Association between the prothrombin time-international normalized ratio and concomitant use of antibiotics in warfarin users: Focus on type of antibiotic and its susceptibility to Bacteroides fragilis

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Research Report

Association between the prothrombin time-international normalized ratio and concomitant use of antibiotics in warfarin users: Focus on type of antibiotic and its susceptibility to *Bacteroides fragilis*

Tatsuya Yagi, PhD[1,2],

Takafumi Naito, PhD[1],

Ayami Kato, MS[1],

Kensho Hirao, MS[1],

Junichi Kawakami, PhD[1]

[1]*Department of Hospital Pharmacy, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

[2]*Department of Medicine Solna, Centre for Pharmacoepidemiology, Karolinska Institutet, Karolinska University Hospital, SE-17176 Stockholm, Sweden*

Correspondence: *Tatsuya Yagi, PhD*

Address: *1-20-1 Handayama, Higashi-ku, Hamamatsu, 431-3192, Japan*

Phone: *+81 53 435 2623;* ***Fax:*** *+81 53 435 2764.*

E-mail: *tatsuya.yagi@ki.se, t.yagi.hamamed@gmail.com*

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ORCID iDs:

Tatsuya Yagi: https://orcid.org/0000-0003-1194-3568

ABSTRACT (250 words)

Background: The difference in type of antibiotics and its susceptibility to *Bacteroides fragilis* may influence warfarin anticoagulation. However, these influences have not been clarified in clinical settings. **Objectives:** This study aimed to investigate association between the prothrombin time-international normalized ratio (PT-INR) and concomitant use of antibiotics in real-world population of warfarin users. **Methods:** This was a single-center cohort study using data from health records and included patients who received β-lactams (BL)/fluoroquinolones (FQ) during ongoing warfarin treatment (2011–2015) at Hamamatsu University Hospital in Japan. Antibiotics were categorized into those which have susceptibility to *Bacteroides fragilis* (BL_{sus}, FQ_{sus}) or non-susceptibility (BL_{non}, FQ_{non}) and into those given orally (BL_{po}, FQ_{po}) or intravenously (BL_{iv}, FQ_{iv}). Outcomes were excessive PT-INR and changes in PT-INR, defined as the ratio (INR ratio) and difference (ΔINR) of maximum PT-INR and baseline PT-INR. Excessive PT-INR was graded as INR ratio of > 1.5 or > 2.5. **Results:** Total of 1,185 warfarin user were included. The proportion of INR ratio > 2.5 in FQ_{iv} was higher than in BL_{iv} (95% CI: 1.59-46.5). The proportions with an INR ratio of > 1.5 in BL_{sus} and FQ_{sus} were higher than in BL_{non} (1.72-14.1) and FQ_{non} (1.05-9.36), respectively. ΔINR values in FQ_{po}, FQ_{iv} and FQ_{sus} were higher than those in BL_{po}, BL_{iv} and FQ_{non}, respectively. **Conclusions and Relevance:** Concomitant use of fluoroquinolones or of antibiotics which are susceptible to *Bacteroides fragilis* is associated with higher risk of excessive anticoagulation. This findings would contribute to safe and proper antibiotic

treatment in warfarin user.

Introduction

Warfarin, an oral anticoagulant, used for the prevention of further coagulation in patients who are diagnosed with deep venous thrombosis, pulmonary embolism, atrial fibrillation.[1,2] Its narrow therapeutic window requires frequent monitoring of the prothrombin time-international normalized ratio (PT-INR) values.[3] PT-INR values outside the recommended therapeutic window are associated with increased risk of bleeding or thrombosis. Warfarin competes with vitamin K, an essential factor for the key reaction of the vitamin K cycle, by binding vitamin K epoxide reductase (VKOR), thereby increasing anticoagulant activity.[4] Warfarin is predominantly metabolized by CYP2C9, CYP1A2, and CYP3A4.[5] The vitamin K-based mechanism of warfarin leads to a potential for drug-drug and drug-food interactions. Examples of such interactions include its concomitant use with antibiotics, carbamazepine, azole antifungals, and HIV protease inhibitors.[6,7]

Antibiotics such as fluoroquinolones and β-lactams are important therapeutic options for the treatment of broad bacterial infections. In both in-hospital and outpatient settings, they are used for the treatment of hospital-acquired respiratory infections and urinary tract infections.[8,9,10] Concomitant use of warfarin and a fluoroquinolone or β-lactam potentially increases the risk of excessive anticoagulation. Nevertheless, warfarin users are often co-treated with fluoroquinolones or β-lactams in clinical settings. Interactions between some antibiotics and warfarin have been partially explained by changes in the intestinal flora resulting in a reduction of intestinal vitamin K synthesis.[6] Prescribers need to consider how

adding and removing antibiotics will affect a patient's PT-INR and the bleeding risk during antibiotic therapy. As such, data on potential interactions between the type of antibiotic and warfarin use is required to improve the safety of antibiotic therapy in warfarin users.

Vitamin K cannot be synthesized by the human body, but is synthesized intestinal bacteria.[11] Vitamin K is commonly supplied from food and gut microbiota. In humans, the major genera of the intestinal flora that can synthesize vitamin K are *Bacteroides spp* and *Bifidobacteria spp.*[12,13,14] The composition of the intestinal bacteria with respect to *Bacteroides spp.* and *Prevotella spp.* is the most influential factor determining fecal vitamin K content.[15] In particular, the *Bacteroides fragilis* strains are critical to systemic and mucosal immunity and host nutrition.[16] These previous reports have indicated that decreasing the content of *Bacteroides fragilis* in intestine can enhance the warfarin anticoagulation activity through declined synthesis of vitamin K. The patients receiving antibiotics with susceptibility to *Bacteroides fragilis* potentially have the higher risk of excessive anticoagulation ability than those with non-susceptibility. To date, the association between excessive anticoagulation ability and concomitant use of antibiotics focused on the susceptibility to *Bacteroides fragilis* of antibiotics remains to be clarified in warfarin users. This assessment can provide safe and proper antibiotic therapy options based on the susceptibility or non-susceptibility to *Bacteroides fragilis* of antibiotics in warfarin users.

The aim of this study was to investigate the risk of excessive anticoagulation ability and bleeding associated with concomitant use of antibiotics categorized according to the type

of antibiotic and its susceptibility to *Bacteroides fragilis* in warfarin users.

Materials and methods

Study Design

This was a cohort study of patients prescribed fluoroquinolones or β-lactams during ongoing treatment with warfarin. Each individual was categorized according to the type of antibiotic and its susceptibility to *Bacteroides fragilis*. Outcomes were changes in PT-INR from initiation of the antibiotic treatment and the incidence of bleeding events (gastrointestinal, respiratory, and intracranial bleeding). The study was approved by the Ethics Committee of the Hamamatsu University School of Medicine. This investigation was performed according to the Declaration of Helsinki.

Data source

Data from the Hamamatsu University Hospital (613 beds, 1140 outpatients per day) analytical clinical information system entitled D*D was used. The database consists of patient background information (age, gender), records of prescriptions, injections, and diagnoses. It contains data beginning in 1999 and includes approximately 400,000 patients.

Patients

We included patients who were above 18 years of age with ongoing warfarin treatment who had been prescribed fluoroquinolones or β-lactams at least once between April 2011 and March 2015. Ongoing warfarin use and stable-state of warfarin therapy were defined as the

prescription of a stable dose of warfarin for ≥ 30 days.[17,18] Patients were included if they were not prescribed any antibiotics and had a PT-INR that was measured within 3 days before the start of the antibiotics treatment (baseline PT-INR). Patients with baseline PT-INR values of < 1.0 or > 3.0 were excluded. The present study excluded patients who were prescribed additional antibiotics or switched to other antibiotics before 30 days and within exposure periods, and who were administered clarithromycin, erythromycin, phenytoin, carbamazepine, phenobarbital, cimetidine, fluconazole, itraconazole, voriconazole, or any drug to treat HIV.

Drug Exposure

Six different drug exposure categories were used based on the route of administration of the antibiotic and *Bacteroides fragilis* sensitivity to the antibiotic (Table 1): Beta-lactams per orally, **BL_{po} group**; Beta-lactams per intravenous, **BL_{iv} group**; Fluoroquinolones per orally, **FQ_{po} group**; Fluoroquinolones per intravenous, **FQ_{iv} group**; *Bacteroides fragilis* sensitivity to beta-lactams per intravenous, BL_{sus} group; *Bacteroides fragilis* non-sensitivity to beta-lactams per intravenous, **BL_{non} group**; *Bacteroides fragilis* sensitivity to fluoroquinolones per orally, **FQ_{sus} group**; *Bacteroides fragilis* non-sensitivity to fluoroquinolones per orally, **FQ_{non} group**.[19]

Exposure periods started at the first prescription date of a fluoroquinolone or β-lactam and ended at 30 days after its prescription date. The patients were prescribed

antibiotics for 2-28 days.

Study outcome

The study outcomes were excessive PT-INR and a diagnosis of gastrointestinal or intracranial bleeding during the exposure period. The PT-INR measured within 3 days before concomitant use of antibiotics was used as the baseline PT-INR, and the highest PT-INR within the exposure period was considered as the maximum PT-INR. The present study defined the days between started at the first prescription date of a fluoroquinolone or β-lactam and the date of a maximum PT-INR as an INR-time. We calculated the ratio of maximum to baseline PT-INR (INR ratio) to assess excessive PT-INR. An excessive PT-INR was graded as an INR ratio of > 1.5 or > 2.5 based on version 4.0 of the National Cancer Institute's CTCAE (Common Terminology Criteria for Adverse Events). Diagnoses of gastrointestinal or intracranial bleeding were based on ICD-10. In addition, we compared the values of the difference between maximum PT-INR and baseline PT-INR (ΔINR) in each group. To minimize the influence of infection itself and antibiotic indication on outcomes, this study compared the incidence of outcomes between the groups of “oral fluoroquinolones and oral β-lactams”, “intravenous fluoroquinolones and intravenous β-lactams”, “the antibiotics which have a susceptibility to Bacteroides fragilis and non-susceptibility”.[20]

Statistical analysis

All statistical tests were performed using SPSS 25.0J statistical software (SPSS Japan Inc., Tokyo). The chi-square test was used to compare the proportion of patients experiencing the investigated outcomes (Fisher's exact test was used for only the comparisons of the proportion of patients experiencing an INR ratio of > 1.5 and > 2.5 between BL_{non} and BL_{sus} or between FQ_{non} and FQ_{sus}), and to estimate the Odds ratio and 95% Confidence intervals (CI). The comparisons between baseline PT-INR and maximum PT-INR were analyzed using the Wilcoxon signed-rank test. INR-time and ΔINR were compared in each group using the Mann-Whitney *U* test. A *P*-value less than 5% was considered to indicate statistical significance. All descriptive statistics for PT-INR values are presented as the median and interquartile range (IQR).

Results

Patient characteristics

Table 2 shows baseline characteristics of this study. A total of 1,185 patients with ongoing warfarin treatment had a recorded concomitant use of fluoroquinolones or β-lactams during the study period. In our study, 820 patients were excluded for the following reasons; prescribed a drug that met an exclusion criteria (n = 16), PT-INR was not measured within 3 days before the start of the antibiotics treatment (n = 329), prescribed additional antibiotics or switched to other antibiotics before 30 days or within the exposure period (n = 235), changes in the warfarin dose within 30 days prior to cohort entry (n = 113), or PT-INR values of < 1.0 or > 3.0 within 30 days prior to cohort entry (n = 127). In total, 365 patients were included in the study population; 131, 132, 84, and 18 patients in the BL_{po} group, BL_{iv} group, FQ_{po} group, and FQ_{iv} group, respectively. In the BL_{iv} group, 64 and 68 patients belonged to the BL_{non} group and BL_{sus} group, respectively. In the FQ_{po} group, 53 and 31 patients belonged to the FQ_{non} group and FQ_{sus} group, respectively. The patients were prescribed antibiotics for 2-28 days.

Changes in PT-INR after concomitant use of antibiotics

Table 3 shows the median and interquartile range for baseline PT-INR, maximum PT-INR, and differences between the maximum PT-INR and baseline PT-INR (ΔINR). Maximum PT-INR values were higher than baseline PT-INR in all groups. The ΔINR in the FQ_{iv} group

and FQ_{po} group were higher than in the BL_{iv} and BL_{po} groups, respectively (95%CI: 0.14 to 0.40 and, 0.03 to 1.29). The ΔINR in the FQ_{sus} group was higher than in the FQ_{non} group.

Excessive PT-INR after concomitant use of antibiotics

Table 4 shows the proportion of patients experiencing an INR ratio of > 1.5 and > 2.5, and median (interquartile range) of INR-time. The proportion of patients with an INR ratio of > 2.5 in the FQ_{iv} group was higher than that in the BL_{iv} group (odds ratio, 95%CI: 8.6, 1.03 to 68.4). The FQ_{sus} group had a higher proportion of patients with an INR ratio of > 1.5 and > 2.5 compared with the FQ_{non} group (odds ratio, 95%CI: 3.13, 0.92 to 11.0 for INR ratio of > 1.5). The BL_{sus} group had a higher proportion of patients with an INR ratio of > 1.5 compared with the BL_{non} group (odds ratio, 95%CI: 4.92, 1.61 to 17.8). The INR-time showed from 4 to 7 days, and there were no differences for INR-time among each group.

Discussion

In this study of patients with ongoing warfarin therapy, concomitant use of fluoroquinolones was associated with an excessive PT-INR compared with concomitant use of β-lactams. In addition, concomitant use of antibiotics that have a susceptibility to *Bacteroides fragilis* has a higher risk of an excessive PT-INR compared to antibiotics that do not have a susceptibility to *Bacteroides fragilis*. The proportion with an INR ratio of > 1.5 was higher in patients receiving concomitant use of antibiotics that have a susceptibility to *Bacteroides fragilis* than non-susceptibility. The proportion of patients with an INR ratio of > 2.5 with intravenous fluoroquinolones was higher than that of patients with intravenous β-lactams, and that of patients receiving fluoroquinolones that have a susceptibility to *Bacteroides fragilis* than fluoroquinolones with non-susceptibility. To the best of our knowledge, this is the first report to investigate the association between concomitant use of antibiotics and warfarin anticoagulation ability in a real-world warfarin population, focusing on the type of antibiotic and its susceptibility to *Bacteroides fragilis*.

The present study compared the difference in excessive PT-INR between oral fluoroquinolones and β-lactams or intravenous fluoroquinolones and β-lactams. Previous studies have demonstrated that concomitant use of a fluoroquinolone such as ciprofloxacin, levofloxacin, or moxifloxacin with warfarin potentially increases the risk of experiencing a PT-INR of 5.0 or more. In contrast, concomitant use of a β-lactam such as cephalexin or amoxicillin-clavulanic acid was not associated with an increase in PT-INR.[20] Our results also

indicate that concomitant use of fluoroquinolones is associated with an increased risk of an excessive PT-INR as compared with concomitant use of β-lactams. In particular, the proportion of patients experiencing an INR ratio of > 2.5 with intravenous fluoroquinolones was higher than that with intravenous β-lactams (odds ratio, 95%CI: 8.6, 1.03-68.4). Fluoroquinolones potentially reduce the protein binding rate of warfarin and inhibit CYP1A2.[21,22] These mechanisms can explain our findings of an association between concomitant use of fluoroquinolones and warfarin anticoagulant ability.

This study revealed that concomitant use of an antibiotic that has a susceptibility to *Bacteroides fragilis* is associated with an increased risk of excessive PT-INR. *Bacteroides fragilis* is the predominant bacterial species in the human gut where they produce vitamin K.[12,13,14] As such, the concomitant use of an antibiotic that has a susceptibility to *Bacteroides fragilis* may increase the risk of excessive anticoagulation ability in warfarin therapy. This study found that the proportions of patients experiencing an INR ratio of > 1.5 in the BL_{sus} and FQ_{sus} groups were 3 and 5 times higher than that in the BL_{non} and FQ_{non} groups, respectively. The proportion of patients with an INR ratio of > 2.5 in the FQ_{sus} group was higher than that in the FQ_{non} group. These data indicate that, whenever possible, it may be prudent to avoid the concomitant use of an antibiotic that has a susceptibility to *Bacteroides fragilis* in warfarin users.

The present study also evaluated the association between concomitant use of antibiotics and bleeding risk. However, owing to the small sample size, the present study

could not analyze in this outcome between fluoroquinolones and β-lactams or between antibiotics that have a susceptibility to *Bacteroides fragilis* and those that do not have a non-susceptibility. A previous retrospective cohort study within a cohort of 22,272 veterans reported that concomitant use of ciprofloxacin or levofloxacin with warfarin was associated with serious bleeding events.[23] In addition, a case-control study nested within a cohort of 38,762 older adult patients demonstrated that concomitant use of oral fluoroquinolones, penicillins, or cephalosporins was associated with an increased risk of bleeding in warfarin users.[24] These previous findings indicated that adverse bleeding events associated with the difference in the type of antibiotics. Further investigations are required to analyze the association between adverse bleeding events and concomitant use of antibiotics focused on the type of antibiotics and its susceptibility.

Our study has several limitations. First, only patients who had attended an outpatient visit or who were hospitalized in Hamamatsu University Hospital were included. Moreover, only treatments provided by this hospital were registered in the medical database system. This may have led to exposure and outcome misclassification. Second, we had no data on adherence to the drugs prescribed. All of the patients receiving intravenous antibiotics were inpatients, while most of those receiving oral antibiotics were outpatients. This may have biased the findings towards the null, particularly in the analyses evaluating antibiotic use in the outpatient setting. Third, the present study compared oral fluoroquinolones with oral β-lactams or intravenous fluoroquinolones with intravenous β-lactams. Our findings may

have been influenced by confounding factors related to indication, in particular with respect to the severity of the infection. The present study design was chosen to minimize the influence of antibiotic indication and infection, however, additional analyses taking into consideration the severity of the infection are required to confirm the reliability of our results. Fourth, the incidences of bleeding events and changes in PT-INR are associated with CYP2C9 and VKORC1 genetic variants.[25] These variants differ between Asian and Western populations. Thus, the generalizability of our findings may be limited in Japanese populations. Fifth, the present database system did not cover information on several potential confounding and risk factors for the outcomes such as over-the-counter medications, diet, and herbal medicines. However, the adequate instructions about interactions of over-the-counter, foods, and supplements with warfarin have been commonly given to patients to avoid the adverse events of warfarin elsewhere.[22] Additionally, the present study could not assess the details of sequelae of infection, and of adverse events of antibiotic therapy (e.g. fever, nausea/vomiting, diarrhoea) which potentially affects the outcomes. Adjustment for the impact of these interactions and changes in each patient condition would confirm the considerable association between the PT-INR and the concomitant use of antibiotics. Sixth, the present study defined the stability of warfarin therapy at each patient as the prescription of a stable dose of warfarin for at least 30 days. Additionally, the study did not include patient data on adherence to the drugs prescribed in warfarin users. An additional design including the evaluation of patient's stability of warfarin therapy prior to introduction of antibiotic

would confirm our findings.[17,18] Finally, the associations in our findings do not mean causation. The present study lacked microbiology data. Thus, we are not certain that susceptibility to *Bacteroides fragilis* causes a higher risk of excessive anticoagulation.

Conclusion and Relevance

The concomitant use of fluoroquinolones and antibiotics that have a susceptibility to *Bacteroides fragilis* was associated with an increased risk of excessive PT-INR in warfarin users. The findings of the present study hopefully will contribute to the optimization of antibiotic treatment in warfarin users.

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Legends for Tables

Table 1. Six different drug exposure categories based on the route of administration of the antibiotic and *Bacteroides fragilis* sensitivity to the antibiotic

Table 2 (a). Baseline characteristics for BLPO, BLIV, FQPO, and FQIV group.

Table 2 (b). Baseline characteristics for BLnon, BLsus, FQnon, and FQsus group.

Table 3. Median and interquartile range for baseline PT-INR and maximum PT-INR and differences between the maximum PT-INR and the baseline PT-INR (ΔINR)

Table 4. Proportion of patients experiencing an INR ratio of > 1.5 and > 2.5, and median (interquartile range) of INR-time.

Table 1. Six different drug exposure categories based on the route of administration of the antibiotic and Bacteroides fragilis sensitivity to the antibiotic

Group	Antibiotics
BL_{po}	oral ampicillin, amoxicillin, sultamicillin, cefdinir, cefpodoxime, cefcapene, cefditores
BL_{iv}	intravenous ampicillin, ampicillin/sulbactam, piperacillin, piperacillin/tazobactam, cefazolin, cefmetazole, ceftriaxone, cefoperazone/sulbactam, cefepime, cefozopran, meropenem, dripenem
FQ_{po}	oral levofloxacin, moxifloxacin, garenoxacin, sitafloxacin
FQiv	intravenous levofloxacin, ciprofloxacin, pazufloxacin
BL_{sus}	ampicillin/sulbactam, piperacillin/tazobactam, cefoperazone/sulbactam, meropenem, dripenem
BL_{non}	intravenous ampicillin, piperacillin, cefazolin, cefepime, cefozopran
FQ_{sus}	moxifloxacin, garenoxacin, sitafloxacin
FQ_{non}	levofloxacin

Abbreviations: BL, β-lactams; FQ, fluoroquinolones; non, non-susceptibility to *Bacteroides fragilis*; sus, susceptibility to *Bacteroides fragilis*

Table 2. Baseline characteristics for BL_{PO}, BL_{IV}, FQ_{PO}, and FQ_{IV} group.

	BL_{PO}		BL_{IV}		FQ_{PO}		FQ_{IV}	
Number of patients (male/female)	131	(79/52)	132	(88/44)	84	(55/29)	18	(13/5)
Age, years[a]	73	(65 - 79)	77	(72 - 83)	75	(68 - 81)	78	(69 - 84)
Duration combined periods, days[a]	5	(3 - 7)	6	(4 - 8)	6	(4 - 7)	7	(5 - 11)
Dose of warfain, mg[a]	2	(1.00 - 2.75)	2	(1.50 - 2.75)	2	(1.50 - 3.00)	1.5	(1.00 - 2.00)
baseline INR[a]	1.79	(1.34 - 2.15)	1.61	(1.43 - 2.09)	1.66	(1.31 - 2.04)	1.63	(1.30 - 1.91)
Diagnosis - Number of patients (%)								

Aortic insufficiency	15	(11.5)	17	(12.9)	6	(7.1)	2	(11.1)
Arterial embolism	1	(0.8)	2	(1.5)	5	(6.0)	0	(0)
Arterial occlusion	3	(2.3)	4	(3.0)	6	(7.1)	0	(0)
Atrial fibrillation	49	(37.4)	49	(37.1)	21	(25.0)	5	(27.8)
Cardiac angina	18	(13.7)	19	(14.4)	11	(13.1)	3	(16.7)
Cerebral infarction	14	(10.7)	10	(7.6)	7	(8.3)	2	(11.1)
Deep venous thrombosis	20	(15.3)	18	(13.6)	17	(20.2)	3	(16.7)
Myocardial infarction	7	(5.3)	8	(6.1)	1	(1.2)	0	(0)
Pulmonary embolism	4	(3.1)	4	(3.0)	10	(11.9)	3	(16.7)
Ventricular aneurysm	0	(0)	1	(0.8)	0	(0)	0	(0)
Antibiotics - Number of patients	Amoxicillin	7	ABPC/SBT	15	Levofloxacin	53	Ciprofloxacin	8

Ampicillin	4	Cefazolin	25	Garenoxacin	1	Levofloxacin	7
Cefaclor	4	Cefepim	5	Moxifloxacin	16	Pazufloxacin	3
Cefcapene	58	Cefozopran	6	Sitafloxacin	14		
Cefdinir	27	Ceftriaxone	23				
Cefditoren	16	CPZ/SBT	14				
Cefpodoxime	9	Dripenem	6				
Sultamicillin	6	Flomoxef	8				
		Meropenem	13				
		Panipenem	2				
		PIPC/TAZ	10				
		Piperacillin	5				

Abbreviations: PT-INR, the prothrombin time-international normalized ratio; ABPC/SBT, ampicillin/sulbactam; CPZ/SBT, cefoperazone/sulbactam; PIPC/TAZ, piperacillin/tazobactam; BL, β-lactams; FQ, fluoroquinolones; po, orally; iv, intravenous

[a]Median (interquartile range)

Table 3. Baseline characteristics for BLnon, BLsus, FQnon, and FQsus group.

	BLnon		BLsus		FQnon		FQsus	
Number of patients (male/female)	64	(43/21)	68	(45/23)	53	(33/20)	31	(22/9)
Age, years[a]	75	(69 - 81)	78	(73 - 83)	75	(66 - 82)	75	(69 - 81)
Duration combined periods, days[a]	6	(3 - 8)	6	(4 - 8)	6	(5 - 7)	6	(4 - 10)
Dose of warfain, mg[a]	2	(1.50 - 3.00)	2	(1.50 - 2.50)	2.5	(1.50 - 3.00)	2	(1.50 - 2.50)
baseline PT-INR[a]	1.72	(1.44 - 2.21)	1.58	(1.39 - 1.97)	1.66	(1.32 - 2.01)	1.64	(1.27 - 2.10)
Diagnosis - Number of patients (%)								
Aortic insufficiency	6	(9.4)	11	(16.2)	4	(7.5)	2	(6.5)
Arterial embolism	1	(1.6)	1	(1.5)	3	(5.7)	2	(6.5)
Arterial occlusion	1	(1.6)	3	(4.4)	5	(9.4)	1	(3.2)

Atrial fibrillation	25	(39.1)	24	(35.3)	13	(24.5)	8	(25.8)
Cardiac angina	13	(20.3)	6	(8.8)	7	(13.2)	4	(12.9)
Cerebral infarction	5	(7.8)	5	(7.4)	3	(5.7)	4	(12.9)
Deep venous thrombosis	8	(12.5)	10	(14.7)	10	(18.9)	7	(22.6)
Myocardial infarction	4	(6.3)	4	(5.9)	0	(0)	1	(3.2)
Pulmonary embolism	0	(0)	4	(5.9)	8	(15.1)	2	(6.5)
Ventricular aneurysm	1	(1.6)	0	(0)	0	(0)	0	(0)

Antibiotics - Number of patients								
	Cefazolin	25	ABPC/SBT	15	Levofloxacin	53	Garenoxacin	1
	Cefepim	5	CPZ/SBT	14			Moxifloxacin	16
	Cefozopran	6	Dripenem	6			Sitafloxacin	14
	Ceftriaxone	23	Flomoxef	8				
	Piperacillin	5	Meropenem	13				
			Panipenem	2				
			PIPC/TAZ	10				

Abbreviations: PT-INR, the prothrombin time-international normalized ratio; ABPC/SBT, ampicillin/sulbactam; CPZ/SBT, cefoperazone/sulbactam; PIPC/TAZ, piperacillin/tazobactam; BL, β-lactams; FQ, fluoroquinolones; non, non-susceptibility to *Bacteroides fragilis*; sus, susceptibility to *Bacteroides fragilis*

[a]Median (interquartile range)

Table 4. Median and interquartile range for baseline PT-INR and maximum PT-INR and differences between the maximum PT-INR and the baseline PT-INR (ΔINR)

	β-Lactam			Fluoroquinolone			
	baseline PT-INR[a]	maximum PT-INR[a]	p-value[b]	baseline PT-INR[a]	maximum PT-INR[a]	p-value[b]	p-value[c]
Oral	1.77 (1.18 - 2.12)	1.85 (1.47 - 2.37)	<0.01	1.66 (1.28 - 2.04)	1.93 (1.43 - 2.40)	<0.01	
ΔINR		0.06 (-0.19 - 0.56)			0.17 (0.002 - 0.69)		<0.001
Intravenous	1.61 (1.43 - 2.10)	1.90 (1.45 - 2.69)	<0.01	1.71 (1.31 - 2.04)	2.80 (1.61 - 4.07)	<0.01	
ΔINR		0.23 (-0.04 - 2.22)			0.4 (0.15 - 2.34)		<0.05

	Non-susceptibility to *Bacteroides fragilis*			Susceptibility to *Bacteroides fragilis*			
	baseline PT-INR[a]	maximum PT-INR[a]	p-value[b]	baseline PT-INR[a]	maximum PT-INR[a]	p-value[b]	p-value[c]
β-Lactam	1.72 (1.44 - 2.22)	1.88 (1.50 - 2.43)	<0.01	1.57 (1.35 - 1.97)	1.92 (1.43 - 3.00)	<0.01	
ΔINR		0.16 (-0.09 - 0.52)			0.33 (0.02 - 0.96)		0.09
Fluoroquinolone	1.66 (1.32 - 2.01)	1.82 (1.40 - 2.31)	<0.01	1.64 (1.27 - 2.10)	2.08 (1.74 - 3.21)	<0.01	

ΔINR	0.12	(-0.04 - 0.51)	0.18	(0.09 - 1.57)	<0.05

Abbreviations: PT-INR, the prothrombin time-international normalized ratio; ΔINR, difference of maximum PT-INR and baseline PT-INR

[a]Median (interquartile range)

[b]P-value for baseline INR vs. maximum INR

[c]P-value for ΔINR in β-Lactam vs. Fluoroquinolone or ΔINR in Non-susceptibility to *Bacteroides fragilis* vs. Susceptibility to *Bacteroides fragilis*

Table 5. Proportion of patients experiencing an INR ratio of > 1.5 and > 2.5, and median (interquartile range) of INR-time.

	INR ratio > 1.5			INR ratio > 2.5			INR-time (days)	
	n (%)	Odds ratio (95% CI)	p-value	n (%)	Odds ratio (95% CI)	p-value	Median (IQR)	p-value
BL_{po}	26 (20)	1.02 (0.48 - 2.13)	0.94	8 (6)	0.77 (0.16 - 2.99)	0.68	7 (3 - 12)	0.73
FQ_{po}	17 (20)			4 (5)			7 (4 - 11)	
BL_{iv}	25 (19)	2.72 (0.80 - 8.58)	0.05	3 (2)	8.6 (1.03 - 68.4)	< 0.01	5 (2 - 8)	0.51
FQ_{iv}	7 (35)			3 (15)			5 (3 - 11)	

	INR ratio > 1.5			INR ratio > 2.5			INR-time (days)	
	n (%)	Odds ratio (95% CI)	p-value	n (%)	Odds ratio (95% CI)	p-value	Median (IQR)	p-value

BL_{non}	5	(8)				0	(0)				5	(3 - 10)	
			4.92	(1.61 - 17.8)	< 0.01			-	-	0.13			0.20
BL_{sus}	20	(29)				3	(4)				4	(2 - 8)	
FQ_{non}	7	(13)				0	(0)				7	(4 - 11)	
			3.13	(0.92 - 11.0)	< 0.05			-	-	< 0.05			0.66
FQ_{sus}	10	(32)				4	(13)				6	(6 - 11)	

Abbreviations: INR ratio, the ratio of maximum the prothrombin time-international normalized ratio and baseline the prothrombin time-international normalized ratio; INR-time, the days between started at the first prescription date of a fluoroquinolone or β-lactam and the date of a maximum the prothrombin time-international normalized ratio ; 95%CI, 95% confidence intervals; IQR, interquartile range; BL, β-lactams; FQ, fluoroquinolones; po, orally; iv, intravenous; non, non-susceptibility to *Bacteroides fragilis*; sus, susceptibility to *Bacteroides fragilis*