Oral Anticoagulant and Antiplatelet Therapy and Peripheral Arterial Disease

The Warfarin Antiplatelet Vascular Evaluation Trial Investigators*

ABSTRACT

BACKGROUND

Atherosclerotic peripheral arterial disease is associated with an increased risk of myocardial infarction, stroke, and death from cardiovascular causes. Antiplatelet drugs reduce this risk, but the role of oral anticoagulant agents in the prevention of cardiovascular complications in patients with peripheral arterial disease is unclear.

METHODS

We assigned patients with peripheral arterial disease to combination therapy with an antiplatelet agent and an oral anticoagulant agent (target international normalized ratio [INR], 2.0 to 3.0) or to antiplatelet therapy alone. The first coprimary outcome was myocardial infarction, stroke, or death from cardiovascular causes; the second coprimary outcome was myocardial infarction, stroke, severe ischemia of the peripheral or coronary arteries leading to urgent intervention, or death from cardiovascular causes.

RESULTS

A total of 2161 patients were randomly assigned to therapy. The mean follow-up time was 35 months. Myocardial infarction, stroke, or death from cardiovascular causes occurred in 132 of 1080 patients receiving combination therapy (12.2%) and in 144 of 1081 patients receiving antiplatelet therapy alone (13.3%) (relative risk, 0.92; 95% confidence interval [CI], 0.73 to 1.16; $P=0.48$). Myocardial infarction, stroke, severe ischemia, or death from cardiovascular causes occurred in 172 patients receiving combination therapy (15.9%) as compared with 188 patients receiving antiplatelet therapy alone (17.4%) (relative risk, 0.91; 95% CI, 0.74 to 1.12; $P=0.37$). Life-threatening bleeding occurred in 43 patients receiving combination therapy (4.0%) as compared with 13 patients receiving antiplatelet therapy alone (1.2%) (relative risk, 3.41; 95% CI, 1.84 to 6.35; $P<0.001$).

CONCLUSIONS

In patients with peripheral arterial disease, the combination of an oral anticoagulant and antiplatelet therapy was not more effective than antiplatelet therapy alone in preventing major cardiovascular complications and was associated with an increase in life-threatening bleeding. (ClinicalTrials.gov number, NCT00125671.)

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PERIPHERAL ARTERIAL DISEASE IS MOST commonly caused by atherosclerosis and is a sign that widespread atherosclerotic vascular disease is present. Patients with peripheral arterial disease have a risk of myocardial infarction, stroke, or death from cardiovascular causes that is three times as high as persons without peripheral arterial disease.[1,2] Antiplatelet therapy reduces the incidence of major cardiovascular events in patients with peripheral arterial disease.[3]

Oral anticoagulant agents, with or without antiplatelet therapy, reduce the rate of major cardiovascular events in patients with coronary artery disease. The American College of Cardiology and the American Heart Association consider oral anticoagulation in combination with aspirin to be an appropriate alternative to aspirin alone in patients who have had a myocardial infarction with ST elevation.[4-7] Information regarding the efficacy and safety of oral anticoagulation, with or without antiplatelet therapy, in patients with peripheral arterial disease is limited.[8] We therefore conducted a randomized trial to determine whether oral anticoagulation (target international normalized ratio [INR], 2.0 to 3.0) in combination with antiplatelet therapy is superior to antiplatelet therapy alone in patients with peripheral arterial disease.

METHODS

STUDY DESIGN

We conducted this randomized, open-label, clinical trial at 80 centers in Canada, Poland, Hungary, Ukraine, China, the Netherlands, and Australia. Details of the study design have been published previously.[8] The study was coordinated by the Population Health Research Institute at McMaster University in Hamilton, Ontario, Canada. The protocol was approved by the ethics review boards of all participating institutions, and all patients provided written informed consent.

The Warfarin Antiplatelet Vascular Evaluation (WAVE) trial was sponsored by the Canadian Institutes of Health Research, the Heart and Stroke Foundation of Ontario, and the Population Health Research Institute. Donations were also provided by Roche Diagnostics (in kind) and DuPont Pharma. In Hungary, acenocoumarol was provided by ICN Pharma. None of the corporate sponsors had any role in the design or conduct of the trial, analysis of the data, or preparation of the manuscript.

PATIENT ELIGIBILITY

Men and women who were 35 to 85 years of age and had peripheral arterial disease were eligible for enrollment in the trial. Peripheral arterial disease was defined as atherosclerosis of the arteries of the lower extremities, the carotid arteries, or the subclavian arteries. Atherosclerosis of the lower extremities was defined as intermittent claudication with objective evidence of peripheral arterial disease, ischemic pain at rest, nonhealing ulcers or focal gangrene, previous amputation, arterial revascularization, or the blue toe syndrome. Carotid artery disease was defined as a transient ischemic attack or stroke more than 6 months before enrollment, carotid endarterectomy, or asymptomatic carotid stenosis of more than 50%. Patients were excluded from the study if they had an indication for oral anticoagulant treatment, were actively bleeding or were at high risk for bleeding, had had a stroke within 6 months before enrollment, or required dialysis.

RANDOMIZATION AND STUDY MEDICATIONS

Patients who provided written informed consent entered an active run-in phase for 2 to 4 weeks, during which they received both oral anticoagulant therapy and antiplatelet therapy. Acceptable antiplatelet agents included aspirin (recommended dose, 81 to 325 mg per day), ticlopidine, and clopidogrel. Warfarin was used for oral anticoagulation in five countries, and acenocoumarol was used in Poland and Hungary.

If a stable INR between 2.0 and 3.0 was achieved during the run-in phase, the patient agreed to continue and adhered to therapy, and no side effects had occurred, a central 24-hour computerized randomization service was used to assign the patient to either the combination of oral anticoagulation and antiplatelet therapy (1080 patients) or antiplatelet therapy alone (1081 patients). A permuted-block randomization stratified according to clinical center was used. All study participants continued taking the antiplatelet agent they were receiving at the time of the active run-in. Dual antiplatelet therapy was not permitted unless the patient had an acute coronary syndrome or placement of a coronary stent during follow-up.

FOLLOW-UP AND ASSESSMENT OF END POINTS

After randomization, INR values were measured every month or more frequently, at the discretion of the local physician. Patients were followed for

a minimum of 2.5 years or a maximum of 3.5 years. Follow-up assessments occurred every 3 months, when information on events, other hospitalizations, and adherence to the assigned treatment regimen was obtained.

STUDY OUTCOMES

Two coprimary composite outcomes were defined. Coprimary outcome 1 was myocardial infarction, stroke, or death from cardiovascular causes; coprimary outcome 2 was myocardial infarction, stroke, severe ischemia of the peripheral or coronary arteries leading to urgent intervention, or death from cardiovascular causes. The safety outcomes were life-threatening, moderate, or minor bleeding episodes. All outcomes were determined by the members of a central adjudication committee who used standard definitions and were unaware of treatment allocation. An independent data and safety monitoring board monitored the study regularly; safety data were assessed every 6 months or more frequently, as requested by the data and safety monitoring board.

Death from cardiovascular causes was defined as any death for which there was no clearly documented noncardiovascular cause. Myocardial infarction was defined as the presence of at least two of the following three findings: typical ischemic chest pain; elevation of the level of serum creatine kinase, serum creatine kinase MB fraction, or serum troponin; and diagnostic electrocardiographic changes. Stroke was defined as a new focal neurologic deficit lasting more than 24 hours. Strokes were classified as ischemic or hemorrhagic (including subarachnoid hemorrhage) if a computed tomographic or magnetic resonance imaging scan or an autopsy report was available. All other strokes were classified as of uncertain cause. Severe coronary ischemia was defined as unstable angina with electrocardiographic changes requiring hospitalization and leading to coronary revascularization. Severe peripheral ischemia was defined as ischemia threatening the viability of the limb and leading to thrombolytic therapy, angioplasty, bypass surgery, or amputation.

Bleeding was categorized as life-threatening, moderate, or minor. Life-threatening bleeding was defined as fatal or intracranial bleeding or bleeding requiring surgical intervention or transfusion of a total of at least 4 units of blood or blood products, including fresh-frozen plasma. Moderate bleeding was defined as intraocular hemorrhage or as bleeding that the treating physician determined required transfusion of 1 to 3 units of blood or blood products. All other bleeding was classified as minor.

STATISTICAL ANALYSIS

The original trial protocol (see the Supplementary Appendix, available with the full text of this article at www.nejm.org) estimated that random assignment of 2400 patients equally to the two treatment groups with a follow-up of 2.5 years would provide more than 80% power to detect an observed risk reduction of 25% in coprimary outcome 1 (estimated event rate in the control group, 13.8%) and more than 90% power to detect risk reduction of 25% in coprimary outcome 2 (estimated event rate in the control group, 24.1%). Both calculations assumed a 15% rate of nonadherence to oral anticoagulation and a 5% rate of use of oral anticoagulation in the control group.

The original power calculation estimated that 2400 patients would be required, but recruitment of patients was slower than expected. Therefore, on September 27, 2002, in order to maintain study power, the steering committee stopped recruitment at 2161 patients and recommended extending the follow-up period from 2.5 years to 3.5 years for the 1396 patients already enrolled in the study.

The primary analysis compared treatment groups with respect to the first occurrence of an event in each of the two coprimary outcomes using a log-rank statistic based on an intention-to-treat analysis. Assessment of the treatment effect of adherence to oral anticoagulation was performed by comparing results from centers with good adherence (at least 70% of patients using oral anticoagulation over the course of follow-up) to results from centers with poor adherence (less than 70% of patients using oral anticoagulation over the course of follow-up).[9] Among patients receiving oral anticoagulation, the time in the therapeutic range was calculated by the linear-interpolation method described by Rosendaal et al.[10] All reported P values are two-sided and are not adjusted for multiple testing.

RESULTS

BASELINE CHARACTERISTICS

Between April 2000 and September 2003, a total of 2417 eligible, consenting patients were entered into the run-in phase of the trial (see the Supple-

mentary Appendix). Of these, 2161 entered the randomized phase. The most common reasons for not continuing into the randomized phase were patient refusal (115 patients), poor adherence to oral anticoagulant therapy (50 patients), inability to maintain a stable INR (43 patients), and bleeding (23 patients).

The baseline characteristics of the patients participating in the randomized phase of the trial are shown in Table 1. The mean age was 64 years, and 73.6% were men. Most of the patients (81.8%) had peripheral arterial disease of the lower extremities. At baseline, 98.4% of the patients were receiving some form of antiplatelet therapy.

FOLLOW-UP AND ADHERENCE TO TREATMENT

The mean duration of follow-up was 35 months (1043 days). A total of 1073 patients (49.7%) were followed for 2.5 years, and 1088 patients (50.3%) were followed for 3.5 years. Two patients (both in the combination-therapy group) withdrew consent and could not be contacted. Therefore, complete data at the end of the study were available for 2159 of the patients randomly assigned to treatment (99.9%); data on the 2 who withdrew that were obtained up to the time of last contact were also included. In the combination-therapy group, oral anticoagulation was permanently discontinued in 319 patients (29.5%) and antiplatelet therapy was permanently discontinued in 53 (4.9%); in the group receiving only antiplatelet therapy, antiplatelet agents were permanently discontinued in 21 patients (1.9%) and 45 patients (4.2%) began using nonstudy oral anticoagulants (see the Supplementary Appendix). Among patients receiving oral anticoagulation, the mean INR was 2.2; 62.0% of the time, INR values were in the therapeutic range (2.0 to 3.0); 30.8% of the time, they were below 2.0; and 7.2% of the time, they were above 3.0.[10]

During follow-up, the use of statins, angiotensin-converting–enzyme inhibitors, and beta-blockers increased moderately while the use of pentoxifylline decreased. Peripheral revascularization was performed in 76 patients (3.5%), limb amputation in 20 (0.9%), and coronary-artery bypass grafting in 25 (1.2%). There were no significant differences in the use of these medications or procedures between the two study groups (see the Supplementary Appendix).

OUTCOMES

The first coprimary composite end point (myocardial infarction, stroke, or death from cardiovascular causes) occurred in 132 of the 1080 patients in the combination-therapy group (12.2%), as compared with 144 of the 1081 patients in the antiplatelet-therapy group (13.3%) (relative risk, 0.92; 95% confidence interval [CI], 0.73 to 1.16; P=0.48). The second coprimary composite end point (myocardial infarction, stroke, severe ischemia of the coronary or peripheral arteries, or death from cardiovascular causes) occurred in 172 patients in the combination-therapy group (15.9%) and 188 patients in the antiplatelet-therapy group (17.4%) (relative risk, 0.91; 95% CI, 0.74 to 1.12; P=0.37). Figure 1 shows the cumulative risks of the two coprimary outcomes for each treatment group. As shown in Table 2, no significant differences were observed between treatment groups with respect to the primary outcome components of death from cardiovascular causes (6.1% vs. 6.0%; relative risk, 1.04), myocardial infarction (5.0% vs. 6.1%; relative risk, 0.82), stroke (3.5% vs. 3.5%; relative risk, 1.01), and severe ischemia (5.7% vs. 5.5%; relative risk, 1.06).

ADVERSE EVENTS

Both life-threatening bleeding (4.0% vs. 1.2%; relative risk, 3.41; 95% CI, 1.84 to 6.35; P<0.001) and moderate bleeding (2.9% vs. 1.0%; relative risk, 2.82; 95% CI, 1.43 to 5.58; P=0.002) were increased in the combination-therapy group as compared with the antiplatelet-therapy group (Table 2). Figure 2 shows the cumulative risk of life-threatening bleeding in the two groups. There were 14 hemorrhagic strokes (1.3%) in the combination-therapy group and none in the antiplatelet-therapy group (relative risk, 15.2; 95% CI, 2.0 to 115.6; P=0.001). Minor bleeding was also significantly increased (38.6% vs. 10.6%; relative risk, 3.63; 95% CI, 3.01 to 4.38; P<0.001) After removal of fatal bleeding and hemorrhagic stroke from coprimary outcome 1, the risk of coprimary outcome 1 was 10.8% in the combination-therapy group as compared with 13.2% in the antiplatelet-therapy group (relative risk, 0.82; 95% CI, 0.64 to 1.05). The relative risk of coprimary outcome 2 after removal of fatal bleeding and hemorrhagic stroke from the outcome was similar (relative risk, 0.83; 95% CI, 0.67 to 1.03) (Table 2).

Characteristic	Oral Anticoagulant plus Antiplatelet Therapy (N = 1080)	Antiplatelet Therapy Alone (N = 1081)	P Value
Age — yr	63.9±9.4	63.8±9.5	0.88
Male sex — no. (%)	796 (73.7)	795 (73.5)	0.93
Hypertension — no. (%)	630 (58.3)	628 (58.1)	0.84
Diabetes — no. (%)	290 (26.9)	298 (27.6)	0.71
Smoking history — no. (%)			
Current smoker	318 (29.4)	315 (29.1)	0.88
Former smoker	518 (48.0)	533 (49.3)	0.53
Coronary artery disease — no. (%)†	483 (44.7)	539 (49.9)	0.02
Stroke — no. (%)	166 (15.4)	177 (16.4)	0.52
Qualifying condition — no. (%)			
Peripheral arterial disease of the lower extremities	880 (81.5)	887 (82.1)	0.73
Other peripheral arterial disease‡	200 (18.5)	194 (17.9)	0.73
Blood pressure — mm Hg			
Systolic	137.0±18.7	137.0±18.6	0.92
Diastolic	78.1±10.5	78.0±10.6	0.89
Ankle–brachial index§			0.82
Median	0.83	0.84	
Interquartile range	0.7–1.0	0.7–1.0	
Medications — no. (%)			
Antiplatelet agents	1062 (98.3)	1065 (98.5)	0.73
Aspirin	999 (92.5)	986 (91.2)	0.27
Ticlopidine	30 (2.8)	44 (4.1)	0.09
Clopidogrel	35 (3.2)	40 (3.7)	0.56
Hydroxymethylglutaryl–coenzyme A reductase inhibitors (statins)	462 (42.8)	489 (45.2)	0.25
Any lipid-lowering medication	588 (54.4)	603 (55.8)	0.53
Angiotensin-converting–enzyme inhibitors	545 (50.5)	544 (50.3)	0.95
Beta-blockers	343 (31.8)	347 (32.1)	0.86

Table 1. Baseline Characteristics of the Patients.*

* Plus–minus values are means ±SD.
† Coronary artery disease is defined as a history of myocardial infarction, angina, percutaneous coronary intervention, or coronary-artery bypass surgery.
‡ Other peripheral arterial disease is defined as subclavian arterial stenosis, prior carotid endarterectomy, transient ischemic attack or stroke more than 6 months before enrollment, or asymptomatic carotid stenosis of more than 50%.
§ Measurements of the ankle–brachial index were available for 771 patients receiving combination therapy and 759 patients receiving antiplatelet therapy alone.

PRESPECIFIED AND EXPLORATORY SUBGROUP ANALYSES

The treatment effect on both efficacy outcomes, as well as on the incidence of bleeding, was statistically consistent in all subgroup analyses (Fig. 3). No differential effect on the first coprimary out-come was detected when centers were categorized according to their level of adherence. The relative risk of death from cardiovascular causes, myocardial infarction, or stroke was 0.98 (95% CI, 0.49 to 1.97) for centers with adherence of 70% or greater and 0.91 (95% CI, 0.71 to 1.17) for centers with

A

B

Figure 1. Cumulative Incidence of the Coprimary End Points in the Two Treatment Groups.

Panel A shows the cumulative incidence of the first coprimary end point (myocardial infarction, stroke, or death from cardiovascular causes). There was no significant difference in outcome between the group receiving combination therapy with an oral anticoagulant and an antiplatelet agent and the group receiving an antiplatelet agent alone (relative risk, 0.92; 95% CI, 0.73 to 1.16; P=0.48). Panel B shows the cumulative incidence of the second coprimary end point (myocardial infarction, stroke, severe ischemia of the peripheral or coronary arteries leading to urgent intervention, or death from cardiovascular causes). There was no significant difference in outcome between the two groups (relative risk, 0.91; 95% CI, 0.74 to 1.12; P=0.37).

adherence of less than 70%.[9] In an exploratory subgroup analysis, the treatment effect among all participating countries was compared, and heterogeneity of borderline statistical significance was observed (chi-square=12.20, P=0.06). The relative risk of the first coprimary outcome appeared to be increased among patients in China (relative risk, 2.62; 95% CI, 1.25 to 5.47), whereas it was lower in other countries (see the Supplementary Appendix).

DISCUSSION

In the WAVE trial, we compared the efficacy and safety of combination antithrombotic therapy with an antiplatelet agent and an oral anticoagulant (tar-

get INR, 2.0 to 3.0) with the efficacy and safety of antiplatelet therapy alone in patients with peripheral arterial disease. We found that combination therapy was not more effective than antiplatelet therapy alone in preventing major cardiovascular complications. Instead, combination therapy was associated with a substantial excess of life-threatening bleeding as well as other bleeding.

Antiplatelet agents reduce the incidence of major cardiovascular events in patients with peripheral arterial disease,[3,11] and therefore it was reasonable to consider the possibility that the addition of an anticoagulant (such as warfarin) to an antiplatelet agent would increase this benefit. This hypothesis was further supported by the favorable

Table 2. Primary and Secondary Outcomes.*

Outcome	Oral Anticoagulant plus Antiplatelet Therapy (N=1080)	Antiplatelet Therapy Alone (N=1081)	Combination Therapy vs. Antiplatelet Therapy Alone	
			Relative Risk (95% CI)	P Value
	no. (%)			
Coprimary outcome 1†	132 (12.2)	144 (13.3)	0.92 (0.73–1.16)	0.48
Coprimary outcome 2‡	172 (15.9)	188 (17.4)	0.91 (0.74–1.12)	0.37
Death from any cause	99 (9.2)	96 (8.9)	1.04 (0.79–1.38)	0.76
Death from cardiovascular causes	66 (6.1)	65 (6.0)	1.04 (0.74–1.46)	0.84
Myocardial infarction	54 (5.0)	66 (6.1)	0.82 (0.57–1.18)	0.28
Stroke	38 (3.5)	38 (3.5)	1.01 (0.65–1.59)	0.96
Ischemic or of uncertain cause	24 (2.2)	38 (3.5)	0.64 (0.38–1.06)	0.09
Hemorrhagic	14 (1.3)	0	15.2 (2.0–115.6)	0.001
Severe ischemia	62 (5.7)	59 (5.5)	1.06 (0.74–1.51)	0.76
Coronary	20 (1.9)	15 (1.4)	1.35 (0.69–2.64)	0.38
Lower extremities	42 (3.9)	44 (4.1)	0.96 (0.63–1.47)	0.86
Fatal bleeding	10 (0.9)	3 (0.3)	3.34 (0.92–12.1)	0.05
Life-threatening bleeding	43 (4.0)	13 (1.2)	3.41 (1.84–6.35)	<0.001
Intracranial bleeding	14 (1.3)	0	15.2 (2.0–115.6)	0.001
Moderate bleeding	31 (2.9)	11 (1.0)	2.82 (1.43–5.58)	0.002
Life-threatening or moderate bleeding	74 (6.9)	24 (2.2)	3.21 (2.02–5.08)	<0.001
Minor bleeding	417 (38.6)	115 (10.6)	3.63 (3.01–4.38)	<0.001
Coprimary outcome 1 with no fatal bleeding or hemorrhagic stroke	117 (10.8)	143 (13.2)	0.82 (0.64–1.05)	0.11
Coprimary outcome 2 with no fatal bleeding or hemorrhagic stroke	157 (14.5)	187 (17.3)	0.83 (0.67–1.03)	0.09

* CI denotes confidence interval.
† Coprimary outcome 1 was myocardial infarction, stroke, or death from cardiovascular causes.
‡ Coprimary outcome 2 was myocardial infarction, stroke, severe ischemia of the peripheral or coronary arteries, or death from cardiovascular causes.

effects of the combination of moderate-intensity oral anticoagulant therapy and antiplatelet therapy in patients with coronary artery disease.[5-7,12] Few randomized trials had tested this hypothesis before our study, and clinical practice was therefore variable.[8,13]

In the WAVE trial, we aimed to maximize adherence to oral anticoagulant therapy and to minimize bleeding. We therefore excluded patients with known risk factors for bleeding, such as long-term use of nonsteroidal antiinflammatory drugs, previous gastrointestinal bleeding, or recent stroke. In addition, the active run-in excluded patients with unstable INR values, minor bleeding, or poor adherence to oral anticoagulant therapy. Despite these efforts, 29.5% of patients discontinued oral anticoagulant therapy during follow-up. This rate is consistent with the adherence levels achieved in other large clinical trials of long-term oral anticoagulation.[4,14] The INR values of participants assigned to oral anticoagulation were in the therapeutic range (2.0 to 3.0) 62% of the time, demonstrating a level of anticoagulant control similar to that achieved in most trials.

On the basis of previous clinical trials,[14] we expected that the rates of minor, and possibly of moderate, bleeding would be significantly increased in the combination-therapy group. However, we also expected that the benefits of treatment would outweigh the risks. Although the P value was nonsignificant, the lower border of the 95% confidence interval does not totally ex-
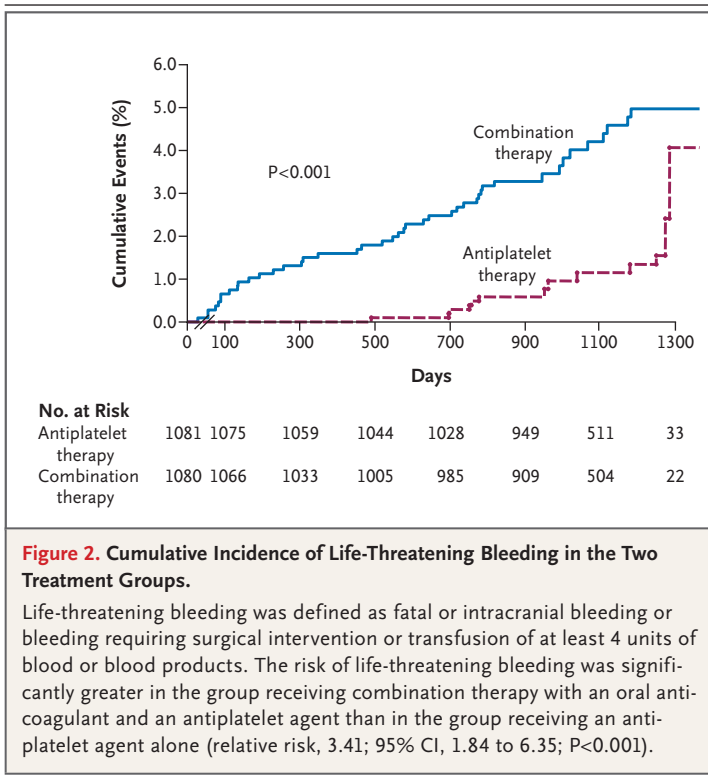
Figure 2. Cumulative Incidence of Life-Threatening Bleeding in the Two Treatment Groups.

Life-threatening bleeding was defined as fatal or intracranial bleeding or bleeding requiring surgical intervention or transfusion of at least 4 units of blood or blood products. The risk of life-threatening bleeding was significantly greater in the group receiving combination therapy with an oral anticoagulant and an antiplatelet agent than in the group receiving an antiplatelet agent alone (relative risk, 3.41; 95% CI, 1.84 to 6.35; P<0.001).

clude a 25% relative risk reduction. Our results are consistent with those of the Department of Veterans Affairs Cooperative Study, the only other large, randomized trial comparing a combination of oral anticoagulant and antiplatelet therapy with antiplatelet therapy alone in patients with peripheral arterial disease.[13] Both trials showed no significant reduction in myocardial infarction, stroke, or death from cardiovascular causes, and both showed a significant increase in life-threatening and moderate bleeding.

We observed a significant increase in life-threatening bleeding complications, including fatal bleeding and hemorrhagic stroke, with combination therapy as compared with antiplatelet therapy alone, despite the fact that very few patients had an INR above 3.0. Excluding fatal bleeding and hemorrhagic stroke from the coprimary outcomes results in risk reductions that are more favorable with combination therapy than with antiplatelet therapy alone and suggests that the excess bleeding that occurred in patients receiving combination therapy "neutralized" any benefit of that therapy.

The rates of serious bleeding and hemorrhagic stroke among patients receiving a combination of oral anticoagulant and antiplatelet therapy were higher in the WAVE trial (5.5 of 100 and 0.51 of 100 patient-years, respectively) than in a trial involving patients with coronary artery disease (0.56 of 100 and 0.12 of 100 patient-years, respectively).[6] However, the WAVE results are similar to those of another large trial involving patients with peripheral arterial disease that compared oral anticoagulation (target INR, 3.0 to 4.5) with aspirin; in that trial the rates of serious bleeding and hemorrhagic stroke among patients receiving oral anticoagulant therapy were 4.1 of 100 and 0.61 of 100 patient-years, respectively.[15] Therefore, it appears that patients with peripheral arterial disease who are treated with oral anticoagulation may be more likely to have bleeding complications, including hemorrhagic stroke, than are patients with coronary artery disease. The reason for this difference may be that patients with peripheral arterial disease are older and have more systemic atherosclerosis, including cerebrovascular disease, and more coexisting conditions.[16]

Secondary analyses revealed that the efficacy and safety of combination therapy did not differ among several patient subgroups of clinical importance. In an exploratory subgroup analysis according to country, some heterogeneity of the treatment effect was observed. The relative risk of the first coprimary outcome (myocardial infarction, stroke, or death from cardiovascular causes) was increased among patients from China. Since this qualitative interaction was unexpected, the most likely explanation for this finding is chance. However, it has been suggested that the optimal target INR may be lower for Chinese patients than for whites,[17] and the possibility of a differential response to combination therapy among Chinese patients therefore cannot be ruled out.

One potential limitation of the trial was the open-label design, which permitted patients and their physicians to know which study regimen they were receiving. This knowledge could have influenced clinical decisions regarding other medical therapy or procedures. However, no significant differences between the two study groups in interim management were identified (see the Supplementary Appendix). Furthermore, all trial end points were centrally adjudicated by a blinded adjudication committee.

On the basis of the WAVE results, oral anticoagulation combined with antiplatelet therapy is not indicated in patients with peripheral arterial dis-
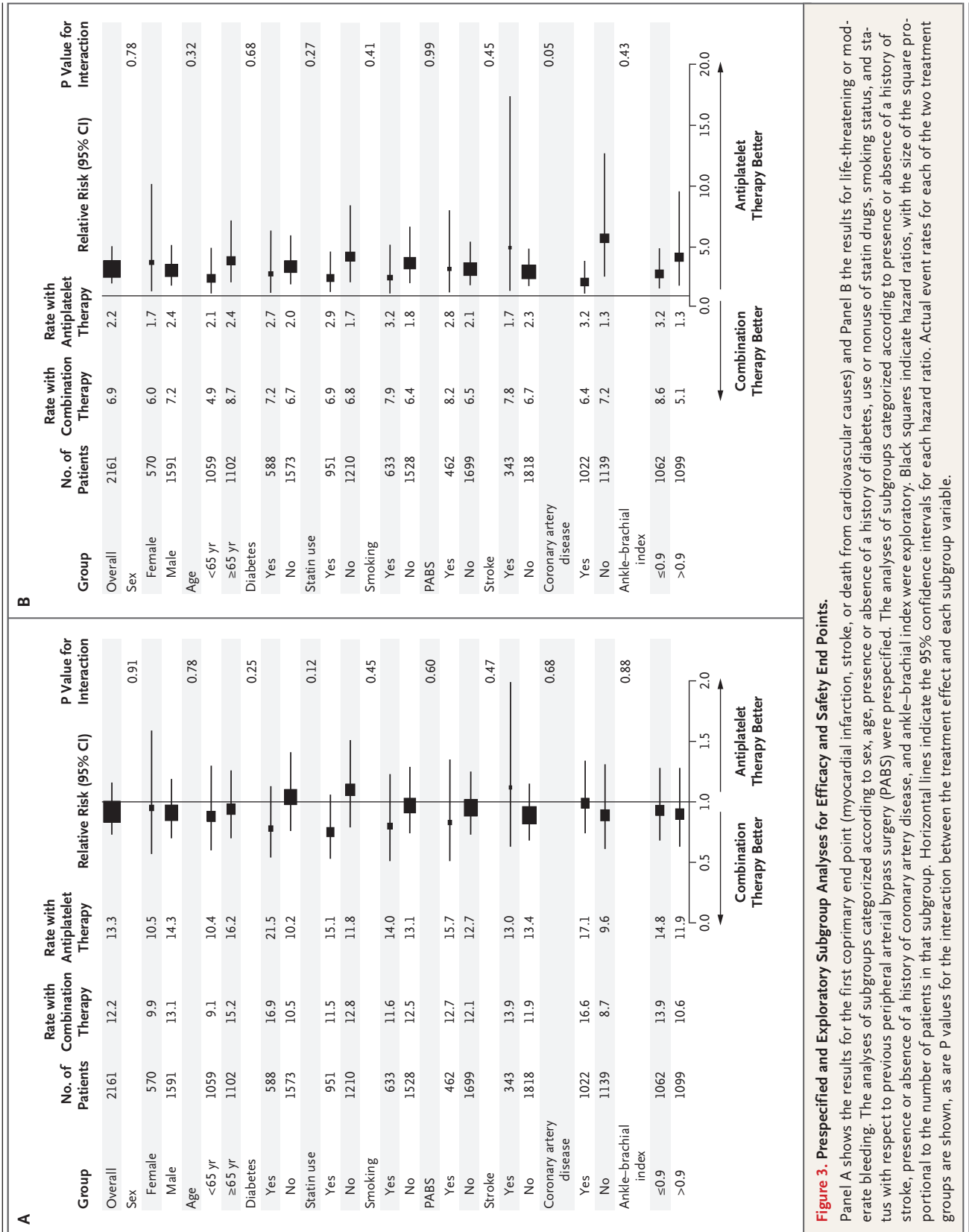
A

Group	No. of Patients	Rate with Combination Therapy	Rate with Antiplatelet Therapy	Relative Risk (95% CI)	P Value for Interaction
Overall	2161	12.2	13.3		
Sex					0.91
Female	570	9.9	10.5		
Male	1591	13.1	14.3		
Age					0.78
<65 yr	1059	9.1	10.4		
≥65 yr	1102	15.2	16.2		
Diabetes					0.25
Yes	588	16.9	21.5		
No	1573	10.5	10.2		
Statin use					0.12
Yes	951	11.5	15.1		
No	1210	12.8	11.8		
Smoking					0.45
Yes	633	11.6	14.0		
No	1528	12.5	13.1		
PABS					0.60
Yes	462	12.7	15.7		
No	1699	12.1	12.7		
Stroke					0.47
Yes	343	13.9	13.0		
No	1818	11.9	13.4		
Coronary artery disease					0.68
Yes	1022	16.6	17.1		
No	1139	8.7	9.6		
Ankle–brachial index					0.88
≤0.9	1062	13.9	14.8		
>0.9	1099	10.6	11.9		

0.0 0.5 1.0 1.5 2.0
Combination Therapy Better — Antiplatelet Therapy Better

B

Group	No. of Patients	Rate with Combination Therapy	Rate with Antiplatelet Therapy	Relative Risk (95% CI)	P Value for Interaction
Overall	2161	6.9	2.2		
Sex					0.78
Female	570	6.0	1.7		
Male	1591	7.2	2.4		
Age					0.32
<65 yr	1059	4.9	2.1		
≥65 yr	1102	8.7	2.4		
Diabetes					0.68
Yes	588	7.2	2.7		
No	1573	6.7	2.0		
Statin use					0.27
Yes	951	6.9	2.9		
No	1210	6.8	1.7		
Smoking					0.41
Yes	633	7.9	3.2		
No	1528	6.4	1.8		
PABS					0.99
Yes	462	8.2	2.8		
No	1699	6.5	2.1		
Stroke					0.45
Yes	343	7.8	1.7		
No	1818	6.7	2.3		
Coronary artery disease					0.05
Yes	1022	6.4	3.2		
No	1139	7.2	1.3		
Ankle–brachial index					0.43
≤0.9	1062	8.6	3.2		
>0.9	1099	5.1	1.3		

0.0 5.0 10.0 15.0 20.0
Combination Therapy Better — Antiplatelet Therapy Better

Figure 3. Prespecified and Exploratory Subgroup Analyses for Efficacy and Safety End Points.

Panel A shows the results for the first coprimary end point (myocardial infarction, stroke, or death from cardiovascular causes) and Panel B the results for life-threatening or moderate bleeding. The analyses of subgroups categorized according to sex, age, presence or absence of a history of diabetes, use or nonuse of statin drugs, smoking status, and status with respect to previous peripheral arterial bypass surgery (PABS) were prespecified. The analyses of subgroups categorized according to presence or absence of a history of stroke, presence or absence of a history of coronary artery disease, and ankle–brachial index were exploratory. Black squares indicate hazard ratios, with the size of the square proportional to the number of patients in that subgroup. Horizontal lines indicate the 95% confidence intervals for each hazard ratio. Actual event rates for each of the two treatment groups are shown, as are P values for the interaction between the treatment effect and each subgroup variable.

ease, since no significant benefit was observed and substantial risk was incurred. According to our data, treating 1000 patients with combination therapy as compared with antiplatelet therapy alone for 3 years would lead to 24 fewer cardio-vascular events but 28 more episodes of life-threatening bleeding, resulting in a net increase in serious adverse outcomes. Our findings highlight the need to evaluate alternatives to vitamin K antagonists in patients with peripheral arterial disease.[18]

In conclusion, we compared the efficacy and safety of antiplatelet therapy combined with oral anticoagulation (target INR, 2.0 to 3.0) with the efficacy and safety of antiplatelet therapy alone in patients with peripheral arterial disease. We found that combination therapy was not more effective than antiplatelet therapy alone in preventing major cardiovascular complications and was associated with a substantial increase in the risk of life-threatening bleeding.

APPENDIX

The following investigators participated in the WAVE trial: **Steering Committee:** principal investigator, S. Anand; chair of steering committee, S. Yusuf; study coordinators, P. Montague, S.L. Chin; regional representatives, A. Budaj, C. Cina, H. Lee (deceased), S. Sauve, R. Guzman, G. Hajjar, G. Gosselin, D. Gossard, B. Sussex, R. Crowell, J. Eikelboom, M. Keltai, A. Parkhomenko, L.S. Liu, H. van Urk; **Investigators** (with the number of patients shown in parentheses): *Australia* — J. Eikelboom (16) (national coordinator); *Canada* — *Alberta*, R. Moore (12); *British Columbia*, W. Leong (6), R. Smith (30), K. Woo, J. Imrie (2); *Manitoba*, R. Guzman (125); *Newfoundland*, B. Sussex (78); *Nova Scotia*, R. Crowell (101); *Ontario*, S. Anand (national coordinator), R. Bhargava (6), Y.K. Chan (19), C. Cina (102), S. Fratesi (103), B. Geerts (7), G. Hajjar (27), G. Kuruvilla (18), C. Lai (17), H. Lee (103), S. Nawaz (11), S. Sauve (37); *Quebec*, P. Bolduc (22), D. Gossard (27), G. Gosselin (49), R. Labbé (37), P. Nault (5), D. Pilon (12), G. Pruneau (14), D. Savard (2), R. St.-Hilaire (11); *China* — L.S. Liu, S.C. Xu, Y.L. Li (national coordinator), L.L. Deng (23), L. Fan (7), X.H. Fang (21), P. Feng (7), B.X. Guo (7), B.L. Hu (8), X.J. Jiang (9), J.H. Liu (2), L.H. Liu (12), X.Q. Liu (6), F.H. Lu (34), X.Y. Shi (8), R.S. Wang (13), Y.X. Wang (114), Q. Yuan, S.B. Wu (38), L. Zhang (23), X.M. Zhang (13), F. Zhao (2); *Hungary* — B. Herczeg (5), M. Jozan-Jilling (16), M. Keltai (national coordinator), E. Mesko (13), S. Olvaszto (16), G. Sipos (1), P. Soltesz (25), F. Szaboki (8), S. Timar (1); *the Netherlands* — H. van Urk (national coordinator), O. Schouten (17); *Poland* — Z. Binio (3), A. Budaj, B. Klosiewicz-Wasek (73) (national coordinator), J. Gorny (11), K. Janik (46), T. Kawka-Urbanek (27), J. Maciejewicz (22), P. Miekus (67), F. Monies (85), M. Ogorek (31), J. Surwilo (12), M. Szpajer (96), T. Waszyrowski (35), J. Wojciechowski (16), B. Zalska (36), M. Zebrowski (5); *Ukraine* — Y. Dykun (8), E. Grishina (2), A. Karpenko (49), L. Kononenko (148), O. Koval (8), V. Kovalenko (3), V. Netyazhenko (1), A. Parkhomenko (national coordinator), M. Perepelytsa (20), T. Pertseva (1), Y. Sirenko (4), A. Skarzhevsky (5); **Adjudication:** B. Sussex, S. Sauve, cochairs; C. Cina, R. Guzman, B. Klosjewicz-Wasek; *adjudication officers:* F. Merali, P. Magloire; *adjudication coordinator:* L. Joldersma; **Operations Committee:** S. Anand, S. Yusuf, B. Sussex, J. Eikelboom, P. Montague, A. Budaj, H. Lee (deceased), G. Gosselin, M. Keltai; **Data and Safety Monitoring Committee:** G. Dagenais (chair), J.S. Ginsberg, A. Hill, W. Taylor; **Project Office:** S. Anand, S. Yusuf, P. Montague, S.L. Chin, L. Joldersma, S. Parkinson, K. Antaya, D. Sloane, B. Nowacki, P. Magloire, F. Merali; **Laboratory:** M. McQueen, K. Hall; **Biostatistics:** C. Xie, J. Pogue, S. Hawken; **Pharmacy Contact:** M. Biljan; **Administration:** B. Cracknell, K. Antaya.

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