

A Korean Multi-Center Survey about Warfarin Management before Gastroenterological Endoscopy in Patients with a History of Mechanical Valve Replacement Surgery

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Background: Guidelines for esophagogastroduodenoscopy (EGD) in the West allow the continued use of warfarin under therapeutic international normalized ratio (INR) level. In Korea, no guidelines have been issued regarding warfarin treatment before EGD. The authors surveyed Korean cardiac surgeons about how Korean cardiac surgeons handle warfarin therapy before EGD using a questionnaire. Participants were requested to make decisions regarding the continuation of warfarin therapy in two hypothetical cases. **Methods:** The questionnaire was administered to cardiac surgeons and consisted of eight questions, including two case scenarios. **Results:** Thirty-six cardiac surgeons at 28 hospitals participated in the survey, and 52.7% of the participants chose to stop warfarin before EGD in aortic valve replacement patients without risk factors for thromboembolism. When the patient's INR level was 2, 31% of the participants indicated that they would choose to continue warfarin therapy. For EGD with biopsy, 72.2% of the participants chose warfarin withdrawal, and 25% of the participants chose heparin replacement. In mitral valve replacement patients, 47.2% of the participants chose to discontinue warfarin, and 22.2% of the participants chose heparin replacement. For EGD with biopsy in patients with a mitral valve replacement, 58.3% of the participants chose to stop warfarin, and 41.7% of the participants chose heparin replacement. **Conclusion:** This study demonstrated that attitudes regarding warfarin treatment for EGD are very different among Korean surgeons. Guidelines specific to the Korean population are required.

Key words: 1. Heart valve prosthesis
2. Anticoagulants
3. Endoscopy
4. Hemorrhage
5. Thromboembolism

Introduction

During esophagogastroduodenoscopy (EGD) examinations and/or the treatment of patients on antith-

rombotic therapy, it is necessary to balance the risk of hemorrhage induced by antithrombotic therapy with the risk of thromboembolism after antithrombotic drug withdrawal [1,2]. The risk of hemorrhage de-

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depends on the nature of the endoscopic procedure, and the risk of thromboembolism depends on comorbidities [2]. Guidelines for EGD in the USA, UK, and Europe allow the continued use of warfarin at the time of an EGD examination, including examinations involving a mucosal biopsy, because the risk of hemorrhage induced by diagnostic EGD with mucosal biopsy is low [3-6]. It is believed, without solid evidence, that Caucasians are more susceptible to thromboembolism than Asians [7]. In 2005, the Japan Gastroenterological Endoscopy Society (JGES) recommended three or four days of withdrawal from warfarin, three days from aspirin, and five days from ticlopidine, even for low-risk endoscopic procedures requiring biopsy [2,8]. However, the JGES guidelines were changed in 2014 and no longer recommended warfarin discontinuation for diagnostic EGD [2]. Furthermore, warfarin discontinuation is not required for EGD with a mucosal biopsy if the international normalized ratio (INR) is in the therapeutic range [2]. In Korea, no ethnicity-specific warfarin management guidelines have been issued for EGD. This multicenter questionnaire-based survey was performed to evaluate current practice with respect to warfarin management for EGD in mechanical valve replacement patients.

Methods

The questionnaire was administered to cardiac surgeons (all board-certified) during the 2015 Korean Society for Thoracic and Cardiovascular Surgery annual meeting. It consisted of eight questions. Two questions gathered general information (participant age and affiliation), four addressed each surgeon's personal judgment regarding warfarin treatment before EGD on the basis of two hypothetical cases, and two requested opinions about ethnic differences regarding bleeding and the risk of thromboembolism. The full questionnaire is provided in Appendix 1.

Results

Thirty-six cardiac surgeons from 28 hospitals participated in the survey. Eleven of the hospitals were in Seoul, 10 were in Incheon and Gyeonggi-do, three were in Busan and Gyeongsangnam-do, four were in Daegu and Gyeongsangbuk-do, one was in Daejeon

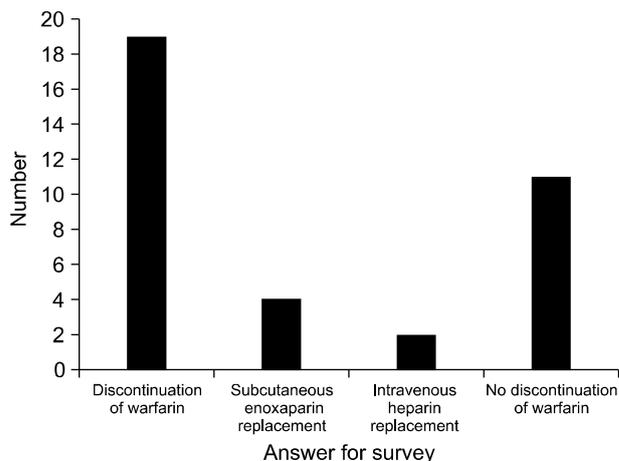


Fig. 1. Policy before EGD for annual health check-up. Policies regarding warfarin discontinuation before an EGD for an annual health check-up in an AVR patient with no risk factors for thromboembolism. Case: 60-year-old male, AVR (mechanical), received warfarin, present international normalized ratio of 2, no risk factors of thromboembolism. EGD, gogastroduodenoscopy; AVR, aortic valve replacement.

and Chungcheongnam-do, and two were in Gwangju and Jeollanam-do. Five of the participants were in their thirties, 21 were in their forties, eight were in their fifties, and two were over sixty.

We asked surgeons to indicate their policies regarding warfarin treatment before EGD conducted during annual health check-ups (Fig. 1). The first case presented in the questionnaire (case 1) was a 60-year-old male on warfarin with an INR level of 2 who had undergone aortic valve replacement with a mechanical valve. Nineteen of the 36 surgeons responded that they would stop warfarin and not replace it with another medication for two to five days (median, three days) prior to EGD. Four stated that they would replace warfarin with subcutaneous enoxaparin, and two that they would replace warfarin with intravenous heparin. Eleven surgeons responded that they would perform EGD without discontinuing warfarin.

Moreover, if EGD with a biopsy was indicated for the patient in case 1, 26 surgeons answered that they would stop warfarin without a replacement for two to seven days (median, three days) prior to EGD (Fig. 2), seven that they would replace warfarin with subcutaneous enoxaparin, and two that they would replace warfarin with intravenous heparin. One surgeon stated that EGD would be performed without

Survey about Warfarin Management before Endoscopy

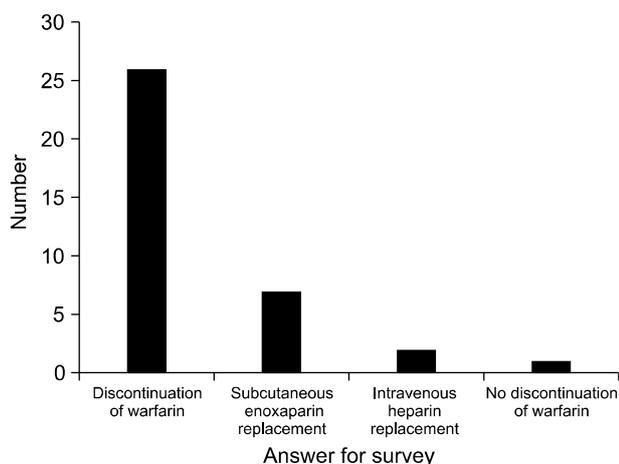


Fig. 2. Policy before EGD with biopsy. Policies regarding warfarin discontinuation before EGD with a biopsy for an AVR patient with no risk factors for thromboembolism. Case: 60-year-old male, AVR (mechanical), received warfarin, present international normalized ratio of 2, no risk factors of thromboembolism. EGD, esophagogastroduodenoscopy; AVR, aortic valve replacement.

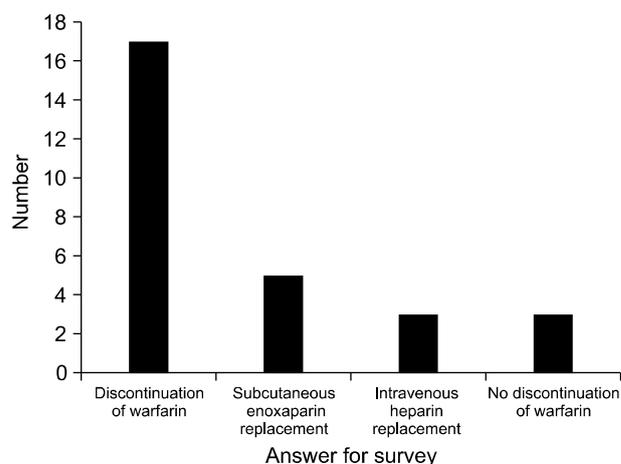


Fig. 3. Policy before EGD for annual health check-up. Policies regarding warfarin discontinuation before EGD in MVR patients with no risk factors for thromboembolism. Case: 60-year-old male, MVR (mechanical), received warfarin, present international normalized ratio of 2.5-3, no risk factors of thromboembolism. EGD, esophagogastroduodenoscopy; MVR, mitral valve replacement.

discontinuing warfarin.

Case 2 involved a 60-year-old male on warfarin with an INR level of 2.5-3 who had undergone mitral valve replacement with a mechanical valve. Before EGD for an annual health check-up, 17 surgeons answered that they would stop warfarin for two to give days (median, three days) prior to EGD (Fig. 3), five that they would replace warfarin with subcutaneous enoxaparin, and three that they would replace warfarin with intravenous heparin. Eleven surgeons stated that they would perform EGD without discontinuing warfarin. If the patient in case 2 underwent EGD with a biopsy, 21 surgeons responded that they would stop warfarin without a replacement for two to seven days (median, three days) prior to EGD (Fig. 4), 10 responded that they would replace warfarin with subcutaneous enoxaparin, and five responded that they would replace warfarin with intravenous heparin. No surgeon responded that EGD would be performed without discontinuing warfarin.

Regarding the relative risks of thromboembolism after warfarin withdrawal in Koreans and Caucasians, two surgeons believed that the risk was higher in Koreans, eight believed that the risk was the same, and 26 thought that the risk was lower in Koreans (Fig. 5). Regarding the relative risks of bleeding during EGD in Koreans and Caucasians without discontinuing warfarin at an INR level of 2-3, 18 sur-

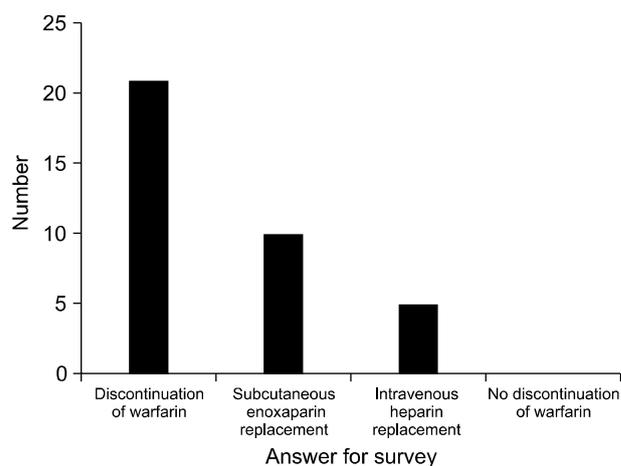


Fig. 4. Policy before EGD with biopsy. Policies regarding warfarin discontinuation before EGD with a biopsy in MVR patients with no risk factors for thromboembolism. Case: 60-year-old male, MVR (mechanical), received warfarin, present international normalized ratio of 2.5-3, no risk factors of thromboembolism. EGD, esophagogastroduodenoscopy; MVR, mitral valve replacement.

geons believed the risk was higher in Koreans, 17 believed the risk was the same, and one considered the risk to be lower in Koreans.

Discussion

The suspension of warfarin therapy causes reversion to a state of hypercoagulability [2], and it has

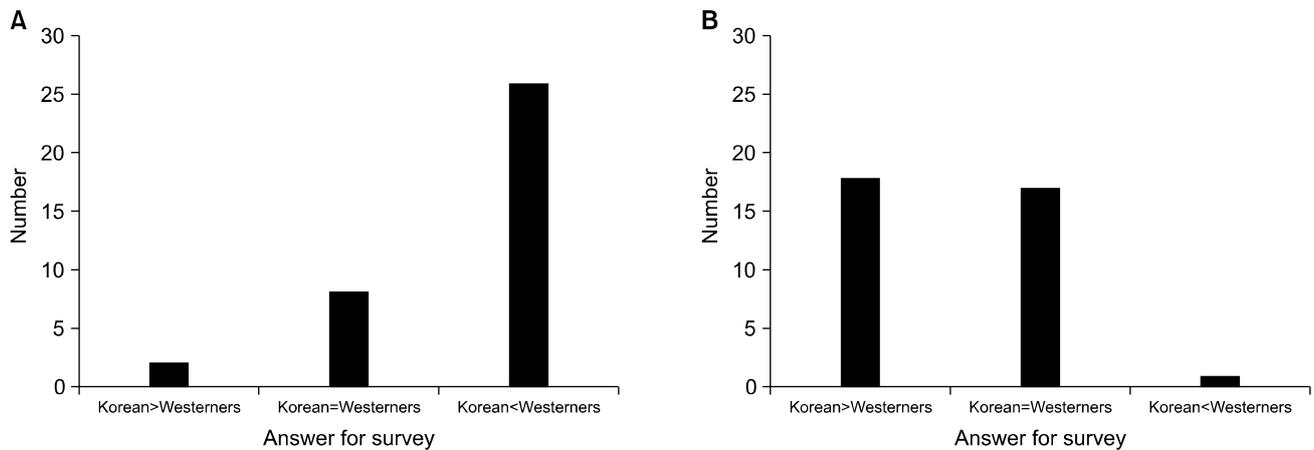


Fig. 5. Cardiac surgeons' opinions regarding the risks of thromboembolism and bleeding during esophagogastroduodenoscopy without warfarin discontinuation. (A) Risk of thromboembolism. (B) Risk of bleeding.

been reported that in 1% of cases, warfarin withdrawal results in thromboembolic complications and poor prognoses [2,9-11]. In addition to drug withdrawal, the risk of thromboembolism may be increased by dehydration caused by preparation for endoscopic examination, and this risk should be addressed by adequate fluid replacement [2]. In the 2014 JGES guidelines, the conditions with a high risk of thromboembolism associated with discontinuing anticoagulant therapy are a history of cardiogenic brain embolism, mechanical mitral valve replacement, thromboembolism following mechanical valve replacement, atrial fibrillation accompanying valvular heart disease, atrial fibrillation without valvular heart disease but with a high risk of stroke, anti-phospholipid antibody syndrome, and deep vein thrombosis/pulmonary thromboembolism [2]. However, the guidelines state that the risk of thromboembolism associated with anticoagulant discontinuation varies considerably [2]. Once thromboembolic complications have occurred, they are often serious, and all patients on anticoagulant therapy should therefore be treated as high-risk patients [2].

The 2014 JGES guidelines classify gastroenterological endoscopic procedures into the following four categories: diagnostic gastroenterological endoscopy without biopsy, endoscopic mucosal biopsy, gastroenterological endoscopy with a low risk of bleeding, and gastroenterological endoscopy with a high risk of bleeding [2]. The incidence of bleeding complications after mucosal biopsy is 0.002% in the stomach and 0.09% in the large intestine, regardless of antith-

rombotic use [12,13]. Several studies, even in Japan, have shown that the bleeding risk after biopsy was not increased by antithrombotics [14,15]. Furthermore, since antithrombotics do not increase the risk of bleeding after diagnostic EGD including a mucosal biopsy, the 2014 JGES guidelines indicate that discontinuing warfarin is not required if the INR is under the therapeutic range [2].

In the present study, 52.7% of the participants responded that they would discontinue warfarin before EGD in the aortic valve replacement patient (case 1) without risk factors for thromboembolism, while 31% answered that they would maintain warfarin therapy with at an INR level of 2. If EGD with a biopsy was to be performed, 72.2% stated that they would stop warfarin, and 25% stated they would replace warfarin with subcutaneous enoxaparin or intravenous heparin. In case 2, the mitral valve replacement patient, 47.2% of participants chose to discontinue warfarin, and 22.2% chose to replace warfarin with intravenous heparin or subcutaneous enoxaparin. These results demonstrate that the percentage of participants who chose heparin replacement was higher for mitral valve replacement patients than for aortic valve replacement patients. In case 2, if EGD was to be performed with a biopsy, 58.3% of participants chose to discontinue warfarin without a replacement and 41.7% chose to replace warfarin with heparin. These findings indicate that Korean cardiac surgeons are prepared to stop warfarin, with varying attitudes towards heparin replacement, before EGD with or without a biopsy, which is not in line with Western

or Japanese guidelines.

One study explored differences between the management practices of Korean and Western endoscopists regarding patients on anticoagulation or antiplatelet medications [16]. The authors found that, although Korean endoscopists appeared to be concerned about the risk of bleeding, they did not seem to be as concerned about thromboembolism, which may have been due to the belief held by Korean endoscopists that Caucasians are more susceptible than Asians to thromboembolism [16].

In the present study, most Korean cardiac surgeons (72%) indicated that the risk of thromboembolism after warfarin withdrawal is lower in Koreans than Caucasians. Half of the participants (50%) believed the risk of bleeding during endoscopy without warfarin withdrawal at an INR of 2–3 to be higher in Koreans, while 47.2% believed the risk to be equivalent in Koreans and Caucasians.

Although some studies have supported the proposal that Caucasians are more susceptible than Asians to thromboembolism [17], the risk of thromboembolism in Asians may be substantial [16], and the cessation of warfarin thus requires careful consideration. Furthermore, the mortality rate associated with embolism is greater than that associated with bleeding [17]. Asians may be predisposed to severe forms of embolism, such as cerebrovascular events [16,18]. Thromboembolism in Caucasians may be more likely to be of the cardiovascular variety, which has less severe clinical consequences than central nervous system thromboembolism, whereas the cerebrovascular system is more likely to be involved in Asians [16,18]. Indeed, a Korean survey indicated that six of 81 endoscopists (7.4%) have experienced a case of embolism in a patient after discontinuing anticoagulation and antiplatelet medications for an endoscopic procedure, and five of these six were cerebrovascular embolisms [19].

Guidelines are useful as references, but the risks of hemorrhage and thromboembolism after withdrawal should be assessed on a case-by-case basis. The 2014 JGES guidelines recommend that when anticoagulants need to be discontinued before gastroenterological endoscopy, the prescribing doctor should be consulted beforehand, because it is important to develop a management plan optimized for the individual based on a consultation between the endoscopist and the

physician responsible for prescribing antithrombotics [2]. In Korea, no guidelines have been issued regarding warfarin management before EGD.

This study has several limitations. First, the number of participants was small, and its methodology involved a questionnaire based on hypothetical clinical cases. Nonetheless, this study revealed that preferences regarding warfarin treatment at the time of EGD vary considerably among Korean surgeons. This is a preliminary study to confirm the necessity of developing new guidelines. Further collaborative studies between cardiac surgeons and endoscopists are necessary to develop new guidelines that take into account ethnic differences and current practice.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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References

1. Bhatt DL, Scheiman J, Abraham NS, et al. *ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents*. *Circulation* 2008;118:1894-909.
2. Fujimoto K, Fujishiro M, Kato M, et al. *Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment*. *Dig Endosc* 2014;26:1-14.
3. ASGE Standards of Practice Committee, Anderson MA, Ben-Menachem T, et al. *Management of antithrombotic agents for endoscopic procedures*. *Gastrointest Endosc* 2009;70:1060-70.
4. Veitch AM, Baglin TP, Gershlick AH, et al. *Guidelines for the management of anticoagulant and antiplatelet therapy in patients undergoing endoscopic procedures*. *Gut* 2008;57:1322-9.
5. Boustiere C, Veitch A, Vanbiervliet G, et al. *Endoscopy and antiplatelet agents*. *European Society of Gastrointestinal Endoscopy (ESGE) Guideline*. *Endoscopy* 2011;43:445-61.
6. Eisen GM, Baron TH, Dominitz JA, et al. *Guideline on the management of anticoagulation and antiplatelet therapy for endoscopic procedures*. *Gastrointest Endosc* 2002;55:

- 775-9.
7. Fujishiro M, Oda I, Yamamoto Y, et al. *Multi-center survey regarding the management of anticoagulation and antiplatelet therapy for endoscopic procedures in Japan.* J Gastroenterol Hepatol 2009;24:214-8.
 8. Ogoshi K, Kaneko E, Tada M; Japan Gastroenterological Endoscopy Society Risk Management Committee. *Use of anticoagulants and antiplatelet agents during endoscopic procedures.* Gastroenterol Endosc 2005;47:2691-5.
 9. Wahl MJ. *Dental surgery in anticoagulated patients.* Arch Intern Med 1998;158:1610-6.
 10. Blacker DJ, Wijdicks EF, McClelland RL. *Stroke risk in anti-coagulated patients with atrial fibrillation undergoing endoscopy.* Neurology 2003;61:964-8.
 11. Palareti G, Legnani C, Guazzaloca G, et al. *Activation of blood coagulation after abrupt or stepwise withdrawal of oral anticoagulants: a prospective study.* Thromb Haemost 1994;72:222-6.
 12. Sieg A, Hachmoeller-Eisenbach U, Eisenbach T. *Prospective evaluation of complications in outpatient GI endoscopy: a survey among German gastroenterologists.* Gastrointest Endosc 2001;53:620-7.
 13. Parra-Blanco A, Kaminaga N, Kojima T, et al. *Hemoclipping for postpolypectomy and postbiopsy colonic bleeding.* Gastrointest Endosc 2000;51:37-41.
 14. Ono S, Fujishiro M, Hirano K, et al. *Retrospective analysis on the management of anticoagulants and antiplatelet agents for scheduled endoscopy.* J Gastroenterol 2009;44:1185-9.
 15. Tono S, Morita Y, Miura M, et al. *Risks associated with endoscopic biopsy procedures undertaken while administering antiplatelet drugs.* Gastroenterol Endosc 2011;53:3326-35.
 16. Lee SY, Tang SJ, Rockey DC, et al. *Managing anticoagulation and antiplatelet medications in GI endoscopy: a survey comparing the East and the West.* Gastrointest Endosc 2008;67:1076-81.
 17. Ido K, Togashi K, Yamamoto H, et al. *How antiplatelets and anticoagulants should be managed in endoscopic treatment.* Gastroenterol Endosc 2004;46:2079-85.
 18. Ogoshi K, Kaneko E, Tada M, et al. *The management of anticoagulation and antiplatelet therapy for endoscopic procedures.* Gastroenterol Endosc 2005;47:2691-5.
 19. Lee SY, Chang DK, Park DI, et al. *Multicenter survey on gastrointestinal endoscopic examination during anticoagulation or antiplatelet medications [abstract].* Korean J Gastrointest Endosc 2006;33(Suppl 2):169-70.

Appendix 1. Survey questionnaire

1. Please indicate your institutional affiliation.
2. How old are you?
 - ① 30-39 years old
 - ② 40-49 years old
 - ③ 50-59 years old
 - ④ Over 60 years old
3. A 60-year-old male patient with a history of aortic valve replacement with a mechanical valve is currently on warfarin. He has no risk factors of thromboembolism, such as arrhythmia, heart failure, or stroke, and his international normalized ratio (INR) level is approximately 2. What would you do for this patient if he requires gastroenterologic endoscopy as part of an annual health check-up?
 - ① Discontinuation of warfarin without a replacement (If you stop warfarin, how many days prior to the gastroenterologic endoscopy do you order warfarin cessation?)
 - ② Replace warfarin with subcutaneous enoxaparin.
 - ③ Replace warfarin with intravenous heparin.
 - ④ Conduct the gastroenterologic endoscopy without discontinuing warfarin.
4. For the same patient described in question 3, what would you do for gastroenterologic endoscopy with a mucosal biopsy?
 - ① Discontinuation of warfarin without a replacement (If you stop warfarin, how many days prior to the gastroenterologic endoscopy do you order warfarin cessation?)
 - ② Replace warfarin with subcutaneous enoxaparin.
 - ③ Replace warfarin with intravenous heparin.
 - ④ Conduct the gastroenterologic endoscopy without discontinuing warfarin.
5. A 60-year-old male patient with a history of mitral valve replacement with a mechanical valve is currently taking warfarin. He has no risk factors for thromboembolism, such as arrhythmia, heart failure, or stroke, and his INR level is 2.5-3. What would you do for this patient if he requires a gastroenterologic endoscopy as part of an annual health check-up?
 - ① Discontinue warfarin without a replacement (If you stop warfarin, how many days prior to the gastroenterologic endoscopy do you order warfarin cessation?)
 - ② Replace warfarin with subcutaneous enoxaparin.
 - ③ Replace warfarin with intravenous heparin.
 - ④ If the INR is 2.5-3, conduct the gastroenterologic endoscopy without discontinuing warfarin.
6. In the same patient presented in question 5, how would you handle gastroenterologic endoscopy with a mucosal biopsy?
 - ① Discontinue warfarin without a replacement (If you stop warfarin, how many days prior to the gastroenterologic endoscopy do you order warfarin cessation?)
 - ② Replace warfarin with subcutaneous enoxaparin.
 - ③ Replace warfarin with intravenous heparin.
 - ④ Conduct the gastroenterologic endoscopy without discontinuing warfarin.
7. Do you think the risk of thromboembolism after warfarin cessation is higher in Koreans or Caucasians?
 - ① The risk is higher in Koreans.
 - ② There is no difference.
 - ③ The risk is lower in Koreans.

8. Do you think that if a gastroenterologic endoscopy is performed without warfarin cessation at an INR of 2-3, the risk of bleeding is higher in Koreans or in Caucasians?
- ① The risk is higher in Koreans.
 - ② There is no difference.
 - ③ The risk is lower in Koreans.