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Antithrombotic therapy in patients with atrial fibrillation and acute coronary syndrome in the real world: Data from the Berlin AFibACS Registry

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Abstract

Background: *Guidelines for the management of atrial fibrillation (AFib) recommend antithromboembolic treatment strategies for patients with AFib and acute coronary syndrome (AFibACS). Our study assessed how current guidelines are implemented in the metropolitan area of Berlin and which therapeutic options were chosen in light of stroke and bleeding risk in everyday practice.*

Methods and Results: *Between April 2008 and January 2012, we included 1,295 AFibACS patients in the AFibACS Registry, as part of the Berlin Myocardial Infarction Registry. Mean age of the patients was 76 years with numerous comorbidities (15.4% former stroke, 35.0% renal failure, 43.5% diabetes, 92.8% hypertension). Of all the patients, 888 were treated with stent implantation, 91 with balloon angioplasty, and 316 conservatively. Overall mortality was 11.6%, and 8.3% in stented patients. At hospital discharge, triple therapy was administered to 49.9% of stented cases. After adjustment, odds of receiving triple therapy were lower with increasing age and renal failure. Odds were higher after stent implantation, with a higher CHA_2DS_2-VASc score, and with any AFib category compared to initially diagnosed AFib. Between 2008 and 2011, triple therapy increased from 33.3% to 49.8% for stented patients and did not change significantly for those treated conservatively or with balloon angioplasty.*

Conclusions: *These data suggest that in AFibACS patients, antithrombotic treatment focused on dual antiplatelet therapy for ACS, rather than on anticoagulation therapy for stroke prevention. Factors influencing therapy at discharge were age, renal failure, stent implantation, AFib category, and CHA_2DS_2-VASc score. During the study period, triple therapy increased for stented patients.* (Cardiol J 2014; 21, 5: 465–473)

Key words: acute myocardial infarction, atrial fibrillation, triple therapy, antithrombotic therapy, registry data

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Introduction

Atrial fibrillation (AFib) is the most common cardiac arrhythmia and it is found in 1–2% of the general population. AFib increases the risk of stroke 5-fold and is responsible for one-fifth of all incidents of stroke — often severe cases with a high degree of disability and a risk of death double to that of patients with other causes of stroke [1, 2]. For prevention of stroke, patients with AFib receive antithrombotic therapy (level of evidence Ia in guidelines) which reduces stroke rates by 64% [3]. In a recent analysis of a large German database, Wilke et al. [4] showed that the use of anticoagulation therapy reduced the stroke rate by 74%.

Patients with AFib and acute coronary syndrome (ACS) pose an even greater challenge. For prevention of stroke, these patients need anticoagulation therapy, and for prevention of further coronary events, they require dual antiplatelet therapy as recommended by current guidelines [5–7]. However, the combination of anticoagulation and dual antiplatelet therapy (triple therapy) may dramatically increase the risk of bleeding, with the incidence of bleeding being reported from 2% to 15% [5] and increased bleeding events will lead to longer therapy duration [8]. At the same time, ACS patients with major bleeding have greater risk of death than patients without bleeding [9, 10].

Considering the dilemma whether anticoagulation medication for stroke prevention on top of dual antiplatelet therapy may increase the risk of bleeding, strong evidence from adequately powered and rigorously conducted trails would be crucial. However, existing recommendations are based on small samples and show inconsistent findings on safety and efficacy. The 20 studies [5] that served as the basis for the AFib guideline recommendations comprised between 27 to 1,247 cases, with 14 studies having included less than 250 cases and 15 studies being single-center or dual-center studies.

For AFibACS patients with a low or intermediate hemorrhagic risk, guidelines recommend triple therapy for 6 months, a combination of anticoagulation and clopidogrel for up to 12 months, and anticoagulation lifelong. For AFibACS patients with a high hemorrhagic risk, guidelines recommend triple therapy for 4 weeks, a combination of anticoagulation and clopidogrel for up to 12 months, and anticoagulation lifelong [11, 12]. A United States consensus document in comparison to the European approach proposes a longer duration of triple therapy for patients with low to moderate bleeding risk and increased stent thrombosis and stroke risk. Trying to avoid thromboembolic complications seems to be greater in North America compared to Europe, where bleeding was more of a concern [13, 14].

Because of the high risk of bleeding, triple therapy is under discussion [15]. The WOEST Study [16], which included AFib patients treated with a stent, and a Danish data [17] analysis with AFibACS patients showed that bleeding risk and mortality were higher in patients treated with triple therapy than those treated with anticoagulation medication and clopidogrel alone (double therapy), with no difference in stent thrombosis and thromboembolic risk. Also, a small study by Yang et al. [18] showed that a dual therapy with aspirin and prasugrel was more potent than a triple therapy with aspirin, clopidogrel and cilostazol.

Our study aimed at showing how guidelines were implemented in the metropolitan area of Berlin and which therapeutic options were taken in light of stroke and bleeding risk in everyday practice. Rubboli et al. [19] were recently able to show that the management of patients with AFib and coronary stenting was variable across Europe and only partially adherent to guidelines.

Methods

The Berlin Myocardial Infarction Registry (BMIR) is a prospective registry, which has continuously been collecting data on treatment of ACS patients in Berlin hospitals since 1999. Our study was carried out on top of the ongoing BMIR [20].

Between April 2008 and January 2012, we collected data on 11,068 ACS patients admitted to 19 hospitals in Berlin within 24 h after ACS symptom onset. ACS was defined as type I myocardial infarction, as universally defined [21]. In our study, we included only those 1,295 ACS patients, who in addition to ACS suffered from non-valvular AFib. AFib data were collected and categorized according to the presentation of arrhythmia: first-diagnosed, paroxysmal, persistent, long-standing persistent, and permanent AFib [11].

Regular monitoring and peer review took place within the BMIR, and site audits were performed in the participating hospitals to ensure that patients are consecutively included in the Registry. Patients were also selected randomly from every institution, with source-data verification in 7.5% of patients. Data entry was performed at the Technische Universität Berlin. All entries were double-checked for errors and inconsistencies. In cases of missing data, institutions were asked to provide the additional necessary information.

Patients' data were collected anonymously. The data registry was approved by the Berlin Board for Data Privacy Monitoring. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Data collection

For the AFibACS Registry, data were collected in each institution on hardcopy or electronic questionnaires by trained cardiovascular specialists, and were subsequently processed on a pseudonymized basis. A booklet with detailed information on definitions and special aspects of data entry was available in every participating hospital. The main sections of the questionnaire covered demographic data (age, sex), pre-existing risk factors (arterial hypertension, smoking, diabetes mellitus, hypercholesterolemia > 200 mg/dL), and medical history. Congestive heart failure and renal failure (with C_{rea} < 2 mg/dL), as well as left ventricular function were diagnosed on admission by the attending physician.

Data on the pre-hospital phase and on patient findings at initial presentation were also collected: e.g., blood pressure, heart rate, and cardiogenic shock at admission. The attending physicians recorded the type of AFib, CHA_2DS_2-VASc, and HAS-BLED scores, as well as treatment, complications, outcome, and medication (including anticoagulation medication at hospital discharge).

Statistical methods

Data are presented as percent values, mean values with standard deviation, and median values with first and third quartiles. We applied Pearson's χ^2 test for univariate comparison of nominal data. We performed the χ^2 test for trend of categorical variables. We performed the t-test for age. Significance was assumed for $p < 0.05$. All tests of statistical significance were 2-tailed.

We applied logistic regression to adjust for age (in years) and female gender, and for those variables that showed a significant influence on triple therapy in univariate analysis: renal failure, stent implantation, type of AFib (paroxysmal compared to new-onset AFib, and persistent or permanent compared to new-onset AFib), and CHA_2DS_2-VASc score as a continuous variable.

Medication at hospital discharge was analyzed for all patients discharged alive from the hospital, and was defined as the following:

— DAPT — patients who received only dual antiplatelet therapy with aspirin and a $P2Y_{12}$ inhibitor;
— triple therapy — patients who received DAPT and anticoagulation medication with either a vitamin K antagonist, heparin, or new direct oral anticoagulants;
— double therapy — patients with a single antiplatelet drug (aspirin, clopidogrel, prasugrel, or ticagrelor), and one anticoagulative drug (phenprocoumon, heparin, or new direct oral anticoagulants);
— mono therapy — patients with aspirin or clopidogrel only;
— rest — other combinations with < 2% (includes also 0.9% of patients who received phenprocoumon only).

Results

Baseline characteristics

A total of 1,295 AFibACS patients were collected during a 46-month study period, which comprised 11.7% of all ACS patients enrolled in the BMIR (2008: 8.2% and 2011: 14.7% of all ACS patients). With a mean age of 75.6 years, the AFib ACS patients were older than all ACS patients (66.5 years), and the percentage of women (38.3%) was higher than in the ACS patient group (31%). Compared to all ACS patients, they suffered more from comorbidities: 15.4% former stroke (for the total cohort: 8.1%), 29.5% former ACS (22.6%), 35% renal failure (17.2%), 43.5% diabetes mellitus (30.5%), 45.6% chronic heart failure (14.8%), and 92.8% hypertension on admission (78.2%). An ST-elevation myocardial infarction (STEMI) was present in 31.5% compared to 45.5% in all ACS patients, with 8% having experienced cardiogenic shock at admission (all: 6.6%) and 17.1% with a left ventricular function of ≤ 30 compared to 9.9% in all ACS patients.

With respect to the type of AFib, 21.2% were categorized as first-diagnosed, 36.0% as paroxysmal, 8.7% as persistent, 1.6% as long-standing persistent, and 32.6% as permanent AFib.

The CHA_2DS_2-VASc score was > 1 in 99.2% of patients. 69.9% of patients had a high bleeding risk with a HAS-BLED score > 2 (Tables 1, 2).

In-hospital treatment and outcome

A total of 888 AFibACS patients were treated with stent implantation: 59% with bare metal stents (BMS) and 41% with drug-eluting stents (DES). In 91 patients, only balloon dilatation was performed, and 316 patients did not undergo intervention. The use of BMS or DES was independent of the HAS-BLED score (HAS-BLED score 0–2: 56% BMS, 44% DES; HAS-BLED score > 2: 60% BMS, 40% DES; $p = 0.256$)

Table 1. Number of atrial fibrillation and acute coronary syndrome patients according to CHA_2DS_2-VASc score.

CHA_2DS_2-VASc score	No. (%) of patients
Score 0	0 (%)
Score 1	10 (0.8%)
Score 2	61 (4.7%)
Score 3	160 (12.4%)
Score 4	279 (21.5%)
Score 5	369 (28.5%)
Score 6	249 (19.2%)
Score 7	112 (8.6%)
Score 8	44 (3.4%)
Score 9	11 (0.8%)

Table 2. Number of atrial fibrillation and acute coronary syndrome patients according to HAS--BLED score.

HAS-BLED score	No. (%) of patients
Score 0	7 (0.5%)
Score 1	84 (6.5%)
Score 2	299 (23.1%)
Score 3	488 (37.7%)
Score 4	311 (24.1%)
Score 5	89 (6.9%)
Score 6	15 (1.2%)
Score 7	0 (0%)
Score 8	0 (0%)
Score 9	0 (0%)

and independent of in-hospital bleeding. Patients with moderate to severe bleeding (GUSTO criteria) received BMS in 66.7% and DES in 33.3% of cases compared to 57.7% with BMS and 42.2% with DES for patients with only minor bleeding or without bleeding ($p = 0.291$).

Patients treated with stent, balloon angioplasty only, and conservatively differed in age, sex, comorbidities, and STEMI (Table 3). They also differed in outcome: 8.3% of patients treated with a stent died in the hospital compared to 13.2% with balloon angioplasty and 20.3% treated conservatively ($p < 0.001$). Overall death rate was 11.6%.

Hospital discharge medication

Figure 1 depicts discharge medication. With a majority of patients on DAPT, main determinants were ACS and stent implantation. Dual antithrombotic therapy was provided to 96.3% of stented patients — of whom approximately half received additional anticoagulation medication. HAS-BLED score 0–2 compared to a score > 2 did not show any differences between the different categories, which may be seen in Figure 1.

Patients on triple therapy after stent placement (n = 406) received phenprocoumon in 55%, heparin in 43%, and dabigatran in 2% of cases indicating anticoagulation therapy. Those patients treated with balloon angioplasty (n = 35) received phenprocoumon in 40% and heparin in 60% of cases, those treated conservatively (n = 50) were on phenprocoumon in 42% and on heparin in 58%.

Prescription of triple therapy at hospital discharge depended on age, renal failure, stent implan-

Table 3. Baseline characteristics of atrial fibrillation and acute coronary syndrome patients treated with stent, balloon angioplasty, or conservatively.

Baseline characteristics	With stent (n = 888)	Balloon angioplasty (n = 91)	Conservatively (n = 316)	P*
Age [years]	74	76	80	< 0.001
Women	34.6%	33.0%	50.3%	< 0.001
ST elevation myocardial infarction	36.8%	37.8%	15.0%	< 0.001
Diabetes mellitus	43.4%	42.9%	44.0%	0.861
Hypertension	92.7%	92.3%	93.4%	0.714
Renal failure	30.3%	37.8%	47.3%	< 0.001
Coronary heart disease	42.8%	56.0%	50.6%	0.008
Former acute coronary syndrome	28.1%	45.5%	28.9%	0.450
Former stroke	14.0%	11.1%	20.6%	0.0009
Atrial fibrillation permanent	29.6%	37.2%	40.1%	< 0.001
CHA_2DS_2-VASc score (7–9)	10.9%	12.1%	19.1%	< 0.001
HAS-BLED score > 2	66.9%	70.3%	77.9%	< 0.001

*χ^2 test for trend

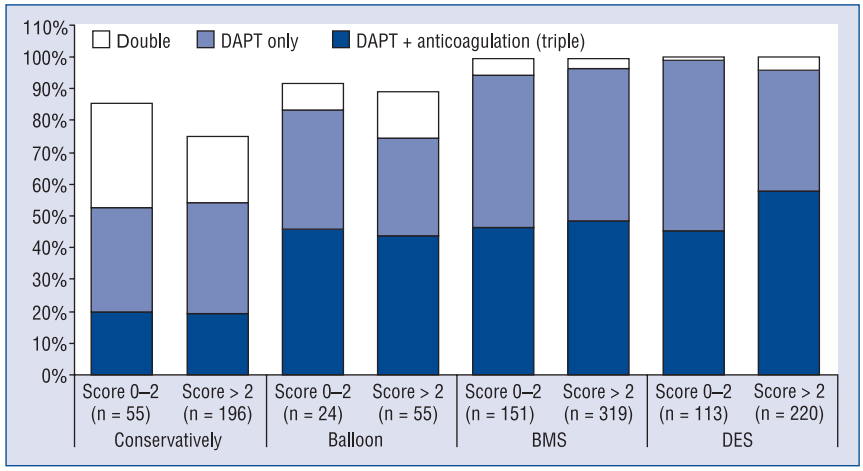

Figure 1. Antithrombotic therapy at hospital discharge for patients with CHA2DS2-VASc score > 1 treated with bare metal stents (BMS) or drug-eluting stents (DES), balloon angioplasty, or conservatively according to HAS-BLED score (in %).

tation, AFib category, and CHA_2DS_2-VASc score (Table 4). According to the odds ratios (OR), stent implantation, and age had the greatest association with triple therapy after adjustment by logistic regression analysis. Another major factor of influence was the CHA_2DS_2-VASc score. For each increasing additional score point, the chance of receiving triple therapy rose by OR = 1.22.

The HAS-BLED score (0–2 vs. > 2) did not show a significant influence on the prescription of triple therapy in the logistic regression analysis (OR 1.15, 95% CI 0.84–1.57). Also, moderate to severe in-hospital bleeding did not significantly influence prescription of triple therapy (results not shown).

Chronological changes in therapy

Patients who were treated with a stent received triple therapy more often in the period 2011–2012 (58.1%) than in 2008 (39.8%) (Fig. 2). An increase was not observed in patients treated conservatively or with balloon angioplasty. A significant share of stent-treated patients were on heparin at hospital discharge (Fig. 3). Dabigatran played only a minor role in 2011–2012 for patients treated with a stent.

Discussion

We collected data from 1,295 AFibACS patients, who comprised 11.7% of all ACS patients collected within the BMIR in the respective period. Our figures correlate well with other studies reporting that between 6% and 21% of patients with ACS suffer from AFib [22].

Table 4. Factors influencing the prescription of triple therapy at discharge for patients with CHA_2DS_2-VASc > 1 (results of a logistic regression analysis).

Variables adjusted for	OR	95% CI
Age [years]	0.98	0.96–0.994
Women	0.82	0.60–1.10
Stent implantation	3.00	2.21–4.06
Renal failure	0.74	0.55–0.98
AFib first-diagnosed (reference)	–	–
AFib paroxysmal	1.73	1.20–2.47
AFib pers./perm.	2.25	1.57–3.23
CHA_2DS_2-VASc (as a continuous variable)	1.20	1.06–1.35
HAS-BLED score (0–2 vs. > 2)	1.15	0.84–1.57

OR — odds ratio; CI — confidence interval; AFib — atrial fibrillation; pers. — persistent; perm. — permanent

There was an increase of AFibACS patients observed between 2008 and 2011. Although the causes of this increase remain unclear, we may assume it happened due to heightened awareness for AFib within our ACS population. An increased awareness for AFib was also the assumption put forward by Schnabel et al. [2]. Stefansdottir et al. [23] showed an increase in prevalence and incidence for patients with AFib for Iceland, and Ahmad and Kirchof [24] argued in a recent Editorial in "Circulation" that prevalence and incidence of AFib increase as the populations get older and that improved treatment of patients with other cardiac disorders than AFib, i.e. ACS, will prolong the lives of the patients at risk of AFib.

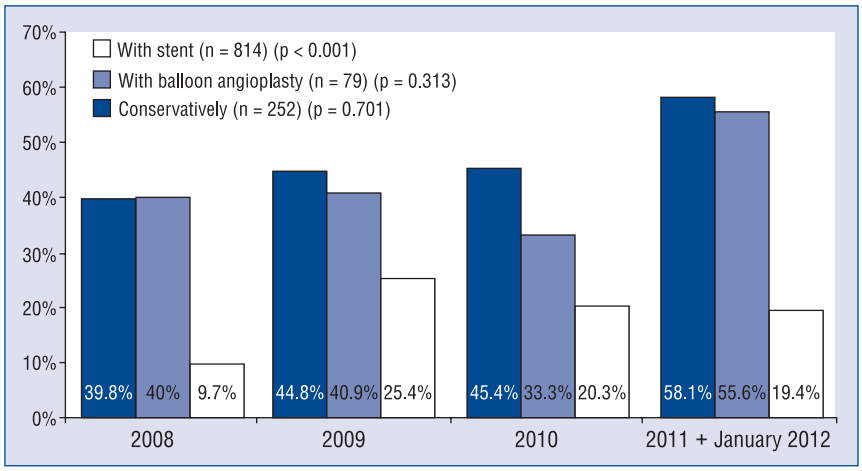

Figure 2. Changes over time regarding the prescription of triple therapy in atrial fibrillation and acute coronary syndrome patients at hospital discharge, treatment with stent, balloon angioplasty, or conservatively (in %).

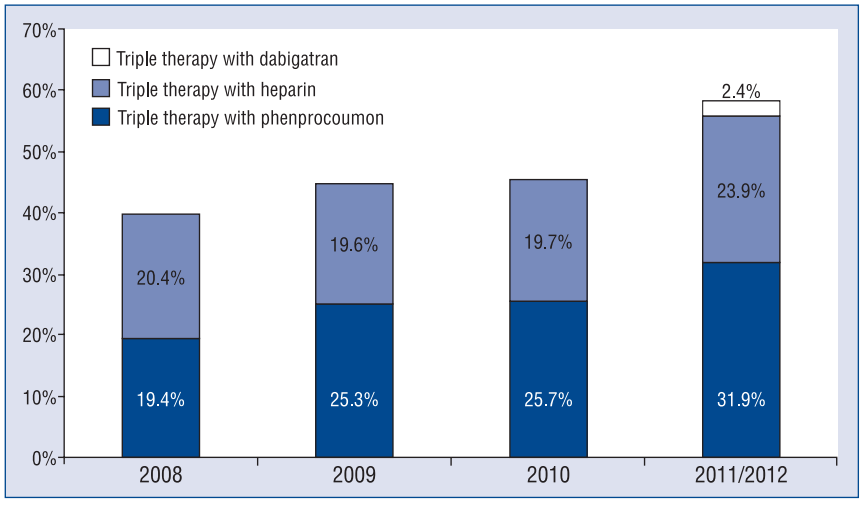

Figure 3. Anticoagulation in stent-treated atrial fibrillation and acute coronary syndrome patients discharged with triple therapy (in %).

AFibACS patients, as high-risk group of patients

In our study, AFibACS patients were in average older than patients with ACS alone. They were also multimorbid to a greater degree and had a higher in-hospital death rate. Similar data were published by the ACTION Registry-GWTG [25], with AFibACS patients being on average of 78 years of age, having a history of hypertension in 84.7% of cases, diabetes mellitus in 38.4%, former ACS in 34.9%, coronary heart disease (CHD) in 34.8%, and former stroke in 16.3%. They also demonstrated a $CHADS_2$ score < 1 in 3.7% of cases and died in hospital in 9.9%. The GRACE registry [26] compared ACS patients with new-onset and pre-existing AFib. The average age of these patients was from 72 to 75. With the combination of new-onset and pre-existing AFib patients in GRACE, the AFibACS patients had a history of hypertension in 71% of cases, of diabetes mellitus in 29%, of former ACS in 37%, and of CHD in 24%. They died in the hospital in 11.2% of cases. These data were very similar to our results. Patients' characteristics in our context compared well with that of previously published registry data underscoring that AFibACS patients constitute a high-risk group.

In-hospital treatment

We divided our AFibACS patients into three groups: those who received interventional reper-

fusion therapy with coronary stenting, those with balloon angioplasty, and those treated conservatively. The three groups differed substantially. Those treated with a stent were younger and less often female. In addition, they suffered less often from renal failure, CHD, and former stroke, and presented with STEMI more often. Mortality for stented patients was 12% lower than for those treated conservatively ($p < 0.001$). Although patients with high risk of bleeding are recommended to receive BMS instead of DES, in our study only 60% of patients with a HAS-BLED score > 2 received DES. This percentage is lower than the one found by Rubboli et al. [19] who showed that 76% of AFib patients with coronary stenting receive BMS.

Hospital discharge medication

At hospital discharge, 96.3% of patients treated with a stent were on DAPT compared to 53.9% of those treated conservatively ($p < 0.001$). Additional anticoagulation (triple therapy) was prescribed only in 49.9% of patients with stent and in 19.5% of conservatively treated patients. These results are in line with the results of the ACTION Registry-GWTG [24]. During years 2008–2009, only 15% of all AFibACS patients were discharged on triple therapy, whereas 63.5% were on DAPT. Lamberts et al. [17], with a Danish cohort of AFib ACS patients, demonstrated similar results from an earlier period (2000–2009) with triple therapy in only 13% of all AFibACS patients, DAPT in 27%, double in 16%, and mono in 36% of patients (8% any other combination). Lamberts et al. [17], however, showed that the risk of bleeding was higher with triple therapy than with other treatment approaches. This risk may be reflected in many physicians' choice not to administer triple therapy to AFibACS patients.

A potential reluctance of hospital-based physicians to make a decision for triple therapy may be indicated by the high number of patients receiving heparin at discharge (40%). This figure suggests that hospital physicians shift the decision to subsequent outpatient care.

Logistic regression analysis identified stent placement as one of the major determinants of triple therapy at discharge after adjustment (OR = 3.0). The results of the logistic regression also showed that triple therapy was lower in older patients and in patients with renal failure, was higher in patients with paroxysmal or persistent/ /permanent AFib (as compared to first-diagnosed AFib) and higher with a higher CHA_2DS_2-VASc score. For each additional point of the CHA_2DS_2-VASc score, the probability of receiving triple therapy increased by OR = 1.22, which indicated that the chances of receiving triple therapy were 2.76 times higher with a score of 9 than with a score of 1. Thus, the CHA_2DS_2-VASc score that had been introduced in the new European Society of Cardiology (ESC) AFib guidelines in 2010 [11] is reflected in everyday practice in Berlin hospitals. In contrast, we could not identify if the HAS-BLED score had a statistically significant influence on the rate of triple therapy at discharge, although it has been shown that the HAS-BLED score predicts bleeding events with a moderate accuracy [27].

Changes of discharge medication in recent years

The number of stent-treated patients receiving triple therapy increased over time, especially since 2011. Therefore, the awareness of AFib and triple therapy has increased since 2011. In August of 2010, new ESC AFib guidelines were published, which recommended triple therapy for AFibACS patients [11]. In 2011, new direct oral anticoagulants were approved for stroke prevention in non-valvular AFib patients (dabigatran in August 2011 [28], rivaroxaban in December 2011 [29], and apixaban in November 2012 [30]). In 2012, a focused update on the management of AFib was published with a special chapter on novel oral anticoagulants [12]. Although, as recorded in our registry, dabigatran use was low in 2011, it is likely that prescription of dabigatran, rivaroxaban, and apixaban will increase with a larger number of patients treated by triple therapy with these agents. However, as voiced in a recent Editorial in the "European Heart Journal" [31], it remains unclear whether the new oral anticoagulants should be preferred over the standard therapy for AFibACS patients. Dedicated randomized trials on triple therapy with the new direct oral anticoagulants are clearly warranted.

Limitations of the study

Since our data are based on a registry, the known limitations of registry data must be taken into consideration. These, for example, do not allow direct comparison of therapies or their efficacy. We do not have follow-up data after hospital discharge on bleeding or stroke or mortality. Our data were collected in a metropolitan area of the city of Berlin and may therefore not be applicable to other regions or rural areas.

Conclusions

Our present analysis illustrates how patients with ACS and AFib were treated under real-world circumstances. We were able to show that AFibACS patients in Berlin were older than ACS patients and multimorbid. Hospital discharge treatment focused more on ACS treatment with high rates of antithrombotic therapy for patients treated with a stent, and with lower rates for patients treated conservatively or with balloon angioplasty. In addition, anticoagulation therapy for stroke prevention was administered less often. After adjustment, higher age and renal failure lowered chances of receiving triple therapy, whereas stent implantation, paroxysmal or persistent/permanent AFib (as compared to first diagnosed AFib), and a higher CHA_2DS_2-VASc score increased chances of receiving triple therapy. Over time, triple therapy increased for patients treated with a stent.

Owing to their great risk of stroke, patients with ACS and AFib pose a therapeutic challenge in cases of treatment with anticoagulation on top of dual antiplatelet therapy. An additional great risk is the one of bleeding associated with triple therapy. Therefore, dedicated randomized trials on triple therapy with the new direct oral anticoagulants are clearly warranted.

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