Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial

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Summary

Background **If percutaneous coronary intervention (PCI) is required in patients taking oral anticoagulants, antiplatelet therapy with aspirin and clopidogrel is indicated, but such triple therapy increases the risk of serious bleeding. We investigated the safety and efficacy of clopidogrel alone compared with clopidogrel plus aspirin.**

Methods **We did an open-label, multicentre, randomised, controlled trial in 15 centres in Belgium and the Netherlands. From November, 2008, to November, 2011, adults receiving oral anticoagulants and undergoing PCI were assigned clopidogrel alone (double therapy) or clopidogrel plus aspirin (triple therapy). The primary outcome was any bleeding episode within 1 year of PCI, assessed by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00769938.**

Findings **573 patients were enrolled and 1-year data were available for 279 (98·2%) patients assigned double therapy and 284 (98·3%) assigned triple therapy. Mean ages were 70·3 (SD 7·0) years and 69·5 (8·0) years, respectively. Bleeding episodes were seen in 54 (19·4%) patients receiving double therapy and in 126 (44·4%) receiving triple therapy (hazard ratio [HR] 0·36, 95% CI 0·26–0·50, p<0·0001). In the double-therapy group, six (2·2%) patients had multiple bleeding events, compared with 34 (12·0%) in the triple-therapy group. 11 (3·9%) patients receiving double therapy required at least one blood transfusion, compared with 27 (9·5%) patients in the triple-therapy group (odds ratio from Kaplan-Meier curve 0·39, 95% CI 0·17–0·84, p=0·011).**

Interpretation **Use of clopiogrel without aspirin was associated with a significant reduction in bleeding complications and no increase in the rate of thrombotic events.**

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Introduction

Long-term treatment with oral anticoagulants is necessary in patients with mechanical heart valves and in most with atrial fibrillation.[1–3] 20–30% of patients have concomitant ischaemic heart disease that requires percutaneous coronary intervention (PCI) with stenting.[3,4] In these cases, double antiplatelet therapy with aspirin and clopidogrel is indicated to prevent stent thrombosis.[3,5] The combination of oral anticoagulants and antiplatelet therapy, however, is associated with a high annual risk (4–16%) of fatal and non-fatal bleeding episodes.[4,6–8] The optimum treatment after PCI is, therefore, unclear when thrombotic and bleeding risks are both taken into account. No indicative data are available from prospective randomised trials. Experts recommend triple antithrombotic therapy, consisting of oral anticoagulants with a revised target international normalisation rate, aspirin, and clopidogrel (for as short a time as possible),[3] but this strategy has not been tested prospectively.[3,9] Omission of oral anticoagulants could lead to an increased risk of thrombotic stroke,[10–12] whereas clopidogrel is essential to prevent stent thrombosis.[6,13–15] The exclusion of aspirin might, therefore, be useful to reduce the bleeding risk in patients with coronary artery disease. Results from two large, randomised trials showed that full-intensity oral anticoagulants alone after myocardial infarction were associated with reduced rates of reinfarction and stroke compared with aspirin, although the risk of bleeding episodes was raised.[16,17]

In this trial we tested the hypothesis that in patients taking oral anticoagulants and undergoing PCI, the use of clopidogrel alone would reduce the risk of bleeding but not increase the risk of thrombotic events compared with clopidogrel plus aspirin.

Methods

Study design and patients

The What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing (WOEST) study was an open-label, randomised, controlled trial done at 15 sites in the Netherlands and Belgium.[18] All eligible patients referred to the study centres from November, 2008, to November, 2011, were included. Inclusion criteria were a long-term

indication for oral anticoagulation treatment (until at least 1 year after the study); a severe coronary lesion (at least 75% stenosis on angiography or fractional flow reserve lower than 0·80) with indication for PCI; and age 18–80 years. Exclusion criteria were history of intracranial bleeding; cardiogenic shock; contraindication to use of aspirin, clopidogrel, or both; peptic ulcer in the previous 6 months; thrombocytopenia (platelet concentration lower than 50×10^9/L); major bleeding (according to the Thrombolysis in Myocardial Infarction [TIMI] criteria) in the past 12 months; and pregnancy. The indication for PCI was based on established European and US guidelines.[19,20]

The study protocol was approved by the central Dutch and Belgian ethics committees and the local ethics review boards of all participating centre. The data management and statistical analysis were performed by the research and development section, Cardiology Department, St Antonius Hospital, Nieuwegein, Netherlands. All patients provided written informed consent.

Randomisation

Patients were randomly assigned in a 1:1 ratio to receive clopidogrel alone (double therapy) or clopidogrel and aspirin (triple therapy). The randomisation sequence was computer generated at St Antonius Hospital (blocked randomisation per centre) and patients' allocations were kept in sequentially numbered sealed envelopes. Group allocations were issued by the secretarial staff of the research department of each centre. Requests for treatment assignments could be made before or up to 4 h after PCI.

Treatment

All patients were pretreated with a maintenance dose of 75 mg clopidogrel per day for at least 5 days, a loading dose of 300 mg at least 24 h before PCI, or a loading dose of 600 mg at least 4 h before PCI. Study treatment was started promptly after randomisation. All patients received 75 mg clopidogrel daily, and those in the triple-therapy group were also given 80–100 mg aspirin daily; a 320 mg loading dose was also given to patients who had not been taking aspirin before the study. During the intervention, oral anticoagulants were continued where possible, with a target international normalisation ratio of 2·0.[18] At the discretion of the treating physician, however, oral anticoagulants could be replaced with low-molecular-weight heparin during PCI. To reduce the risk of bleeding, use of radial access, proton-pump inhibitors, and access-site-closure devices (when PCI was done through a femoral access site) were recommended but not mandatory.[18] After PCI, oral anticoagulants were restarted, with the target international normalisation ratio being that indicated for the underlying disease.

The allocated antiplatelet treatment was continued for at least 1 month, up to 1 year at the discretion of the attending physician, in patients who received a bare-metal stent for stable coronary disease. In patients with acute coronary syndromes or who received drug-eluting stents, clopidogrel was administered for at least 1 year. Other cardiac medications were given at the discretion of the attending physician.[18]

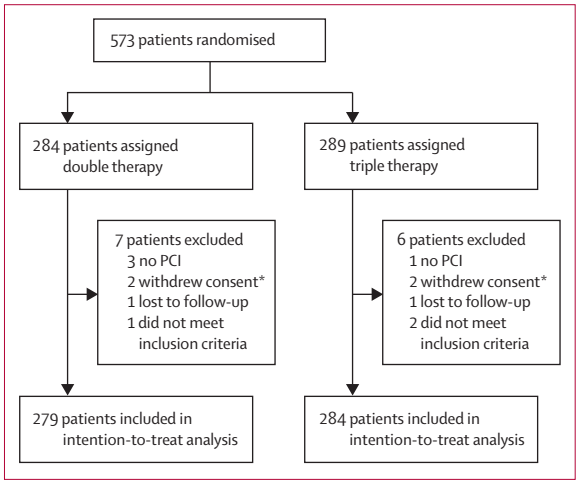

Figure 1: **Trial profile**
PCI=percutaneous coronary intervention. *Two patients in the double-therapy group and one in the triple-therapy group were included in the intention-to-treat analysis until the day of withdrawal.

Assessments and follow-up

All data were collected prospectively and were entered into a central database. Follow-up stopped 1 year after inclusion, at the time of death, or on Aug 1, 2012, whichever came first.

Patients were assessed with electrocardiography before and 2 h and 6 h after PCI, or more frequently if clinically indicated. Creatine kinase concentration and the creatinine kinase MB fraction were measured in all patients before and after PCI in those who had recurrent angina pectoris, or in any patient in whom the electrocardiography results before and after PCI differed.

Myocardial infarction was defined as detection of rise and fall of cardiac biomarkers, including troponin, with at least one value above the 99th percentile of the upper reference limit, together with evidence of myocardial ischaemia with at least one of the following: clinical symptoms, electrocardiographic changes (new ST–T changes or new left-bundle-branch block), development of pathological Q waves, or new loss of viable myocardium or new regional wall-motion abnormality on imaging. Periprocedural infarction was defined as rises in cardiac biomarker concentrations to more than three times the 99th percentile of the upper reference limit.[21] Stroke was defined as focal loss of neurological function caused by an ischaemic or haemorrhagic event. A diagnosis of stroke was made by the treating neurologist. CT or MRI was used to distinguish ischaemic from haemorrhagic strokes. All events were adjudicated by a clinical events committee that was unaware of treatment allocations.

Follow-up data after discharge were obtained during routinely scheduled outpatient visits at 3, 6, and 12 months and in telephone calls to patients at 1 month and 12 months. Standardised questions were used to assess bleeding episodes, thrombotic events, and use of medications. All thrombotic and bleeding events requiring medical attention were verified by an events committee that was unaware of the patient's study group, by use of medical records obtained from referring family doctors and hospitals.

	Double therapy (n=279)	Triple therapy (n=284)
Clinical baseline characteristics		
Mean (SD) age (years)	70·3 (7·0)	69·5 (8·0)
Sex (male/female)	214 (77%)/65 (23%)	234 (82%)/50 (18%)
Risk factors		
Mean (SD) BMI (kg/m²)	27·5 (4·3)	27·9 (4·2)
Diabetes	68 (24%)	72 (25%)
Hypertension	193 (69%)	193 (68%)
Hypercholesterolaemia	191 (68%)	205 (72%)
Current smoker	60 (22%)	42 (15%)
Family history of CAD	116 (42%)	122 (43%)
History of myocardial infarction	96 (34%)	100 (35%)
History of heart failure	71 (25%)	70 (25%)
History of stroke	49 (18%)	50 (18%)
History of PCI	86 (31%)	101 (36%)
History of CABG	56 (20%)	74 (26%)
History of gastrointestinal bleeding	14 (5%)	14 (5%)
History of renal failure	51 (18%)	48 (17%)
$CHADS_2$ score at baseline for AF patients*		
1	19 (12%)	20 (12%)
2	52 (32%)	42 (26%)
3	53 (32%)	58 (36%)
4	26 (16%)	25 (15%)
5	11 (7%)	12 (7%)
>5	2 (1%)	4 (2%)
Medication on admission		
β blocker	211 (76%)	230 (81%)
ACE inhibitor or ARB	193 (69%)	188 (66%)
Calcium-channel blocker	75 (27%)	89 (31%)
Diuretic	129 (46%)	143 (50%)
Statin	196 (70%)	226 (80%)
Digoxin	30 (11%)	38 (13%)
Nitrate	81 (29%)	93 (33%)
Aspirin	74 (27%)	118 (42%)
Clopidogrel	124 (44%)	154 (54%)
Insulin	21 (8%)	27 (10%)
Oral antidiabetic	58 (21%)	50 (18%)
Fibrate	7 (3%)	5 (2%)
PPI use	95 (34%)	110 (39%)
Omeprazole	50 (18%)	65 (23%)
Other	45 (16%)	45 (16%)

(Continues in next column)

Statistical analysis

The primary endpoint was the occurrence of any bleeding episode during 1-year follow-up. Each bleeding event was classified separately according to the TIMI criteria (minimal, minor, or major), the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria (mild, moderate, or severe), and the Bleeding Academic Research Consortium (BARC) criteria (score 1, 2, 3, 4, or 5, where 1 is minor and 5 is fatal).[22–24] We assessed a composite secondary endpoint of death, myocardial infarction, stroke, target-vessel revascularisation, and stent thrombosis (according to the Academic Research Consortium criteria),[25] and separately assessed each individual component of the primary and secondary endpoints.

The trial was powered to assess whether clopidogrel alone was better than clopidogrel and aspirin in the prevention of bleeding in patients taking oral anticoagulants and undergoing PCI. We assumed a 12% occurrence rate of any bleeding complication at 1 year in the triple-therapy group and of 5% in the double-therapy group, on the basis of data from the largest retrospective study that was available at the time this study was designed.[6] We used a two-sided χ^2 test and calculated that a minimum sample size of 248 patients in each group would be required to achieve an α level of 0·05 and statistical power of 0·80.

Primary and secondary endpoints based on time to first event were assessed by comparison of Kaplan-Meier-based cumulative incidence rates with the log-rank test. The primary analysis was assessed by intention to treat. As a measure of strength of the treatment effect, we calculated hazard ratios (HRs) and

	Double therapy (n=279)	Triple therapy (n=284)
(Continued from previous column)		
Indication for oral anticoagulation		
Atrial fibrillation/atrial flutter	164/236 (69%)	162/234 (69%)
Mechanical valve	24/236 (10%)	25/234 (11%)
Other (eg, apical aneurysm, pulmonary embolus, PAD, EF <30%)	48/236 (20%)	47/234 (20%)
Acute coronary syndrome at baseline		
Yes	69 (25%)	86 (30%)
Ejection fraction		
Mean (SD) at baseline (%)	46 (15)	47 (13)
EF <30%	40/190 (21%)	37/206 (18%)

Values are n (%) unless stated otherwise. Categories do not add up to 100% for all variables owing to missing values. BMI=body-mass index. CAD=coronary artery disease. PCI=percutaneous coronary intervention. CABG=coronary artery bypass graft. AF=atrial fibrillation. ACE-inhibitor=angiotensin-converting-enzyme inhibitor. ARB=angiotensin-II-receptor blocker. PPI=proton-pump inhibitor. PAD=peripheral artery disease. EF=ejection fraction. *n=163 in the double-therapy group and n=161 in the triple-therapy group.

Table 1: **Clinical characteristics and treatments at baseline**

95% CIs for double therapy versus triple therapy by means of Cox's proportional hazards regression analysis. When applicable, we used multivariate Cox's proportional hazard regression to correct for baseline imbalances. We assessed the robustness of the primary endpoint by subgroup analyses (age, sex, presentation of an acute coronary syndrome, indication for oral anticoagulation, and stent type), for which we computed likelihood-ratio-test p values for interaction in the Cox's proportional hazards regression analysis. We also constructed a forest plot for visual inspection. All calculations were done with R software (version 2.15). This study is registered with ClinicalTrials.gov, number NCT00769938.

	Double therapy (n=279)	Triple therapy (n=284)
Procedural characteristics		
Arterial access		
Radial	74 (27%)	71 (25%)
Femoral	204 (73%)	208 (75%)
Mean (SD) INR on day of PCI	1·86 (1·00)	1·94 (1·09)
Angiographic characteristics		
PCI vessel		
LAD	111 (40%)	118 (42%)
RCA	92 (33%)	72 (25%)
LCX	59 (21%)	76 (27%)
Venous or arterial graft	16 (6%)	16 (6%)
Number of vessels treated		
1	202 (72%)	199 (70%)
2	57 (20%)	68 (24%)
3	13 (5%)	13 (5%)
Predilatation	194 (70%)	212 (75%)
Stent type		
None	5 (2%)	4 (1%)
Bare metal	89 (32%)	86 (30%)
Drug eluting	181 (65%)	183 (64%)
Bare metal and drug eluting	3 (1%)	11 (4%)
Non-ACS patients with electively fitted bare metal stents	61 (22%)	52 (19%)
Mean (SD) diameter (mm)*	3·16 (0·55)	3·11 (0·49)
Mean (SD) total length (mm)†	23·4 (13·0)	24·0 (12·7)
Closure device		
No	70 (25%)	85 (30%)
Angioseal‡	166 (60%)	167 (59%)
Other	43 (15%)	29 (10%)
ACC lesion type		
A	44 (16%)	34 (12%)
B1	82 (29%)	92 (32%)
B2	84 (30%)	83 (30%)
C	45 (16%)	65 (23%)
Periprocedural treatment		
Continuation of OAC	128 (46%)	113 (40%)
Bolus of heparin	251 (91%)	257 (90%)
Bridging with LMWH	66 (24%)	68 (24%)
GPIIbIIIa	25 (9%)	26 (9%)
Fondaparinux	3 (1%)	2 (1%)

Data are n (%) unless stated otherwise. Categories do not add up to 100% for all variables owing to missing values. INR=international normalised ratio. PCI=percutaneous coronary intervention. LAD=left anterior descending coronary artery. RCA=right coronary artery. LCX=left circumflex coronary artery. ACS=acute coronary syndrome. ACC=American College of Cardiology. OAC=oral anticoagulation. LMWH=low-molecular-weight-heparin. GPIIbIIIa=glycoprotein-IIbIIIa-receptor blocker. *If more than one stent used, the smallest stent diameter is reported. †If more than one stent used, the stent length denotes the sum of all stent lengths. ‡St Jude Medical, St Paul, MN, USA.

Table 2: **Baseline procedural characteristics**

See Online for appendix

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for the publication.

Results

573 patients were enrolled, of whom 284 were assigned to the double-therapy group and 289 to the triple-therapy group (figure 1). Baseline and procedural characteristics were similar in the two groups (tables 1, 2). Complete follow-up was obtained for 98·3% of the patients (figure 1). The final collection of follow-up data occurred on Aug 1, 2012. The median follow-up for both groups was 365 days, and the mean follow-up was 358 (minimum 16 and maximum 365) days for the double-therapy group and 351 (2 and 365) days for the triple-therapy group. At 1 year oral anticoagulation was being used by 258 (92·5%) of 279 patients in the double-therapy group and 259 (91·2%) of 284 in the triple-therapy group. Clopidogrel was being used by 225 (80·6%) at 1 year in the double-therapy group, and in the triple-therapy group aspirin was being used by 189 (66·5%) and clopidogrel by 224 (78·9%) patients (appendix pp 1–2).

At 1-year follow-up, any bleeding had occurred in 54 (19·4%) patients in the double-therapy group and in 126 patients (44·4%) in the triple-therapy group (table 3, figure 2, appendix p 3). In the double-therapy group, six (2·2%) patients had had multiple bleeding events, compared with 34 (12·0%) in the triple-therapy (table 4). At 1 year, at least one blood transfusion had been required in 11 (3·9%) patients who received double therapy, compared with 27 (9·5%) of those who received triple therapy (odds ratio from Kaplan-Meier curve 0·39, 95% CI 0·17–0·84, p=0·011; table 3). For the individual bleeding classifications, significant differences in favour of the double-therapy group were seen for TIMI minor, TIMI minimal, GUSTO moderate, GUSTO mild, and BARC 3, 2, and 1. Combined TIMI major and minor, combined GUSTO severe and moderate, and combined BARC 3 and 2 bleeding episodes all showed results in favour of double therapy (table 3). For TIMI major, GUSTO severe, and BARC 3a and 3b bleeding, double therapy seemed to be associated with

fewer episodes, but the differences between groups were not significant (table 3). The numbers of intracranial bleeds were the same in the two treatment groups, but at other sites, numbers were lower in the double therapy group (table 4, appendix p 4). Lower rates of any bleeding were seen in the double-therapy group in all subgroups (age, sex, presentation of an acute coronary syndrome, indication for oral anticoagulation, and stent type; appendix p 5).

The combined secondary endpoint of death, myocardial infarction, stroke, target-vessel revascularisation, and stent thrombosis was reported in 31 (11·1%) patients in the double-therapy group and in 50 (17·6%) in the triple-therapy group (table 5, figure 3). After correction for imbalance in baseline characteristics, the HR remained similar (0·56, 95% CI 0·35–0·91). Seven (2·5%) in the double-therapy group and 18 (6·3%) in the triple-therapy group had died from any cause at 1 year (table 5, appendix p 6). The rates for the other individual components of the secondary endpoint did not differ significantly between the two treatment groups (table 5, appendix p 6).

	Double therapy (n-279)	Triple therapy (n=284)	Hazard ratio (95% CI)	p value
Any bleeding event	54 (19·4%)	126 (44·4%)	0·36 (0·26–0·50)	<0·0001
TIMI bleeding				
Major	9 (3·2%)	16 (5·6%)	0·56 (0·25–1·27)	0·159
Major and minor	39 (14·0%)	89 (31·3%)	0·40 (0·27–0·58)	<0·0001
GUSTO bleeding				
Severe	4 (1·4)	10 (3·5%)	0·40 (0·12–1·27)	0·119
Severe and moderate	15 (5·4%)	35 (12·3%)	0·42 (0·23–0·76)	0·003
BARC bleeding				
3	18 (6·5%)	36 (12·7%)	0·49 (0·28–0·86)	0·011
3c	3 (1·1%)	3 (1·1%)	1·00 (0·20–4·90)	0·996
3b	6 (2·2%)	14 (5·0%)	0·43 (0·17–1·10)	0·074
3a	9 (3·2%)	19 (6·7%)	0·47 (0·21–1·00)	0·054·
2	23 (8·2%)	59 (20·8%)	0·36 (0·23–0·59)	<0·0001
2+3	40 (14·3%)	90 (31·7%)	0·40 (0·28–0·58)	<0·0001
1	18 (6·5%)	45 (15·8%)	0·38 (0·22–0·66)	0·0004
Any blood transfusion	11 (3·9%)	27 (9·5%)	0·39* (0·17–0·84)	0·011

Percentages are calculated from the Kaplan-Meier curve. TIMI= Thrombolysis in Myocardial Infarction criteria. GUSTO=Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria. BARC=Bleeding Academic Research Consortium criteria. *Odds ratio.

Table 3: **Results for the primary endpoint at 1 year**

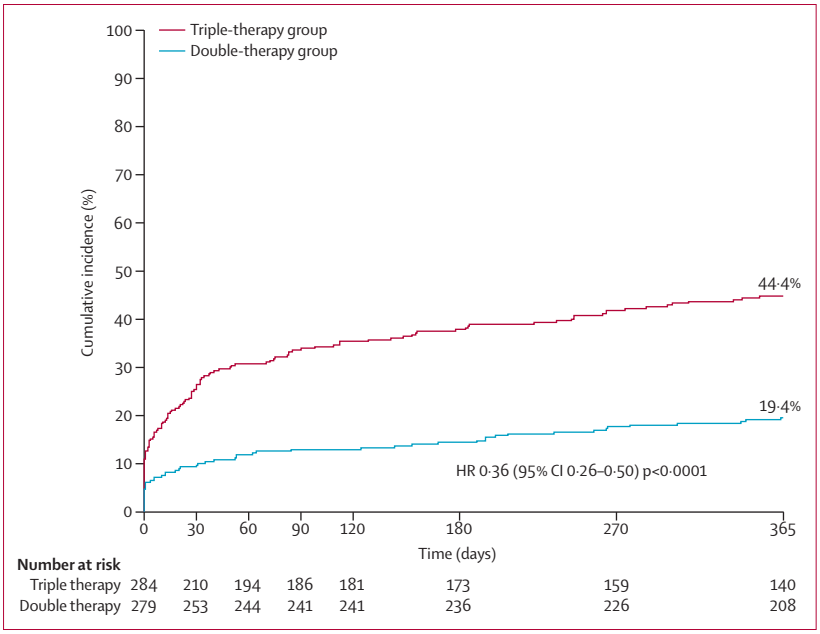

Figure 2: **Incidence of the primary endpoint (any bleeding)**
HR=hazard ratio.

Discussion

The WOEST trial clearly shows that clopidogrel alone administered to patients taking oral anticoagulants who require PCI is associated with a significantly lower rate of bleeding complications at 1 year than is use of clopidogrel plus aspirin.

As anticipated, the frequency of gastrointestinal bleeding episodes was substantially lower in the double-therapy than in the triple-therapy group, which is probably related to the local erosive effect of aspirin. When assessed by the BARC criteria, the incidence of serious (BARC 3) bleeding episodes was significantly higher in the triple-therapy group than in the double-therapy group. The number of TIMI major bleeding episodes was also higher in the triple-therapy group than in the double-therapy group, but the overall difference in TIMI bleeding events was largely driven by minimal and minor events. Nevertheless, when we assessed differences between TIMI minor and major and GUSTO moderate and severe bleeding epsodes, the rates were significantly higher for both combined endpoints in the triple-therapy group. This finding indicates that even without the least serious bleeding classifications (TIMI minimal and GUSTO mild), there is still a significant difference in favour of double therapy. Finally, despite rates of TIMI major bleeding not differing significantly between treatment groups, the number needed to harm was 40 (data not shown), which we believe is clinically relevant if all aspects of the effects of double therapy on bleeding risk are taken into account. Therefore, we view the reduction in bleeding complications in the WOEST trial as being clinically meaningful.

The role of non-major bleeding should not be underestimated. Discontinuation of antiplatelet therapy in affected patients can lead to subsequent thrombotic complications, such as stent thrombosis.[3,8,26–28] Gastrointestinal bleeding episodes that require urgent gastroscopy and blood transfusion but lead to decreases in haemoglobin concentrations of up to 30 g/L might be classified as TIMI minor. Blood transfusions have been associated with increased risk of death in previous

	Double therapy (n=279)	Triple therapy (n=284)
Total number of bleeding events		
≥1	54 (19·4%)	126 (44·4%)
2	3 (1·1%)	30 (10·6%)
≥3	3 (1·1%)	4 (1·4%)
Location of worst bleeding event		
Intracranial	3 (1·1%)	3 (1·1%)
Access site	16 (5·7%)	20 (7·0%)
Gastrointestinal	8 (2·9%)	25 (8·8%)
Skin haematoma requiring medical attention	7 (2·5%)	30 (10·6%)
Nose	10 (3·6%)	21 (7·4%)
Retroperitoneal	1 (0·3%)	3 (1·1%)
Urogenital	3 (1·1%)	8 (2·8%)
Percardial	0	2 (0·7%)
Eye	1 (0·4%)	3 (1·1%)
Respiratory tract	2 (0·7%)	3 (1·1%)
Muscle	1 (0·4%)	0
Mouth	0	3 (1·1%)
Bleeding after surgery at any location	1 (0·4%)	2 (0·7%)
ICD/pacemaker pocket	1 (0·4%)	3 (1·1%)

ICD=implantable cardioverter defibrillator.

Table 4: **Location of worst bleeding per patient**

	Double therapy (n=297)	Triple therapy (n=284)	Hazard ratio (95% CI)	p value
Combined secondary endpoint	31 (11·1%)	50 (17·6%)	0·60 (0·38–0·94)	0·025
Death				
All-cause	7 (2·5%)	18 (6·3%)	0·39 (0·16–0·93)	0·027
Cardiac	3 (1·1%)	7 (2·5%)	0·43 (0·11–1·66)	0·207
Non-cardiac	4 (1·4%)	11 (3·9%)	0·36 (0·11–1·13)	0·069
Myocardial infarction				
Any	9 (3·2%)	13 (4·6%)	0·69 (0·29–1·60)	0·382
STEMI	1 (0·4%)	3 (1·1%)	0·34 (0·04–3·25)	0·325
Non-STEMI	8 (2·9%)	10 (3·5%)	0·79 (0·31–2·01)	0·625
Target-vessel revascularisation				
PCI or CABG	20 (7·2%)	19 (6·7%)	1·05 (0·56–1·97)	0·876
PCI	17 (6·1%)	16 (5·6%)	1·06 (0·54–2·10)	0·869
CABG	3 (1·1%)	3 (1·1%)	1·00 (0·20–4·90)	0·998
Stroke				
Any	3 (1·1%)	8 (2·8%)	0·37 (0·10–1·40)	0·128
Ischaemic	2 (0·7%)	8 (2·8%)	0·25 (0·05–1·17)	0·056
Haemorrhagic	1 (0·4%)	0	NA	0·321
Disabling	2 (0·7%)	2 (0·7%)	0·99 (0·14–6·99)	0·988
Non-disabling	1 (0·4%)	7 (2·5%)	0·14 (0·02–1·16)	0·034
Stent thrombosis				
Any	4 (1·4%)	9 (3·2%)	0·44 (0·14–1·44)	0·165
Definite	1 (0·4%)	3 (1·1%)	0·33 (0·03–3·22)	0·319
Probable	0	2 (0·7%)	NA	0·161
Possible	3 (1·1%)	4 (1·4%)	0·75 (0·17–3·30)	0·708

Percentages are calculated from the Kaplan-Meier curve. STEMI=ST-elevation myocardial infarction. PCI=percutaneous coronary intervention. CABG=coronary artery bypass graft. NA=not applicable.

Table 5: **Secondary and safety endpoints at 1 year**

studies,[8] and in this study a significantly lower rate of transfusions were required in the double-therapy group than in the triple-therapy group.

The bleeding rate in the WOEST trial could be viewed as very high. For instance, the bleeding rate in the largest Danish registry of more than 70 000 patients with atrial fibrillation who were discharged with oral anticoagulants for stroke prevention was notably lower: the bleeding rates at 1 year were 13·9% and 15·7%, respectively,[4] in the double-therapy and triple-therapy groups, compared with 19·4% and 44·4% in this study. This difference might have occurred because we collected data on all rather than only major bleeding events, and because our study was specifically designed to assess bleeding episodes as an endpoint. Another reason for higher bleeding rates in our study could have been the long duration of clopidogrel therapy because of the high rate of drug-eluting-stent placement (appendix p 7). Although the use of bare-metal stents was recommended, the severity of coronary artery disease (eg, long lesions and multivessel disease) in this study population probably led to a high use of drug-eluting stents.[29]

Bleeding episodes might have been prevented with increased use of proton-pump inhibitors and radial access for PCI. The goal of our study, however, was to include a population that reflected the usual clinical situation to generate meaningful answers for cardiologists. Therefore, the use of proton-pump inhibitors were recommended but not mandatory. Today, in this type of patient, radial access is the preferred strategy in Europe and the USA. Proton-pump inhibitors are also recommended for use in these patients (panel).[3,30]

This study was designed before the HAS-BLED score[3] and the CHA_2DS_2 VASC$_2$ score[30] were established and, therefore, they were not used to estimate bleeding risk and make decisions about the use of oral anticoagulants.

A noteworthy outcome is that most bleeding episodes occurred within 180 days of PCI, whereas most deaths occurred after 180 days. In patients prone to bleeding, episodes frequently occur shortly after starting a new treatment, which could be the reason for most events occurring within 180 days in this study. Similar timeframes have been reported in other studies of antiplatelet therapy.[31,32] The number of deaths, however, was small and, therefore, we were unable to assess whether there was a link between the timings of the bleeding episodes and the deaths.

Another important finding in the WOEST trial is that the rates of thrombotic and thromboembolic events did not differ between patients who did and did not receive aspirin. We hypothesised that inhibition of thrombin (a strong platelet activator) with oral anticoagulants and inhibition of P2RY12 with clopidogrel would lessen the importance of cyclo-oxygenase-1 (PTGS1) inhibition for protection against thrombotic and thromboembolic events. This hypothesis was based on the results of two

large randomised trials done in patients who survived after myocardial infarction to compare oral anticoagulation with aspirin in the prevention of reinfarction and stroke. Lower recurrence rates but higher risks of bleeding were associated with oral anticoagulation.[16,17] Thus, oral anticoagulation was at least as good as aspirin in protecting patients from thrombotic events. The results of the WOEST trial support the hypothesis that aspirin is not needed in patients who receive stents. Nevertheless, this study was not powered to detect differences in the occurrence of thrombotic events, such as stent thrombosis, when aspirin was omitted, and this feature would need to be studied in a larger trial. A very large trial, however, is unlikely to be done because of lack of interest to sponsors. Therefore, on the basis of our findings, we think that aspirin does not need to be used in patients receiving oral anticoagulants and undergoing PCI.

We did not test oral anticoagulants plus aspirin without clopidogrel or aspirin plus clopidogrel without oral anticoagulants. In patients with atrial fibrillation assessed in the ACTIVE-W study,[10] however, full-intensity oral anticoagulation protected better against ischaemic complications than did double antiplatelet therapy with aspirin and clopidogrel. The withholding of oral anticoagulation in patients with atrial fibrillation undergoing coronary-artery stenting is associated with increased major cardiovascular events and mortality, and does not seem to reduce bleeding,[12] and the omission of clopidogrel in patients receiving coronary stents has been associated with an increased risk of thrombotic events, such as myocardial infarction and stent thrombosis.[6] Therefore, only the option of combining oral anticoagulants with clopidogrel was feasible. Improvements in stent designs have led to shortened durations of clopidogrel therapy[33–35] and, therefore, improved treatment safety. Furthermore, new oral anticoagulants have been developed for stroke prevention in atrial fibrillation.[36] Whether the routine use of these agents will improve the safety of PCI in patients with atrial fibrillation patients should be tested. The new strong antiplatelet agents, such as prasugrel[31] and ticagrelor,[37] however, might increase the risk of major bleeding, and their effect on coronary intervention patients with atrial fibrillation who are taking oral anticoagulants is unknown.

This study has several limitations. First, it was an open-label study, which has inherent bias. Nevertheless, all events for which medical attention was sought were adjudicated by a bleeding events committee that was unaware of treatment allocation. Classification of self-reported bleeding episodes for which patients did not consult a health-care professional, however, was subjective. That the rate of all bleeding events was lower in the double-therapy group than in the triple-therapy group is reassuring. The study was powered to assess superiority of double therapy on the primary bleeding endpoint, but not non-inferiority on the secondary endpoints. Third, because of limited resources of the study, a placebo was not used instead of aspirin in the double-therapy group. Although the open nature of the study might have led to reporting bias, we do not think this feature plays an important part in a comparison of two versus three drugs. Major bleeding episodes are likely to come to the attention of investigators and, therefore, discontinuation of treatment was more likely to be based on bleeding than on other factors. Aspirin seems to have been stopped after bleeding events

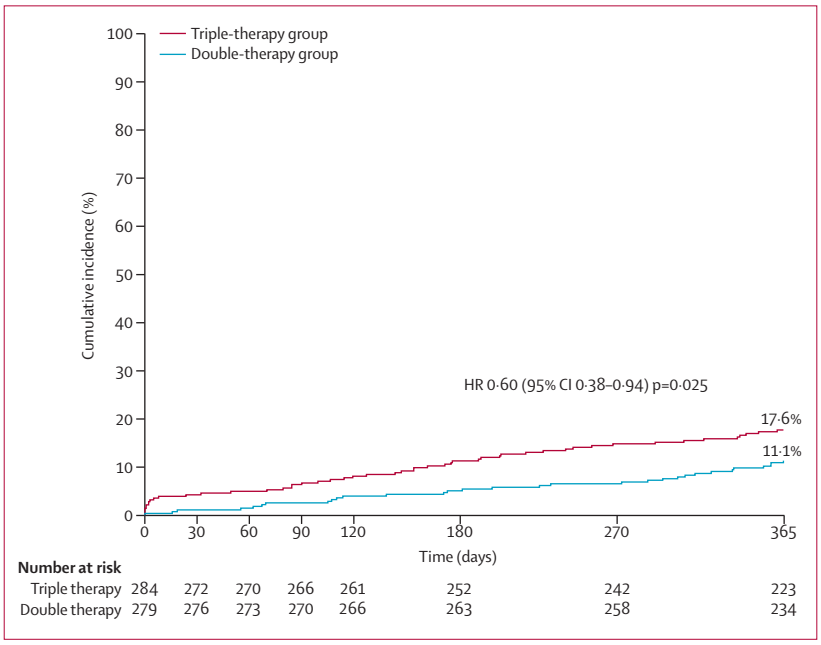

Figure 3: **Cumulative incidence of the secondary endpoint (death, myocardial infarction, stroke, target-vessel revascularisation, and stent thrombosis)**
HR=hazard ratio.

Panel: **Research in context**

Systematic review

If percutaneous coronary intervention is required in patients taking long-term anticoagulation (because of a mechanical valve or atrial fibrillation), European and US experts recommend the use of triple therapy with aspirin, clopidogrel, and oral anticoagulation. These recommendations are based on expert opinions.[3,30] So far, no randomised trials have been done to assess the optimum treatment in these patients.

Interpretation

In this randomised trial of patients taking oral anticoagulants and undergoing percutaneous coronary intervention, treatment with clopidogrel and oral anticoagulants was associated with a significantly lower risk of bleeding complications than tripe therapy that included aspririn. We also found no evidence of increased thrombotic risk without the use of aspirin.

(appendix p 7). Finally, we do not have information on how much anticoagulation in the therapeutic range was achieved, because control of the international normalised ratio was left to the specialised thrombosis service, which operates independently from hospitals in the Netherlands. We do know from the RELY trial,[38] however, that the quality of oral anticoagulation control by this service is good, with a mean of 70% of patients being in the therapeutic range at any given time.

In this randomised trial of patients taking oral anticoagulants and undergoing PCI, treatment with clopidogrel and oral anticoagulants was associated with a significantly lower risk of bleeding complications than was aspirin, clopidogrel, and oral anticoagulation. Although the trial was small, we saw no evidence of an increased risk of thrombotic events by the withholding of aspirin (panel).

Contributors

WJMD and JMtB designed the study. WJMD did the literature search. WJMD, TO, BJGLDS, J-PH, TA, AACMH, MMV, AWv'tH, and JMtB did the data collection, analysis, and interpretation. JCK and JGPT did the statistical analysis and interpretation of statistical data. WJMD, FWAV, JGPT, and JMtB wrote the paper. WJMD created the figures. TO, BJGLDS, J-PH, TA, MV, AACMH, MMV, JGPT, and AWv'tH reviewed the drafts of the paper.

WOEST study groups

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Conflicts of interest

We declare that we have no conflicts of interest.

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