

# The optimal anticoagulant therapy for mechanical heart valves in a gallbladder cancer patient with hepatic metastases

## A case report

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### Abstract

**Rationale:** Developing an optimal anticoagulant strategy poses a challenging task in patients with mechanical heart valves (MHVs) throughout their lifetime. We report an optimal anticoagulant therapy in a cancer patient with hepatic metastases after MHV replacement.

**Patient concerns:** A 68-year-old female with MHVs suffered from gallbladder cancer with hepatic metastases. Her international normalized ratio (INR) fluctuated owing to the declined hepatic function.

**Diagnoses:** Gallbladder cancer and hepatic metastases, with a history of mechanic aortic valve replacement and mitral valve replacement.

**Interventions:** Warfarin was discontinued and Vitamin K1 was immediately administered via intravenous infusion. low-molecular-weight heparin (LMWH) was regarded as a preferable option, and nadroparin at the dosage of 4100IU daily was administered.

**Outcomes:** No adverse event occurred during the patient's hospitalization and two-week follow up after discharge.

**Lessons:** LMWH may represent a reasonable alternative regarding the inhibition of thrombus and bleeding in MHVs carriers with cancer and hepatic metastases.

**Abbreviations:** INR = international normalized ratio, LMWH = low-molecular-weight heparin, MHVs = mechanical heart valves, NCCN = National Comprehensive Cancer Network, NOACs = nonvitamin K antagonist oral anticoagulants, UFH = unfractionated heparin, VKAs = vitamin K antagonists, VTE = venous thromboembolism.

**Keywords:** anticoagulant, cancer, hepatic metastases, low-molecular-weight heparin, mechanical heart valves

## 1. Introduction

Patients with mechanical heart valves (MHVs) require lifelong anticoagulation to prevent valve thrombosis that could lead to

deleterious complications or even death.<sup>[1]</sup> Guidelines recommend anticoagulant treatment with warfarin, which is predominantly metabolized in liver after administration. Since liver is the major source of coagulation factors, hepatic insufficiency can affect coagulation and international normalized ratio (INR) control in general. Venous thromboembolism (VTE) is also a complication in cancer patients, with a fourfold to sevenfold greater risk when compared to patients without cancer.<sup>[2,3]</sup> At present, medical strategies of cancer-associated VTE recommended in guidelines include low-molecular-weight heparin (LMWH), vitamin K antagonists (VKAs), and nonvitamin K antagonist oral anticoagulants (NOACs).<sup>[4]</sup> Nevertheless, in cancer patients with hepatic metastases, coexistence of a coagulopathy may be a potential barrier to use warfarin.<sup>[4]</sup> Therefore, the choice of antithrombotic management in this fragile population should be individually tailored. Here, we report a heart valve bearer complicated with gallbladder cancer and hepatic metastases who suffered from INR fluctuation when using warfarin. Finally, LMWH was chosen as an optimal anticoagulant in consideration of available evidence and patient's characteristics.

## 2. Case report

Approval for the study by the local institution review board was not required because it was a case report. Written informed consent was obtained from the patient for publication of the details of this case report. A 68-year-old woman, on 5-year oral

Editor: N/A.

*Funding:* This work was supported by Research Funds of Shanghai health and family planning commission (20184Y0022), Program for Key Discipline of Clinical Pharmacy of Shanghai (2016-40044-002), and Program for Key but Weak Discipline of Shanghai Municipal Commission of Health and Family Planning (2016ZB0304).

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The authors have no conflicts of interest to disclose.

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Medicine (2018) 97:37(e12368)

Received: 19 May 2018 / Accepted: 20 August 2018

<http://dx.doi.org/10.1097/MD.00000000000012368>

anticoagulation with warfarin because of mechanic aortic valve replacement and mitral valve replacement, suffered from gallbladder cancer with hepatic metastases for 1 year. Outside the hospital, the patient's INR was maintained within the therapeutic range (2.5–3.5) at the dosage of warfarin 2.5 mg daily. After admission, her INR was detected at a high value of 7.67 but without bleeding. At this juncture, warfarin was discontinued temporarily and intravenous vitamin K 10 mg was administrated by slow infusion, resulting in a decreased INR value of 1.39 on the next day. Of note, due to hepatic metastases, the patient's hepatic function markedly declined accompanied with elevated alanine aminotransferase of 101 U/L (reference: 0–75 U/L), aspartate aminotransferase of 289 U/L (reference: 10–28 U/L), direct bilirubin of 223.6  $\mu\text{mol/L}$  (reference: 0.1–5  $\mu\text{mol/L}$ ), and total bilirubin of 323.2  $\mu\text{mol/L}$  (reference: 3.4–17.1  $\mu\text{mol/L}$ ). Thus, regarding the metabolic pathway of warfarin and hepatic insufficiency of the present patient, warfarin seemed to be not suitable for the present patient. Finally, nadroparin at the dosage of 4100 IU daily was managed via subcutaneous injection and the INR value ranged from 1.20 to 1.45 during the nadroparin treatment. On discharge, the patient continues to use nadroparin 4100 IU daily, without adverse event occurring during hospitalization and 2-week follow-up after discharge.

### 3. Discussion

In patients with MHVs, in addition to the thrombogenicity of the intravascular prosthetic material, mechanical valves impose abnormal flow conditions, with zones of low flow within their components, as well as areas of high-shear stress.<sup>[5]</sup> Above reasons promote platelet activation, leading to valve thrombosis and embolic events. A meta-analysis from the 1990s including studies of all valve types and locations found a 5.6 times of thromboembolic events with no therapy than VKA therapy (95% confidence interval: 4.2–7.5).<sup>[6]</sup> For above reasons, life-long therapy with VKA is now recommended in patients with MHVs.

It is of note that effective oral antithrombotic therapy in patients with MHVs requires the management of warfarin with an appropriate INR in the target range. However, the anticoagulation effects of warfarin vary with changes in liver function, food–drug and drug–drug interaction, and inpatient genetic variability. The liver plays an essential role within the clotting cascade via synthesis of plasma clotting factors. Therefore, liver dysfunction has been well-documented to impact this cascade, resulting in defective hemostasis with prothrombin time prolongation.<sup>[7,8]</sup> Moreover, warfarin is stereo selectively metabolized by hepatic cytochrome P-450 microsomal enzymes to inactive hydroxylated metabolites and by reductases to reduced metabolites with minimal anticoagulant activity.<sup>[9]</sup> Thus, hepatic impairment can potentiate the response to warfarin through decreased metabolism of warfarin. Several retrospective studies revealed that patients with liver disease were significantly more likely to have a high INR when taking warfarin, and worsening liver dysfunction was found to be strongly associated with bleeding episodes.<sup>[10]</sup> In this kind of patients, more frequent monitoring of INR and clinically related bleeding should be conducted when using warfarin. In the present patient, laboratory testing showed that her liver function deteriorated because of hepatic metastases followed with gallbladder cancer. Thus, warfarin was not appropriate for her because of the difficulty in maintaining the therapeutic levels of INR.

Other optimal antithrombotic therapy should be considered in such fragile population. According to National Comprehensive

Cancer Network (NCCN) clinical practice guidelines, the LMWHs, fondaparinux, and subcutaneous unfractionated heparin (UFH) are category 1 options for the venous thromboembolism (VTE) prophylaxis in cancer inpatients.<sup>[11]</sup> Previous studies comparing different anticoagulant regimens for the prevention of VTE in cancer patients have not clearly identified a particular regimen to have superior efficacy.<sup>[12,13]</sup> Akl et al<sup>[14]</sup> conducted a meta-analysis to compare outcomes of perioperative VTE prophylaxis with LMWH versus UFH in cancer patients, and found no difference in rates of mortality, suspected VTE, or bleeding events. Therefore, LMWH is an optimal antithrombotic treatment in cancer patients. However, LMWH is not approved for patients with MHVs, and only temporary off-label use is considered as a treatment option in this clinical setting. Steger et al<sup>[15]</sup> followed a cohort of 256 patients who underwent MHV implantation and were treated with a fixed dose of enoxaparin (40 mg, twice daily, subcutaneously). In this study, with a mean follow-up of 38 days, LMWHs were shown to be safe, without prosthesis thrombosis and major bleeding.<sup>[15]</sup> A meaningful meta-analysis study also has been conducted on the focus of this issue by pooling nine studies with 1042 patients and demonstrated that the use of LMWH seem to be as effective and safe as UFH/VKA for the VTE prophylaxis in patients with MHVs.<sup>[16]</sup> Meanwhile, unlike warfarin, LMWH (nadroparin) is not metabolized by hepatic cytochrome P-450 microsomal enzymes owing to relatively low molecular weight of 3500 to 5000 Da.<sup>[11]</sup> Thus, the efficiency of nadroparin with normal dosage will not be affected by impaired hepatic function. Based on above-mentioned information, LMWH is likely to be an alternative with a good balance between thrombosis and bleeding in cancer patients with MHVs.

Based on the clinical setting of this case and current evidence, LMWH may represent a reasonable alternative regarding the inhibition of thrombus and bleeding in MHVs carriers with cancer and hepatic metastases. However, several limitations should be addressed in this case. Firstly, the long-term effects of thrombosis prevention are uncertain due to relatively short follow-up duration in this case. In addition, no RCTs have been conducted to evaluate the optimal drug strategy for these fragile patients with MHVs and cancer, thus further high-quality real-world studies on evaluation of this issue are necessary.

### Author contributions

**Conceptualization:** Yi-Dan Yan, Ying-Jie Su, Bo-Ya Chen, Jiu-Jie Cui, Zai-Li Zhang, Qi Xu, Zhichun Gu.

### References

- [1] Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2017;70:252–89.
- [2] Blom JW, Doggen CJ, Osanto S, et al. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *JAMA* 2005;293:715–22.
- [3] Heit JA, Silverstein MD, Mohr DN, et al. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. *Arch Intern Med* 2000;160:809–15.
- [4] Yan YD, Zhang C, Shen L, et al. Net clinical benefit of non-vitamin K antagonist oral anticoagulants for venous thromboembolism prophylaxis in patients with cancer: a systematic review and trade-off analysis from 9 randomized controlled trials. *Front Pharmacol* 2018;9:575.
- [5] Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63:e57–185.

- [6] Forsberg P, DeSancho MT. Role of novel anticoagulants for patients with mechanical heart valves. *Curr Atheroscler Rep* 2014;16:448.
- [7] Ageno W, Gallus AS, Wittkowsky A, et al. Oral anticoagulant therapy: antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(2 suppl):e44S–88S.
- [8] Demirkan K, Stephens MA, Newman KP, et al. Response to warfarin and other oral anticoagulants: effects of disease states. *South Med J* 2000;93:448–54. quiz 455.
- [9] Clark NP, Hoang K, Delate T, et al. Warfarin interaction with hepatic cytochrome P-450 enzyme-inducing anticonvulsants. *Clin Appl Thromb Hemost* 2018;24:172–8.
- [10] Self TH, Owens RE, Sakaan SA, et al. Effect of diseases on response to vitamin K antagonists. *Curr Med Res Opin* 2016;32:613–20.
- [11] Streiff MB, Holmstrom B, Ashrani A, et al. Cancer-associated venous thromboembolic disease, Version 1.2015. *J Natl Compr Canc Netw* 2015;13:1079–95.
- [12] Efficacy and safety of enoxaparin versus unfractionated heparin for prevention of deep vein thrombosis in elective cancer surgery: a double-blind randomized multicentre trial with venographic assessment. ENOXACAN Study Group. *Br J Surg* 1997; 84: 1099–1103
- [13] Mismetti P, Laporte S, Darmon JY, et al. Meta-analysis of low molecular weight heparin in the prevention of venous thromboembolism in general surgery. *Br J Surg* 2001;88:913–30.
- [14] Akl EA, Terrenato I, Barba M, et al. Low-molecular-weight heparin vs unfractionated heparin for perioperative thromboprophylaxis in patients with cancer: a systematic review and meta-analysis. *Arch Intern Med* 2008;168:1261–9.
- [15] Steger V, Bail DH, Graf D, et al. A practical approach for bridging anticoagulation after mechanical heart valve replacement. *J Heart Valve Dis* 2008;17:335–42.
- [16] Caldeira D, David C, Santos AT, et al. Efficacy and safety of low molecular weight heparin in patients with mechanical heart valves: systematic review and meta-analysis. *J Thromb Haemost* 2014;12:650–9.