Internal and Emergency Medicine (2020) 15:311–318
https://doi.org/10.1007/s11739-019-02229-7

EM - ORIGINAL

Thirty-day mortality in atrial fibrillation patients with gastrointestinal bleeding in the emergency department: differences between direct oral anticoagulant and warfarin users

Gianni Turcato[1] · Antonio Bonora[2] · Elisabetta Zorzi[3] · Arian Zaboli[1] · Massimo Zannoni[2] · Giorgio Ricci[3] · Norbert Pfeifer[1] · Antonio Maccagnani[2] · Andrea Tenci[4]

Received: 24 May 2019 / Accepted: 2 November 2019 / Published online: 21 November 2019

Abstract
More clinical data are required on the safety of direct oral anticoagulants (DOACs). Although patients treated with warfarin and DOACs have a similar risk of bleeding, short-term mortality after a gastrointestinal bleeding (GIB) episode in DOAC-treated patients has not been clarified. The objective of this study was to assess differences in 30-day mortality in patients treated with DOACs or warfarin admitted to the emergency department (ED) for GIB. This was a multicentre retrospective study conducted over 2 years. The study included patients evaluated at three different EDs for GIB. The baseline characteristics were included. Subsequently, we assessed the differences in past medical history and clinical data between the two study groups (DOAC and warfarin users). Differences between the two groups were evaluated using Kaplan–Meier curves. Among the 284 patients presenting GIB enrolled in the study period, 39.4% (112/284) were treated with DOACs and 60.6% (172/284) were treated with warfarin. Overall, 8.1% (23/284) of patients died within 30 days. Among the 172 warfarin-treated patients, 8.7% (15/172) died within 30 days from ED evaluation. In the 112 DOAC-treated patients, the mortality rate was 7.1% (8/112). The Cox regression analysis, adjusted for possible clinical confounders, and the Kaplan–Meier curves did not outline differences between the two treatment groups. The present study shows no differences between DOACs and warfarin in short-term mortality after GIB.

Keywords Gastrointestinal bleeding · Warfarin · Direct oral anticoagulant · Atrial fibrillation · Emergency department

Introduction

Gastrointestinal bleeding (GIB) complications (such as the need for blood transfusion, hospitalisation, medium–short-term mortality) in atrial fibrillation (AF) patients treated with direct oral anticoagulants (DOACs) remain unclear [1, 2].

Landmark trials have shown that DOACs are not inferior in thromboembolic risk prevention compared to warfarin in AF [3–5]. However, the selected patients showed slightly higher GIB risk [6, 7], especially those aged > 75 years who were treated with concomitant antiplatelet therapy [6, 8]. A meta-analysis published in 2013 by Holster et al. that included previous randomized controlled trials (RCTs, total 75,081 patients) proved that DOAC users had a higher risk of GIB compared to patients treated with standard care, with an odds ratio (OR) of 1.45 [9].

Post-approval observational studies performed with administrative datasets have shown conflicting results about GIB risk. Some studies proved greater safety with warfarin [10, 11]; others described a non-significant difference between DOACs and warfarin [12, 13]. Hence, the original aim of these studies was not to assess the outcome of GIB. Their main focus was evaluating the efficacy of these drugs

✉ Gianni Turcato
gianni.turcato@yahoo.it

[1] Department of Emergency Medicine, Franz Tappeiner Hospital of Merano, Azienda Sanitaria Dell'Alto Adige, Merano, Bolzano, Italy

[2] Department of Emergency Medicine, University of Verona, Verona, Italy

[3] Department of Cardiology and Intensive Care Cardiology, Girolamo Fracastoro Hospital of San Bonifacio, Azienda Ospedaliera Scaligera, San Bonifacio, Verona, Italy

[4] Department of Emergency Medicine, Girolamo Fracastoro Hospital of San Bonifacio, Azienda Ospedaliera Scaligera, San Bonifacio, Verona, Italy

in reducing stroke incidence [12–14]. Therefore, these studies did not use a standard definition of GIB, which led to reduced data interpretation. Moreover, patients enrolled in clinical trials are frequently not representative of real-world practice. These groups often have strict inclusion and exclusion criteria, leading to complicated interpretation of the data from all of our patients [13, 14].

A recent observational real-world study found that warfarin users had fourfold risk of GIB and described lower intrahospital mortality in DOAC-treated patients [14]. However, there is some evidence on the prognosis in DOAC-treated patients with GIB.

Here, we aimed to evaluate the difference in 30-day mortality risk between GIB patients treated with DOACs or warfarin.

Materials and methods

We considered all patients who were evaluated at the emergency departments (ED) of the Policlinico Universitario (Verona, Italy), Ospedale Civile Maggiore (Verona, Italy) and Ospedale Girolamo Fracastoro (San Bonifacio, Italy) for GIB. These EDs all have a 24-h endoscopy service. The analysis spanned from 1 January 2016 to 31 December 2017.

GIB was defined according to the International Society of Thrombosis and Haemostasis and subsequently divided into major bleeding and/or clinically relevant non-major bleeding [15, 16].

Clinically major GIB was defined as overt or occult GI blood loss resulting in hospitalisation and was associated with a decline in haemoglobin by ≥ 2 g/dl, hemodynamic instability (systolic blood pressure < 90 mmHg or heart rate > 100 beats per minute) within 24 h of presentation, and/or the need for endoscopic evaluation, angiography or surgery [15].

Clinically relevant non-major GIB was defined as any sign or symptom of haemorrhage that did not fit the criteria for the definition of major bleeding but that did meet at least one of the following criteria: required medical intervention by a healthcare professional and leading to hospitalisation, increased level of care or prompting a face-to-face (i.e., not just telephone or electronic communication) evaluation [16].

During the study period, all patients with ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification) diagnosis codes related to GIB were extracted using First Aid software (Dedalus Healthcare System Group, Firenze, Italy). All identified cases were then evaluated via manual review of the patient's medical records to ascertain presence of GIB and concomitant oral anticoagulant therapy. Patients with assessed GIB were divided into two groups according to the ongoing therapy: DOACs and warfarin. We excluded patients treated with anticoagulant therapy for other reasons than AF (i.e., mechanical heart valve, previous pulmonary thromboembolism).

Baseline demographic characteristics, comorbidities, pharmacologic therapy and laboratory data were recorded at the moment of manual revision of the ED folders.

The primary outcome was 30-day mortality from ED evaluation. The survival rate was obtained directly from the registry office.

The secondary outcomes were the need for blood transfusion in ED, urgent endoscopic evaluation and hospital admission after ED stabilisation. This retrospective observational study was performed according to the Declaration of Helsinki and under the terms of the relevant local legislation.

Statistical analysis

Continuous variables are reported as the median and interquartile ranges. Categorical variables are reported as the percentage and number of events.

The two treatment groups (DOACs vs. warfarin) were compared to evaluate any possible imbalance in the past medical history or clinical characteristics. Here, the use of propensity score matching had to be considered to equilibrate the two groups and to obtain a homogeneous cohort of patients for prognostic evaluation.

The 30-day mortality is reported as the percentage and number of total events. Comparison with the clinical and past medical history variables was performed using the Mann–Whitney U test and with Fisher's exact test, as appropriate. Cox regression, adjusted for all variables that were significant to the previous univariate analysis, was performed to verify differences in mortality between the two treatment groups. Finally, the Kaplan–Meier method was used to compare 30-day survival between DOAC and warfarin users. Each analysis was considered significant at $p < 0.05$. The statistical analysis was performed using STATA 14.0 (StataCorp, College Station, Texas, USA).

Results

During the study period, 284 patients with ongoing oral anticoagulant therapy and concomitant GIB were evaluated. We excluded 34 patients with no confirmed bleeding at the moment of the visit, 7 patients because they lacked past medical history data and 5 patients without follow-up.

Among the 284 patients, 39.4% (112/284) were treated with DOACs, and 60.6% (172/284) were treated with warfarin. Among the DOAC-treated patients, 29.5% (33/112) were treated with dabigatran, 25.9% (29/112) with rivaroxaban, 37.5% (42/112) with apixaban and 7.1% (8/112) with edoxaban.

Within 30 days from ED evaluation, 8.1% of the patients (23/284) died.

Table 1 lists the demographic, past medical history and clinical characteristics of the two treatment groups (DOACs vs. warfarin) (Table 1).

Propensity score matching was not needed, as the two groups did not show significant differences except for the concomitant platelet therapy (11.6% vs. 2.7%, $p = 0.007$) (Table 1). Table 2 shows the past medical history and clinical characteristics recorded at ED admission and 30-day mortality univariate analysis. The factors associated with 30-day mortality risk were age, history of chronic renal disease, active cancer, HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly) value, and bleeding type (major GIB) and site (upper GIB). After the univariate analysis, neither of the two anticoagulant treatments resulted in higher 30-day mortality risk (warfarin 8.7% vs. DOACs 7.1%, $p = 0.824$) (Table 2).

Table 1 Clinical history, demographic and laboratory data recorded in 284 patients admitted to the ED for a GIB

Variable	Warfarin	DOACs	*P*
Patients, *n* (%)	172 (60.6)	112 (39.4)	
Age, years, median (IQR)	82 (77–88)	83 (79–87)	0.473
Age > 75 years	142 (82.6)	101 (90.2)	0.085
Sex, *n* (%)			0.466
Male	88 (51.2)	63 (56.3)	
Female	84 (48.8)	49 (43.8)	
Clinical history, *n* (%)			
Ischemic heart disease	45 (26.2)	26 (23.2)	0.674
Hypertension	156 (90.7)	101 (90.2)	1.000
Heart failure disease	50 (29.1)	41 (36.6)	0.195
Cancer	25 (14.5)	26 (23.2)	0.081
Gastrointestinal cancer	17 (9.9)	11 (9.8)	1.000
Liver disease	8 (4.7)	7 (6.3)	0.594
Previous stroke	26 (15.1)	23 (20.5)	0.262
Previous VTE	3 (1.7)	1 (0.9)	1.000
Vascular disease	39 (22.7)	27 (24.3)	0.775
Diabetes	44 (25.6)	26 (23.6)	0.778
Chronic kidney disease	42 (24.4)	27 (24.1)	1.000
Antiplatelet therapy	20 (11.6)	3 (2.7)	0.007
Bleeding			0.395
Upper gastrointestinal bleeding	85 (49.4)	49 (43.8)	
Lower gastrointestinal bleeding	87 (50.6)	63 (56.3)	
CHA_2DS_2-VASc score, median (IQR)	4 (3–5)	4 (3–5)	0.112
HAS-BLED score, median (IQR)	3 (2–4)	2 (2–3)	0.680
Laboratory exams			
Haemoglobin (g/dL)	100.4 (82.0–122.0)	95.5 (75.4–116.1)	0.184
Creatinine (mg/dL)	1.10 (0.84–1.53)	1.14 (0.94–1.54)	0.373
Platelet (10^9/L)	211 (166–284)	229 (182–290)	0.337
PT (INR)	2.97 (2.19–4.48)	1.32 (1.16–1.70)	0.001
aPTT (ratio)	1.40 (1.09–1.68)	1.19 (0.98–1.47)	0.016
Type of bleeding			0.468
Clinically relevant non-major GIB	83 (48.3)	49 (43.9)	
Major GIB	89 (51.7)	63 (56.3)	
30-day mortality	15 (8.7)	8 (7.1)	0.824
Secondary outcomes			
Transfusion in ED	69 (40.1)	53 (47.3)	0.270
Fresh frozen plasma in ED	35 (20.3)	21 (18.7)	0.763
Urgent endoscopy	32 (18.4)	23 (20.3)	0.865
Hospital admission	65 (38.1)	49 (43.9)	0.510

Table 2 Univariate analysis for predicting 30- and 90-day mortality after ED admission for GIB

Variable	30 days alive	30 days death	*p*
Patients, *n* (%)	261 (91.9)	23 (8.1)	
Age, years, median (IQR)	82 (79–87)	88 (81–92)	0.009
Sex, *n* (%)			0.278
Male	136 (52.1)	15 (65.2)	
Female	125 (47.9)	8 (34.8)	
Oral anticoagulation treatment			0.824
Warfarin	157 (60.2)	15 (65.2)	
DOACs	104 (39.8)	8 (34.8)	
Clinical history, *n* (%)			
Ischemic heart disease	64 (24.5)	7 (30.4)	0.615
Hypertension	235 (90.0)	22 (95.7)	0.709
Heart failure disease	80 (30.7)	11 (47.8)	0.105
Cancer	43 (16.5)	8 (34.8)	0.043
Gastrointestinal cancer	24 (9.2)	4 (17.4)	0.261
Liver disease	14 (5.4)	1 (4.3)	1.000
Previous stroke	43 (16.5)	6 (26.1)	0.252
Previous VTE	4 (1.5)	0 (0)	1.000
Vascular disease	57 (21.9)	9 (39.1)	0.073
Diabetes	62 (23.9)	8 (34.8)	0.312 0.001
Chronic kidney disease	54 (20.7)	15 (65.2)	1.000
Antiplatelet therapy	21 (8.0)	2 (8.7)	
CHA_2DS_2-VASc score, median (IQR)	4 (3–5)	5 (4–7)	0.116
HAS-BLED score, median (IQR)	2 (2–3)	3 (2–4)	0.025
Laboratory exam			
Haemoglobin (g/dL)	100 (82–122)	96 (76–108)	0.227
Creatinin (mg/dL)	1.11 (0.87–1.54)	1.38 (1.16–1.95)	0.064
Platelet (10^9/L)	219 (172–294)	206 (171–307)	0.997
PT (INR)	2.02 (1.32–3.19)	2.52 (1.51–4.56)	0.106
aPTT (ratio)	1.25 (1.04–1.62)	1.38 (1.08–2.52)	0.404
Type of bleeding			0.016
Clinically relevant non-major GIB	127 (48.7)	5 (21.7)	
Major GIB	134 (51.3)	18 (78.3)	
Bleeding			0.048
Lower	128 (49)	6 (21.1)	
Upper	133 (51)	17 (73.9)	

Cox analysis adjusted for age, chronic renal disease, major GIB, upper GIB and baseline HAS-BLED showed no difference in mortality within 30 days of the GIB episode between the two groups [p = not significant (ns)] (Fig. 1). The Kaplan–Meier curves showed no difference in 30-day survival after the GIB episode between warfarin and DOAC users (p = ns) (Fig. 2).

No difference was recorded between warfarin and DOACs users for secondary outcomes (Table 1).

Discussion

This real-world retrospective study involved 284 episodes of acute GIB. All patients had concomitant anticoagulant therapy (DOACs, 112 vs. warfarin, 172) for preventing thromboembolism in non-valvular AF.

No difference between DOAC- and warfarin-treated patients was recorded in 30-day mortality after an acute

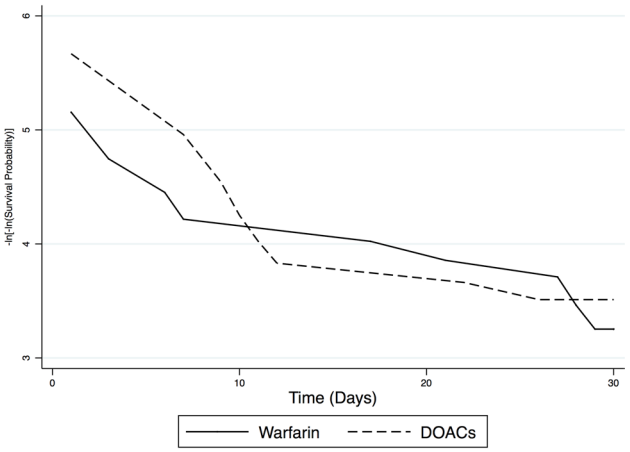

Fig. 1 Cox regression analysis of 30-day morality risk between DOAC-treated patients versus warfarin-treated patients

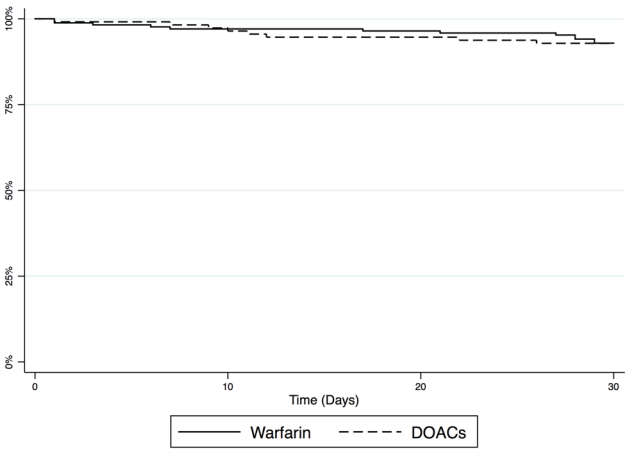

Fig. 2 Kaplan–Meier curves for differences in 30-day survival between DOACs and warfarin users

GIB episode evaluated in ED. Even after adjustment for variables associated with the risk of 30-day mortality (age, chronic renal disease, major GIB, upper GIB, HAS-BLED), no differences were recorded within 30 days of the GIB episode between the DOAC and warfarin users.

GIB is a common problem that ranges from self-limited bleeding to haemorrhagic emergency [17]. In the latter, patients can present hemodynamic instability with altered mental status and rapidly progress to generalised shock [17, 18]. Even haemodynamically stable patients need accurate diagnostic evaluation and clinical follow-up [19]. The estimated global mortality after a GIB is > 10% [20, 21] and its severity is influenced by old age [22, 23] and comorbidities [22, 23]. Oral anticoagulant therapy (warfarin) represents a risk factor for the prognosis of patients with GIB, with a fatality rate of almost 6% [24, 25].

Interestingly, several studies have evaluated the GIB risk for DOACs compared with warfarin in patients with non-valvular AF, and reported contradictory findings [14, 26, 27]. Moreover, none of these studies explored prognostic differences after an acute episode of GIB in patients receiving oral anticoagulant, comparing DOACs and warfarin users [14, 26]. In the Randomised Evaluation of Long-term anticoagulation therapY, dabigatran (RE-LY) study, patients treated with dabigatran (150 mg) has higher GIB risk compared with warfarin-treated patients [hazard ratio (HR): 1.50, 95% confidence interval (95%CI): 1.19–1.89, $p < 0.001$] [3]. Similarly, the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in AF, rivaroxaban (ROCKET AF trial) reported an increased rate of GIB in patients taking rivaroxaban compared to warfarin (HR 1.42; 95%CI 1.22–1.66) [5]. However, in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE trial), the risk of major GIB with 20 mg apixaban was similar to that of warfarin, but patients taking apixaban rather than warfarin had a lower risk of non-major bleeding (HR 0.69; 95%CI 0.63–0.75) [4, 28]. Lastly, the ENGAGE study (edoxaban) showed a higher GIB risk for high edoxaban doses compared to warfarin (HR 1.23, 95%CI 1.02–1.50, $p = 0.03$) [29]. These landmark trials were not originally designed to assess the outcome of GIB, and no standard definition of GIB was used across these studies, restricting the data interpretation [14, 26]. Moreover, none of these landmark studies has specified prognosis or mortality after acute GIB during the follow-up of DOAC- or warfarin-treated patients [3–5, 28].

A real-life retrospective study in New Zealand reported that dabigatran-treated patients had slightly higher annual GIB rate compared to the warfarin-treated patients (3.70% vs. 3.35%), but the two treatments had similar relative risk for GIB [30]. The revision of other national registries demonstrated no differences between DOACs and warfarin, except DOACs in older patients and with higher dosages [31, 32].

In a retrospective study of 46,163 patients (dabigatran, 4907; rivaroxaban, 1649; warfarin, 39,607), Chang et al. demonstrated that the dabigatran group had higher GIB incidence (9.01 per 100 person-years), but the cumulative risk for GIB adjusted for confounding variables was not different for the DOAC and warfarin users [12]. Abraham et al. showed that, in a cohort of 758 patients well adjusted for the past medical history, the relative risk for GIB for dabigatran and rivaroxaban was 0.79 (95%CI: 0.61– 1.03) and 0.93 (95%CI: 0.69–1.25), respectively, compared with warfarin [13].

Recently, Cangemi et al. performed an observational study (163 GIB cases) and showed that GIB risk was > four-fold higher for patients using warfarin compared to those

using DOACs (2.5% vs. 0.6%, OR 4.13; 95%CI 1.69–10.09) [14]. Furthermore, they show for the first time some prognostic indications after GIB in warfarin users with higher transfusion incidence (64.6% vs. 20%, $p=0.042$), longer hospital stay (mean 7.7 vs. 3.8 days, $p=0.068$) and higher 90-day mortality in hospitalised warfarin users (warfarin group, 7.6%) [14].

The present study has some interesting features. It is a real-life study performed in three different centres with an endoscopy unit working 24 h a day, analysed a high number of GIB patients, compared warfarin to all DOAC therapies available (dabigatran, apixaban, rivaroxaban, edoxaban) and explored short-term mortality. Unlike previous analysis based on anticoagulated patient registries, the present study directly considers individual episodes of acute GIB in the ED. Moreover, we considered only AF anticoagulation patients compared to previous studies that considered all therapeutic anticoagulation indications, thus including patients with higher warfarin dosage (i.e., mechanical heart valve) and patients with major bleeding risk (i.e., pulmonary thromboembolism).

The cohort of patients enrolled did not show any differences in baseline characteristics between DOACs and warfarin users. Therefore, there was no need for statistical matching (for example, propensity score matching).

To the best of our knowledge, our results are the first to explore the prognosis of DOAC-treated patients with GIB. The short-term mortality is aligned with the mortality data in other studies in the case of GIB in patients treated with oral anticoagulants (warfarin, anti-vitamin K [AVK]) [19–23].

Limitations

Our study has some limitations. First, the retrospective design exposes it to biases typical for these studies. Second, major GIB and clinically relevant non-major GIB were initially distinguished but later grouped under one single outcome. Recent studies have suggested that all non-major bleeding occurring during oral anticoagulant therapy are not trivial for either patients or health care systems [16, 19, 33–35]. Finally, we considered every therapeutic procedure that was carried out in the ED. Subsequent therapeutic procedures after patient stabilisation were not considered for statistical analysis.

Despite these limitations, the lack of prognostic information in the case of GIB in patients treated with oral anticoagulants is important data for ED evaluation of the anticoagulated patient. The rapid diffusion of these drugs should involve the gathering of more real-life evidence. However, further studies should take into account subsequent bleeding therapies in anticoagulated patients with GIB.

Conclusions

The present study shows no difference in short-term mortality between DOAC and warfarin users. DOACs represent a real innovation of the last decade. Despite their rapid diffusion, the available evidence is lacking, and the GIB prognosis of anticoagulated patients remains unclear. We believe that all information from actual clinical settings are important, given the global burn of thromboembolic pathology and the growing anticoagulant necessity in populations with comorbidities.

Compliance with ethical standards

Conflict of interest Authors have no conflict of interest to declare.

Statement of human and animal rights This retrospective study was conducted in accordance with the current rules of the local ethics committee.

Informed consent Consent to the study's participation was requested at their access in the emergency department.

References

1. Cheung KS, Leung WK (2017) Gastrointestinal bleeding in patients on novel oral anticoagulants: Risk, prevention and management. World J Gastroenterol. 23(11):1954–1963. https://doi.org/10.3748/wjg.v23.i11.1954
2. Miller CS, Dorreen A, Martel M, Huynh T, Barkun AN (2017) Risk of gastrointestinal bleeding in patients taking non-vitamin k antagonist oral anticoagulants: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 15(11):1674–1683. https://doi.org/10.1016/j.cgh.2017.04.031 **(Epub 2017 Apr 27)**
3. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L, RE-LY Steering Committee, and Investigators (2009) Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 361(12):1139–1151. https://doi.org/10.1056/NEJMoa0905561 **(Epub 2009 Aug 30)**
4. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L, ARISTOTLE Committees, and Investigators (2011) Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 365(11):981–992. https://doi.org/10.1056/NEJMoa1107039 **(Epub 2011 Aug 27)**
5. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM, ROCKET AF Investigators (2011) Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 365(10):883–891. https://doi.org/10.1056/NEJMoa1009638 **(Epub 2011 Aug 10)**

6. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM (2014) Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 383(9921):955–962. https://doi.org/10.1016/S0140-6736(13)62343-0 **(Epub 2013 Dec 4)**
7. Liew A, O'Donnell M, Douketis J (2014) Comparing mortality in patients with atrial fibrillation who are receiving a direct-acting oral anticoagulation or warfarin: a meta-analysis of randomized trials. J Thromb Haemost. 12(9):1419–1424. https://doi.org/10.1111/jth.12651 **(Epub 2014 Jul 2015)**
8. Komócsi A, Vorobcsuk A, Kehl D, Aradi D (2012) Use of new-generation oral anticoagulant agents in patients receiving antiplatelet therapy after an acute coronary syndrome: systematic review and meta-analysis of randomized controlled trials. Arch Intern Med. 172(20):1537–1545. https://doi.org/10.1001/archinternmed.2012.4026
9. Holster IL, Valkhoff VE, Kuipers EJ, Tjwa ET (2013) New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis. Gastroenterology 145:105–112. https://doi.org/10.1053/j.gastro.2013.02.041 **(Epub 2014 Aug 12)**
10. Sarrazin MS, Jones M, Mazur A, Chrischilles E, Cram P (2014) Bleeding rates in veterans affairs patients with atrial fibrillation who switch from warfarin to dabigatran. Am J Med. 127(12):1179–1185. https://doi.org/10.1016/j.amjmed.2014.07.024
11. Lauffenburger JC, Farley JF, Gehi AK, Rhoney DH, Brookhart MA, Fang G (2015) Effectiveness and safety of dabigatran and warfarin in real-world US patients with non-valvular atrial fibrillation: a retrospective cohort study. J Am Heart Assoc. 4(4):e001798. https://doi.org/10.1161/JAHA.115.001798
12. Chang HY, Zhou M, Tang W, Alexander GC, Singh S (2015) Risk of gastrointestinal bleeding associated with oral anticoagulants: population based retrospective cohort study. BMJ 24(350):h1585. https://doi.org/10.1136/bmj.h1585
13. Abraham NS, Singh S, Alexander GC, Heien H, Haas LR, Crown W, Shah ND (2015) Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population based cohort study. BMJ 24(350):h1857. https://doi.org/10.1136/bmj.h1857
14. Cangemi DJ, Krill T, Weideman R, Cipher DJ, Spechler SJ, Feagins LA (2017) A comparison of the rate of gastrointestinal bleeding in patients taking non-vitamin K antagonist oral anticoagulants or warfarin. Am J Gastroenterol. 112(5):734–739. https://doi.org/10.1038/ajg.2017.39 **(Epub 2017 Feb 28)**
15. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific, and Standardization Committee of the International Society on Thrombosis and, Haemostasis (2005) Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 3(4):692–694. https://doi.org/10.1111/j.1538-7836.2005.01204.x
16. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S, Subcommittee on Control of Anticoagulation (2015) Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost. 13(11):2119–2126. https://doi.org/10.1111/jth.13140
17. Farrar FC (2018) Management of acute gastrointestinal bleed. Crit Care Nurs Clin N Am. 30(1):55–66. https://doi.org/10.1016/j.cnc.2017.10.005 **(Epub 2017 Nov 21)**
18. Grace ND (1997) Diagnosis and treatment of gastrointestinal bleeding secondary to portal hypertension: American College of Gastroenterology Practice Parameters Committee. Am J Gastroenterol. 92(7):1081–1091
19. Hopper AD, Sanders DS (2011) Upper GI bleeding requires prompt investigation. Practitioner. 255(1742):15–92
20. Hearnshaw SA, Logan RF, Lowe D, Travis SP, Murphy MF, Palmer KR (2011) Acute upper gastrointestinal bleeding in the UK: patient characteristics, diagnoses and outcomes in the 2007 UK audit. Gut 60(10):1327–1335. https://doi.org/10.1136/gut.2010.228437 **(Epub 2011 Apr 13)**
21. Desai J, Kolb JM, Weitz JI, Aisenberg J (2013) Gastrointestinal bleeding with the new oral anticoagulation—defining the issues and the management strategies. Thromb Haemost. 110(2):205–212. https://doi.org/10.1160/TH13-02-0150 **(Epub 2013 May 23)**
22. Abraham NS, Hartman C, Richardson P, Castillo D, Street RL Jr, Naik AD (2013) Risk of lower and upper gastrointestinal bleeding, transfusions, and hospitalizations with complex antithrombotic therapy in elderly patients. Circulation 128(17):1869–1877. https://doi.org/10.1161/CIRCULATIONAHA.113.004747 **(Epub 2013 Sep 11)**
23. Chen WC, Chen YH, Hsu PI, Tsay FW, Chan HH, Cheng JS, Lai KH (2014) Gastrointestinal hemorrhage in warfarin anticoagulated patients: incidence, risk, factor, management, and outcome. Biomed Res Int. https://doi.org/10.1155/2014/463767
24. Leonard CE, Brensinger CM, Bilker WB, Kimmel SE, Han X, Nam YH, Gagne JJ, Mangaali MJ, Hennessy S (2016) Gastrointestinal bleeding and intracranial hemorrhage in concomitant users of warfarin and antihyperlipidemics. Int J Cardiol. 228:761–770
25. Gallagher AM, van Staa TP, Murray-Thomas T, Schoof N, Clemens A, Ackermann D, Bartels DB (2014) Population-based cohort study of warfarin-treated patients with atrial fibrillation: incidence of cardiovascular and bleeding outcomes. BMJ Open. 4:e003839. https://doi.org/10.1136/bmjopen-2013-003839
26. Lanas-Gimeno A, Lanas A (2017) Risk of gastrointestinal bleeding during anticoagulant treatment. Expert Opin Drug Saf. 16(6):673–685. https://doi.org/10.1080/14740338.2017.1325870 **(Epub 2017 May 17)**
27. Xu WW, Hu SJ, Wu T (2017) Risk analysis of new oral anticoagulants for gastrointestinal bleeding and intracranial hemorrhage in atrial fibrillation patients: a systematic review and network meta-analysis. J Zhejiang Univ Sci B. 18(7):567–576. https://doi.org/10.1631/jzus.B1600143
28. Bahit MC, Lopes RD, Wojdyla DM, Held C, Hanna M, Vinereanu D, Hylek EM, Verheugt F, Goto S, Alexander JH, Wallentin L, Granger CB (2017) Non-major bleeding with apixaban versus warfarin in patients with atrial fibrillation. Heart 103(8):623–628. https://doi.org/10.1136/heartjnl-2016-309901 **(Epub 2016 Oct 24)**
29. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM, ENGAGE AF-TIMI 48 Investigators (2013) Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 369(22):2093–2104. https://doi.org/10.1056/NEJMoa1310907 **(Epub 2013 Nov 19)**
30. Nishtala PS, Gnjidic D, Jamieson HA, Hanger HC, Kaluarachchi C, Hilmer SN (2016) "Real-world" haemorrhagic rates for warfarin and dabigatran using population-level data in New Zealand. Int J Cardiol. 15(203):746–752. https://doi.org/10.1016/j.ijcard.2015.11.067 **(Epub 2015 Nov 10)**
31. Larsen TB, Rasmussen LH, Skjøth F, Due KM, Callréus T, Rosenzweig M, Lip GY (2013) Efficacy and safety of dabigatran etexilate and warfarin in "real-world" patients with atrial fibrillation: a prospective nationwide cohort study. J Am Coll Cardiol. 61(22):2264–2273. https://doi.org/10.1016/j.jacc.2013.03.020 **(Epub 2013 Apr 3)**
32. Graham DJ, Reichman ME, Wernecke M, Zhang R, Southworth MR, Levenson M, Sheu TC, Mott K, Goulding MR, Houstoun

M, MaCurdy TE, Worrall C, Kelman JA (2015) Cardiovascular, bleeding, and mortality risks in elderly Medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. Circulation 131(2):157–164. https://doi.org/10.1161/CIRCULATIONAHA.114.012061 **(Epub 2014 Oct 30)**

33. Abraham NS (2014) Gastrointestinal bleeding in cardiac patients: epidemiology and evolving clinical paradigms. Curr Opin Gastroenterol. 30(6):609–614. https://doi.org/10.1097/MOG.0000000000000122
34. Franco L, Becattini C, Vanni S, Sbrojavacca R, Nitti C, Manina G, Masotti L, Pomero F, Cattinelli S, Cappelli R, Re R, Agnelli G (2018) Clinically relevant non-major bleeding with oral anticoagulants: non-major may not be trivial. Blood Transfus. 16(4):387–391. https://doi.org/10.2450/2017.0335-16 **(Epub 2017 Mar 15)**
35. Laporte S, Chapelle C, Bertoletti L, Ollier E, Zufferey P, Lega JC, Merah A, Décousus H, Schulman S, Meyer G, Cucherat M, Mismetti P (2017) Assessment of clinically relevant bleeding as a surrogate outcome for major bleeding: validation by meta-analysis of randomized controlled trials. J Thromb Haemost. 15(8):1547–1558. https://doi.org/10.1111/jth.13740 **(Epub 2017 Jul 5)**