Oral Anticoagulant Therapy in Patients With Coronary Artery Disease: A Meta-analysis

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Context Despite years of use in coronary artery disease (CAD) and several studies of its effectiveness, the role of oral anticoagulants (OAs) remains controversial.

Objective To determine the effects of long-term OA therapy, stratified by the intensities of anticoagulation and aspirin therapy, on outcomes in patients with CAD.

Data Sources Studies were identified by MEDLINE, EMBASE, and CURRENT CONTENTS searches (1960-July 1999) and by reviewing reference lists and inquiring with experts and pharmaceutical companies.

Study Selection Studies were included if they were published between 1960 and July 1999, were randomized, had recruited patients with CAD, who had used OA therapy for at least 3 months. Of 43 articles identified, 30 articles (31 trials) were analyzed.

Data Extraction Information on type, duration, and method of monitoring OA therapy, as well as rates of death, myocardial infarction (MI), thromboembolic complications, stroke, and bleeding were abstracted by 2 independent observers.

Data Synthesis With high-intensity (international normalized ratio [INR], 2.8-4.8) OAs vs control (16 trials, 10 056 patients), clear reductions in mortality (odds reduction [ORed], 22%; 95% confidence interval [CI], 13%-31%), MIs (ORed, 42%; 95% CI, 34%-48%), and thromboembolic complications including stroke (ORed, 63%; 95% CI, 53-71%) were observed, but were associated with a 6.0-fold (95% CI, 4.4- to 8.2-fold) increase in major bleeding. For moderate OAs (INR, 2-3) vs control (4 trials, 1365 patients) the ORed for death was 18% (95% CI, –6% to 37%); for MI, 52% (95% CI, 37%-64%); and for stroke, 53% (95% CI, 19%-73%), but it increased bleeding by 7.7-fold (95% CI, 3.3- to 18-fold). For moderate- to high-intensity OAs (INR, $\geq$2) vs aspirin (7 trials, 3457 patients), no reduction in death, MI, or stroke was observed, and it was associated with a 2.4-fold (95% CI, 1.6- to 3.6-fold) increase in major bleeding. For moderate- to high-intensity OAs and aspirin vs aspirin alone (3 trials, 480 patients), the ORed for death, MI, or stroke was 56% (95% CI, 17%-77%) and major bleeding increased by 1.9-fold (0.6- to 6.0-fold). For low-intensity OAs (INR, $<$2.0) and aspirin vs aspirin alone (3 trials, 8435 patients), no significant reduction in death, MI, or stroke was observed, and major bleeding increased by 1.3-fold (95% CI, 1.0- to 1.8-fold).

Conclusions Among patients with CAD, high-intensity and moderate-intensity OA are effective in reducing MI and stroke but increase the risk of bleeding. In the presence of aspirin, low-intensity OA does not appear to be superior to aspirin alone, while moderate- to high-intensity OA and aspirin vs aspirin alone appears promising and the bleeding risk is modest, but this requires confirmation from ongoing trials.

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ORAL ANTICOAGULANTS (OAs) have been used in patients with vascular disease for 40 years, but their role is still controversial because of multiple reasons. First, several small, randomized trials provided conflicting results in patients who had experienced a myocardial infarction (MI). Second, OAs are inconvenient to use as they require careful monitoring and dose adjustments. Third, there are concerns whether the risk of bleeding with OAs justify their use. Fourth, antiplatelet therapies have been proven to be effective in reducing vascular complications and to be safe.

Whether OAs are effective in reducing cardiovascular events in patients who had experienced an MI has been the subject of previous overviews.[1,2] The International Anticoagulant Review group[1] published a combined analysis of 9 trials (5 randomized), which were conducted between 1950 and 1965. Although they observed a statistically significant 40% risk reduction in mortality in men younger than 55 years using OAs, this group could not reach a consensus. In 1977, Chalmers et al[2] published a more formal systematic overview of the available trials of OA in patients who had experienced an MI and reported a 21% reduction in mortality ($P<.001$), a 50% reduction in thromboembolic events including recurrent MI and ischemic stroke, and a 2-fold increase in bleeding events with OA.[2] This analysis failed to gain acceptance partly because meta-analysis was new, and partly because trials that used historical or nonrandomized controls were included.

Subsequently, 2 important findings have directed research involving OA in vascular disease. First, the rates of recurrent vascular events in patients with established vascular disease remains high, despite the use of antiplatelet agents.[3] Second, there is evidence of a persistent biochemical stimulus to thrombosis for several months after an acute coronary syndrome even in the presence of aspirin.[4] This stimulated the conduct of a number of large, well-

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controlled trials testing OA at varying intensities with or without concomitant aspirin therapy. Initially, trials tested high-intensity OA (international normalized ratio [INR], 2.8-4.8) in the absence of aspirin,[5,6] or high- and moderate-intensity OA (INR, 2-3) compared with aspirin or control.[7] More recent trials have evaluated the combination of OA and aspirin vs aspirin alone in the moderate-intensity (INR, 2-3), and low-intensity (INR, <1.5)[8,9] ranges. To more reliably determine the role of OA with and without antiplatelet therapy, we conducted an overview of all available trials of OA in established coronary artery disease (CAD), stratified by intensity (target INR) and by aspirin use. Our objectives were to comprehensively assess the effects of OA on death, recurrent MI, stroke, and bleeding in patients with established CAD, and to determine if the effects vary by intensity of OA and aspirin use.

METHODS

We tried to identify all unconfounded randomized trials between 1960 and July 1999 by searching the conventional databases of MEDLINE, EMBASE, and CURRENT CONTENTS, reviewing reference lists, and inquiring with experts in the field, and pharmaceutical companies. Computer searches used combinations of key words related to OA (eg, warfarin sodium, coumarins) and vascular disease (eg, CAD, MI, unstable angina, coronary artery bypass graft surgery). Studies were included if they (1) were published after 1960, (2) were randomized, (3) recruited patients with established CAD, (4) used OA, and (5) continued treatment for 3 or more months. Data were extracted from the published reports independently by 2 reviewers and a consensus was achieved for any discrepancies. Extra information was requested from 2 trials,[10,11] but only obtained for 1 trial.[10]

The reported events of death, MI, and stroke were taken from the published reports. In the trials that provided data on fatal and nonfatal events, a composite rate of death or nonfatal MI or nonfatal stroke was calculated. The reporting of bleeding events was incomplete, and the definitions of bleeding differed substantially in the trials conducted prior to 1980. However, all trials reported the rates of total bleeding, and wherever possible bleeds that required transfusion, surgical intervention, or hospitalization were identified and coded as major bleeding events.

Trials conducted prior to 1980 predated the widespread use of the INR.[12] In trials that reported the prothrombin ratio and the type of thromboplastin used, the INR was reasonably approximated using a validated nomogram.[13] In 3 trials in which the thromboplastin was not reported, the intensity of anticoagulation was classified based on the period in which the study was conducted.[10,14,15] All INR classifications were independently reviewed by a thrombosis expert (Jack Hirsh, MD, September 1998).

Although a variety of OAs (eg, warfarin sodium, dicoumarol, marcoumar, phenprocoumon, acencoumarin, bishydroxycoumarin) were used across the trials, all agents work by inhibiting the production of vitamin K-dependent coagulation factors (factors VII, IX, X, II), and there are no data which suggest that the pharmacologic action of these agents differ from one another.[13]

The modified Mantel-Haenszel method was used to combine the data from individual trials.[16] This method has been extensively used in previous meta-analyses[17] and entailed calculating the observed (number of events in the treatment group) minus the expected (average number of events for treatment and control groups) events and determining the variance for each. Grand totals were calculated for each and the ratio of the 2 was used to estimate the odds ratio (OR). The OR (and its 95% confidence interval [CI]) was calculated for each trial. The odds reduction (ORed) was calculated using 1 minus the OR, and was expressed as a percentage. For each study event, patients were counted in each category (eg, a patient with fatal MI was counted in the MI category and in the total mortality category). For combined events (eg, death, MI, stroke), patients were counted only once. In unevenly randomized trials in which fewer patients were randomized to control, the number of patients randomized (and number of events reported) were adjusted to match the treatment group, using methods previously described.[16] Trials were examined for heterogeneity by dividing them into strata based on the intensity of anticoagulation (low, moderate, high) and the concomitant use of aspirin. The χ^2 tests for heterogeneity were approximated by summing the N separate χ^2 test statistics ($O\text{-}E^2/V$) for each trial and subtracting the overall χ^2

Table 1. Baseline Characteristics in High-, Moderate- and Low-Intensity OA Trials*

Baseline Characteristics	High OA Intensity (95% CI)	Moderate OA Intensity (95% CI)	Low OA Intensity (95% CI)
No. of trials	20	8	3
No. of patients	11 692	3270	8435
Mean age, y	61.8 (61.6-61.9)	59.9 (59.7-60.1)	64.3 (64.2-64.3)
Men	80.0 (79.3-80.7)	76.0 (74.5-77.5)	79.0 (78.1-79.9)
Initiation of therapy			
In hospital	37.7 (36.8-38.6)	78.0 (76.6-79.4)	3.7 (3.3-4.1)
Hospital to 3 mo	52.0 (51.1-52.9)	22.0 (20.5-23.4)	80.3 (79.4-81.1)
After 3 mo	11.0 (10.4-11.6)	0.0 (NA)	16.0 (15.3-16.8)
Duration of treatment, y			
<1	11.3 (10.7-11.9)	16.5 (15.2-17.8)	4.0 (3.6-4.4)
1-2	22.9 (22.1-23.7)	6.9 (6.0-7.8)	80.0 (71.9-88.0)
>2	65.8 (64.9-66.7)	76.9 (75.4-78.3)	16.0 (8.6-23.3)
Discontinued OA by the end of trial	32.0 (30.6-33.4)	20.0 (18.0-22.0)	22.0 (19.1-24.9)

*Values are expressed as percentages of patients unless otherwise indicated. OA indicates oral anitcoagulant; CI, confidence interval; NA, not available. High intensity is defined by the international normalized ratio >2.8; moderate, 2-3; and low, <2.

Table 2. Results of Prolonged Oral Anticoagulant (OA) Therapy Compared With Control in High-, Moderate-, and Low-Intensity Trials on Total Mortality*

Source, y	Level of Intensity	No./Total (%) of Subjects Allocated to OA Therapy	No./Total (%) of Subjects Allocated to Control Therapy	*P* Value
High-Intensity OA vs Control†				
MacMillan et al,[14] 1960	High	8/27 (29.6)	0.23 (0)	.005
Borchegrevink,[32] 1960	High	1/103 (1.0)	8/100 (8.0)	.02
Clausen et al,[33] 1961	High	15/93 (16.1)	13/99 (13.1)	.56
Harvald et al,[34] 1961	High	34/145 (23.4)	45/171 (26.3)	.54
Apenstrom and Korsan-Bengtsen,[35] 1964	High	39/118 (33.1)	50/113 (44.2)	.08
Conrad et al,[36] 1964	High	9/52 (17.3)	8/34 (23.5)	.48
Wasserman et al,[15] 1966	High	12/77 (15.6)	15/70 (21.4)	.36
Loeliger et al,[37] 1967	High	8/128 (6.3)	11/112 (9.8)	.41
Lovell et al,[38] 1967	High	33/178 (18.5)	39/172 (22.7)	.53
Seaman et al,[39] 1969	High	36/88 (40.9)	31/87 (35.6)	.47
Sorensen et al,[40] 1969	High	30/156 (19.2)	43/120 (35.8)	.002
Sixty Plus Reinfarction,[41] 1980	High	51/439 (11.6)	69/439 (15.7)	.08
WARIS,[5] 1990	High	94/607 (15.5)	123/607 (20.3)	.03
ASPECT,[6] 1994	High	170/1700 (10.0)	189/1704 (11.1)	.30
Meuwissen et al,[42] 1969	High	1/68 (1.5)	8/70 (11.4)	.02
Drapkin and Merskey,[20,43] 1974 and 1972	High	111/745 (14.9)	166/782 (21.2)	.007
Breddin et al,[44] 1980	High	39/320 (12.2)	32/309 (10.4)	.47
Total		**691/5044** (13.7)	**850/5012** (17.0)	<.001
High- or Moderate-Intensity OA vs Aspirin‡				
Breddin et al,[44] 1980	High	39/320 (12.2)	27/317 (8.5)	.13
CABADAS,[45] 1993	High	3/307 (1.0)	8/309 (2.6)	.13
Eritsland et al,[11] 1996	High	5/319 (1.6)	9/291 (3.1)	.21
ATACS,[46] 1990	High	1/24 (4.2)	0/32 (0)	.25
McEnany et al,[47] 1982	Moderate	1/68 (1.5)	1/71 (1.4)	.98
Kraska et al,[10] 1981	Moderate	5/60 (8.3)	7/60 (11.7)	.03
EPSIM,[7] 1982	Moderate	67/652 (10.3)	72/651 (11.1)	.65
Total		**120/1726** (7.0)	**124/1731** (7.2)	.78
Moderate-Intensity OA vs Control§				
COOP,[48] 1969	Moderate	120/385 (31.2)	114/350 (32.6)	.68
MRC Anticoagulant,[49] 1964	Moderate	29/195 (14.9)	40/188 (21.3)	.10
Williams et al,[50] 1986	Moderate	1/51 (2.0)	4/51 (7.8)	.17
McEnany et al,[47] 1982	Moderate	1/68 (1.5)	3/77 (3.9)	.38
Total		**151/699** (21.6)	**161/666** (24.2)	.14
High- or Moderate-Intensity OA and Aspirin vs Aspirin‖				
ATACS,[46] 1990	High	0/37 (0)	0/32 (0)	.25
OASIS Pilot 2,[51] 1998	Moderate	2/98 (2.0)	5/99 (5.1)	.26
ATACS-Main,[52] 1994	Moderate	2/105 (1.9)	2/109 (1.8)	.97
Total		**4/240** (1.7)	**7/240** (2.9)	.61
Low-Intensity OA and Aspirin vs Aspirin¶				
OASIS Pilot,[51] 1998	Low	2/155 (1.3)	3/154 (1.9)	.65
Post-CABG,[9] 1997	Low	28/674 (4.2)	39/677 (5.8)	.17
CARS,[8] 1997	Low	118/3382 (3.5)	102/3393 (3.0)	.26
Total		**148/4211** (3.5)	**144/4224** (3.4)	.79

*WARIS indicates Warfarin Re-infarction Study; ASPECT, Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis; CABADAS, Prevention of Coronary Artery Bypass Graft Occlusion by Aspirin, Dipyridamole, Acenocoumarol/Phenoprocoumon Study; ATACS, Antithrombotic Therapy in Acute Coronary Syndromes; EPSIM, Enquete de Prevention Secondaire de Infarctus du Myocarde; COOP, Veterans Administration Cooperative Study; MRC Anticoagulant, Medical Research Council Anticoagulant Study; and OASIS, Organization to Assess Strategies for Ischemic Syndromes. CI indicates confidence interval; OR, odds ratio.
†Pooled OR, 0.78 (95% CI, 0.69-0.87); *P*<.001. Events prevented/1000 patients treated = 33.
‡Pooled OR, 0.93 (95% CI, 0.69-1.28); *P*>.10. Events prevented/1000 patients treated = 2.
§Pooled OR, 0.82 (95% CI, 0.63-1.06); *P*>.10. Events prevented/1000 patients treated = 26.
‖Pooled OR, 0.74 (95% CI, 0.23-2.33); *P*>.10. Events prevented/1000 patients treated = 12.
¶Pooled OR, 1.03 (95% CI, 0.82-1.30); *P*>.10. Events prevented/1000 patients treated = −1.

value (GT^2/SIV) from this, using N-1 degrees of freedom.[18] The number of events prevented or caused per 1000 patients treated was calculated by subtracting the absolute event rate of the treatment group from the control or placebo group, and multiplying this number by 10.[17]

RESULTS

We identified 43 reports of 44 trials of patients with CAD that evaluated OA, and excluded 13 trials.[19-31] Two trials had duplicate reports,[19,20] 4 trials administered OA to both the treatment and control groups,[21-24] 5 trials included patients with other vascular conditions (ie, coronary stents),[25-29] and 2 trials[30,31] reported only surrogate outcomes. Of the remaining 30 reports of 31 trials included in the analysis, 20 were classified as high intensity (INR, >2.8),[5,6,11,14,15,32-46] 8 as moderate intensity (INR, 2-3),[7,10,47-52] and 3 as low intensity (INR, <2).[8,9,50]

High Intensity

Twenty trials (N = 11 692) were classified as high intensity (TABLE 1).[5,6,11,14,15,32-46] In 16 trials (N = 10 056), no patients received aspirin and in 4 trials (N = 1853),[11,44-46] OAs were compared directly with aspirin. Trials that evaluated OA vs control and OA vs aspirin were analyzed separately. Thirty-four percent of patients were treated with warfarin for up to 2 years, and 66% of patients were treated for longer duration. Thirty-two percent of patients discontinued OA therapy before the scheduled end of follow-up (Table 1).

For studies that compared high intensity vs control, 5044 patients received OAs and 5012 were randomized to placebo or control (totals adjusted for uneven randomization). The OReds for OA vs control for mortality, MI, and thromboembolic complications including stroke were 22% (95% CI, 13%-31%; *P*<.001; TABLE 2), 42% (95% CI, 34%-48%; *P*<.001; TABLE 3), and 63% (95% CI, 53%-71%; *P*<.001; TABLE 4), respectively (FIGURE 1). Where stroke was reported separately, an ORed of 48% (95% CI, 33%-60%; *P*<.001) in favor of OA was observed. For the combination of

death, MI or stroke, data from 13 trials[5,6,32,34-42,44] indicated an ORed of 43% (95% CI, 37%-49%; $P<.001$; TABLE 5), although a relative increase in total and major bleeding occurred with OA; OR of 4.7 (95% CI, 4.0-5.6; $P<.001$; TABLE 6) and 6.0 (95% CI, 4.4-8.2; $P<.001$; TABLE 7), respectively. In the 3 trials (N = 5496)[5,6,41] in which hemorrhagic stroke could be reliably separated from total stroke, a 5-fold (95% CI, 2.6-10.3; $P<.001$) relative increase in hemorrhagic strokes with OA was observed, although the absolute rates were low (1.1% vs 0.1%). However, given the substantial ORed reduction in nonhemorrhagic strokes of 65% (95% CI, 52%-74%; $P<.001$), overall, there was a 46% reduction (95% CI, 28%-59%; $P<.001$) in stroke with OA (TABLE 8). For every 1000 patients treated with high-intensity OA, 98 vascular events were prevented and 39 major bleeds were caused.

Moderate Intensity

Eight trials were classified as moderate intensity (N = 3270) (Table 1). In 3 trials[7,10,47] (N = 1562), OAs were compared with aspirin, 4 trials[47-49,52] (N = 1365) compared OA with control, and 2 trials[50,52] (N = 361) compared OA and aspirin vs aspirin alone.

Moderate Intensity OA vs Control. Data from 1365 patients from 4 trials were available. The OA OReds for mortality, MI, and stroke were 18% (95% CI, –6% to 37%; $P>.10$; Table 2), 52% (95% CI, 37%-64%; $P<.001$; Table 3), and 53% (95% CI, 19%-73%; $P = .02$; Table 8), respectively (Figure 1). The relative increase in the odds of major bleeding with OA was 7.7 (95% CI, 3.3-18; $P<.001$; Table 7). For every 1000 patients treated, the number of vascular events prevented was 24 (with wide CIs), yet 35 major bleeds were caused.

Moderate- or High-Intensity OAs vs Aspirin. Data were available from 7 trials (3457 patients).[7,10,11,44-47] Nonsignificant OReds with OAs for death [7% (95% CI, –28% to 31%); $P>.10$; Table 2], and MI [12% (95% CI, –24% to 37%); $P>.10$; Table 3], and no reduction in the combination of death, MI, or stroke were observed (Table 5). Stroke and major bleeding are increased 2.37 times (95% CI, 0.83-6.78; $P>.10$; Table 8), and 2.4 times (95% CI, 1.6-3.6; $P<.001$; Table 7), respectively (FIGURE 2).

Moderate- to High-Intensity OA and Aspirin Compared With Aspirin Alone. Data from 3 trials[46,50,52] were combined although the total number of patients is small (n = 480). The point

Table 3. Results of Prolonged Oral Anticoagulant (OA) Therapy Compared With Control in High-, Moderate-, and Low-Intensity Trials on Fatal and Nonfatal Myocardial Infarction*

Source, y	Level of Intensity	No./Total (%) of Subjects Allocated to OA Therapy	No./Total (%) of Subjects Allocated to Control Therapy	*P* Value
High-Intensity OA vs Control†				
MacMillan et al,[14] 1960	High	6/27 (22.2)	4/23 (17.4)	.67
Borchegrevink ,[32] 1960	High	1/103 (1.0)	6/100 (6.0)	.05
Clausen et al,[33] 1961	High	22/93 (23.7)	21/99 (21.2)	.69
Harvald et al,[34] 1961	High	52/145 (35.9)	67/171 (39.2)	.52
Apenstrom and Korsan-Bengtsen,[35] 1964	High	20/118 (16.9)	45/113 (39.8)	0
Conrad et al,[36] 1964	High	9/52 (17.3)	6/34 (17.6)	.97
Loeliger et al,[37] 1967	High	2/128 (1.6)	12/112 (10.7)	0
Lovell et al,[38] 1967	High	12/178 (6.7)	17/172 (9.9)	.38
Seaman et al,[39] 1969	High	35/88 (39.8)	33/87 (37.9)	.80
Sorensen et al,[40] 1969	High	24/156 (15.4)	37/120 (30.8)	.13
Sixty Plus Reinfarction,[41] 1980	High	29/439 (6.6)	64/439 (14.6)	0
WARIS,[5] 1990	High	82/607 (13.5)	124/607 (20.4)	0
ASPECT,[6] 1994	High	114/1700 (6.7)	242/1704 (14.2)	0
Meuwissen et al,[42] 1969	High	5/68 (7.4)	7/70 (10.0)	.58
Drapkin and Merskey,[20,43] 1974 and 1972	High	88/745 (11.8)	102/782 (13.0)	.55
Breddin et al,[44] 1980	High	16/320 (5.0)	25/309 (8.1)	.12
Total		**501/4647** (10.8)	**812/4942** (16.4)	<.001
High- or Moderate-Intensity OA vs Aspirin‡				
CABADAS,[45] 1993	High	24/307 (7.8)	25/309 (8.1)	.90
Breddin et al,[44] 1980	High	16/320 (5.0)	16/317 (5.0)	.98
ATACS,[46] 1990	High	3/24 (12.5)	1/32 (3.1)	.28
EPSIM,[7] 1982	Moderate	20/652 (3.1)	32/651 (4.9)	.09
Kraska et al,[10] 1981	Moderate	7/60 (11.7)	1/60 (1.7)	.03
McEnany et al,[47] 1982	Moderate	1/68 (1.5)	1/71 (1.4)	.98
Total		**71/1431** (5.0)	**76/1440** (5.3)	.99
Moderate-Intensity OA vs Control§				
COOP,[48] 1969	High	60/385 (15.6)	73/350 (20.9)	.06
MRC Anticoagulant,[49] 1964	Moderate	34/195 (17.4)	81/188 (43.1)	<.001
McEnany et al,[47] 1982	Moderate	1/68 (1.5)	5/77 (6.5)	.13
Williams et al,[50] 1986	Moderate	2/51 (3.9)	3/51 (5.9)	.65
Total		**97/699** (13.9)	**162/666** (24.3)	<.001
High- or Moderate-Intensity OA and Aspirin vs Aspirin‖				
ATACS,[46] 1990	High	0/37 (0)	1/32 (3.1)	.28
ATACS-Main,[52] 1994	Moderate	6/105 (5.7)	9/109 (8.3)	.47
OASIS Pilot 2,[51] 1998	Moderate	4/98 (4.1)	8/99 (8.1)	.24
Total		**10/240** (4.2)	**18/240** (7.5)	.32
Low-Intensity OA and Aspirin vs Aspirin¶				
OASIS Pilot 1,[51] 1998	Low	8/155 (5.2)	2/154 (1.3)	.06
Post-CABG,[9] 1997	Low	35/674 (5.2)	40/677 (5.9)	.54
CARS,[8] 1997	Low	210/3382 (6.2)	230/3393 (6.8)	.34
Total		**253/4211** (6.0)	**272/4224** (6.4)	.71

*For expansion of study names, see the first footnote to Table 2. CI indicates confidence interval; OR, odds ratio.
†Pooled OR, 0.58 (95% CI, 0.52-0.66); $P<.001$. Events prevented/1000 patients treated = 56.
‡Pooled OR, 0.88 (95% CI, 0.63-1.24); $P>.10$. Events prevented/1000 patients treated = 3.
§Pooled OR, 0.48 (95% CI, 0.36-0.63); $P<.001$. Events prevented/1000 patients treated = 104.
‖Pooled OR, 0.55 (95% CI, 0.26-1.19); $P>.10$. Events prevented/1000 patients treated = 33.
¶Pooled OR, 0.93 (95% CI, 0.78-1.12); $P>.10$. Events prevented/1000 patients treated = 4.

estimates favor the combination of OA and aspirin over aspirin alone, and differ markedly from the results of the direct comparison of OA with aspirin. For the combined outcome of death, MI, or stroke, the ORed was 56% (95% CI, 17%-77%; $P = .01$; Table 5). Separate analyses by individual outcomes indicate consistent mortality, MI, and stroke reductions of 26% ($P>.10$; Table 3), 45% ($P>.10$; Table 4), and 86%, ($P = .08$; Table 8), respectively, but the numbers are too small for each individual estimate to be reliable (Figure 2). The relative increase in major bleeding with OA and aspirin was 1.9 (95% CI, 0.6-6.0; $P>.10$; Table 7). For every 1000 patients treated, 54 vascular events were prevented, and 16 major bleeding events were caused.

Low Intensity

Three trials[8,9,50] (N = 8435 patients) comparing low-intensity OA and aspirin with aspirin were identified (Table 1). The CARS trial[8] was a 3-arm trial that compared fixed-dose 1-mg warfarin and aspirin with fixed-dose 3-mg warfarin and aspirin with aspirin alone. The INR values in the OA group receiving 1 milligram increased minimally, therefore data for only the arm receiving 3 milligrams was used and compared with the aspirin-only arm.[8]

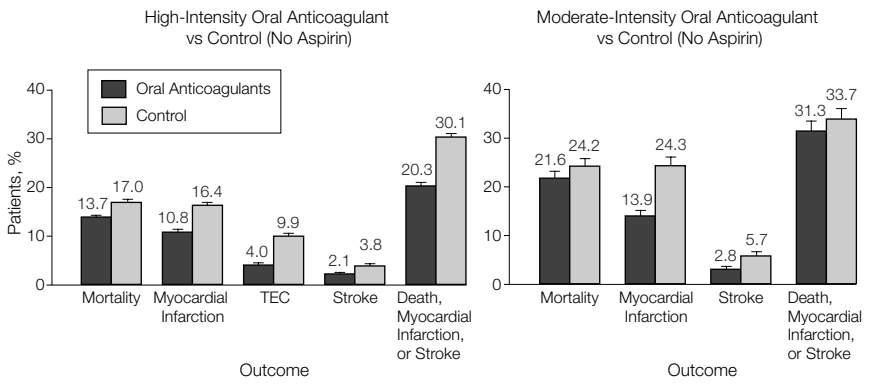
No significant benefit in favor of OA and aspirin vs aspirin alone for mortality (OR, 1.03; 95% CI, 0.81-1.30; $P>.10$; Table 3), MI (OR, 0.93; 95% CI, 0.78-1.11; $P>.10$; Table 4), stroke (OR, 1.00; 95% CI, 0.65-1.55; $P>.10$; Table 8) or their combination (OR, 0.91; 95% CI, 0.79-1.06; $P>.10$; Table 5) is observed (Figure 2). Oral anticoagulants were associated with a relative increase in major bleeding (OR, 1.3; 95% CI, 1.0-1.7; $P = .09$; Table 7).

Table 4. Results of Prolonged Oral Anticoagulant (OA) Therapy Compared With Control in High-Intensity Trials on Thromboembolic Complications*

Source, y	Level of Intensity	No./Total (%) of Subjects Allocated to OA Therapy	No./Total (%) of Subjects Allocated to Control Therapy	*P* Value
High-Intensity OA vs Control†				
Borchegrevink ,[32] 1960	High	0/103 (0)	2/100 (2.0)	.15
Clausen et al,[33] 1961	High	5/93 (5.4)	9/99 (9.1)	.32
Harvald et al,[34] 1961	High	10/145 (6.9)	28/171 (16.4)	.01
Apenstrom and Korsan-Bengtsen,[35] 1964	High	4/118 (3.4)	28/113 (24.8)	<.001
Wasserman et al,[15] 1966	High	1/77 (1.3)	2/70 (2.9)	.51
Loeliger et al,[37] 1967	High	2/128 (1.6)	15/112 (13.4)	<.001
Seaman et al,[39] 1969	High	7/88 (8.0)	11/87 (12.6)	.31
Sorensen et al,[40] 1969	High	4/156 (2.6)	13/120 (10.8)	.005
Sixty Plus Reinfarction,[41] 1980	High	9/439 (2.1)	33/439 (7.5)	<.001
Drapkin and Merskey,[20,43] 1974 and 1972	High	52/745 (7.0)	90/782 (11.5)	.01
Breddin et al,[44] 1980	High	2/320 (0.6)	7/309 (2.3)	.08
Total		**96/2412** (4.0)	**238/2402** (9.9)	<.001

*Data only available for high-intensity trials.
†Pooled odds ratio, 0.37 (95% confidence interval, 0.29-0.47); $P<.001$. Events prevented/1000 patients treated = 59.

Figure 1. Rates of Major Cardiovascular Outcomes for High- and Moderate-Intensity Oral Anticoagulant vs Control



Compliance

We defined noncompliance as the discontinuation of OA prior to the intended duration of treatment. Discontinuation rates were reported inconsistently across the trials. The average rate of noncompliance with OA for high intensity was 32% (95% CI, 30.6-33.4), for moderate intensity was 20.0% (95% CI, 18.0-22.0), and for low intensity was 22.0% (95% CI, 19.1-24.9) (Table 1). The major reason for discontinuation was concern about bleeding.

Exploring Heterogeneity

We detected a significant degree of heterogeneity in the high-intensity vs control strata. Many of the trials included in this strata were small and were conducted in the early 1960s and 1970s; however, after 1980, 3 large and well-controlled trials testing high-intensity OA were conducted.[5,6,41] To explore the causes of heterogeneity in the high-intensity strata, we divided all high-intensity trials into pre-1980 and post-1980 groups. Most of the variation in the treatment effect across individual trials was derived from the small, older trials in which the ORs vary from as small as 0.19 to as large as 8.6, compared with the modern trials in which the ORs are similar, and the variances smaller (available from authors on request). Therefore, given that the summary estimates of the modern trials are significant, not heterogeneous, and are consistent with the overall conclusions of the treatment effect in favor of high-intensity OA, the overall estimates are likely valid.

We also explored the heterogeneity of ORs between strata based on intensity of OA and subdivided the trials by whether the control group received as-

pirin. Three comparison groups were defined: trials that compared OA with control, trials that compared OA with aspirin, and trials in which the combination of OA and aspirin were compared with aspirin. Within each comparison group, strata were defined by level of intensity (high, moderate, and low) and compared for the outcome of death, MI, and bleeding. Overall, no significant heterogeneity was observed consistently across outcomes (TABLE 9).

COMMENT

Based on this meta-analysis of randomized trials that includes data from more than 21 319 patients, clear reductions in total mortality, MI, and stroke occur among CAD patients treated with OA at high intensity (INR, 2.8-4.8). Although a significant increase in major bleeding is also observed with high-intensity OA therapy, the benefits clearly outweigh the risks. By contrast, low-intensity OA (INR, <2.0) in the presence of aspirin is not beneficial, but increases bleeding. In a relatively smaller number of patients, we analyzed 3 categories of patients, moderate OA vs control, moderate to high OA vs aspirin, and moderate to high OA and aspirin vs aspirin alone. Moderate-intensity OAs are more effective than control in reducing recurrent ischemic events, moderate to high OA appear to be as effective but not superior to aspirin (although small [10% to 15%] but important differences between the therapies cannot be excluded), and some additional benefit appears to be gained when aspirin is added to moderate to high OA compared with aspirin alone. However, the CIs are wide and this hypothesis requires confirmation from other trials, many of which are ongoing.

The trials included in this systematic overview span a period of almost 40 years. Despite the variable practice of OA, and monitoring, our analysis of major vascular outcomes indicates the consistency of these results over time. In the early high-intensity trials, aspirin was not used. Aspirin has been clearly shown to reduce the vascular events (MI, stroke, vascular death) by about 25% to 30%, total mortality by 16%, vascular death by 18%, nonfatal reinfarction by 34%, and nonfatal stroke by 28%.[17] The point estimates for the same outcomes when comparing OA with control appear to be generally larger. However, indirect comparisons can be misleading. By contrast, the direct comparison trials of OA with aspirin are too small to reliably detect a 15% to 20% difference between OA and aspirin. Therefore, the currently available data do not provide reliable information on the relative benefits of OA and aspirin. A more relevant question is the combined impact of OA and as-

Table 5. Results of Prolonged Oral Anticoagulant (OA) Therapy Compared With Control in High-, Moderate-, and Low-Intensity Trials on the Combined Outcome of Death, Myocardial Infarction, or Stroke*

Source, y	Level of Intensity	No./Total (%) of Subjects Allocated to OA Therapy	No./Total (%) of Subjects Allocated to Control Therapy	*P* Value
High-Intensity OA vs Control†				
Borchegrevink,[32] 1960	High	1/103 (1.0)	9/100 (9.0)	.008
Harvald et al,[34] 1961	High	64/145 (44.1)	78/171 (45.6)	.76
Apenstrom and Korsan-Bengtsen,[35] 1964	High	46/118 (39.0)	71/113 (62.8)	.001
Conrad et al,[36] 1964	High	14/52 (26.9)	9/34 (26.5)	.96
Loeliger et al,[37] 1967	High	10/128 (7.8)	23/112 (20.5)	.01
Lovell et al,[38] 1967	High	39/178 (21.9)	46/172 (26.7)	.49
Seaman et al,[39] 1969	High	68/88 (77.3)	46/87 (52.9)	.09
Sorensen et al,[40] 1969	High	33/156 (21.2)	49/120 (40.8)	.13
Sixty Plus Reinfarction,[41] 1980	High	75/439 (17.1)	158/439 (36.0)	<.001
WARIS,[5] 1990	High	146/607 (24.1)	225/607 (37.1)	<.001
ASPECT,[6] 1994	High	286/1700 (16.8)	445/1704 (26.1)	<.001
Meuwissen et al,[42] 1969	High	6/68 (8.8)	8/70 (11.4)	.61
Breddin et al,[44] 1980	High	45/320 (14.1)	47/309 (15.2)	.68
Total		**833/4102** (20.3)	**1214/4038** (30.1)	<.001
High- and Moderate-Intensity OA vs Aspirin‡				
Breddin et al,[44] 1980	High	45/320 (14.1)	38/317 (12.0)	.44
ATACS-Pilot,[46] 1990	High	4/24 (16.7)	5/32 (15.6)	.08
McEnany et al,[47] 1982	Moderate	2/68 (2.9)	1/71 (1.4)	.54
EPSIM,[7] 1982	Moderate	10/128 (7.8)	23/112 (20.5)	.56
Total		**61/540** (11.3)	**67/532** (12.6)	.78
Moderate-Intensity OA vs Control§				
COOP,[48] 1969	Moderate	153/385 (39.7)	149/350 (42.6)	.44
Williams et al,[50] 1986	Moderate	3/51 (5.9)	7/51 (13.7)	.19
McEnany et al,[47] 1982	Moderate	2/68 (2.9)	5/77 (6.5)	.32
Total		**158/504** (31.3)	**161/478** (33.7)	.22
High- or Moderate-Intensity OA and Aspirin vs Aspirin‖				
ATACS,[46] 1990	High	0/37 (0)	1/32 (3.1)	.03
OASIS Pilot 2,[51] 1998	Moderate	5/98 (5.1)	13/99 (13.1)	.05
ATACS-Main,[52] 1994	Moderate	8/105 (7.6)	12/109 (11.0)	.40
Total		**13/240** (5.4)	**26/240** (10.8)	.01
Low-Intensity OA and Aspirin vs Aspirin¶				
OASIS Pilot 1,[51] 1998	Low	10/155 (6.5)	5/154 (3.2)	.19
Post CABG,[9] 1997	Low	68/674 (10.1)	94/677 (13.9)	.03
CARS,[8] 1997	Low	295/3382 (8.7)	308/3393 (9.1)	.61
Total		**373/4211** (8.9)	**407/4224** (9.6)	.22

*For expansion of study names, see the first footnote to Table 2. CI indicates confidence interval; OR, odds ratio.
†Pooled OR, 0.57 (95% CI, 0.51-0.63); *P*<.001. Events prevented/1000 patients treated = 98.
‡Pooled OR, 1.04 (95% CI, 0.80-1.34); *P*>.10. Events prevented/1000 patients treated = 13.
§Pooled OR, 0.84 (95% CI, 0.80-1.34); *P*>.10. Events prevented/1000 patients treated = 24.
‖Pooled OR, 0.44 (95% CI, 0.23-0.83); *P* = .01. Events prevented/1000 patients treated = 54.
¶Pooled OR, 0.91 (95% CI, 0.79-1.06); *P*>.10. Events prevented/1000 patients treated = 7.

pirin compared with aspirin alone in high-risk patients, as aspirin by itself is only of modest efficacy. Other antiplatelet agents or their combinations are also being evaluated in patients with CAD. Trials of new glycoprotein IIb/IIIa antiplatelet agents have not been demonstrated to be superior to aspirin during long-term treatment,[53] whereas long-term use of clopidogrel (a thienopyridine compound) in patients with established vascular disease was associated with an 8.7% risk reduction in recurrent cardiovascular events when compared with aspirin.[54] In addition, the combination of a thienopyridine (eg, ticlopidine and clopidogrel) and aspirin also appears to confer an additional benefit over aspirin alone in patients with coronary stents, and large trials testing the efficacy and safety profile of this combination in patients with prior cardiovascular disease are under way.

No benefit was observed in the large trials testing low-intensity OA and aspirin compared with aspirin, but major bleeding events increased. This result may seems at odds with the recent results of the Thrombosis Prevention Trial in which low-intensity OA and aspirin were evaluated in the primary prevention setting and resulted in a significant reduction in coronary death and MI.[55] In this trial, 1268 patients were randomized to OA alone, 1268 to aspirin alone, 1277 to OA and aspirin, and 1272 to placebo. The mean INR in the OA group was 1.47 with an average dose of 4 mg/day. The combined treatment of OA and aspirin was found to be significantly more effective than placebo, and a modest but nonsignificant 15.5% risk reduction compared with aspirin was observed. In the Post-Coronary Artery Bypass Graft trial,[9] the risk reduction with OA and aspirin compared with aspirin was modest and nonsignificant (11%), and a similar dosing schedule and mean INR of 1.4 was obtained. However, in the CARS trial,[8] unlike the other 2, a fixed-dose regimen (3 mg/day) was used and a target INR intensity was not chosen. The mean INR was 1.19 and only a 3.1% risk reduction (P = NS), in favor of OA (3 mg) and aspirin vs aspirin alone was observed. Therefore, although it is clear that low-intensity OA with INR values of less than 1.5 are not effective in preventing ischemic events, the possibility remains of a beneficial effect of low-intensity OA (INR, 1.5-2.0) used together with aspirin, and this question requires further evaluation.

In contrast to the low-intensity strata, several small trials in which moderate-intensity OA and aspirin in patients with unstable angina or non-Q wave MI have suggested a moderate benefit[51,53] when compared with aspirin alone. As well, there is evidence to support the efficacy of moderate intensity OA and aspirin compared with aspirin alone in patients with atrial fibrillation,[56] and with mechanical valves.[57] The additional benefit of moderate OA when added to aspirin in these trials is supportive of an independent mechanism of benefit of combined antiplatelet and antithrombotic treatment, but this requires confirmation. Ongoing trials include WARIS-2, ASPECT-2, and CHAMP, which are evaluating the efficacy of moderate-intensity OA (INR, 2-3) and aspirin compared with aspirin alone in patients following unstable angina or MI.

The risk of bleeding with OA is directly related to the intensity of anticoagulation, clinical factors, the duration of therapy, and the concomitant use of antiplatelet therapies.[13] In our analysis we observed an increase in the absolute rate of major bleeding with an increase in INR intensity (FIGURE 3). No significant heterogeneity was identified in a formal comparison of ORs across intensity strata. The highest rate of bleeding was observed in the high-intensity stratum, in which the monitoring of anticoagulation was highly variable across studies, and the duration of treatment was significantly longer than in most modern trials. In both the low-intensity and moderate-intensity strata, OAs were used in combination with aspirin, however despite this, a graded increase in bleeding by INR intensity was observed. This suggests that in patients taking OAs, the more important predictor of bleeding is the INR and not whether aspirin was used concomitantly. However, at each intensity the rates of major bleeding with OA were significantly higher than in the comparison group (no OA or aspirin alone), and this is a justifiable con-

Table 6. Results of Prolonged Oral Anticoagulant (OA) Therapy Compared With Control in High-Intensity Trials on Total Bleeds*

Source, y	Level of Intensity	No./Total (%) of Subjects Allocated to OA Therapy	No./Total (%) of Subjects Allocated to Control Therapy	*P* Value
High-Intensity OA vs Control†				
MacMillan et al,[14] 1960	High	8/27 (29.6)	1/23 (4.3)	.02
Borchegrevink,[32] 1960	High	10/103 (9.7)	1/100 (1.0)	.01
Clausen et al,[33] 1960	High	59/93 (63.4)	15/99 (15.2)	<.001
Harvald et al,[34] 1961	High	86/145 (59.3)	9/171 (5.3)	<.001
Apenstrom and Korsan-Bengtsen,[35] 1964	High	56/118 (47.5)	17/113 (15.0)	<.001
Conrad et al,[36] 1964	High	23/52 (44.2)	0/34 (0)	<.001
Wasserman et al,[15] 1966	High	13/77 (16.9)	6/70 (8.6)	.13
Loeliger et al,[37] 1967	High	17/128 (13.3)	7/112 (6.3)	.04
Lovell et al,[38] 1967	High	48/178 (27.0)	0/172 (0)	<.001
Seaman et al,[39] 1969	High	59/88 (67.0)	44/87 (50.6)	.80
Sorensen et al,[40] 1969	High	47/156 (30.1)	2/120 (1.7)	<.001
Meuwissen et al,[42] 1969	High	8/68 (11.8)	0/70 (0)	.003
WARIS,[5] 1990	High	52/607 (8.6)	25/607 (4.1)	.001
Drapkin and Merskey,[20,43] 1974 and 1972	High	96/745 (12.9)	42/782 (5.4)	<.001
Breddin et al,[44] 1980	High	12/320 (3.8)	0/309 (0)	<.001
Total		**594/2905** (20.4)	**169/2869** (5.9)	<.001

*WARIS indicates Warfarin Re-infarction Study.
†Pooled odds ratio, 4.7 (95% confidence interval, 4.0-5.6); P<.001.

cern when considering using OA and aspirin (TABLE 10).

Among patients with CAD, high-intensity (INR, 2.8-4.8) OAs are effective in reducing death, MI, and stroke, but are associated with a significant risk of bleeding. When compared with control, moderate-intensity OA (INR, 2-3) are effective in reducing MI, and stroke, but a significant increase in bleeding remains. When compared with aspirin, moderate- to high-intensity OAs appear equivalent, but the CIs are wide and are consistent with a moderate but clinically important difference. In the presence of aspirin, low-intensity OAs (INR<2.0) are not superior to aspirin alone, while moderate- to high-intensity OAs (INR, 2-3) and aspirin appear promising, but further trials are needed.

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Table 7. Comparisons of Results of Prolonged Oral Anticoagulant (OA) Therapy Compared With Control in High-, Moderate- and Low-Intensity Trials on Major Bleeding*

Source, y	Level of Intensity	No./Total (%) of Subjets Allocated to OA Therapy	No./Total (%) of Subjects Allocated to Control Therapy	*P* Value
High-Intensity OA vs Control†				
Borchegrevink ,[32] 1960	High	1/103 (1.0)	0/100 (0)	.32
Clausen et al,[33] 1961	High	8/93 (8.6)	0/99 (0)	.003
Harvald et al,[34] 1961	High	26/145 (17.9)	0/171 (0)	<.001
Apenstrom and Korsan-Bengtsen,[35] 1964	High	6/118 (5.1)	6/113 (5.3)	<.001
Loeliger et al,[37] 1967	High	1/128 (0.8)	1/112 (0.9)	.97
Lovell et al,[38] 1967	High	11/178 (6.2)	0/172 (0)	.003
Sorensen et al,[40] 1969	High	12/156 (7.7)	0/120 (0)	.002
Breddin et al,[44] 1980	High	12/320 (3.8)	0/309 (0)	<.001
Sixty Plus Reinfarction,[41] 1980	High	27/439 (6.2)	3/439 (0.7)	<.001
WARIS,[5] 1990	High	8/607 (1.3)	0/607 (0)	.005
ASPECT,[6] 1994	High	73/1700 (4.3)	19/1704 (1.1)	<.001
Total		**185/3987** (4.6)	**29/3946** (0.7)	<.001
High- or Moderate-Intensity OA vs Aspirin‡				
Breddin et al,[44] 1980	High	12/320 (3.8)	16/317 (5.0)	<.001
CABADAS,[45] 1993	High	25/307 (8.1)	16/309 (5.2)	.14
Eritsland et al,[11] 1996	High	3/319 (0.9)	5/291 (1.7)	.40
ATACS,[46] 1990	High	2/24 (8.3)	3/32 (9.4)	.89
Kraska et al,[10] 1981	Moderate	4/60 (6.7)	0/60 (0)	.04
EPSIM,[7] 1982	Moderate	21/652 (3.2)	5/651 (0.8)	.002
McEnany MT et al,[47] 1982	Moderate	3/68 (4.4)	0/71 (0)	.07
Total		**70/1750** (3.7)	**45/1731** (1.0)	<.001
Moderate-Intensity OA vs Control§				
COOP,[48] 1969	Moderate	4/385 (1.0)	0/350 (0)	.05
MRC Anticoagulant,[49] 1964	Moderate	16/195 (8.2)	0/188 (0)	<.001
McEnany et al,[47] 1982	Moderate	3/68 (4.4)	0/77 (0)	.06
Total		**23/648** (3.5)	**0/615** (0)	<.001
High- or Moderate-Intensity OA and Aspirin vs Aspirin‖				
ATACS,[46] 1990	High	3/37 (8.1)	3/32 (9.4)	.85
OASIS Pilot 2,[51] 1998	Moderate	2/98 (2.0)	1/99 (1.0)	.55
ATACS-Main,[52] 1994	Moderate	3/105 (2.9)	0/109 (0)	.07
Total		**8/240** (3.3)	**4/240** (1.7)	.28
Low-Intensity OA and Aspirin vs Aspirin¶				
OASIS Pilot 1,[51] 1998	Low	2/155 (1.3)	1/154 (0.6)	.05
Post-CABG,[9] 1997	Low	20/674 (3.0)	20/677 (3.0)	.99
CARS,[8] 1997	Low	75/3382 (2.2)	57/3393 (1.7)	.11
Total		**97/4211** (2.3)	**78/4224** (1.8)	**.09**

*For expansion of study names, see the first footnote to Table 2.
†Pooled OR, 6.0 (95% confidence interval [CI], 4.4-8.2); *P*<.001.
‡Pooled OR, 2.4 (95% CI, 1.6-3.6); *P*<.001.
§Pooled OR, 7.7 (95% CI, 3.3-17.6); *P*<.001.
‖Pooled OR, 1.88 (95% CI, 0.59-6.00); *P*>.10.
¶Pooled OR, 1.29 (95% CI, 0.96-1.75); *P* = .09.

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Table 8. Results of Prolonged Oral Anticoagulant (OA) Therapy Compared With Control in High-, Moderate-, and Low-Intensity Trials on Stroke*

Source, y	Level of Intensity	No./Total (%) of Subjects Allocated to OA Therapy	No./Total (%) of Subjects Allocated to Control Therapy	*P* Value
High-Intensity OA vs Control†				
Apenstrom and Korsan-Bengtsen,[35] 1964	High	6/118 (5.1)	2/113 (1.8)	.17
Loeliger et al,[37]1967	High	0/128 (0)	2/112 (1.8)	.15
Lovell et al,[38] 1967	High	2/178 (1.1)	7/172 (4.1)	.10
Sorensen et al,[40] 1969	High	2/156 (1.3)	6/120 (5.0)	.07
Sixty Plus Reinfarction,[41] 1980	High	13/439 (3.0)	21/439 (4.8)	.01
WARIS,[55] 1990	High	20/607 (3.3)	44/607 (7.2)	.02
ASPECT,[6] 1994	High	37/1700 (2.2)	62/1704 (3.6)	.03
Drapkin and Merskey,[20,43] 1974 and 1972	High	13/745 (1.7)	18/782 (2.3)	.08
Breddin et al,[44] 1980	High	1/320 (0.3)	2/309 (0.6)	.54
Total		**94/4391** (2.1)	**164/4358** (3.8)	.002
High- and Moderate-Intensity OA vs Aspirin‡				
CABADAS,[45] 1993	High	3/307 (1.0)	1/309 (0.3)	.31
Breddin et al,[44] 1980	High	1/320 (0.3)	2/309 (0.6)	.32
McEnany et al,[47] 1982	Moderate	1/68 (1.5)	0/71 (0)	.31
EPSIM,[7] 1982	Moderate	5/652 (0.8)	3/651 (0.5)	.48
Total		**10/1347** (0.7)	**6/1340** (0.4)	.46
Moderate-Intensity OA vs Control§				
COOP,[48] 1969	Moderate	15/385 (3.9)	27/350 (7.7)	.03
MRC Anticoagulant,[49] 1964	Moderate	2/195 (1.0)	8/188 (4.3)	.05
McEnany et al,[47] 1982	Moderate	1/68 (1.5)	0/77 (0)	.29
Total		**18/648** (2.8)	**35/615** (5.7)	.03
Moderate-Intensity OA and Aspirin vs Aspirin‖				
OASIS Pilot 2,[51] 1998	Moderate	0/98 (0)	2/99 (2.0)	.16
ATACS-Main,[52] 1994	Moderate	0/105 (0)	1/109 (0.9)	.33
Total		**0/203** (0)	**3/208** (1.4)	.09
Low-Intensity OA and Aspirin vs Aspirin¶				
Post-CABG,[9] 1997	Low	10/674 (1.5)	20/677 (3.0)	.07
CARS,[8] 1997	Low	31/3382 (0.9)	21/3393 (0.6)	.16
Total		**41/4056** (1.0)	**41/4070** (1.0)	.99
High-Intensity OA vs Control (Hemorrhagic Stroke)#				
Sixty Plus Reinfarction,[41] 1980	High	7/439 (1.6)	1/439 (0.2)	.03
WARIS,[5] 1990	High	5/607 (0.8)	0/607 (0)	.02
ASPECT,[6] 1994	High	17/1700 (1.0)	2/1704 (0.1)	.001
Total		**29/2746** (1.1)	**3/2750** (0.1)	0
High-Intensity OA vs Control (Nonhemorrhagic Stroke)**				
Sixty Plus Reinfarction,[41] 1980	High	6/439 (1.4)	20/439 (4.6)	.005
WARIS,[5] 1990	High	15/607 (2.5)	44/607 (7.2)	0
ASPECT,[6] 1994	High	20/1700 (1.2)	60/1704 (3.5)	0
Total		**41/2746** (1.5)	**124/2750** (4.5)	0
High-Intensity OA vs Control (Overall Stroke)††				
Sixty Plus Reinfarction,[41] 1980	High	13/439 (3.0)	21/439 (4.8)	.16
WARIS,[5] 1990	High	20/607 (3.3)	44/607 (7.2)	.003
ASPECT,[6] 1994	High	37/1700 (2.2)	62/1704 (3.6)	.009
Total		**70/2746** (2.5)	**127/2750** (4.6)	0

*For expansion of study names, see the first footnote to Table 2. CI indicates confidence interval; OR, odds ratio.
†Pooled OR, 0.52 (95% CI, 0.40-0.68); *P* = .002. Events prevented/1000 patients treated = 17.
‡Pooled OR, 2.37 (95% CI, 0.83-6.78); *P*>.10. Events prevented/1000 patients treated = –3.
§Pooled OR, 0.47 (95% CI, 0.27-0.81); *P* = .02. Events prevented/1000 patients treated = 29.
‖Pooled OR, 0.14 (95% CI, 0.01-1.32); *P* = .08.
¶Pooled OR, 1.00 (95% CI, 0.65-1.55); *P*>.10.
#Pooled OR, 5.13 (95% CI, 2.6-10.3); *P*<.001.
**Pooled OR, 0.35 (95% CI, 0.26-0.48); *P*<.001.
††Pooled OR, 0.54 (95% CI, 0.41-0.72); *P*<.001.

Figure 2. Rates of Major Cardiovascular Outcomes by Oral Anticoagulant Intensity and Aspirin Use

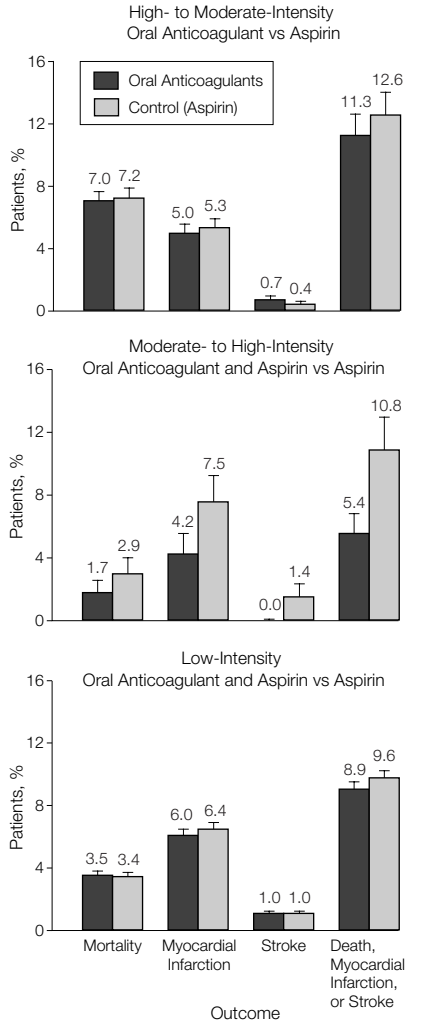

Table 9. Summary of Results With the Analysis Stratified by Oral Anticoagulant (OA) Intensity and Aspirin Use*

Outcome	Level of OA Intensity	OA vs Control	Level of Intensity	OA vs Aspirin	Level of Intensity	OA and Aspirin vs Aspirin
Death	High	0.78 (0.69-0.87)	High	1.05 (0.68-1.61)	Moderate	0.74 (0.23-2.33)
	Moderate	0.82 (0.23-2.33)	Moderate	1.03 (0.73-1.44)	Low	1.03 (0.82-1.30)
Myocardial infarction	High	0.58 (0.52-0.66)	High	0.97 (0.62-1.53)	Moderate	0.55 (0.26-1.19)
	Moderate	0.48 (0.36-0.63)	Moderate	0.79 (0.48-1.31)	Low	0.93 (0.66-1.30)
Major bleeding	High	6.0 (4.4-8.2)	High	5.37 (2.34-12.3)	Moderate	1.88 (0.59-6.00)
	Moderate	7.7 (3.3-17.6)	Moderate	3.43 (1.8-6.5)	Low	1.29 (0.96-1.75)

*All values are expressed as odds ratio (95% confidence interval). No significant differences exist for the high and moderate, or moderate- and low-intensity groups.

Figure 3. Major Bleeding Rates in Patients With Vascular Disease

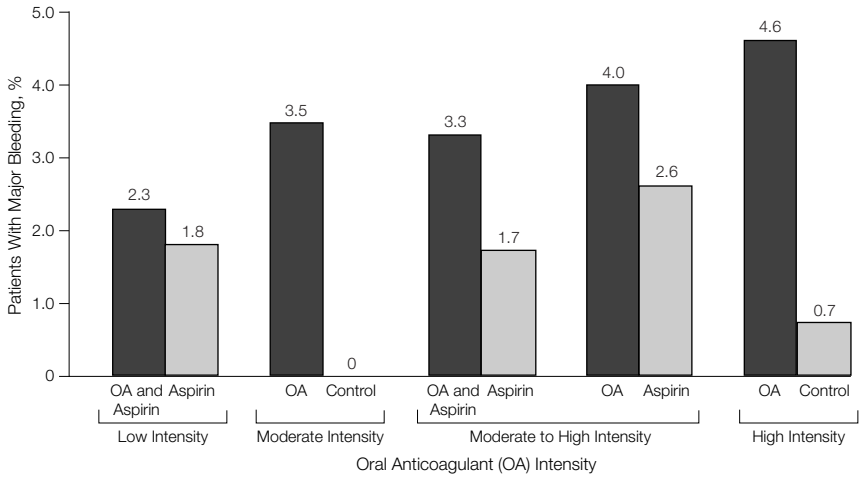

Table 10. Risk-Benefit per Thousand Patients Treated With Oral Anticoagulant (OA) Intensity*

	Events Prevented per 1000 Patients Treated (95% Confidence Interval)	Major Bleeds Caused per 1000 Patients Treated (95% Confidence Interval)
High-intensity OA vs control	98 (73-123)	39 (35-43)
Moderate-intensity OA vs control	24 (22-26)	35 (21-49)
Moderate- to high-intensity OA and aspirin vs aspirin	54 (43-65)	16 (10-22)
Moderate- to high-intensity OA vs aspirin	13 (11-14)	14 (12-16)
Low-intensity OA and aspirin vs aspirin	7 (6-8)	5 (4-6)

*Combination of death, myocardial infarction, or stroke.

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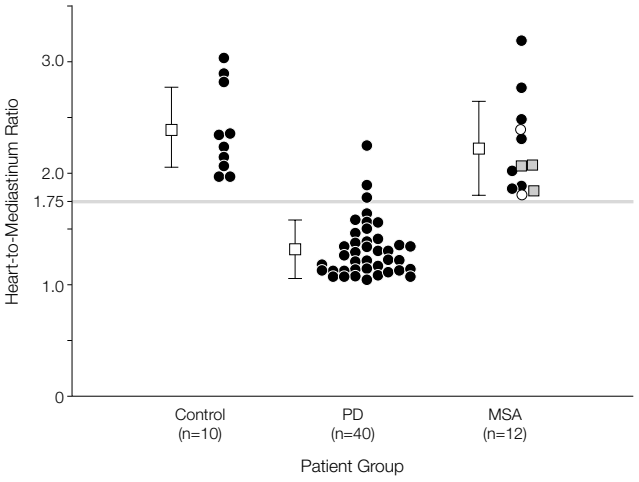
Figure. Scintigraphic Differentiation of Parkinson Disease and Multiple System Atrophy by Cardiac Iodine-123 Metaiodobenzylguanidine Accumulation



Uptake of iodine-123 metaiodobenzylguanidine (I-123 MIBG) was semiquantitatively evaluated by heart-to-mediastinum (H-M) ratios. Each circle or square shows H-M ratios of each patient or control subject. In the multiple-system atrophy (MSA) group, closed circles represent olivopontocerebellar atrophy, open circles represent striatonigral degeneration, and closed squares represent Shy-Drager syndrome. Open squares and bars represent means (SDs) of each group. Differences of H/M ratios between control vs Parkinson disease (PD) and PD vs MSA were both statistically significant. Gray line marks H/M 1.75 ratio used to discriminate between PD and MSA. As a result, patients with PD were scintigraphically differentiated from MSA patients with high sensitivity and specificity.

Comment. These results suggest that the underlying mechanism causing autonomic disorders may differ pathophysiologically between PD and MSA. In the present study, diagnosis of PD and MSA was based on clinical features and not on pathological findings. Therefore, the final diagnosis may be different when a postmortem study is performed. However, cardiac I-123 MIBG accumulation may be a useful marker in differentiating PD from MSA.

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CORRECTION

Tables and Figures Errors: In the Review entitled "Oral Anticoagulant Therapy in Patients With Coronary Artery Disease: A Meta-analysis" published in the December 1, 1999, issue of THE JOURNAL (1999;282:2058-2067), there were errors in the figures and tables. On page 2060, Table 2, under "High-Intensity OA vs Control," MacMillan et al, the value for "No./Total (%) of Subjects Allocated to Control Therapy" should have been 0/23 (0); under "High- or Moderate-Intensity OA vs Aspirin," the total value for "No./Total (%) of Subjects Allocated to OA Therapy" should have been 121/1750 (6.9) and the *P* value for Kraska et al should have been .54; under "High- or Moderate-Intensity OA and Aspirin vs Aspirin," ATACS, the value for "No./Total (%) of Subjects Allocated to Control Therapy" should have been 1/32 (3.1) and the total line for this column should have been 8/240 (3.3); and the events prevented/1000 patients treated in the double dagger footnote should have been 3 and the events prevented/1000 patients treated in the parallel footnote should have been 16. On page 2061, Table 3, the *P* values that were zeros should have been <.001; under "High-Intensity OA vs Control," for "No./Total (%) of Subjects Allocated to OA Therapy," the total value should have been 517/4967 (10.4); and the events prevented/1000 patients treated in the dagger footnote should have been 60. On page 2062, Figure 1, under "High-Intensity Oral Anticoagulant vs Control (No Aspirin)," the oral anticoagulant bar value for "Myocardial Infarction" should have been 10.4. On page 2063, Table 5, under "High-Intensity OA vs Control," the *P* value for Seaman et al should have been .001; under "High- and Moderate-Intensity OA vs Aspirin," EPSIM, the "No./Total (%) of Subjects Allocated to OA Therapy" should have been 84/652 (12.9), the "No./Total (%) of Subjects Allocated to Control Therapy" should have been 91/651 (14.0), and the total line should have been 135/1064 (12.7), 135/1071 (12.6), .78; and the events prevented/1000 patients treated in the double daggar footnote should have been –1. On page 2064, Table 6, the *P* value for Seaman et al should have been .03. On page 2065, Table 7, under "High-Intensity OA vs Control," the *P* value for Apenstrom and Korsan-Bengtsen should have been .94; under "High- or Moderate-Intensity OA vs Aspirin," the *P* value for Breddin et al should have been .43, and the total line should have been 70/1750 (4.0), 45/1731 (2.6), <.001; and under "Low-Intensity OA and Aspirin vs Aspirin," OASIS Pilot I, the "No./Total (%) of Subjects Allocated to OA Therapy" should have been 4/155 (2.3), the "No./Total (%) of Subjects Allocated to Control Therapy" should have been 0/154 (0), and the total line should have been 99/4211 (2.3), 77/4244 (1.8), .09. On page 2066, Table 8, the *P* values that were zeros should have been <.001 and under "High-Intensity OA vs Control," the *P* value for Drapkin and Merskey should have been .44. In Figure 2, under "High- to Moderate-Intensity Oral Anticoagulant vs Aspirin," the oral anticoagulant bar value for "Mortality" should have been 6.9 and for "Death, Myocardial Infarction, or Stroke" the oral anticoagulant bar value should have been 12.7; and under "Moderate- to High-Intensity Oral Anticoagulant and Aspirin vs Aspirin," the control bar value for "Mortality" should have been 3.3. These corrections do not change the study conclusions.