



Effects of Triple Therapy in Patients With Non-Valvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention Regarding Thromboembolic Risk Stratification

Antonia Sambola, MD; Maria Mutuberría, MD; Bruno García del Blanco, MD;
Albert Alonso, MD; José A. Barrabés, MD; Fernando Alfonso, MD; Héctor Bueno, MD;
Angel Cequier, MD; Javier Zueco, MD; Oriol Rodríguez-Leor, MD;
Eduard Bosch, MD; Pilar Tornos, MD; David García-Dorado, MD

Background: The effects of dual antiplatelet therapy (DAPT) and triple therapy (TT: DAPT plus oral anticoagulation) in patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) regarding to CHA₂DS₂-VASc score remain undefined. We compare the effect of TT vs. DAPT in this setting regarding the CHA₂DS₂-VASc score.

Methods and Results: In a prospective multicenter registry, 585 patients (75.2% male, 73.2±8.2 years) with AF undergoing PCI were followed up during 1 year. Of them, 157 (26.8%) had a CHA₂DS₂-VASc=1, and 428 (73.2%) had a CHA₂DS₂-VASc ≥2. TT was prescribed in 51.6% with CHA₂DS₂-VASc=1 and in 55.5% with CHA₂DS₂-VASc ≥2. Patients with CHA₂DS₂-VASc=1 receiving TT had a similar thromboembolism rate to those on DAPT (1.2% vs. 1.3%, P=0.73), but more total (19.5% vs. 6.9%, P=0.01) and a tendency to more major (4.9% vs. 0%, P=0.06) bleeding. However, patients with CHA₂DS₂-VASc ≥2 receiving TT had a lower thromboembolism rate (1.7% vs. 5.3%, P=0.03) and a trend towards more bleeds (21.8% vs. 15.6%, P=0.06), with an excess of major bleeding (8.4% vs. 3.1%, P=0.01). Rates of major adverse cardiac events (MACE) in both CHA₂DS₂-VASc subgroups were similar, irrespective of treatment. In a Cox multivariate analysis, TT was associated to major bleeding, but not with MACE.

Conclusions: In patients with AF and CHA₂DS₂-VASc=1 undergoing PCI, the use of TT involves a high risk of bleeding without a significant benefit in preventing thromboembolism. (*Circ J* 2016; **80**: 354–362)

Key Words: Anticoagulation; Atrial fibrillation; Dual antiplatelet therapy; Percutaneous coronary intervention; Thromboembolic risk

Atrial fibrillation (AF) is associated with an increased risk of systemic embolization, with cerebral embolism being the most catastrophic consequence. In patients with non-valvular AF, oral anticoagulation (OAC) is especially recommended for those at medium or high risk of embolization, mainly to reduce the risk of stroke.¹⁻³ The CHADS₂ score was widely used in clinical practice to assess the thromboembolic risk of patients with AF,^{4,5} but current recommendations for OAC in the ACC/AHA and ESC guidelines are based on the new CHA₂DS₂-VASc score that incor-

porates other risk factors (vascular disease, age 65–74 years, and female sex), thereby widening the spectrum of patients with OAC indication by including those with lower embolic risk. Therefore, patients with CHA₂DS₂-VASc=1 have a 1-year risk of embolism of 1.3% whereas patients with CHA₂DS₂-VASc=2 have a risk of embolism of 2.2%.^{1,2,6}

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In this respect, for the management of patients with AF,

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Cardiology Department, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona (A.S., M.M., B.G.d.B., A.A., J.A.B., P.T., D.G.-D.); Cardiology Department, Hospital Universitario Clínico San Carlos, Madrid (F.A.); Cardiology Department, Hospital General Universitario Gregorio Marañón, Madrid (H.B.); Cardiology Department, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat (Barcelona) (A.C.); Cardiology Department, Hospital Universitario Marqués de Valdecilla, Santander (J.Z.); Cardiology Department, Hospital Universitari Germans Trias, Badalona (Barcelona) (O.R.-L.); and Cardiology Department, Hospital Universitari Parc Taulí, Sabadell (Barcelona) (E.B.), Spain

Mailing address: Antonia Sambola, MD, FESC, Department of Cardiology, Hospital Universitari Vall d'Hebron, Autonomous University of Barcelona, P. Vall d'Hebron 119-129, 08035 Barcelona, Spain. E-mail: asambola@vhebron.net

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ESC/AHA/ACC/HRS guidelines recommend triple therapy (TT: OAC plus aspirin plus clopidogrel) for patients with CHA₂DS₂-VASc ≥ 2 while for patients with CHA₂DS₂-VASc=1 TT is recommended or preferred,^{1,2,6,7} although aspirin alone may be considered.¹ On the other hand, dual antiplatelet therapy (DAPT) is essential to prevent the risk of stent thrombosis or myocardial ischemic events in patients treated with percutaneous coronary intervention (PCI).⁶⁻¹³ However, to date, the strategy of TT vs. DAPT has not been prospectively compared in randomized trials in this setting of patients, and specific recommendations remain undefined.^{1,2,6-8,10} In this observational study, we compared the effect of TT and DAPT on thromboembolism and bleeding rates in patients with non-valvular AF undergoing PCI with regard to their CHA₂DS₂-VASc score (1 vs. ≥ 2).

Methods

Patient Selection and Study Design

We analyzed a prospective cohort study of consecutive patients with AF who underwent PCI and were treated with TT or DAPT. The population consisted of 2 distinct prospective cohorts: the first cohort enrolled patients from January 2003 to December 2006 in 6 Spanish teaching centers¹⁴ and the second cohort was recruited from a single center (University Hospital Vall d'Hebron) between 2007 and 2012. There were no significant differences in baseline characteristics between cohorts 1 and 2, except in the type of drug-eluting stent (DES) implanted. In the first cohort, all DES implanted were 1st-generation and in the second cohort, 78.6% of DES implanted were 2nd-generation.

Patients with a preexisting diagnosis of permanent, persistent or paroxysmal AF and those who developed new-onset AF during their index admission were included. The risk of stroke or systemic embolism was assessed using the CHA₂DS₂-VASc score.^{1,2,7} Bleeding risk was estimated by the HAS-BLED score.^{1,2,6,7}

At each participating hospital, demographic and clinical data, CHA₂DS₂-VASc score, bleeding risk (estimated by the HAS-BLED score^{1,2,6,7} as low (<3) or high (≥ 3)), PCI details, therapeutic regimen prescribed and recommended duration after stent implantation were recorded by the local investigator.

Because this was an observational study, decisions as to the type of revascularization performed or type of stent used or choice of antithrombotic therapies at discharge were left to the discretion of the attending cardiologists. In all patients the recommended duration of the prescribed treatment was collected; in patients discharged with DAPT (aspirin 100 mg once daily and clopidogrel 75 mg once daily), it was recommended that 1 antiplatelet agent should be stopped at least 1 month following PCI when a bare-metal stent (BMS) was used, and between 3 and 12 months when a DES was used. All patients treated with OAC received vitamin K antagonists plus DAPT or plus clopidogrel alone following the regimen described previously and the specific time schedule for each patient was collected. Thereafter, patients were followed as part of the routine clinical practice of each hospital. Target international normalized ratio values were between 2 and 2.5 for prevention of hemorrhagic events.^{8,9,15}

Clinical and demographic characteristics, risk factors for thromboembolism, and the use of antithrombotic therapy before PCI and at discharge were collected. Clinical follow-up was performed by telephone interviews and review of clinical records of patients with hospital readmissions and/or outpatient clinic visits to confirm the ongoing antithrombotic regi-

men after discharge, and to ascertain the occurrence of adverse events. Bleeding and thromboembolic events were collected by a predefined questionnaire. All adverse events were collected with the antithrombotic therapy at the moment of occurrence.

The effects of TT and DAPT on thromboembolic and bleeding events were analyzed according to CHA₂DS₂-VASc and HAS-BLED scores. We compared the incidence of thromboembolic events in patients with low to intermediate risk (CHA₂DS₂-VASc=1) vs. high risk (CHA₂DS₂-VASc ≥ 2), and bleeding events in relation to the HAS-BLED score according to the ESC guidelines.⁶

The 2 cohort studies complied with the Declaration of Helsinki and were approved by the institutional review boards of all the hospitals involved.¹⁰ The current study was approved by the Vall d'Hebron University Institutional Review Board. Prior to participating in this study, each investigator obtained local ethics committee approval and patients gave their written informed consent.

Endpoints and Definition of Adverse Events

The primary endpoint was the occurrence of any thromboembolic event (stroke or peripheral embolism) and the secondary endpoint was any major bleeding event. In addition, the occurrence of major adverse cardiac events (MACE) defined as death, myocardial infarction (MI), stent thrombosis or target vessel revascularization and major adverse event (MAE) defined as the incidence of any cardiac adverse event, including bleeding and/or thromboembolism occurring during follow-up, were estimated.

Stroke was defined as the sudden onset of a neurologic deficit in an area consistent with the territory of a major cerebral artery, and was categorized as ischemic, hemorrhagic or unspecified. Hemorrhagic transformation was not considered as a hemorrhagic stroke. Intracranial hemorrhage was defined as a hemorrhagic stroke or a subarachnoid or subdural hemorrhage. Stroke could be diagnosed by techniques such as brain computed tomography or magnetic resonance imaging.¹⁶ Systemic embolism was an acute vascular occlusion of the limbs or any organ (kidneys, mesenteric arteries, spleen, retina or grafts) and had to be documented by angiography, surgery, scintigraphy or autopsy. Any degree of bleeding (major or minor) was defined according to the classification scheme of the TIMI and PRISM-PLUS trials (major bleeding was defined as a decrease in the blood hemoglobin level of more than 4.0 g/dl, the need for the transfusion of ≥ 2 units of blood, the need for corrective surgery, the occurrence of any intracranial or retroperitoneal hemorrhage, or any combination of these).^{17,18} Acute MI was defined following the criteria of the ESC/ACC/AHA/WHF.¹⁹ Stent thrombosis was defined according to the criteria of The Academic Research Consortium.²⁰

Statistical Analysis

Descriptive analysis was made using mean \pm standard deviation and range for continuous variables. Absolute and relative frequencies of patients in each category were analyzed for categorical variables. Comparison of continuous variables between the 2 treatment groups was made by Student's t-test and by chi-square test for categorical variables.

The probability of adverse events during follow-up for each therapeutic group was calculated by Kaplan-Meier analysis and compared by the Mantel-Cox log-rank test in a multivariable model. In this model, we also included variables that showed a probability value < 0.15 in the univariate analysis when patients with and without OAC at discharge were

Table 1. Characteristics of Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention Regarding Treatment Received at Discharge

	Total population (n=585)	TT (n=319)	DAPT (n=266)	P value
Women (%)	145 (24.8)	80 (25.1)	63 (23.7)	0.38
Age, years	73.2±8.2	73±8	73±8	0.67
Smoking (%)	286 (48.9)	146 (45.8)	147 (55.2)	0.01
Hypertension (%)	436 (74.7)	254 (79.9)	185 (69.5)	0.006
Diabetes (%)	219 (37.6)	129 (40.4)	91 (34.2)	0.07
Dyslipidemia	319 (54.7)	174 (54.4)	121 (45.4)	0.22
History of HF (%)	329 (56.4)	180 (56.3)	150 (56.4)	0.52
Previous stroke (%)	85 (14.5)	57 (17.9)	28 (10.5)	0.008
Renal failure (%)	94 (16.1)	48 (15.1)	46 (17.4)	0.25
PAD (%)	78 (13.3)	37 (11.5)	43 (16.2)	0.06
CHA ₂ DS ₂ -VASc ≥2 (%)	428 (73.2)	177 (55.5)	118 (44.5)	0.22
HAS-BLED ≥3 (%)	229 (39.2)	132 (41.6)	99 (37.2)	0.07
COPD (%)	108 (18.5)	62 (19.4)	49 (18.5)	0.44
Previous PCI (%)	186 (31.8)	129 (40.3)	63 (23.6)	0.0001
History of CABG (%)	63 (10.8)	41 (12.9)	24 (8.9)	0.08
Previous MI (%)	193 (33)	116 (36.5)	80 (30.2)	0.06
ACS (%)	428 (73.2)	218 (68.3)	211 (79.2)	0.002
Patients with DES (%)	233 (39.8)	125 (39.3)	110 (41.2)	0.35

CHA₂DS₂-VASc is an acronym for thromboembolism factors (Congestive heart failure, Hypertension, Diabetes, Vascular disease, Age 65–74 years and Sex (female), all with a score=1, while age ≥75 years and history of previous stroke have a score=2.^{1,2} A score ≥2 indicates 'high risk' for stroke or embolism. HAS-BLED is an acronym for bleeding factors: Hypertension, Renal/liver failure, Stroke, Bleeding predisposition, INR liability, Age >65 years, concomitant Drugs or alcohol. ACS, acute coronary syndrome as index event at the time of PCI; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; HF, heart failure; PCI, percutaneous coronary intervention; MI, myocardial infarction; PAD, peripheral arterial disease; TT, triple therapy.

compared, as well as all demographic, clinical or procedural variables. A Cox proportional hazards model was used to assess the association between the therapeutic regimen at discharge and cardiovascular events. A 2-tailed P-value <0.05 was considered significant. Statistical analysis was performed using the statistical package SPSS 20.0 (Chicago, IL, USA).

Results

Baseline Characteristics

There were 585 patients with non-valvular AF who underwent PCI (women: 24.4%, mean age 74.1±8.1 years). In the whole cohort, 157 (26.2%) patients had CHA₂DS₂-VASc score=1. The remaining 428 patients (73.2%) had a CHA₂DS₂-VASc score ≥2. The main characteristics of patients treated with TT compared with those treated with DAPT are summarized in **Table 1**. No differences were observed regarding sex or age but patients who received TT were more frequently smokers, had a higher frequency of hypertension, history of previous stroke, previous PCI and acute coronary syndrome (ACS) as index event, and they also more frequently had a CHA₂DS₂-VASc score ≥2 than patients who received DAPT (**Table 1**).

In the patients with CHA₂DS₂-VASc=1, 1st-generation DES were implanted in 52.3% of patients and 2nd-generation DES were implanted in 47.7%. Among patients with CHA₂DS₂-VASc ≥2, 1st-generation DES were implanted in 55.5% of patients and 2nd-generation DES in 44.5%. There were no differences in the use of TT in patients with 1st-generation DES, in respect of CHA₂DS₂-VASc=1 vs. CHA₂DS₂-VASc ≥2: (56.3% vs. 69.2%, P=0.12), nor in patients who received 2nd-generation DES (48.2% vs. 49.4%, P=0.13).

Antithrombotic Therapy

The prescription of TT at hospital discharge was similar in patients with CHA₂DS₂-VASc=1 or CHA₂DS₂-VASc ≥2 (TT, 51.6% vs. 55.5%, P=0.22). In patients receiving BMS, the use of TT was similar through time in both subgroups of patients (1.5±1.0 vs. 1.6±1.2 months, respectively, P=0.56), as it was in patients receiving DES (7.3±3.6 vs. 6.5±4.2 months, respectively, P=0.35). Time in the therapeutic range data could only be collected for patients included by the coordinating center (University Hospital Vall d'Hebron). Of patients with CHA₂DS₂-VASc=1 on TT, 57 (70%) were from this center and 64% of all INR values drawn on OAC were in the therapeutic range, while for patients with CHA₂DS₂-VASc ≥2 on TT, 181 (76.8%) were from this center and 65.5% of all INR values drawn on OAC were in the therapeutic range.

Influence of TT on Outcomes in Patients With CHA₂DS₂-VASc=1

No differences were observed regarding sex, age, cardiovascular risk factors or HAS-BLED score among patients who received TT and DAPT, except in the prevalence of previous PCI, which was higher among the patients on TT (45% vs. 25%, P=0.01). Patients on TT in this subgroup, compared with those on DAPT, had a similar incidence of stroke (1.2% vs. 1.3%, P=0.73), but a higher incidence of bleeding events (19.5% vs. 6.9%, P=0.01; hazard ratio [HR], 3.18; confidence interval [CI], 1.16–8.69; P=0.02). Of these patients, 93.3% had a HAS-BLED score <3. In addition, no patient treated with DAPT suffered a major bleeding event (4.9% vs. 0%, P=0.06). The incidence of MACE was similar between treatment groups (11.1% vs. 13.3%, P=0.42), as was the incidence of MAE (27.2% vs. 21.3%, P=0.47) (**Figure 1**).

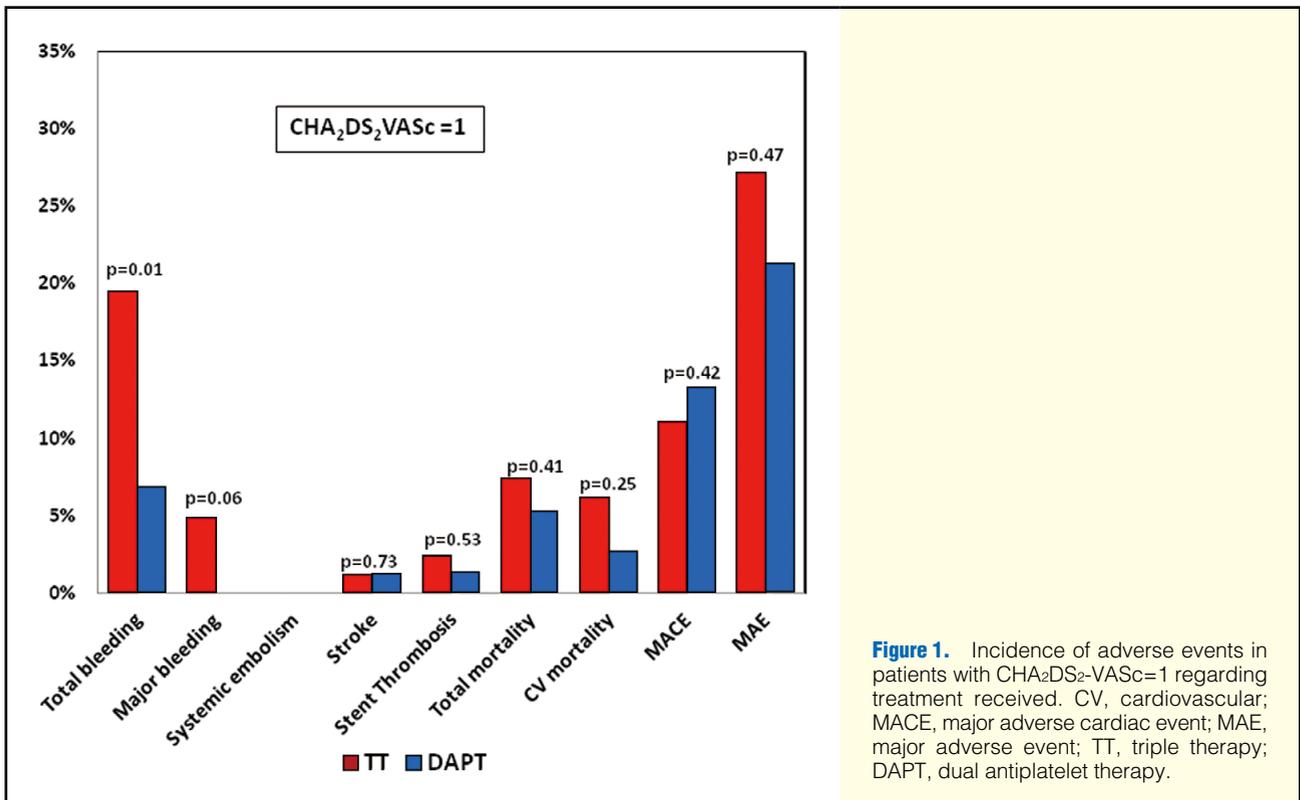


Figure 1. Incidence of adverse events in patients with CHA₂DS₂-VASc=1 regarding treatment received. CV, cardiovascular; MACE, major adverse cardiac event; MAE, major adverse event; TT, triple therapy; DAPT, dual antiplatelet therapy.

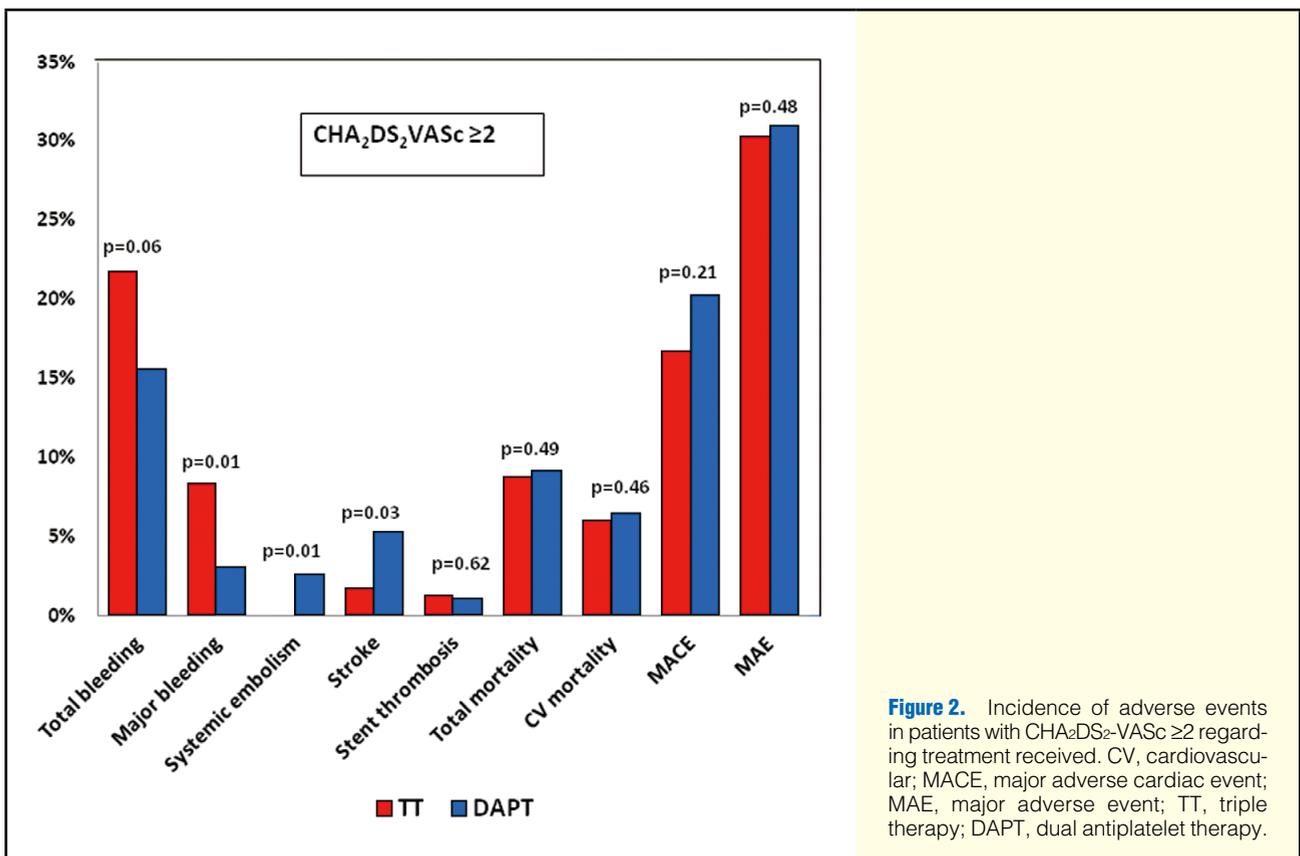


Figure 2. Incidence of adverse events in patients with CHA₂DS₂-VASc ≥ 2 regarding treatment received. CV, cardiovascular; MACE, major adverse cardiac event; MAE, major adverse event; TT, triple therapy; DAPT, dual antiplatelet therapy.

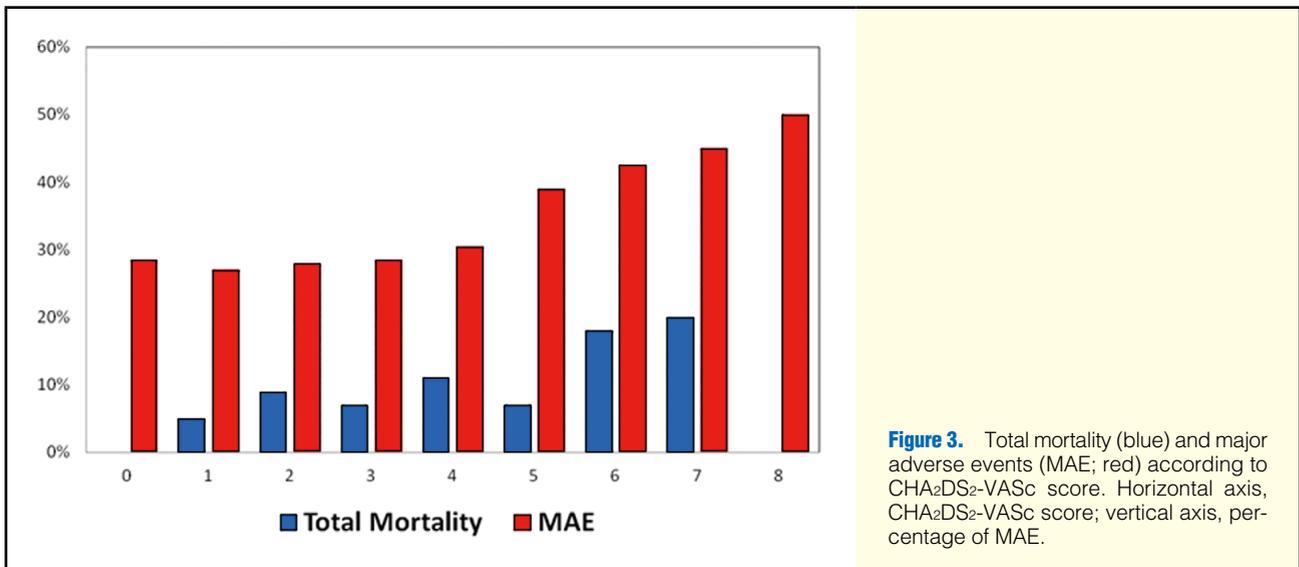


Figure 3. Total mortality (blue) and major adverse events (MAE; red) according to CHA₂DS₂-VASc score. Horizontal axis, CHA₂DS₂-VASc score; vertical axis, percentage of MAE.

Influence of TT on Outcomes in Patients With CHA₂DS₂-VASc ≥2

No differences were observed regarding sex, age or cardiovascular risk factors among patients who received TT and DAPT except in the prevalence of hypertension (90.3% vs. 77.9%, $P=0.0001$) and diabetes (49.2% vs. 39.5%, $P=0.02$). The rates of previous stroke (23.9% vs. 14.7%, $P=0.001$) and previous PCI (38.8% vs. 22.9%, $P=0.0001$) were higher in patients on TT. There were no differences in HAS-BLED scores between treatment groups.

In this subgroup, patients on TT had a lower incidence of stroke (1.7% vs. 5.3%, $P=0.03$; HR 3.23; 95% CI, 1.01–10.30, $P=0.04$) and systemic embolism (1.7% vs. 7.5%, $P=0.01$; HR 4.49; 95% CI, 1.48–13.6, $P=0.02$) than those on DAPT. Nevertheless, these patients tended to have a higher incidence of bleeding events (21.8% vs. 15.6%, $P=0.06$; HR 1.36; 95% CI, 0.87–2.1, $P=0.16$), with an excess of major bleeding (8.4% vs. 3.1%, $P=0.01$; HR 2.6; 95% CI, 1.03–6.5, $P=0.04$). Among patients who presented with a bleeding event, 39.2% had a HAS-BLED score ≥ 3 . The incidence of MACE was similar between treatment groups (16.8% vs. 20.3%, respectively, $P=0.21$), as was the incidence of MAE (30.3% vs. 31.0%, $P=0.48$) (Figure 2).

Consequences of TT on Mortality and Other Adverse Events in Relation to CHA₂DS₂-VASc Score

The relation of CHA₂DS₂-VASc score to total mortality and MAE is shown in Figure 3. In the overall population, 52 patients (8.9%) died during follow-up, with the cardiovascular mortality rate being 6.2% (6.6% with CHA₂DS₂-VASc=1 vs. 9.7% with CHA₂DS₂-VASc ≥ 2 , $P=0.16$). In the subgroup of patients with CHA₂DS₂-VASc=1, there were not differences in mortality rate between patients who received TT and those who received DAPT (7.4% vs. 5.5%, respectively, $P=0.41$), nor in the subgroup with CHA₂DS₂-VASc=2 (9.2% vs. 10.6%, respectively, $P=0.38$). However, 3 patients with CHA₂DS₂-VASc=1 died from complications of bleeding events: 1 had an intracranial hemorrhage and the other 2 patients had stent thrombosis after discontinuation of DAPT.

The probability of stroke or systemic embolism and bleeding events in patients with CHA₂DS₂-VASc=1 and CHA₂DS₂-

VASc ≥ 2 with regard to both treatments is shown in Figures 1 and 2. The treatment did not influence the probability of embolic events in patients with CHA₂DS₂-VASc=1. However, the probability of bleeding events was higher in patients with CHA₂DS₂-VASc=1 who received TT (Figures 4A,B). In contrast, patients with CHA₂DS₂-VASc ≥ 2 who received TT had a lower probability of embolic events and their probability of bleeding events was similar to that of patients who received DAPT (Figures 4C,D).

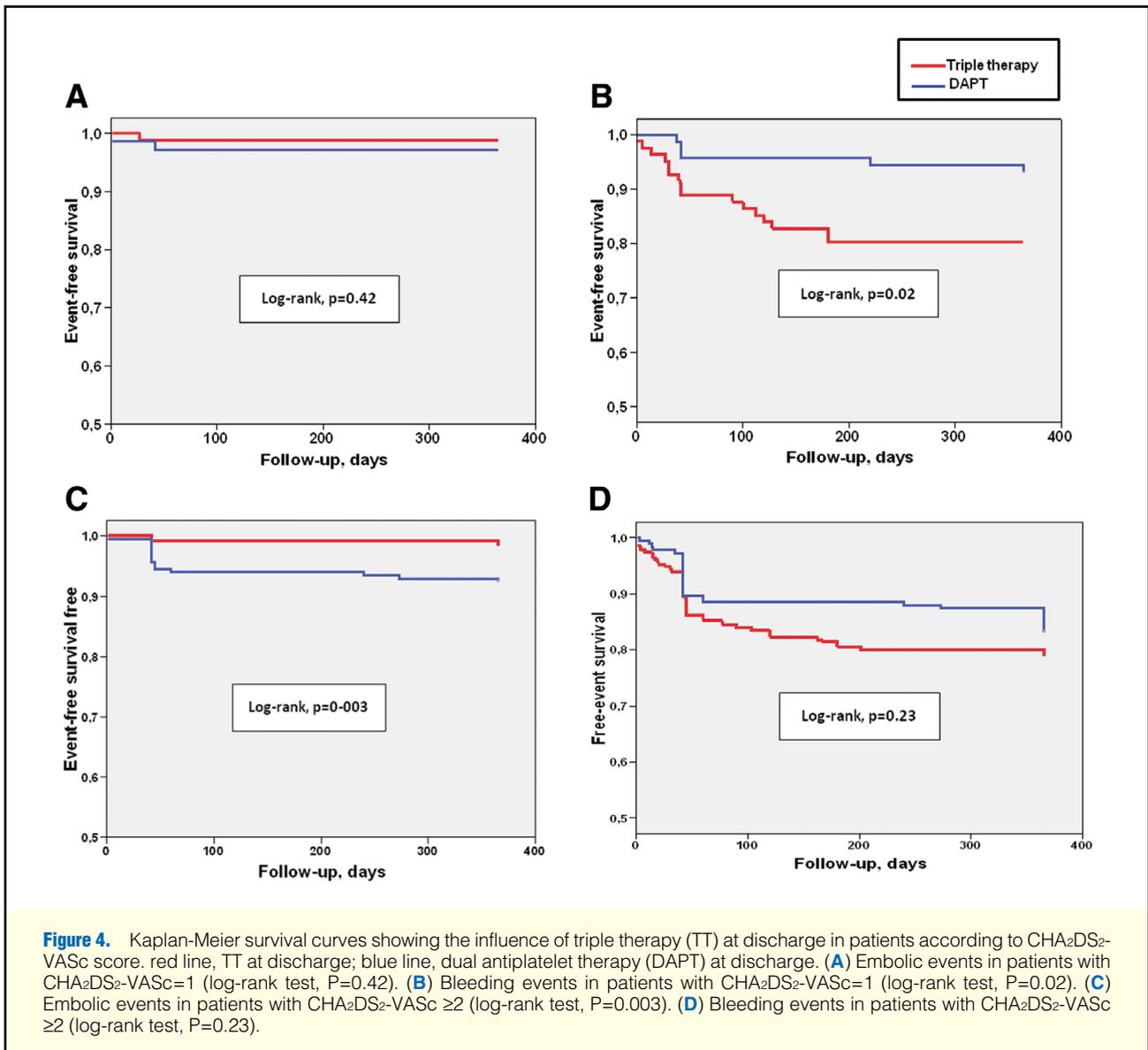
In a multivariate analysis of the overall population adjusted by confounding variables, TT was a predictor of major bleeding (HR, 2.97; 95% CI, 1.25–7.02, $P=0.01$) and MAE (HR, 1.38; 95% CI, 1.01–1.89; $P=0.04$), without a significant reduction of MACE (HR, 1.05; 95% CI, 0.67–1.86; $P=0.81$). Other predictors of major bleeding were age, and previous stroke. Renal failure, previous acute MI, previous PCI, and ejection fraction $<40\%$ were associated with MACE. Predictors of MAE were age, renal failure, and previous MI, but previous PCI was a protective factor (Table 2).

Specifically, in the subgroup with CHA₂DS₂-VASc=1, multivariate analysis showed a tendency towards a higher incidence of major bleeding in the subgroup of patients who received TT (HR 2.79; 95% CI, 0.97–8.00; $P=0.05$) after adjusting for age, renal failure, and vascular access. Neither the MACE nor MAE rate was associated with the use of TT in several models adjusted for confounding variables.

Discussion

This is the first prospective study showing that treatment with TT in patients with AF undergoing PCI with a CHA₂DS₂-VASc=1 carries a high risk of bleeding with apparently no benefit in the prevention of thromboembolic events. However, in patients with CHA₂DS₂-VASc ≥ 2 , TT was also associated with an increased incidence of bleeding but a lower rate of thromboembolism.

The use of the new risk scale, CHA₂DS₂-VASc, has expanded the number of patients with non-valvular AF who have an indication for OAC. The risk of stroke in patients with AF is feared because of the physical disability and socioeconomic costs involved.²⁰ A previous study by our group suggested that



DAPT might be a safe strategy after coronary stenting in patients with AF and low thromboembolic risk.¹⁴

In our current study of patients with CHA₂DS₂-VASc=1, only 1 patient treated with DAPT presented with a transient thromboembolic event, which represents an annual risk of thromboembolism of 1.3% (0.10% per month). The incidence of thromboembolism in our cohort is exactly the same as found by Lip et al, who refined clinical risk stratification for predicting stroke and thromboembolism in AF using the novel risk score CHA₂DS₂-VASc.^{4,6}

Furthermore, we observed a higher incidence of bleeding events (19.5% vs. 6.9% P=0.01) in patients with a CHA₂DS₂-VASc score=1 on TT as compared with those on DAPT. In addition, no patient treated with DAPT suffered a major bleeding event (4.9% vs. 0%, P=0.06). In previous studies, there have not been data available on bleeding events rates in patients with CHA₂DS₂-VASc=1.¹⁷⁻³⁰ However, we found a lower incidence of major bleeding than Ruiz-Nodar et al²⁵ and Menozzi et al,³⁰ and similar to those found by Karjalainen et al²³ and Nguyen et al²⁴ for patients on TT, irrespective of

CHA₂DS₂-VASc score. In this respect, it is remarkable that in our cohort no patients on DAPT suffered a major bleeding event.

Major bleeding has been associated with a 3- to 7-fold higher mortality rate among ACS patients compared with patients without bleeding.^{29,30} This higher mortality rate is not only caused by the bleeding event itself but also by its consequences such as discontinuation of antithrombotic treatment leading to thrombotic complications.²⁹⁻³⁸ In our study, 3 patients with CHA₂DS₂-VASc=1 and treated with TT died from complications of bleeding events.

Conversely, the present results confirm that patients with CHA₂DS₂-VASc ≥2 benefit from TT despite excessive bleeding. In agreement with other authors, we also found a strong correlation between stroke and bleeding risk scores, with patients with CHA₂D₂S-VASc ≥2 being those with the highest bleeding risk, defined as HAS-BLED ≥3.³⁹ In contrast, we found no association between CHA₂D₂S-VASc score and MACE or MAE. Therefore, decisions concerning the optimal antithrombotic management of patients with AF undergoing

Table 2. Multivariate Cox Regression Analyses for Prediction of Adverse Outcomes					
Variable	Beta	SE	HR	95% CI	P value
Predictors of major bleeding					
Age	0.63	0.03	1.06	1.00–1.13	0.04
Renal failure	0.58	0.43	1.79	0.76–4.25	0.18
Previous stroke	0.83	0.42	2.30	1.00–5.28	0.04
CHA ₂ DS ₂ -VASc	–0.05	0.61	0.99	0.30–3.30	0.99
Use of DES	0.05	0.38	1.05	0.49–2.25	0.88
TT	1.09	0.43	2.97	1.25–7.02	0.01
Predictors of MACE					
Age	0.03	0.01	1.03	0.99–1.07	0.05
Renal failure	0.77	0.25	2.17	1.31–3.59	0.002
Peripheral vasculopathy	0.19	0.31	1.21	0.65–2.24	0.54
Previous PCI	0.65	0.17	1.50	0.44–2.50	0.0001
Previous AMI	0.33	0.25	1.39	0.86–2.25	0.01
Ejection fraction	–0.02	0.008	0.98	0.96–0.99	0.009
CHA ₂ DS ₂ -VASc	–0.16	0.37	0.84	0.40–1.76	0.65
TT	0.05	0.23	1.05	0.67–1.86	0.81
Predictors of MAE					
Age	0.03	0.01	1.03	1.01–1.05	0.004
Renal failure	0.47	0.18	1.60	1.10–2.32	0.01
Peripheral vasculopathy	0.23	0.22	1.26	0.81–1.94	0.29
Previous stroke	0.25	0.20	1.28	0.86–1.91	0.22
Previous MI	0.39	0.17	1.48	0.10–2.08	0.02
Previous PCI	–0.68	0.19	0.50	0.34–0.73	0.0001
Previous CABG	–0.03	0.24	0.97	0.60–1.57	0.90
CHA ₂ DS ₂ -VASc	–0.34	0.24	0.71	0.44–1.14	0.15
TT	0.32	0.15	1.38	1.01–1.89	0.04

CHA₂DS₂-VASc is an acronym for thromboembolism factors (Congestive heart failure, Hypertension, Diabetes, Vascular disease, Age 65–74 years and Sex (female), all with a score=1, while age ≥75 years and history of previous stroke have a score=2.^{1,2} A score ≥2 indicates 'high risk' for stroke or embolism. Abbreviations as in Table 1.

PCI are not easy.

On the other hand, although there is some evidence supporting the strategy of combining OAC plus clopidogrel in this setting,⁴⁰ this regimen was rarely prescribed in our series, probably because of the widely accepted notion that the omission of DAPT could determine a greater incidence of early and late stent thrombosis.^{14,39,41,42} The use of OAC plus clopidogrel was very rare in our cohort and those patients were excluded (data not shown). Therefore, DAPT was preferred over a single antiplatelet agent, likely because 73% of patients had an ACS as index event, in accordance with other studies.^{24,39}

In agreement with our results, both Tomita et al⁴³ and Okumura et al⁴⁴ recently reported that patients with AF and modified CHA₂DS₂-VASc score=1 (registry did not include peripheral artery disease or aortic plaque) had a truly low risk of thromboembolism (0.86%), even when female sex was excluded (1.0%), suggesting that the use of anticoagulation must be avoided in this subgroup of patients.^{43,44}

On the other hand, Abe et al⁴⁵ found no significant sex difference in the annual incidence of thromboembolism (1.2% for women, 1.6% for men; odds ratio 0.72, 95% CI 0.28–1.62; P=0.44). That study also confirmed there were no significant differences between the CHA₂DS₂-VASc score and their proposed CHA₂DS₂-VA score (a modified risk scoring system that excludes female sex as a variable from the CHA₂DS₂-VASc score) in both men and women.⁴⁵ In our cohort, sex was not an independent factor for bleeding, concurring with other bleeding risk scores (HAS-BLED and ORBIT-AF) that did

not identify female sex as an independent predictor for bleeding. We think that female sex was not an independent factor for bleeding “per se”; we believe it is more likely that weight <60 kg is the true independent factor for bleeding.

In short, our data suggested that in patients with CHA₂DS₂-VASc=1 undergoing PCI, bleeding risk far exceeds thromboembolic risk. However, the recommendations of current guidelines are undefined. In this respect, we add valuable information for determining clinical practice in this setting of patients, pending results of randomized trials comparing TT vs. DAPT or new anticoagulants.^{46–48}

Study Limitations

The major limitations of the current study are possible selection bias and confounding not accounted for in the multivariable analysis, inherent to all observational studies. The number of patients with CHA₂DS₂-VASc=1 was small, but the proportion of this subgroup must be low in all series, because CHA₂DS₂-VASc stroke risk score assigns 1 point to peripheral vascular disease (including MI) and the studies in this subgroup are particularly scarce.⁶ On the other hand, the choice of antithrombotic therapy regimen was at the discretion of the attending physician and was non-randomized, inherent to a “real world” registry. It is noteworthy that the subgroup of patients with CHA₂DS₂-VASc ≥2 received DAPT in a similar proportion to those who received TT, despite the high risk of thromboembolism in this population. The reasons why this decision was made are unknown. However, the decision to

treat with TT or DAPT was not in relation to the risk of bleeding, because numbers of patients with HAS-BLED ≥ 3 were similar in both groups. Another limitation is that data on time in the therapeutic range for patients on OAC could not be obtained for the overall population, although the subgroup with these data available was probably representative of the overall sample.

Conclusions

In summary, the use of TT in patients with a CHA₂DS₂-VASC=1 carries a high risk of bleeding with no apparent benefit in preventing thromboembolic events, while in patients with CHA₂DS₂-VASC ≥ 2 , TT decreases the thromboembolism rate despite an increase in major bleeding. Decisions in these patients regarding the type and duration of antithrombotic therapy should be individualized, with the need for careful clinical assessment and regular follow-up. Randomized trials are warranted to establish the optimal management in this complex setting.

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Disclosures

None. The authors are solely responsible for the design and conduct of this study, all study analyses, drafting and editing of the paper and its final contents.

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