Safety and efficacy of combined antiplatelet-warfarin therapy after coronary stenting

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Aims The aim of this study was to evaluate the antithrombotic treatment adopted after coronary stenting in patients requiring long-term anticoagulation.

Methods and results We analysed retrospectively all consecutive patients on warfarin therapy ($n = 239$, mean age 70 years, men 74%) who underwent percutaneous coronary intervention (PCI) in 2003–04 in six hospitals. An age- and sex-matched control group with similar disease presentation (unstable or stable symptoms) was selected from the study period. Primary endpoint was defined as the occurrence of death, myocardial infarction, target vessel revascularization, or stent thrombosis at 12 months. Warfarin treatment was an independent predictor of both primary endpoint (OR 1.7, 95% CI 1.0–3.0, $P = 0.05$) and major bleeding (OR 3.4, 95% CI 1.2–9.3, $P = 0.02$). Triple therapy with aspirin and clopidogrel was the most common (48%) option in stented patients in warfarin group, and there was a significant ($P = 0.004$) difference between the drug combinations in stent thrombosis with the highest (15.2%) incidence in patients receiving warfarin plus aspirin combination.

Conclusion Our study shows that the prognosis is unsatisfactory in warfarin-treated patients irrespective of the drug combination used. Aspirin plus warfarin combination seems to be inadequate to prevent stent thrombosis.

Introduction

The optimal antiplatelet therapy following coronary stenting consists of a combination of aspirin and clopidogrel for the prevention of stent thrombosis,[1–3] but the optimal antithrombotic strategy is unclear for patients in whom long-term anticoagulation (AC) with warfarin is recommended because of atrial fibrillation, mechanical heart valve, previous systemic or venous thromboembolism, or other conditions. Addition of both aspirin and clopidogrel in the drug regimen of patients already on AC increases the risk of bleeding, whereas withholding antiplatelet therapy increases the risk of stent thrombosis. Even a temporary discontinuation of AC may increase the risk of thromboembolism,[4] and the increasing use of drug-eluting stents (DES) may increase the overall risk of late stent thrombosis.[5–7] Thus, it is not surprising that the antithrombotic strategies adopted after percutaneous coronary intervention (PCI) in this patient subset appear highly variable.

The aim of this study was to evaluate the current PCI practice and treatment results in this patient subset requiring long-term AC.

Methods

Study design and patient population

This study is part of a wider protocol in progress to assess thrombotic and bleeding complications of cardiac procedures in Western Finland.[7–9] This retrospective analysis was based on computerized PCI databases in six Western Finnish hospitals. All patients undergoing PCI and having an indication for long-term AC with warfarin were identified between 2003 and 2004 in two hospitals and in 2004 in other hospitals. In each centre, an age- (± 5 years) and sex-matched control group with similar disease (unstable or stable symptoms) was collected from a total PCI population of ~4200 patients treated during the study period. Matching was successful except for differences in disease type in three pairs and in age (6–10 years) in four pairs.

Lesions were treated according to current standard interventional techniques, with the final strategy (including direct stenting, post-dilatation, periprocedural glycoprotein IIb/IIIa inhibitor, and the use of intravascular ultrasound) left entirely up to the

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operator's discretion. Procedural success was defined as a residual stenosis <30% by visual analysis in the presence of Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 without death, occurrence of Q-wave myocardial infarction (MI), or coronary artery bypass graft surgery (CABG).

All medical records of the cases and controls were reviewed and the patients were interviewed by telephone if needed in order to determine the length of antithrombotic therapy and incidence of bleeding and other clinical events during the follow-up period of 1 year. CHADS score, based on the patient's age and other medical conditions (score from 0 to 6), was recorded for all patients. The CHADS score estimates the yearly risk of stroke if AC with warfarin is not used in patients with non-valvular atrial fibrillation.[10] Hospital records and death certificates from the Central Statistical Office of Finland were used to record and classify deaths.

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

Endpoint definitions and clinical follow-up

The primary endpoint was defined as the occurrence of death, MI, target vessel revascularization (TVR), or stent thrombosis at 12 months. The secondary safety endpoint consisted of major bleeding complications and stroke at 12 months.

MI was diagnosed if any troponin elevation with symptoms suggestive for acute coronary syndromes (ACS) was detected. The presence of new pathological Q-waves in ECG was also diagnosed as MI. TVR was defined as a reintervention driven by any lesion located in the stented vessel. Indication for repeat revascularization was based on anginal symptoms and/or proven myocardial ischaemia in the target vessel territory, and a significant luminal stenosis (>50% diameter stenosis). Stent thrombosis was diagnosed in the presence of ACS with angiographic evidence of either thrombotic vessel occlusion or thrombus within the stent, or in autopsy. 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 events.[11] Stroke was defined as an ischaemic cerebral infarction caused by an embolic or thrombotic occlusion of a major intracranial artery.

Adverse events were recorded at hospital discharge and at 12 months.

Statistical analysis

Continuous variables are presented as means (standard deviations) and categorical variables are presented as frequencies (percentages). Paired t-test was used to compare the difference between the study groups in continuous variables. The difference in categorical variables between the study groups were tested by binary logistic regression analysis with matched pair as a random effect.[12]

Univariate and multivariable logistic regression analyses with matched pair as a random effect were performed to identify independent predictors for primary endpoint and bleeding complications at 12 months among all stented patients. Because of multiple testing, only variables with a two-sided $P < 0.05$ in the univariate analysis were entered into multivariable model. Results of logistic regression are presented as odds ratios (OR) with 95% confidence interval (CI). The differences between the treatment combinations in the warfarin group were tested with ANOVA and a Bonferroni correction for P-values were performed to account for multiple comparisons. The χ^2 or Fisher's exact test was used for comparison of categorical variables in the warfarin group. A two-sided $P < 0.05$ was considered statistically significant. Data was analysed using SAS System for Windows, version 9.1 and SPSS, version 11.[13]

Results

Baseline characteristics

We identified 239 patients with an indication of long-term AC with warfarin who underwent PCI during the study period. Complete follow-up data could be gathered for all patients and also for all the 239 control patients without prior AC. The baseline clinical characteristics of the study population and the indications for AC are displayed in *Table 1*. The patients who received AC with warfarin had more often co-morbidities such as hypertension ($P = 0.03$), heart failure ($P < 0.001$), and diabetes ($P = 0.01$), and they also had more often previous stroke ($P < 0.001$), MI ($P = 0.005$), and CABG ($P < 0.001$) in their medical history than patients in the control group. Permanent atrial fibrillation (70% of cases) was the most frequent indication for AC.

Table 1 Baseline characteristics of the study population

	Warfarin patients (n = 239)	Control patients (n = 239)	P-value
Male, n (%)	177 (74)	177 (74)	1.0
Age, (years)	70 ± 9	70 ± 9	0.29
Diabetes, n (%)	71 (30)	47 (20)	0.012
Hypercholesterolaemia, n (%)	167 (70)	164 (69)	0.77
Current smoking, n (%)	70 (29)	55 (23)	0.12
Hypertension, n (%)	160 (67)	136 (57)	0.025
Ejection fraction,[a] %	50 ± 14	56 ± 11	0.003
Previous heart failure, n (%)	58 (24)	12 (5)	<0.001
Previous stroke, n (%)	49 (21)	13 (5)	<0.001
Previous MI, n (%)	99 (41)	69 (29)	0.005
Previous PCI, n (%)	35 (15)	33 (14)	0.79
Previous CABG, n (%)	48 (20)	21 (9)	<0.001
Acute STEMI, n (%)	22 (9)	33 (14)	0.11
Acute NSTEMI, n (%)	60 (25)	55 (23)	0.58
Unstable angina, n (%)	46 (19)	41 (17)	0.54
Medications at discharge			
Beta-blockers, n (%)	212 (89)	225 (94)	0.038
Lipid-lowering agents, n (%)	186 (78)	200 (84)	0.11
ACE-inhibitors/ARB, n (%)	157 (66)	121 (51)	0.001
Indications for AC			
Atrial fibrillation, n (%)	168 (70)		
Previous cerebrovascular accident, n (%)	26 (11)		
Mechanical heart valve, n (%)	10 (4)		
Pulmonary embolus or venous thromboembolism, n (%)	23 (10)		
Other indication, n (%)	12 (5)		

Data are mean (SD) or percentage. STEMI, ST-elevation MI; NSTEMI, non ST-elevation MI; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers.
[a]Ejection fraction available in 159 patients in warfarin group and in 117 patients in control group.

Table 2 Procedural characteristics

	Warfarin patients (*n* = 239)	Control patients (*n* = 239)	*P*-value
Thrombolysis within 24 h, *n* (%)	4 (2)	8 (3)	0.25
Glycoprotein IIb/IIIa inhibitor, *n* (%)	66 (28)	84 (35)	0.07
Number of lesions treated per patient	1.19 ± 0.43	1.21 ± 0.45	0.75
Stent diameter used, (mm)	3.15 ± 0.43	3.08 ± 0.41	0.12
Total stent length, (mm)	23.2 ± 12.2	22.6 ± 11.6	0.79
Stents implanted, *n*	290	296	
Patients with DES, *n* (%)	101 (42)	97 (41)	0.71
Balloon angioplasty, *n* (%)	20 (8)	12 (5)	0.15
Procedural success, *n* (%)	232 (97)	234 (98)	0.56
Femoral sheath, *n* (%)	189 (79)	174 (73)	0.10
Radial sheath, *n* (%)	50 (21)	65 (27)	0.10
Use of access-site closure devices, *n* (%)	62 (26)	57 (24)	0.60
INR on the day of the PCI	2.19 ± 0.54		
Length of hospitalization (days)	3.6 ± 6	2.4 ± 3	0.003

Data are mean (SD) or percentage.

Table 3 Antithrombotic regimens adopted in stented patients after PCI

	Warfarin patients (*n* = 219)	Control patients (*n* = 227)
Aspirin + clopidogrel, *n* (%)	34 (15.5)	214 (94.3)
Warfarin + aspirin + clopidogrel, *n* (%)	106 (48.4)	1 (0.4)
Warfarin + aspirin, *n* (%)	33 (15.1)	0 (0)
Warfarin + clopidogrel, *n* (%)	45 (20.5)	0 (0)
Warfarin monotherapy, *n* (%)	1 (0.5)	0 (0)
Clopidogrel monotherapy, *n* (%)	0 (0)	10 (4.4)
Aspirin monotherapy, *n* (%)	0 (0)	2 (0.9)

Figure 1 Duration of clopidogrel treatment after stenting in the various subgroups in warfarin group.
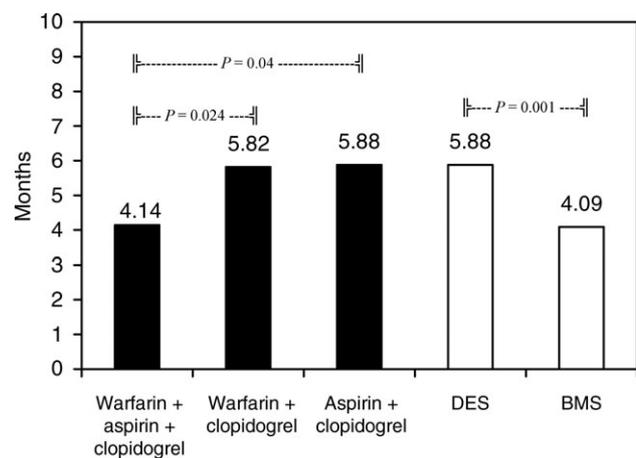
Procedural variables

The procedural characteristics are summarized in *Table 2*. Glycoprotein IIb/IIIa inhibitors tended to be less often (*P* = 0.07) used in the AC group. Coronary stenting was performed on 219 patients in the warfarin group and on 227 patients in the control group. The use of DES (~40%) and other deployment and implantation features were comparable in the two groups. The mean international normalized ratio (INR) value on the day of the PCI was 2.19 ± 0.54.

Antithrombotic therapy

Table 3 shows different antithrombotic regimens adopted after coronary stenting. In the warfarin group, triple therapy with dual antiplatelet regimen plus warfarin was most commonly used (48.4%). Temporary switching (mean duration 177 days) from warfarin to dual antiplatelet therapy with aspirin and clopidogrel was used in 15.5% of patients. Duration of clopidogrel prescription was significantly shorter in triple therapy group than in both dual therapy groups (*Figure 1*). Clopidogrel treatment was longer in patients receiving DES than in patients with bare metal stents (BMS) (*P* = 0.001). Patients treated with dual antiplatelet therapy had significantly longer (difference 7–11 mm, *P* = 0.001) total stent length compared with all the other groups. Procedural INR level was significantly lower in the triple therapy group compared with all other groups (difference 0.1–0.3, *P* = 0.02).

Hospital complications

Summary of outcome events at discharge in stented patients are shown in *Table 4*. Major bleeding tended to be more common (4 vs. 0) in warfarin group, but the other outcomes were comparable in the two groups. The duration of hospitalization after PCI was longer in warfarin-treated patients (*Table 2*).

In warfarin group, three patients suffering primary endpoint were discharged, and all of them received the initially prescribed antithrombotic regimens for the whole 12-month period (triple therapy in one patient and warfarin plus aspirin combination in two patients). The in-hospital bleeding events and stroke were non-fatal and four of the patients received triple therapy (for 3 to 12 months), and one patient was treated with aspirin plus clopidogrel for 3 months.

Outcome at 12 months

The primary and secondary endpoints in stented patients are listed in *Table 4*. At 12 months, the rate of primary endpoint (death, MI, TVR, or stent thrombosis) was higher in the warfarin group (*P* = 0.003). This was mainly driven by a significant difference (19 vs. 4, *P* = 0.003) in mortality, but also the incidence of MI was higher in the warfarin group. The rate of stent thrombosis did not differ significantly

Table 4 Summary of outcome events during follow-up in stented patients

	Warfarin patients (n = 219)	Control patients (n = 227)	OR (95% CI)[a]	P-value
At discharge				
Primary endpoint				
Death, n (%)	3 (1.4)	1 (0.4)		
MI, n (%)	4 (1.8)	3 (1.3)		
TVR, n (%)	3 (1.4)	1 (0.4)		
Stent thrombosis, n (%)	4 (1.8)	1 (0.4)		
Overall, n (%)	6 (2.7)	3 (1.3)	2.1 (0.5–8.6)	0.30
Secondary endpoint				
Major bleeding, n (%)	4 (1.8)	0 (0)		
Stroke,[b] n (%)	1 (0.5)	0 (0)		
At 12 months[c]				
Primary endpoint				
Death,[d] n (%)	19 (8.7)	4 (1.8)	5.3 (1.8–16.0)	0.003
MI, n (%)	22 (10.0)	11 (4.8)	2.2 (1.0–4.7)	0.041
TVR, n (%)	24 (11.0)	17 (7.5)	1.5 (0.8–2.9)	0.21
Stent thrombosis, (%)	9 (4.1)	3 (1.3)	3.2 (0.8–12.1)	0.09
Overall, n (%)	48 (21.9)	25 (11.0)	2.3 (1.3–3.8)	0.003
Secondary endpoint				
Major bleeding, n (%)	18 (8.2)	6 (2.6)	3.3 (1.3–8.6)	0.014
Stroke,[b] n (%)	7 (3.2)	5 (2.2)	1.5 (0.5–4.7)	0.52
Overall, n (%)	25 (11.4)	11 (4.8)	2.5 (1.2–5.3)	0.014

[a]Binary logistic regression analysis with matched pair as random effect.
[b]Intracranial bleedings not included.
[c]Including hospital complications.
[d]12 of 19 in warfarin group and one of four in control group suffered cardiovascular death.

($P = 0.09$) between the warfarin and control groups. There were no acute stent thrombosis and all subacute occlusions occurred within 7 days of the procedure.

Major bleeding was more common in the warfarin group ($P = 0.01$). Detailed data on bleeding complications in warfarin group is presented in *Table 5*. Two of the bleeding events were fatal. In the control group, four patients had gastro-intestinal bleeding and two other patients had a significant decrease in the blood haemoglobin level more than 4.0 g/dL.

The incidence of stroke was comparable in the two groups. The CHADS score was not significantly higher in patients who suffered stroke during the follow-up ($P = 0.4$).

Balloon angioplasty

Balloon angioplasty without stenting was not a more frequently chosen option in the warfarin group than in the controls (20 vs. 12 patients). A total of 16 patients in the warfarin group received combination of warfarin and aspirin, and nine patients in the control group received dual therapy with aspirin and clopidogrel. Five patients in the warfarin group and four controls had reached the primary endpoint within 12 months. Major bleeding complications occurred in two patients in both groups.

Complications with various drug regimens in warfarin group

Complications with various drug regimens adopted after stenting in the warfarin group are shown in *Figures 2* and *3*. There was a significant ($P = 0.004$) difference between

Table 5 Major bleeding complications in 18 patients in warfarin group during 12 months follow-up

Intracranial bleeding[a]	3
Gastrointestinal bleeding	2
Groin haematoma[b]	4
Retroperitoneal bleeding	1
Decrease in the blood haemoglobin (4.0 g/dL)[c]	17
Urinary bleeding	1

[a]Two patients related to trauma.
[b]Three patients needed corrective surgery.
[c]Six patients needed transfusion of two or more units of blood.

the groups in the incidence of stent thrombosis with highest (15.2%) incidence in patients receiving warfarin plus aspirin combination. Two patients (1.9%) in the triple therapy group had stent thrombosis during the follow-up. In the triple therapy group, stent thrombosis occurred in one patient 16 days after the clopidogrel treatment was stopped, and majority of MIs occurred after stopping clopidogrel (*Figure 2*). In the control group, all three patients with stent thrombosis were on dual treatment with aspirin and clopidogrel. Four of the nine patients with stent thrombosis in warfarin group and one patient in control group were treated with DES.

There were no significant differences in major bleeding events between the subgroups (*Figure 2*). Most of the bleeding events occurred while on scheduled drug regimens, and 13 of 18 patients were receiving clopidogrel. The incidence of stroke was highest (8.8%) in the patients with warfarin
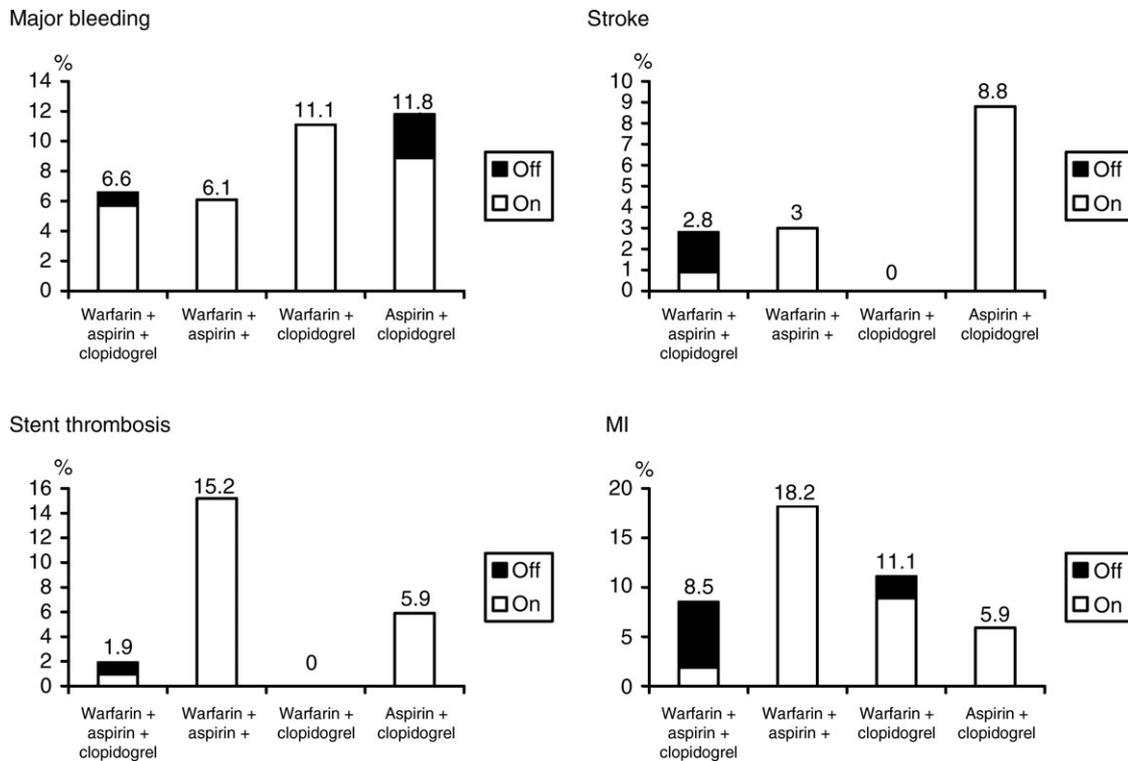
Figure 2 Complications during 12-month follow-up with various drug regimens adopted after stenting in warfarin group (prescribed drug combinations either On or Off at the time of the event).
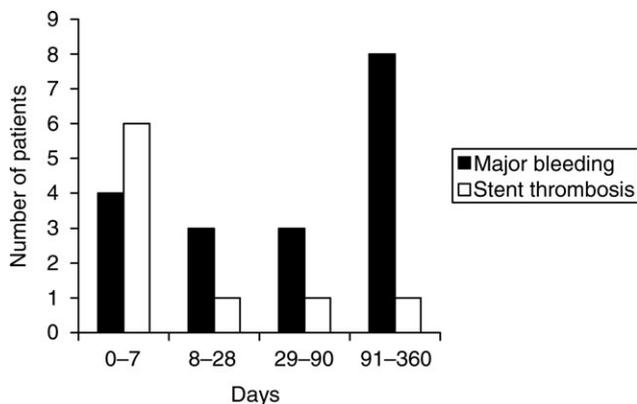

Figure 3 Timing of major bleeding events and stent thrombosis during follow-up. The bleeding risk remained high throughout the treatment period, whereas most of the definite stent thrombosis occurred early after PCI.

substituted by double antiplatelet therapy, but the difference to other groups was not significant.

Predictors of adverse events

Warfarin group (OR 3.3, 95% CI 1.3–8.6, $P = 0.01$), female gender (OR 3.7, 95% CI 1.6–8.7, $P = 0.003$), current smoking (OR 3.0, 95% CI 1.3–7.0, $P = 0.01$), acute non-Q-wave MI (OR 2.4, 95% CI 1.0–5.7, $P = 0.05$), and use of glycoprotein receptor blocker (OR 2.6, 95% CI 1.1–6.0, $P = 0.03$) were significant predictors of major bleeding within 12 months in univariate analyses. Multivariable analysis with these variables in the model showed that in addition to warfarin group (OR 3.4, 95% CI 1.2–9.3, $P = 0.02$), current smoking (OR 6.6, 95% CI 2.2–19.9, $P < 0.001$), use of

glycoprotein receptor blocker (OR 2.6, 95% CI 1.0–6.5, $P = 0.05$), and female gender (OR 7.6, 95% CI 2.5–23.0, $P < 0.001$) predicted major bleeding.

In univariate analyses, warfarin group (OR 2.3, 95% CI 1.3–3.8. $P = 0.003$), history of heart failure (OR 3.0, 95% CI 1.6–5.5, $P < 0.001$), and previous CABG (OR 3.1, 95% CI 1.7–5.8, $P < 0.001$) predicted primary endpoint at 12 months. In the multivariable analysis, previous CABG (OR 2.5, 95% CI 1.3–4.7, $P = 0.006$), history of heart failure (OR 2.1, 95% CI 1.1–4.1, $P = 0.02$), and warfarin group (OR 1.7, 95% CI 1.0–3.0, $P = 0.05$) remained significant independent predictors for primary endpoint.

Discussion

The major finding of our case–control study was that the prognosis of warfarin-treated patients is unsatisfactory irrespective of the antithrombotic combinations used. Frequent co-morbidities are likely to have a major contribution to some of the differences, but the problems of antithrombotic therapy seem to also have a crucial role, especially for the bleeding complications. Stent thrombosis and MI were frequent, particularly in patients without clopidogrel in the drug combination and the risk of stroke seems to be increased if warfarin is withdrawn after stenting. Not unexpectedly, major bleeding complications were common, particularly during the most popular triple therapy, and also in the dual therapy group with warfarin and clopidogrel.

Current guidelines

The combination of aspirin and clopidogrel is the current standard antithrombotic therapy after PCI.[14] The

recommended duration of dual antiplatelet therapy is at least 1 month in patients receiving BMS, 3 months in patients receiving sirolimus-eluting stent(s), and 6 months of aspirin and clopidogrel in patients receiving paclitaxel eluting stent(s).[15–17] In patients with ACS, clopidogrel is recommended up to 1 year after PCI.[18–20] However, nearly 10% of patients referred for PCI also have clear evidence-based indications for long-term AC. There are no evidence-based guidelines on the management of these patients and so various antithrombotic combinations are used in everyday practice as shown by the present report.

Previous randomized studies on AC

Four randomized trials (ISAR, FANTASTIC, STARS, and MATTIS) have shown that warfarin plus aspirin combination after PCI is not as effective as ticlodipine plus aspirin in preventing stent thrombosis.[21–23] On the other hand, recent ACTIVE-W study had to be stopped early because of clear superiority of oral AC over dual antiplatelet therapy in stroke prevention in patients with atrial fibrillation.[4] Of note, the difference was most obvious in those patients already on AC before the study. This finding suggests that the switch to antiplatelet therapy may predispose also a PCI patient to an extra risk during a warfarin withdrawal. Unfortunately, there are no randomized trials comparing various antiplatelet drug combinations during baseline warfarin therapy.

Observational studies on AC after angioplasty

To our knowledge, there are only few small observational studies on the antiplatelet treatment of anticoagulated patients after coronary angioplasty, and all of these have focused on bleeding complications.[24–26] In accordance with our findings, Orford et al.[24] showed overall bleeding rate of 9.2% with triple therapy with warfarin, aspirin, and thienopyridine in a group of 66 consecutive patients. Another recent study reported a 6.6% incidence of major bleeding with triple therapy.[25] On the other hand, short-term triple therapy after PCI was not associated with prohibitively high (~2%) incidence of major bleeding complications in two other small studies.[26,27]

Limitations and strengths of the present study

This lack of knowledge emphasizes the importance of the present study for shedding light on the unresolved issue of antithrombotic treatment in PCI patients with evidence-based indication for AC. The importance of this issue is further emphasized by the fact that the prognosis of this population seems to be unsatisfactory. Our case–control study is the largest so far. The small sample size is, however, limited for subgroup analysis. Our study carries all the inherent limitations of a retrospective study. Decisions to use specific drug combinations were made by the local physicians, according to their perceptions of risks and benefits for particular patients. Such treatment allocation probably results in an imbalance in risk factors between the drug combinations. Non-blinded outcome assessment, limited data on drug compliance, and missing data on e.g. mild bleeding complications are among the limitations of our study. 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 AC undergoing PCI, and is helpful in planning future prospective studies on this topic.

Conclusions

Our study shows that the long-term prognosis of warfarin-treated patients is unsatisfactory irrespective of the drug combinations used. Although general guidelines are available concerning antithrombotic therapy after PCI and acute MI, the optimal strategy for treating patients requiring AC is complex and will depend on individual patient's risk factors for thromboembolism and bleeding. On the basis of previous randomized trials and present findings, it seems that dual treatment with aspirin and AC is associated with frequent stent thrombosis[21–23] and MI, although this combination has proved to be a good option after MI.[28–31] ACTIVE W study[4] together with our results suggests that even a short withdrawal of AC after PCI is associated with a significant risk of stroke and cannot be recommended. Our findings support the view that dual antiplatelet treatment combined with AC is currently the best option for the majority of the patients. This full-dose triple therapy predisposes, however, to an increased risk of bleeding, which may require stopping AC and expose these patients to thrombosis and thromboembolism. The favourable outcome in clopidogrel–warfarin subgroup suggests that this combination might be a reasonable option in patients with increased bleeding risks. The risks and benefits of glycoprotein receptor blockers in this high-risk population should be kept in mind in view of the observed high risk of bleeding complications.

Acknowledgements

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