Oral Anticoagulant Therapy in Patients with Coronary Artery Disease

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ABSTRACT

Oral anticoagulation (OA) has been used to treat patients with coronary artery disease (CAD) for more than 40 years and has been a subject of intense controversy since that time. Seven to 10% of patients with acute myocardial infarction (MI) develop recurrent MI, stroke, or death in the 6 weeks following the index event and approximately 20% after 4 years, despite optimal background therapy with aspirin. Recent large studies and systematic reviews have greatly clarified the role of OA in the modern era. On the weight of the evidence, which is reviewed in detail in this article, long-term, moderate-intensity OA (International Normalized Ratio 2.0 to 3.0) should be considered an option for the prevention of recurrent CAD, particularly in high-risk patients.

KEYWORDS: Oral anticoagulants, coronary artery disease, prevention

Educational Objectives: On completion of this article, the reader should have an understanding of (1) the rationale for using oral anticoagulants in patients with coronary artery disease (CAD), (2) the risks and benefits of different intensity levels of oral anticoagulation for CAD, and (3) clinical situations in which oral anticoagulants for patients with CAD should be considered.

BACKGROUND

Oral anticoagulation (OA) has been used to treat patients with coronary artery disease (CAD) for more than 40 years, and its use has been the subject of intense controversy since that time.[1] One reason for the continuing debate is the inconsistent results of multiple clinical trials that have evaluated the efficacy and safety of varying intensities of OA, with or without concomitant antiplatelet therapy, for the secondary prevention of CAD. A number of recent, large, clinical trials have clarified the role of OA in the modern era.[1–7]

The impetus to study OA and other long-term antithrombotic therapies is provided by the natural history of CAD and the acute coronary syndromes (ACSs) in particular. On average, 7 to 10% of patients with acute myocardial infarction (MI) will develop recurrent ischemic events or death in the 6 weeks following the index event, despite optimal background therapy.[8] Long-term recurrence rates also remain high; in one large, controlled trial, 20% of aspirin-treated patients suffered death, recurrent MI, or stroke over a 4-year period.[4] It is well known that a highly thrombogenic milieu may persist in patients for up to 6 months following an MI.[9–11] Increased levels of circulating active thrombin are apparent following ACS, which may cause persistent platelet stimulation, formation of soluble fibrin products that polymerize to form blood clots, and activation of coagulation factors V, VIII, and XIII.[12]

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Aspirin is the most well-studied antiplatelet agent for the prevention of vascular disease in a wide range of settings.[13] A recently updated overview of randomized controlled trials of antiplatelet agents (mostly aspirin) reported absolute reductions in the risk of serious vascular event of 3.6% among patients with a previous MI and 3.8% among patients in the 1st month following acute MI.[14] Despite its proven efficacy and safety, many patients with CAD suffer recurrent ischemic events while taking aspirin. This has prompted the study of a number of additional strategies to inhibit platelet activation and prevent thrombus formation.[15,16]

Oral anticoagulants, well established for the thromboprophylaxis and treatment of deep vein thrombosis, pulmonary embolism, mechanical heart valves, and atrial fibrillation, represent one such strategy.[17] Warfarin (coumadin) is the most frequently used oral anticoagulant. OAs exert their anticoagulant actions as vitamin K antagonists. The reduced form of vitamin K (vitamin KH_2) is required as a cofactor for the gamma-carboxylation of glutamic acid residues in clotting factors II, VII, IX, and X. OAs block the reductase enzymes that are required to recycle vitamin K epoxide to vitamin KH_2 after the gamma-carboxylation reaction, thereby depleting active vitamin K. OAs such as warfarin have a relatively narrow therapeutic index and in clinical practice are monitored by the use of the International Normalized Ratio (INR). The INR has largely replaced the prothrombin time (PT) as the standard measure of intensity of OA with warfarin. The INR's main advantage over the PT is that it enables standardization of the latter between different laboratories.

Two of the authors (SSA and SY) previously reported a meta-analysis of all randomized trials published up to the year 1999 studying the use of OA of varying intensities, with or without the coadministration of aspirin, in patients with CAD.[1] This review demonstrated that high-intensity anticoagulation (INR > 2.8) clearly reduced cardiovascular (CV) events (albeit at the expense of an increase in major bleeding episodes), whereas low-intensity anticoagulation (INR < 2.0) did not.

Few large studies up to that point, however, had examined the strategy of moderate-intensity anticoagulation (INR 2.0 to 3.0) for the prevention of recurrent ischemic events, an approach that may maintain the efficacy of high-intensity OA while minimizing the risk of major bleeding. In the past several years, a number of completed trials have addressed the role of moderate-intensity anticoagulation in patients with CAD.[2–7] Together with the original meta-analysis, a total of 37 trials involving 35,906 patients have now been studied. Some of these trials used OA together with aspirin, whereas others did not. The purpose of this article is to examine the aggregate data on the efficacy and safety of various intensities of OA, with or without aspirin therapy, and provide clinical recommendations on the use of OA in patients with CAD.

RECENT TRIALS

Since the original meta-analysis, 6 additional trials involving 14,587 patients have been completed.[2–7] Three of these trials compared three treatments: moderate-intensity OA plus aspirin, moderate to high-intensity OA alone, and aspirin alone.[4–6] Three trials compared moderate-intensity OA and aspirin to aspirin alone.[2,3,7] The characteristics of these six recent trials are found in Table 1 and their results are summarized subsequently.

Table 1 Characteristics of Recent Trials

Trial	Population	Randomized Comparisons	Sample Size (*n*)	Achieved INR	Compliance (Final, %)	Duration of Study
ASPECT-II[7]	ACS	OA (2–2.5) + A (80 mg)	332	2.4	77	26 months
		OA (3–4.0)	325	3.2	80	
		A (80 mg)	336		87	
BAAS[6]	Angioplasty	OA (2.1–4.8) + A (100 mg)	530	3.0	NA	12 months
		A (100 mg)	528			
CHAMP[3]	AMI	OA (1.5–2.5) + A (81 mg)	2522	1.8	71	2.7 years
		A (162 mg)	2537			
Huynh et al.[5]	ACS prior CABG	OA (2–2.5) + (80 mg)	44	NA	86	12 months
		OA (2–2.5)	45			
		A (80 mg)	46			
OASIS[2]	ACS	OA (2–2.5) + A (325 mg)	1848	2.1	64	5 months
		A (325 mg)	1864			
WARIS-II[4]	AMI	OA (1.5–2.5) + A (75 mg)	1208	2.2	NA	4 years
		OA (2.8–4.8)	1216	2.8		
		A (160 mg)	1206			

Values represent means, unless otherwise specified. ACS: acute coronary syndromes, AMI: acute myocardial infarction, A: aspirin, CABG: coronary artery bypass graft, INR: International Normalization Ratio, NA: not available, OA: oral anticoagulants.

Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis II

Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis II (ASPECT-II) was a multicenter, open trial involving 53 sites randomizing 993 patients who suffered an ACS, defined as an MI or episode of unstable angina within the preceding 8 weeks.[7] Patients were randomly assigned within 8 weeks of hospital discharge to receive combined moderate-intensity OA targeting an INR of 2.0 to 2.5 and low-dose aspirin (80 mg/day, n = 333), high-intensity OA targeting an INR of 3.0 to 4.0 (n = 330), or low-dose aspirin alone (80 mg/day, n = 336). Patients were followed for a maximum of 26 months (median of 12 months).

The primary outcome was the first occurrence of MI, stroke, or death. A significant 50% risk reduction was observed when the combination of moderate-intensity OA and aspirin was compared with aspirin alone (4.8 vs. 9.2%, $p < 0.05$). Moreover, a significant 45% risk reduction was observed when high-intensity OA was compared with aspirin alone (5.2 vs. 9.2%, $p < 0.05$). Although the composite outcome was lower in the combination group compared with high-intensity OA alone, this difference was not significant. A trend for more major bleeding occurred among patients taking the combination of OA and aspirin (2.1%) than aspirin or OA alone (0.9% for each of the latter, p = 0.2 for difference). Therefore, from this trial, in patients who were hospitalized with ACS, either combined aspirin and oral anticoagulants at moderate-intensity (INR 2.0 to 2.5) or high-intensity OA (INR 3.0 to 3.5) are more effective than aspirin alone in reducing subsequent CV events.

Balloon Angioplasty and Anticoagulation Study

A total of 1058 patients were randomized in the Balloon Angioplasty and Anticoagulation Study (BAAS).[6] Five hundred thirty patients were randomly assigned to coumadin (INR = 2.1 to 4.8) plus aspirin (100 mg/day) and 528 patients were randomized to receive aspirin alone (100 mg/day). Patients were treated with coumadin (median of 6 days before percutaneous coronary intervention) and aspirin prior to the angioplasty; anticoagulation was continued through the procedure. The mean INR prior to the angioplasty was 2.7 ± 1.1 and during follow-up was 3.0 ±1.1.

At 30 days the composite end point of death, MI, target revascularization, and stroke occurred in 3.4% patients treated with coumadin plus aspirin compared with 6.4% of patients treated with aspirin alone, which is associated with a relative risk (RR) reduction of 47% (95% confidence interval, CI: 8 to 70%, p = 0.04). At 1 year, the event rate was 14.3% in the combination group versus 20.3% in the aspirin-alone group for a RR reduction of 29% (95% CI: 7 to 46%). The incidence of major bleeding during the index hospitalization was 3.2% in the combination group versus 1.0% in the aspirin-alone group. Therefore, in this study, coumadin in addition to aspirin started before the angioplasty and continued for at least 6 months appears to be more effective than aspirin alone in the prevention of acute and late complications after coronary angioplasty.

Combination Hemotherapy and Mortality Prevention

The Combination Hemotherapy and Mortality Prevention (CHAMP) study was a randomized, open trial comparing warfarin targeting an INR of 1.5 to 2.5, combined with aspirin (81 mg/day), with aspirin monotherapy (162 mg/day) in patients following acute MI.[3] Five thousand fifty-nine patients were enrolled within 14 days of acute MI and followed for a median of 2.7 years. The primary outcome was total mortality and was experienced by 17.6% of the patients randomized to OA and aspirin versus 17.3% of patients randomized to aspirin alone (p = 0.76). Recurrent MI occurred in 13.3% of patients taking OA and aspirin versus 13.1% taking aspirin alone (p = 0.78). Stroke occurred in 3.1% of patients taking OA and aspirin versus 3.5% on aspirin (p = 0.52). No significant differences in the composite of CV death, stroke, and MI were observed. Major bleeding occurred more frequently with combination therapy versus aspirin with 1.28 versus 0.72 events per 100 persons per year, respectively (p = 0.001). The mean INR achieved in the anticoagulant group was 1.8, and by the end of the trial 30% of patients had discontinued OA therapy.

Huynh et al.

This was a double-blind, randomized trial of patients with non-ST segment elevation ACS who had undergone prior CABG surgery. The duration of treatment was 12 months.[5] One hundred thirty-five patients were randomized to receive warfarin plus aspirin to target an INR of 2.0 to 2.5 (n = 44), warfarin alone (n = 45), or aspirin alone (n = 46). The primary outcome was the composite of death, MI, or unstable angina requiring hospitalization and occurred in 11.3% in the combination therapy group, 14.6% in the OA-alone group, and 11.5% in the aspirin-alone group (overall p = 0.76). This trial was stopped early due to poor recruitment and was underpowered to show a statistical difference between the treatment groups.

Organization to Assess Strategies for Ischemic Syndromes II

In the Organization to Assess Strategies for Ischemic Syndromes II (OASIS-II) study, 3712 with ACS were randomized within 12 to 48 hours of receiving intra-

venous antithrombotic treatment to receive either OA therapy (n = 1848) or standard therapy (n = 1864).[2] All patients were encouraged to take aspirin (mean dose 325 mg/day). Patients were followed for 5 months after study entry; 7.6% of patients in the combination group suffered a CV death, MI, or stroke versus 8.3% of patients in the standard therapy group, for a RR reduction of 10% (95% CI: −14 to 28%, p = 0.40).

There was an excess of major bleeding experienced by the combination group compared with the aspirin-alone group (2.7 vs. 1.3%, p = 0.004), respectively. The mean INR among patients on OA was 2.1 ± 0.9, and compliance to OA was 64% at the end of the trial. Interestingly, a retrospective subgroup analysis indicated that, among countries with good compliance, there was an apparent benefit (risk reduction of 32%, 95% CI: 5 to 52%) compared with no benefit in countries with poor compliance (RR = 1.17, 95% CI: 0.86 to 1.60).

Warfarin–Aspirin Reinfarction Study II

The Warfarin–Aspirin Reinfarction Study II (WARIS-II) was a randomized, open study in which 3600 patients with acute MI from 20 hospitals in Norway were randomly allocated to 1 of 3 treatment arms: warfarin to target an INR of 2.0 to 2.5 plus aspirin (75 mg/day, n = 1208), warfarin to target an INR of 2.8 to 4.8 (n = 1216), or aspirin alone (160 mg/day, n = 1206).[4] Patients were enrolled between January 1994 and June 1998 and followed up for 4 years. Approximately half of the patients received thrombolytic therapy as treatment for their acute MI.

The primary end point of the study was the composite of death, recurrent MI, or stroke. The combination of OA (mean INR = 2.2) and aspirin compared with aspirin alone reduced the primary end point by 29% (95% CI: 14 to 42%, p = 0.0005). OA alone (mean INR = 2.8) compared with aspirin alone reduced the primary end point by 19% (95% CI: 11 to 33%, p = 0.028). Major bleeding was significantly increased in patients treated with OA and aspirin (2.3%) and OA alone (2.7%) compared with patients who received aspirin alone (0.7%, p < 0.001 for comparison with both OA groups with aspirin).

ANALYSIS OF OA STRATEGIES

High-Intensity OA (INR > 2.8) versus Control

Data from 13 trials involving 8140 patients were available to compare high-intensity OA with control (Fig. 1).[18–29] Death, MI, or stroke occurred in 20.3% of patients treated with OA versus 30.3% of patients who received no therapy, translating into an odds reduction of 43% (95% CI: 37 to 49%, p < 0.0001). Among 11 trials involving 7933 patients for which data were available, major bleeding occurred in 4.6% of OA patients versus 0.7% of control patients, for an odds increase of 4.5 (95% CI: 2.5 to 6.0, p < 0.00001; Fig. 2).[18–20,22–27,29,30]

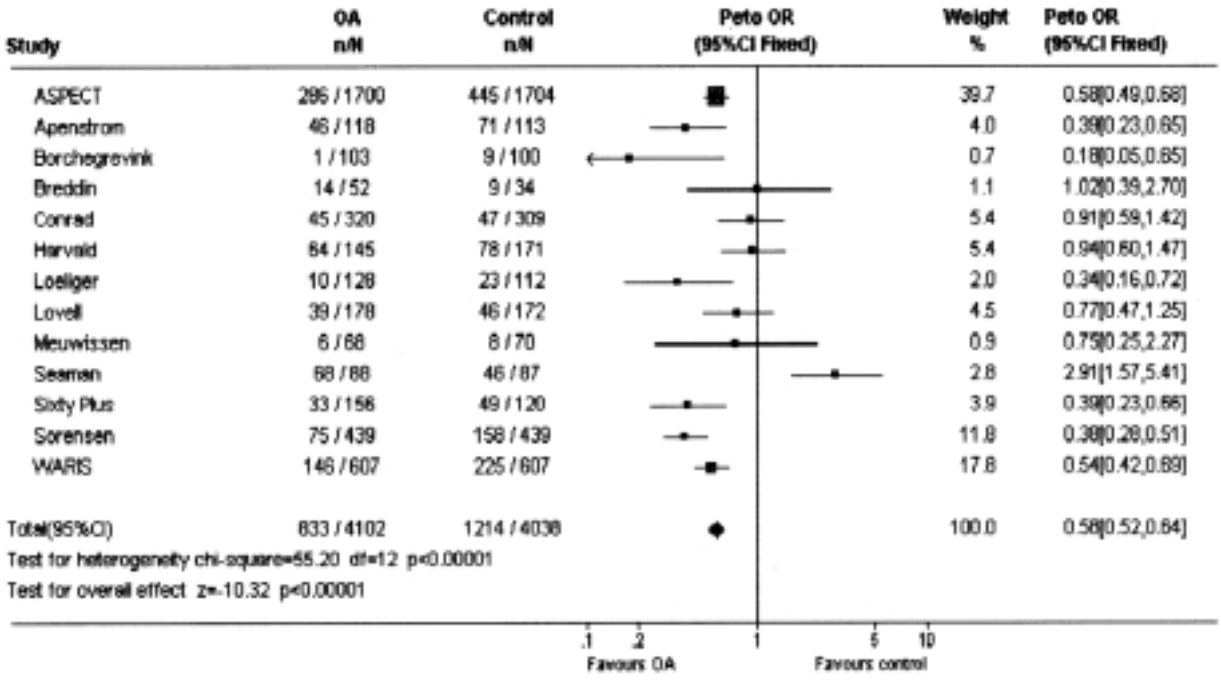

Figure 1 High-intensity OA vs. control.

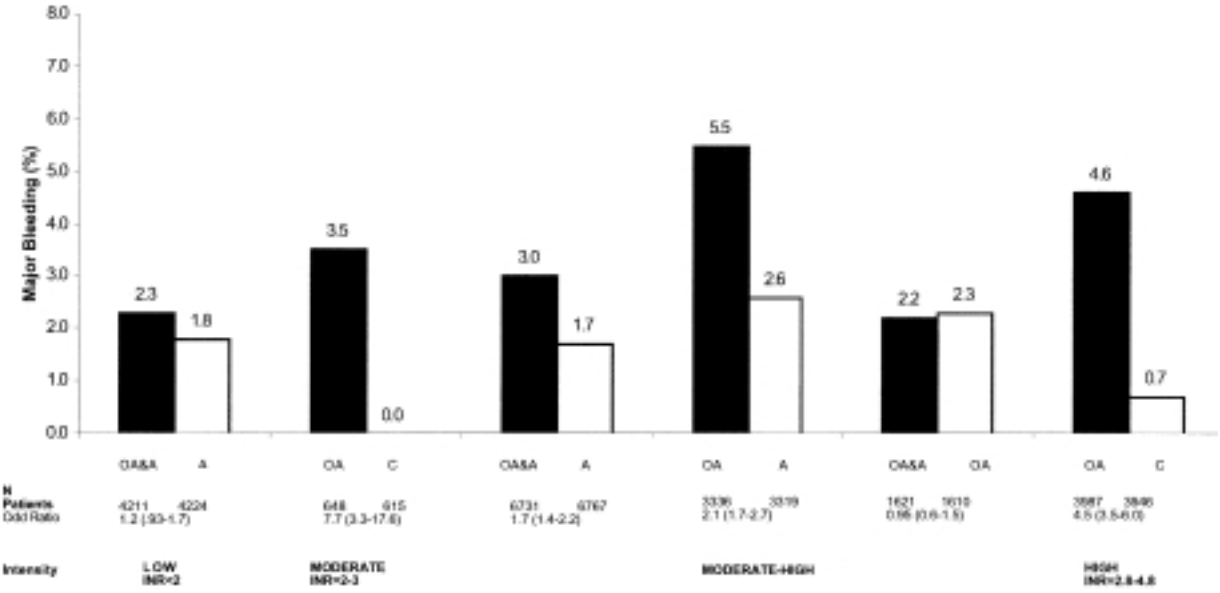

Figure 2 Major bleeding rates in patients with vascular disease.

Moderate-Intensity OA (INR 2.0 to 3.0) versus Control

Data from three trials are available.[31–33] A nonsignificant 16% reduction (95% CI: −11 to 37%, $p = 0.20$) in CV death, MI, and stroke was observed among patients receiving OA versus control (Fig. 3). Major bleeding occurred in 3.5% of patients on OA versus no patients receiving control, for an odds increase of 7.7 (95% CI: 3.3 to 18, $p < 0.0001$; Fig. 2).

Moderate to High-Intensity OA versus Aspirin

Data from 6 trials and 4155 patients in which OA and aspirin were directly compared were available to evaluate the outcome of death, MI, or stroke (Fig. 4).[4,7,25,31,34,35] This outcome occurred in 13.5% of people receiving OA versus 16.3% of patients receiving aspirin alone, resulting in an odds reduction of 21% (95% CI: 6 to 33%, $p = 0.008$). Using data from 10 trials involving 6655 patients, major bleeding was increased by 2.1-fold (95% CI: 1.7 to 2.1, $p < 0.00001$) among patients taking OA (Fig. 2).[4,5,7,21,25,31,36–38]

Moderate to High-Intensity OA Plus Aspirin vs. Aspirin Alone

Data from 7 trials involving 12,333 patients are available for the combined outcome of CV death, MI, or stroke (Fig. 5).[2–4,7,39–41] The combined outcome occurred in 12.6% who received OA plus aspirin versus 15.9% who received aspirin alone, resulting in a significant 12% odds reduction (95% CI: 3 to 20%, $p = 0.01$).

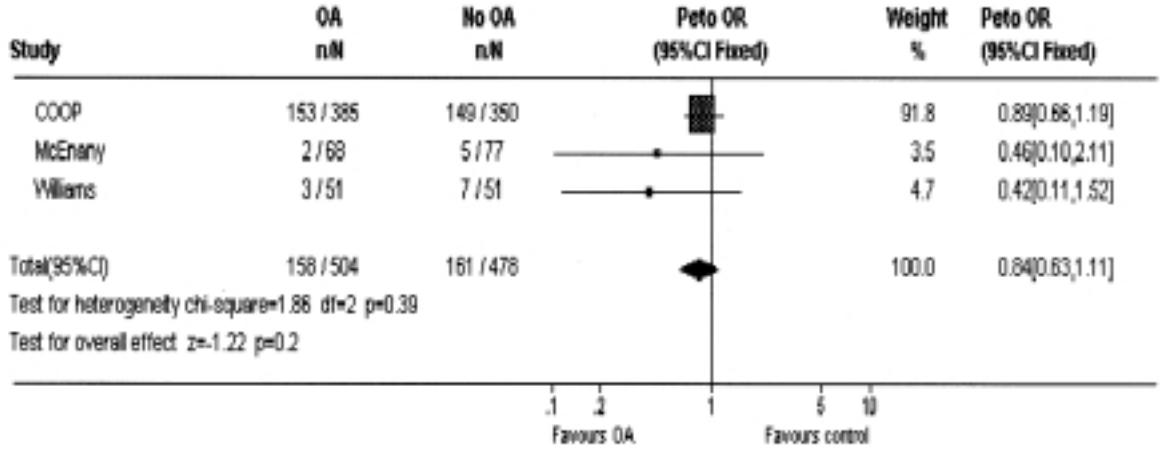

Figure 3 Moderate-high-intensity OA vs. control.

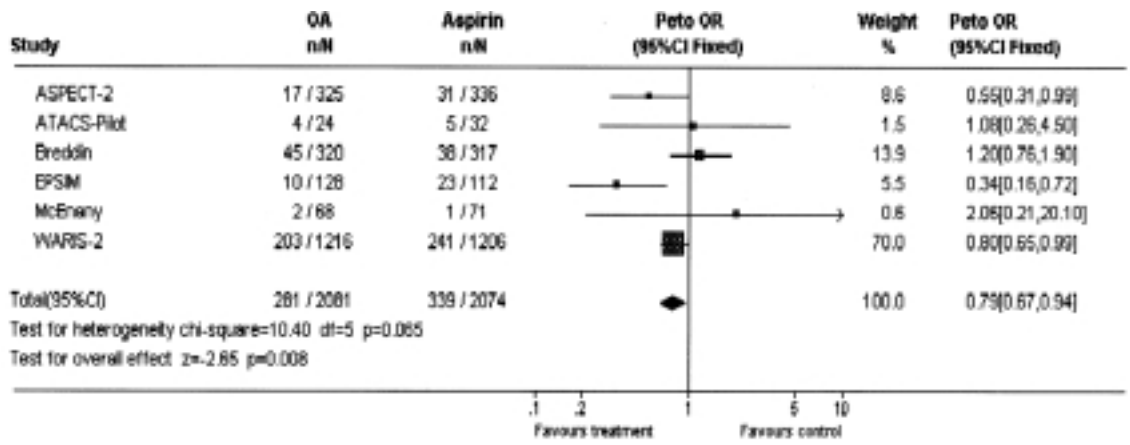

Figure 4 Moderate-high-intensity OA vs. aspirin.

Using data from 9 trials involving 13,498 patients, major bleeding occurred in 3.0% of patients receiving the combination versus 1.7% of patients receiving aspirin only, for a relative increase of 1.74 (95% CI: 1.39 to 2.17; Fig. 2).[2–7,39–41] Therefore, an increase in absolute risk of bleeding of 1.8% is clearly outweighed by a 3.3% absolute risk reduction in CV death, MI, and stroke.

Moderate to High-Intensity OA and Aspirin versus OA alone

Data from 3 trials involving 3142 patients are available to compare the end point of CV death, MI, and stroke (Fig. 6).[4,7,39] This occurred in 12.5% of patients receiving combination therapy versus 14.3% receiving OA alone, for an odds reduction of 14% (95% CI: −6 to 30%, $p = 0.15$). Using data from 4 trials involving 3231 patients, no substantial difference in major bleeding episodes was observed between the combination therapy (2.2%) and OA alone (2.3%), for an odds ratio, OR, of 0.95 (95% CI: 0.60 to 1.51, $p = 0.80$; Fig. 2).[4,5,7,39]

Low-Intensity INR < 2.0

Three trials ($n = 8435$ patients) compared low-intensity OA plus aspirin with aspirin alone.[40,42,43] The CARS study was a three-arm trial that compared fixed-dose, 1-mg warfarin plus aspirin with fixed-dose, 3-mg warfarin plus aspirin with aspirin alone.[42] The INR values in the 1-mg OA group increased minimally (0.03 increase compared with the aspirin-only arm, median INR < 1.05); therefore, data for only the 3-mg arm (median INR = 1.5) was used and compared with the aspirin-alone arm. No significant benefit in favor of OA and aspirin versus aspirin alone for the combination of CV death, MI, and stroke was observed (OR: 0.91, 95% CI: 0.79 to 1.06, $p > 0.10$), as this outcome occurred in 8.8% of patients who received combination therapy ver-

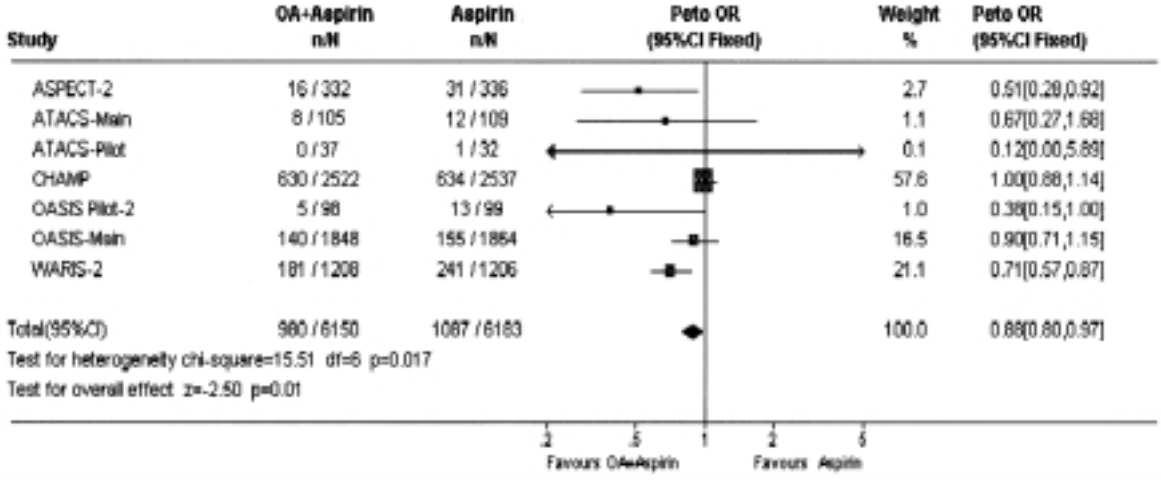

Figure 5 Moderate-high-intensity OA + aspirin vs. aspirin.

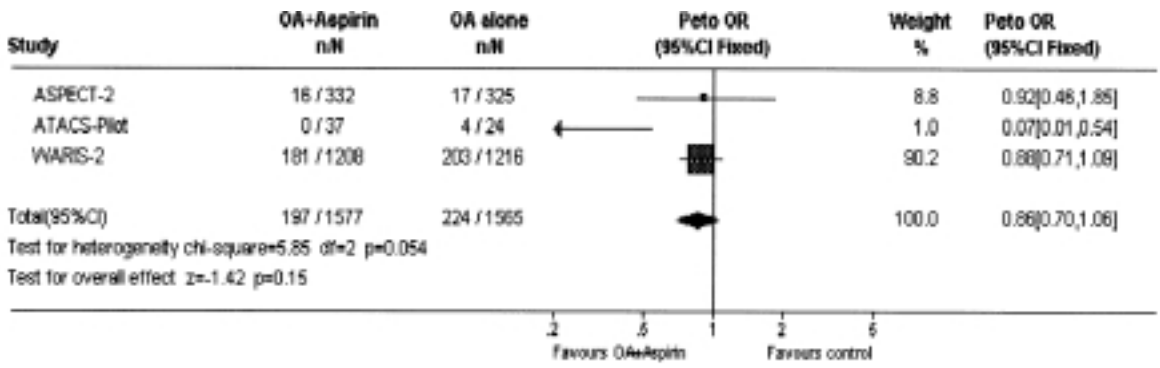

Figure 6 Moderate-intensity OA + aspirin vs. moderate-high-intensity OA.

sus 9.6% who received aspirin (Fig. 7). Major bleeding occurred in 2.3% of patients on combination therapy versus 1.8% of patients who received aspirin, resulting in a nonsignificant 25% increase in bleeding (Fig. 2).

DISCUSSION

We previously reported a systematic review of oral anticoagulants in patients with CAD, comprising 31 trials involving more than 21,000 patients studied across nearly 40 years.[1] The major findings from that analysis were (1) high-intensity OA (INR > 2.8) clearly prevents CV complications but markedly increases the risk of bleeding; (2) low-intensity, fix-dosed OA (INR < 2.0) is ineffective in reducing CV risk compared with aspirin alone and probably increases the risk of major bleeding; and (3) the combination of moderate-intensity OA and aspirin appeared promising, but insufficient clinical trial data were available to be conclusive.

In the 3 years since this meta-analysis was published, a number of additional trials specifically focused on moderate-intensity OA have been completed. Their data, in conjunction with the previous literature, enable a more rigorous examination of moderate-intensity OA for the prevention of recurrent CV events. It is now more clear that moderate-intensity OA, with or without co-administration of aspirin, is more effective than aspirin alone, albeit with a modest increase in the risk of bleeding. Furthermore, moderate OA plus aspirin may be more effective than OA alone (odds reduction of 14%, 95% CI: −6% to 30%, $p = 0.15$), with no apparent increase in bleeding; however, more data are needed to be definitive. Thus, there appears to be a threshold level of anticoagulation (INR = 2.0 to 3.0) required to maximize the prevention of thrombotic events (MI, stroke) and minimize hemorrhagic risk, a situation analogous to the use of OA in the thromboprophylaxis of venous thromboembolism, atrial fibrillation, and prosthetic heart valves.[17]

There is no apparent large increase in bleeding with the combination of moderate OA and aspirin compared with aspirin or OA alone. This supports other evidence that it is the INR intensity, rather than the simultaneous use of antiplatelet agents, that is the strongest determinant of bleeding episodes.[17,44,45] For instance, Massel and Little recently reported a meta-analysis of the risks and benefits of adding antiplatelet therapy to coumadin in patients with prosthetic heart valves.[44] They found that the addition of aspirin to coumadin was associated with an increase in the risk of major bleeding (OR: 1.50, 95% CI: 1.03 to 2.18, $p = 0.033$), which was nullified when they considered contemporary trials separately in which lower doses of aspirin (average, 100 mg) were used (OR for bleeding: 0.88 vs. 2.23 for later, low-dose trials vs. early, high-dose trials, $p = 0.025$).

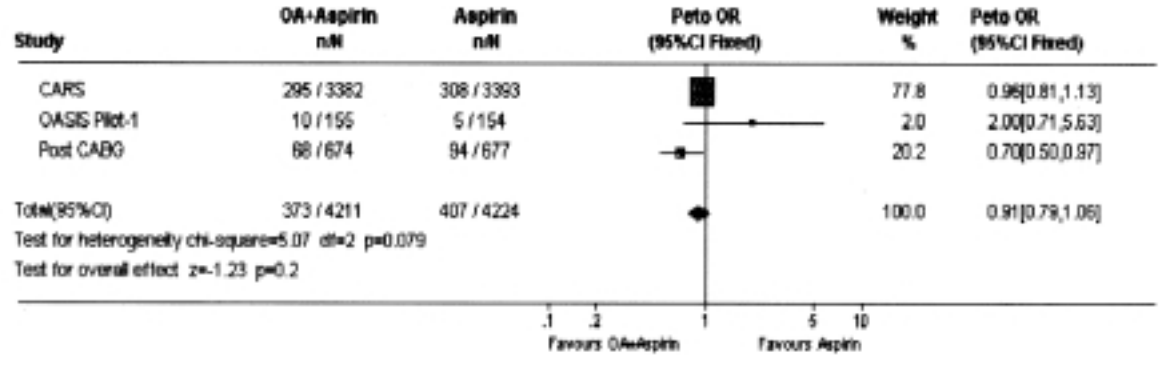

Figure 7 Low-intensity OA + aspirin vs. aspirin.

The data presented here represent the *observed* treatment effects because the summary estimates include all patients regardless of whether they were actually compliant with the intended therapy. Because, in most trials of OA, nonadherence was substantial, these estimates are conservative, represent an intention to treat analysis, and are likely to be an underestimate of the *true* risk reduction achievable with OA when adherence is higher and the target INR is achieved in most patients.

An example of the effect of nonadherence on the overall estimate of treatment effect comes from the OASIS-II study.[2] In this trial, OA and aspirin versus aspirin alone was associated with a small, nonsignificant reduction in CV death, MI, and stroke (7.6 vs. 8.3%, RR = 0.90, 95% CI: 0.72 to 1.14). However, at the end of the follow-up period, only 63.7% of patients who were randomized to receive OA and aspirin were actually taking OA. Adherence to OA varied significantly among the 14 countries that participated in the trial. Countries were divided into those in which compliance with OA was at least 70% at 35 days and those countries in which compliance was less than 70% at 35 days. In the good-compliance countries, the combination of OA and aspirin was associated with a significant 32% reduction in CV death, MI, and stroke (6.1 vs. 8.9%, RR = 0.68; 95% CI: 0.48 to 0.95, $p = 0.02$) compared with aspirin alone. Conversely, in poor-compliance countries, no reduction in the composite outcome was observed. Therefore, in the high-compliance subgroup, OA and aspirin use was associated with a RR reduction that was more than three times as great as the risk reduction with OA and aspirin observed using the intention-to-treat approach.

Despite clear evidence of efficacy, the use of OA in the management of patients with CAD has not been widely adopted, particularly in North America, where antiplatelet therapy has become the standard of care.[46] The reasons may have more to do with the perceived disadvantages and inconvenience of OA rather than an understanding of the published evidence. Clearly, the use of OA therapy requires careful monitoring and dose adjustment and is not as easy to administer or follow as antiplatelet agents. Moreover, recent data suggest that dual-antiplatelet blockade, with clopidogrel and aspirin, has clinical benefit over aspirin alone, particularly for patients with non-ST-elevation ACS and/or patients undergoing percutaneous coronary intervention.[15,47,48] Oral direct thrombin inhibitors (such as ximelagatran) appear promising for the treatment and prophylaxis of venous thromboembolism, and such agents may require less monitoring and dose adjustment than conventional OA; however, ongoing trials in patients with CAD have not yet been reported.[49,50] Therefore, clinical trials directly comparing these emerging strategies with OA and antiplatelet therapy in patients with CAD are warranted.

CLINICAL RECOMMENDATIONS

Aspirin is likely to remain the standard of care for the vast majority of patients with CAD, for a number of reasons. First, the evidence supporting aspirin in acute and chronic CAD settings is substantial.[14,46] Second, aspirin has been proven very safe, particularly in low doses (<100 mg/day). Third, aspirin is inexpensive and easy to administer and does not require dose titration or intensive monitoring. There are, however, a number of drawbacks to aspirin, such as the high long-term recurrence rate after MI (e.g., 20% over 4 years) and the presence of aspirin resistance in many patients with CAD.[51–53]

Moderate-intensity OA, with or without aspirin, is an acceptable alternative to aspirin monotherapy in a number of circumstances. Patients with CAD and coexistent atrial fibrillation, large anterior MI, prosthetic heart valves, mural thrombi, or aspirin allergy should be considered for OA therapy. In addition, very-high-risk patients, including those with vascular disease in multiple arterial territories (coronary, cerebral, and/or peripheral), are likely to benefit from more-intensive treatment than aspirin alone. Individuals who suffer recurrent events despite aspirin therapy may have aspirin-resistant platelets and thus may be candidates for enhanced treatment with OA and aspirin. Dual-antiplatelet blockade may be an acceptable alternative, although head-to-head trials comparing dual-antiplatelet therapy with OA and antiplatelet strategies are needed. Additionally, it is possible that, in very-high-risk patients, the combination of moderate-intensity OA, low-dose aspirin, and clopidogrel may prove to be even more effective. However, this hypothesis also requires large, prospective, controlled studies with careful evaluation of the risk-to-benefit ratio. Therefore, at present, in these selected situations, combination therapy with moderate-intensity OA and antiplatelet therapy, with regular INR monitoring, should be considered.

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