatin, carvedilol, furosemide, levothyroxine, losartan, melatonin, polyethylene glycol, quetiapine, oral semaglutide, and senna. Upon arrival at the ED, her vital signs were as follows: temperature 36.8 degrees Celsius, heart rate 64 beats per minute, respiratory rate 24 breaths per minute, blood pressure 101/62 mm Hg, and oxygen saturation of 94% on room air. Her BMI was at 34.68 kg/m^2. Laboratory tests indicated anemia, with hemoglobin of 10.4 g/dL, and thrombocytopenia at 71 x 10^9/L. Her routine chemistry indicated worsening renal function, as shown by her serum creatinine of 3.88 mg/dL (2.37 mg/dL, two months ago) and an eGFR of 11 mL/minute/1.73 m^2 (20 mL/minute/1.73 m^2, two months ago and creatinine clearance was at 15 milliliters per minute. Her TSH was elevated at 68 uIU/mL.

The chest CT without contrast revealed mild cardiomegaly and moderate pericardial effusion, along with pleural effusions. The patient was admitted to telemetry for an acute exacerbation of heart failure then she was transferred to intermediate care and started furosemide via continuous infusion and dobutamine drip. She resumed home rivaroxaban 2.5 mg daily. During hospitalization, she developed atrial fibrillation. Echocardiography showed a normal-sized left ventricle, ejection fraction of 61.6%, and a small pericardial effusion. The pericardiocentesis was not recommended as pericardial effusion was likely developed from volume overload, uremia, or poorly controlled hypothyroidism and the patient did not have the evidence of tamponade. Furthermore, apixaban 2.5 mg twice daily was recommended to replace rivaroxaban due to the patient's new onset of atrial fibrillation. On hospital day 5, following a discussion with the patient's family regarding the prognosis and goals of care, the care was transitioned to comfort measures, and the patient expired.

Case 3

A 70-year-old South Asian male with past medical histories significant for atrial fibrillation, HFpEF, stage IV large B-cell lymphoma with metastasis to the lung, status post five cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), pancytopenia secondary to chemotherapy, depression, type 2 DM, obesity, and obstructive sleep apnea was sent to the ED from the heart failure clinic for CHF exacerbation. He experienced worsening exertional shortness of breath during normal daily activity and weight gain over the past two weeks.

The patient started apixaban 5 mg twice daily approximately 400 days earlier for atrial fibrillation. He began his first cycle of R-CHOP 194 days before presenting to the ED. Throughout his R-CHOP cycles, apixaban was held when the platelet count dropped below 100 x 10^9/L and the fifth cycle of R-CHOP started.

His home medications included allopurinol, atorvastatin, bumetanide, diltiazem, ergocalciferol, glipizide, loratadine, metformin, metolazone, and oral potassium chloride. Upon arrival at the ED, his vital signs were as follows: temperature 36.2 degrees Celsius, heart rate 80 beats per minute, respiratory rate 18 breaths per minute, blood pressure 94/57 mm Hg, and SpO2 97 % on room air.

Laboratory tests showed anemia at Hb 8.1 g/dL and thrombocytopenia of 99 x 10^9/L. The routine chemistry panel indicated acute renal impairment as the patient's serum creatinine was elevated at 2.22 mg/dL compared to 1.27 mg/dL from two months ago. His eGFR was at 29 mL/minute/1.73 m^2.

During hospital days 1 through 4, the patient was treated with IV furosemide, and oral metolazone was added on hospital day 3. On hospital day 4, the patient was transferred to the intensive care unit, as he required a vasopressor for hypotension. His diuretic regimen changed to a continuous infusion of furosemide and dobutamine. On hospital day 5, the patient's ECG revealed low voltage throughout all leads, a ventricular rate of 109 beats per minute, atrial fibrillation, and ventricular premature complexes. The echocardiogram showed an ejection fraction of 39%, right ventricular systolic pressure of 56 mmHg, a moderate-sized pericardial effusion with tamponade physiology, and a large pleural effusion. Before starting apixaban in the past, echocardiography did not indicate pericardial effusion in the past. Fifteen days after beginning the first cycle of R-CHOP (while on apixaban), trace pericardial effusion was noted in the echocardiogram. Then three days after starting the fifth cycle of R-CHOP (while on apixaban), moderate-sized pericardial effusion and pleural effusion were noted in the echocardiogram. The patient underwent pericardiocentesis and had 900 mL of dark-colored bloody fluid removed. Immediately following the procedure, the patient's blood pressure significantly improved, and the dobutamine was discontinued. Pericardial fluid analysis showed red blood cell counts of 3,238,148 and red/turbid fluid.

The patient improved over the next two days, requiring

Table 2: P-glycoprotein +/- CYP3A4 Drug Interactions with Direct Oral Anticoagulants.

Direct Oral Anticoagulant	Type of Drug Interaction	Manufacturer Listed Interacting Drugs	Manufacturer Recommended Intervention
Apixaban 5 mg, or 10 mg BID [3]	P-glycoprotein inhibitor + strong CYP3A4 inhibitor	Itraconazole, ketoconazole, ritonavir	Reduce the dose of apixaban by 50%
Dabigatran 150 mg BID for SPAF, CrCl 30-50 [4]	P-glycoprotein inhibitor	Dronedarone, ketoconazole	Reduce the dose of dabigatran by 50%
Dabigatran 150 mg BID for SPAF, CrCl 15-30 [4]	P-glycoprotein inhibitor	Dronedarone, ketoconazole	Avoid using dabigatran
Dabigatran for DVT/PE prophylaxis, treatment, preventing recurrences, CrCl < 50 [4]	P-glycoprotein inhibitor	Not specified by the manufacturer. The package inserts pharmacology section listed amiodarone, dronedarone, ketoconazole, quinidine, ticagrelor, verapamil	Avoid using dabigatran
Edoxaban 60 mg once daily for DVT/PE [5]	P-glycoprotein inhibitor	Azithromycin, clarithromycin, erythromycin, oral itraconazole, oral ketoconazole, quinidine, verapamil)	Reduce the dose of edoxaban by 50%
Rivaroxaban [6]	P-glycoprotein inhibitor + strong CYP3A4 inhibitor	Ketoconazole, ritonavir	Avoid using rivaroxaban
Rivaroxaban, CrCl 15-79 [6]	P-glycoprotein inhibitor + moderate CYP3A4 inhibitor	Erythromycin	Avoid using rivaroxaban

BID = twice daily; CrCl = creatinine clearance in milliliters/minute; DVT = deep vein thrombosis; PE = pulmonary embolism; SPAF = stroke prevention in atrial fibrillation.

fewer doses of furosemide, and kidney function was also improved. On hospital day 8, the pericardial drain was removed, draining an additional 250 mL with a total net output of 1.15 L. The patient was discharged the next day on oral bumetanide, and apixaban was continued to be held.

Discussion

Spontaneous hemopericardium has been reported for all the DOACs marketed in the United States of America [8-25]. The incidence of this rare adverse effect has not been established - we report the hemopericardium cases, one patient on dabigatran and another on apixaban required urgent pericardiocentesis at our institution. From 2018 to 2024, the incidence of hemopericardium resulting in pericardiocentesis was 0.45% for 220 dabigatran recipients and 0.05% for 2,117 apixaban recipients. One out of 1,073 (0.09%) rivaroxaban recipients developed a small pericardial effusion.

While our case 1 patient's most likely cause of death was cardiopulmonary collapse related to PEA from cardiac tamponade with underlying acute exacerbation of heart failure, other contributors deserve mention. Dabigatran is a known substrate of the efflux transporter protein p-glycoprotein. Our patient had an eGFR at 26 mL/minute/1.73 m^2 and took dabigatran with two p-glycoprotein inhibitors: carvedilol [26,27] and simvastatin [28]. The European Society of Cardiology states that there is limited data on the safety and efficacy of using DOACs for morbidly obese patients requiring stroke prevention for atrial fibrillation [29]. Our patient showed signs of coagulopathy, with an INR of 5.2 on admission. The manufacturer recommends lowering the dose of dabigatran by 50% if a patient has a creatinine clearance of 30 to 50 milliliters per minute and takes dronedarone or ketoconazole [4]. The package insert does not list other potential p-glycoprotein inhibitor drug interactions with dabigatran. Our patient underwent prolonged CPR, which could have contributed to the development of pericardial effusion.

Our rivaroxaban patient (case 2) had multiple underlying conditions that could have caused her to develop pericardial effusion. Severe hypothyroidism, uremia, and volume overload secondary to acute heart failure exacerbation can lead to pericardial effusion [30-32]. However, our patient presented with a creatinine clearance of 15 milliliters per minute and took two p-glycoprotein inhibitors (atorvastatin [33] and carvedilol [26,27]) with rivaroxaban 2.5 mg daily. She received an off-label dose of rivaroxaban to prevent the recurrence of DVT. The manufacturer recommends avoiding rivaroxaban for this indication if patients have a creatinine clearance below 15 milliliters per minute. Furthermore, rivaroxaban undergoes dual elimination – hepatic metabolism through CYP3A4/CYP2J2 and renal excretion through p-glycoprotein-mediated secretion [6]. It is possible that our patient's poor renal function, combined with the drug interactions, could have increased the effects of rivaroxaban.

Our apixaban patient (case 3) had two comorbidities that increased his risk for developing pericardial effusion: congestive heart failure and B-cell lymphoma status post five cycles of R-CHOP [32,34]. Two drugs in the R-CHOP regimen, cyclophosphamide and doxorubicin, may increase the risk of developing pericardial effusion [34]. Before starting apixaban and fifteen days after starting his first cycle of R-CHOP (while on apixaban), his echocardiogram did not show clinically relevant pericardial effusion. He developed a moderate-sized pericardial effusion 3 days after starting his fifth cycle of R-CHOP (while on apixaban). He took apixaban concomitantly with diltiazem, a p-glycoprotein inhibitor, and a moderate CYP3A4 inhibitor [35]. The manufacturer recommends reducing the dose of apixaban by 50% if a patient takes a combined p-glycoprotein inhibitor and a strong CYP3A4 inhibitor such as itraconazole, ketoconazole, or ritonavir [3]. Our patient's apixaban therapy was held for 107 days before undergoing urgent pericardiocentesis. However, it is possible that the combined effects of many months of potentially supratherapeutic levels of apixaban, five cycles of R-CHOP, and stage IV B-cell lymphoma could have contributed to developing a hemopericardium. Table 2 summarizes key drug interactions that require dose reduction or avoidance of apixaban, dabigatran, edoxaban, and rivaroxaban.

This report underscores the importance of considering patients' underlying medical conditions and drug interactions before initiating and during DOAC therapy. Pericardial effusion is a rare occurrence with DOAC therapy, but it can lead to fatal outcomes. The DOAC manufacturers do not include comprehensive lists of drug interactions, making it challenging for clinicians to avoid potentially harmful interactions. An alert triggered in electronic health records, providing a list of p-glycoprotein inhibitor drug interactions before prescribing and dispensing DOACs in hospitals and clinics, would help prevent serious adverse events

Limitations

Our study has limitations as the results are based on only three clinical case series in a single center therefore, it cannot be extrapolated to a wider population.

Conclusion

The incidence of DOAC-associated hemopericardium was less than 0.5% at our institution. Clinicians need to be vigilant about drug interactions with p-glycoprotein inhibitors and underlying conditions predisposing patients to developing pericardial effusion.

Consent

The San Joaquin General Hospital Institutional Review Board approved waiving the patient's informed consent for this retrospective review.

Ethical declarations

This article was published after the San Joaquin General Hospital Institutional Review Board approved waiving the patients' informed consent. The patients' personal information was not mentioned so the case series report was published anonymously.

Disclaimer (Artificial Intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

Acknowledgment

We would like to express our sincere gratitude to Dr. Syung Min Jung for invaluable support of this research.

References

1. Joglar JA, Chung MK, Armbruster AL, Benjamin EJ, Chyou JY, Cronin EM, et al. 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2024;149:e1–e156. Available from: https://doi.org/10.1161/cir.0000000000001193
2. Stevens SM, Woller SC, Kreuziger LB, Bounameaux H, Doerschug K, Geersing GJ, et al. Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report. Chest. 2021;160:e545–e608. Available from: https://doi.org/10.1016/j.chest.2021.07.055
3. Apixaban (Eliquis) prescribing information. Princeton (NJ): Bristol-Myers Squibb Company and New York (NY): Pfizer Inc.; 2025.
4. Dabigatran etexilate (Pradaxa) prescribing information. Ridgefield (CT): Boehringer Ingelheim Pharmaceuticals, Inc.; 2023.
5. Edoxaban (Savaysa) prescribing information. Basking Ridge (NJ): Daiichi Sankyo, Inc.; 2024.
6. Rivaroxaban (Xarelto) prescribing information. Titusville (NJ): Janssen Pharmaceuticals, Inc.; 2025 Apr.
7. Dy EA, Shiltz DL. Hemopericardium and cardiac tamponade associated with dabigatran use. Ann Pharmacother. 2012;46:e18. Available from: https://doi.org/10.1345/aph.1r112
8. Sheikh AB, Shah I, Sagheer S, Javed N, Minhas AMK, Lopez ED, et al. Hemopericardium in the setting of direct oral anticoagulant use: an updated systematic review. Cardiovasc Revasc Med. 2022;39:73–83. Available from: https://doi.org/10.1016/j.carrev.2021.09.010
9. Barton CA, McMillian WD, Raza SS, Keller RE. Hemopericardium in a patient treated with dabigatran etexilate. Pharmacotherapy. 2012;32(5):e103–7. Available from: https://doi.org/10.1002/j.1875-9114.2012.01036.x
10. Kızılırmak F, Gunes HM, Guler E, Demir GG, Karaca O, Canpolat HG. Hemopericardium and cardiac tamponade in a patient treated with dabigatran etexilate. Korean Circ J. 2016;46(1):99–101. Available from: https://doi.org/10.4070/kcj.2016.46.1.99
11. Jelani QU, Gordon R, Schussheim A. Dabigatran-induced spontaneous hemopericardium and cardiac tamponade. Tex Heart Inst J. 2017;44(5):370–2. Available from: https://doi.org/10.14503/thij-16-6073
12. Song S, Cook J, Goulbourne C, Meade M, Salciccioli L, Lazar J. First reported case of hemopericardium related to dabigatran use reversed by new antidote idarucizumab. Case Rep Cardiol. 2017;2017:6458636. Available from: https://doi.org/10.1155/2017/6458636
13. Yu JH, Liu HH, Hsieh MJ, Hsieh IC, Chu PH, Chen DY. Spontaneous bilateral haemothorax with haemopericardium secondary to rivaroxaban. J Clin Pharm Ther. 2020;45(5):1175–8. Available from: https://doi.org/10.1111/jcpt.13116
14. Shivamurthy P, Brar N, Therrien ML. Isolated hemopericardium associated with rivaroxaban: first case report. Pharmacotherapy. 2014;34(9):e169–72. Available from: https://doi.org/10.1002/phar.1474
15. Mehta A, Burkland D, Mathuria N. Isolated hemopericardium after initiation of rivaroxaban: implications and potential mechanisms. Clin Pract. 2019;9(1):1096. Available from: https://doi.org/10.4081/cp.2019.1096
16. Shastri P, Bhuta S, Oostra C, Monroe T. Hemopericardium with subsequent cardiac tamponade secondary to rivaroxaban treatment: a case report. Eur Heart J Case Rep. 2020;5(1):ytaa482. Available from: https://doi.org/10.1093/ehjcr/ytaa482
17. Menendez D, Michel J. Hemopericardium with tamponade following rivaroxaban administration and its attenuation by CYP3A4 inhibitors. Proc (Bayl Univ Med Cent). 2016;29(4):414–5. Available from: https://doi.org/10.1080/08998280.2016.11929492
18. Basnet S, Tachamo N, Tharu B, Dhital R, Ghimire S, Poudel DR. Life-threatening hemopericardium associated with rivaroxaban. Case Rep Cardiol. 2017;2017:4691325. Available from: https://doi.org/10.1155/2017/4691325
19. Ioppolo AM, Longobardo L, D'Isa S, De Gregorio P, Manfredi M, De Cesare NB. An uncommon case of spontaneous hemopericardium in a patient treated with rivaroxaban. J Cardiovasc Echogr. 2019;29(4):180–2. Available from: https://doi.org/10.4103/jcecho.jcecho_57_19
20. Olagunju A, Khatib M, Palermo-Alvarado F. A possible drug-drug interaction between Eliquis and amiodarone resulting in hemoperi-cardium. Cureus. 2021;13(2):e13486. Available from: https://doi.org/10.7759/cureus.13486

21. Cinelli M, Uddin A, Duka I, Soomro A, Tamburrino F, Ghavami F, Lafferty J. Spontaneous hemorrhagic pericardial and pleural effusion in a patient receiving apixaban. Cardiol Res. 2019;10(4):249–52. Available from: https://doi.org/10.14740/cr902

22. Sigawy C, Apter S, Vine J, Grossman E. Spontaneous hemopericardium in a patient receiving apixaban therapy: first case report. Pharmacotherapy. 2015;35(7):e115–7. Available from: https://doi.org/10.1002/phar.1602

23. Sablani N, Garg J, Hasan B, Patel R, Martinez MW. First reported case series in the United States of hemopericardium in patients on apixaban. HeartRhythm Case Rep. 2017;4(2):82–4. Available from: https://doi.org/10.1016/j.hrcr.2017.11.015

24. Tsai TY, Leu HB, Lo LW, Chen SA, Hsu PF. Spontaneous hemopericardium complicated with hemothorax in a patient receiving edoxaban therapy: a case report. Acta Cardiol Sin. 2019;35(3):342–4. Available from: https://doi.org/10.6515/acs.201905_35(3).20190212a

25. Tsai TY, Leu HB, Lo LW, Chen SA, Hsu PF. Spontaneous hemopericardium complicated with hemothorax in a patient receiving edoxaban therapy: a case report. Acta Cardiol Sin. 2019;35:342–4. Available from: https://doi.org/10.6515/acs.201905_35(3).20190212a

26. Bader FM, Hagan ME, Crompton JA, Gilbert EM. The effect of beta-blocker use on cyclosporine level in cardiac transplant recipients. J Heart Lung Transplant. 2005;24:2144–7. Available from: https://doi.org/10.1016/j.healun.2005.05.002

27. Souza FC, Neri JS, Marques EB, Barros RB, Scaramello CB. Should pharmacotherapy of digoxin be reviewed in male patients with heart failure in the case of association with carvedilol? Int J Cardiol. 2015;191:4–6. Available from: https://doi.org/10.1016/j.ijcard.2015.04.247

28. Chung H, Kim JM, Park JW, Noh J, Kim KA, Park JY. Effects of simvastatin on pharmacokinetics and anticoagulant effects of dabigatran in healthy subjects. Pharmaceuticals (Basel). 2023;16:364. Available from: https://doi.org/10.3390/ph16030364

29. Hindley B, Lip GYH, McCloskey AP, Penson PE. Pharmacokinetics and pharmacodynamics of direct oral anticoagulants. Expert Opin Drug Metab Toxicol. 2023;19:911–23. Available from: https://doi.org/10.1080/17425255.2023.2287472

30. Chahine J, Ala CK, Gentry JL, Pantalone KM, Klein AL. Pericardial diseases in patients with hypothyroidism. Heart. 2019;105:1027–33. Available from: https://doi.org/10.1136/heartjnl-2018-314528

31. Rehman KA, Betancor J, Xu B, Kumar A, Rivas CG, Sato K, et al. Uremic pericarditis, pericardial effusion, and constrictive pericarditis in end-stage renal disease: insights and pathophysiology. Clin Cardiol. 2017;40:839–46. Available from: https://doi.org/10.1002/clc.22770

32. Zhai G, Zhang B, Wang J, Liu Y, Zhou Y. Prognostic value of pericardial effusion size in patients with acute heart failure. Curr Vasc Pharmacol. 2022;20:508–16. Available from: https://doi.org/10.2174/1570161120666220721094739

33. Boyd RA, Stern RH, Stewart BH, Wu X, Reyner EL, Zegarac EA, et al. Atorvastatin coadministration may increase digoxin concentrations by inhibition of intestinal P-glycoprotein-mediated secretion. J Clin Pharmacol. 2000;40:91–8. Available from: https://doi.org/10.1177/00912700022008612

34. Lorenzo-Esteller L, Ramos-Polo R, Pons Riverola A, Pons Riverola A, Morillas H, Berdejo J, et al. Pericardial disease in patients with cancer: clinical insights on diagnosis and treatment. Cancers (Basel). 2024;16:1–14. Available from: https://doi.org/10.3390/cancers16203466

35. Frost CE, Byon W, Song Y, Wang J, Schuster AE, Boyd RA, et al. Effect of ketoconazole and diltiazem on the pharmacokinetics of apixaban, an oral direct factor Xa inhibitor. Br J Clin Pharmacol. 2015;79:838–46. Available from: https://doi.org/10.1111/bcp.12541