ESC European Society of Cardiology

European Heart Journal - Cardiovascular Pharmacotherapy (2020) **6**, 14–21
doi:10.1093/ehjcvp/pvz025

**ORIGINAL ARTICLE**
*Acute coronary syndromes*

# Antithrombotic treatment and major adverse cardiac events after bleeding in patients with myocardial infarction: a retrospective analysis of nationwide registry data

**Hafsah Nabi[1], Rasmus Rørth[1], Daniel H. Tajchman [1], Lene Holmvang[1], Christian Torp-Pedersen[2,3], Gunnar Gislason [4,5,6], Emil L. Fosbøl[1], Lars Køber[1], and Rikke Sørensen[1]***

[1]Department of Cardiology, Copenhagen University Hospital, Afsnit 2142, Opgang 2, 14. Sal, Inge Lehmanns vej 7, 2100 København Ø, Denmark; [2]Department of Cardiology and Epidemiology/Biostatistics, Aalborg University Hospital, Hobrovej 18-22, 9000 Aalborg, Denmark; [3]Department of Health Science and Technology, Aalborg University, Fredrik Bajers Vej 7 D2, 9220 Aalborg Øst, Denmark; [4]Department of Cardiology, Copenhagen University Hospital, Herlev and Gentofte, Gentofte Hospitalsvej 6, 3. Sal, 2900 Hellerup, Denmark; [5]The Danish Heart Foundation, Vognmagergade 7, 3.sal, 1120 København K, Denmark; and [6]The National Institute of Public Health, University of Southern Denmark, Studiestræde 6, 1455 København K, Denmark

*Received 2 May 2019; revised 10 June 2019; editorial decision 27 June 2019; accepted 3 July 2019; online publish-ahead-of-print 5 July 2019*

**Aims** The aim of this study was to describe the use of antithrombotic therapy following a bleeding event among patients with myocardial infarction (MI), and the associated risk of major adverse cardiac events (MACE).

**Methods and results** Using Danish nationwide registries, patients hospitalized with a bleeding event within 1 year after MI were identified. Antithrombotic treatment with aspirin, clopidogrel, and/or vitamin K antagonists (VKA) was determined at the bleeding and at Day 90 and 180 post-bleed. Based on guidelines, patients were stratified into four groups: expected, reduced, discontinued, or intensified treatment. Risk of MACE (ischaemic stroke, MI, or death) within the first year was assessed by Cox proportional hazard models. A total of 3324 patients with a bleeding after MI were included. At Day 90 post-bleed, 1052 (31.7%) received expected antithrombotic treatment, 1301 (39.2%) reduced, 164 (4.9%) intensified, and 807 (24.3%) no treatment. Major adverse cardiac events occurred in 637 (19.2%) patients. With dual antiplatelet therapy as reference, adjusted hazard ratios for MACE were: aspirin 1.81 (1.06–3.09), clopidogrel 1.08 (0.64–1.82), VKA 1.08 (0.47–2.48), VKA + aspirin 1.97 (0.95–4.07), VKA + clopidogrel 0.26 (0.03–1.91), triple 1.73 (0.50–5.95), and no treatment 1.93 (1.11–3.36).

**Conclusion** The majority of MI patients reduced or discontinued their antithrombotic therapy post-bleed. Patients in monotherapy with aspirin or no treatment post-bleed had a higher risk of MACE Further studies of optimal antithrombotic treatments after a bleed are needed.

**Keywords** Myocardial infarction • Bleeding • Antithrombotic treatment

## Introduction

Antithrombotic therapy is a cornerstone of treatment in patients with acute myocardial infarction (MI).[1,2] Along with an early invasive strategy of coronary angiography and revascularization, antiplatelet treatments have reduced the incidence of recurrent thrombotic events and death.[3] However, many MI patients have additional indications for oral anticoagulation (OAC), i.e. atrial fibrillation (AF) or mechanical prosthetic heart valves,[3,4] and combinations of antithrombotic drugs are widely used.[5,6] In addition to the desired antithrombotic effect, antithrombotic pharmacotherapy is associated with an increased risk of bleeding, this risk is accentuated with the number of drugs used, and with certain combinations.[5] Several randomized trials have shown 30 days risk of major bleeding of 1–8%

* Corresponding author. Tel: +45 23962884, Email: rikke.soerensen@regionh.dk

among MI patients, whereas observational studies suggest an even higher bleeding rate up to 12%.[7–9]

It is well-established that patients who experience a bleeding have a higher risk of recurrent thrombotic events and death following the bleed.[10–13] Discontinuation of antithrombotic drugs leading to progressive recovery of platelet function and coagulation activity has been put forward as one of the underlying mechanisms. However, the clinical use of antithrombotic treatment in MI patients after a bleeding event is sparsely described. In addition, it is unknown, whether there is an association between antithrombotic treatment strategy post-bleed and the risk of recurrent thrombotic events and death.

The purpose of this study was to describe antithrombotic treatment therapy after a bleeding event among MI patients and in addition to assess the associated risk of major adverse cardiac events (MACE).

# Methods

## Data sources

This study was conducted by use of four nationwide registries, which were linked on an individual level by a unique personal identification number: (i) Danish National Patient Registry: contains information about all hospital admissions since 1978 and the associated discharge diagnoses according to the International Classification of Diseases (ICD-8 and ICD-10). (ii) The Danish Registry of Medicinal Product Statistics (The National Prescription Register): holds information about all claimed prescriptions since 1995. This includes information about date of dispensing, total quantity, strength, and the international anatomical therapeutic chemical classification system (ATC) code. (iii) The Danish Civil Registry: holds information on vital status, residency, migration, and ancestry of each Danish citizen. (iv) The Danish Registry of Causes of Death: contains information on death since 1970.

## Ethics

Registry studies in which individuals cannot be identified do not require ethical approval in Denmark. This study was approved by the Danish Data Protection Agency (No. 2007-58-0015; internal reference: GEH 2014-014, I-Suite no. 02732).

## Study population

By use of the Danish National Patient Registry, we identified patients aged 30 years or above who were hospitalized with first time MI (ICD-10 code I21 or I22) between the years 2000 and 2012. We included those admitted with a bleeding event within the first year post-MI. Inclusion date was the day of hospital admission due to bleeding. A bleeding admission was defined as admission to hospital with a bleeding diagnosis (ICD-10 codes for bleeding diagnoses listed in Supplementary material online, *Appendix I*).[14,15] The period of 1 year was chosen as patients during this period are recommended intensified antithrombotic treatment. Patients, who were in no antithrombotic treatment at the bleeding event were excluded. No treatment was defined as no claimed prescriptions/no tablets available from previous claimed prescriptions. Furthermore, patients, who died within 90 days post-bleed, were excluded to avoid immortal lifetime bias.[16] A flowchart is shown as *Figure 1*.

## Comorbidity and pharmacotherapy

Hospitalizations within the year prior to the bleeding were used to define comorbidities according to the Modified Ontario acute MI mortality prediction rules.[17] Because of low sensitivity of heart failure diagnoses, claimed prescriptions of loop diuretics within 90 days before admission as a proxy for heart failure.[18] Patients with claimed prescriptions for glucose-lowering agents were considered to have diabetes. Patients were classified by percutaneous coronary intervention (PCI), using the Danish procedure codes KFNG02 and KFNG05. Baseline pharmacotherapy (angiotensin-converting enzyme-inhibitors, beta-blockers, antidiabetics, PPI, NSAIDs, loop diuretics, spironolactone, and statins) was assessed, if a prescription was dispensed within 180 days prior to the bleeding event. Likewise, prescriptions of antithrombotics were used to assess antithrombotic treatment regimen.[5,19] Because the inclusion period was from 2000 to 2012 only 5.4% of the MI patients received prasugrel/ticagrelor or NOAC after the MI and we chose to exclude these patients to uniform the population.[AQ: Please spell out NOAC, PPI, NSAIDs (if necessary).]

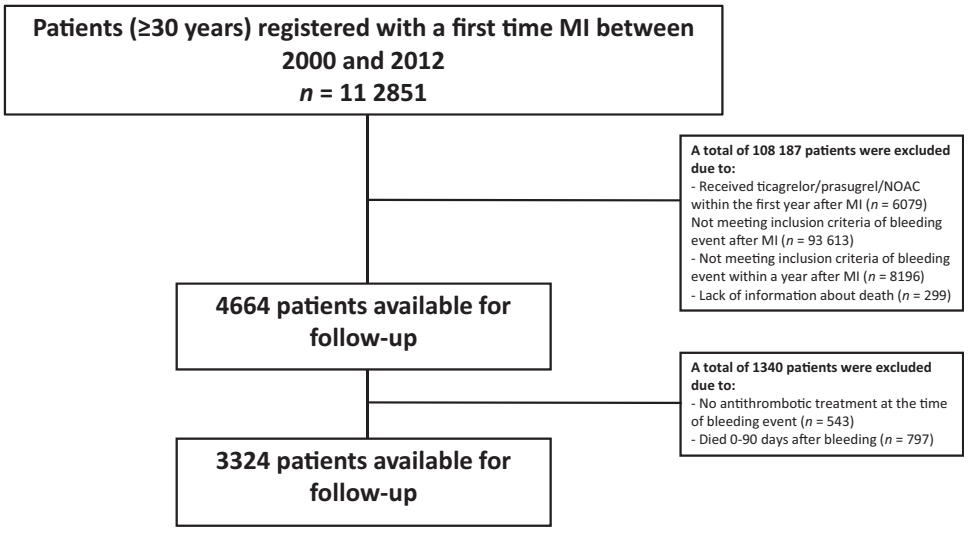


**Figure 1** A flowchart of patient selection.

## Endpoints

The following endpoints were defined:

(1) *Antithrombotic* treatment at the following time points: at baseline, first claimed antithrombotic regimen within 90 days post-bleed, at Day 90 and Day 180 post-bleed.

(2) *Claimed antithrombotic treatment vs. expected treatment*: Patients were classified in the following groups: expected treatment, reduced treatment, no treatment, or intensified treatment. The ongoing antithrombotic treatment was evaluated at baseline, at the first claimed regimen post-bleed, at Day 90 and Day 180 post-bleed.

The following criteria were used to define expected regimens:

- *Antiplatelet therapy:* According to Guidelines 12 months treatment with dual antiplatelet therapy (DAPT) was expected after the MI diagnose. After 12 months, patients were expected to be in lifelong monotherapy with aspirin or clopidogrel, unless they had an indication of OAC.[3,20,21] If the patient had an elective PCI within the first year post-MI, the DAPT period was extended 6 months after the date of PCI.[22]
- *Oral anticoagulation:* Lifelong therapy of OAC was expected in patients with a diagnosis of mechanical heart valve, recurrent pulmonary embolism/deep venous thrombosis (≥1 event) and/or AF and $CHA_2DS_2$-VASc-score ≥1 at inclusion. In patients with first time pulmonary embolism or deep venous thrombosis, 6 months of OAC was expected (diagnose codes and definition of CHA2DS2-VASc in Supplementary material online, *Appendix I*).
- *Combinations of antiplatelets and oral anticoagulation:* OAC and DAPT were expected for 1 year after the MI, if the indication of OAC was present at the MI diagnosis. If the indication of oral coagulation arose after the MI, or if it was temporary (first time pulmonary embolism/deep venous thrombosis) the expected period was adjusted accordingly.

The following criteria were used to define reduced treatment: The patient was classified to have reduced treatment if he/she claimed less antithrombotic medication than expected (Supplementary material online, *Figure S2*) and intensified treatment: The patient was classified to have intensified treatment if he/she claimed more antithrombotic medication than expected (Supplementary material online, *Figure S2*).

(3) *Associated risk of MACE:* The associated risks of MACE were defined as recurrent MI, ischaemic stroke, or all-cause death, within the first year post-bleed, calculated from Day 90 post-bleed. Definitions listed in the Supplementary material online, *Appendix*.[23] Patients were censored at first event.

## Additional analyses

A sub-analysis of recurrent bleeding events was carried out, starting from Day 90 post-bleed. A recurrent bleeding event was defined using the same ICD-10 discharge codes as at baseline (Supplementary material online, *Appendix I*). Patients were censored at first event.

Furthermore, a sub-analysis of the patients with or without OAC at baseline and related outcomes were assessed.

## Statistical analyses

Categorical variables are presented in number and percentages, and continuous variables are presented with a mean/standard deviation or median/interquartile ranges. The antithrombotic treatments post-bleed were assessed as first regimen within 90 days post-bleed, at Day 90 and Day 180 post-bleed. Sensitivity analyses on shorter intervals were tested (antithrombotic treatment at Day 30 and Day 60), but due to largely varying prescription lengths, we chose 90 days as the period. To assess the risk of MACE we used two different Cox Proportional Hazard Models. One included the antithrombotic drug exposure groups as time-varying covariates. Days where the patients were admitted was covered by medicine supplied by the hospital. With this model, patients were only considered at risk for each exposure group while taking the corresponding antithrombotic drug or were without treatment. Each patient was allowed in one drug exposure group at a time; however, it was possible to change exposure group based on claimed prescriptions, as done previously.[5,19] The analyses were adjusted for relevant covariates as age groups, sex, comorbidity, concomitant medical therapy, and PCI status. Due to non-linear distribution, age was included as age groups of <60 years, 60–70 years, 70–80 years, and >80 years. The second model included information of antithrombotic treatment after the bleeding categorized in the following categories: no change, discontinued, reduced, or intensified treatment. This model was adjusted for age groups, sex, comorbidity, concomitant medical therapy, and PCI status. The models were tested for absence of relevant interactions and found to be valid. Results are presented as hazard ratios with 95% confidence intervals.

All statistical analyses were done using SAS version 9.4 (SAS institute Inc., Cary, NC, USA).

# Results

This study included 3324 patients with first-time MI, who were admitted with a bleeding event within 1-year post-MI (*Figure 1*). *Table 1* shows the baseline characteristics. Mean age was 71.2 (SD 11.5) for men and 75.4 (SD 11.4) for women.

## Antithrombotic treatment post-bleed

Mean time from bleeding to claimed prescription of antithrombotic treatment varied from 24.2 days (SD 25.3) for triple therapy to 42.2 days (SD 26.8) for monotherapy with aspirin (*Table 2*). The majority of patients (78.8%) were in monotherapy with aspirin or clopidogrel or in no treatment within the first 90 days post-bleed. Treatment patterns at Day 90 and Day 180 post-bleed are shown in *Table 2*. At Day 180 post-bleed, the largest group was in monotherapy with aspirin (33.0%) followed by DAPT (24.2%). *Table 3* shows the proportion of patients in expected, reduced, intensified, or no treatment. A discontinuation or reduction was observed in >70% of the patients after the bleeding event. Baseline characteristics according to expected treatment are presented in the Supplementary material online, *Tables S1a*, *S1b*, and *S1c*. Comparing patients with or without OAC: Patients without OAC were more likely to be in expected treatment (at all time points), more discontinued treatment at first regimen and Days 90, whereas patients with OAC at all time points were more likely to received reduced or intensified treatment. Numbers are shown in Supplementary material online, *Table S3*.

## Major adverse cardiac events

A total of 637 (19.2%) patients experienced MACE: 149 (4.5%) had a recurrent MI, 73 (2.1%) had a stroke, and 415 (12.5%) died. Results from the Cox analyses are shown in *Figure 2A and B*. Compared with DAPT, no antithrombotic treatment and monotherapy with aspirin were associated with an increased risk of MACE, the remaining antithrombotic exposure groups were not significantly associated with an increased or decreased 1-year risk of MACE. Other variables associated with increased risk of MACE were: increasing age, renal

**Table 1 Baseline, according to antithrombotic treatment at bleeding event**

| | | | Monotherapy | | | Dual therapy | | Triple therapy |
|---|---|---|---|---|---|---|---|---|
| | All patients (*n* = 3324) | Aspirin (*n* = 888) | Clopidogrel (*n* = 332) | VKA (*n* = 62) | Aspirin + clopidogrel (*n* = 1536) | Aspirin + VKA (*n* = 354) | Clopidogrel + VKA (*n* = 67) | Aspirin + clopidogrel + VKA (*n* = 85) |
| Inclusion year, *n* (%) | | | | | | | | |
| 2000–2003 | 871 (26) | 453 (51) | 58 (18) | 22 (35) | 205 (13) | 120 (34) | 8 (12) | 5 (6) |
| 2004–2006 | 970 (29) | 201 (23) | 113 (34) | 9 (15) | 503 (33) | 99 (28) | 22 (33) | 23 (27) |
| 2007–2009 | 899 (27) | 139 (15) | 101 (30) | 14 (23) | 503 (33) | 91 (26) | 19 (28) | 32 (38) |
| 2010–2012 | 584 (18) | 95 (11) | 60 (18) | 17 (27) | 325 (21) | 44 (12) | 18 (27) | 25 (29) |
| Demographics | | | | | | | | |
| Men, *n* (%) | 2176 (65) | 542 (61) | 218 (66) | 39 (63) | 1037 (68) | 230 (65) | 49 (73) | 61 (71) |
| Age (men), mean (SD) | 71.2 (11.5) | 73.4 (11.9) | 70.9 (11.8) | 73.2 (12.2) | 69.6 (11.6) | 73.3 (9.4) | 72.2 (6.9) | 71.5 (9.4) |
| median (IQR) | 72.2 (15.9) | 75.1 (16.0) | 72.4 (15.6) | 74.9 (13.0) | 70.3 (16.7) | 74.9 (12.1) | 71.6 (9.2) | 73.0 (12.0) |
| Age (women), mean (SD) | 75.4(11.4) | 77.9 (11.4) | 76.2 (9.5) | 76.0 (9.8) | 73.2 (11.8) | 75.6 (10.9) | 75.9 (6.9) | 79.5 (9.1) |
| median (IQR) | 77.3(14.6) | 80.0 (15.2) | 78.5 (11.9) | 75.3 (11.3) | 74.6 (16.6) | 77.9 (13.4) | 76.3 (11.9) | 82.1 (11.3) |
| Comorbidity, *n* (%) | | | | | | | | |
| Congestive heart failure | 892 (27) | 261 (29) | 89 (27) | 20 (32) | 323 (21) | 131 (37) | 31 (46) | 37 (44) |
| Cerebrovascular disease | 374 (11) | 131 (15) | 36 (11) | 15 (24) | 125 (8) | 41 (12) | 15 (22) | 11 (13) |
| Diabetes with complication | 318 (9) | 89 (10) | 40 (12) | 10 (16) | 124 (8) | 38 (11) | 7 (10) | 10 (12) |
| Atrial fibrillation | 1020 (31) | 247 (28) | 65 (20) | 47 (76) | 275 (18) | 273 (77) | 48 (72) | 65 (76) |
| Other cardiac dysrhythmias | 268 (8) | 58 (7) | 14 (4) | 11 (18) | 106 (7) | 59 (17) | 8 (12) | 12 (14) |
| Recurrent VTE (>1) | 51 (2) | 5 (1) | 6 (2) | 5 (8) | 14 (1) | 16 (5) | 1 (1) | 4 (5) |
| Acute renal failure | 102 (3) | 36 (4) | 8 (2) | 3 (5) | 38 (3) | 14 (4) | 1 (1) | 2 (2) |
| Chronic renal failure | 163 (5) | 55 (6) | 18 (5) | 4 (6) | 55 (4) | 21 (6) | 3 (4) | 7 (8) |
| Malignant disease | 225 (7) | 73 (8) | 29 (9) | 3 (5) | 86 (6) | 30 (8) | 3 (4) | 1 (1) |
| Shock | 27 (1) | 6 (1) | 2 (1) | 2 (3) | 11 (0.7) | 4 (1) | 1 (1) | 1 (1) |
| Pulmonary oedema | 77 (2) | 34 (4) | 8 (2) | 3 (5) | 21(1) | 9 (3) | 2 (3) | 0 (0) |
| PCI | 1437 (43) | 162 (18) | 171 (52) | 7 (11) | 920 (60) | 99 (28) | 34 (51) | 44 (52) |
| Pharmacotherapy, *n* (%) | | | | | | | | |
| ACEI | 1948 (59) | 465 (52) | 211 (64) | 32 (52) | 880 (57) | 245 (69) | 55 (82) | 60 (71) |
| Anti-diabetics | 468 (14) | 133 (15) | 56 (17) | 15 (24) | 178 (12) | 59 (17) | 13 (19) | 14 (16) |
| Beta-blocker | 2639 (79) | 611 (69) | 278 (84) | 47 (76) | 1274 (83) | 294 (83) | 59 (88) | 76 (89) |
| Loop-diuretics | 1439 (43) | 445 (50) | 142 (43) | 38 (61) | 496 (32) | 226 (64) | 43 (64) | 49 (58) |
| Spironolactone | 395 (12) | 121 (14) | 34 (10) | 6 (10) | 129 (8) | 73 (21) | 19 (28) | 13 (15) |
| NSAID | 669 (20) | 194 (22) | 63 (19) | 9 (15) | 328 (21) | 55 (16) | 9 (13) | 11 (13) |
| PPI | 1090 (33) | 300 (34) | 120 (36) | 20 (32) | 490 (32) | 108 (31) | 24 (36) | 28 (33) |
| Statins | 2497 (75) | 474 (53) | 280 (84) | 26 (42) | 1331 (87) | 255 (72) | 60 (90) | 71 (84) |
| First bleeding event | | | | | | | | |
| Cerebral, *n* (%) | 132 (4) | 44 (5) | 10 (3) | 6 (10) | 54 (3) | 12 (3) | 3 (5) | 3 (4) |
| Gastrointestinal, *n* (%) | 925 (28) | 259 (29) | 88 (27) | 10 (16) | 441 (29) | 92 (26) | 12 (18) | 23 (27) |
| Respiratory tract, *n* (%) | 838 (25) | 144 (16) | 86 (26) | 26 (42) | 416 (27) | 111 (31) | 24 (36) | 31 (36) |
| Urogenital, *n* (%) | 720 (22) | 197 (22) | 78 (23) | 7 (11) | 352 (23) | 62 (18) | 11 (16) | 13 (15) |
| Anaemia from acute or chronic bleeding, *n* (%) | 709 (21) | 244 (28) | 70 (21) | 13 (21) | 273 (18) | 77 (22) | 17 (25) | 15 (18) |
| Time from MI to bleeding (days), mean (SD) median (IQR) | 145 (104.6) 124 (179.0) | 149(108.1) 132 (187.5) | 165(99.4) 156(160.5) | 158(103.5) 150 (178.0) | 139 (104.0) 110 (175.0) | 139 (105.3) 115.0 (168.0) | 165 (97.5) 154.0 (159.0) | 143 (93.3) 112.0 (131.0) |

failure, heart failure, malignancy, and use of proton pump inhibitors. In relation to expected treatment discontinuation was at all time points associated with increased risk of MACE. At Day 90, intensified treatment was also associated with increased risk of MACE, but not at first regimen or at Day 180. In the subgroup analysis of patients with OAC no treatment at Day 90 was associated with a higher risk of MACE, as was both no and reduced treatment at Day 180.

**Table 2** Antithrombotic treatments post-bleed

| Antithrombotic regimen | At the time of bleeding event (baseline) (*n* = 3324), *n* (%) | First antithrombotic regimen within 90 days post-bleed[a] (*n* = 3324), *n* (%) | Antithrombotic regimen Day 90 post-bleed (*n* = 3324), *n* (%) | Antithrombotic regimen Day 180 post-bleed (*n* = 3123), *n* (%) |
|---|---|---|---|---|
| None | | 736 (22.1) | 807 (24.3) | 567 (18.2) |
| Aspirin | 888 (26.7) | 984 (29.6) | 820 (24.7) | 1031 (33.0) |
| Clopidogrel | 332 (9.9) | 901 (27.1) | 485 (14.6) | 396 (12.7) |
| VKAs | 62 (1.9) | 189 (5.7) | 95 (2.9) | 96 (3.1) |
| Aspirin + clopidogrel (DAPT) | 1536 (46.2) | 424 (12.8) | 870 (26.1) | 756 (24.2) |
| Aspirin + VKA | 354 (10.7) | 54 (1.6) | 129 (3.9) | 176 (5.6) |
| Clopidogrel + VKA | 67 (2.0) | 22 (0.6) | 47 (1.4) | 46 (1.5) |
| Aspirin + clopidogrel + VKA | 85 (2.5) | 14 (0.4) | 71 (2.1) | 55 (1.8) |

Aspirin: 42.2 ± 26.8 (median 41).
Clopidogrel: 31.5 ± 24.3 (median 26).
VKAs: 34.4 ± 22.9 (median 32).
Aspirin + clopidogrel (DAPT): 35.8 ± 26.4 (median 32).
Aspirin + VKA: 34.7 ± 26.4 (median 31).
Clopidogrel + VKA: 29.2 ± 21.4 (median 26).
Triple therapy: 24.2 ± 25.3 (median 13).
[a]Time from bleeding event to prescription claim [days, mean (SD)].

**Table 3** Assessment of antithrombotic treatment post-bleed

| | At the time of bleeding event (baseline) (*n* = 3324), *n* (%) | First regimen within 90 days post-bleed (*n* = 3324), *n* (%) | Day 90 post-bleed (*n* = 3324), *n* (%) | Day 180 post-bleed (*n* = 3123), *n* (%) |
|---|---|---|---|---|
| Expected treatment | 1555 (46.8) | 565 (17.0) | 1052 (31.7) | 1185 (37.9) |
| Discontinued treatment | — | 736 (22.1) | 807 (24.3) | 567 (18.2) |
| Reduced treatment | 1374 (41.3) | 1914 (57.6) | 1301 (39.2) | 1089 (34.9) |
| Intensified treatment | 395 (11.9) | 109 (3.2) | 164 (4.9) | 282 (9.0) |

## Recurrent bleeding events

A total of 431 (12.9%) patients had a recurrent bleeding event within 1 year. The distribution was following: urogenital bleeding event in 115 patients (3.5%), gastrointestinal bleeding 108 patients (3.2%), anaemia of acute or chronic bleeding 95 patients (2.8%), respiratory tract bleedings 88 patients (2.6%), and cerebral bleeding in 25 patients (0.8%). The Cox analyses did not show any significant associations between antithrombotic treatment regimen post-bleed and risk of recurrent bleeding events (Supplementary material online, *Table S1*), expect in the subgroup of patients with OAC, where no treatment at first regimen and Day 90 was associated with a lower risk of bleeding.

# Discussion

This study is one of the first to describe the pattern of antithrombotic treatment after a bleeding event among patients with recent MI and the associated risk of MACE. The main findings are: (i) The majority of patients (79.7%) either discontinued or were reduced in their antithrombotic treatment within the first 90 days after the bleed. At Day 90 and Day 180 post-bleed, this number had declined; however, more than 50% of the patients were still in no or reduced antithrombotic treatment. (ii) We found that the risk of MACE was significantly increased among patients, who were in no antithrombotic treatment or monotherapy with aspirin post-bleed. (iii) We found no associations between the antithrombotic treatment post-bleed and risk of recurrent bleeding events.

Bleeding is a frequent complication among patients with acute coronary syndrome (ACS); up to 30% experience bleeding events of varying severity during the hospitalization.[11,24,25] Patients who bleed are in our and in other studies older and have more comorbidities, including a history of prior stroke, heart failure, diabetes mellitus, and PCI prior to the event.[8,9] Previous studies have investigated the prognostic impact of bleeding episodes among patients with ACS, and have reported, that a major bleeding event was associated with a five-fold increase in risk of death during the first 30 days.[10] The association was weaker between 30 days and 6 months, however, mortality was still increased, and a similar

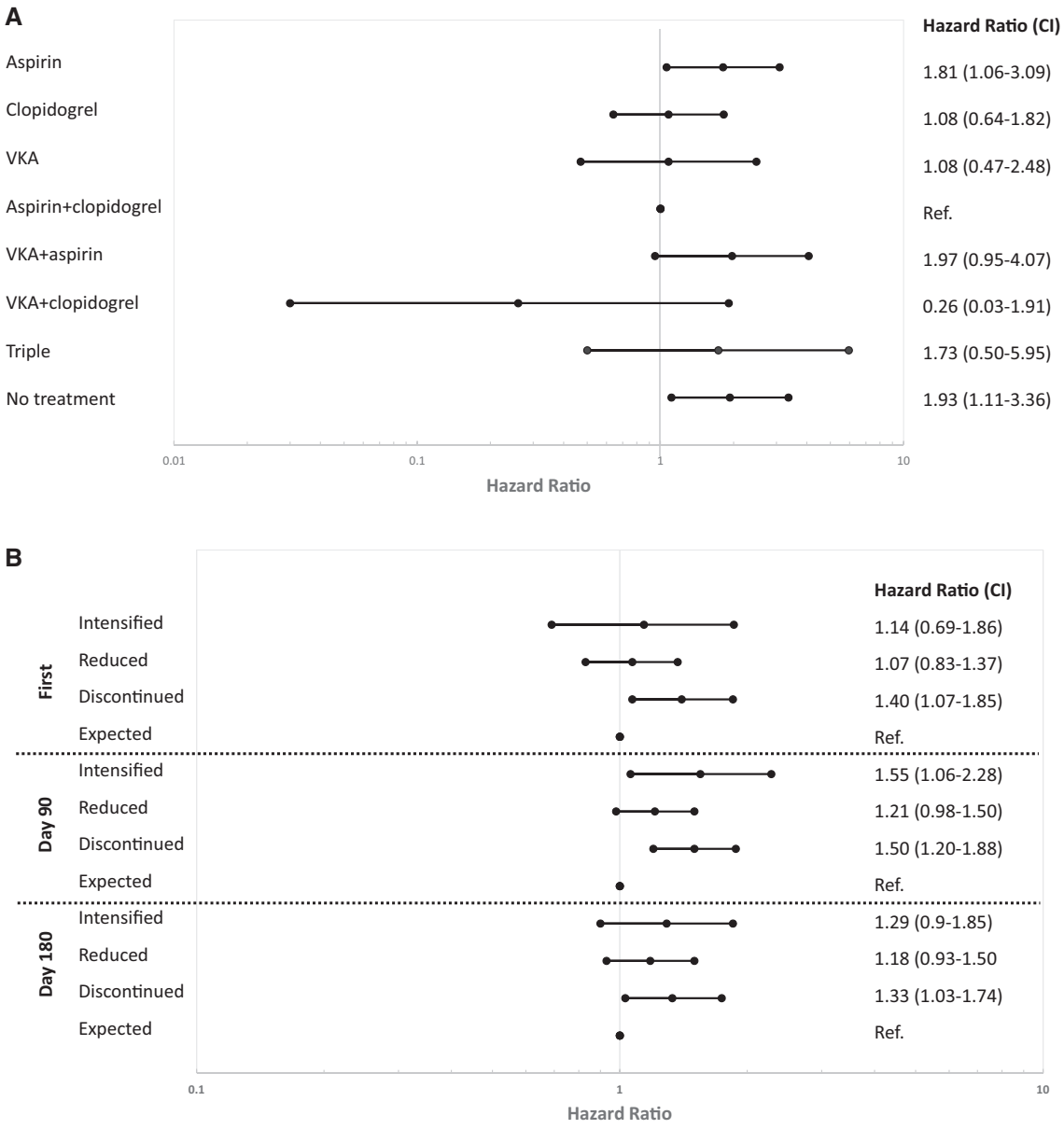


**Figure 2** (*A* and *B*) Adjusted 1-year risk of major adverse cardiac events in myocardial infarction patients with a bleeding event risk of within the first year post-bleed. (*A*) Risk of major adverse cardiac events (recurrent myocardial infarction, ischaemic stroke, or death) related to different antithrombotic treatments within the first year post-bleed. (The Cox proportional hazard model had the antitrombotic combinations included as time-dependent variables. The model was adjusted for age groups, sex, comorbidity, concomitant medical therapy, and percutaneous coronary intervention status.) (*B*) Risk of major adverse cardiac events (recurrent myocardial infarction, ischaemic stroke, or death) related to expected treatment within the first year post-bleed. (The Cox proportional hazard model was adjusted for age groups, sex, comorbidity, concomitant medical therapy, and percutaneous coronary intervention status.)

pattern was seen for recurrent ischaemic events (MI and stroke).[10] Another study by Rao *et al.*[11] showed a stepwise increase in 30-day and 6-month mortality associated with increasing bleeding severity. These findings have been supported by others.[8,26,27] Thus major bleeding is associated with a higher short-term and long-term mortality, and even minimal bleeding is of clinical significance.[26,28]

Lopes *et al.*[9] reported a lower likelihood of receiving clopidogrel at discharge after an in-hospital bleeding among ACS patients treated with a PCI, whereas there was no significant difference in the use of aspirin. In a study by Chan *et al.*,[29] discharge antithrombotic use was examined among 8582 ACS patients with in-hospital bleeding. Almost 1 of 10 patients with bleeding was discharged without antiplatelets, and these patients had a higher risk of death, MI, and stroke at

6 months, compared with patients receiving antiplatelets at discharge. This supports our findings that absence of antithrombotic therapy post-bleed may contribute to the increased risk of ischaemic events.[29] Wang *et al.*[30] found differences in antiplatelet use after bleeding during index acute MI hospitalization, a difference that persisted up to 6 months, but disappeared after 1 year. Our results also indicate that some patients resume their antithrombotic treatment within 6 months post-bleed.

The Patterns of non-adherence to Antiplatelet Regimens in stented Patients (PARIS) study investigated DAPT cessation among patients undergoing PCI. They found that approximately 3% had ceased DAPT within 30 days and 20% within the first year after PCI.[31] The majority disrupted DAPT due to non-compliance or bleeding. Physician recommended cessation was associated with a lower risk of MACE, while no difference was found among the group of temporary interruption due to surgical procedure. A disruption due to bleeding or non-compliance was associated with a higher risk of MACE.[31]

Clearly, it is a clinical challenge to assess the risk and benefit of antithrombotic treatment after a bleeding event. Several studies have published recommendations on the acute management of bleeding; however, less is known about the management of antithrombotic treatment after the bleeding event among MI patients. The European Society of Cardiology recently published a consensus paper, where it is recommended to consider resumption of antithrombotic drugs in patients with a clear indication, except if the bleeding is life-threatening.[32] Our findings support this approach as we found increased risk of MACE among patients receiving no treatment/or aspirin monotherapy post-bleed. Our study demonstrates that it is most common to reduce/or discontinue treatment after the bleeding event, and resume treatment after a period of time, a practice that is supported by the same consensus document.

The patients that discontinued or reduced treatment were older, with more comorbidity as congestive heart failure, cerebrovascular disease, renal failure, and AF compared with the patients in expected treatment. In addition, a lower number had been treated with PCI. Patients treated with OAC were likewise older with more comorbidity compared with those in DAPT and were more likely to received reduced or intensified treatment at all time-point. This probably indicates a clinical dilemma where patients have both high risk of bleeding and thrombotic events. At Day 90, we found that intensified treatment was also associated with increased risk of MACE, but not at other time points. The findings are in a small patient group and might be explained by patients initiating OAC due to AF and concurrent increased risk stroke.[4]

## Strengths and limitations

The main strength of our study is the completeness of data with a large nationwide unselected cohort of MI patients with complete information of prescriptions. However, our study has several limitations. We only included MI patients who were admitted for a bleeding and survived >90 days, thus our population represents a small proportion of an all-comer MI population and minor bleedings are not considered. Our data do not comprise reasons for prescription or cessation of medication, which is important in evaluation of the risk/benefit among different patient groups. Also, the accuracy of the antithrombotic regimens post-bleed is dependent on a prescription claim, and indirectly on the number of tablets from the previous prescription. If patients had claimed a large number of tablets before the bleeding, they would have a longer period until the next prescription but might have initiated treatment sooner, with tablets available from the previous purchase. We have implemented a 90-day period after bleeding to minimize this problem. The observational study design increases the risk of residual confounding, even after adjustment. At last, MACE was defined as admittance to a Danish hospital with recurrent MI, stroke, or death. Those patients not admitted with MI or stroke/or admitted outside Denmark could not be classified, however, the problem is considered minor, and data on vital status was complete in all patients.

# Conclusion

In conclusion, among patients with a bleeding post-MI, the majority reduced or discontinued antithrombotic therapy post-bleed. A higher risk of MACE was related to discontinuation of antithrombotic therapy or reduction to monotherapy with aspirin. Further studies of optimal antithrombotic treatments after a bleeding event are needed.

# Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

**Conflict of interest:** none declared.

## References


1. Lewis HD, Davis JW, Archibald DG, Steinke WE, Smitherman TC, Doherty JE, Schnaper HW, LeWinter MM, Linares E, Pouget JM, Sabharwal SC, Chesler E, DeMots H 3rd. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of a Veterans Administration Cooperative Study. *N Engl J Med* 1983;**309**:396–403.
2. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;**345**:494–502.
3. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns W, Zahger D; ESC Committee for Practice Guidelines. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the task force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2011;**32**:2999–3054.
4. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GY, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL, Zeppenfeld K. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016;**18**:1609–1678.
5. Sorensen R, Hansen ML, Abildstrom SZ, Hvelplund A, Andersson C, Jorgensen C, Madsen JK, Hansen PR, Køber L, Torp-Pedersen C, Gislason GH. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. *Lancet* 2009;**374**:1967–1974.

6. Manzano-Fernández S, Pastor FJ, Marín F, Cambronero F, Caro C, Pascual-Figal DA, Garrido IP, Pinar E, Valdés M, Lip GYH. Increased major bleeding complications related to triple antithrombotic therapy usage in patients with atrial fibrillation undergoing percutaneous coronary artery stenting. *Chest* 2008;**134**:559–567.
7. CURRENT-OASIS 7 Investigators, Mehta SR, Bassand JP, Chrolavicius S, Diaz R, Eikelboom JW, Fox KA, Granger CB, Jolly S, Joyner CD, Rupprecht HJ, Widimsky P, Afzal R, Pogue J, Yusuf S. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *N Engl J Med* 2010;**363**:930–942.
8. Budaj A, Eikelboom JW, Mehta SR, Afzal R, Chrolavicius S, Bassand JP, Fox KA, Wallentin L, Peters RJ, Granger CB, Joyner CD, Yusuf S; OASIS 5 Investigators. Improving clinical outcomes by reducing bleeding in patients with non-ST-elevation acute coronary syndromes. *Eur Heart J* 2009;**30**:655–661.
9. Lopes RD, Subherwal S, Holmes DN, Thomas L, Wang TY, Rao SV, Magnus Ohman E, Roe MT, Peterson ED, Alexander KP. The association of in-hospital major bleeding with short-, intermediate-, and long-term mortality among older patients with non-ST-segment elevation myocardial infarction. *Eur Heart J* 2012;**33**:2044–2053.
10. Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation* 2006;**114**:774–782.
11. Rao SV, O'Grady K, Pieper KS, Granger CB, Newby LK, Van de Werf F, Mahaffey KW, Califf RM, Harrington RA. Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes. *Am J Cardiol* 2005;**96**:1200–1206.
12. Rao SV. Bleeding as a predictor of mortality risk. *Rev Cardiovasc Med* 2006;**7(Suppl 3)**:S12–S18.
13. Staerk L, Fosbøl EL, Lamberts M, Bonde AN, Gadsbøll K, Sindet-Pedersen C, Holm EA, Gerds TA, Ozenne B, Lip GYH, Torp-Pedersen C, Gislason GH, Olesen JB. Resumption of oral anticoagulation following traumatic injury and risk of stroke and bleeding in patients with atrial fibrillation: a nationwide cohort study. *Eur Heart J* 2018;**39**:1698–1705a.
14. Buresly K, Eisenberg MJ, Zhang X, Pilote L. Bleeding complications associated with combinations of aspirin, thienopyridine derivatives, and warfarin in elderly patients following acute myocardial infarction. *Arch Intern Med* 2005;**165**:784–789.
15. Jackevicius CA, Tu JV, Demers V, Melo M, Cox J, Rinfret S, Kalavrouziotis D, Johansen H, Behlouli H, Newman A, Pilote L. Cardiovascular outcomes after a change in prescription policy for clopidogrel. *N Engl J Med* 2008;**359**:1802–1810.
16. Suissa S. Immortal time bias in pharmaco-epidemiology. *Am J Epidemiol* 2008;**167**:492–499.
17. Tu JV, Austin PC, Walld R, Roos L, Agras J, McDonald KM. Development and validation of the Ontario acute myocardial infarction mortality prediction rules. *J Am Coll Cardiol* 2001;**37**:992–997.
18. Gislason GH, Rasmussen JN, Abildstrøm SZ, Gadsbøll N, Buch P, Friberg J, Rasmussen S, Køber L, Stender S, Madsen M, Torp-Pedersen C. Long-term compliance with beta-blockers, angiotensin-converting enzyme inhibitors, and statins after acute myocardial infarction. *Eur Heart J* 2006;**27**:1153–1158.
19. Andersson C, Vaag A, Selmer C, Schmiegelow M, Sørensen R, Lindhardsen J, Gislason GH, Køber L, Torp-Pedersen C. Risk of cancer in patients using glucose-lowering agents: a nationwide cohort study of 3.6 million people. *BMJ Open* 2012;**2**:e000433.
20. Bertrand ME, Simoons ML, Fox KAA, Wallentin LC, Hamm CW, McFadden E, De Feyter PJ, Specchia G, Ruzyllo W. Management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2002;**23**:1809–1840.
21. Task Force for Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of European Society of Cardiology, Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernández-Avilés F, Fox KA, Hasdai D, Ohman EM, Wallentin L, Wijns W. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J* 2007;**28**:1598–1660.
22. Silber S, Albertsson P, Aviles FF, Camici PG, Colombo A, Hamm C, Jorgensen E, Marco J, Nordrehaug JE, Ruzyłło W, Urban P, Stone GW, Wijns W; European Society of Cardiology. [Percutaneous coronary interventions. Guidelines of the European Society of Cardiology-ESC]. *Kardiol Pol* 2005;**63**:265–320; discussion 321–323.
23. Helweg-Larsen K. The Danish Register of causes of death. *Scand J Public Health* 2011;**39**:26–29.
24. Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, Wang TY, Gibler WB, Ohman EM, Roe MT, Pollack CV, Peterson ED, Alexander KP. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score. *Circulation* 2009;**119**:1873–1882.
25. Berger JS, Frye CB, Harshaw Q, Edwards FH, Steinhubl SR, Becker RC. Impact of clopidogrel in patients with acute coronary syndromes requiring coronary artery bypass surgery: a multicenter analysis. *J Am Coll Cardiol* 2008;**52**:1693–1701.
26. Ben-Dor I, Torguson R, Scheinowitz M, Li Y, Delhaye C, Wakabayashi K, Maluenda G, Syed AI, Collins SD, Gonzalez MA, Gaglia MA, Xue Z, Kaneshige K, Satler LF, Suddath WO, Kent KM, Pichard AD, Waksman R. Incidence, correlates, and clinical impact of nuisance bleeding after antiplatelet therapy for patients with drug-eluting stents. *Am Heart J* 2010;**159**:871–875.
27. Yoon YH, Kim YH, Kim SO, Lee JY, Park DW, Kang SJ, Lee SW, Lee CW, Park SW, Park SJ. Impact of in-hospital bleeding according to the Bleeding Academic Research Consortium classification on the long-term adverse outcomes in patients undergoing percutaneous coronary intervention. *Catheter Cardiovasc Interv* 2015;**85**:63–71.
28. Roy P, Bonello L, Torguson R, de Labriolle A, Lemesle G, Slottow TLP, Steinberg DH, Kaneshige K, Xue Z, Satler LF, Kent KM, Suddath WO, Pichard AD, Lindsay J, Waksman R. Impact of "nuisance" bleeding on clopidogrel compliance in patients undergoing intracoronary drug-eluting stent implantation. *Am J Cardiol* 2008;**102**:1614–1617.
29. Chan MY, Sun JL, Wang TY, Lopes RD, Jolicoeur ME, Pieper KS, Rao SV, Newby LK, Mahaffey KW, Harrington RA, Peterson ED. Patterns of discharge antiplatelet therapy and late outcomes among 8,582 patients with bleeding during acute coronary syndrome: a pooled analysis from PURSUIT, PARAGON-A, PARAGON-B, and SYNERGY. *Am Heart J* 2010;**160**:1056–1064, 1064.e2.
30. Wang TY, Xiao L, Alexander KP, Rao SV, Kosiborod MN, Rumsfeld JS, Spertus JA, Peterson ED. Antiplatelet therapy use after discharge among acute myocardial infarction patients with in-hospital bleeding. *Circulation* 2008;**118**:2139–2145.
31. Mehran R, Baber U, Steg PG, Ariti C, Weisz G, Witzenbichler B, Henry TD, Kini AS, Stuckey T, Cohen DJ, Berger PB, Iakovou I, Dangas G, Waksman R, Antoniucci D, Sartori S, Krucoff MW, Hermiller JB, Shawl F, Gibson CM, Chieffo A, Alu M, Moliterno DJ, Colombo A, Pocock S. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. *Lancet* 2013;**382**:1714–1722.
32. Halvorsen S, Storey RF, Rocca B, Sibbing D, Ten Berg J, Grove EL, Weiss TW, Collet JP, Andreotti F, Gulba DC, Lip GYH, Husted S, Vilahur G, Morais J, Verheugt FWA, Lanas A, Al-Shahi Salman R, Steg PG, Huber K; ESC Working Group on Thrombosis. Management of antithrombotic therapy after bleeding in patients with coronary artery disease and/or atrial fibrillation: expert consensus paper of the European Society of Cardiology Working Group on Thrombosis. *Eur Heart J* 2017;**38**:1455–1462.