ANSWERING REVIEWERS

September 18, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 12653-edited.docx).

Title: Is Cholecystectomy a Reasonable Treatment Option for Simple Gallbladder Polyps Larger Than 10 mm?

Author: Hye Yon Park, Se Hoon Oh, Kwang Hyuck Lee, Jong Kyun Lee, Kyu Taek Lee

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 12653

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) GBPs with gallstones which are common in HBP practice may have higer risk for gallbladder cancer. In the study, this type of patient were excluded and only simple GBPs patients were involved. So the title and the conclusion of the manuscript is not appopriate. I recommend that the tilte could be writed as "Cholecystectomy a Reasonable treatment for simple Gallbladder Polyps Greater Than 10mm? " and the short title could be replaced as "Validation of surgical indication for simple gallbladder polyp".
Ans) We corrected the main title and short title as reviewer's suggestion.

(2) This study is a retrospective study from single center. Thus the defect should be pointed out in discussion.
Ans) We mentioned it in conclusion.

(3) The manuscript needs careful editing by someone with expertise in technical English editing paying particular attention to English grammar, spelling, and sentence structure so that the goals and results of the study are clear to the reader.
Ans) Our manuscript was corrected by a specialized English editing company (www.harrisco.net).

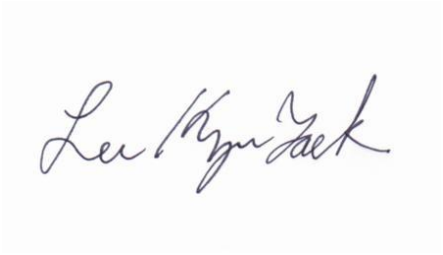
(4) The total number of cholecystectomies (for all reasons)performed during the study's period should be mentioned
Ans) The total number of cholecystectomies in 2012 was 712 cases. So, total number of cholecystectomies for 16 years in Samsung Medical Center was about 10,000 cases. Many portion of operative cases were symptomatic GB stones and cholecystitis cases. We think it is not necessary to mention this in our paper.

(5) It should be add to the text a table or grafh showing the polyps' distribution according to size, i.e., how many polyps had 8mm, how many had 9mm, etc. The English must be improved.
Ans) We added it in Table 3. Our manuscript was corrected by a specialized English editing company (www.harrisco.net).

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,



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Response to Editor's comment

To Editor-in-Chief

I'm Dr. Park, the first author of the manuscript (No. 12653)

We are grateful for your insightful and detailed comments. We followed all of your suggestions.

We believe that the manuscript is improved because we responded to the reviewers' comments.

All coauthors have read the final version of the manuscript. This paper has not been published in whole or in part in any language, except for an abstract presented in a national meeting.

There is no conflict of interests related to this work. Your favorable consideration will be greatly appreciated.

Sincerely.

Hye Yeon Park, MD

Reviewer #2: Lee and colleagues present a retrospective analysis of 430 patients with diagnosis of AF and peptic ulcer disease and compare patients who received oral anticoagulation during follow-up period with those who did not. This is a well-written report asking an important question of (1) efficacy and (2) safety of OAC in such patients. An essential statement which underlines the importance of this paper is "hidden" in discussions (and should be in the introduction): such patients oftentimes are excluded from randomized trials.

Response) We thanks the reviewer for the insightful comments. In response to the reviewer, we changed the abstract as follows; We evaluated the efficacy and safety of OAC in nonvalvular atrial fibrillation (AF) patients with ulcer history (Page 2, line 3-4).

We moved a part of discussion to the introduction, and changed the introduction as follows; However, the risk of bleeding after OAT and optimal OAT in AF patients with a previous ulcer is poorly understood, because these patients were usually excluded from most OAT studies (Page 3, line 5-7).

Major concerns:

Table 1 shows that there were significant differences between comparison groups. Given about 60 and 80 events in the 2 comparison groups, the proportional hazards model should be adjusted at least for the potential main sources for confounding: age, hypertension, CHF, stroke and concomitant aspirin use. This would easily pass the rule of thumb to include no more than 1 adjusting variable per 10 events. The authors should include such analysis.

Response) In response to the reviewer's comment, we added adjusted hazard model in the result (Page 7, line 1-2; Page 7, line 8-9; Page 8, line 2-3).

Although I typically favor data-driven approaches to analyses, I believe any reader would be surprised that patients with INRs of 1.5-3 were considered in target range. I understand that this was a safe target range in this study, but would not apply to clinical practice (plus there are other studies that have shown lower INRs than 2 to be associated with relatively steep increases of incident stroke. Therefore the subgroup analysis should be repeated in patients who were >/=60% in TTR of INR 2-3 vs. patients <60%.

Response) We thank the reviewer for the insightful comments. In response to the reviewer's

comment, we changed INRs of 1.5-3.0 to 2.0-3.0, and repeated the analysis. The OAT+ patients with TTR ≥ 60% had higher cumulative survival free of the composite endpoint than OAT- (p=0.01) and those with TTR <60% (p=0.03). The result was presented in page 8 (line 3-4) and in the revised figure 4.

Minor concerns:

The introduction should be kept to a few sentences and the reader should understand the aim and context of the study within 2-3 sentences. Most of this text belongs in Discussion.

Response) In response to the reviewer, we shortened introduction, and changed the aim as follows; The aim of this study was to evaluate the clinical courses, including thromboembolic and bleeding events, of AF patients with a history of gastrointestinal ulcer according to whether or not they received OAC. Second, we also evaluated the clinical outcomes of patients according to the quality of anticoagulation represented as time in the therapeutic rage (TTR) of INR (Page 3, line 11-14).

It is not clear how patients were identified (by ICD-9 codes from electronic medical records, or other databases?) This should be clarified.

Response) Patients were identified by ICD-9 codes from electronic medical records. In response to the reviewer, we changed the method as follows; Between January 2001 and July 2011, using ICD-9 codes, we identified 810 consecutive patients with nonvalvular AF and GI ulcer disease (page3, line 18-20).

Also it appears that all patients between 2001 and 2011 have been screened and enrolled if they meet exclusion and inclusion criteria. I suspect that many patients were excluded. Some may have not fit criteria other may have had missing data. It would be helpful if possible to compare included and excluded patients in a table (possibly as electronic appendix).

Response) We added exclusion and inclusion criteria in methods as follows; Between January 2001 and July 2011, using ICD-9 codes, we identified 810 consecutive patients with nonvalvular AF and gastrointestinal ulcer disease. Patients with chronic liver disease (n=162), thrombocytopenia (n=57), endoscopic findings with malignancy, Mallory-Weiss tear, angiodysplasia or Dieulafoy's lesion (n=56), previous intracerebral hemorrhage (n=12), and

insufficient clinical data (n=93) were excluded (Page 3, line 18-23).We added the comparison between excluded and included patients in supplementary table.

How was congestive heart failure defined (abnormal LVEF, diastolic dysfunction, prior admission for heart failure)?

Response) Heart failure was defined when hospitalized patients have appropriate symptoms (shortness of breath, fatigue, fluid retention, or any combination of these symptoms) and clinical signs of fluid retention (pulmonary or peripheral) with explainable abnormality of cardiac structure and function (Cowie MR, et al. *Lancet* 1997;350:1349-1353) (Page 4, line 6-9).

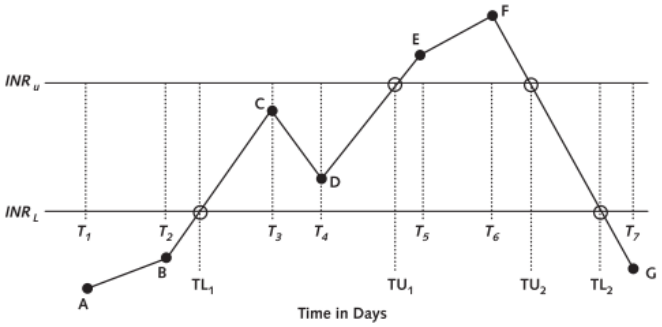
How was missing data dealt with? Imputation? Exclusion of patients?

Response) Patients with an interval of 56 days or more between INR tests were excluded. And we did not impute values for missed INRs but used the linear interpolation method as proposed by Rosendaal et al (Rosendaal FR, et al. *Thromb Haemost* 1993;69:236-239). This method assumes that the INR values between 2 consecutive measurements vary linearly. We quote a figure that explains this method very well at the next page (Schulman S, et al. *Ann Intern Med*, 2011;155:653-659).

We explained in the method as follows: To calculate TTR, INR values between the actual tests were estimated using the linear interpolation method as proposed by Rosendaal et al. (Rosendaal FR, et al. *Thromb Haemost* 1993;69:236-239). This method assumes that the INR values between 2 consecutive measurements vary linearly. Patients with an interval of 56 days or more between INR tests were excluded from the analysis (Page 5, line 18-21).

Appendix Figure 2. **Description of TTR calculation.**

The raw data consist of a series of k INR and data pairs (INR_i and T_i for $i = 1,2,...k$) for each patient observed during the study period, and the fixed upper and lower limits of the acceptable INR therapeutic range (INR_U, INR_L). In the example below, there are $k = 7$ assessment dates (from T_1 to T_7) with INR levels (from INR_1 to INR_7) that demonstrate the most common situations (labeled A, B, C, D, E, F, G).



The TTR can be calculated easily if one assumes that the "instantaneous" unobserved INRs between observation times follow a linear path (i.e., "you join the dots"). Therefore, the table below summarizes the number of days that the patient remained within and outside of (either below or above) the therapeutic range, depending on the location of the segments relative to the INR boundaries.

Segment (1)	Days in Therapeutic Range (2)	Days out of Therapeutic Range	
		Below Lower Limit (3)	Above Upper Limit (4)
AB	0	$T_2 - T_1$	0
BC	$T_3 - TL_1$	$TL_1 - T_2$	0
CD	$T_4 - T_3$	0	0
DE	$TU_1 - T_4$	0	$T_5 - TU_1$
EF	0	0	$T_6 - T_5$
FG	$TL_2 - TU_2$	$T_7 - TL_2$	$TU_2 - T_6$

In statistical analysis, it should be mentioned how non-normal distributed data were compared.

Response) Mann-Whitney test was used for non-normal distributed data. We also added the method as follows; Continuous variables that were normally distributed were reported as mean ± SD and were compared by use of a Student's *t*-test for parametric data and Mann-Whitney test for nonparametric data (Page 5, line 22 – Page 6, line 1).

Please include follow-up time between the 2 comparison groups to demonstrate that patients in both groups had equal opportunity to develop events.

Response) Follow time was not different between the 2 groups. In response to the reviewer's comments, we added the result as follows; There was no difference in the follow-up duration between the 2 groups (3.5 ±2.6 vs. 3.2 ±2.7 years, p=0.23) (Page 6, line 18-19).

The authors should mention (in Results and Limitations) that a trend in difference of composite outcome was seen and there was potentially a lack of power that was responsible for this result.

Response) In response to the reviewer's comment, we added the sentences in Result and Limitation as follows; There was no significant difference between the 2 groups, although OAT- patients tended to have more composite endpoint (P=0.08) (Page 7, line 14-16)

There was a trend in difference of composite outcome and there was potentially a lack of power due to small study size (Page 10, line 3-5)