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ORIGINAL PAPER

Prognosis of patients with atrial fibrillation undergoing percutaneous coronary intervention receiving drug eluting stents

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Abstract
Background Atrial fibrillation (AF) is increasingly prevalent in elderly patients and adversely affects clinical outcomes after coronary artery bypass grafting, non-cardiac surgery or myocardial infarction. Aim of the present analysis was to investigate the prognostic impact of AF in patients undergoing drug eluting stent (DES) implantation during a 1-year follow-up.
Patients and methods 5,772 consecutive patients undergoing percutaneous coronary intervention were enrolled into the German Drug Eluting Stent Registry (DES.DE) and were followed for 12 months. Of these 455 had AF and 5,317 in sinus rhythm served as controls. Univariate and multivariate logistic regression analyses were used to determine the risk of major adverse cardiac and cerebrovascular events (MACCE) and bleeding complications.
Results Patients with AF were older (71.3 ± 7.6 vs. 64.7 ± 10.5 years) and had a higher prevalence of diabetes, hypertension, renal insufficiency as well as more prior bypass surgery, stroke and peripheral arterial disease. Cardiogenic shock (2.9 vs. 1.4 %; $p < 0.05$), left ventricular ejection fraction ≤40 % (21.0 vs. 11.4 %; $p < 0.0001$) and triple vessel disease (44.4 vs. 37.9 %; $p < 0.01$) were more frequent in patients with AF than in controls. MACCE (OR 2.08, 95 % CI 1.56–2.77), total mortality (OR 3.27, 95 % CI 2.32–4.62) and non-fatal stroke (OR 2.03, 95 % CI 1.03–4.00) as well as bleeding complications (OR 1.88, 95 % CI 1.13–3.12) during the 1-year follow-up were more frequent in patients with AF (univariate analysis). In multivariate analyses adjusting for covariates determined to be relevant at baseline, the risk for total mortality remained elevated (OR 1.63, 95 % CI 1.05–2.52).
Conclusions AF is an important predictor of long-term mortality in patients undergoing DES implantation.

Keywords Atrial fibrillation · Drug eluting stent · MACCE · Mortality

For the DES.DE Study Group.

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Introduction

Atrial fibrillation (AF) is associated with structural heart disease and leads to a fivefold increased risk for stroke, heart failure and a 50–90 % increase in the risk of death [1–4]. The incidence of AF in patients with acute coronary syndromes varies between 2 and 21 % [3, 5–7]. AF can adversely affect clinical outcomes after coronary artery bypass grafting (CABG) [8, 9], other non-cardiac surgery [10], acute myocardial infarction (AMI) [3, 11, 12] and percutaneous coronary intervention (PCI) [13].

Data on the prognosis of patients with AF undergoing elective or emergent PCI procedures with implantation of drug eluting stents (DES) are scarce [14–17]. Ruiz-Nodar et al. [14] evaluated a retrospectively identified cohort of 604 patients with AF undergoing BMS or DES implantation with a follow-up of 7 years. They found higher incidence rate of major bleeding with DES but no difference in MACE or all-cause mortality. A more recent Australian registry in 3,307 patients with or without AF reported increased mortality (9.9 vs. 2.2 %, $p < 0.0001$) and readmission rates at 30 days ($p = 0.01$).

Existing data are, however, frequently retrospective and limited by their missing long-term (>90 days) follow-up. To investigate the impact of AF in patients with DES implantation and the role of anticoagulation for prognosis in clinical practice at 1 year, we analyzed data of the German Drug Eluting Stent Registry (Deutsches Drug Eluting Stent Register, DES.DE) [18].

Methods

Patients and data collection

Consecutive patients undergoing elective or non-elective PCI procedures were enrolled into DES.DE on an intention-to-treat basis by the coordinating center in Ludwigshafen. DES.DE is a German multi-center, multi-stent registry for DES aiming at demonstrating the treatment of patients with coronary artery disease (CAD) giving further insight into daily practices beyond randomized trials. Details of the registry were previously described [18–21]. The registry was approved by the research and ethics committees at the institutions involved, and patients gave written consent for processing their anonymous data. The first patients were enrolled in October 2005. During phase I, only CYPHER™, TAXUS™ and selected patients with BMS were included. For the present analysis only DES patients were considered. Follow-up was completed at 3, 6, 9 and 12 months.

Documentation

Patient baseline characteristics, angiographic as well as interventional data and in-hospital outcomes were documented on a case report form (paper based or electronic) and transferred for data management to the Institut für Herzinfarktforschung, Ludwigshafen. The data were checked for completeness and consistency, and queries were generated when necessary for all centers. Clinical outcomes and in-hospital death were documented by the attending physicians, in some cases hospital mortality was obtained by the hospital administration office.

Endpoints

All deaths were documented, and differentiation made between cardiac, non-cardiac, and unknown causes. Target vessel revascularization was defined as either percutaneous intervention or bypass surgery for the initially treated coronary vessel. Stent thrombosis was defined as probable, possible, and certain [22]. Myocardial infarction was defined as either ST elevation or non-ST elevation myocardial infarction [23]. The endpoint major adverse cardiac and cerebrovascular event (MACCE) was the composite of cumulative death, myocardial infarction, or stroke/transitory ischemic attack (TIA) analyzed from hospital discharge to 12 months.

The $CHADS_2$ [cardiac failure, hypertension, age, diabetes, stroke (doubled)] risk index is based on a point system in which 2 points are assigned for a history of stroke or TIA and 1 point each is assigned for age >75 years, a history of hypertension, diabetes, or recent cardiac failure. Information on major bleeding complications was based on physician assessment.

Statistical analysis

Frequencies of patient characteristics and outcomes are presented as percentages. The distribution of metric variables is described with medians and quartiles. All descriptive statistics are based on available cases. Interventional characteristics are reported for the first procedure performed during hospital stay in an individual patient. For the comparison of patient characteristics between subgroups crude odds ratios with 95 % confidence intervals are shown, or p values of the Mann–Whitney–Wilcoxon test in case of metric variables.

Survival curves were estimated for a 12-month period after PCI by the Kaplan–Meier method and compared by log-rank test. Unadjusted and adjusted odds ratios with 95 % confidence intervals were calculated by logistic regression for the outcomes mortality/MACCE, as well as MI, stroke and major bleeding. In addition to the presence of AF, the following variables were entered into backward selection procedures applying a level of $p > 0.05$ for removal: age, gender, diabetes, hypertension, positive family history, impaired renal function, prior MI, bypass, PCI, stroke, PAD, cardiogenic shock, heart failure, EF <40 %, triple vessel

disease, and left main disease. p values ≤ 0.05 were considered significant (two-tailed). The statistical analyses were performed using SAS, version 9.2 (Cary, NC, USA).

Results

5,772 patients recruited at 98 sites were available for the present analysis of which 455 had AF at hospital admission and 5,317 in sinus rhythm served as controls. Patients with AF were about 6.5 years older (71.3 ± 7.6 vs. 64.7 ± 10.5 years) and had a higher prevalence of diabetes, hypertension, and renal insufficiency. Further, they had an increased cardiovascular co-morbidity burden, with prior CABG, stroke and PAD being more frequent (Table 1).

Cardiac status at hospital admission

More patients in this registry underwent elective (56.2 %) than emergency PCI (40.8 %) (Table 2). There were no further significant differences with respect to the target segment or the degree of stenosis prior to and after PCI, except for slight differences in lesion length (median: 16 vs. 15 mm; $p < 0.01$), the proportion of patients with type C stenosis (33.2 vs. 26.9 %; $p < 0.05$), the proportion of in-stent stenoses (11.9 vs. 15.9 %; $p < 0.05$) and the proportion of successfully positioned stents (97.3 vs. 98.7 %; $p < 0.05$). Substantial differences were noticed with respect to the cardiac status. More patients with AF had cardiogenic shock (OR 2.00, 95 % CI 1.10–3.63), heart failure (OR 2.13, 95 % CI 1.69–2.69), an ejection fraction ≤ 40 % (OR 2.07, 95 % CI 1.58–2.72) and triple vessel disease (OR 1.31, 95 % CI 1.08–1.59).

In-hospital outcomes and 1-year incidence of adverse events

Patients with AF received a high loading dose of clopidogrel (600 mg; 58.7 vs. 49.0 %; $p < 0.01$) more frequently. Other peri-procedural medication was equally distributed between groups. There were no statistically significant differences with respect to in-hospital MACCE rates or severe bleeding complications.

At the 1-year follow-up, the presence of AF was associated with an increase in mortality, MACCE and major bleeding complications in univariate comparisons (Fig. 1). The risk increase for mortality was most pronounced (OR 3.22, 95 % CI 2.14–4.84), followed by the increased risk for major bleeding (OR 2.10, 95 % CI 1.25–3.55). Multivariable analyses, however, revealed that after adjusting for differences at baseline the elevation of mortality (OR 1.79, 95 % CI 1.16–2.77) remained significant. The cumulative survival of patients with or without AF in a Kaplan–Meier analysis is displayed in Fig. 2 (log-rank $p < 0.0001$).

Anticoagulation in AF patients undergoing DES implantation

At hospital discharge, 4.9 % of patients had a $CHADS_2$ score of 0, 29.9 % a score of 1 and 65.3 % had a score of at

Table 1 Patient characteristics at hospital admission

	AF ($n = 455$)	No AF ($n = 5{,}317$)	OR (95 % CI)
Demographic data			
Age (mean ± SD)	**71.3 ± 7.6**	**64.7 ± 10.5**	***p* < 0.0001***
Age >75 years (%)	**36.7**	**17.0**	**2.83 (2.31–3.47)**
Male (%)	73.8	74.7	0.96 (0.77–1.19)
BMI (kg/m^2)	27.5 (25.3–29.7)	27.4 (25.0–30.2)	$p > 0.99$*
Risk factors (%)			
Diabetes	**42.2**	**31.0**	**1.62 (1.34–1.98)**
Hypertension	**88.3**	**83.4**	**1.50 (1.11–2.01)**
Smoking	**13.2**	**23.0**	**0.51 (0.37–0.69)**
Hyperlipidemia	78.6	80.6	0.89 (0.70–1.13)
Family history	**29.0**	**37.3**	**0.68 (0.53–0.89)**
Renal insufficiency	**24.4**	**11.5**	**2.48 (1.97–3.13)**
Comorbidity (%)			
Prior MI	33.3	29.9	1.17 (0.95–1.44)
Prior CABG	**19.8**	**13.9**	**1.53 (1.20–1.95)**
Prior PCI	40.5	45.0	0.83 (0.68–1.01)
Prior stroke	**8.0**	**4.0**	**2.07 (1.43–3.01)**
PAD	**16.0**	**8.9**	**1.06 (1.48–2.59)**

BMI body mass index, *CABG* coronary artery bypass graft, *MI* myocardial infarction, *PAD* peripheral arterial disease, *PCI* percutaneous coronary intervention, *SD* standard deviation

Bold values indicate that both values of the CI are either below or above 1

* Mann–Whitney–Wilcoxon test

Table 2 Indication for PCI and cardiac status

	AF (n = 455)	No AF (n = 5,317)	OR (95 % CI)
Indication for PCI (%)			
ACS	38.2	41.0	0.89 (0.73–1.08)
STEMI (ongoing)	8.4	10.8	0.75 (0.53–1.06)
STEMI (stabilized)	1.5	2.1	0.73 (0.34–1.57)
NSTEMI	14.1	12.7	1.13 (0.86–1.49)
Unstable AP	14.1	15.3	0.91 (0.69–1.20)
Elective PCI	57.2	56.1	1.04 (0.86–1.27)
Other	**4.6**	**2.9**	**1.65 (1.03–2.63)**
Cardiac status (%)			
Cardiogenic shock	**2.9**	**1.4**	**2.00 (1.10–3.63)**
Anamnestic HF	**25.9**	**14.1**	**2.13 (1.69–2.69)**
Ejection fraction ≤40 %	**21.0**	**11.4**	**2.07 (1.58–2.72)**
3 vessel disease	**44.4**	**37.9**	**1.31 (1.08–1.59)**

AP angina pectoris, *CAD* coronary artery disease, *NSTEMI* mean non-ST elevation myocardial infarction, *LAD* left anterior descendens, *LVEF* left ventricular ejection fraction, *PCI* percutaneous coronary intervention, *STEMI* ST elevation myocardial infarction, *HF* heart failure

Bold values indicate that both values of the CI are either below or above 1

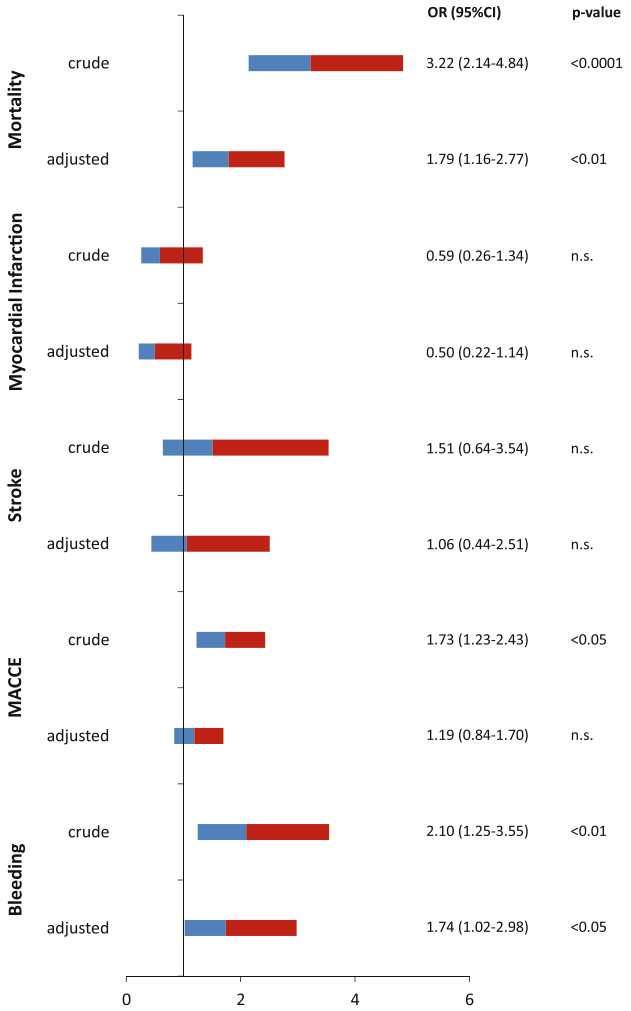

Fig. 1 Clinical complications during 12 months follow-up in patients with DES: AF vs. no AF (univariate and multivariate analysis). *MACCE* major adverse cardiac and cardiovascular events, *MI* myocardial infarction, *OR* odds ratio, *CI* confidence interval. Crude or adjusted for age, gender, diabetes, hypertension, positive family history, kidney failure, prior MI, bypass, PCI, stroke, PAD, cardiogenic shock, heart failure, EF <40 %, KHK3, LMA, stenosis

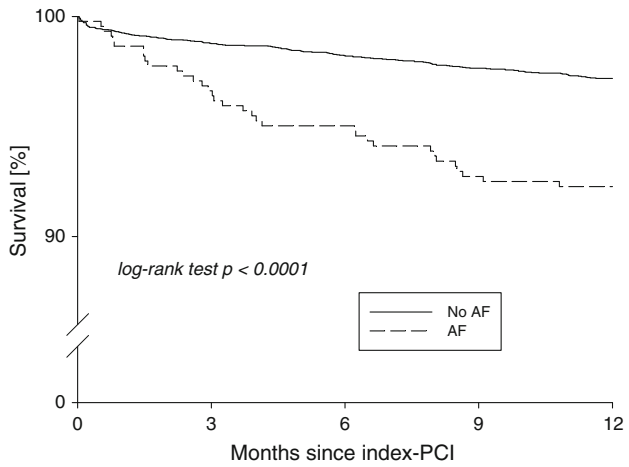

Fig. 2 Survival of patients with or without AF after PCI. *AF* atrial fibrillation. Adjusted for age, gender, diabetes, hypertension, positive family history, kidney failure, prior MI, bypass, PCI, stroke, PAD, cardiogenic shock, heart failure, EF <40 %, KHK3, LMA, stenosis

least 2. Patients with AF received less ASA (92.3 vs. 98.9 %, OR 0.14, 95 % CI 0.09–0.21) while clopidogrel use was comparable (98.9 vs. 99.5 %, OR 0.46, 95 % CI 0.18–1.20). Use of vitamin-K antagonists (VKA) was significantly more frequent in patients with AF (26.3 vs. 1.8 %, OR 17.27, 95 % CI 12.37–24.11).

A total of 26.8 % received VKA in any combination at a $CHADS_2$ score of 2 or more which is considered an obligation of VKA use (Fig. 3). On the contrary of those with a $CHADS_2$ score of 0, a total of 31.8 % received a VKA although guidelines consider this to be no indication. In patients with a $CHADS_2$ score of 2 or more there was no difference in clinical complications at months 12 whether or not patients received VKA (Table 3) or whether they underwent elective or emergency PCI. The only difference was evident when comparing patients receiving a combination of VKA and clopidogrel with or without ASA with a 10 % rate of non-fatal myocardial infarction in patients

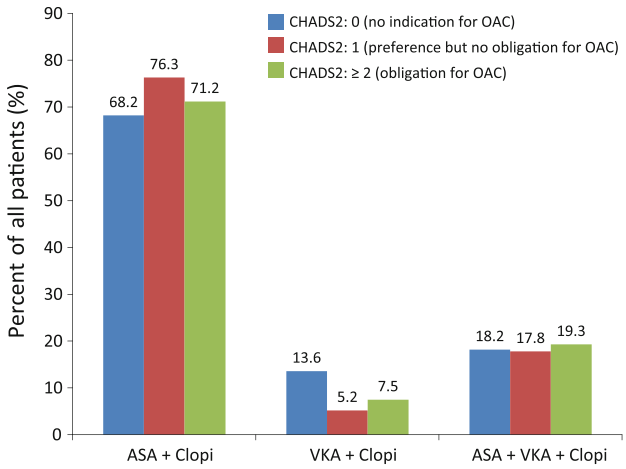

Fig. 3 $CHADS_2$ score of patients with AF and pharmacotherapy. *ASA* acetylsalicylic acid, *clopi* clopidogrel, *VKA* vitamin-K antagonists, *OAC* oral anticoagulation, *AF* atrial fibrillation

with the triple combination versus 0 % in those receiving VKA and clopidogrel only ($p < 0.05$).

Discussion

This analysis demonstrates that patients with AF undergoing PCI with DES implantation are at a substantially increased risk for subsequent cardio- and cerebrovascular events and bleeding complications over the course of a prolonged 1-year follow-up (Fig. 2). This increased risk in patients with AF persists even after adjusting for differences in baseline characteristics and co-morbidity. While bleeding complications were more frequent in the AF group, we were not able to associate this risk to the use of oral anticoagulants or triple antithrombotic therapy.

Comparison to previous data

The results are in principal agreement with prior analyses in patients undergoing coronary angiography with [6, 13–17] or without PCI [24]. The studies reported higher rates of major bleeding complications in DES than in BMS-treated AF patients [14], that new onset AF during PCI predicted a high 90-day mortality and increased adverse outcomes [16] and that AF resulted in a twofold increase in short-term major adverse cardiac events at a fourfold increase in mortality [17]. While there are a number of reports on bleeding complications with antithrombotic treatments in patients with AF, there is no report, however, focussing on the relative impact of AF on thromboembolic events or bleeding complications in patients undergoing DES implantation. Against this background it is important to note that AF, independent of baseline patient characteristics

Table 3 Clinical complications during 12 months follow-up in patients with AF, a CHADS2 ≥2 and DES implantation

Pts with AF and CHADS2 ≥2	VKA (%)	No VKA (%)	OR (95 % CI)	*p* value
Mortality	5.1	9.6	0.50 (0.17–1.52)	0.21
Myocardial infarction in survivors	2.9	1.7	1.74 (0.28–10.6)	0.54
Stroke/TIA in survivors	1.4	1.7	0.86 (0.09–8.44)	0.90
MACCE	8.9	12.0	0.71 (0.29–1.72)	0.45
Major bleeding in survivors	3.0	4.8	0.63 (0.13–8.28)	0.56
Pts with AF and CHADS2 ≥2	VKA + ASA + Clopi (%)	VKA + Clopi (%)	OR (95 % CI)	*p* value
Mortality	5.4	4.5	1.19 (0.12–12.1)	0.88
Myocardial infarction in survivors	**0**	**10.0**	–	**<0.05**
Stroke/TIA in survivors	2.1	0.0	–	0.52
MACCE	7.1	13.6	0.49 (0.10–2.38)	0.37
Major bleeding in survivors	4.3	0.0	–	0.37
Pts with AF and CHADS2 ≥2	ACS (%)	Elective PCI (%)	OR (95 % CI)	*p* value
Mortality	11.4	6.1	2.00 (0.84–4.72)	0.11
Myocardial infarction in survivors	1.1	2.7	0.38 (0.04–3.49)	0.38
Stroke/TIA in survivors	0.0	2.7	–	0.10
MACCE	12.3	10.3	1.22 (0.57–2.58)	0.61
Major bleeding in survivors	2.2	5.8	0.38 (0.08–1.81)	0.21

AP angina pectoris, *CAD* coronary artery disease, *NSTEMI* mean non-ST elevation myocardial infarction, *LAD* left anterior descendens, *LVEF* left ventricular ejection fraction, *PCI* percutaneous coronary intervention, *STEMI* ST elevation myocardial infarction

Bold values indicate that both values of the CI are either below or above 1

and co-morbidity, increased mortality by a factor of 1.8. A similar increase was seen for major bleeding complications with an increase by a factor of 1.7 (see Fig. 2).

AF in patients with DES implantation

Patients in the present analysis were participants of the Germany DES.DE registry and all patients considered for the analysis received DESs. On the one hand, DES have been shown to result in a substantial reduction of target lesion revascularization in comparison with BMS (19 vs. 5 % per year) [25]. On the other hand, DES have never been sufficiently studied in patients with AF. AF has actually been a common exclusion criterion in clinical trials of DES implantation. A recent analysis of two propensity score matched cohorts (DES vs. BMS) of patients with AF reported similar incidence rates of MACE and all-cause mortality with a higher incidence of major bleeding in the DES group ($p = 0.03$) [14]. The DES.DE registry does not allow for such a comparison because of low absolute patient numbers with AF in the BMS arm ($n = 67$) [18]. Within the DES-treated group, however, analyses indicated a substantial increase of bleeding complications in the AF group. This is important given the data from the Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) [26] and Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS) trials [27]. In these trials, 30-day mortality was increased in those developing major or minor bleeding complications (independent of stent type).

Anticoagulation

There were no randomized controlled trial data on the use of antithrombotic drugs in patients with AF after PCI at the time of this registry, and there are conflicting positions on antithrombotic use [28, 29]. There is a recent position statement [30] and a consensus guideline [31], however, that may be referred to when looking for guidance. Based on expert consensus, but without conclusive evidence [32,33], a combination of an oral anticoagulant with clopidogrel is considered by the guidelines of the ACC/AHA and ESC as the antithrombotics of choice in patients requiring an oral anticoagulant on a medium-term [31, 34]. A triple combination is recommended for 1 or 6 months, depending on stent type and an oral anticoagulant with clopidogrel for 12 months in ACS and patients with drug-eluting stent implantation, after which the oral anticoagulant may be continued as monotherapy in the absence of a subsequent coronary event [31, 34].

Therefore, it was important to note that the vast majority of patients with DES implantation received a dual combination of ASA and clopidogrel but no oral anticoagulant irrespective of the $CHADS_2$ score which would indicate an obligation for oral anticoagulation in case of a score of 2 or more (Fig. 3). For the remaining patients, the triple combination was preferred over the dual VKA/clopidogrel combination therapy—again without major differences as to the patient's $CHADS_2$ score. Bleeding risk overall was in accordance with other estimates for "real world" AF patients (3.0 %) [31].

On the other hand, it was interesting to see that rates of vascular events and major bleeding complications were not statistically different between those receiving oral anticoagulants or not and whether ASA was dismissed from the typical triple combination therapy recommended for stented patients with AF. The only difference was related to a low rate of MI in the triple combination therapy group which was significantly lower than that in patients receiving a dual combination of OACs and clopidogrel ($p < 0.05$). This is in contrast to previous work performed by Gao et al. [35] who found a reduction of MACE rates at an overall increased bleeding rate. Rogacka and Pasceri et al. [36, 37] documented that there was no difference in this respect between BMS and DES.

More recently, the WOEST study [38] compared two regimens with and without aspirin in patient on oral anticoagulant therapy undergoing elective coronary stenting (with both BMS and DES). Patients were randomized to either receive a dual combination of oral anticoagulants and clopidogrel or a triple combination including aspirin. They found that at 1 year the risk more than halved with dual versus triple therapy (HR 0.36; 95 % CI 0.26–0.50) and demonstrated that also vascular events were nominally but not significantly reduced. The exception was all-cause death which was 2.6 % in the dual and 6.4 % in the triple therapy group ($p = 0.027$).

Limitations

The present analysis had the inherent limitations of any non-randomized multicenter registry with the inherent substantial risk of bias. We aimed to reduce the extent of bias in our analyses using multivariable logistic regression analysis; propensity score analyses would have been another valid option. The registry findings can further be limited by low rates of enrollment and underreporting of events, although reflecting the real world better than controlled randomized studies. Moreover, DES.DE was closely monitored by a critical event committee, despite its comprehensive structure. Further, incident AF prior to PCI, during PCI or long-term follow-up was not obtained and only AF diagnosed at baseline was considered for this analysis. Another critical issue is the selection of variables

for adjusting the impact of AF on long-term vascular events. Heart failure for example is a risk factor for the development of AF but also a direct consequence. Adjusting for dependent variables like heart failure (or stroke), however, might underestimate the true impact of AF on vascular events. It might be tempting to speculate, that patients with a history of but no current AF do better during long-term follow-up of PCI than patients with current AF, but the aforementioned analyses of the VALIANT studies have reported similar outcomes (37 with current vs. 38 % without current AF) [39].

Clinical implications

Patients with AF are at an increased risk for vascular events and this risk increase is reflected in the higher odds for developing adverse events after PCI. While the risk increase could be rather due to the associated risk factors than AF itself, it might still be a useful and readily available risk marker for an unfavorable long-term outcome after PCI. There is, however, no mentioning of AF as such in STEMI guidelines [40, 41] including the recent ACC/AHA update for the management of patients with STEMI [42] or the respective PCI guidance [43, 44]. It appears to be reasonable to consider AF in assessing the long-term risks of PCI not only because of the increased risk for mortality even after multivariable analysis, but because high-risk patients can thus easily be identified.

Conclusions

Atrial fibrillation is an important predictor of vascular risk in patients undergoing PCI. While increasing risk might be mostly incurred by comorbidity and risk factors rather than by AF itself, AF should be considered a condition to monitor a given patient even closer to prevent future vascular events.

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