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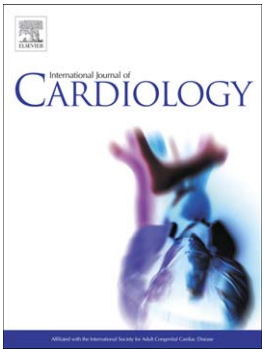

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Bridging therapy with low molecular weight heparin in patients with atrial fibrillation undergoing percutaneous coronary intervention with stent implantation: the AFCAS study

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Conflicts of interest: None declared.

Key words: Coronary Heart Disease; Atrial Fibrillation; Anticoagulation; Bridging therapy

Structured abstract

Background: Recent reports have provided evidence that bridging therapy with low-molecular-weight heparin (LMWH) may increase bleeding complications in patients with atrial fibrillation (AF) on oral anticoagulation undergoing percutaneous coronary intervention (PCI). We sought to assess mid-term bleeding and thromboembolic events in patients from the AFCAS registry discharged on triple therapy (TT).

Methods: AFCAS is a multicenter, prospective registry enrolling patients with AF undergoing PCI. The primary endpoints were: 1) bleeding complications as defined by the bleeding academic research criteria (BARC); 2) a composite of cardiac and cerebrovascular events (MACCE) at 3 and 12 months follow-up.

Results: Altogether 663 out of 929 consecutive patients were discharged on TT, either on oral vitamin K antagonist (VKA-TT) (n=498) or bridging LMWH-TT (n=165). Patients on LMWH-TT had more often diabetes, heart failure, and hypertension compared to those on VKA-TT. The rates of major bleeding events (BARC ≥3) (11.5% vs. 6.0%, p=0.03) as well as MACCE (11.5% vs. 5.0%, p=0.006) were higher in the LMWH-TT group compared to VKA-TT group at 3 months follow-up. In a Cox multivariate regression model and propensity-score matched analysis LMWH-TT increased the risk for major BARC bleeding events at 3 and 12 months follow-ups.

Conclusions: In this large, prospective, real-world population of patients with AF undergoing PCI patients discharged on LMWH-TT had a significantly higher risk for major bleeds in comparison to patients discharged on VKA-TT. LMWH-bridging therapy appeared harmful in this subset of patient on oral anticoagulation.

Introduction

In accordance with current guidelines, the antithrombotic therapy for patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention with stent implantation (PCI) should consist of triple therapy (TT) of vitamin K-antagonist (VKA), aspirin, and clopidogrel when the thromboembolic risk is moderate to high (CHA_2DS_2VASC score ≥2) [1]. TT is the treatment of choice at least in the first month after stent implantation [1, 2]. Data on patients after PCI who have an indication for VKA are limited [3, 4]. Previously bridging treatment with low-molecular-weight heparin (LMWH) has been the standard recommendation for patients if VKA has to be interrupted or introduced[5, 6]. However, recent expert recommendations suggest that in patients on oral anticoagulation with CHA2DS2-VASc ≥2 and stable angina, an uninterrupted anticoagulation strategy with no additional heparin boluses during PCI is the preferred strategy (Class IIa, level of evidence C)[1]. Little is known about the outcomes of LMWH-bridging therapy in long-term follow-up as well as in patients presenting with acute coronary syndrome.

In this pre-specified analysis, we prospectively assessed the effect of LMWH-bridging therapy vs. uninterrupted oral anticoagulation therapy on thrombotic and bleeding events in patients with AF undergoing stent implantation with an indication for TT.

Methods

Study population

AFCAS is an observational, multicenter, prospective registry including patients with AF who are referred for PCI (Clinicaltrials.gov identifier NCT00596570). Inclusion criteria were elective or urgent/emergency PCI and 1) history of AF (paroxysmal, persistent, or permanent), or 2) AF during the index hospital stay. Because of the observational design, the only exclusion criterion was unwillingness/inability to participate in the study or to give written informed consent. Coronary angiography and PCI were performed using either radial or femoral approach for arterial access and haemostasis was obtained according to the local practice. Lesions were treated according to contemporary interventional techniques.

LMWH (enoxaparin sodium, dalteparin), unfractionated heparin, bivalirudin and glycoprotein IIb/IIIa inhibitors were administered entirely at the operator's discretion. Moreover, the choice of the combination of antithrombotic treatment after the procedure was at the treating physician's discretion.

Details of the study have been published elsewhere [7-10]. At each participating center, patients were treated according to local policies, and were followed up for 12 months (phone call at 3, 6 and 12 months and when needed by assessment of patient records in the hospitals and in health centers of catchment areas. Each event was adjudicated according to the pre-specified definitions for myocardial infarction, target vessel revascularization, stent thrombosis transient ischemic attack and stroke [7-10]. Bleeding events were centrally adjudicated based on the patient record data on case report forms. The study complied with the Declaration of

Helsinki. Ethic committees of participating centers approved the study protocol, and written informed consent was obtained from every patient.

This analysis included patients discharged on TT including VKA, aspirin and clopidogrel (VKA-TT) and those on LMWH–bridging therapy, aspirin and clopidogrel (LMWH-TT).

Study endpoints

Endpoints included any bleeding complications defined according to the bleeding academic research consortium (BARC) criteria as any (BARC 2-5), minor (BARC 2) and major (BARC 3a, 3b, 3c and 5)[11]; a composite of major adverse cardiac and cerebrovascular events (MACCE) and its derivatives all-cause mortality, non-fatal myocardial infarction, stent thrombosis according ARC criteria[12], repeat revascularization (excluding staged planned procedures), and arterial embolism (stroke, transient ischaemic attack, peripheral arterial embolism).

Statistical analysis

Data are presented as means ± standard deviations, median [interquartile range] and frequencies (%) where appropriate. Normality was tested using Kolmogorov-Smirnov and Shapiro-Wilk tests. Continuous variables were analyzed using independent samples t-test and independent samples Mann-Whitney U test where appropriate. Categorical variables were analyzed using chi-square tests. Cox regression analysis was performed using stepwise backward Wald method. The study groups significantly differed in a number of baseline and procedural characteristics. Such differences were accounted for propensity score analysis. A propensity score was estimated by logistic regression initially including all baseline and operative variables and after that by a stepwise backward method. The area under the receiver operating characteristic (ROC) curve was used to represent the discriminatory ability of the

regression model. Propensity score was used for risk adjustment as a covariate in multivariate analyses assessing all predefined outcome end-points. Furthermore, one-to-one propensity score matching was performed by using a caliper of 0.02 of the standard deviation of propensity score. Significance was set at p value <0.05. Analysis was performed with SPSS version 16.0 (SPSS Inc., Chicago, IL).

Results

Out of 663 patients discharged on TT, 498 (75.1%) were on VKA-TT and remaining 165 (24.9%) on LMWH-TT. Baseline and procedural characteristics according to VKA-TT vs. LMWH-TT are presented in Tables 1 and 2. Median [IQR] dosage of LMWH per day was 100 [60] mg (mean SD 107±41 mg) in patients in the LMWH-TT arm. The use of glycoprotein 2b/3a inhibitors was (11.6% vs. 31.5%, p<0.001) and bivalirudin (5.5% vs. 0.6%, p=0.006) in the VKA-TT and LMWH-TT arms, respectively. Patients on VKA-TT had less often hypertension, diabetes, and congestive heart failure; but more often permanent/persistent AF. Patients on LMWH-TT had higher CHA_2DS_2-VASc-score and modified HAS-BLED-score and more often a history of peptic ulcer. However, no differences were found in the indication for PCI, left ventricular ejection fraction or the use of drug-eluting stents. As expected, periprocedural INR was significantly higher in patients on VKA-TT compared to those on LMWH-TT at discharge. The median [IQR] duration of hospital stay was longer in patients on LMWH-TT compared to those on VKA-TT (3.0 [5.0] days vs. 2.0 [4.0] days, p<0.001). In patient on LMWH-TT, the median interruption of VKA therapy was 5.5 [12.0] days (mean 10.4 ± 14.6 days), and 66/162 (40.7%) of them had VKA treatment re-initiated at the time of hospital discharge.

Adverse events at 3 months as well as 12 months follow-up are presented in Table 3. The rate of major bleeding events (BARC ≥3) was significantly higher in the LMWH-TT group compared to VKA-TT group at 3 months follow-up. The rate of MACCE was also significantly higher in the LMWH-TT group compared to VKA-TT group. Figure 1 presents the freedom from major bleeding at 3 months follow-up and Figure 2 freedom from MACCE at 12 months follow-up. Patients on LMWH-TT group had more major bleeding events early within 30 days after the index procedure compared to those on VKA-TT. A significant difference in the occurrence of MACCE was also observed throughout the entire follow-up.

Since the study groups differed significantly in certain baseline characteristics as shown in Tables 1 and Table 2, a multivariate Cox-regression analysis adjusted for the presence of diabetes, hypertension, congestive heart failure, renal impairment, anemia, the use of bivalirudin or glycoprotein 2b/3a inhibitors, and acute coronary syndrome was carried out. Here, LMWH-TT remained a significant predictor for major BARC bleeding events at 3 months (HR 3.51, 95%CI 1.76-6984, p<0.001) and at 12 months follow-up (HR 2.22, 95%CI 1.04-3.06, p=0.007), respectively. LMWH-TT was also significantly associated with increasing rate of MACCE at 3 months (HR 2.73, 95%CI 1.47-5.09, p=0.002) persisting up to 12 months follow-up (HR 1.72, 95%CI 1.24-3.97, p=0.008). Multivariate models remained unchanged when patients on periprocedural bivalirudin or glycoprotein 2b/3a inhibitors were excluded (data not shown).

Propensity score analysis

To further adjust for baseline differences, a propensity score was calculated by logistic regression (Hosmer-Lemeshow test: p=0.173) and had an area under the ROC curve of 0.880 (95%CI 0.844-0.915). The matching caliper chosen was 0.05. One-to-one propensity score matching provided 76 pairs with similar baseline and operative characteristics (Tables 1-3).

Patients discharged on LMWH-TT showed an increased (non-significant) risk for major bleeding at 3 months (HR 3.45, 95%CI 0.95-12.6, p=0.06), and 12 months (HR 2.97, 95%CI 0.95-9.34, p=0.06) (Table 3). Similarly, LMWH-TT was associated with a non-significant increased risk of MACCE at 12 months (21.3% vs. 13.5%, p=0.191), driven by trends to increased mortality (10.5% vs. 4.2%, p=0.229) and repeat revascularization (10.4% vs. 4.2%, p=0.166) (Table 3).

Propensity score adjusted analysis showed that at 12 months, the risk of mortality (p=0.637), myocardial infarction (p=0.601), repeat revascularization (p=0.109), stent thrombosis (p=0.678), arterial thromboembolism (p=0.192) and MACCE (p=0.409) were similar between the study groups.

Discussion

Bridging therapy with LMWH in addition to dual antiplatelet therapy appeared to increase the rate of major bleeding events compared to uninterrupted oral VKA-TT in this "real world" registry of patients with AF undergoing PCI. Moreover, LMWH-TT was associated with increased rate of thrombotic/thromboembolic events and prolonged hospital stay, and a 3-fold increase of bleeding events in the propensity score matched model.

Anticoagulation therapy is recommended in patients with AF and a moderate to high risk for strokes as defined by a CHA_2DS_2-VASC-score ≥2 to avoid stroke and other thromboembolic events [1]. In patients undergoing PCI with stent implantation, clinical decision-making is challenging since the combination of aspirin and a $P2Y_{12}$-inhibitor is also indicated to prevent stent thrombosis. TT should always be considered to carry an increased risk of overall bleeding and should therefore be reserved for those patients for whom the expected net clinical benefit is favorable. Consequently, guidelines recommend in patients with an indication for oral

anticoagulation after PCI the combination of VKA, aspirin and clopidogrel (VKA-TT) for at least one month, although risk for severe bleedings increases substantially under VKA-TT[1]. In addition, VKA plus clopidogrel treatment may be considered in patients at low bleeding risk [1, 13].

Recent randomized trials showed that uninterrupted oral anticoagulation therapy was associated with substantially decreased 0.19-fold risk in the rate of major bleeding events after pacing-device implantation [14] and 0.08-fold risk in the catheter ablation of AF compared to bridging therapy [15]. There are, however, no randomized trials assessing the safety or risks of bridging therapy during PCI. In the earlier non-randomized studies, the strategy of uninterrupted oral anticoagulation has been at least as safe as warfarin pause combined with heparin bridging, but the low methodological quality of studies precludes any definitive conclusions [4, 16]. The present analysis gives important additional information on this topic. It is the first to focus on patients with an indication for TT and also assess the 1-year outcome of the patients using also propensity score-matching to adjust for differences in the patient groups.

Our study supports the view that uninterrupted oral anticoagulation strategy should be preferred in patients on VKAs. Warfarin prolongs activated clotting time (ACT) in a predictable fashion. In addition, therapeutic (International Normalized Ratio (INR) ≥2.0) uninterrupted anticoagulation with warfarin is not associated with increased periprocedural thromboembolic or bleeding complications in patients who underwent PCI[17]. Large INR fluctuations after VKA interruption and suppression of proteins C and S occurring upon VKA re-initiation can be avoided using uninterrupted oral anticoagulation. In line with previous reports, the incidence of bleeding and thromboembolic complications appeared to increase during the early varying phase of anticoagulation. LMWH-bridging seems also to be less advantageous from an economic

point of view since hospital stay was significantly longer in patients on LMWH-TT compared to those on VKA-TT in line with a previous report[18].

Finally, the question of whether uninterrupted oral anticoagulation is associated with a higher risk of bleeding because of difficulties in controlling haemorrhage appears not valid, because rapid reversal of anticoagulation can be obtained using plasma and/or coagulation proteins. Of note, reversal of the anticoagulant effect of enoxaparin and fondaparinux, which are the recommended anticoagulants in acute coronary syndromes, may be more cumbersome, since protamine sulphate (the established antidote to unfractionated heparin) has little or no effect in neutralizing these agents.

Limitations

Significant baseline differences between the study groups were accounted using multivariate Cox regression modeling and propensity score matched pairs. The large differences between the study populations led to a propensity score with a rather large under the ROC curve. This in turn led to a reduced, but very tightly matched pairs. The difference between the results of multivariate analysis and propensity-adjusted analysis could be due to a reduced number of patients available for propensity score calculation as well as the fact that propensity score has dealt with a much larger number of variables. Nevertheless, major bleeding events were more frequent with all these methods.

Conclusion

In this large, prospective, real-world population of patients with AF undergoing PCI patients discharged on LMWH-TT had a significantly higher risk for major bleeds in comparison to patients discharged on VKA-TT. LMWH-bridging therapy appeared harmful in this subset of patient on oral anticoagulation.

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Table 1 Baseline clinical characteristics of the two study subgroups

	Whole cohort			Propensity score matched pairs		
Variable	**VKA-TT (n = 498)**	**LMWH-TT (n = 165)**	**p-value**	**VKA-TT (N=76)**	**LMWH-TT (N=76)**	***p* value**
Age (years)	74.0 [10]	73.0 [9]	0.30	74.0 [13]	74.0 [8]	0.588
Female gender	146 (29.3)	45 (27.3)	0.69	21 (27.6)	19 (25.0)	0.713
Diabetes mellitus	161 (32.3)	84 (50.9)	<0.001	32 (42.1)	32 (42.1)	1.000
Hypercholesterolemia	338 (67.9)	111 (67.3)	0.92	47 (61.8)	53 (69.7)	0.393
Body mass index (kg/m^2)	27.8 [6.0]	28.0 [6.3]	0.45	28.3 [7.1]	28.1 [6.7]	0.956
Current or ex-smoking	43 (8.6)	26 (15.8)	0.01	5 (6.6)	9 (11.8)	0.401
Hypertension	397 (79.7)	158 (95.8)	<0.001	70 (92.1)	73 (96.1)	0.303
Paroxysmal atrial fibrillation	137 (27.5)	78 (47.3)	<0.001	31 (40.8)	31 (40.8)	1.000
CHA_2DS_2-VASC score	4.0 [2.0]	5 [2.0]	0.004	5.0 [2.0]	4.0 [6.0]	0.721
HAS-BLED score	3.0 [1.0]	3.0 [0]	0.007	3.0 [0]	3.0 [0]	0.145
History of peptic ulcer	15 (3.0)	13 (7.9)	0.01	2 (2.6)	7 (9.2)	0.167
History of cerebral haemorrhage	4 (0.8)	1 (0.6))	1.0	0	0	-
History of GI haemorrhage	11 (2.2)	4 (2.4)	0.77	1 (1.3)	1 (1.3)	1.000
History of heart failure	80 (16.1)	54 (32.7)	<0.001	29 (38.2)	24 (31.6)	0.395
eGFR below 60 ml/min	135 (33.3)	57 (39.3)	0.22	24 (35.8)	28 (39.4)	0.661
Pre-procedural anemia (WHO)	131 (29.2)	45 (28.0)	0.84	3 (3.9)	1 (1.3)	0.620
Prior transient ischaemic attacks	28 (5.6)	4 (2.4)	0.14	6 (7.9)	2 (2.6)	0.276
Prior stroke	68 (13.7)	16 (9.7)	0.22	10 (13.2)	10 (13.2)	1.000
Prior MI	126 (25.3)	38 (23.0)	0.60	22 (28.9)	17 (22.4)	0.353
Prior PCI	70 (14.1)	34 (20.6)	0.05	9 (11.8)	17 (22.4)	0.085
Prior coronary bypass surgery	82 (16.5)	19 (11.5)	0.14	12 (15.8)	11 (14.5)	0.821
Left ventricular ejection fraction (%)	50 [20]	50 [25]	0.55	47 [21]	50 [18]	0.429

Stable angina pectoris	228 (45.8)	88 (53.3)	0.86	39 (51.3)	37 (48.7)	0.746
ACS						
Unstable angina pectoris	76 (15.3)	30 (18.2)	0.39	13 (17.1)	19 (25.0)	0.233
Non-ST-elevation MI	129 (25.9)	38 (23.0)	0.54	18 (23.7)	14 (18.4)	0.426
ST-elevation MI	65 (13.1)	20 (12.1)	0.89	6 (7.9)	6 (7.9)	1.000

Continuous variables are presented as median [interquartile range], whereas categorical variables are presented as frequency (percentage). ACS indicates acute coronary syndrome; eGFR: estimated glomerular filtration rate; GI: gastrointestinal, IQR: inter-quartile range; MI: myocardial infarction; PCI: percutaneous coronary intervention. TT: Triple Therapy consisting of anticoagulation, aspirin and clopidogrel.

Table 2 Procedural data of the two study subgroups

Variable	Whole cohort			Propensity score matched pairs		
	VKA-TT (n = 498)	LMWH-TT (n = 165)	p-value	VKA-TT (N=76)	LMWH-TT (N=76)	*p* value
Femoral access	315 (63.3)	144 (87.3)	<0.001	61 (80.3)	67 (88.2)	0.182
Number of treated vessels	1 [0]	1 [0]	0.77	1.0 [0]	1.0 [0]	0.120
Drug-eluting stent	119 (25.0)	35 (21.5)	0.40	22 (29.3)	20 (26.3)	0.679
Plain balloon angioplasty	28 (5.6)	1 (0.6)	0.004	4 (5.3)	0	0.120
Peri-procedural INR	2.1 [1.0]	1.6 [1.0]	<0.001	1.7 [1.0]	1.4 [1.0]	0.193
Stent diameter (mm)	3.0 [0.5]	3.0 [0.5]	<0.001			
Total stent length (mm)	19 [15]	18 [14]	0.45	21.0 [17.0]	18.0 [9.0]	0.017
Procedural success	487 (97.8)	160 (97.0)	0.48			

Continuous variables are presented as mean ± SD or median [interquartile range], whereas categorical variables are presented as frequency (percentage). INR: international normalized ratio; TT: Triple Therapy consisting of anticoagulation, aspirin and clopidogrel.

Table 3 Clinical outcome at 3 and 12-month follow-up in the two study subgroups

	Whole cohort			Propensity score matched pairs		
Variable	**VKA-TT (n = 498)**	**LMWH-TT (n = 165)**	**p-value**	**VKA-TT (N=76)**	**LMWH-TT (N=76)**	***p* value**
3 months						
Any bleeding (BARC 2-5)	59 (11.8)	27 (16.4)	0.14	7 (9.1)	15 (19.7)	0.065
Major bleeding (BARC 3a, 3b, 3c, 5)	30 (6.0)	19 (11.5)	0.03	3 (3.9)	10 (13.2)	0.078
Minor bleeding (BARC 2)	29 (5.8)	8 (4.8)	0.85	4 (5.3)	5 (6.6)	1.000
MACCE	25 (5.0)	19 (11.5)	0.006	3 (3.9)	8 (10.5)	0.209
All-cause mortality	13 (2.6)	9 (5.5)	0.08	1 (1.3)	3 (3.9)	0.620
Non-fatal myocardial infarction	11 (2.2)	4 (2.4)	0.77	2 (2.6)	2 (2.6)	1.000
Definite/probable stent thrombosis	1 (0.2)	3 (1.8)	0.05	0 (0)	0 (0)	-
Repeat revascularization	3 (0.6)	9 (5.5)	<0.001	1 (1.3)	3 (3.9)	0.620
Stroke/TIA/Arterial embolism	1 (0.2)	2 (1.2)	0.16	0 (0)	1 (1.3)	1.000
12 months						
Any bleeding (BARC 2-5)	83 (16.7)	32 (19.4)	0.41	14.9%	24.0%	0.138
Major bleeding (BARC 3a, 3b, 3c, 5)	46 (9.2)	22 (13.3)	0.14	4.5%	16.6%	0.034
Minor bleeding (BARC 2)	38 (7.6)	10 (6.1)	0.60	9.9%	8.7%	0.884
MACCE	86 (17.3)	48 (29.1)	0.002	13.5%	21.3%	0.191
All-cause mortality	44 (8.8)	18 (10.9)	0.44	5.3%	10.5%	0.229
Non-fatal myocardial infarction	32 (6.4)	9 (5.5)	0.85	2.7%	4.3%	0.618
Definite/probable stent thrombosis	4 (0.8)	4 (2.4)	0.11	1.4%	0%	0.331
Repeat revascularization	27 (5.4)	27 (16.4)	<0.001	4.2%	10.4%	0.166
Stroke/TIA/Arterial embolism	12 (2.8)	4 (2.4)	1.0	2.8%	1.4%	0.598

Variables are presented as frequency (percentage). MACCE indicates major adverse cardiac and cerebrovascular events; TIA: transient ischemic attacks; BARC: Bleeding Academic Research Consortium.

Figure legends

Figure 1. Kaplan-Meier analysis with log-rank test: Freedom from major bleeding (BARC 3a, b, c, and 5) at 90 days follow-up after percutaneous coronary intervention with stent implantation in patients with atrial fibrillation according to VKA-TT (black line) and LMWH-TT (grey line) at discharge.

Figure 2. Kaplan-Meier analysis with log-rank test: Freedom from major cardiac and cerebrovascular events (MACCE) after percutaneous coronary intervention with stent implantation in patients with atrial fibrillation according to VKA-TT (black line) and LMWH-TT (grey line) at discharge.

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Appendix

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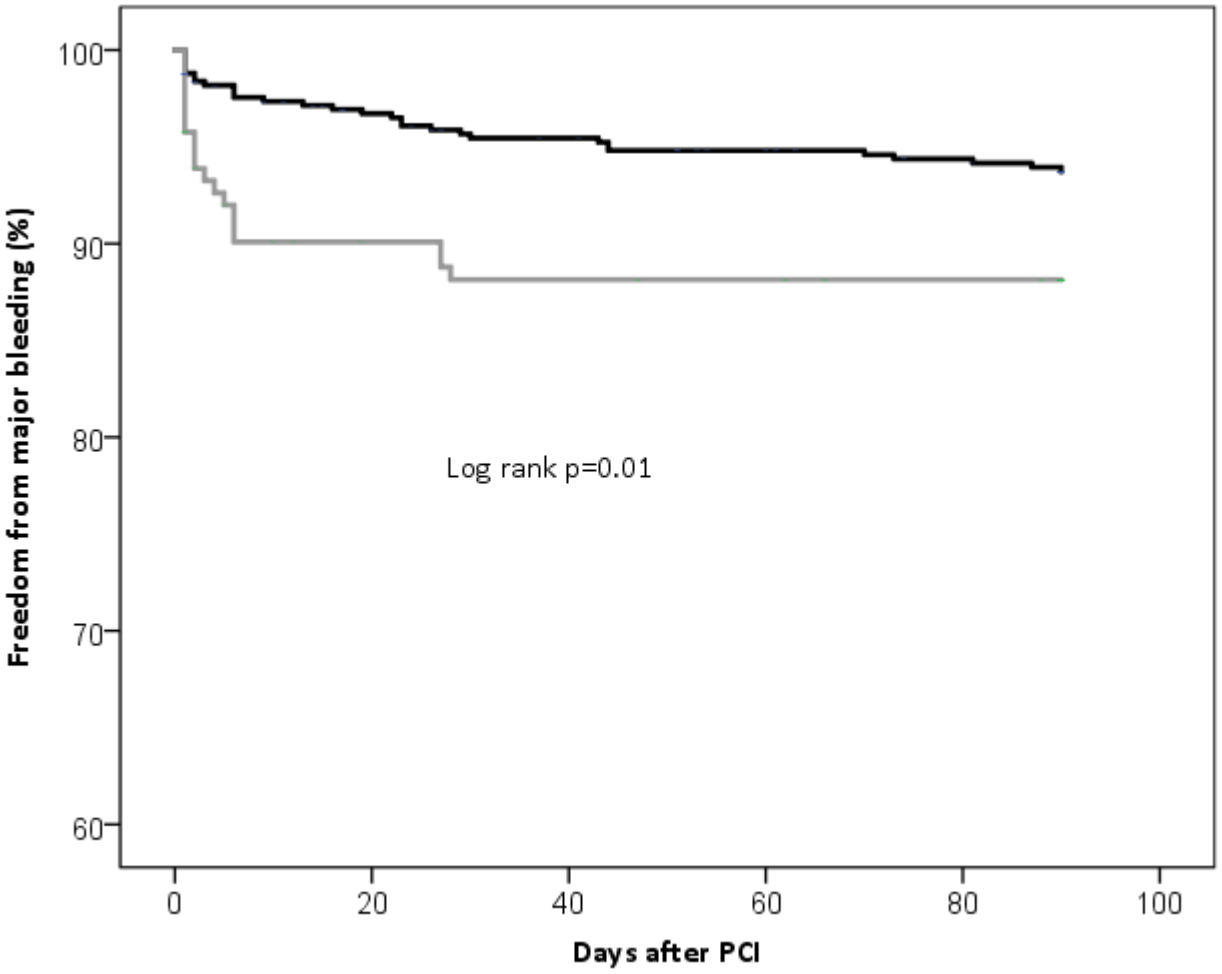

Figure 1

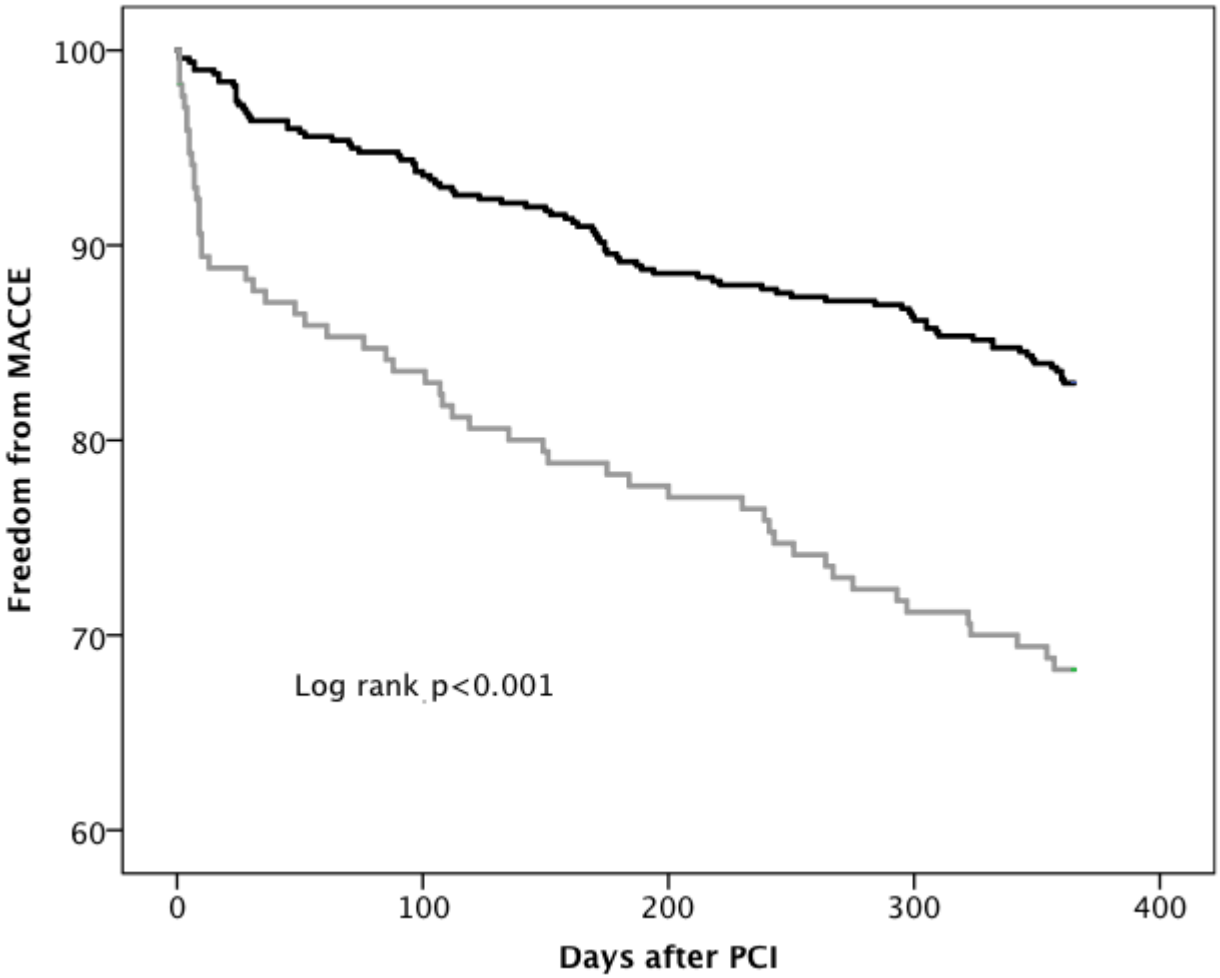

Figure 2

Highlights

- Bridging treatment with low-molecular-weight heparin (LMWH) has been the standard recommendation for patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI).
- In this large, prospective, real-world population we prospectively assessed the effect of LMWH-bridging therapy vs. uninterrupted oral anticoagulation therapy on thrombotic and bleeding events in this patient subset with an indication for anticoagulation plus dual antiplatelet therapy.
- Patients with AF undergoing PCI discharged on LMWH-triple therapy had a significantly higher risk for major bleeds in comparison to patients discharged on uninterrupted oral anticoagulation and dual antiplatelet therapy.
- LMWH-bridging therapy appeared harmful in this subset of patient on oral anticoagulation.