The Role of Combination Therapy with Antiplatelet and Oral Anticoagulant Agents in Cardiovascular Disease

Thomas L. Lenz, PharmD and Daniel E. Hilleman, PharmD

ABSTRACT This review examines the use of combinations of oral antiplatelet agents with oral anticoagulant agents for long-term secondary prevention in patients with cardiovascular diseases such as myocardial infarction (MI), mechanical valve replacement, coronary artery stent implantation, and chronic atrial fibrillation (AF).

Anticoagulant and antiplatelet agents are indicated in the prevention and treatment of a variety of thromboembolic disorders. Antiplatelet agents predominantly effect the development of clot formation in the arterial circulation, where platelets play a more pivotal role than in the venous circulation. Anticoagulants affect clot formation in both the arterial and venous circulation by inhibiting the activity (production) of clotting factors. As these agents affect the clotting process by different mechanisms, the combined use of these drugs might be more effective than the use of either agent alone.

REVIEW OF STUDY RESULTS
Published articles and abstracts were identified from a Medline search (January 1966–January 2001) using the terms anticoagulant, antiplatelet, coronary artery disease, mechanical valve, coronary artery stent, and atrial fibrillation. Pertinent articles written in English were considered for review. Additional articles were identified from the references of retrieved literature.

Myocardial Infarction
The risk of recurrent adverse cardiovascular events among patients experiencing myocardial infarction (MI) is high. The mortality rate for these individuals is 10% during the first year, and 5% annually thereafter.1 Patients who have suffered an MI have a six-fold increased risk of death compared to patients who do not have coronary artery disease (CAD).

Antiplatelet Monotherapy Trials
The American College of Cardiology (ACC) and the American Heart Association (AHA) currently recommend using the antiplatelet agent aspirin for the secondary prevention of MI.2 Other available oral antiplatelet agents such as clopidogrel, ticlopidine, and dipyridamole are not recommended by the ACC/AHA unless a patient has a true aspirin allergy or is unresponsive to aspirin.2

The Antiplatelet Trialist Collaboration evaluated the outcomes of 145 trials that used aspirin as the main antiplatelet therapy.3 After a one-month follow-up of the 20,000 patients with MIs who were included in these studies, adverse cardiovascular events occurred in 14% of control patients and 10% of antiplatelet-treated patients. After two years of follow-up, 17% of control patients had an adverse event compared to 14% of antiplatelet agents. This represents a relative risk reduction of 18%. Overall, approximately 40 vascular events were avoided per 1,000 patients treated (P<0.00001).3

Oral Anticoagulation Monotherapy Trials
The ACC/AHA recommends the use of oral anticoagulants for the secondary prevention in post-MI patients if the patient is unable to take aspirin or another antiplatelet agent.2 In addition, oral anticoagulants are indicated in post-MI patients who have other indications for anticoagulants such as atrial fibrillation (AF) or left ventricular (LV) thrombus.

Long-term use of oral anticoagulants in post-MI patients without AF or LV thrombus remains controversial. Several trials have compared oral anticoagulation versus placebo in post-MI patients. Initial studies with oral anticoagulants showed promising results, but were questioned because of poor study design.4-7 The Sixty-Plus Reinfarction Study found a significant reduction in mortality (P=0.017) and recurrent MI (P=0.0001) with oral anticoagulants following MI.8 In a similar study, Smith et al. randomized post-MI patients to either an oral anticoagulant or placebo. A 24% reduction in mortality (P=0.027) and a 34% reduction in reinfarction (P=0.0007) was observed with oral anticoagulants.9 More recently, the Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) trial found no significant difference in mortality between oral anticoagulant therapy and placebo in post-MI patients. The ASPECT trial showed that oral anticoagulant therapy significantly reduced recurrent MI and cerebrovascular events compared to placebo.10

Antiplatelet versus oral anticoagulation trials
Four trials dating back to 1980 examined the risks and benefits of administering antiplatelet agents versus oral anticoagulants for the secondary prevention of myocardial infarction.11-14 None of the four trials was able to show a significant difference in primary endpoints between these agents in post-MI patients, how-

Dr. Lenz is a Cardiovascular Research Fellow at The Cardiac Center of Creighton University, Omaha, Nebraska. Dr. Hilleman is Professor and Chair of the Pharmacy Practice Department in the School of Pharmacy and Allied Health Professions at Creighton University, Omaha, Nebraska.
ever. The Antithrombotics in the Prevention of Reocclusion in Coronary Thrombolysis (APRICOT-1) study showed that aspirin was superior to placebo in event-free combined endpoints at three months (P<0.001). No difference was seen when aspirin was compared with warfarin (Table 1).

### Combination Antiplatelet/Anticoagulant Trials

The Coumadin Aspirin Reinfarction Study (CARS) compared a fixed-dose combination of warfarin and aspirin to aspirin alone in post-MI patients. The study randomly assigned 8,803 patients, who were three to 21 days post-infarction, to one of three treatment arms. The treatment arms consisted of 160 mg of aspirin, 3 mg of warfarin plus 80 mg of aspirin, or 1 mg of warfarin plus 80 mg of aspirin.

The results of the CARS study found that a fixed low dose of warfarin (1 or 3 mg) plus 80 mg of aspirin was no more effective than aspirin monotherapy in reducing adverse cardiovascular events. The relative risk of a primary event (reinfarction, non-fatal ischemic stroke or cardiovascular death) occurring at one year in the 160-mg aspirin group compared with the 1-mg warfarin plus 80-mg aspirin group was 1.03 (95% CI, 0.87–1.22, P=0.74). Aspirin monotherapy, compared to the warfarin 3-mg plus aspirin 80-mg group, had a relative risk of a primary event at one year of 0.95 (95% CI, 0.81–1.12, P=0.57). The risk of major hemorrhage at one year was significantly lower in the 160-mg aspirin monotherapy group compared to the 3-mg warfarin plus 80-mg aspirin group (0.74%, 95% CI 0.43–1.1 vs. 1.4%, 0.94–1.8, P=0.014). Major hemorrhages in the 1-mg warfarin/80-mg aspirin group were not statistically different compared to aspirin monotherapy (P>0.62). The median International Normalized Ratios (INRs) at six months with the three treatment groups were 1.02 with 160 mg of aspirin; 1.04 with 1 mg of warfarin plus 80 mg of aspirin; and 1.19 with 3 mg of warfarin plus 80 mg of aspirin.

There are currently three ongoing trials in post-MI patients that are evaluating the effectiveness of the combination of warfarin and aspirin. The Combination Hemotherapy and Mortality Prevention (CHAMP) study compared the efficacy of 161 mg per day of aspirin versus the combination of aspirin 81 mg per day plus warfarin titrated to achieve an INR of 1.5 to 2.5 in 5,059 patients. Preliminary results have found no statistical significance between the two groups with regard to mortality, non-fatal MI, non-fatal stroke, or intracranial or fatal bleeds. However, combination therapy was associated with a two-fold increase in major hemorrhage; these were primarily gastrointestinal in nature (statistical significance not reported).

The WARIS II (Warfarin-Aspirin Reinfarction Study) was designed to measure the efficacy and safety of warfarin alone (INR 2.8–4.2), aspirin alone (160 mg daily), and the combination of warfarin (INR 2.0–2.5) and 75 mg of aspirin in 3,606 post-MI patients. Composite endpoints for the study included death, non-fatal reinfarction, and stroke. There is no available data yet from the WARIS II trial results.

The APRICOT-2 trial randomized 308 post-MI patients with TIMI 3 flow who were within 48 hours of obtaining a thrombolytic agent to one of two treatment groups. Patients enrolled in APRICOT-2 received either 80 mg of aspirin daily or the combination of 80 mg of aspirin daily plus warfarin (INR 2.0–3.0). Preliminary results show the combination therapy to have a lower reocclusion rate at three months compared to aspirin monotherapy: 18% versus 30%, respectively (P<0.05). Event-free survival was achieved by 70% of aspirin-alone patients and by 83% of patients assigned to combination therapy (P<0.01). A slight trend towards minor bleeding was shown in the combination therapy group, but there was no difference in major bleeding between the two groups.

The Antithrombotic Therapy in Acute Coronary Syndromes (ATACS) trial compared the efficacy and safety of the combination of aspirin plus warfarin versus aspirin alone in 214 patients with unstable rest angina or non-Q wave myocardial infarction. Patients enrolled in the study received either aspirin 162.5 mg daily or aspirin 162.5 mg daily plus warfarin titrated to an INR of 2.0 to 3.0. Trial therapy lasted 12 weeks with the primary endpoints including recurrent angina, myocardial infarction, and/or death. At 14 days, there was a significant reduction in total ischemic events in the combination group versus aspirin alone (10.5% vs. 27%, P<0.004). A primary endpoint analysis at 12 weeks, although not significant, showed a strong trend favoring the combination group over aspirin alone (13% [14/105] vs. 25% [27/109], P=0.06). No major bleeding events occurred in the...
aspirin-only treatment group, whereas three of 105 (2.9%) patients in the combination groups experienced bleeding.19

Valve Replacement

Lifelong oral anticoagulation (INR 2.5–3.5) has been recommended to reduce the incidence of systemic embolism in patients receiving mechanical prosthetic heart valves.20 Despite adequate oral anticoagulation, the incidence of thromboembolic events in this patient population is still approximately 2% per year.20 As a result, several studies have attempted to decrease this risk by adding aspirin or other antiplatelet agents to oral anticoagulation regimens.

Cappelleri et al. conducted a meta-analysis that evaluated the safety and efficacy of combined anticoagulant and antiplatelet therapy versus anticoagulant monotherapy in mechanical heart valve patients.21 Included in the meta-analysis were five placebo-controlled randomized trials.22-26 Treatment regimens and results for each study are listed in Table 2. This meta-analysis found that combined antiplatelet and anticoagulant therapy significantly reduced the risk of embolism by approximately 67% (0.33, 95% CI 0.16–0.69, \(P=0.0032\)) versus anticoagulant monotherapy. Mortality data showed a 40% reduction in death favoring combination therapy, but the difference was not statistically significant (0.60, 95% CI 0.32–1.12, \(P=0.11\)).

In addition, the combination-therapy group experienced an estimated risk of bleeding that was 1.6 times greater than the monotherapy group (1.65, 95% CI 1.15–2.39, \(P=0.0069\)). The risk of major gastrointestinal hemorrhage was also significantly higher in the combination group compared to the monotherapy group (3.47, 95% CI 1.43–8.40, \(P=0.0058\)). The authors estimated that for every 1.6 patients who had a stroke prevented by combination therapy, there was one major gastrointestinal bleed.

Since the Cappelleri et al. meta-analysis, one other prospective, randomized study had been published regarding combination antiplatelet/anticoagulation therapy in heart valve replacement patients. In an attempt to reduce the number of gastrointestinal bleeding events associated with combination therapy, Meschengieser et al. conducted a study that compared low-intensity anticoagulation plus aspirin versus high-intensity anticoagulation monotherapy.20 Two hundred and fifty-eight patients were randomized to the treatment regimen of 100 mg per day of aspirin plus an unspecified oral anticoagulant (INR 2.5–3.5). In the high-intensity oral anticoagulation group, 245 patients did not receive aspirin, but were titrated on the oral anticoagulation to an INR of 3.5 to 4.5. Patients were followed for a median of 23 months.

The results show that both treatment arms had a similar number of embolic episodes. The aspirin/low-intensity anticoagulation group had an incidence of embolic episodes of 1.32 per 100 patient years (95% CI, 0.53–2.7).20 The high-intensity anticoagulation group had an incidence of embolic episodes of 1.48 per 100 patient years (95% CI, 0.59–3.03). The less intense anticoagulation arm showed a 52% reduction in the risk of major bleeding compared to the more intense anticoagulation arm. This difference, however, did not reach statistical significance (95% CI, 0.19–1.38, \(P=0.273\)).20

The American College of Chest Physicians (ACCP) currently has several alternative grade 2C recommendations (very weak recommendations; other alternatives might be equally reasonable) regarding the addition of an antiplatelet agent to anticoagulation therapy in mechanical prosthetic heart valve patients.27 The ACCP recommends that patients with tilting disk valves, bileaflet mechanical valves in the mitral position, or bileaflet mechanical valves in the aortic position plus atrial fibrillation, have a goal INR of 2.5 (range=2.0–3.0) in combination with aspirin at a dose of 80 to 100 mg per day (grade 2C recommendation).27 The ACCP also recommends that patients with a caged ball or with caged disk valves, have a goal INR of 3.0 (range=2.5–3.5) in combination with aspirin 80 to 100 mg per day (grade 2A recommendation; interme-

---

**Table 2 Combination Oral Anticoagulation/Antiplatelet Therapy Versus Oral Monotherapy Anticoagulation in Mechanical Heart Valve Patients**

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Regimen</th>
<th>Number of Patients (%)</th>
<th>Rate of Thromboembolic Event (%)</th>
<th>RRR (%)</th>
<th>Rate of Major Bleeding (%)</th>
<th>RRR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sullivan et al.22</td>
<td>D 400mg/d + W (INR 3–4.5) W (INR 3–4.5)</td>
<td>79</td>
<td>1*</td>
<td>93</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Altman et al.23</td>
<td>A 500 mg/d + AC (INR 1.8–2.3) AC (INR 1.8–2.3)</td>
<td>57</td>
<td>5#</td>
<td>75</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Dale et al.24</td>
<td>A (1000mg/d) + UA (INR 2–2.2) UA (INR 2–2.2)</td>
<td>75</td>
<td>3*</td>
<td>81</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>Chesebro et al.25</td>
<td>A 500mg/d + W (INR 2.4–7.5)</td>
<td>170</td>
<td>4</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turpie et al.26</td>
<td>A 100 mg/d + W (INR 3–4.5) W (INR 3–4.5)</td>
<td>186</td>
<td>3.9#</td>
<td>61</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Meschengieser et al.20</td>
<td>A 100mg/d + LDA (INR 2.5–3.5) HDA (INR 3.5–4.5)</td>
<td>258</td>
<td>2.7</td>
<td>3.6</td>
<td>2.3</td>
<td>52</td>
</tr>
</tbody>
</table>

* \(P<0.01\); #\(P<0.005\); A=aspirin; AC=acenocoumarin; D=dipyridamole; HAD=high-dose anticoagulant; LDA=low-dose anticoagulant; NA=not reported; UA=unspecified anticoagulant; W=warfarin; RRR=relative risk reduction.
Atrial Fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia requiring medical intervention. Its prevalence increases with age, doubling with each advancing decade of life. Approximately 2.2 million Americans have AF. The main treatment goal is to restore sinus rhythm and to prevent thromboembolic complications and recurrences of AF. Aggressive treatment involves converting and maintaining sinus rhythm. However, this treatment has a risk of toxicity from exposure to antiarrhythmic therapy. A more conservative strategy is to allow patients to remain in AF. These patients typically require long-term anticoagulation with drugs to control heart rate.

The ACCP offers specific anticoagulation guidelines for AF patients. They recommend that patients with AF and at least one high risk factor, or more than one moderate risk factor, take warfarin with an INR of 2.0 to 3.0. For patients with one moderate risk factor, aspirin 325 mg per day or warfarin (INR 2.0–3.0) is recommended. Patients without high moderate risk factors are advised by the ACCP to take 325 mg per day of aspirin. High risk factors include prior TIA or stroke, systemic embolus, hypertension, poor left ventricular function, rheumatic mitral valve disease, a prosthetic heart valve, and age over 75. Moderate risk factors include age 65 to 75, diabetes mellitus, and coronary artery disease with preserved LV function. The ACCP currently does not recommend the use of aspirin plus low-dose warfarin therapy in patients with lone AF (grade 1A; strong recommendation).

Several studies have attempted to compare oral anticoagulation versus aspirin versus the combination of the two to decrease thromboembolic complications in AF patients. In 1989, the first of two Copenhagen AFASAK (Atrial Fibrillation, Aspirin, and Anticoagulation Study) trials was published. Chronic AF patients were randomized to receive warfarin (INR 2.8–4.2), 75 mg of aspirin or placebo and followed for two years with the intent of preventing thromboembolic complications. The warfarin group had a significantly lower incidence of thromboembolic complications (stroke, TIA, embolic complications to the viscera and extremities) compared with the aspirin and placebo groups (P<0.05).

The Copenhagen AFASAK II trial was published in 1998. Like the AFASAK I study, chronic AF patients were recruited and thromboembolic events and stroke were recorded over a 42-month period. The treatment regimens for AFASAK II consisted of warfarin 1.25 mg per day, aspirin 300 mg per day, combination of the two to decrease thromboembolic complications and stroke, and thromboembolic complications (stroke, TIA, embolic complications to the viscera and extremities) compared with the aspirin and placebo groups (P<0.05).

The cumulative primary event rate (stroke or systemic thromboembolic event) in the 677 patients enrolled at one and three years showed no significant difference between the four treatment groups. The low-dose warfarin group had a cumulative primary event rate at one year of 5.8% and at two years of 11.9%, whereas the aspirin monotherapy group experienced rates of 3.6% and 8.4%, respectively (P=0.67). The warfarin-plus-aspirin groups had a cumulative primary event rate at one and three years of 7.2% and 12.8%, respectively, and the adjusted-dose warfarin group rates were 2.8% and 8.3%, respectively (P=0.67).

Bleeding occurred in 19% (130/677) of the patients enrolled. Thirteen patients experienced major bleeding, which was fatal in two cases. During treatment with low-dose warfarin

Table 3 Combination Oral Anticoagulation and Antiplatelet Therapy in Patients with Chronic Atrial Fibrillation

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Mean Follow-up (yr)</th>
<th>OAC INR Range</th>
<th>ASA OAC/ OAC Dose</th>
<th>Rate of Primary Events (%)</th>
<th>RRR (%)</th>
<th>Rate of Major Bleeding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFASAK I</td>
<td>1007</td>
<td>1.2</td>
<td>2.8-4.2</td>
<td>75 —</td>
<td>OAC 2.7 ASA 5.2</td>
<td>48*</td>
<td>OAC 0.6 ASA 0.3</td>
</tr>
<tr>
<td>AFASAK II</td>
<td>677</td>
<td>NA</td>
<td>2.0-3.0</td>
<td>300 ASA 300 mg W 1.25 mg</td>
<td>OAC 3.4 OAC + ASA 3.2</td>
<td>-6</td>
<td>OAC 1.7 OAC + ASA 03</td>
</tr>
<tr>
<td>SPAF I</td>
<td>1330</td>
<td>2.2</td>
<td>2.0-4.5</td>
<td>325 —</td>
<td>OAC 2.3 P 7.4</td>
<td>67*</td>
<td>OAC P 1.5 1.6</td>
</tr>
<tr>
<td>SPAF II</td>
<td>1100</td>
<td>2.7</td>
<td>2.0-4.5</td>
<td>325 —</td>
<td>OAC ≤75 1.3 ASA 1.9</td>
<td>33 ≤75 OAC ASA 1.7 0.9</td>
<td></td>
</tr>
<tr>
<td>SPAF III</td>
<td>1044</td>
<td>1.1</td>
<td>2.0-3.0</td>
<td>ASA 325mg W (INR 1.2 to 1.5)</td>
<td>OAC 1.9 OAC + ASA 7.9</td>
<td>74</td>
<td>OAC 21 OAC + ASA 24</td>
</tr>
</tbody>
</table>

*P<0.01; #P<0.005; ASA=aspirin; NA=not reported; OAC=oral anticoagulant; P=placebo; W=warfarin; RRR=relative risk reduction.
alone, warfarin plus aspirin, aspirin monotherapy, and adjusted-dose warfarin, the annual rate of major bleeding was 0.8%, 0.3%, 1.4%, and 1.1%, respectively (P = 0.20). After three years of treatment, the cumulative rate of any bleeding in the treatment groups was 25%, 24%, 30%, and 41% (P = 0.003), respectively. The adjusted-dose warfarin group had a significantly higher cumulative incidence of bleeding; however, the authors attribute the difference to a higher rate of minor bleeding. Excessive INR values (P = 0.001) and prior myocardial infarction (P = 0.001) were independent risk factors for bleeding. Advanced age was determined not to be an independent risk factor for bleeding.35

A series of three Stroke Prevention in Atrial Fibrillation (SPAF) studies were initially conducted to evaluate whether aspirin or warfarin worked better to prevent stroke in patients with atrial fibrillation.36,37 SPAF I found that both aspirin and warfarin reduced the rate of primary events (ischemic stroke and systemic embolism) or death by 32% (P = 0.02) and 58% (P = 0.01), respectively, versus placebo.36 SPAF II compared warfarin versus aspirin in the same primary events as SPAF I and found no significant difference in patients under 75 years of age (P = 0.24) and patients over 75 years of age (P = 0.39).37

The SPAF III trial compared the combination of a fixed dose of warfarin (0.5–3.0 mg/day to range INR of 1.2–1.5) plus aspirin 325 mg per day versus adjusted-dose warfarin (INR 2.0–3.0) in 1,044 AF patients.38 Participants were required to have at least one thromboembolic risk factor (congestive heart failure, left ventricular ejection fraction ≤ 25%, previous thromboembolism, systemic blood pressure > 160 mm Hg at study enrollment, or being female and > 75 years). The mean follow-up was 1.1 years. Ischemic stroke or systemic embolism were the primary events, whereas secondary events consisted of TIA, MI, major hemorrhage, or death.

The results of SPAF III overwhelmingly favor adjusted-dose warfarin over combination therapy. Adjusted-dose warfarin showed the rate of primary events to be 1.9% versus 7.9% in the combination group (P = 0.0001). The risk of primary event or vascular death combined in the adjusted-dose warfarin group was 6.4% compared with 11.8% in the combination group (P = 0.0002). The mean INR in the combination group was 1.3, compared to 2.4 in the adjusted-dose warfarin group. The rate of major bleeding was similar in both groups and not statistically different—adjusted-dose warfarin, 2.1%; combination group, 2.4% (Table 3).38

**Coronary Stent Implantation**

The role of antiplatelet therapy following coronary stent implantation is well-established. The ACCP currently recommends that 80 to 325 mg of aspirin be administered at least two hours prior to stent placement and continued indefinitely at a dose of 80 to 325 mg daily.39 As an adjunct, the ACCP recommends a clopidogrel 300-mg oral loading dose and a 75-mg daily dose for 14 to 30 days, or a ticlopidine 500-mg loading dose and 250 mg twice daily for at least 10 to 14 days after the procedure.39

Several studies have compared the use of aspirin and ticlopidine versus aspirin and warfarin in patients receiving coronary artery stents. In general, the consensus of these studies is that the combination of aspirin and ticlopidine is significantly better than the combination of aspirin and warfarin or aspirin monotherapy for thrombus prevention. Because of this, the ACCP no longer recommends the use of warfarin following stent implantation unless other indications exist. Warfarin is only indicated for patients who have poor left ventricular function, atrial fibrillation, or mechanical heart valves in addition to coronary artery stent implantation.40

Leon et al. randomized 1,653 patients undergoing coronary stenting to one of three treatment arms.41 Treatment regimens consisted of aspirin monotherapy 325 mg per day or aspirin 325 mg per day plus IV heparin, followed by warfarin titrated to INR 2.0 to 2.5 for four weeks or 325 mg of aspirin daily with 250 mg of ticlopidine twice daily for four weeks. Primary endpoints included death, revascularization of the target lesion, angiographically evident thrombosis, or myocardial infarction within 30 days. Patients in the aspirin plus ticlopidine group had significantly fewer combined primary events at 30 days than the other two treatment regimens (P = 0.001). The rate of hemorrhagic complications, however, was significantly lower in the aspirin monotherapy group (1.8% [10/557]) than in the aspirin/ticlopidine group (5.5% [30/546]) or the aspirin/warfarin group (6.2% [34/550]) (P = 0.001). There was no significant difference in hemorrhagic complications between the aspirin/ticlopidine and aspirin/warfarin groups (P = 0.99).

The FANTASTIC (The Full Anticoagulation Versus Aspirin and Ticlopidine) study randomized 473 patients from 13 centers undergoing unplanned and elective coronary stenting.42 Treatment groups consisted of either aspirin (100–325 mg/day) plus 250 mg of ticlopidine twice daily for six weeks or aspirin (100–325 mg/day) plus warfarin (INR 2.5–3.0) for six weeks. The anticoagulation group was initially started on heparin, which was discontinued when the INR was in the target range on two consecutive days. All patients in both groups continued aspirin therapy indefinitely. The primary endpoint of the study was the rate of bleeding complications in the six weeks after stent implantation. Secondary endpoints consisted of acute or subacute stent occlusion, clinical cardiac-related events (death, Q-wave or non-Q-wave MI) and duration of hospitalization.42

The incidence of overall bleeding complications was lower in the aspirin/ticlopidine group (13.5% [33/243]) compared to the aspirin/warfarin group (21% [21/230]) (P = 0.03). The aspirin/ticlopidine group showed a 41% relative risk reduction in bleeding compared with the aspirin/warfarin group (95% CI, 0.35–0.98). The overall rate of stent occlusions did not differ significantly between the two treatment regimens (P = 0.53). However, acute (< 24 hours) stent occlusions were more frequent in the aspirin/ticlopidine group (2.4%) than in the aspirin/warfarin group (0.4%) (P = 0.06). The aspirin/ticlopidine groups had significantly less subacute (< 24 hours) stent occlusions (3.5% vs. 0.4%) (P = 0.01). Although not statistically significant, there was a lower overall cardiac event rate in the antiplatelet group (5.7%) compared to the anticoagulation group (8.3%) (P = 0.37). In addition, antiplatelet therapy patients had a significantly shorter average hospital stay (4.3 vs. 6.4 days) compared to the anticoagulation therapy patients (P = 0.00001).42
The MATTIS (Multicenter Aspirin and Ticlopidine Trial After Coronary Stenting) study was conducted to evaluate outcomes in high-risk coronary stent implantation patients. The study randomized 350 patients to one of two treatment arms: aspirin (250 mg daily) plus ticlopidine (250 mg twice daily) or aspirin (250 mg daily) plus warfarin (INR 2.5–3.0) daily. Both groups received IV heparin following the procedure. An analysis at 30 days showed 5.6% (10/177) of the patients in the aspirin/ticlopidine group and 11% (19/173) of patients in the aspirin/warfarin group suffered an adverse event (death, myocardial infarction, repeat percutaneous intervention or CABG). The relative risk of developing an adverse event was 1.94 (95% CI, 0.95–4.06) (P=0.07). The secondary endpoint of major vascular access site and/or bleeding complications was seen in 3 of 177 patients (1.7%) in the aspirin/ticlopidine group (95% CI, 0.4–4.9) and in 12 of 173 patients (6.9%) in the aspirin/warfarin group (95% CI, 3.6 to 11.8) (P=0.02). 43

**DISCUSSION**

The major concern when treating patients with combination antiplatelet/anticoagulant therapy is the increased risk of bleeding. The relative risk of upper gastrointestinal bleeding in patients taking aspirin monotherapy, compared with non-aspirin users, is approximately two to 3.5 times greater. The relative risk of gastrointestinal bleeding in patients who receive oral anticoagulants alone is estimated to be two to five times greater than in non-users. Patients receiving a combination of an antiplatelet agent and an oral anticoagulant agent have an even greater risk of bleeding.

The CARS and the ATACS trials for secondary prevention in post-MI/post-unstable angina, respectively, showed somewhat similar results with regard to bleeding events. In the CARS trial, 3 mg of warfarin plus 80 mg of aspirin had a significantly greater risk of spontaneous major hemorrhages compared to 160 mg of aspirin monotherapy (P=0.014). The combined rates of any major hemorrhages, however, showed no difference between the warfarin/aspirin group versus the aspirin-only group (P=0.11). In the ATACS trial, the warfarin/aspirin therapy group experienced a 2.9% (3/105) major-bleed rate compared with no major bleeding events (0/109) in the aspirin monotherapy group.

The valve replacement studies showed somewhat conflicting results. The Cappelleri et al. meta-analysis (1,337 total patients) reported that when patients received combination antiplatelet/anticoagulant therapy, there was one major gastrointestinal bleed for every 1.6 patients in whom stroke was prevented. The risk of major bleeding in patients taking combination therapy was significantly greater than in patients taking anticoagulation monotherapy (P=0.0069). The Meschengieser et al. study, however, showed the combination group to have a decreased risk of bleeding compared to the anticoagulation monotherapy group. Meschengieser et al. compared a total of 503 patients randomized to either low-intensity anticoagulation (INR 2.5–3.5) plus aspirin or high-intensity anticoagulation (INR 3.5–4.5) monotherapy. A 52% reduction in the risk of major bleeding was seen in the combination group, but this difference did not reach statistical significance (P=0.27).

The two major combination therapy versus monotherapy studies (AFASAK II and SPAF III) in atrial fibrillation patients showed similar and interesting results. Both studies experienced an overall low rate of major bleeding events (AFASAK II, 2.3%; SPAF III, 2.4%). In the SPAF III study, the difference in major bleeding rates was not statistically significant between the patients receiving the combination of aspirin 325 mg/day plus a fixed dose of warfarin (0.5–3 mg/day) versus adjusted-dose warfarin (INR 2.0 to 3.0) monotherapy. During the AFASAK II study, the annual rate of major bleeding among the four treatment groups was also not statistically significant (P=0.20). The AFASAK II trial did show a statistically greater number of bleeding events (P=0.003) after three years in the adjusted-dose warfarin group compared to the other three groups (mini-dose warfarin, warfarin plus aspirin, aspirin monotherapy). The authors, however, attribute this difference to a greater number of minor bleeding events in the adjusted-dose warfarin group compared with the other three groups. Both the SPAF III and the AFASAK III trials showed no difference in major bleeding events in combination antiplatelet/anticoagulant therapy patients versus monotherapy-treated patients.

In the studies in which patients received coronary artery stent implantation, a combination of aspirin plus ticlopidine was compared with a combination of aspirin plus warfarin in three separate trials. A study conducted by Leon et al. added a third aspirin monotherapy arm. Leon et al. found aspirin monotherapy to have a significantly lower risk of bleeding complications than both the aspirin/ticlopidine group and the aspirin/warfarin group (P=0.001). No difference, however, was seen when comparing the bleeding risk of aspirin/ticlopidine therapy with aspirin/warfarin therapy (P=0.99).

With respect to bleeding, the results from the FANTASTIC trial were different from the results obtained by Leon et al. In the FANTASTIC trial, patients who received the aspirin/ticlopidine combination had a lower risk of bleeding compared to the aspirin/warfarin group (P=0.03). Patients in the MATTIS trial were also shown to have a decreased risk of bleeding if they were randomized to the aspirin/ticlopidine group rather than the aspirin/warfarin group (P=0.02).

**CONCLUSION**

It is evident that the studies published on patients who have had previous heart attacks indicate that aspirin monotherapy is superior to the combination of aspirin and warfarin in the secondary prevention of MI. The unpublished results of the WARIS-II trial, however, might shed further light on the use of combination therapy in post-MI patients. There appears to be no long-term benefit (at 12 weeks and beyond) from the combination of warfarin and aspirin over aspirin alone in patients with unstable angina/non-Q wave MI.

Patients with mechanical valve replacement have a decreased risk of embolism with combination therapy compared to anticoagulation alone. A 67% reduction in the risk of embolism was seen in the combination group over the anticoagulation group in a meta-analysis of approximately 1,300 patients (P=0.0032). However, a study not included in the meta-analysis refuted these results. No

*continued on page 571*
significant difference in embolic episodes was seen in about 500 patients with mechanical valve replacements who were taking either combination therapy versus anticoagulation therapy alone.

Studies comparing combination therapy with anticoagulation alone in patients with chronic AF have produced conflicting results. Only two published studies have compared combination therapy to monotherapy in patients with AF, and these studies reached different conclusions. The AFASAK II study, which showed no significant difference between the two treatments, used a low fixed dose of warfarin of 1.25 mg per day (median INR 2.0–3.0) was significantly better than combination therapy. The combination therapy in this study used a fixed-dose warfarin of 0.5 to 3.0 mg per day. At this time, it is unclear which therapy is better. The ACCP currently does not recommend the use of aspirin plus low-dose warfarin therapy in patients with lone AF.

More studies will have to be completed in this area, and in particular with adjusted-dose warfarin in combination with aspirin.

Patients receiving intracoronary artery stent implantation clearly achieve a greater benefit from taking the combination of aspirin/ticlopidine or aspirin/clopidogrel in comparison to the combination of aspirin/warfarin or aspirin/monotherapy, as demonstrated in three large randomized trials. As a result, the ACCP no longer recommends the use of warfarin for post-intracoronary stent patients. The ACCP recommends the combination of aspirin/ticlopidine or aspirin/clopidogrel in these patients.

REFERENCES