Cellular Physiology and Biochemistry

Cell Physiol Biochem 2018;50:1164-1177

DOI: 10.1159/000494543

Published online: 24 October 2018

Accepted: 16 October 2018

Original Paper

Predictors and Management of Antiplatelet-Related Bleeding Complications for Acute Coronary Syndrome in Chinese Elderly Patients

Jindong Wan[a,b] Peijian Wang[a,b] Peng Zhou[a,b] Sen Liu[a,b] Dan Wang[a,b] Jingyu Kan[a,b] Jixin Hou[a,b] Li Zuo[a,b] Shuangtao Ma[c] Yongjian Yang[d]

[a]Department of Cardiology, The First Affiliated Hospital, Chengdu Medical College, Chengdu, [b]Key Laboratory of Aging and Vascular Homeostasis of Sichuan Higher Education Institutes, Chengdu, China, [c]Division of Nanomedicine and Molecular Intervention, Department of Medicine, Michigan State University, East Lansing, MI, USA, [d]Department of Cardiology, Chengdu Military General Hospital, Chengdu, China

Key Words

Bleeding • Antiplatelet therapy • Acute coronary syndrome • Major adverse cardiac and cerebrovascular events

Abstract

Background/Aims: Bleeding complications after percutaneous coronary intervention (PCI) are strongly associated with adverse patient outcomes. However, there are no specific guidelines for the predictors and management of antiplatelet-related bleeding complications in Chinese elderly patients with acute coronary syndrome (ACS). ***Methods:*** A retrospective analysis of 237 consecutive patients (aged ≥ 75 years) with ACS who had undergone successful PCI from January 2010 to December 2016 was performed to identify predictors and management of antiplatelet-related bleeding complications. Multivariate logistic regression analysis was conducted to investigate independent predictors of antiplatelet-related bleeding complications. We defined antiplatelet-related bleeding complications as first hospitalization received long-term oral antiplatelet therapy and required hospitalization, including gastrointestinal and intracranial bleedings. ***Results:*** After multivariable adjustment, independent risk predictors of antiplatelet-related bleeding complications included female gender (odds ratio [OR]: 2.96; 95% confidence interval [CI]: 1.98 to 4.15; $P = 0.011$), body mass index (OR: 1.54; 95% CI: 1.06 to 1.94; $P = 0.034$), previous history of bleeding (OR: 4.03; 95% CI: 1.84 to 6.12; $P = 0.004$), fasting blood glucose (OR: 2.79; 95% CI: 1.23 to 4.46; $P = 0.025$), and chronic total occlusion lesion (OR: 4.69; 95% CI: 2.19 to 7.93; $P = 0.007$). Of 46 patients with antiplatelet-related bleeding complications, 54.3% were treated short-term dual antiplatelet therapy (DAPT) cessation (0–7 days) and 45.7%

J. Wan, P. Wang and P. Zhou contributed equally to this work.

Peijian Wang and Yongjian Yang

Department of Cardiology, The 1st Affiliated Hospital of Chengdu Med. College 278 Baoguang Avenue, Chengdu, Sichuan 610500 (China); Department of Cardiology, Chengdu Military General Hospital, 270 Tianhui Rd, Chengdu, Sichuan 611083 (China), E-Mail wpjmed@aliyun.com; yangyongjian38@sina.com

underwent long-term DAPT cessation (>7 days). Among these, 14 patients presented major adverse cardiac and cerebrovascular events (MACCE), whereas no re-bleeding happened over all available follow-up. The incidence of MACCE was not significantly different between the two groups one year after PCI (36.0% for short-term DAPT cessation versus 23.8% for long-term DAPT cessation, P = 0.522). ***Conclusion:*** For elderly patients with ACS, multiple factors were likely to contribute to antiplatelet-related bleeding complications, especially previous history of bleeding and chronic total occlusion lesion. Better individualized, tailored and risk-adjusted antiplatelet therapy after PCI is urgently needed in this high-risk population.

Introduction

Elderly people represent an increasing proportion of the acute coronary syndrome (ACS) population worldwide, accounting for up to a third of patients [1], and a trend also observed in Chinese elderly adults [2]. In parallel, these frail patients have frequent comorbidities, including age-related changes in cardiovascular structure and function, other organ systems dysfunction (including the kidneys, liver, skeletal muscle, and brain), and multiple medications received, exposing them to an increased risk of iatrogenic complications [3, 4]. As a result, current evidence-based practice guidelines suffer inherent gaps in providing recommendations for managing older adults with ACS, the majority of whom would not have been eligible for participation in most of the major randomized clinical trials [3]. Hence, there are currently no specific guidelines concerning the management of antiplatelet therapy for ACS in elderly patients, especially for Chinese elderly adults (≥ 75 years of age) [3, 5, 6].

Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor reduces ischaemic recurrences in patients with ACS treated with percutaneous coronary intervention (PCI), but increases bleeding [7]. In this regard, approximately half of the major bleeds in patients aged 75 years or older are gastrointestinal bleeding (GIB) [8], an uncommon but devastating complication of regular antiplatelet use is intracerebral haemorrhage (ICH) [9]. An increasing number of data indicates that the Asian population that present with ACS or undergo PCI display highly variable risk profiles for bleeding when compared with the Western population [10]. Of note, the identification of distinct predictors for antiplatelet-related bleeding complications may provide opportunities to further tailor post-PCI care for those at high bleeding risk, yet studies dedicated to the risk predictors of antiplatelet-related bleeding complications after PCI in Chinese elderly people are rarely done [3, 6, 11]. Furthermore, bleeding is strongly associated with the occurrence of mortality within one year after bleeding complications [12]. Timely cessation of antiplatelet therapy is a critical component of the successful management of antiplatelet-related bleeding complications in patients with ACS [13]. However, much less is known about the contemporary timing relations between physician-guided DAPT cessation and subsequent major adverse cardiac and cerebrovascular events (MACCE) in Chinese elderly patients with ACS.

Our aim of this study was to identify risk predictors of antiplatelet-related bleeding complications (GIB or ICH) for ACS in elderly patients, assess the management associated with these patients, and synthesize the available information of our clinical experience to provide clinicians with a new interpreting to appropriate antiplatelet strategies.

Materials and Methods

Subjects

This study was a single-center retrospective study involved consecutive patients who had undergone successful PCI referred to the First Affiliated Hospital of Chengdu Medical College from January 2010 to December 2016. The inclusion criteria for the study were as follows: aged ≥ 75 years old; fulfill the ACS criteria [13, 14]; successful PCI in at least one major coronary artery; received standard antithrombotic treatment for the PCI procedure [7]; and angiographically documented PCI. Patients were excluded if they

had any of the following conditions: atrial fibrillation or atrial flutter, history of other types of operations including coronary artery bypass graft (CABG); subjects who were previously on long-term DAPT; subjects who were on oral anticoagulation therapy; bleeding complications not related to antithrombotic origin such as trauma, tumor, arterial aneurysm, vascular malformation, and hemorrhagic conversion of arterial or venous infarction; bleeding complications not related to gastrointestinal or intracranial site; severe concomitant medical illness including liver and kidney dysfunction, severe anemia; and other chronic diseases leading to limited life expectancy. A total of 53 patients that met initial inclusion criteria was collected (bleeding group). After matching the age (± 3 years) with cases in 1:3 or greater ratio (perfect matching was not feasible), 184 patients who did not present bleeding complications were matched as a control (without bleeding group) during the same time period. The study received ethical approval from the Committee for Medical Ethics of the First Affiliated Hospital of Chengdu Medical College, Chengdu, China. Written informed consent was obtained.

Data Collection

Medical chart reviews undertaken by the research nurse and the self-administered questionnaires were used to collect participants' medical history, health behaviors, and index ACS characteristics; clinical risk profile; and medical management data. Information on demographics (age and sex), comorbidities, lifestyle variables (smoking status, alcohol consumption, and body mass index), and biological data was extracted from the database or medical chart reviews.

For the present study, the SYNTAX score for each angiogram was assessed by two experienced interventional cardiologists blinded to treatment assignment and clinical outcomes [15]. The GRACE score calculator was applied on all selected patients for the weighing of ischemic risk [16]. The CRUSADE bleeding risk score was calculated for each patient by assigning certain number of points for weighted integers of each of the eight independent predictors (gender, diabetes mellitus, peripheral arterial disease, heart rate, systolic blood pressure, heart failure, haematocrit and creatinine clearance) of in-hospital bleeding events [17].

Definitions

The primary bleeding complications of interest after PCI were classified as GIB or ICH. GIB was defined as overt or occult bleeding within the gastrointestinal tract that occurred during a period of antiplatelet therapy [18]. An overt bleed was classified as melena, hematochezia, hematemesis, and coffee ground emesis. An occult bleed was defined as an acute drop in hemoglobin with positive fecal occult blood test and negative upper and lower endoscopies. ICH was diagnosed according to the World Health Organization criteria [19], and confirmed by head computed tomography (CT) or magnetic resonance imaging (MRI). Major bleeding was diagnosed according to the standardized bleeding definitions for cardiovascular clinical trials by the American Bleeding Academic Research Consortium, and types 3 and 4 were defined as major bleeding [20]. Antiplatelet-related bleeding complications were defined as first hospitalization received long-term oral antiplatelet therapy and required hospitalization, including gastrointestinal and intracranial bleedings [21]. DAPT cessation was defined as cessation of antiplatelet treatment due to bleeding [22]. Once hemostasis had been assured and no continuing or recurrent hemorrhage, DAPT cessation did not preclude that low or standardized dose of clopidogrel monotherapy was timely restarted. Additionally, DAPT cessation did not preclude patients from subsequently resuming DAPT after this time interval, including length of DAPT >7 days. MACCE were defined as the composite of cardiac death, definite or probable stent thrombosis, spontaneous myocardial infarction, clinically indicated target lesion revascularisation or nonfatal ischemic stroke [22-24]. Re-bleeding was defined as further hematemesis and/or melena and/or hypovolemic shock after first endoscopy [25], or defined as a change of at least four points in the National Institutes Health stroke scale (NIHSS) score within the first 72 h after hospital admission together with an increase of intracranial bleeding on brain imaging [26].

DAPT cessation for subjects with antiplatelet-related bleeding complications

All the patients with antiplatelet-related bleeding complications had a DAPT cessation after initial bleeding, and further classified by duration of cessation as either short-term (0–7 days), or long-term (> 7 days). In addition, follow-up by standardized telephone interview or outpatient clinical visits were scheduled at 30 days, 3 months, 6 months, and 12 months after DAPT cessation. Of the initial 53 patients

with antiplatelet-related bleeding complications, 7 were ineligible for one year follow-up, including 4 patients in short-term DAPT cessation group and 3 patients in long-term DAPT cessation group. 3 patients were lost to phone contact, 2 patients denied verbal consent, and 2 patients failed to complete all required information. Eventually, a total of 46 patients with antiplatelet-related bleeding complications treated by DAPT cessation were followed. During the telephone interview, the site staff obtained information regarding major adverse events and deaths. All major adverse events were adjudicated by an independent clinical events committee blinded to treatment assignment.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were expressed as a percentage. Continuous variables were compared using Student's t-test, while categorical variables were compared using chi-square tests. Since this study was retrospective design and sample size was limited due to the availability of samples, we estimated the power of our study. However, 1:3 (or greater) case:control matching was used to maximize statistical power. Univariable logistic regression analysis was used to estimate the effect of various variables on the hazard of bleeding complications. Multivariate logistic regression analysis was then performed to identify independent predictors of bleeding complications. Variables in these models were selected based on univariate *p*-values of < 0.05 and overall clinical significance. Odds ratios (ORs) and their 95% confidence intervals (CIs) along with corresponding *p* values were presented. Kaplan-Meier survival curves were constructed for MACCE occurrence in patients treated with short-term or long-term DAPT cessation and compared with the log-rank test. All statistical analyses were conducted using STATA (version 12.0) and SPSS (version 22.0). Two-sided $P < 0.05$ was considered statistically significant.

Results

Characteristics of study patients

Baseline characteristics of the initial 237 patients studied are shown in Table 1. Compared with patients without bleeding, those with bleeding were significantly associated with the following parameters: greater proportion of female genger, lower values of body mass index (BMI), lower presence of non-ST segment elevation myocardial infarction (NSTEMI), higher levels of systolic blood pressure, fasting blood glucose (FBG), length of stent, GRACE score, CRUSADE score, and the prevalence of smoking, alcohol consumption, and the presence of ST-segment elevation myocardial infarction (STEMI), diabetes, hypertension, dyslipidemia, previous history of bleeding, and chronic total occlusion (CTO) lesion.

Table 1. Baseline Characteristics of Study Patients with or without Bleeding. Values are mean ± SD or n (%). BMI, body mass index; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST segment elevation myocardial infarction; LVEF, left ventricular ejection fraction; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; FBG, fasting blood glucose; CTO, chronic total occlusion; GRACE, Global Registry of Acute Coronary Events; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines. A p-value of < 0.05 was considered statistically significant

Variable	Bleeding (n= 53)	Without bleeding (n= 184)	P Value
Age (years)	77.39 ± 2.56	77.63 ± 1.71	0.449
Female	22 (41.5)	37 (20.1)	0.003
BMI (kg/m^2)	22.67 ± 3.18	25.96 ± 3.02	< 0.001
Clinical presentation			
STEMI	40 (75.5)	92 (50.0)	0.001
NSTEMI	9 (17.0)	71 (38.6)	0.003
Unstable angina	4 (7.5)	21 (11.4)	0.612
Comorbidities			
Smoking	32 (60.4)	75 (40.8)	0.020
Alcohol consumption	24 (45.3)	46 (25.0)	0.006
Diabetes	28 (52.8)	59 (32.1)	0.009
Hypertension	31 (58.5)	66 (35.9)	0.004
Dyslipidemia	25 (47.2)	52 (28.3)	0.012
Previous history of bleeding	11 (20.8)	3 (1.6)	< 0.001
Clinical data			
Killip class > I on admission	32 (60.4)	121 (65.8)	0.728
Systolic blood pressure (mmHg)	138 ± 12	134 ± 11	0.031
Diastolic blood pressure (mmHg)	81 ± 7	80 ± 6	0.181
Heart rate (bpm)	80 ± 10	81 ± 11	0.506
LVEF (%)	52 ± 10	53 ± 11	0.532
Total cholesterol (mg/dl)	4.47 ± 1.21	4.18 ± 1.22	0.309
HDL-C (mg/dl)	1.27 ± 0.17	1.28 ± 0.14	0.801
LDL-C (mg/dl)	3.93 ± 1.26	3.76 ± 0.88	0.284
Triglycerides (mg/dl)	3.70 ± 1.56	3.52 ± 0.92	0.161
FBG (mmol/L)	9.57 ± 1.47	7.60 ± 1.60	< 0.001
Serum creatinine (μmol/L)	88.48 ± 8.52	85.89 ± 8.83	0.074
Angiographic features			
Single-vessel disease	9 (17.0)	35 (19.0)	0.843
Double-vessel disease	18 (34.0)	72 (39.1)	0.525
Triple-vessel disease	26 (49.0)	77 (41.8)	0.432
Bifurcation lesion	17 (32.1)	72 (39.1)	0.422
CTO lesion	15 (28.3)	23 (12.5)	0.010
Length of stent (mm)	65.48 ± 7.84	40.30 ± 11.26	< 0.001
SYNTAX score	14 ± 7	14 ± 8	0.376
Risk score for in-hospital			
GRACE score	126 ± 23	116 ± 21	0.005
CRUSADE score	32 ± 8	27 ± 12	0.004

Multivariate analysis

The associations of patients' baseline characteristics with bleeding complications, estimated by univariable logistic regression analysis, are presented in Table 2. The results of multivariate logistic regression analysis on bleeding complications after PCI are shown in Fig. 1. On multivariate analysis, female gender (OR: 2.96; 95% CI: 1.98 to 4.15; P = 0.011), BMI (OR: 1.54; 95% CI: 1.06 to 1.94; P = 0.034), previous history of bleeding (OR: 4.03; 95% CI: 1.84 to 6.12; P = 0.004), FBG (OR: 2.79; 95% CI: 1.23 to 4.46; P = 0.025), and CTO lesion (OR: 4.69; 95% CI: 2.19 to 7.93; P = 0.007) were independent predictors of bleeding complications (Fig. 1).

Characteristics and clinical outcomes of DAPT cessation

Characteristics and clinical outcomes of short-term or long-term DAPT cessation for patients with antiplatelet-related bleeding complications are presented in Table 3. Of 46 patients with antiplatelet-related bleeding complications, 54.3% were treated short-term DAPT cessation and 45.7% underwent long-term DAPT cessation. Among these, 14 patients presented MACCE, whereas no re-bleeding happened over all available follow-up. The incidence of MACCE was not significantly different between the two groups one year after PCI (36.0% for short-term DAPT cessation versus 23.8% for long-term DAPT cessation, P = 0.522) (Table 3). Kaplan-Meier survival curves and cumulative event rates for MACCE in patients with short-term DAPT cessation or long-term DAPT cessation are shown in Fig. 2. There was no significant difference in MACCE rate between the groups with short-term DAPT cessation or long-term DAPT cessation (log-rank P = 0.481 [Fig. 2]). Not surprisingly, two interesting cases illustrating the judicious tailoring of antiplatelet therapy were described in Supplemental information (for all supplementary material see www.karger.com/doi/10.1159/000494543).

Table 2. Univariate logistic regression analysis on bleeding complications. OR, odds ratio; CI, confidence interval; A p-value of < 0.05 was considered statistically significant

Variable	OR	95% CI	P-Value
Female	3.41	2.22-5.27	0.004
BMI	1.79	1.29-2.49	< 0.001
STEMI	2.14	0.75-3.63	0.188
NSTEMI	1.35	0.78-2.32	0.287
Smoking	1.19	0.87-1.63	0.823
Alcohol consumption	2.71	0.74-4.33	0.071
Diabetes	1.68	0.88-2.60	0.343
Hypertension	2.75	1.53-6.28	0.029
Dyslipidemia	3.17	0.69-5.94	0.062
Previous history of bleeding	2.47	1.14-4.38	0.018
FBG	4.31	1.94-9.57	0.004
CTO lesion	2.56	1.17-5.62	0.019
Length of stent	1.59	0.66-3.83	0.682
GRACE score	5.83	0.85-11.99	0.453
CRUSADE score	7.24	0.71-14.33	0.298

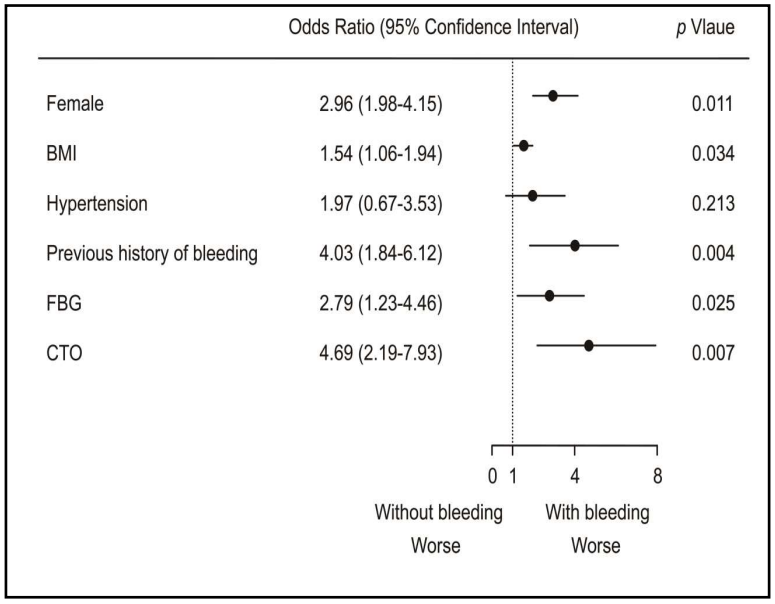

Fig. 1. Forest plot showing results of multivariate logistic regression analysis of bleeding complications. Female, BMI, previous history of bleeding, FBG, and CTO lesion were independent predictors of bleeding complications.

Discussion

This study reports the predictors and treatment experience of antiplatelet-related bleeding complications after PCI for ACS in elderly patients in a single center. Furthermore, our findings show that patients who had physician-guided long-term DAPT cessation did not have an obviously increased rate of MACCE events, compared with those on short-term DAPT cessation.

These results permit several conclusions. First, bleeding complications are associated with adverse outcomes after PCI [12], risk stratification is important for such patients to enable an appropriate therapeutic approach for each individual case. In contemporary primary PCI, the occurrence of access site bleeds is rare even in high risk population [27, 28]. In fact, access-related bleedings (i.e., femoral, or radial artery) were not associated with an excess in 30 day mortality, but the rest of the bleeds (i.e., GIB or ICH) were [27, 28]. Therefore, emphasis, among those PCI patients with ACS, needs to now focus on how to reduce non-access site bleeds. Antithrombotic drugs are associated with a clinically significant risk of GIB or ICH [5]. Regarding the independent predictors of bleeding complications on multivariate analysis (female, low BMI, previous history of bleeding, and FBG), our results are mostly consistent with those of previous studies [17, 29,

Table 3. Characteristics and clinical outcomes of short-term or long-term DAPT cessation for patients with antiplatelet-related bleeding complications. Values are n (%). DAPT, dual antiplatelet therapy; MACCE, major adverse cardiac and cerebrovascular events. A p-value of < 0.05 was considered statistically significant

Variable	DAPT cessation		P Value
	Short-term (n= 25)	Long-term (n= 21)	
Gastrointestinal bleeding	23 (92.0)	16 (76.2)	0.220
Intracerebral haemorrhage	2 (8.0)	5 (23.8)	0.220
Major bleeding	18 (72.0)	19 (90.5)	0.151
One-year clinical outcomes			
Total MACCE	9 (36.0)	5 (23.8)	0.522
Cardiac death	2 (8.0)	1 (4.8)	0.658
Spontaneous myocardial infarction	3 (12.0)	1 (4.8)	0.614
Definite or probable stent thrombosis	1 (4.0)	1 (4.8)	0.900
Target lesion revascularisation	2 (8.0)	1 (4.8)	0.658
Stroke	1 (4.0)	1 (4.8)	0.900
All-cause death	4 (16.0)	3 (14.3)	0.872

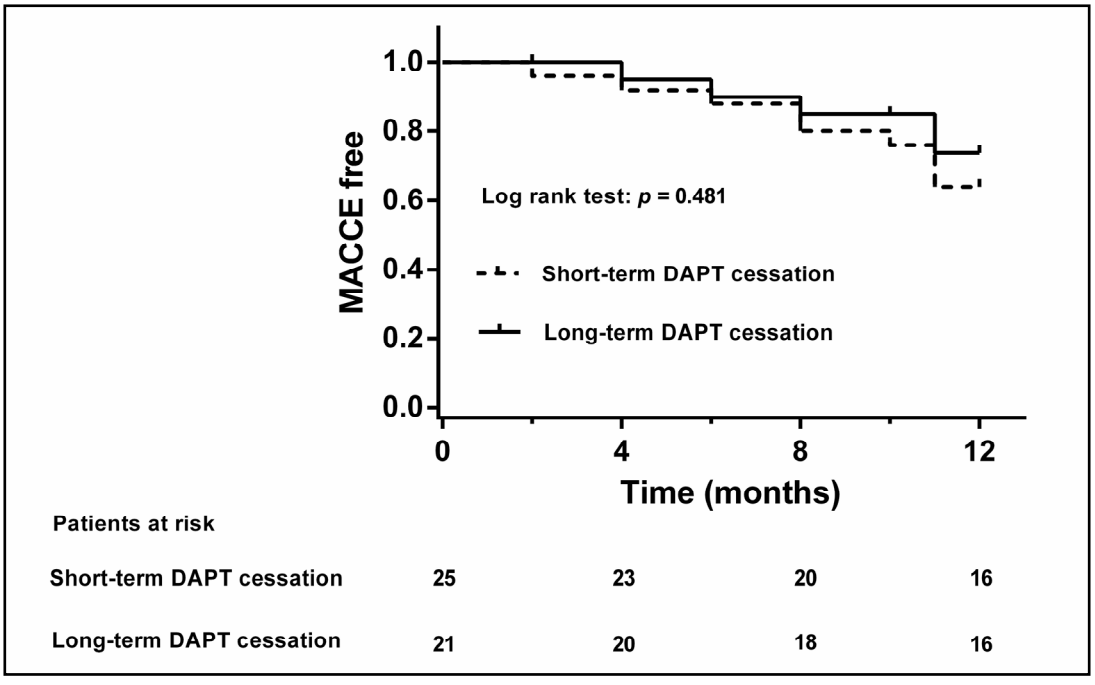

Fig. 2. Kaplan-Meier curve for MACCE according to DAPT cessation for patients with antiplatelet-related bleeding complications. DAPT, dual antiplatelet therapy; MACCE, major adverse cardiac and cerebrovascular events.

30]. In addition to these common factors, PCI for CTO lesions is also independent predictor of bleeding complications in our study, perhaps on the basis of the advent of newly developed devices and techniques, sufficient procedural success and acceptable complication rates have been achieved [31]. It should be noted, however, that previous studies did not focused on the older adult. Accordingly, age over 75 years was a mandatory inclusion criterion in our study. Second, compared with those on short-term DAPT cessation, patients who had physician-guided long-term DAPT cessation did not have an obviously increased rate of MACCE events. These results are consistent with those of Mehran *et al.* [22] who found that cardiac events after DAPT cessation depend on the clinical circumstance and reason for cessation and attenuates over time; yet the authors did not focus on Chinese population. Nonetheless, in a meta-analysis of the duration of DAPT in patients treated with second-generation drug-eluting stents, major bleeding was reduced by shorter DAPT (OR: 0.60; 95% CI: 0.42 to 0.96), emphasizing the need for an individualized approach to balance the competing risks of bleeding and myocardial infarction when deciding on the optimal DAPT duration for each patient [32]. Third, in general, management of antiplatelet-related bleeding complications includes identification and treatment of the bleeding source, haemostatic intervention (manual, endoscopic, and surgical), discontinuation of antithrombotic drugs (partial or complete), replacement therapy, and antidotes if available, depending on bleeding severity and risk of ischaemic recurrence [5, 33, 34]. Transfusions are recommended in haemodynamically unstable patients or with haematocrit < 25% or haemoglobin < 7 g/dL [5, 35]. Well-established scores of ischemic and bleeding risk, such as GRACE and CRUSADE, are imperative for sound decision-making regarding drug cessation or continuation [36, 37]. Moreover, knowledge of the mechanism of action, half-life and elimination route of the antiplatelet agent, as well as timing of last administration and kidney function, are important for optimal management [5].

Management of GIB in the elderly

Antiplatelet agents increase the risk of major bleeding complications after PCI, among which GIB is the commonest manifestation [38]. The association between GIB and antiplatelet agents is well recognized [39]. The current state-of-the-art management of GIB also should consider the following important approaches. Firstly, Aspirin is a cyclooxygenase (COX) inhibitor that inhibits both COX-1 and COX-2 and causes irreversible inhibition of platelet function [40]. The time required to recover adequate platelet function after aspirin use is 7 to 10 days. The thienopyridine agents, clopidogrel, prasugrel, and ticagrelor, inhibit the $P2Y_{12}$ receptor on the platelet to inhibit platelet aggregation. Inhibition is irreversible for clopidogrel and prasugrel and reversible for ticagrelor [40]. The antiplatelet effect can last between 3 and 9 days depending on the agent [38]. Following ACS, regardless of whether the patient has been medically treated or undergone PCI, the most dangerous period of time to alter DAPT is in the first 90 days following the event [41]. Elective diagnostic endoscopy can safely be performed without cessation of DAPT [38]. Secondly, the European guidelines recommend a PPI with DAPT to reduce GIB events [5, 42]. With clopidogrel, PPIs with low CYPC19 inhibitory capacity (e.g. pantoprazole) are preferred [5, 42]. Thirdly, other measures include blood pressure control, avoidance, or limited use of other drugs that enhance bleeding (e.g. NSAIDs, steroids), avoidance of heavy alcohol intake [5, 42]. Fourthly, once endoscopic hemostasis has been assured, antiplatelets should be restarted; on the same day of the procedure, in most cases. In situations in which hemostasis is uncertain, discussion with the patient's cardiologist, hematologist, or gastroenterologist is important to ensure an individualized approach for each patient.

Management of ICH in the elderly

Antiplatelet therapy might slightly increase the incidence of ICH [42]. The effect of antiplatelet drugs on the outcome of ICH is uncertain [43]. Previous observational studies showed that reduced platelet activity is associated with early ICH growth, and poor functional outcome [44, 45]. Another study reported that the use of antiplatelet medication at the

onset of ICH symptoms was not associated with increased hemorrhage volume, hematoma expansion, or poor functional outcome [46]. The current state-of-the-art management of ICH also should consider the following important approaches. Firstly, platelet transfusion is used prophylactically and therapeutically in many clinical settings; however, few randomised trials have investigated its effectiveness for active bleeding disorders [47, 48]. In the findings of the PATCH trial, platelet transfusion cannot be recommended for the treatment of acute intracerebral haemorrhage in people taking antiplatelet therapy because platelet transfusion seemed to worsen their outcome [49]. Secondly, the condition of patients with ICH frequently deteriorates within the first 24 or 48 hours after symptom onset because of secondary injuries caused by hematoma expansion, intraventricular hemorrhage extension, fever, and high blood pressure [50]. Preliminary studies have suggested that therapeutic cooling may reduce perihematomal edema [51]. On the other hand, intensive blood pressure reduction is thought to reduce hematoma expansion and improve the clinical outcomes in patients with ICH. However, the therapeutic goals of blood pressure reduction in the early phase of ICH are not clearly defined. The key point to debate is whether acute blood pressure reduction results in ischemic insult to perihematomal penumbral lesions surrounding the hemorrhage [50, 52, 53]. Overall, the current evidence supports that early intensive blood pressure lowering is safe and feasible, and is associated with a modestly better functional outcome. Thirdly, hyperglycemia on admission is associated with an increased 28-day case fatality in both nondiabetic and diabetic patients with ICH [19]. Therefore, hyperglycemia should be controlled adequately, glucose level should be monitored regularly and both hyperglycemia and hypoglycemia should be avoided [19, 54]. Fourthly, after ICH, resuming antiplatelet therapy should be considered with great caution, especially after lobar bleeds that have higher recurrence rates than deep cerebral bleeds [5, 42].

There are several possible explanations for our findings. First, there is a wide consensus that antiplatelet drugs provide first-line antithrombotic therapy for the management of acute ischemic syndromes (both coronary and cerebrovascular) and for the prevention of their recurrence [55]. Current guidelines advocate a DAPT with aspirin and clopidogrel for up to 12 months [33]. It is important to emphasize that this intensification of treatment is associated with an increased risk of bleeding. In addition, evidence has been accumulating for a strong association of bleeding with subsequent mortality, the causes of which are thought to be multifactorial [56]. Various mechanisms can explain this association: bleeding can directly lead to death (in case of severe hemorrhage or intracranial bleeding, for example), prompt cessation of antithrombotic therapy and thus induce ischemic events, and coupled with medications required to treat bleeding (such as transfusion) can also affect prognosis [57]. Second, to date, there are no randomized control trials that systematically explore the timing of restarting antithrombotic drugs after bleeding complications [5, 42]. Given the risk of thrombotic events and recurrent bleeding, few studies recommends individualized timelines. Moreover, there is a pervasive lack of evidence to guide clinical decision making in older patients with cardiovascular disease, as well as a paucity of data on the impact of diagnostic and therapeutic interventions on key outcomes that are particularly important to older patients, such as quality of life, physical function, and maintenance of independence [3]. Third, physicians appropriately discontinue DAPT in patients with bleeding complications accounting for improving MACCE events after discontinuation. Additionally, one potential explanation is that patients undergoing PCI are indeed different; their levels of platelet activation, their comorbidities, and demographics all may lead to a completely different balance of risk and benefit. Fourth, the pharmacodynamic response to clopidogrel is associated with a large interindividual variability, especially in those with the lowest on-clopidogrel reactivity the risk of bleeding is increased [58]. More importantly, certain studies have already suggested that Asian patients may respond differently to antithrombotic therapy in comparison with the Western population [10]. Platelet function testing is still being used in many centres and international guidelines still recommend platelet function testing in high-risk situations. However, attempts have not been made to characterize the efficacy of antiplatelet therapy using platelet function testing in our centre mainly based

on current information, its routine use is not recommended particularly as costs and cost effectiveness have not been established, and agreement between laboratorymethods is lacking. Moreover, several studies have demonstrated that platelet function monitoring with treatment adjustment did not improve the clinical outcome of elderly patients treated with coronary stenting for an ACS [4, 59].

The main strength of our study is that it provides new insight on the options for individual risk assessment and strategies to personalize antiplatelet therapy in Chinese elderly patients with bleeding complications (GIB or ICH). Given the differing risk profiles between Chinese patients and those in the Western population [60], we not only specifically addressed predictors of bleeding complications after PCI, but also tested interactions between DAPT cessation and cardiovascular risk. Our findings may have significant clinical implications, as individuals' characteristics and angiographic factors are all independently associated with bleeding complications after PCI, and therefore need to be considered separately for precise prediction of bleeding risk. Furthermore, these findings might provide the foundation for future evidence-based guidelines applicable to older patients, thereby enhancing patient-centered evidence-based care of older people with cardiovascular disease in China and around the world.

Limitations of our study warrant consideration. First, this was a retrospective study, residual and uncontrolled confounding might still be present. Although we performed multivariate logistic regression analysis to adjust for possible confounding variables, some selection bias might not have been completely adjusted for in our statistical model. In addition, information on comorbidities, such as smoking, alcohol consumption, hypertension, diabetes, and dyslipidemia, was self-reported by participants, which potentially can lead to error. Second, the incidence of bleeding complications after PCI was low [61, 62], and we exclusively recruited patients with definite antiplatelet-related bleeding complications after PCI; hence, the study sample was relatively small. Third, this was a single-center study based on clinical data from our hospital database. Fourth, we were not able to assess the actual dosage of antiplatelet therapy that patients received, raising the question of whether specific dosage-related factors may have had an influence on the risk of bleeding after PCI. Thus, these findings have to be confirmed by further prospective, well-designed multicenter studies.

Conclusion

For elderly patients with ACS, multiple factors were likely to contribute to antiplatelet-related bleeding complications, especially previous history of bleeding and chronic total occlusion lesion. Better individualized, tailored and risk-adjusted antiplatelet therapy after PCI is urgently needed in this high-risk population.

Acknowledgements

This research was supported by grants from the National Natural Science Foundation of China (81400289, 81641058) and the outstanding young academic and technological leaders of Sichuan Province (2016JQ0032).

Disclosure Statement

The authors declare that there is no conflict of interest regarding the publication of this paper.

References

1 Schoenenberger AW, Radovanovic D, Windecker S, Iglesias JF, Pedrazzini G, Stuck AE, Erne P; AMIS Plus Investigators: Temporal trends in the treatment and outcomes of elderly patients with acute coronary syndrome. Eur Heart J 2016;37:1304-1311.

2 Li J, Li X, Wang Q, Hu S, Wang Y, Masoudi FA, Spertus JA, Krumholz HM, Jiang L; China PEACE Collaborative Group: ST-segment elevation myocardial infarction in China from 2001 to 2011 (the China PEACE-Retrospective Acute Myocardial Infarction Study): a retrospective analysis of hospital data. Lancet 2015;385:441-451.

3 Rich MW, Chyun DA, Skolnick AH, Alexander KP, Forman DE, Kitzman DW, Maurer MS, McClurken JB, Resnick BM, Shen WK, Tirschwell DL; American Heart Association Older Populations Committee of the Council on Clinical Cardiology, Council on Cardiovascular and Stroke Nursing, Council on Cardiovascular Surgery and Anesthesia, and Stroke Council; American College of Cardiology; American Geriatrics Society: Knowledge gaps in cardiovascular care of the older adult population: a scientific statement from the American Heart Association, American College of Cardiology, and American Geriatrics Society. J Am Coll Cardiol 2016;67:2419-2440.

4 Cayla G, Cuisset T, Silvain J, Leclercq F, Manzo-Silberman S, Saint-Etienne C, Delarche N, Bellemain-Appaix A, Range G, El Mahmoud R, Carrié D, Belle L, Souteyrand G, Aubry P, Sabouret P, du Fretay XH, Beygui F, Bonnet JL, Lattuca B, Pouillot C et al.: Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomised controlled superiority trial. Lancet 2016;388:2015-2022.

5 Andreotti F, Rocca B, Husted S, Ajjan RA, ten Berg J, Cattaneo M, Collet JP, De Caterina R, Fox KA, Halvorsen S, Huber K, Hylek EM, Lip GY, Montalescot G, Morais J, Patrono C, Verheugt FW, Wallentin L, Weiss TW, Storey RF; ESC Thrombosis Working Group: Antithrombotic therapy in the elderly: expert position paper of the European Society of Cardiology Working Group on Thrombosis. Eur Heart J 2015;36:3238-3249.

6 Jiang L, Krumholz HM, Li X, Li J, Hu S: Achieving best outcomes for patients with cardiovascular disease in China by enhancing the quality of medical care and establishing a learning health-care system. Lancet 2015;386:1493-1505.

7 Costa F, van Klaveren D, James S, Heg D, Räber L, Feres F, Pilgrim T, Hong MK, Kim HS, Colombo A, Steg PG, Zanchin T, Palmerini T, Wallentin L, Bhatt DL, Stone GW, Windecker S, Steyerberg EW, Valgimigli M; PRECISE-DAPT Study Investigators: Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet 2017;389:1025-1034.

8 Li L, Geraghty OC, Mehta Z, Rothwell PM: Age-specific risks, severity, time course, and outcome of bleeding on long-term antiplatelet treatment after vascular events: a population-based cohort study. Lancet 2017;390:490-499.

9 Bath PM, Woodhouse LJ, Appleton JP, Beridze M, Christensen H, Dineen RA, Duley L, England TJ, Flaherty K, Havard D, Heptinstall S, James M, Krishnan K, Markus HS, Montgomery AA, Pocock SJ, Randall M, Ranta A, Robinson TG, Scutt P, Venables GS, Sprigg N; TARDIS Investigators: Antiplatelet therapy with aspirin, clopidogrel, and dipyridamole versus clopidogrel alone or aspirin and dipyridamole in patients with acute cerebral ischaemia (TARDIS): a randomised, open-label, phase 3 superiority trial. Lancet 2018;391:850-859.

10 Levine GN, Jeong YH, Goto S, Anderson JL, Huo Y, Mega JL, Taubert K, Smith SC Jr: World Heart Federation expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. Nature Reviews Cardiology 2014;11:597-606.

11 Tegn N, Abdelnoor M, Aaberge L, Endresen K, Smith P, Aakhus S, Gjertsen E, Dahl-Hofseth O, Ranhoff AH, Gullestad L, Bendz B; After Eighty study investigators: Invasive versus conservative strategy in patients aged 80 years or older with non-ST-elevation myocardial infarction or unstable angina pectoris (After Eighty study): an open-label randomised controlled trial. Lancet 2016;387:1057-1065.

12 Palmerini T, Bacchi Reggiani L, Della Riva D, Romanello M, Feres F, Abizaid A, Gilard M, Morice MC, Valgimigli M, Hong MK, Kim BK, Jang Y, Kim HS, Park KW, Colombo A, Chieffo A, Ahn JM, Park SJ, Schüpke S et al.: Bleeding-related deaths in relation to the duration of dual-antiplatelet therapy after coronary stenting. J Am Coll Cardiol 2017;69:2011-2022.

13 De Silva K, Myat A, Cotton J, James S, Gershlick A, Stone GW: Bleeding associated with the management of acute coronary syndromes. Heart 2017;103:546-562.
14 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.
15 Palmerini T, Genereux P, Caixeta A, Cristea E, Lansky A, Mehran R, Dangas G, Lazar D, Sanchez R, Fahy M, Xu K, Stone GW: Prognostic value of the SYNTAX score in patients with acute coronary syndromes undergoing percutaneous coronary intervention. J Am Coll Cardiol 2011;57:2389-2397.
16 Berger PB, Bhatt DL, Fuster V, Steg PG, Fox KA, Shao M, Brennan DM, Hacke W, Montalescot G, Steinhubl SR, Topol EJ; CHARISMA Investigators: Bleeding complications with dual antiplatelet therapy among patients with stable vascular disease or risk factors for vascular disease: results from the clopidogrel for high atherothrombotic risk and ischemic stabilization, management, and avoidance (CHARISMA) trial. Circulation 2010;121:2575-2583.
17 Abu-Assi E, Gracía-Acuña JM, Ferreira-González I, Peña-Gil C, Gayoso-Diz P, González-Juanatey JR: Evaluating the performance of the can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA guidelines (CRUSADE) bleeding score in a contemporary spanish cohort of patients with non-ST-segment elevation acute myocardial infarction. Circulation 2010;121:2419-2426.
18 Singh G, Albeldawi M, Kalra SS, Mehta PP, Lopez R, Vargo JJ: Features of patients with gastrointestinal bleeding after implantation of ventricular assist devices. Clin Gastroenterol Hepatol 2015;13:107-114.
19 Jin C, Li G, Rexrode KM, Gurol ME, Yuan X, Hui Y, Ruan C, Vaidya A, Wang Y, Wu S, Gao X: Prospective study of fasting blood glucose and intracerebral hemorrhagic risk. Stroke 2018;49:27-33.
20 Vranckx P, White HD, Huang Z, Mahaffey KW, Armstrong PW, Van de Werf F, Moliterno DJ, Wallentin L, Held C, Aylward PE, Cornel JH, Bode C, Huber K, Nicolau JC, Ruzyllo W, Harrington RA, Tricoci P: Validation of BARC bleeding criteria in patients with acute coronary syndromes: the TRACER trial. J Am Coll Cardiol 2016;67:2135-2144.
21 Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H: Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736-2747.
22 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.
23 Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium: Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344-2351.
24 Achilles A, Mohring A, Dannenberg L, Piayda K, Levkau B, Hohlfeld T, Zeus T, Kelm M, Polzin A: Analgesic medication with dipyrone in patients with coronary artery disease: relation to MACCE. Int J Cardiol 2017;236:76-81.
25 Shafi MA: Continuing medical education questions: January 2018: "Weekend Effect" in patients with upper gastrointestinal hemorrhage: a systematic review and meta-analysis. Am J Gastroenterol 2018;113:22-31.
26 Llull L, Thiel S, Amaro S, Cervera Á, Planas AM, Chamorro Á: Ficolin-1 levels in patients developing vasospasm and cerebral ischemia after spontaneous subarachnoid hemorrhage. Mol Neurobiol 2017;54:6572-6580.
27 Kilic S, Van't Hof AW, Ten Berg J, Lopez AA, Zeymer U, Hamon M, Soulat L, Bernstein D, Deliargyris EN, Steg PG: Frequency and prognostic significance of access site and non-access site bleeding and impact of choice of antithrombin therapy in patients undergoing primary percutaneous coronary intervention. The EUROMAX trial. Int J Cardiol 2016; 211:119-123.
28 Dauerman HL: Nonlinear mathematics of death and vascular access. Circulation 2016;133:1634-1646.

29 Ndrepepa G, Schulz S, Neumann FJ, Byrne RA, Hoppmann P, Cassese S, Ott I, Fusaro M, Ibrahim T, Tada T, Richardt G, Laugwitz KL, Schunkert H, Kastrati A: Bleeding after percutaneous coronary intervention in women and men matched for age, body mass index, and type of antithrombotic therapy. Am Heart J 2013;166:534-540.

30 Young K, Earl T, Selzer F, Marroquin OC, Mulukutla SR, Cohen HA, Williams DO, Jacobs A, Kelsey SF, Abbott JD: Trends in major entry site complications from percutaneous coronary intervention (from the Dynamic Registry). Am J Cardiol 2014;113:626-630.

31 Inohara T, Kohsaka S, Miyata H, Ueda I, Hayashida K, Maekawa Y, Kawamura A, Numasawa Y, Suzuki M, Noma S, Nishi Y, Fukuda K: Real-world use and appropriateness of coronary interventions for chronic total occlusion (from a Japanese Multicenter Registry). Am J Cardiol 2015;116:858-864.

32 D'Ascenzo F, Moretti C, Bianco M, Bernardi A, Taha S, Cerrato E, Omedè P, Montefusco A, Frangieh AH, Lee CW, Campo G, Chieffo A, Quadri G, Pavani M, Zoccai GB, Gaita F, Park SJ, Colombo A, Templin C, Lüscher TF, Stone GW: Meta-analysis of the duration of dual antiplatelet therapy in patients treated with second-generation drug-eluting stents. Am J Cardiol 2016;117:1714-1723.

33 Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L, Mehran R, Mukherjee D, Newby LK, O'Gara PT, Sabatine MS, Smith PK, Smith SC Jr: 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines: An update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non–ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. Circulation 2016;134:e123-e155.

34 Valgimigli M, Costa F, Lokhnygina Y, Clare RM, Wallentin L, Moliterno DJ, Armstrong PW, White HD, Held C, Aylward PE, Van de Werf F, Harrington RA, Mahaffey KW, Tricoci P: Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the thrombin receptor antagonist for clinical event reduction in acute coronary syndrome (TRACER) randomized trial. Eur Heart J 2017;38:804-810.

35 Holst LB, Petersen MW, Haase N, Perner A, Wetterslev J: Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomised trials with meta-analysis and trial sequential analysis. BMJ 2015;350:h1354.

36 Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, Wang TY, Gibler WB, Ohman EM, Roe MT, Pollack CV Jr, 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.

37 Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, Baumgartner H, Gaemperli O et al.; Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology: 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37:267-315.

38 ASGE Standards of Practice Committee, Acosta RD, Abraham NS, Chandrasekhara V, Chathadi KV, Early DS, Eloubeidi MA, Evans JA, Faulx AL, Fisher DA, Fonkalsrud L, Hwang JH, Khashab MA, Lightdale JR, Muthusamy VR, Pasha SF, Saltzman JR, Shaukat A, Shergill AK, Wang A, Cash BD, DeWitt JM: The management of antithrombotic agents for patients undergoing GI endoscopy. Gastrointest Endosc 2016;83:3-16.

39 Abraham NS: New clinical paradigms for treating and preventing antiplatelet gastrointestinal bleeding. Curr Opin Gastroen 2017;33:467-472.

40 Geisler T, Gawaz M, Steinhubl SR, Bhatt DL, Storey RF, Flather M: Current strategies in antiplatelet therapy—Does identification of risk and adjustment of therapy contribute to more effective, personalized medicine in cardiovascular disease? Pharmacol Ther 2010;127:95-107.
41 Ho PM, Tsai TT, Wang TY, Shetterly SM, Clarke CL, Go AS, Sedrakyan A, Rumsfeld JS, Peterson ED, Magid DJ: Adverse events after stopping clopidogrel in post-acute coronary syndrome patients: Insights from a large integrated healthcare delivery system. Circ Cardiovasc Qual Outcomes 2010;3:303-308.
42 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.
43 Kim JY, Bae H: Spontaneous Intracerebral Hemorrhage: Management. J Stroke 2017;19:28-39.
44 Naidech AM, Bernstein RA, Levasseur K, Bassin SL, Bendok BR, Batjer HH, Bleck TP, Alberts MJ: Platelet activity and outcome after intracerebral hemorrhage. Ann Neurol 2009;65:352-356.
45 Naidech AM, Jovanovic B, Liebling S, Garg RK, Bassin SL, Bendok BR, Bernstein RA, Alberts MJ, Batjer HH: Reduced platelet activity is associated with early clot growth and worse 3-month outcome after intracerebral hemorrhage. Stroke 2009;40:2398-2401.
46 Sansing LH, Messe SR, Cucchiara BL, Cohen SN, Lyden PD, Kasner SE; CHANT Investigators: Prior antiplatelet use does not affect hemorrhage growth or outcome after ICH. Neurology 2009;72:1397-1402.
47 Kumar A, Mhaskar R, Grossman BJ, Kaufman RM, Tobian AA, Kleinman S, Gernsheimer T, Tinmouth AT, Djulbegovic B; AABB Platelet Transfusion Guidelines Panel: Platelet transfusion: a systematic review of the clinical evidence. Transfusion 2015;55:1116-1127.
48 Kaufman RM, Djulbegovic B, Gernsheimer T, Kleinman S, Tinmouth AT, Capocelli KE, Cipolle MD, Cohn CS, Fung MK, Grossman BJ, Mintz PD, O'Malley BA, Sesok-Pizzini DA, Shander A, Stack GE, Webert KE, Weinstein R, Welch BG, Whitman GJ, Wong EC, Tobian AA; AABB: Platelet transfusion: a clinical practice guideline from the AABB. Ann Intern Med 2015;162:205-213.
49 Baharoglu MI, Cordonnier C, Al-Shahi Salman R, de Gans K, Koopman MM, Brand A, Majoie CB, Beenen LF, Marquering HA, Vermeulen M, Nederkoorn PJ, de Haan RJ, Roos YB; PATCH Investigators: Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial. Lancet 2016;387:2605-2613.
50 Morotti A, Boulouis G, Romero JM, Brouwers HB, Jessel MJ, Vashkevich A, Schwab K, Afzal MR, Cassarly C, Greenberg SM, Martin RH, Qureshi AI, Rosand J, Goldstein JN; ATACH-II and NETT investigators: Blood pressure reduction and noncontrast CT markers of intracerebral hemorrhage expansion. Neurology 2017;89:548-554.
51 Kollmar R, Staykov D, Dörfler A, Schellinger PD, Schwab S, Bardutzky J: Hypothermia reduces perihemorrhagic edema after intracerebral hemorrhage. Stroke 2010;8:1684-1689.
52 Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL, Moy CS, Silbergleit R, Steiner T, Suarez JI, Toyoda K, Wang Y, Yamamoto H, Yoon BW; ATACH-2 Trial Investigators and the Neurological Emergency Treatment Trials Network: Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. New Engl J Med 2016;375:1033-1043.
53 Li W, Jin C, Vaidya A, Wu Y, Rexrode K, Zheng X, Gurol ME, Ma C, Wu S, Gao X: Blood pressure trajectories and the risk of intracerebral hemorrhage and cerebral infarction: a prospective study. Hypertension 2017;70:508-514.
54 Hemphill JC, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, Fung GL, Goldstein JN, Macdonald RL, Mitchell PH, Scott PA, Selim MH, Woo D; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology: Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2015;46:2032-2060.
55 Patrono C, Morais J, Baigent C, Collet JP, Fitzgerald D, Halvorsen S, Rocca B, Siegbahn A, Storey RF, Vilahur G: Antiplatelet agents for the treatment and prevention of coronary atherothrombosis. J Am Coll Cardiol 2017;70:1760-1776.
56 Amin AP, Wang TY, McCoy L, Bach RG, Effron MB, Peterson ED, Cohen DJ: Impact of bleeding on quality of life in patients on DAPT: Insights from TRANSLATE-ACS. J Am Coll Cardiol 2016;67:59-65.

57 Doyle BJ, Rihal CS, Gastineau DA, Holmes DR: Bleeding, blood transfusion, and increased mortality after percutaneous coronary intervention. J Am Coll Cardiol 2009;53:2019-2027.
58 Price MJ, Berger PB, Teirstein PS, Tanguay JF, Angiolillo DJ, Spriggs D, Puri S, Robbins M, Garratt KN, Bertrand OF, Stillabower ME, Aragon JR, Kandzari DE, Stinis CT, Lee MS, Manoukian SV, Cannon CP, Schork NJ, Topol EJ; GRAVITAS Investigators: Standard-vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. JAMA 2011;305:1097-1105.
59 Collet JP, Cuisset T, Rangé G, Cayla G, Elhadad S, Pouillot C, Henry P, Motreff P, Carrié D, Boueri Z, Belle L, Van Belle E, Rousseau H, Aubry P, Monségu J, Sabouret P, O'Connor SA, Abtan J, Kerneis M, Saint-Etienne C et al.: Bedside monitoring to adjust antiplatelet therapy for coronary stenting. N Engl J Med 2012;367:2100-2109.
60 Jose PO, Frank AT, Kapphahn KI, Goldstein BA, Eggleston K, Hastings KG, Cullen MR, Palaniappan LP: Cardiovascular disease mortality in Asian Americans. J Am Coll Cardiol 2014;23:2486-2494.
61 Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dangas GD, Kirtane AJ, Parise H, Fahy M, Manoukian SV, Feit F, Ohman ME, Witzenbichler B, Guagliumi G, Lansky AJ, Stone GW: A risk score to predict bleeding in patients with acute coronary syndromes. J Am Coll Cardiol 2010;55:2556-2566.
62 Mahaffey KW, Hager R, Wojdyla D, White HD, Armstrong PW, Alexander JH, Tricoci P, Lopes RD, Ohman EM, Roe MT, Harrington RA, Wallentin L: Meta-analysis of intracranial hemorrhage in acute coronary syndromes: incidence, predictors, and clinical outcomes. J Am Heart Assoc 2015;4:e001512.