

Safety of percutaneous coronary intervention during uninterrupted oral anticoagulant treatment

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Aims

Uninterrupted anticoagulation (UAC) is assumed to increase bleeding and access-site complications. A common consensus is to postpone percutaneous coronary interventions (PCI) to reach international normalized ratio (INR) levels < 1.5–1.8.

Methods and results

To assess the safety and feasibility of UAC, we analysed retrospectively all consecutive patients ($n = 523$) on warfarin therapy referred for PCI in four centres with a policy to interrupt anticoagulation (IAC) before PCI and in three centres with a long experience on UAC during PCI. Major bleeding, access-site complications, and major adverse cardiac events (death, myocardial infarction, target vessel revascularization, and stent thrombosis) were recorded during hospitalization. In the IAC group, warfarin was withdrawn for a mean of 3 days prior to PCI (mean INR 1.7). In the UAC group, mean INR value was 2.2. Glycoprotein IIb/IIIa (GP) inhibitors ($P < 0.001$) and low-molecular-weight heparins ($P < 0.001$) were more often used in the IAC group. Major bleeding and access-site complications were more common in the IAC group (5.0% vs. 1.2%, $P = 0.02$ and 11.3% vs. 5.0%, $P = 0.01$, respectively) than in the UAC group. After adjusting for propensity score, the group difference in access-site complications remained significant [OR (odds ratio) 2.8, 95% CI (confidence interval) 1.3–6.1, $P = 0.008$], but did not remain significant in major bleeding (OR 3.9, 95% CI 1.0–15.3, $P = 0.05$). In multivariable analysis, femoral access (OR 9.9, 95% CI 1.3–75.2), use of access-site closure devices (OR 2.1, 95% CI 1.1–4.0), low-molecular-weight heparin (OR 2.7, 95% CI 1.1–6.7) and old age predicted access-site complications, and the use of GP inhibitors (OR 3.0, 95% CI 1.0–9.1) remained as a predictor of major bleeding.

Conclusion

Our study shows that PCI is a safe procedure during UAC with no excess bleeding complications.

Keywords

Angioplasty • Warfarin • Anticoagulation • Complications • Bleeding

Introduction

The management of patients anticoagulated with warfarin and referred for percutaneous coronary intervention (PCI) represents a substantial challenge to the physician who must balance the risks of periprocedural haemorrhage, thrombotic complications, and thromboembolism. Currently, a standard recommendation for

these patients is to discontinue warfarin before invasive cardiac procedures, since uninterrupted anticoagulation (UAC) is assumed to increase bleeding and access-site complications. The periprocedural INR (international normalized ratio) level < 1.8 is most often recommended.^{1,2} Unfractionated (UFH) or low molecular weight heparins (LMWH) are often administered as a

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bridging therapy until INR levels have risen back to the therapeutic levels.³ The bridging therapy with heparins is feasible, but this practice is associated with prolonged hospitalization, extra inconvenience of heparin administration, and potential thromboembolism associated with subtherapeutic anticoagulation (AC).^{3–5}

In spite of the current recommendations, it is not possible to draw firm conclusions on the relative efficacy and safety of different management strategies, since randomized controlled studies are missing and even the cohort studies are few and based on small and heterogeneous patient populations. So it is not surprising that the clinical practice is varying and many centres have a long experience of performing coronary angiography and PCI during full oral anticoagulation (OAC). In this study, we sought to determine the safety and efficacy of various periprocedural antithrombotic strategies in patients on long-term OAC with warfarin undergoing PCI in seven Finnish hospitals. Our special interest was to assess the safety of the simplistic UAC strategy.

Methods

Study design and patient population

This study is a part of a wider protocol in progress to assess thrombotic and bleeding complications of cardiac procedures in Western Finland.^{6–8} This retrospective analysis was based on computerized PCI databases in seven Finnish hospitals. We analysed all consecutive patients ($N = 523$) on warfarin therapy referred for PCI in four centres with a main policy to interrupt anticoagulation (IAC) before PCI and in three centres with a long experience on UAC during PCI. However, in each hospital, the treatment strategies varied between individual physicians. Therefore, in hospitals with IAC policy, a total of 20 patients underwent PCI with the UAC strategy. Similarly in the UAC group, a total of 51 patients had IAC policy during PCI, in some of the cases INR was, however, above the therapeutic range. The study period in the participating hospitals ranged from 3 to 5 years between years 2002 and 2006.

Coronary angiography and PCI were performed using either radial or femoral approach for arterial access and the haemostasis was obtained according to the local practice. Immediate post-operative sheath removal was preferred in all but one hospital, where the femoral sheaths were removed 2 h post-operatively. Lesions were treated according to current standard interventional techniques.

The medical records of the eligible patients were reviewed in order to determine the perioperative antithrombotic strategies and the incidence of major bleeding or access-site complications and major adverse cardiac events (MACE) during hospitalization. We also gathered data on other hospital complications, length of hospitalization, patient demographics including indications for warfarin use and the levels of AC (INR level). The Congestive heart failure, Hypertension, Age, Diabetes, Stroke (CHADS) score quantifying the annual stroke risk for patients who have non-valvular atrial fibrillation was also recorded for all patients.⁹

This study complies with the Declaration of Helsinki. The study protocol was approved by the Ethics Committees of the coordinating Satakunta Central Hospital and the participating hospitals.

Definitions

Vascular access-site complications included pseudoaneurysm or arteriovenous fistula, the occurrence of retroperitoneal haemorrhage and the need for corrective surgery. A decrease in the blood

haemoglobin level of more than 4.0 g/dL or the need for the transfusion of two or more units of blood or prolongation of index hospitalization because of access-site bleeding were also considered as access-site complications.

Major bleeding was defined as a decrease in the blood haemoglobin level of more than 4.0 g/dL, the need for the transfusion of two or more units of blood, the need for corrective surgery, the occurrence of an intracranial or retroperitoneal haemorrhage, or any combination of these.¹⁰

MACE was defined as the occurrence of any of the following during hospitalization: death, Q-wave or non-Q-wave MI (myocardial infarction), revascularization of the target vessel (emergency or elective coronary artery bypass grafting or repeated coronary angioplasty) or stent thrombosis.

MI was diagnosed when a rise in the myocardial injury marker level (troponin I or T) was detected together with symptoms suggestive of acute myocardial ischaemia. For the diagnosis of myocardial reinfarction, a new rise of >50% above the baseline injury marker level was required. Periprocedural MI was not routinely screened, but if procedural MI was suspected, a troponin level > 3 × normal 99th percentile level was required for the diagnosis. Target vessel revascularization was defined as a reintervention driven by any lesion located in the stented vessel. Stent thrombosis was diagnosed with angiographic evidence of either thrombotic vessel occlusion or thrombus within the stent, or in autopsy.

All outcome events were gathered only from the period of index hospitalization.

Statistical analysis

Continuous variables are presented as means (SD) and study groups were compared by Student's unpaired *t*-test. Categorical variables are presented as counts and percentages and were compared by the χ^2 or Fisher's exact test. In order to identify the independent predictors for major bleeding, access-site complications, MACE, and death during hospitalization, first univariate logistic regression for each baseline clinical characteristics and procedural variables was applied. At the second stage, the variables significantly ($P < 0.05$) associated with dependent variables in univariate analyses were included in multivariable analyses. The number of outcome events was quite low and therefore interaction terms were not investigated in multivariable models. For logistic models, age was categorized into four classes consisting of the age groups 38–59, 60–69, 70–79, and 80–88 years, because of the non-linear relation of age and logit-function. The fit of the logistic regression models was adequate according to Hosmer and Lemeshow goodness-of-fit tests.

Propensity scores were used to adjust for potential bias in the comparison between non-randomized IAC and UAC groups. Propensity scores were calculated as the predicted probability that patient was treated by UAC as opposed to IAC using logistic regression. Propensity score model 1 ($n = 523$) included the main effects of all baseline and procedural variables except INR and model 2 ($n = 478$, due to 45 missing INR values) included the main effects of all baseline and procedural variables. The differences between UAC and IAC groups in outcome variables were compared after adjustment for propensity score (linear term) by using logistic regression. Propensity score was also included in multivariable models. Results of the logistic regression are presented using odds ratios (OR) and their 95% confidence intervals (CI). A two-sided P -value < 0.05 was required for statistical significance. All data were analysed with the use of SPSS version 11¹¹ and SAS System for Windows version 9.1 (SAS Institute Inc., Cary, NC, USA).

The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

Results

Baseline clinical characteristics

We identified 523 patients with an indication for long-term OAC with warfarin who underwent PCI during the study period. A total of 241 patients underwent PCI without pauses in warfarin therapy (The UAC group). In 254 patients (The IAC group), OAC treatment with warfarin was stopped before the procedure (mean 3.0 days, range 1–30 days). Furthermore, a total of 28 patients underwent PCI when warfarin treatment was interrupted on the day of the index procedure. A total of 27 patients were prescribed a combination of aspirin and clopidogrel at discharge, and one patient received only clopidogrel at discharge.

The baseline clinical characteristics of the study population and the indications for OAC are further detailed in *Table 1*. There were more patients with prior MI ($P = 0.03$) and PCI ($P = 0.007$) in the UAC group compared with the IAC group. Female gender ($P = 0.007$) and history of heart failure ($P = 0.006$) were more common in the IAC group. Permanent non-valvular atrial fibrillation was the most frequent indication for OAC in both study groups (71% in the UAC group and 73% in the IAC group). The mean CHADS score was similar in the two groups.

Procedural variables

The procedural variables are summarized in *Table 2*. Femoral access was used in the majority of patients in both groups (78% in the UAC group and 80% in the IAC group) with no difference in the use of closure devices, but drug-eluting stents were more commonly used in the IAC group ($P < 0.001$). The mean INR on the day of the procedure was higher in the UAC group (2.2 vs.

Table 1 Baseline clinical characteristics of the study population

	UAC (n = 241)	IAC (n = 282)	P-value
Male, n (%)	191 (79)	194 (69)	0.007
Age (years)	69 ± 9	70 ± 9	0.28
CHADS score	1.8 ± 1.3	1.7 ± 1.1	0.44
Risk factors, n (%)			
Diabetes	60 (25)	92 (33)	0.054
Hypercholesterolemia	161 (67)	204 (72)	0.18
Current or ex-smoker	61 (25)	76 (27)	0.69
Hypertension	146 (61)	194 (69)	0.054
Medical history, n (%)			
Heart failure	40 (17)	75 (27)	0.006
Stroke	58 (24)	55 (20)	0.24
Myocardial infarction	103 (43)	94 (33)	0.03
PCI	48 (20)	32 (11)	0.007
CABG	50 (21)	62 (22)	0.75
Indication for PCI, n (%)			
Stable angina	115 (48)	147 (52)	0.34
STEMI	29 (12)	20 (7)	0.07
NSTEMI	61 (25)	72 (26)	1.0
Unstable angina	36 (15)	43 (15)	1.0
Medications at discharge, n (%)			
Beta-blockers	218 (90)	250 (89)	0.57
Lipid-lowering agents	199 (83)	220 (78)	0.23
ACE inhibitors/ARB	165 (68)	205 (73)	0.29
Indications for OAC, n (%)			
Atrial fibrillation	170 (71)	207 (73)	0.49
Prior cerebrovascular accident	25 (10)	33 (12)	0.68
Mechanical heart valve	19 (8)	5 (2)	0.001
Other indication	27 (11)	37 (13)	0.59

Data are mean (SD) or percentage. UAC, uninterrupted anticoagulation; IAC, interrupted anticoagulation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; OAC, oral anticoagulation.

Table 2 Procedural variables

	UAC (n = 241)	IAC (n = 282)	P-value
Lesions treated per patient	1.23 ± 0.5	1.22 ± 0.5	0.84
Lesion type, n (%)			
A	60 (25)	73 (26)	0.84
B/C	181 (75)	209 (74)	0.84
Stents, n	290	346	
Patients with drug eluting stents, n (%)	76 (32)	140 (50)	<0.001
Stent diameter (mm)	3.19 ± 0.58	3.17 ± 0.45	0.76
Total stent length (mm)	22.3 ± 11.5	23.7 ± 13.0	0.23
Balloon angioplasty, n (%)	29 (12)	15 (5)	0.007
Procedural success, n (%)	226 (94)	272 (96)	0.22
Femoral sheath, n (%)	189 (78)	225 (80)	0.75
Radial sheath, n (%)	52 (22)	57 (20)	0.75
Haemostasis, n (%)			
Manual compression	71 (29)	120 (43)	0.002
Device ^a	99 (41)	75 (27)	0.001
Access-site closure device ^b	71 (29)	87 (31)	0.78
INR on the day of the PCI ^c	2.2 ± 0.5	1.7 ± 0.5	<0.001

Data are mean (SD) or percentage. UAC, uninterrupted anticoagulation; IAC, interrupted anticoagulation; INR, international normalized ratio.

^aFemoStop[®], pneumatic compression device (Radi medical system, Sweden).

^bAngioseal[®], closure device (St Jude medical, USA).

^cPeriprocedural INR was not available for four patients in the UAC group and for 41 patients in the IAC group.

1.7, $P < 0.001$) compared with the IAC group. The INR value on the day of the procedure was not available in four (2%) patients in the UAC group and in 41 (15%) patients in the IAC group.

Periprocedural antithrombotic therapy

A total of 33 patients (13%) in the UAC group and 109 patients (39%) in the IAC group were pre-treated with clopidogrel for at least 24 h ($P < 0.001$). Table 3 shows supplemental periprocedural antithrombotic therapies used during and after the index PCI. In the IAC group, LMWH ($P < 0.001$) and glycoprotein IIb/IIIa (GP) inhibitors ($P < 0.001$) were more often utilized during the intervention. Post-procedural (>12 h) use of LMWH ($P = 0.002$) and GP inhibitors ($P < 0.001$) were also more frequent in the IAC group. There were 115 (48%) patients in the UAC group and 36 (13%) patients in the IAC group ($P < 0.001$) who received warfarin as the only anticoagulant during the PCI.

Antithrombotic regimens adopted after PCI are listed in Table 3. Dual therapy with warfarin and aspirin (22%) or warfarin and clopidogrel (21%) was utilized more often in the UAC group. In the IAC group, warfarin was discontinued in 90 patients (32%) and replaced by dual antiplatelet therapy with aspirin and clopidogrel, which was continued after discharge.

Uninterrupted anticoagulation vs. interrupted anticoagulation and outcome events during hospitalization

The in-hospital rates of adverse events in the two groups are presented in Table 4. The c-statistics for the propensity score models indicated good discrimination (for model 1 c-statistic 0.77 and for model 2 c-statistic 0.84). Several baseline and procedural variables were imbalanced before adjusting for propensity score, but after adjusting the differences between UAC and IAC groups, were non-significant and the balance was achieved. Propensity score was a significant covariate ($P = 0.03$) only for MACE in model 2. Major bleeding occurred more often in the IAC group compared with the UAC group (5.0% vs. 1.2%, $P = 0.02$). After adjusting for propensity score based on model 2, the difference in major bleeding between UAC and IAC groups remained significant (OR 5.7, 95% CI 1.4–24.1, $P = 0.02$), but did not remain significant after adjusting for propensity score based on model 1 (OR 3.9, 95% CI 1.0–15.3, $P = 0.05$). Detailed data on bleeding complications in both study groups are presented in Table 5. Two patients (0.7%) in the IAC group and one patient (0.4%) in the UAC group died after major bleeding during the index hospitalization.

Access-site complications occurred more frequently in the IAC group than in the UAC group (11.3% vs. 5.0%, $P = 0.01$) and the group difference remained significant after adjusting for propensity score (for model 1 OR 2.8, 95% CI 1.3–6.1, $P = 0.008$ and for model 2 OR 3.5, 95% CI 1.5–8.2, $P = 0.003$). Major bleeding events or access-site complications were not significantly related to INR levels in either group (Figure 1). MACE occurred in a total of 22 patients, 9 (3.2%) assigned to the IAC group and 13 (5.4%) assigned to the UAC group ($P = 0.28$). Adjusting for propensity score did not reveal significant association between UAC and MACE or death during hospitalization.

Predictors of adverse events

Univariate and multivariable logistic regression analyses to identify independent predictors for major bleeding, access-site complications, MACE, and death are shown in Table 6. Multivariable analysis showed, that the use of GP inhibitors (OR 3.0, 95% CI 1.0–9.1) was a predictor of borderline significance for major bleeding. Multivariable analysis showed, that the use of femoral access (OR 9.9, 95% CI 1.3–75.2), closure device (OR 2.1, 95% CI 1.1–4.0), LMWH (OR 2.7, 95% CI 1.1–6.7) and old age remained significant independent predictors for access-site complications. If clopidogrel was not utilized after the procedure, it predicted MACE. After multivariable models were adjusted for propensity score, the UAC and IAC group difference in access-site complication was significant (for model 2, OR 3.0, 95% CI 1.2–7.8, $P = 0.02$). Propensity score was not significant in any of the models. Figure 2 illustrates outcome events in certain subgroups of patients. As shown in Figure 2, major bleeding was common in the IAC group especially in patients presenting with acute coronary syndrome.

'Standard' uninterrupted anticoagulation vs. bridging therapy

There were 66 patients with 'standard' UAC (i.e. INR 2.0–3.5; clopidogrel and aspirin during PCI; no extra AC except warfarin) in

Table 3 Periprocedural antithrombotic treatment

	UAC (n = 241)	IAC (n = 282)	P-value
During PCI, n (%)			
Thrombolysis within 12 h	3 (1)	8 (3)	0.24
Unfractionated heparin	22 (9)	26 (9)	1.0
Low molecular weight heparin	101 (42)	209 (74)	<0.001
Bivalirudin	3 (1)	11 (4)	0.10
No additional anticoagulation	115 (48)	36 (13)	<0.001
Glycoprotein IIb/IIIa inhibitor	43 (18)	100 (35)	<0.001
Post-PCI (>12 h), n (%)			
Unfractionated heparin	3 (1)	1 (0.4)	0.34
Low molecular weight heparin	39 (16)	78 (28)	0.002
Glycoprotein IIb/IIIa inhibitor	41 (17)	98 (35)	<0.001
Antithrombotic regimens adopted after PCI, n (%)			
Aspirin + clopidogrel	0 (0)	90 (32)	<0.001
Warfarin + aspirin + clopidogrel	127 (53)	158 (56)	0.48
Warfarin + aspirin	54 (22)	14 (5)	<0.001
Warfarin + clopidogrel	50 (21)	17 (6)	<0.001
Warfarin monotherapy	10 (4)	1 (0.4)	0.004
Clopidogrel monotherapy	0 (0)	1 (0.4)	1.0
Aspirin monotherapy	0 (0)	1 (0.4)	1.0

UAC, uninterrupted anticoagulation; IAC, interrupted anticoagulation; PCI, percutaneous coronary intervention.

Table 4 Summary of outcome events at discharge

	UAC (n = 241)	IAC (n = 282)	P-value
MACE, n (%)	13 (5.4)	9 (3.2)	0.28
Death	8 (3.3) ^a	2 (0.7)	0.05
Myocardial infarction	8 (3.3)	6 (2.1)	0.43
Target vessel revascularization	4 (1.7)	2 (0.7)	0.42
Stent thrombosis	4 (1.7)	1 (0.4)	0.19
Stroke, n (%)	1 (0.4)	2 (0.7)	1.0
Major Bleeding, n (%)	3 (1.2)	14 (5.0)	0.024
Patients with access-site complications, n (%)			
Pseudoaneurysm	3 (1.2)	8 (2.8)	0.24
Bleeding delaying discharge	8 (3.3)	23 (8.2)	0.025
Need for corrective surgery	0 (0)	4 (1.4)	0.13
Haemoglobin decrease > 4 g/dL	1 (0.4)	5 (1.8)	0.13
Transfusion of blood	0 (0)	7 (2.5) ^b	0.02

UAC, uninterrupted anticoagulation; IAC, interrupted anticoagulation; MACE, number of patients with major adverse cardiac events including death, myocardial infarction, target vessel revascularization, and/or stent thrombosis.

^aTwo patients died from myocardial infarction, one from stent thrombosis, and one patient died of stroke. Three deaths occurred with no acute cardiovascular or bleeding complications after PCI (percutaneous coronary intervention).

^bOne patient with access-site complication received only 1 unit of blood.

the UAC group and 78 patients with LMWH bridging therapy in the IAC group. In these subgroups of patients, there were more major bleeding (11.5% vs. 1.5%, $P = 0.02$) and access-site complications (21.8% vs. 7.6%, $P = 0.02$) with the bridging therapy compared with the UAC. MACE was comparable with these subgroups (6.4% vs. 3.0%, $P = 0.5$, respectively). In multivariable analysis, use of access-site closure devices (OR 3.1, 95% CI 1.2–8.4) and the bridging therapy (OR 4.1, 95% CI 1.4–12.5) remained significant predictors for access-site complications.

Discussion

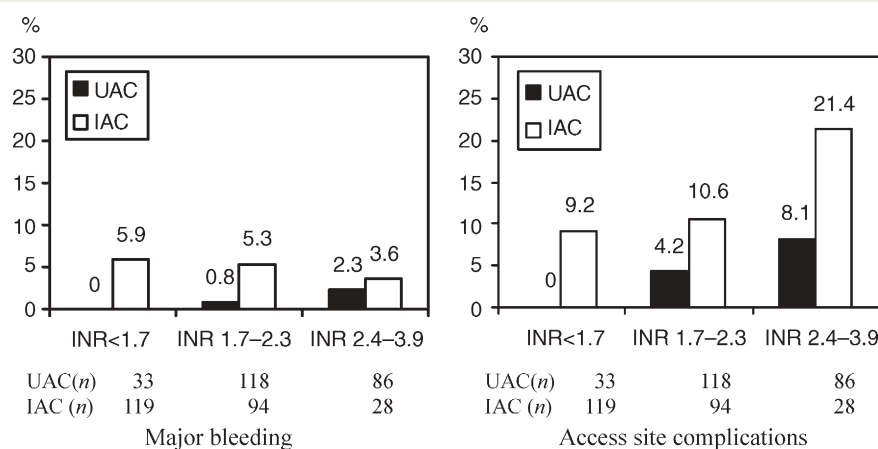
Major findings

It is estimated that more than 5% of patients undergoing PCI require long-term OAC because of underlying chronic medical condition.¹² In this multicentre study, we evaluated bleeding and access-site complications in this increasing subgroup of patients. Our major finding was that the simple strategy of UAC is at least as safe as that of more complicated IAC strategy in the every day clinical practice of PCI. Unexpectedly, both the bleeding and access-site complications were more common in patients with IAC, but this difference was explained largely by more frequent use of GP inhibitors and LMWH in the IAC group. The incidence of bleeding or thrombotic complications was not related to periprocedural INR levels. The subgroup analyses suggested that the bridging therapy with LMWH might lead to increased risk of access-site complications compared with 'standard' UAC.

Table 5 Characteristics of individual cases of major bleeding

Patient No.	Age, gender	Bleeding event	INR	GP inhibitor	LMWH	Antithrombotic therapy after PCI
UAC						
1	53, male	Decrease in Hb > 4 g/dL, transfusion of blood	3.0	+	0	W + A + C
2	84, male	Decrease in Hb > 4 g/dL	2.1	0	+	W + A + C
3	75, male	Groin access-site bleeding, decrease in Hb > 4 g/dL, cardiac death 2 days after PCI	3.3	0	+	W + A
IAC						
1	63, female	Pseudoaneurysm, transfusion of blood	2.0	0	+	W + A + C
2	70, male	Groin access-site bleeding, decrease in Hb > 4 g/dL, Corrective surgery, Transfusion of blood	2.6 ^a	+	+	W + A + C
3	71, female	Decrease in Hb > 4 g/dL	1.6	+	0	W + C
4	74, male	Decrease in Hb > 4 g/dL	2.1	+	+	A + C
5	74, male	Decrease in Hb > 4 g/dL	2.0	+	+	W + A + C
6	75, female	Groin access-site bleeding, decrease in Hb > 4 g/dL, transfusion of blood	1.3	+	+	W + A + C
7	76, male	Pseudoaneurysm, decrease in Hb > 4 g/dL, transfusion of blood	2.7	+	+	W + A + C
8	78, female	Pseudoaneurysm, corrective surgery	1.5	+	+	W + A + C
9	78, male	Radial access, haematuria, decrease in Hb > 4 g/dL	1.4	+	+	A + C
10	79, female	Decrease in Hb > 4 g/dL, Transfusion of blood	2.0	0	+	W + A + C
11	80, female	Decrease in Hb > 4 g/dL, transfusion of blood, died 4 days after PCI	2.0	+	+	A + C
12	81, female	Pseudoaneurysm, decrease in Hb > 4 g/dL, corrective surgery, transfusion of blood	1.5	+	+	W + A + C
13	83, female	Groin access-site bleeding, decrease in Hb > 4 g/dL, transfusion of blood, died 13 days after PCI	1.5	0	+	W + A
14	83, female	Groin access-site bleeding, corrective surgery	1.4	0	+	A + C

UAC, uninterrupted anticoagulation; IAC, interrupted anticoagulation; INR, international normalized ratio; GP, glycoprotein IIb/IIIa; LMWH, low molecular weight heparin; PCI, percutaneous coronary intervention; Hb, haemoglobin; W, warfarin; A, aspirin; C, clopidogrel.
^aINR was obtained 2 days prior PCI.

**Figure 1** Major bleeding and access-site complications in the two study groups according to the international normalized ratio (INR) levels.

Current guideline

It is generally recommended that warfarin should be discontinued a few days prior to elective coronary angiography or intervention,

and the periprocedural INR level should be <1.5–1.8.^{1,2} For patients requiring temporary discontinuation of OAC, current guidelines recommend the use of bridging therapy with UFH or

Table 6 Univariate and multivariable logistic regression analyses of baseline and procedural characteristics as predictors of major bleeding and access-site complications

	Univariate analyses: Odds ratio ^a (95% CI)	P-value	Multivariable analyses: Odds ratio ^a (95% CI)	P-Value
Major Bleeding				
GP inhibitors	5.2 (1.9–14.3)	0.001	3.0 (1.0–9.1)	0.051
Acute coronary syndrome	7.9 (1.8–35.0)	0.006	3.8 (0.8–19.1)	0.1
Female gender	3.3 (1.2–8.7)	0.02	2.0 (0.7–6.2)	0.2
LMWH during hospitalization	4.9 (1.1–21.7)	0.04	1.8 (0.3–9.3)	0.5
IAC group	4.1 (1.2–14.6)	0.03	2.5 (0.6–9.8)	0.2
Age				
38–59 vs. 60–69 years	2.8 (0.2–45.6)	0.47	3.0 (0.2–50.9)	0.5
70–79 vs. 60–69 years	8.1 (1.0–64.1)	0.047	6.1 (0.8–50.1)	0.09
80–88 vs. 60–69 years	15.5 (1.8–135.8)	0.01	7.5 (0.8–72.5)	0.08
Access-site complications				
Femoral access	12.5 (1.7–92.0)	0.01	9.9 (1.3–75.2)	0.03
Use of closure device	3.1 (1.7–5.8)	<0.001	2.1 (1.1–4.0)	0.03
LMWH during hospitalization	3.6 (1.6–8.3)	0.002	2.7 (1.1–6.7)	0.03
IAC group	2.4 (1.2–4.9)	0.01	1.8 (0.9–3.8)	0.1
Age				
38–59 vs. 60–69 years	2.4 (0.7–8.3)	0.16	3.1 (0.9–10.8)	0.08
70–79 vs. 60–69 years	3.4 (1.4–8.5)	0.009	3.8 (1.5–9.6)	0.006
80–88 vs. 60–69 years	4.9 (1.7–14.3)	0.004	4.3 (1.4–13.1)	0.01
MACE				
No clopidogrel post-PCI	3.4 (1.4–8.4)	0.008	3.2 (1.3–7.9)	0.01
Previous heart failure	2.6 (1.1–6.2)	0.03	2.4 (1.0–5.8)	0.055
Death				
Previous heart failure	8.8 (2.2–34.4)	0.002	6.7 (1.6–28.7)	0.01
No clopidogrel post-PCI	5.8 (1.7–20.7)	0.006	3.1 (0.8–12.5)	0.1
Acute coronary syndromes	9.3 (1.2–74.1)	0.04	5.9 (0.7–50.0)	0.1
LAD as a target vessel	5.2 (1.1–24.9)	0.04	4.1 (0.8–20.7)	0.09
IAC group	0.2 (0.04–1.0)	0.048	0.3 (0.05–1.4)	0.1

CI, confidence interval; GP, glycoprotein; LMWH, low molecular weight heparin; IAC, interrupted anticoagulation; PCI, percutaneous coronary intervention.

^aVariables significantly associated with major bleeding, access-site complications, MACE, and death in univariate and multivariable analyses. Significant predictors in univariate analyses were included in multivariable analyses.

LMWH in patients considered to be at risk of thromboembolism, such as those with prosthetic heart valves or atrial fibrillation. If emergent coronary intervention is required due to acute coronary syndromes, radial approach should be considered since haemostasis is rarely an issue with this access-site. The current consensus is, however, based on circumstantial evidence and there are no large-scale randomized trials to support the recommendations.

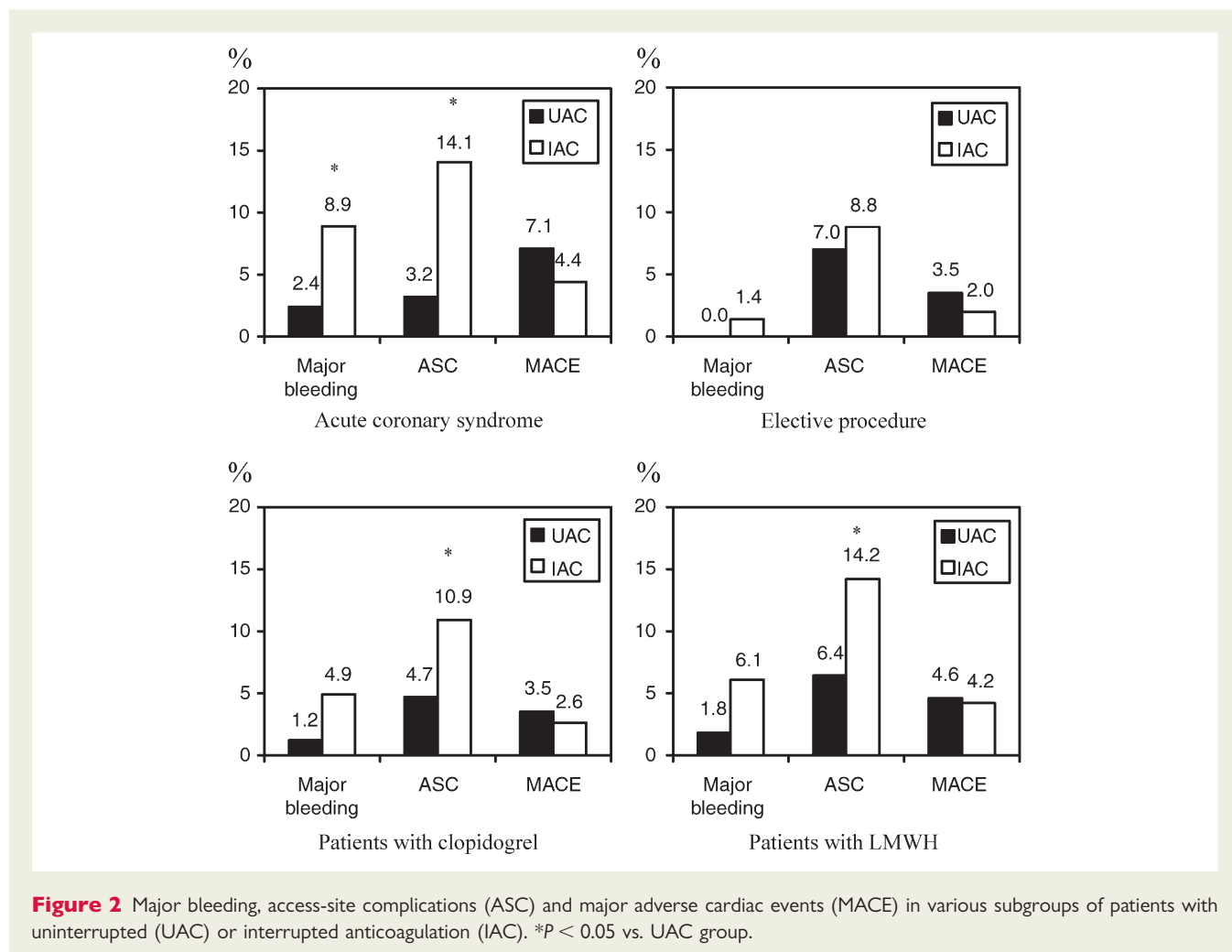
Bridging therapy and bleeding complications

Heparin bridging therapy has been used in patients who receive long-term OAC and require interruption of OAC for elective surgery or an invasive procedure,^{13–19} but the optimal strategy has not been established. Spyropoulos *et al.*¹³ showed a major bleeding rate of 3.3% with UFH and 5.5% with LMWH in 901

patients with bridging therapy for an elective surgical or invasive procedure. Another recent study reported a 6.7% incidence of major bleeding with LMWH bridging therapy in patients at risk of arterial embolism undergoing elective non-cardiac surgery or an invasive procedure,¹⁴ but also lower (2.9%) rates of major bleeding have been reported.¹⁶ Reports focusing on PCI are missing, but in the study by MacDonald *et al.*²⁰ only 4.2% of 119 patients developed enoxaparin-associated access-site complications during LMWH bridging therapy after cardiac catheterization.

Theoretical advantages of uninterrupted anticoagulation

In contrast to non-cardiac surgery, PCI requires procedural AC not only to avoid thromboembolic complications, but also thrombotic



complications of the intervention. Periprocedural AC has traditionally been performed with UFH or more recently with LMWH or direct thrombin inhibitors. Theoretically, OAC may be similarly used to facilitate PCI, since warfarin is known to increase activated coagulation time in a predictable fashion²¹ and stable OAC is not modified by the addition of clopidogrel.²² It is also well established that the more intense the OAC with warfarin, the greater the risk of long-term bleeding.²² Performing PCI without interrupting warfarin avoids the potential thrombotic risks associated with periods of subtherapeutic AC if the interruption is not fully covered by LMWH. Wide fluctuations in INR values are known to be common and long lasting after interruption necessitating prolonged bridging therapy.²³ Secondly, warfarin re-initiation may cause a transient prothrombotic state due to protein C and S suppression.²³ Bleeding was observed to be higher in those patients who crossed over from one AC to the other in the SYNERGY trial, which is of potential relevance also in this context.²⁴ The fear for 'unopposed' fatal bleedings may also be overemphasized, since the anticoagulant effect of warfarin can be rapidly overcome by a combination of activated blood clotting factors II, VII, IX, and X in case of severe bleeding. The anticoagulant effect of warfarin can also be reduced by fresh frozen plasma or by low doses of vitamin K. Our findings suggest that therapeutic OAC with warfarin could possibly replace other modes

of procedural AC with a favourable balance between bleeding and thrombotic complications.

UAC may be most useful for the patients with high risk of thrombotic and thromboembolic complications, since warfarin reinitiation may cause a transient prothrombotic state. Another potential strategy is a temporary adjustment of warfarin dosing to reach a perioperative INR of 1.5–2.4. Such moderate-dose OAC therapy (INR 1.5–2.0) with warfarin has been shown to be safe and effective in the prevention of thromboembolism after orthopaedic surgery, but the low AC level is probably not sufficient for PCI.²⁵ Temporary replacement of OAC by dual antiplatelet therapy is neither a good option in the light of ACTIVE-W study nor our recent results on coronary stenting.^{7,26}

Previous studies

In the current literature, there are no randomized trials comparing different strategies to manage long-term OAC during PCI. El-Jack *et al.*²⁷ recently randomized 61 patients undergoing coronary angiography either to therapeutic OAC treatment or to warfarin withdrawal (≥ 48 h). There was no major bleedings in either group, although all procedures were performed using transfemoral route. Of importance, it took a median of 9 days for INR to return to the therapeutic level.

Prospective Balloon Angioplasty and Anticoagulation Study compared the effects of aspirin alone and aspirin plus coumarins started before PCI with a target INR of 2.1–4.8 on subsequent restenosis. Both strategies led to a low incidence of thrombotic events. Major bleeding or false aneurysm formation was reported in 3.2% of warfarin-treated patients compared with 1% in the aspirin alone group. Surprisingly, there were more bleeding episodes in patients with an INR below the target range than in patients with an INR in the range. All patients were given, however, a high-dose of heparin, 10 000 U bolus plus infusion, during PCI performed via femoral approach.²⁸

Data on safety of uninterrupted long-term warfarin treatment during PCI is minimal. In a small series of patients ($n = 23$), Jessup *et al.*²⁹ showed that cardiac catheterization and PCI may be considered to be feasible in the setting of UAC, since no bleeding or thrombotic complications occurred in spite of the use of femoral route. An early report suggested that stenting could be performed safely under full OAC with no subacute thrombosis or femoral bleeding complications in spite of 8Fr femoral sheaths. Warfarin was started, however, only after successful stenting.³⁰

Vascular closure devices have emerged as an alternative to mechanical compression in order to achieve vascular haemostasis after puncture of the femoral artery. Their efficacy and safety have been evaluated in a number of clinical trials, but to date there is still a lack of randomized clinical trials with sample sizes large enough to reveal their superiority or non-inferiority compared with mechanical compression.^{31–33}

Limitations

Our study carries all the inherent limitations of a retrospective study including individual risk-based decision making in the treatment choices. On the other hand, the strength of our analysis is that we could identify and include all consecutive warfarin-treated patients from the records and avoid potential selection bias of prospective studies. In addition to the differences in the perioperative use of warfarin, other differences in the management strategies and patient selection are likely to modify our results, and multivariable analysis will not cover, e.g. potential differences in the adequacy of manual pressure haemostasis or overall perioperative patient management in the participating hospitals. In addition, physicians are aware of the bleeding risk with the use of GP inhibitors and may have avoided their use in the UAC group. The outcome assessment was not blinded and it was not possible to gather reliable information on, for example, mild bleeding complications retrospectively from patient records. Similarly, criteria for the bleeding that caused prolonged hospitalization may have varied between the institutions. Although our study is the largest so far, the sample size may not be sufficient to cover small, but clinically significant differences in bleeding and thrombotic complications between the main strategies, and the sample size is limited for subgroup analyses. In spite of these limitations, we feel that our data may be used to guide the treatment of patients with an indication of long-term OAC undergoing PCI, and is helpful in planning future prospective studies on this topic.

Conclusions

Our study shows that PCI is a relatively safe procedure during UAC with no excess bleeding or access-site complications compared with IAC. The bleeding events or MACE were not related to the INR levels when not exceeding the therapeutic range. This simplistic strategy of UAC may lead to considerable cost savings compared with the conventional bridging therapy, since the majority of PCIs are currently performed because of acute coronary syndromes. Our findings clearly indicate that radial approach leads to less access-site complications irrespective of AC strategy. The optimal perioperative strategy for treating patients requiring OAC is, however, complex and will depend on individual patient's risk factors for thromboembolism and bleeding. Old age, female gender, and other known bleeding risk factors should be taken into account especially when considering the use of GP inhibitors and LMWH in these patients. Prospective studies are urgently warranted to compare different treatment strategies in patients on long-term warfarin therapy undergoing PCI.

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