Original article

Effects of pre- and postprandial aspirin on gastric bleeding based on clinical data and in vitro study

Kang Jiang^{1,2}, Xueting Wang², Yan Jiang¹, Hansheng Bai¹, Guangjun Fan^{1,2*}

¹Department of pharmacy, The Second Hospital of Dalian Medical University, Dalian, 116021 Liaoning, China;

²School of pharmacy, Dalian Medical University, Dalian, 116044 Liaoning, China

*Corresponding author: Prof. Guangjun Fan, Department of pharmacy, The Second Hospital of Dalian Medical University, No. 467 Zhongshan Road, Shahekou District, Dalian, Liaoning, China. E-mail: 17709875899@163.com; Tel: +86-17709875899

Received June 13, 2019; Accepted October 27, 2019

Aspirin is a common anti-inflammatory agent. Clinical pharmacists have found an inconsistency in the timing of taking the medicine mentioned in the instructions of different brands of aspirin (100mg). To compare the effects of pre- and postprandial aspirin on gastric bleeding and assess the potential risk factors of aspirin caused gastric bleeding. Data from 100 patients taking enteric-coated aspirin tablets in the Second Hospital of Dalian Medical University were retrospectively analyzed. They included demography, medical history, brand of aspirin, time of taking medicine (pre-prandial or postprandial), gastric bleeding situation. The dissolution rates of aspirin were conducted in different pH media (1.0-6.8) by *in vitro* study. Clinical data showed that enteric-coated aspirin tablets had no significant changes in the incidence of gastric bleeding before or after meals (10%). The *in Vitro* dissolution text suggested that enteric-coated aspirin tablets had no obvious release at pH 1.0-5.0 for 2h; however, at pH > 6.8, about 80% of the drug was released within 45min. The results suggest that patients with an upset stomach should be advised to take aspirin before meals to prevent aspirin release in advance.

Key Words: Aspirin; Gastric bleeding; Drug release; Medication time; Adverse

INTRODUCTION

Aspirin, discovered for more than 100 years, is an analgesic, antipyretic, and anti-inflammatory agent.¹ It can also reduce the risk of coronary artery and cerebrovascular diseases.²⁻⁶ Emerging data suggest that aspirin also reduces the risk of multiple cancers, such as colorectal, prostate, esophageal, laryngeal, and gastric cancers.⁶⁻⁸ It is used preferentially for long-term primary and secondary prevention of cardiovascular diseases, that is, myocardial infarction and stroke.⁹⁻¹³ It is one of the most widely used medications in developed and developing countries, and more than 100 billion tablets are consumed every year.¹⁴ However, the use of aspirin may induce a wide range of adverse side effects in the upper gastrointestinal (GI) tract, ranging from troublesome symptoms to life-threatening peptic ulcer bleeding, perforation.^{10,15-17} The adverse effects of aspirin-induced gastric mucosal injury are mediated by both direct and indirect mechanisms. Direct gastric mucosal injury results from the trapping of high concentrations of acidic aspirin within gastric epithelial cells.^{18,19} The indirect effects are mediated primarily via its inhibition of cyclooxygenase (COX), which both inhibits COX-1 and COX-2.²⁰ It can suppress the formation of cytoprotective prostaglandins and thromboxane via COX-1 in gastric mucosa and leading to GI

bleeding.²¹⁻²⁴ Modified release formulations, like enteric-coated, is a common agent used to prevent GI bleeding. Clinical pharmacists have found an inconsistency in the timing of taking the medicine mentioned in the instructions of different brands of enteric-coated aspirin. Domestic "Original" (Shenyang, China) aspirin instructions say, "Take the medicine after meals," while imported "Bayer" (Leverkusen, Germany) aspirin instructions say, "Take the medicine before meals". As we knew, Bayer company first coined aspirin as the trade name for acetylsalicylic acid. In many countries, it remains a registered trademark of this company, whereas in other aspirin has become the generic name of this substance.²⁵ The "Original" enteric-coated aspirin is a generic drug product by

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: weda-h@weda-h.org

How to cite this article: Jiang K, Wang XT, Jiang Y, Bai HS, Fan GJ. Effects of pre- and postprandial aspirin on gastric bleeding based on clinical data and in vitro study. *J ADV HEALTH* 2019; 1(4): 259-264.

Original Pharmacolabo Company in China. It was the first domestic generic drug approved by China Food and Drug Administration on May 18, 2009, for primary prevention of myocardial infarction, in addition to the original drug by Bayer, Germany. In view of this inconsistent situation, it was found that the debates were mainly about whether food or drug could affect the release of enteric-coated aspirin tablets in the GI tract in advance, leading to GI bleeding. This study aimed to compare the effects of pre- and postprandial aspirin on gastric bleeding and explore the rational administration time of enteric-coated aspirin tablets through retrospective analysis and *in vitro* drug dissolution test.

METHODS

Retrospective analysis of clinical cases

Clinical data of 100 patients were collected from September 2016 to November 2016 from the Second Hospital of Dalian Medical University, China. Patient data were obtained from the hospital's information system and telephonic interviews, which included baseline information, medical history, type of aspirin ("Bayer" or "Original"), time of taking the medicine (before or after meals), and gastric hemorrhage condition. The inclusion criteria were as follows: Patients aged more than 18 years who were taking the same brand of enteric-coated aspirin tablets for more than 3 months before hospitalization, and those with GI tumors, hematological diseases, and vitamin K deficiency. The exclusion criteria were as follows: Patients with a history of any clinically significant bleeding before taking aspirin in recent 12 months; those administered with a gastric mucosal protective agent, proton pump inhibitors (PPIs), and H₂ receptor antagonists; and those who did not adhere to the rules of their medication. The hemorrhage criteria included spitting blood, black stool, positive fecal occult blood tests, mucous hyperemia in the stomach and duodenum, edema, punctate and linear erosion, diffuse bleeding, or ulcers. The 100 enrolled patients were categorized into two groups: medication time and brand of aspirin. The first group was further subdivided into before-meal and after-meal groups and the second into Bayer and domestic groups.

In vitro drug dissolution test

Reagents

Standard enteric-coated aspirin tablets were purchased from Zhongke Biotechnology (Beijing, China). Bayer's enteric-coated aspirin tablets were obtained from Bayer HealthCare Pharmaceuticals (Shanghai, China). Domestic enteric-coated aspirin tablets were purchased from Original Pharmaceutical (Shenyang, China). The high-performance liquid chromatography (HPLC)-grade acetonitrile, tetrahydrofuran, and methanol were obtained from Bo Di Chemical (Tianjin, China).

Apparatus used and HPLC

The HPLC system was equipped with a model 3000 pump, a sample injector (AS230), and an ultraviolet detector (UV230II) set at 276 nm. The column was C₁₈ (250 × 4.6 mm²). All items were obtained from Elite (Dalian, China). The chromatogram

data collection and data processing was accomplished using the EC2006 V1.80 software. The ZBS-8L dissolution tester (Tianda Tianfa, Tianjin, China) and pHS-3C audiometer (Weiye, Shanghai, China) were used for the drug-release test. The C18 column (5 μm) was used for separation. The mobile phase consisted of 20.0% acetonitrile, 70.0% H₂O, 5.0% tetrahydrofuran, and 5.0% glacial acetic acid, with a flow rate of 1.0 mL/min. The injection volume was 25-μL. The runtime for all tests was 8 min. The column oven temperature was set at 30°C.

Preparation of standard stock solution

Standard aspirin (25 mg) tablets were weighed, and 1% methanol and glacial acetic acid solution were added to dissolve the drug to obtain a concentration of 25mg/mL stock solutions. Appropriate stock solutions were diluted with 1% methanol and glacial acetic acid solution to obtain 0, 0.05, 0.15, 0.20, and 0.25 mg/mL of aspirin standard solutions. Five solutions were prepared with the desired concentration range for calibration. The standard aspirin solutions were injected, and the chromatogram was recorded.

Preparation of sample solution

Twenty of Bayer's enteric-coated aspirin tablets were accurately weighed, and their mean weight was calculated. Then, they were crushed and 10 mg of tablet powder was transferred into a 100-mL volumetric flask. The sample was diluted with 1% methanol-glacial acetic acid solution and shaken for a few minutes. The solution was filtered using a 0.45-μm membrane filter paper and marked as Bayer's aspirin test solution. Then, the 25-μL test solution was injected into the HPLC system and the chromatogram was recorded. The "Original" aspirin test solution was prepared in the same way. According to the linear regression equation of the standard curve, the content of aspirin in enteric-coated aspirin tablets was calculated.

Drug-release test

The drug-release experiments (20 tablets) were carried out according to the Chinese Pharmacopoeia (2015 edition) using the rotating basket method in a hemispherical dissolution bath equipped with 1000-mL vessels (37°C, 100 rpm). Each condition used six groups of parallel tests to ensure accuracy. The *in vivo* condition was simulated using pH 1.0 Hydrochloric acid solution for 2 h, followed by pH 3.0 phosphate buffer for 2 h, then by pH 5.0 phosphate buffer for 2 h, and finally by pH 6.8 phosphate buffer for 0.75 h. The solutions were filtered using a 0.45-μm membrane filter paper as sample solutions. Released samples (25-μL) were injected into the HPLC system with 276-nm UV detector and the dissolution rate was calculated.

Clinical statistical analysis

The Student *t* test and χ^2 test were used for comparison among groups. Statistical analyses were performed using Prism5 program (GraphPad Software Inc, CA, USA) and IBM SPSS 20.0 (IBM, IL, USA). The data were presented as mean ± standard deviation. A *P* value <0.05 was considered statistically significant for all analyses.

RESULTS

Retrospective analysis of clinical cases

Among the 100 patients included in this study, 49 were male and 51 were female, aged 44-87 years, with an average age of 69.03 ± 9.60 years. Ten cases of GI bleeding occurred due to the administration of enteric-coated aspirin tablets, including four males and six females, aged 59-82 years, with an average age of 71.5 ± 7.82 years. The bleeding rate under different clinical conditions is shown in Table 1. The average age of each group with *P* values is shown in Table 2.

Table 1 Comparison of aspirin-induced bleeding rate under different medication times and different brands.

	Numbers	Bleeding (%)	No bleeding (%)	χ^2	<i>P</i>
Medication time					
Before meals	26	2 (7.7)	24 (92.3)	0.208	0.648
After meals	74	8 (10.8)	66 (89.2)		
Brands of aspirin					
Bayer's aspirin	86	9 (10.5)	77 (89.5)	0.148	0.701
Domestic aspirin	14	1 (7.1)	13 (92.9)		

Table 2 Average age of patients with *P* values

	Average age	<i>P</i>
Medication time		
Before meals	69.5 ± 9.75	0.77
After meals	68.86 ± 9.61	
Brands of aspirin		
Bayer's aspirin	68.73 ± 9.95	0.45
Domestic aspirin	70.86 ± 7.19	

Table 3 Linearity data of standard aspirin

Concentration (mg·mL ⁻¹)	0	0.05	0.1	0.15	0.20	0.25
Peak area	1.65	134.72	276.38	417.73	552.05	688.26

Figure 2 Calibration curve of standard aspirin

The accuracy of an analytical method is the agreement between the actual value of an analysis in the sample and the value obtained by analysis. The recovery tests were carried out using three different concentration levels (0.05, 0.10, and 0.15 mg/mL). The average recoveries obtained for aspirin are 96.78%, 99.99% and

In vitro release experiments

Method validation of HPLC

The system suitability test was applied to the chromatograms under optimum conditions to check various parameters such as theoretical plates (column efficiency >3000), asymmetric factor (0.95-1.05), sensitivity (≥ 10), and resolution (>1.5). The results ensured the adequacy of the proposed HPLC method for the routine analysis of aspirin. The system suitability results were fitted to the standard of the Chinese Pharmacopoeia. Figure 1 shows a typical chromatogram obtained from the analysis of the standard solution using the proposed method. The retention time observed was 5.86 min for aspirin. No interfering peaks and false-positive results were observed in the chromatogram.

Figure 1 Typical HPLC chromatogram of aspirin at 276 nm with a theoretical tower number of 8270.37 and retention time is 5.86.

Linearity was performed using different test concentrations. Five different standard solutions within the linear range containing 0, 0.05, 0.15, 0.20, and 0.25 mg/mL were prepared and injected into the HPLC system. The standard curve was shown in figure 2 and data were suggested in table 3. The corresponding linear regression equation was $y = 2757X + 0.389$ with the square of correlation coefficient R^2 of 0.999 for aspirin, which indicates that the peak area of aspirin ranged from 0 mg/mL ~0.2 mg/mL has better linear relation with the sample size.

100.30%, respectively, which were satisfactory (%RSD=1.61).

The precision of the method was demonstrated by interday and intraday analyses for each concentration at three different concentration levels (0.05, 0.10, and 0.15 mg/mL). For the intraday precision, standard solutions at three concentrations were injected thrice in a day and the percent relative standard deviation (%RSD) was calculated. In the interday studies, standard solutions were injected on three consecutive days and the %RSD for intraday is 1.22, 1.06 and 0.66, respectively. The %RSD for interday precision is 0.94, 0.15 and 0.21, respectively. The data showed that the HPLC method developed was precise (%RSD < 2).

The 0.05, 0.10, and 0.15 mg/mL standard solution peak areas were tested for an interval of 0, 24, 48, and 72 h at room temperature for stability. The average peak area of 0.05, 0.1, and 0.15 mg/mL standard solutions was 134.44, 275.31, and 416.77, respectively, and their RSD was 1.05%, 0.94%, and 0.56% (%RSD < 2), respectively, indicating that the sample solution was stable at 72 h.

Standard aspirin (25 mg) tablets were weighed, change the solvent solvents pH 1.0 hydrochloric acid solution, pH 3.0 phosphate buffer solution, pH 5.0 phosphate buffer solution, pH6.8 phosphate buffer solution and 1% methanol and glacial acetic acid solution, respectively, to dissolve the drug to obtain three different concentration levels (0.05, 0.10, and 0.15 mg/mL). The average peak area of 0.05, 0.1, and 0.15 mg/mL standard solutions was 136.852, 284.912, 419.22, respectively, and their RSD was 1.65%, 1.80%, 0.74% (%RSD<2), respectively, indicating that there was no significant difference for determination the content of aspirin among the five solvents mentioned above.

Content determination

The contents of Bayer's aspirin and domestic aspirin are depicted in Table 4.

Table4 Content measurement parameters of aspirin(n=20)

Parameter	Bayer's aspirin	Domestic aspirin
Weight (mg)	137.5 ±2.70	127.8 ± 2.51
Peak area (mv)	304.72±6.67	301.13±10.03
Aspirin content per tablet (mg)	109.25±1.76	107.55±1.82
Content uniformity (%)	12.51	12.07
RSD (%)	1.70	1.97

3.2.2 Drug-release performances

The *in vitro* release experimental results were examined. At pH 1, no release of Bayer's aspirin and domestic aspirin was detected due to the special solution environment. Data are shown in Tables 5, which included the dissolution rate of Bayer's aspirin and domestic aspirin in different pH media.

Table 5 Drug-release performances of aspirin in different pH media

	Dissolution rate (%)		P
	Bayer's aspirin(n=6)	Domestic aspirin(n=6)	
pH=1	—	—	—
pH=3	0.08±0.02	0.06±0.03	0.12
pH=5	1.13±0.27	1.22±0.22	0.58
pH=6.8	80.12±7.45	81.37±7.44	0.73

DISCUSSION

The widespread use of aspirin in clinic has drawn attention owing to its side effects, especially on GI bleeding. In this retrospective analysis of clinical cases, 100 patients who fulfilled the inclusion criteria were identified. GI bleeding occurred in 10% of these patients. No statistically significant difference in age was observed between patients taking aspirin before meals or after meals ($P>0.05$). Previous trials have shown that up to 15-20% of patients developed gastrointestinal symptoms with aspirin monotherapy.¹⁹ And a latest Retrospective Study of 612,509 Patients showed that the patients with long-term use of aspirin reported a GI bleeding incidence of 5.04% over 20 years' follow up.²⁶ These differences may relate to race and collecting data methods. In this study, it also

confirmed that Bayer's aspirin and domestic aspirin had no significant difference in the incidence of GI bleeding ($P<0.05$). GI bleeding caused by aspirin had no relevance with the medication time (before or after meals; $P<0.05$).

The question then was whether food-induced pH changes led to the release of enteric-coated aspirin tablets in advance. To further explore this, an *in vitro* experiment with two kinds of aspirin was performed. The dissolution rate of aspirin in different pH solutions was determined. Different pH media were simulated in the stomach before or after the patients had a meal to suggest the dissolution of enteric-coated aspirin tablets. However, statistical analysis results showed no significant difference between domestic and Bayer's aspirin in terms of weight variation ($\pm 7.5\%$), content uniformity (≤ 15.0), and content ($P>0.05$). No obvious release of enteric-coated aspirin tablets was found at pH 1.0-5.0 for 2 h. However, at pH>6.8, about 80% of the drug was released within 45 min. The dissolution rates of domestic aspirin and Bayer's aspirin showed no significant statistical difference in different pH solvents ($P>0.05$).

The pH within the human stomach changed following the ingestion of a food substance.²⁷ Reported in the studies on pH changes in the stomach before or after meals were analyzed thoroughly. Nokhodchi et al and Annaert et al reported that the typical median values for the gastric pH in the fasted state ranged from 1.7 to 3.3 (median of 2.5).^{28,29} Gardner et al suggested that median gastric pH was 1, increased to pH 4.5 with ingestion of the meal, and then returned to approximately pH 1, 3-4 h after the start of the meal.³⁰ Ramdanl et al reported that for 90% of the time, the gastric pH in the fasted state remained below 3.³¹ Dressman et al and Birk et al reported that pH was usually below 3 in the normal stomach, and after a moderate meal, it increased to approximately 5.0.^{27,32} Annaert's report also suggested that after ingesting a meal, the gastric pH in the fed state ranged from 2.7 to 6.4.²⁹ Therefore, it was concluded that the gastric pH in the fasted state was around 1-3, and increases to approximately 5.0 after a meal. These findings suggested that no obvious release of enteric-coated aspirin tablets occurred in the fasted state. However, after a meal the pH in stomach increased, when it increased to 6.8, about 80% of the drug released.

PPIs, which inhibit the function of the proton pump responsible for the terminal step in gastric acid secretion, are considered to be the most effective medical treatment for patients with acid-related diseases such as peptic ulcers.^{33,34} Concomitant use of aspirin and proton-pump inhibitors (PPIs) has been recommended in patients with a history of GI hemorrhage,³⁵ especially for the patients who take aspirin for secondary CV protection.^{10,11,36} Humorous studies have shown that these agents significantly reduce the risk of upper GI adverse events in aspirin-treated patients.³⁷⁻⁴⁴ PPIs inhibit gastric acid secretion, which increases gastric pH and can alter the pharmacokinetics of aspirin. This might account for a decline in bioavailability and therapeutic effects of combination therapy with aspirin and PPIs.⁴⁵⁻⁴⁷ However, previous studies have found that PPIs can alter the acidic environment of the stomach rapidly (pH>4) and some of them can raise the pH approximately 7.^{31,35,48-50} This means that administering PPIs and alkaline food may lead to the release of enteric-coated aspirin tablets in advance and increase the possibility of GI bleeding. Several published studies revealed that 4-12 h after taking PPIs, the pH in the stomach decreased to less than 4.^{48,49,51,52} Therefore, according to the study we suggest patients avoid taking PPI and aspirin simultaneously. Instead, they should take aspirin 12 h after taking the PPI to avoid aggravating

the effect of aspirin in the GI tract.

CONCLUSIONS

Postprandial aspirin has a risk of gastric bleeding. Some food or drug can alter pH in the stomach dramatically. Therefore, patients with upset stomach should be advised to take aspirin before meals to prevent aspirin release in advance, and reduce damage to the stomach.

REFERENCES

- Steiner TJ, Voelker M. Gastrointestinal tolerability of aspirin and the choice of over-the-counter analgesia for short-lasting acute pain. *J Clin Pharm Ther* 2009; 34(2): 177-86.
- Collaboration TA. Collaborative Meta-Analysis Of Randomised Trials Of Antiplatelet Therapy For Prevention Of Death, Myocardial Infarction, And Stroke In High Risk Patients Collaborative Meta-Analysis Of Randomised Trials Of Antiplatelet Therapy For Prevention Of Death, Myoca. *British Medical Journal* 2002; 324(7329): 71-86.
- Colin B, Lisa B, Rory C, Jonathan E, Jon G, Richard P, Julie B, Charles H, Patricia K, Tom M. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2010; 373(9678): 1849-60.
- Calonge N, Petitti DB, Dewitt TG, Gordis L, Gregory KD, Harris R, Isham G, Lefevre ML, Loveland-Cherry C, Marion LN. Aspirin for the prevention of cardiovascular disease: U.S. Preventive Services Task Force recommendation statement. *Annals of Internal Medicine* 2009; 150(6): 396-404.
- Bhatt DL, James S, Abraham NS, Antman EM, Chan FKL, Furberg CD, Johnson DA, Mahaffey KW, Quigley EM. 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. *American Journal of Gastroenterology* 2008; 52(18): 1502-17.
- Chan FKL, Ki ELL, Wong GLH, Ching JYL, Tse YK, Au KWL, Wu JCY, Ng SC. Risks of Bleeding Recurrence and Cardiovascular Events With Continued Aspirin Use After Lower Gastrointestinal Hemorrhage. *Gastroenterology* 2016; 151(2): 271-77.
- Raluca E. Effect of daily aspirin on long-term risk of death due to cancer. *Mdica* 2010; 377(9759): 31-41.
- Cuzick J, Thorat MA, Bosetti C, Brown PH, Burn J, Cook NR, Ford LG, Jacobs EJ, Jankowski JA, La Vecchia C, Law M, Meyskens F, Rothwell PM, Senn HJ, Umar A. Estimates of benefits and harms of prophylactic use of aspirin in the general population. *Ann Oncol* 2015; 26(1): 47-57.
- Smith SC Jr, Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, Gibbons RJ, Grundy SM, Hiratzka LE, Jones DW, Lloyd-Jones DM, Minissian M, Mosca L, Peterson ED, Sacco RL, Spertus J, Stein JH, Taubert KA; World Heart Federation and the Preventive Cardiovascular Nurses Association. AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients with Coronary and other Atherosclerotic Vascular Disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation* 2011; 124(22): 2458-73.
- Tsai TJ, Hsu PI. Low-Dose Aspirin-Induced Upper Gastrointestinal Injury-Epidemiology, Management and Prevention. *Journal of Blood Disorders & Transfusion* 2015; 6(6).
- Lavie CJ, Howden CW, Scheiman J, Tursi J. Upper Gastrointestinal Toxicity Associated With Long-Term Aspirin Therapy: Consequences and Prevention. *Curr Probl Cardiol* 2017; 42(5): 146-64.
- Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L. 2016ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease. *Journal of the American College of Cardiology* 2016.
- Amsterdam EA, Wenger NK, Brindis RG, Jr DEC, Ganiats TG, Jr DRH, Jaffe AS, Jneid H, Kelly RF, Kontos MC. 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes : A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology* 2014; 64(24): 2645-87.
- Warner TD, Mitchell JA. Cyclooxygenase-3 (COX-3): filling in the gaps toward a COX continuum? *Proc Natl Acad Sci U S A* 2002; 99(21): 13371-3.
- Taha AS, Angerson WJ, Prasad R, McCloskey C, Gilmour D, Morran CG. Clinical trial: the incidence and early mortality after peptic ulcer perforation, and the use of low - dose aspirin and nonsteroidal anti - inflammatory drugs. *Alimentary Pharmacology & Therapeutics* 2010; 28(7): 878-85.
- McCarthy DM. GI bleeding: problems that persist. *Gastrointestinal Endoscopy* 2009; 70(2): 225-28.
- Ajani UA, Ford ES, Greenland KJ, Giles WH, Mokdad AH. Aspirin use among U.S. adults: Behavioral Risk Factor Surveillance System. *Am J Prev Med* 2006; 30(1): 74-7.
- Fries JF. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med* 1999; 340(24): 1888-99.
- Fanaroff AC, Roe MT. Contemporary Reflections on the Safety of Long-Term Aspirin Treatment for the Secondary Prevention of Cardiovascular Disease. *Drug Saf* 2016; 39(8): 715-27.
- Konstantinopoulos PA, Lehmann DF. The cardiovascular toxicity of selective and nonselective cyclooxygenase inhibitors: comparisons, contrasts, and aspirin confounding. *Journal of Clinical Pharmacology* 2005; 45(7): 742.
- Sharma T, Bliden K, Chaudhary R, Tantry U, Gurbel PA. Efficacy of aspirin (325 mg) + omeprazole (40 mg) in treating coronary artery disease. *Expert Opin Pharmacother* 2017; 18(1): 123-31.
- Huang XZ, Chen Y, Wu J, Zhang X, Wu CC, Zhang CY, Sun SS, Chen WJ. Aspirin and non-steroidal anti-inflammatory drugs use reduce gastric cancer risk: A dose-response meta-analysis. *Oncotarget* 2017; 8(3): 4781-95.
- Zayachkivska O, Bula N, Khyrivska D, Gavrilyuk E, Wallace JL. Exposure to non-steroid anti-inflammatory drugs (NSAIDs) and suppressing hydrogen sulfide synthesis leads to altered structure and impaired function of the oesophagus and oesophagogastric junction. *Inflammopharmacology* 2015; 23(2-3): 91-99.
- Gyllfors P, Bochenek G, Overholt J, Drupka D, Kumlin M, Sheller J, Nizankowska E, Isakson PC, Mejza F, Lefkowitz JB, Dahlén S-E, Szczeklik A, Murray JJ, Dahlén B. Biochemical and clinical evidence that aspirin-intolerant asthmatic subjects tolerate the cyclooxygenase 2-selective analgetic drug celecoxib. *Journal of Allergy and Clinical Immunology* 2003; 111(5): 1116-21.
- Cadavid AP. Aspirin: The Mechanism of Action Revisited in the Context of Pregnancy Complications. *Frontiers in Immunology* 2017; 8.
- Kkf T, Chan F, Hirai HW, Jyy S. Risk of Gastrointestinal Bleeding and Benefit from Colorectal Cancer Reduction from Long-term Use of

- Low Dose Aspirin. A Retrospective Study of 612,509 Patients. *Journal of Gastroenterology & Hepatology* 2018; 33(10).
27. Birk T, Kristensen K, Harboe A, Hansen TB, Ingmer H, De Jonge R, Takumi K, Aabo S. Dietary proteins extend the survival of Salmonella Dublin in a gastric acid environment. *J Food Prot* 2012; 75(2): 353-8.
 28. Nokhodchi A, Asare-Addo K. Drug release from matrix tablets: physiological parameters and the effect of food. *Expert Opin Drug Deliv* 2014; 11(9): 1401-18.
 29. Annaert P, Brouwers J, Bijlens A, Lammert F, Tack J, Augustijns P. Ex vivo permeability experiments in excised rat intestinal tissue and in vitro solubility measurements in aspirated human intestinal fluids support age-dependent oral drug absorption. *Eur J Pharm Sci* 2010; 39(1-3): 15-22.
 30. Gardner JD, Ciociola AA, Robinson M. Measurement of meal-stimulated gastric acid secretion by in vivo gastric autotitration. *J Appl Physiol* (1985) 2002; 92(2): 427-34.
 31. Ramdanl A. Effect of pantoprazole versus other proton pump inhibitors on 24-hour intragastric pH and basal acid output in Zollinger-Ellison syndrome. *Gastroenterol Clin Biol* 2001; 25(3): 4.
 32. Dressman JB, Berardi RR, Dermentzoglou LC, Russell TL, Schmaltz SP, Barnett JL, Jarvenpaa KM. Upper gastrointestinal (GI) pH in young, healthy men and women. *Pharm Res* 1990; 7(7): 756-61.
 33. Katsube T, Adachi K, Kawamura A, Amano K, Uchida Y, Watanabe M, Kinoshita Y. Helicobacter pylori infection influences nocturnal gastric acid breakthrough. *Alimentary Pharmacology & Therapeutics* 2000; 14(8): 1049.
 34. Kim YG, Jang BI, Kim TN. A Matched Case-Control Study of a Novel Acid-Pump Antagonist and Proton-Pump Inhibitor for the Treatment of Iatrogenic Ulcers Caused by Endoscopic Submucosal Dissection. *Gut & Liver* 2010; 4(1): 25.
 35. Tsai Y-W, Wen Y-W, Huang W-F, Chen P-F, Kuo KN, Hsiao F-Y. Cardiovascular and gastrointestinal events of three antiplatelet therapies: clopidogrel, clopidogrel plus proton-pump inhibitors, and aspirin plus proton-pump inhibitors in patients with previous gastrointestinal bleeding. *Journal of Gastroenterology* 2011; 46(1): 39-45.
 36. Joseph J Y S, James Y W L, Jessica Y L C, Justin C Y W, Yuk T L, Philip W Y C, Vincent K S L, Vincent W S W, Francis K L C. Continuation of low-dose aspirin therapy in peptic ulcer bleeding: a randomized trial. *Chinese General Practice* 2010; 152(1): 1-9.
 37. Rodríguez LAG, Martín-Pérez M, Hennekens CH, Rothwell PM, Lanan A. Bleeding Risk with Long-Term Low-Dose Aspirin: A Systematic Review of Observational Studies. *Plos One* 2016; 11(8): e0160046.
 38. Lanan A, Polo-Tomas M, Casado-Arroyo R. The aspirin cardiovascular/gastrointestinal risk calculator--a tool to aid clinicians in practice. *Aliment Pharmacol Ther* 2013; 37(7): 738-48.
 39. Yeomans N, Lanan A, Labenz J, van Zanten SV, van Rensburg C, Racz I, Tchernev K, Karamanolis D, Roda E, Hawkey C, Naucier E, Svedberg LE. Efficacy of esomeprazole (20 mg once daily) for reducing the risk of gastroduodenal ulcers associated with continuous use of low-dose aspirin. *Am J Gastroenterol* 2008; 103(10): 2465-73.
 40. Sylvester KW, Cheng JW, Mehra MR. Esomeprazole and aspirin fixed combination for the prevention of cardiovascular events. *Vasc Health Risk Manag* 2013; 9: 245-54.
 41. Scheiman JM, Devereaux PJ, Herlitz J, Katelaris PH, Lanan A, Veldhuyzen van Zanten S, Naucier E, Svedberg LE. Prevention of peptic ulcers with esomeprazole in patients at risk of ulcer development treated with low-dose acetylsalicylic acid: a randomised, controlled trial (OBERON). *Heart* 2011; 97(10): 797-802.
 42. Lin KJ, Hernández-Díaz S, Rodríguez LAG. Acid Suppressants Reduce Risk of Gastrointestinal Bleeding in Patients on Antithrombotic or Anti-Inflammatory Therapy. *Gastroenterology* 2011; 141(1): 71-79.
 43. Saini SD, Fendrick AM, Scheiman JM. Cost-effectiveness analysis: cardiovascular benefits of proton pump inhibitor co-therapy in patients using aspirin for secondary prevention. *Aliment Pharmacol Ther* 2011; 34(2): 243-51.
 44. Lanan A, Wu P, Medin J, Mills EJ. Low doses of acetylsalicylic acid increase risk of gastrointestinal bleeding in a meta-analysis. *Clin Gastroenterol Hepatol* 2011; 9(9): 762-68 e6.
 45. Giraud MN, Sanduja SK, Felder TB, Illich PA, Dial EJ, Lichtenberger LM. Effect of omeprazole on the bioavailability of unmodified and phospholipid-complexed aspirin in rats. *Aliment Pharmacol Ther* 1997; 11(5): 899-906.
 46. Hu W, Tong J, Kuang X, Chen W, Liu Z. Influence of proton pump inhibitors on clinical outcomes in coronary heart disease patients receiving aspirin and clopidogrel: A meta-analysis. *Medicine (Baltimore)* 2018; 97(3): e9638.
 47. Morten W, Grove EL, Kristensen SD, Anne-Mette H. The antiplatelet effect of aspirin is reduced by proton pump inhibitors in patients with coronary artery disease. *Heart* 2010; 55(5): 368.
 48. Pisegna JR, Sostek MB, Monyak JT, Miner PB, Jr. Intravenous esomeprazole 40 mg vs. intravenous lansoprazole 30 mg for controlling intragastric acidity in healthy adults. *Aliment Pharmacol Ther* 2008; 27(6): 483-90.
 49. Hurt RT, Frazier TH, McClave SA, Crittenden NE, Kulisek C, Saad M, Franklin GA. Stress prophylaxis in intensive care unit patients and the role of enteral nutrition. *JPEN J Parenter Enteral Nutr* 2012; 36(6): 721-31.
 50. von Rosenvinge EC, Song Y, White JR, Maddox C, Blanchard T, Fricke WF. Immune status, antibiotic medication and pH are associated with changes in the stomach fluid microbiota. *ISME J* 2013; 7(7): 1354-66.
 51. Wilder-Smith CH, Röhss K, Bondarov P, Hallerbäck B, Svedberg LE, Ahlbom H. Esomeprazole 40 mg i.v. provides faster and more effective intragastric acid control than pantoprazole 40 mg i.v.: results of a randomized study. *Alimentary Pharmacology & Therapeutics* 2004; 20(10): 1099.
 52. Hunt RH, Armstrong D, James C, Chowdhury SK, Yuan Y, Fiorentini P, Taccon A, Cohen P. Effect on intragastric pH of a PPI with a prolonged plasma half-life: comparison between tenatoprazole and esomeprazole on the duration of acid suppression in healthy male volunteers. *Am J Gastroenterol* 2005; 100(9): 1949-56.