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Optimal antiplatelet therapy for prevention of gastrointestinal injury evaluated by ANKON magnetically controlled capsule endoscopy: Rationale and design of the OPT-PEACE trial

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Background Gastrointestinal injury is a common complication in patients treated with antiplatelet agents after percutaneous coronary intervention (PCI). However, the effects of different antiplatelet regimens on the incidence and severity of gastrointestinal injury have not been well studied, principally due to the lack of a low-risk sensitive and accurate detection system.

Trial design OPT-PEACE is a multicenter, randomized, double-blind, placebo-controlled trial. Gastrointestinal injury will be evaluated with the ANKON magnetically controlled capsule endoscopy system (AMCE), a minimally invasive approach for detecting mucosal lesions in the stomach, duodenum and small intestine. Patients without AMCE-detected gastrointestinal erosions, ulceration or bleeding after drug-eluting stent implantation are enrolled and treated with open-label aspirin (100 mg/d) plus clopidogrel (75 mg/d) for 6 months. Thereafter, 480 event-free patients will undergo repeat AMCE and are randomly assigned in a 1:1:1 ratio to receive aspirin plus clopidogrel, aspirin plus placebo or clopidogrel plus placebo for an additional 6 months. A final AMCE is performed at 12 months. The primary endpoint is the incidence of gastric or intestinal mucosal lesions (erosions, ulceration, or bleeding) within 12 months after enrollment.

Conclusions OPT-PEACE is the first study to investigate the incidence and severity of gastrointestinal injury in patients receiving different antiplatelet therapy regimens after stent implantation. This trial will inform clinical decision-making for personalized antiplatelet therapy post-PCI. (Am Heart J 2020;228:8-16.)
endoscopy. Moreover, gastroenterologists may decline to perform gastroscopy in patients on DAPT given the bleeding risk. Finally, upper endoscopy can only detect lesions in the stomach and duodenum, as it does not visualize the remainder of the small intestine. Thus, the extent to which a shortened DAPT strategy reduces primary gastrointestinal mucosal injury (with or without overt bleeding) and whether aspirin or clopidogrel monotherapy is safer are unknown.

ANKON® magnetically controlled capsule endoscopy (AMCE) is a minimally invasive, active controlled system capable of visualizing the stomach and entire small intestine. Patient acceptance of AMCE is higher than standard endoscopy as the procedure involves only swallowing a small capsule endoscope. Discontinuation of antiplatelet drugs during AMCE is not necessary. Previous studies have confirmed that the sensitivity and specificity of AMCE for the detection of focal lesions of the gastrointestinal tract are similar compared with standard endoscopy. We are therefore performing a double-blind, placebo-controlled randomized trial examining the incidence of gastrointestinal injury evaluated by AMCE in patients treated with a 12-month DAPT regimen versus a 6-month DAPT regimen followed by 6 months of aspirin monotherapy or clopidogrel monotherapy after DES implantation.

### Study design and methods

#### Study objectives and hypothesis

The principal hypothesis of the trial is that following 6 months of DAPT, antiplatelet monotherapy with aspirin or clopidogrel between 6 and 12 months after DES implantation is superior to 12 months of DAPT for preventing gastrointestinal injury detected by AMCE. Thus, the primary study objective is to determine the risks of 12 months of DAPT vs a 6 months of DAPT followed by 6 months of aspirin monotherapy or clopidogrel monotherapy on gastrointestinal mucosal injury after DES implantation. The secondary objective is to evaluate the feasibility and safety of AMCE as a method for detecting gastrointestinal mucosal injury and bleeding in patients receiving APT.

In addition, an exploratory objective is to establish a gastrointestinal mucosal injury scoring system that may identify patients at future risk for clinical gastrointestinal bleeding during long-term APT. For this purpose, 2 previously developed scoring systems will be used to assess the degree of mucosal injury observed by AMCE: (1) The modified Lanza score (MLS), and (2) a separate 5-point scoring system (Table I).

### Study organization

OPT-PEACE is a multicenter, randomized, double-blind, placebo-controlled trial. The trial organization and key committees appear in the Appendix. The investigator team at each center consists of cardiologists and gastroenterologists or endoscopists. Executive and steering committees are responsible for the medical, scientific, and operational conduct of the study. The executive committee is responsible for the integrity of data analysis and reporting of results. An independent clinical events committee will adjudicate all cardiovascular and gastrointestinal events. Endoscopic images will be analyzed by an independent core laboratory.

An independent data safety monitoring board (DSMB) will review unblinded interim data at regular intervals. The data to be reviewed will consist of gastrointestinal mucosal lesions, all bleeding, major adverse cardiovascular events, stent thrombosis as well as other serious adverse events, in order to identify potential safety issues. Based on the safety data, the DSMB may advise the Steering Committee if, in their view, the randomized data provide evidence that may warrant early termination for either efficacy or safety. All final decisions regarding trial modifications rest with the Executive Committee.

The OPT-PEACE trial is approved by the institutional ethics committee of the General Hospital of Northern Theater Command and is conducted in accordance with the Declaration of Helsinki. The study is registered at Clinicaltrials.gov (Identifier: NCT03198741).

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### Table I. Scoring systems to assess gastrointestinal mucosal injury

| Category | Score |
|----------|-------|
| No erosion | 0     |
| 1–2 erosions localized in the gastric antrum, body or bottom | 1     |
| 3–5 erosions localized in one area of the stomach | 2     |
| Erosions localized in 2 different areas of the stomach (total 6–9 lesions) | 3     |
| Gastric ulcer or ≥ 10 erosions | 4     |

| Category | Score |
|----------|-------|
| Normal | 0     |
| Petechiae/red spot (demarcated, usually circular, area of crimson mucosa with preservation of villi) | 1     |
| Small number of erosions (1–4 erosions) | 2     |
| High number of erosions (>4 erosions) | 3     |
| Mucosal breaks (large erosion and/or ulcer) | 4     |
Table II. Study enrollment criteria

Inclusion criteria (all must be present) *:

1) Adult patients with age 18–80 years;
2) Presentation with silent ischemia, stable angina, or non-ST-segment elevation acute coronary syndrome with GRACE score < 140 at admission;
3) PCI with implantation of contemporary drug-eluting stent(s)** during the present admission;
4) Complete revascularization (successful PCI treatment of all epicardial coronary lesions with diameter stenosis >70% or intermediate lesions with FFR ≤ 0.80);
5) Planned DAPT with aspirin and clopidogrel for at least 6 months;
6) Agreement to comply with all study procedures;
7) Written informed consent provided.

Exclusion criteria (all must be absent):
1) Presentation with STEMI;
2) Left main disease (diameter stenosis >30%);
3) Any prior coronary stent implantation during the last year prior to the index procedure;
4) Implantation of first-generation drug-eluting stents or bioabsorbable scaffolds during the index procedure;
5) Implantation of >4 stents during the index procedure;
6) Any prior stent thrombosis;
7) Any active gastrointestinal bleeding or ulcers, or prior gastrointestinal bleeding or ulcers within the last 24 months;
8) Prior gastrointestinal tract or abdominal surgery other than simple procedures which would not change the gastrointestinal tract anatomy, such as polyp removal, cholecystectomy or appendectomy;
9) Contraindications to the AMCE test, including suspected or known gastrointestinal obstruction, stenosis, fistula, diverticula, etc; presence of gastrointestinal obstruction symptoms such as pain or dysphagia; inoperative conditions or refusal to undergo abdominal surgery if required (ie, if the capsule will not pass and cannot be removed by endoscopy);
10) Severe hemorrhoids (phase 3–4 according to guidelines of American Society of Colon and Rectal Surgery);
11) LVEF < 0.40 on admission by echocardiography;
12) Renal dysfunction (eGFR < 30 ml/min/1.73 m²);
13) Active hepatitis or ALT > 3 times upper limits of normal at admission;
14) Uncontrolled severe hypertension (> 180/110 mmHg);
15) Hemoglobin < 100 g/L;
16) Platelet count < 100 × 10⁹/L;
17) Planned use of a proton pump inhibitor, gastric mucosa protectant or any other antacid agent after study enrollment;
18) Required use of oral anticoagulation (warfarin or other factor II or factor X inhibitors);
19) Inability to take 12-month DAPT for any reason;
20) Mandatory use of > 6-month DAPT;
21) Any comorbidity with estimated survival time < 12 months (eg, progressive cancer, chronic obstructive lung disease, etc);
22) Any contraindication to MRI examination, including implantation of an MRI-incompatible pacemaker, defibrillator, or other ferromagnetic material, etc;
23) Pregnant or plan to be pregnant within 1 year;
24) Any condition that may interfere with any study procedures, such as dementia, immobility, alcohol use, etc;
25) Planned surgery within 1 year;
26) Taking iron supplement;
27) Participating in any other clinical trial of an investigational drug or device that has not met its primary endpoint.

* Patients who are unable to comply with the baseline AMCE test, or in whom a suboptimal baseline AMCE test result is obtained (inadequate visualization of the upper GI tract for any reason) are excluded from the study. The analysis population will consist of the modified intention-to-treat (ITT) population, consisting of all patients with an evaluable AMCE test at baseline.

** Contemporary DES refers to DES with thin cobalt-chromium or platinum-chromium struts, with a durable or biodegradable polymer eluting a rapamycin-analogue antiproliferative agent. The current major DES available in China market include: EXCEL and EXCEL 2 (JW Medical System, Weihai, China), TiVo(Essen Technology, Beijing, China), Endeavor Resolute (Medtronic Inc, Minneapolis, USA), FireHawk (MicroPort Medical [Group] Co, Ltd, Shanghai, China), SuMA(SinoMedical, China), Xience V (Abbott, Abbott Park, Illinois, USA), Xience Prime (Abbott Laboratories, Abbott Park, Illinois, USA), Promus Element and Synergy (Boston Scientific, Massachusetts, USA).

Study population and AMCE procedure

Patients with either stable coronary artery disease or low-risk acute coronary syndromes without ST-segment elevation (GRACE score <140) after complete coronary revascularization with at least 1 but not more than 4 contemporary DES will be considered for enrollment. Clinical inclusion and exclusion criteria are listed in Table II. Patients meeting all entry criteria will provide informed written consent and then undergo a screening AMCE examination 30–120 hours after successful PCI.
allows movements of 2 mm and changes in viewing angle of 3°. The dimensions of any visualized lesions are measured by the ANKON ESNavi software. Representative examples of normal and abnormal gastric and intestinal findings are shown in Figure 2. Multicenter randomized studies have demonstrated that the AMCE system provides 93.4% accuracy in diagnosis of focal lesions in the stomach compared with standard gastroscopy.12,13

Subjects do not eat or drink any colored liquid or syrup after 8 PM the day before AMCE examination. On the following morning the subject is administered 10 ml of simethicone (Menarini Group, Florence, Italy) as a defoaming agent to clean the stomach cavity 40 minutes before the examination, and drinks water (~500–1000 mL) until feeling stomach fullness. During examination, if the gastric cavity is not filled with sufficient liquid to enable navigation of the capsule, the subject will drink additional water.

After the whole stomach is examined, subjects continue to wear the portable recorder for visualization of the duodenum and small intestine. The capsule is ultimately excreted. Standard magnetic resonance imaging procedures are prohibited before capsule excretion. If the capsule is not found to be excreted within 2 weeks after examination, the subject returns to the hospital for detection of the capsule by a position detector or abdominal x-ray to confirm whether the capsule is still in the body. If it is, endoscopy may be performed to remove the capsule.

Those undergoing successful screening AMCE exam (visualization of the entire upper gastrointestinal tract and small intestine) and with no sites of erosion, ulceration or bleeding will be enrolled in the trial. Consented patients
in whom the baseline screening AMCE was not performed, was not evaluable or was positive (ie, erosion, ulceration or bleeding present) will be followed for 30 days only for safety surveillance.

Study treatments, randomization and follow-up

All enrolled patients with a negative screening AMCE examination will be treated with open-label aspirin (100 mg/d) plus clopidogrel (75 mg/d) for 6 months. Proton pump inhibitors or other gastric mucosal protectant agents may not be used after study enrollment unless a clear clinical indication has developed (eg, new gastrointestinal bleeding or documented ulcer). Eligibility for randomization (including medication adherence and the interval occurrence of adverse events) will be evaluated in this group at 6 months (+/-2 weeks). At this time patients free from interval major adverse ischemic or clinically overt bleeding events and otherwise without any exclusion criteria (Table III) will undergo a second AMCE examination before randomization. Patients successfully completing this exam are then randomly assigned in a 1:1:1 ratio to receive aspirin plus clopidogrel, aspirin plus clopidogrel-placebo or clopidogrel-plus-aspirin-placebo for an additional 6 months in a double blinded manner. The placebo of aspirin and clopidogrel, having an identical appearance to the original agents, were produced by a GMP certificated manufacturing company. All drugs (including placebos) were packaged and coded by a contract research organization. A final in-person visit will be performed at 6 months (+/-2 weeks) after randomization during to assess study medication adherence and adverse events, after which a third AMCE examination will be performed (Figure 3).

A Helicobacter pylori (HP) breath test will be performed after the screening AMCE exam to document HP infection status. HP eradication therapy is not mandatory but is allowed per physician discretion. Serum hemoglobin levels and assessment for occult fecal blood will be performed at baseline and every 2 months after enrollment, until withdrawal or termination of the study. Platelet function testing, including adenosine diphosphate-induced platelet aggregation by light transmission aggregometry and VerifyNow aspirin and P2Y12 testing assessment, will be performed at baseline screening, randomization and at the end of the study in first 102 enrolled patients (34 per group) as a platelet function substudy.

Blinding and unblinding

The study utilizes a double-blind design with matching placebo for aspirin and clopidogrel. The patients, study site research personnel, and treating physicians will not be aware of treatments received. In emergency situations the blind may be broken if absolutely necessary for the treating physician to provide optimal management.

Study endpoints and definitions

The primary and secondary endpoints are shown in Table IV. The primary endpoint is the incidence of gastric or intestinal mucosal injury occurring within 12 months after enrollment, defined as erosion, ulceration or bleeding<sup>18,19</sup> detected by either planned AMCE or clinically-driven endoscopy. Specifically, gastrointestinal erosion is defined as superficial mucosal breaks with a diameter of <5 mm. Gastrointestinal ulcer is defined as a mucosal break with a diameter ≥5 mm, typically covered with fibrin.

Secondary endpoints include the primary endpoint assessed between enrollment and 6 months, and between 6 and 12 months; clinically evident gastrointestinal hemorrhage<sup>19</sup>; gastrointestinal symptoms (graded by the severity and frequency of abdominal pain, bloating, acid regurgitation and eructation); any bleeding events as defined by the BARC definition (types 1–5)<sup>20</sup>; target lesion failure (TLF, defined as the composite of cardiac death, target-vessel myocardial infarction, or clinically-driven target lesion revascularization); net adverse clinical events (defined as the composite of TLF or BARC type 2–5 bleeding); and stent thrombosis according to the Academic Research Consortium (ARC) definite or probable criteria.<sup>21</sup>
The primary endpoint will be assessed in the 12-month DAPT group compared to the pooled 6-month DAPT plus 6-month aspirin and clopidogrel monotherapy groups. Secondary endpoints will also be assessed in these groups. The primary endpoint and all secondary endpoints will also be compared across the 3 groups, and for all single group versus group comparisons (12-month DAPT vs 6-month DAPT plus 6-month aspirin monotherapy; 12-month DAPT vs 6-month DAPT plus 6-month clopidogrel monotherapy; and 6-month DAPT plus 6-month aspirin monotherapy versus 6-month DAPT plus 6-month clopidogrel monotherapy).

Subgroup analyses
The primary and secondary endpoints will be also analyzed in the following clinically relevant pre-specified subgroups: age (65-year cut-off), sex, diabetes mellitus, chronic kidney disease (eGFR 60 mL/min/1.73m² cut-off), acute coronary syndrome, prior history of gastrointestinal bleeding (24 month cut-off), HP infection status, and DAPT duration prior to randomization (>6 months vs ≤6 months). Stratum-specific odds ratios or hazard ratios with 95% confidence intervals will be calculated for each subgroup using either logistic or Cox proportional hazards models as appropriate. Formal interaction testing will be performed using the subgroup × treatment allocation as an additional term in the multivariable models.

Sample size determination and adjustment
The cumulative incidence of the primary endpoint of gastric or intestinal mucosal lesions within 12 months is
Table IV. Study endpoints.

| Primary endpoint* |
|-------------------|
| The incidence of gastric or intestinal mucosal injuries within 12 months after enrollment, defined as erosion, ulceration or bleeding detected by planned AMCE or clinically-driven endoscopy. |

Secondary endpoints

1) The incidence and severity of gastric and intestinal mucosal lesions during the first 6 months after study enrollment (prior to randomization);
2) The incidence and severity of gastric and intestinal mucosal lesions after randomization (ie, between 6 months and 12 months after study enrollment);
3) The incidence of clinically evident gastrointestinal hemorrhage attributed to the upper GI tract (or of unknown origin) during 6 months after study enrollment (prior to randomization);
4) The incidence of clinically evident gastrointestinal hemorrhage attributed to the upper GI tract (or of unknown origin) after randomization (ie, between 6 months and 12 months after study enrollment);
5) The incidence of clinically evident gastrointestinal hemorrhage attributed to the upper GI tract (or of unknown origin) during 12 months after study enrollment;
6) Gastrointestinal symptoms (pain, nausea/vomiting, dysphagia, other) during the 12 months after enrollment;
7) All bleeding (BARC types 1–5) during the 12 months after enrollment;
8) The incidence of target lesion failure (TLF; cardiac death, target-vessel MI, or clinically-driven target lesion revascularization), during the 12 months after enrollment;
9) The incidence of net adverse clinical events (NACE, defined as TLF or BARC type 2–5 bleeding) during the 12 months after enrollment;
10) The incidence of stent thrombosis (ARC definite, probable, or definite/probable) during the 12 months after enrollment.

* Patients will be evaluable for the primary endpoint if either: a) an AMCE test is performed at 12 months (±2 weeks) and is either positive (whether or not the entire GI tract is visible) or is negative with complete visualization of the GI tract; OR b) if a 6-month AMCE test was done and was positive, even if a 12-month test was not done; OR c) if overt GI bleeding occurred anytime during the 12-month follow-up and an AMCE or endoscopy test was positive.

Estimated to be 47% in patients who received 12 months of DAPT and 30% in those treated with either aspirin or clopidogrel monotherapy beginning at 6 months after enrollment. With a 2:1 ratio in patients treated with either aspirin or clopidogrel monotherapy after 6-month DAPT versus DAPT for 12 months, 384 evaluable patients (256 and 128 respectively) provide 90% power to detect a 17% absolute risk reduction (36% relative risk reduction) with a 2-sided type I error of 0.05. Assuming 20% loss of evaluable primary endpoint outcome assessments due to patient withdrawal, loss to follow-up between 6 and 12 months or suboptimal AMCE visualization of the GI tract at 12 months, 480 patients are planned to be randomized. Assuming that an additional 10% of enrolled patients will not be randomized at 6 months because of adverse clinical events, non-compliance with antiplatelet therapy or lost to follow-up or withdrawal, 534 patients were initially planned to be enrolled after baseline screening. Finally, assuming that 10% of patients who undergo a screening AMCE examination will be excluded due to gastrointestinal ulcer or bleeding, approximately 593 patients were initially planned to be consented and undergo the screening AMCE examination.

Among the first 200 patients enrolled, ~25% had gastrointestinal injury at baseline by screening AMCE (despite clinically absent bleeding or gastrointestinal complaints). Of those who passed the initial exam, only ~65% were eligible for randomization; 17% of patients were noncompliant with the 6-month repeat AMCE exam, and new gastrointestinal ulceration or bleeding was found on the 6-month AMCE examination in 18% of patients. The study sample size was adjusted accordingly so 1000 patients will be screened by AMCE at baseline, with 750 patients enrolled and followed to the 6-month randomization eligibility period to achieve the 480 patient randomized goal (Figure 3).
different antiplatelet regimens beyond 6 months (continued
daptive DAPT vs clopidogrel monotherapy vs aspirin monotherapy
between 6 and 12 months) after PCI, which will be informative for clinical decision-making on personalized
APT. In addition, the OPT-PEACE study will provide useful
insights as to the safety of AMCE as a noninvasive method for
detecting gastrointestinal mucosal injury in patients receiv-
ing APT.

Declaration of competing interest

Drs. Yi Li, Xiaozeng Wang, Dan Bao, Zhuan Liao, Jing Li,
Xiao Han, Heyang Wang, Kai Xu, Zhaoshen Li and Yaling
Han have no competing interests to declare. Dr. Gregg W.
Stone has received speaker or other honoraria from Cook,
Terumo, QOOL Therapeutics and Orchestra Biomed; has
served as a consultant to Valfix, TherOx, Vascular
Dynamics, Robocath, HeartFlow, Gore, Ablative Solu-
tions, Miracor, Neovasc, V-Wave, Abiomed, Ancora, MAIA
Pharmaceuticals, Vectorious, Reva, Matrixyme, Cardiomech;
and has equity/options from Ancora, Qool
Therapeutics, Cagent, Applied Therapeutics, Biostar
family of funds, SpectraWave, Orchestra Biomed, Aria,
Cardiac Success, MedFocus family of funds, Valfix.

Appendix A. OPT-PEACE organization
and participating investigators

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References

1. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines
on myocardial revascularization: The Task Force on Myocardial
Revascularization of the European Society of Cardiology (ESC) and
the European Association for Cardio-Thoracic Surgery (EACTS)
Developed with the special contribution of the European Association
of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J
2014;35(37):2541-619.

2. American College of Emergency Physicians; Society for
Cardiovascular Angiography and Interventions, O’Gara PT, Kushner
FG, Ascheim DD, et al. . 2013 ACCF/AHA guideline for the
management of ST-elevation myocardial infarction: a report of the
American College of Cardiology Foundation/American Heart
Association Task Force on Practice Guidelines. J Am Coll Cardiol
2013;61:e78-140.

3. Parekh PJ, Oldfield 4th EC, Johnson DA. Current strategies to reduce
gastrointestinal bleeding risk associated with antiplatelet agents.
Drugs 2015;75(14):1613-25.

4. Lavie CJ, Howden CW, Scheiman J, et al. Upper gastrointestinal
toxicity associated with long-term aspirin therapy: consequences and
prevention. Curr Probl Cardiol 2017;42(5):146-64.

5. Zhang L, Li Y, Jing QM, et al; CREATE Investigators. Dual antiplatelet
therapy over 6 months increases the risk of bleeding after
biodegradable polymer-coated sirolimus eluting stents implantation:
insights from the CREATE study. J Interv Cardiol 2014;27(2):119-26.

6. Han Y, Xu B, Xu K, et al. Six versus 12 months of dual antiplatelet
therapy after implantation of biodegradable polymer sirolimus-
eluting stent: randomized substudy of the I-LOVE-IT 2 Trial. Circ
Cardiovasc Interv 2016;9(2), e003145.

7. Sharma A, Agrawal S, Garg A, et al. Duration of dual antiplatelet
therapy following drug-eluting stent implantation: a systemic review
and meta-analysis of randomized controlled trials with longer follow
up. Catheter Cardiovasc Interv 2017;90(1):500-7.

8. Yin SH, Xu P, Wang B, et al. Duration of dual antiplatelet therapy
after percutaneous coronary intervention with drug-eluting stent:
systematic review and network meta-analysis. BMJ 2019;365:l2222.

9. Sharma A, Garg A, Elmahor S, et al. Duration of dual antiplatelet
therapy following drug-eluting stent implantation in diabetic and non-
diabetic patients: a systematic review and meta-analysis of random-
ized controlled trials. Prog Cardiovasc Dis 2018;60(4–5):500-7.
10. Vaduganathan M, Bhatt DL, Cryer BL, et al, COGENT Investigators. Proton-pump inhibitors reduce gastrointestinal events regardless of aspirin dose in patients requiring dual antiplatelet therapy. J Am Coll Cardiol 2016;67:1661-71.

11. Guo Y, Wei J. Clinical outcomes of various continued antiplatelet therapies in patients who were administered DAPT following the implantation of drug-eluting stents and developed gastrointestinal hemorrhage. Exp Ther Med 2016;12(2):1125-9.

12. Zou WB, Hou XH, Xin L, et al. Magnetic-controlled capsule endoscopy vs. gastroscopy for gastric diseases: a two-center self-controlled comparative trial. Endoscopy 2015;47(6):525-8.

13. Liao Z, Hou X, Lin-Hu EQ, et al. Accuracy of Magnetically Controlled Capsule Endoscopy, Compared With Conventional Gastroscopy, in Detection of Gastric Diseases. Clin Gastroenterol Hepatol. 2016;14(9):1266–1273.e1.

14. Chen X, Gao F, Zhang J. Screening for gastric and small intestinal mucosal injury with magnetically controlled capsule endoscopy in asymptomatic patients taking enteric-coated aspirin. Gastroenterol Res Pract 2018;2018:2524698.

15. Qian Y, Bai T, Li J, et al. Magnetic-guided capsule endoscopy in the diagnosis of gastrointestinal diseases in minors. Gastroenterol Res Pract 2018;2018:4248792.

16. Lanza FL, Royer Jr GL, Nelson RS, et al. A comparative endoscopic evaluation of the damaging effects of nonsteroidal anti-inflammatory agents on the gastric and duodenal mucosa. Am J Gastroenterol 1981;75(1):17-21.

17. Scarpignato C, Dalak W, Lanas A, et al. Rifaximin reduces number and severity of intestinal lesions associated with use of non-steroidal anti-inflammatory drugs in humans. Gastroenterology 2017;152(5):980-2.

18. Malfertheiner P, Chan FK, McColl KE. Peptic ulcer disease. Lancet 2009;374:1449-61.

19. Kim BSM, Li BT, Engel A, et al. Diagnosis of gastrointestinal bleeding: a practical guide for clinicians. World J Gastrointest Pathophysiol 2014;5(4):467-78.

20. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123(23):2736-47.

21. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115(17):2344-51.

22. Uemura N, Sugano K, Hiraishi H, et al, MAGIC Study Group. Risk factor profiles, drug usage, and prevalence of aspirin-associated gastroduodenal injuries among high-risk cardiovascular Japanese patients: the results from the MAGIC study. J Gastroenterol 2014;49(5):814-24.

23. Shiotani A, Honda K, Murao T, et al. Combination of low-dose aspirin and thienopyridine exacerbates small bowel injury. Scand J Gastroenterol 2011;46(3):281-6.