Journal of
Gastroenterology and Hepatology Research

Online Submissions: http: //www.ghrnet.org/index./joghr/
doi: 10.17554/j.issn.2224-3992.2019.08.864

Journal of GHR 2019 December 21; 8(6): 3009-3013
ISSN 2224-3992 (print) ISSN 2224-6509 (online)

ORIGINAL ARTICLE

Safety of Hepatobiliary and Pancreatic Surgery in Patients Receiving Direct oral Anticoaulants (DOACs)

Takahisa Fujikawa[1], MD, FACS; Akira Tanaka[1], MD

1 Department of Surgery, Kokura Memorial Hospital, Kitakyushu, Fukuoka 802-8555, Japan.

Conflict-of-interest statement: The authors declare that there is no conflict of interest regarding the publication of this paper.

Correspondence to: Takahisa Fujikawa, MD, PhD, FACS, Department of Surgery, 3-2-1 Asano, Kokurakita-Ku, Kitakyushu, Fukuoka 802-8555, JAPAN.
Email: fujikawa-t@kokurakinen.or.jp
Telephone: +12368633325

Received: October 6, 2019
Revised: October 25, 2019
Accepted: October 28, 2019
Published online: December 21, 2019

ABSTRACT

BACKGROUND: The safety and optimal perioperative management of patients receiving direct oral anticoagulants (DOACs) during hepatobiliary and pancreatic (HBP) surgery is still controversial.

METHODS: Between 2012 and 2018, 115 anticoagulant-prescribed patients who underwent elective HBP surgery (65 benign and 50 malignant diseases, 69 laparoscopic and 46 open-fashioned operations) in our department were enrolled in this study. Patients undergoing emergency operations were excluded from the study. The patients were divided into two groups; patients receiving DOACs (DOAC group, n = 35) and patients undergoing warfarin therapy (WF group, n = 80). Background characteristics, surgical blood loss, and postoperative complications, including bleeding and thrombotic complications, were compared between the groups.

RESULTS: In the DOAC group, dabigatran, apixaban, rivaroxaban, and edoxaban were used in 10, 8, 10, and 7 patients, respectively, and only 11 patients (31.4%) received perioperative heparin bridging. There were no differences in patients' background characteristics and mode of surgery (open or laparoscopic). The duration of operation (p = 0.148), surgical blood loss (p = 0.782), and the rate of intraoperative red blood cell transfusion (p = 1.000) were similar between the groups. Overall, any thromboembolic complications were not observed in the current cohort, and only 1 patient (2.9%) suffered from postoperative bleeding complication in the DOAC group. The mortality was zero, and the length of postoperative stay was also identical between the groups (p = 0.998).

CONCLUSION: HBP surgery is safely performed in patients receiving DOAC therapy, without increase in bleeding or thromboembolic complications compared with warfarin therapy.

Key words: Direct oral anticoagulant (DOAC); Hepatobiliary and pancreatic surgery; Anticoagulation therapy; Bleeding complication; Thromboembolic complication

Fujikawa T, Tanaka A. Safety of Hepatobiliary and Pancreatic Surgery in Patients Receiving Direct oral Anticoaulants (DOACs). *Journal of Gastroenterology and Hepatology Research* 2019; **8(6)**: 3009-3013 Available from: URL: http://www.ghrnet.org/index.php/joghr/article/view/2705

INTRODUCTION

After the clinical trials have showed non-inferiority or superiority in terms of safety and efficacy compared with vitamin K antagonist (warfarin)[1-5], the number of patients receiving treatment with direct oral anticoagulants (DOACs) is increasing. Recent reports also demonstrated that approximately 10-15% of DOAC-treated patients will have to interrupt their anticoagulant before an invasive procedure every year[6,7].

The potential advantages of DOACs over warfarin are rapid onset and offset of action, fewer effect of dietary vitamin K intake or drug interaction on their activity, and the predictable anticoagulant effects without the need for routine monitoring[5,8]. Although some updated guidelines regarding the digestive endoscopy procedures currently show the optimal perioperative management of DOAC-treated

patients[9,10], the perioperative management during major surgery such as hepatobiliary and pancreatic (HBP) surgery has not yet been established and is still challenging. In the present study, we reviewed 115 consecutive anticoagulant-received patients undergoing HBP surgery, and investigated the effect of perioperative management of DOACs on bleeding and thromboembolic complications.

PATIENTS AND METHODS

Our institutional review board approved the current study. Potentially relevant cases were searched from the single institution prospectively collected surgery database. After excluding cases with emergency surgery, a total of 115 consecutive HBP surgery (69 benign and 50 malignant diseases, 69 laparoscopic and 46 open-fashioned operations) were included in the current study (Figure 1). The patients were divided into two groups according to the preoperative status of anticoagulation; patients receiving warfarin therapy (WF group, $n = 80$) and patients receiving DOACs (DOAC group, $n = 35$). All procedures were executed by or under the guidance of one of the board-certified attending surgeons in our institution.

To assess the predicted thromboembolic risk of patients in each group, we adopted revised $CHADS_2$ scoring system[11-14]. The $CHADS_2$ score is cumulative on the basis of 6 clinical features: congestive heart failure, hypertension, diabetes mellitus, and age ≥ 75 years (counted as 1 point each), and a history of stroke or TIA (2 points); revised CHADS2 scoring system defines that the patients are categorized as high-risk group if the score is 2 or higher. The status of patients' symptoms and functions regarding ambulatory status was reported according to the ECOG scale of performance status (PS)[15]. Postoperative complications were assessed and categorized by Clavien-Dindo classification (CDC) and CDC class 2 or higher was considered significant[16].

Postoperative bleeding and thromboembolic complications were defined as previously reported[17,18]. Briefly, thromboembolism included cerebral infarction, myocardial infarction, mesenteric infarction, pulmonary thromboembolism, and acute arterial embolism; bleeding complication included luminal bleeding (e.g. gastrointestinal bleeding), abdominal bleeding, and abdominal wall hematoma. Operative mortality was defined as death within 30 d after surgery.

The primary outcome included intraoperative blood loss and postoperative bleeding complications. The background characteristics, perioperative factors, and surgical outcome of included patients were compared between the groups.

Statistical analysis

Continuous values were expressed as mean (SD) or median (interquartile range), while categorical variables were presented as absolute numbers and persentages. For univariate comparisons, Fisher's exact probability test was used to evaluate categorical variables; alternatively, continuous variables were analyzed by Student's t test and Kruskal-Wallis tests for normally and nonnormally distributed data, respectively. All P-values were two sided and P-values less than 0.05 were considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Centre, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, version 2.13.0)[26].

RESULTS

A total of 115 patients were enrolled in the current study, which consisted of 80 patients in the WF group and 35 patients in the DOAC group (Figure 1). Figure 2 shows the type of anticoagulation agents in this cohort. Warfarin was the dominant agent with the rate of 70%, whereas DOAC was used in 30% of patients. In the WF group, most patients were managed perioperatively by heparin bridging (79/80, 98.7%). In the DOAC group, dabigatran, apixaban, rivaroxaban, and edoxaban were used in 10, 8, 10, and 7 patients, respectively, and only 11 patients (31.4%) received perioperative heparin bridging.

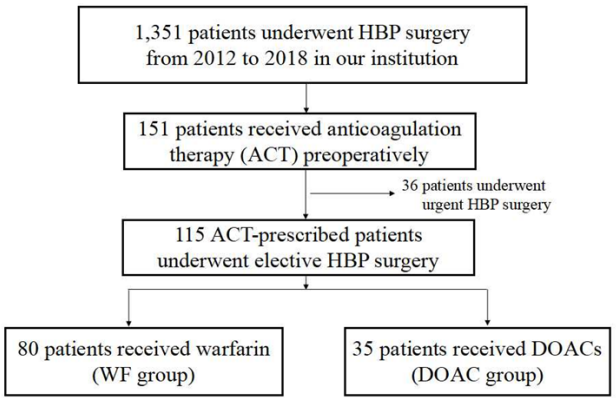

Figure 1 Consort diagram in the current study. Abbreviation: HBP; hepatobiliary and pancreatic, ACT; anticoagulation therapy, WF; warfarin, DOAC; direct oral anticoagulant.

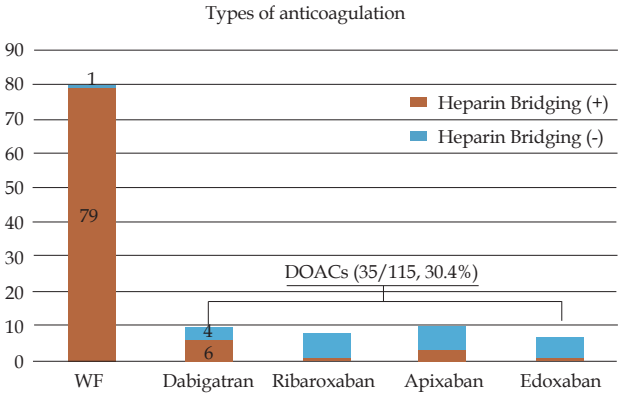

Figure 2 The types of anticoagulation agents in the current cohort. Warfarin is the dominant agent with the rate of 70%, whereas DOACs was used in 30% of patients. In the WF group, most patients were managed perioperatively by heparin bridging (79/80, 98.7%), although only 31.4% (11/35) of DOAC-treated patients used heparin bridging. Abbreviations: WF; warfarin, DOAC; direct oral anticoagulant.

Table 1 shows background characteristics in each group. The median ages in the WF and DOAC groups were 74 years and 73 years, respectively ($p = 0.922$). The occurrence of patients with poor performance status (grade 2-4) ($p = 1.000$), diabetes mellitus ($p = 0.643$), history of congestive heart failure ($p = 0.286$), history of percutaneous coronary intervention or coronary artery bypass graft ($p = 0.408$), history of cerebral infarction or transient ischemic attack ($p = 0.229$), and maintenance of peritoneal dialysis or hemodialysis ($p = 0.312$) were also similar between the groups. The rates of high risk category according to the revised $CHADS_2$ score in the WF and DOAC groups were 69.9% and 54.2%, respectively ($p = 0.686$).

Table 2 shows factors regarding operative procedures in the whole cohort. The present cohort consisted of 65 benign and 50 malignant diseases, and 63 cholecystectomy, 35 liver resection and 15 pancreatic resection were included. The mode of surgery consisted of 69 laparoscopic and 46 open-fashioned operations. There was no difference in the type of diseases ($p = 0.541$), the type of surgery

Table 1 Background characteristics of patients in the current cohort.

Variables	WF (n = 80)	DOAC (n = 35)	p value
Age, y, median (range)	74 (48-87)	73 (44-86)	0.922
Gender, n (%)			
Female	25 (31.2)	8 (22.9)	0.502
Male	55 (68.8)	27 (77.1)	
BMI, kg/m^2, median (range)	23.8 (16.1-30.0)	23.7 (18.4-36.7)	0.886
Performance status, n (%)			1
0, 1	74 (92.5)	32 (91.4)	
2-4	6 (7.5)	3 (8.6)	
Concurrent diseases, n (%)			
Hypertension	38 (47.5)	17 (48.6)	1
Diabetes mellitus	19 (23.8)	10 (28.6)	0.643
Hx of congestive heart failure	30 (37.5)	9 (25.7)	0.286
Vascular diseases	34 (44.2)	12 (34.3)	0.408
Hx of cerebral infarction/TIA	20 (25.0)	5 (14.3)	0.229
Current hemo-/peritoneal dialysis	19 (23.8)	10 (28.6)	0.312
Antiplatelet therapy, n (%)	43 (53.8)	9 (25.7)	0.008
Periop. heparin bridging, n (%)	79 (98.8)	11 (31.4)	<0.001
CHADS$_2$ score, n (%)			0.686
Score 0	6 (7.5)	3 (8.6)	
Score 1	18 (22.5)	13 (37.1)	
Score 2 or higher	56 (69.9)	19 (54.2)	

Bald value indicates statistically significant. *Abbreviations: WF: warfarin; DOAC: direct oral anticoagulant; BMI: body mass index; Hx: history; TIA: transient ischemic attack; Periop.: perioperative.

Table 2 Factors regarding operative procedures in the cohort.

Variables	WF (n = 80)	DOAC (n = 35)	p value
Type of diseases, n (%)			0.541
Benign diseases	47 (58.8)	18 (51.4)	
Malignant diseases	33 (41.2)	17 (48.6)	
Type of surgery, n (%)			0.766
Cholecystectomy	45 (56.2)	18 (51.4)	
Liver resection			
Partial resection	18 (22.5)	6 (17.1)	
Sub- or Mono-sectionectomy	5 (6.2)	4 (11.4)	
Di- or Tri-sectionectomy	2 (2.5)	0 (0.0)	
Extrahepatic bile duct resection	1 (1.2)	1 (2.9)	
Pancreatic resection			
Pancreaticoduodenectomy	6 (7.5)	4 (11.4)	
Distal pancreatectomy	3 (3.8)	2 (5.7)	
Mode of surgery, n (%)			0.836
Laparoscopic surgery	47 (58.8)	22 (62.9)	
Open surgery	33 (41.2)	13 (37.1)	
Duration of operation, min, median (range)	146 (50-587)	151 (45-659)	0.148
Surgical blood loss, mL, median (range)	35 (0-3050)	35 (0-2100)	0.782
Intraoperative RBC transfusion, n (%)	9 (11.2)	3 (8.6)	1

Bald value indicates statistically significant. *Abbreviations: WF: warfarin; DOAC: direct oral anticoagulant; RBC: red blood cell.

Table 3 Factors concerning postoperative morbidity and mortality in the cohort.

Variables	WF (n = 80)	DOAC (n = 35)	p value
Postoperative complication, n (%)			0.064
C-D class 0	69 (86.2)	24 (68.6)	
C-D class 1	3 (3.8)	3 (8.6)	
C-D class 2	8 (10.0)	6 (17.1)	
C-D class 3 or higher	0 (0.0)	2 (5.8)	
Postop. bleeding complication, n (%)	0 (0.0)	1 (2.9)	0.304
Postop. thrombotic complication, n (%)	0 (0.0)	0 (0.0)	NA
Operative mortality, n (%)	0 (0.0)	0 (0.0)	NA
Length of postop. stay, d, median (range)	11 (3-121)	10 (3-147)	0.998

Bald value indicates statistically significant. *Abbreviations: WF: warfarin; DOAC: direct oral anticoagulant; C-D: Clavien-Dindo; Postop.: postoperative; NA: not available.

(p = 0.766) and the mode of surgery (p = 0.836). Concerning intraoperative bleeding events, there were no patients who suffered uncontrollable excessive intraoperative bleeding due to the treatment of ACT or heparin bridging. The duration of operation (p = 0.148), surgical blood loss (p = 0.782), and the rate of intraoperative red blood cell transfusion (p = 1.000) were similar between the groups.

Table 3 shows factors regarding postoperative morbidity and mortality in the cohort. Postoperative complications developed in 19.1% (22/115) of overall patients. The occurrence of severe postoperative complications (CDC class 3 or higher) in the WF and DOAC groups were 0.0% and 5.8%, respectively (p = 0.064). There were no thromboembolic events in the both groups and only 1 patient (2.9%) suffered from postoperative bleeding complication in the DOAC group. This patient, receiving combination of warfarin and aspirin therapy preoperatively, experienced postoperative bleeding from the abdominal wound after pancreaticoduodenectomy, which required repeated hemostasis in the operating room. The mortality was zero in the whole cohort, and the length of postoperative stay was also identical between the groups (11 d vs 10 d, p = 0.998).

DISCUSSION

In the current paper, reviewing 115 consecutive patients undergoing elective HBP surgery, the occurrence of postoperative overall complication, bleeding complication, and thromboembolism were 19.1%, 0.9% and 0%, respectively. In the DOAC group, only 11 patients (31.4%) received perioperative heparin bridging. The background and operative characteristics were similar between the WF and DOAC groups. The mortality was zero, and any thromboembolic complications were not observed in the current cohort. Only 1 patient (2.9%) suffered from postoperative bleeding complication in the DOAC group. It is concluded that HBP surgery is safely performed in patients receiving DOAC therapy, without increase in bleeding or thromboembolic complications.

Currently, DOACs, also known as non-vitamin K antagonist oral anticoagulants (NOACs), are increasingly prescribed for the purpose of preventing arterial or venous thromboembolism. DOAC is a direct thrombin or factor Xa inhibitor. The former includes dabigatran, and the latter includes rivaroxaban, apixaban, and edoxaban. In 2011, dabigatran was approved and indicated for the prevention of ischemic stroke and systemic embolism in patients with non-valvular atrial fibrillation. Factor Xa inhibitors were then launched with the same indications. Compared with warfarin, DOAC has superior pharmacological properties such as better dose-response, less difference in anticoagulant activity between individuals, no effect by vitamin K intake, and very few drug interactions[5,19]. Clinically, there are also many advantages including 19% reduction in mortality and 52% reduction in intracranial hemorrhage compared with warfarin[5,19].

DOACs are fast-acting agents, reaching their peak blood concentration 0.5-5 hours after administration. The half-life of

DOAC is also short (approximately 12 hours), and their anticoagulant effect is reduced within 48 hours after its withdrawal.[9] Reportedly, Xa inhibitors diminish anti-Xa activity 48 hours after the last intake in patients receiving them once daily (e.g. rivaroxaban and edoxaban), and 36 hours after the last intake in those receiving them twice daily (e.g. apixaban)[20,21]. Therefore, if DOACs are stopped for periods longer than 36-48 hours, the risks and benefits need to be carefully assessed.

The recently updated guideline concerning the gastroenterological endoscopy and antithrombotic therapy[9] currently recommends that in case of the procedures with a high risk of bleeding, patients receiving DOAC therapy should discontinue DOAC on the morning of the procedure, and resume DOAC administration on the morning after the procedure. However, there are so far no evidence or guidelines regarding HBP surgery in patients with DOACs, and safety of every surgical type, including HBP surgery, should be assessed. The current study showed that HBP surgery in DOAC-treated patients is safe and feasible without increase in bleeding or thromboembolic complications compared with warfarin.

Concerning the perioperative management of DOAC-treated patients, bridging therapy with heparin after cessation of DOACs was initially recommended to avoid a perioperative gap with insufficient anticoagulation. The recommendations of the European Society of Anaethesiology (ESA) published in 2013[22] suggested that heparin bridging could be used when DOAC had a long preoperative interruption (5 days prior to surgery) in patients at high TE risk. The previous Japanese guidelines (2012) of digestive endoscopy also recommended replacing DOAC with heparin in case of high risk of bleeding[23]. However, as with heparin, the therapeutic effect of DOAC is reduced shortly after the onset of action and the most updated guidelines proposed withdrawing DOAC for only a short period (36-48 hours) during the surgery or procedures. The updated guidelines currently describe that heparin bridging during perioperative cessation of DOACs is not recommended.

Several review and large-scale cohort studies[24,25] also suggest safety and feasibility of perioperative management of DOACs without heparin bridging during noncardiac surgery. Especially, recently published prospective, multicenter cohort study ("PAUSE study") examined outcomes in 3,007 adult DOAC-treated patients with atrial fibrillation who underwent an elective surgery or procedure[25]. DOACs were interrupted 1-2 days prior and resumed 1-2 days after the surgery or procedure. At 30-days, the rates of major bleeding ranged from 0.90-1.85%. The rates of arterial thromboembolism ranged from 0.16-0.60%. The study suggests that a standardized perioperative DOAC management strategy without heparin bridging can be safely used for atrial fibrillation patients undergoing surgery. Although this study included relatively small numbers of major digestive surgery, the optimal DOAC management without heparin bridging was suggested even in case of high bleeding risk surgery such as HBP surgery.

The current study has some limitations. First, it is a retrospective review from a single center, which lessens the efficacy of the conclusion. This limitation will be mitigated in a later follow-up study. Second, our institution is a high-volume tertiary referral hospital for surgical patients receiving antithrombotic therapy; consequently, our findings may not be generalizable to relatively low-volume centers. This restriction will be alleviated by multi-institutional prospective studies.

CONCLSIONS

Analyzing 115 patients receiving anticoagulation therapy, it is concluded that HBP surgery is safely performed in patients receiving DOAC therapy, without increase in bleeding or thromboembolic complications compared with warfarin therapy.

REFERENCES

1. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009; **361(12)**: 1139-1151. [PMID: 19717844]; [DOI: 10.1056/NEJMoa0905561]
2. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011; **365(10)**: 883-891. [PMID: 21830957]; [DOI: 10.1056/NEJMoa1009638]
3. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011; **365(11)**: 981-992. [PMID: 21870978]; [DOI: 10.1056/NEJMoa1107039]
4. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2013; **369(22)**: 2093-2104. [PMID: 24251359]; [DOI: 10.1056/NEJMoa1310907]
5. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014; **383(9921)**: 955-962. [PMID: 24315724]; [DOI: 10.1016/S0140-6736(13)62343-0]
6. Healey JS, Eikelboom J, Douketis J, Wallentin L, Oldgren J, Yang S, Themeles E, Heidbuchel H, Avezum A, Reilly P, Connolly SJ, Yusuf S, Ezekowitz M; RE-LY Investigators. Periprocedural Bleeding and Thromboembolic Events With Dabigatran Compared With Warfarin. *Circulation*. 2012; **126(3)**: 343-348. [PMID: 22700854]; [DOI: 10.1161/CIRCULATIONAHA.111.090464]
7. Sherwood MW, Douketis JD, Patel MR, Piccini JP, Hellkamp AS, Lokhnygina Y, Spyropoulos AC, Hankey GJ, Singer DE, Nessel CC, Mahaffey KW, Fox KA, Califf RM, Becker RC; ROCKET AF Investigators. Outcomes of Temporary Interruption of Rivaroxaban Compared With Warfarin in Patients With Nonvalvular Atrial Fibrillation. *Circulation*. 2014; **129(18)**: 1850-1859. [PMID: 24552831]; [PMCID: PMC4206548]; [DOI: 10.1161/CIRCULATIONAHA.113.005754]
8. Dubois V, Dincq AS, Douxfils J, Ickx B, Samama CM, Dogné JM, Gourdin M, Chatelain B, Mullier F, Lessire S. Perioperative management of patients on direct oral anticoagulants. *Thromb J.* 2017; **15(1)**: 14. [PMID: 28515674]; [PMCID: PMC5433145]; [DOI: 10.1186/s12959-017-0137-1]
9. Kato M, Uedo N, Hokimoto S, Ieko M, Higuchi K, Murakami K, Fujimoto K. Guidelines for Gastroenterological Endoscopy in Patients Undergoing Antithrombotic Treatment: 2017 Appendix on Anticoagulants Including Direct Oral Anticoagulants. *Dig Endosc.* 2018; **30(4)**: 433-440. [PMID: 29733468]; [DOI: 10.1111/den.13184]
10. ASGE Standards of Practice Committee, Acosta RD, Abraham

NS, Chandrasekhara V, Chathadi KV, Early DS, Eloubeidi MA, Evans JA, Faulx AL, Fisher DA, Fonkalsrud L, Hwang JH, Khashab MA, Lightdale JR, Muthusamy VR, Pasha SF, Saltzman JR, Shaukat A, Shergill AK, Wang A, Cash BD, DeWitt JM. The management of antithrombotic agents for patients undergoing GI endoscopy. *Gastrointest Endosc*. 2016; **83(1)**: 3-16. [PMID: 26621548]; [DOI: 10.1016/j.gie.2015.09.035]

11. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001; **285(22)**: 2864-2870. [PMID: 11401607]; [DOI: 10.1001/jama.285.22.2864]
12. Rietbrock S, Heeley E, Plumb J, van Staa T. Chronic atrial fibrillation: Incidence, prevalence, and prediction of stroke using the Congestive heart failure, Hypertension, Age > 75, Diabetes mellitus, and prior Stroke or transient ischemic attack (CHADS2) risk stratification scheme. *Am Heart J*. 2008; **156(1)**: 57-64. [PMID: 18585497]; [DOI: 10.1016/j.ahj.2008.03.010]
13. Zhu W-G, Xiong Q-M, Hong K. Meta-Analysis of $CHADS_2$ versus CHA_2 DS_2 -VASc for Predicting Stroke and Thromboembolism in Atrial Fibrillation Patients Independent of Anticoagulation. *Texas Hear Inst J*. 2015; **42(1)**: 6-15. [PMID: 25873792]; [PMCID: PMC4378047]; [DOI: 10.14503/THIJ-14-4353]
14. Mitchell LB, Southern DA, Galbraith D, et al. Prediction of stroke or TIA in patients without atrial fibrillation using $CHADS_2$ and CHA_2 DS_2 -VASc scores. *Heart*. 2014; **100(19)**: 1524-1530. [PMID: 24860007]; [DOI: 10.1136/heartjnl-2013-305303]
15. Sorensen JB, Klee M, Palshof T, Hansen HH. Performance status assessment in cancer patients. An inter-observer variability study. *Br J Cancer*. 1993; **67(4)**: 773-775. [PMID: 8471434]; [PMCID: PMC1968363]; [DOI: 10.1038/bjc.1993.14016]
16. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004; **240(2)**: 205-213. [PMID: 15273542]; [PMCID: PMC1360123]; [DOI: 10.1097/01.sla.0000133083.54934.ae]
17. Fujikawa T, Tanaka A, Abe T, Yoshimoto Y, Tada S, Maekawa H, Shimoike N. Does antiplatelet therapy affect outcomes of patients receiving abdominal laparoscopic surgery? Lessons from more than 1,000 laparoscopic operations in a single tertiary referral hospital. *J Am Coll Surg*. 2013; **217(6)**: 1044-1053. [PMID: 24051069]; [DOI: 10.1016/j.jamcollsurg.2013.08.005]
18. Fujikawa T, Tanaka A, Abe T, Yoshimoto Y, Tada S, Maekawa H. Effect of antiplatelet therapy on patients undergoing gastroenterological surgery: thromboembolic risks versus bleeding risks during its perioperative withdrawal. *World J Surg*. 2015; **39(1)**: 139-149. [PMID: 25201469]; [DOI: 10.1007/s00268-014-2760-3]
19. Desai J, Granger CB, Weitz JI, Aisenberg J. Novel oral anticoagulants in gastroenterology practice. *Gastrointest Endosc*. 2013; **78(2)**: 227-239. [PMID: 23725876]; [DOI: 10.1016/j.gie.2013.04.179]
20. Frost C1, Wang J, Nepal S, Schuster A, Barrett YC, Mosqueda-Garcia R, Reeves RA, LaCreta F. Apixaban, an oral, direct factor Xa inhibitor: single dose safety, pharmacokinetics, pharmacodynamics and food effect in healthy subjects. *Br J Clin Pharmacol*. 2013; **75(2)**: 476-487. [PMID: 22759198]; [PMCID: PMC3558798]; [DOI: 10.1111/j.1365-2125.2012.04369.x]
21. Frost C, Song Y, Barrett YC, Wang J, Pursley J, Boyd RA, LaCreta F. A randomized direct comparison of the pharmacokinetics and pharmacodynamics of apixaban and rivaroxaban. *Clin Pharmacol*. 2014; **6**: 179-187. [PMID: 25419161]; [PMCID: PMC4235474]; [DOI: 10.2147/CPAA.S61131]
22. Kozek-Langenecker SA, Afshari A, Albaladejo P, Santullano CA, De Robertis E, Filipescu DC, Fries D, Görlinger K, Haas T, Imberger G, Jacob M, Lancé M, Llau J, Mallett S, Meier J, Rahe-Meyer N, Samama CM, Smith A, Solomon C, Van der Linden P, Wikkelsø AJ, Wouters P, Wyffels P. Management of severe perioperative bleeding. *Eur J Anaesthesiol*. 2013; **30(6)**: 270-382. [PMID: 23656742]; [DOI: 10.1097/EJA.0b013e32835f4d5b]
23. Fujimoto K, Fujishiro M, Kato M, Higuchi K, Iwakiri R, Sakamoto C, Uchiyama S, Kashiwagi A, Ogawa H, Murakami K, Mine T, Yoshino J, Kinoshita Y, Ichinose M, Matsui T; Japan Gastroenterological Endoscopy Society. Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment. *Dig Endosc*. 2014; **26(1)**: 1-14. [PMID: 24215155]; [DOI: 10.1111/den.12183]
24. Verma A, Ha ACT, Rutka JT, Verma S. What Surgeons Should Know About Non-Vitamin K Oral Anticoagulants. *JAMA Surg*. April 2018. [PMID: 29710221]; [DOI: 10.1001/jamasurg.2018.0374]
25. Douketis JD, Spyropoulos AC, Duncan J, Carrier M, Le Gal G, Tafur AJ, Vanassche T, Verhamme P, Shivakumar S, Gross PL, Lee AYY, Yeo E, Solymoss S, Kassis J, Le Templier G, Kowalski S, Blostein M, Shah V, MacKay E, Wu C, Clark NP, Bates SM, Spencer FA, Arnaoutoglou E, Coppens M, Arnold DM, Caprini JA, Li N, Moffat KA, Syed S, Schulman S. Perioperative Management of Patients With Atrial Fibrillation Receiving a Direct Oral Anticoagulant. *JAMA Intern Med*. August 2019. [PMID: 31380891]; [PMCID: PMC6686768]; [DOI: 10.1001/jamainternmed.2019.2431]