

# An Appraisal of Dual Antiplatelet Therapy with Clopidogrel and Aspirin for Prevention of Cardiovascular Events

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**Combination antiplatelet therapy, typically with clopidogrel and aspirin, is commonly used for the prevention of cardiovascular events. When used for appropriate indications and duration, its benefits clearly outweigh its risks. However, it is not uncommon for the combination to be used outside of recommended indications or for longer than recommended durations. In these circumstances data are at best unclear and, at worst, indicative of harm. Furthermore, use for one of its indications—prevention of cardiac events after deployment of a coronary stent—is complicated by the type of stent used. This report reviews the evidence surrounding combination antiplatelet therapy with clopidogrel and aspirin, with an emphasis on identifying appropriate indications for and durations of therapy. (J Am Board Fam Med 2009;22:51–56.)**

Primary care physicians (PCPs) often find themselves in the situation in which a patient's cardiologist institutes therapy with clopidogrel in combination with low-dose aspirin, but then defers routine follow-up back to the PCP. This combination offers certain theoretical benefits. Platelet activation is a critical step in the formation of thrombotic clots. Aspirin inhibits the production of thromboxanes, which play a prominent role in platelet activation. Clopidogrel, a thienopyridine, acts by inhibiting adenosine receptors, which play a major role at a different step in platelet activation. Thus, their mechanisms are complementary and may decrease clot formation over either agent alone. Furthermore, resistance to the effects of each agent has been well reported,<sup>1</sup> but resistance to both agents in a given patient should be less frequent. Although this combination of antiplatelet agents has been demonstrated to offer *clinical* benefits under certain circumstances, it does raise problems as well. Most significantly, the reiterative

platelet inhibition increases the likelihood of bleeding. Thus, it is incumbent on the PCP to understand the evidence behind the use of combination therapy and the point at which potential benefits may be offset by its risks. Only then can the PCP make an informed decision about when to return the patient to monotherapy with antiplatelets. Unfortunately, although the literature on this combination of agents is extensive, data regarding the benefits and risks of long-term use are often conflicting. Newer thienopyridines, such as prasugrel, seem to offer both greater benefit and greater risk and may confuse the situation further.<sup>2</sup> This article will outline what is known and make reasonable recommendations for the PCP.

## Indications for Combination Therapy

The primary determinant of using combination therapy is, of course, the indication. An overview of clinical trials investigating the efficacy of the combination of clopidogrel and aspirin has been provided (Table 1). These trials have identified some conditions where combination therapy offers no benefits over monotherapy. Combination therapy has been shown to be no more effective than aspirin alone in primary prevention of coronary or cerebral events in patients at high risk.<sup>3</sup> Aspirin, at a dose of 75 to 162 mg daily, is the preferred treatment for primary prevention; clopidogrel alone is useful in patients with an aspirin allergy.<sup>4</sup> Likewise, combination therapy is inappropriate in patients with a

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**Table 1. Efficacy of Clopidogrel Plus Aspirin in Selected Clinical Trials**

Trial	Patient Population	Endpoint	Event Rate Combination (%)	Event Rate Monotherapy (%)	P
CHARISMA (3)	CAD	CV death, MI, or CVA at 28 months	6.8	7.3	.22
MATCH (5)	CVA	CVA, MI, CV death, or CV hospitalization at 18 months	15.7	16.7*	.244
CLARITY (6)	STEMI	Occlusion, death, or recurrent MI at 8 days	15	21.7	<.001
CURE (9)	NSTEMI	CV death, MI, or CVA at 12 months	9.3	11.4	<.001
PCI-CURE (12)	NSTEMI with PCI	CV death or MI at 8 months	8.8	12.6	.002
CREDO (11)	PCI	Death, MI, or CVA at 12 months	8.5	11.5	.02

\*Clopidogrel monotherapy.

CHARISMA, Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; MATCH, Management of Atherothrombosis with Clopidogrel in High-Risk Patients; CLARITY, Clopidogrel as Adjunctive Reperfusion Therapy; CURE, Clopidogrel in Unstable Angina to Prevent Recurrent Events; PCI-CURE, Percutaneous Coronary Intervention in the Clopidogrel in Unstable Angina to Prevent Recurrent Events; CREDO, Clopidogrel for the Reduction of Events During Observation; CAD, coronary artery disease; CVA, cardiovascular accident; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; CV, cardiovascular; MI, myocardial infarction.

recent stroke or transient ischemic attack because it increases the incidence of major and minor bleeds without offering any therapeutic benefit over clopidogrel alone.<sup>5</sup> The most appropriate indications for the use of combined clopidogrel and aspirin therapy are the treatment of acute coronary syndromes and the prevention of coronary events after placement of a stent.

#### **Acute Coronary Syndromes**

For patients who suffer an ST-segment elevation myocardial infarction and who do not receive stent placement in the course of treatment, current evidence only supports short-term use of combination therapy (roughly 1 to 2 weeks).<sup>6,7</sup> Longer duration of use has not been addressed in these patients, although recent guideline updates consider combination clopidogrel and aspirin therapy reasonable for up to a year.<sup>8</sup> Patients with unstable angina or non-ST-segment elevation myocardial infarction have stronger evidence of benefit from long-term therapy.<sup>9</sup> Treatment with combination therapy for an average duration of 9 months lowered the incidence of cardiovascular death, myocardial infarction, and stroke at 12 months to 9.3% as compared with 11.4% in patients receiving aspirin alone. It should be noted that a significant proportion of patients subsequently received some form of revascularization (balloon angioplasty, stent placement,

or coronary artery bypass graft) during their initial hospitalization, but results remained similar regardless of whether the procedure was performed or not.

#### **Coronary Stents**

Combination therapy is particularly important in the patient receiving coronary stents. It is used for a minimum of 28 days peri- and post-procedurally to lower the incidence of acute (<24 hour) and subacute (1 to 30 days) stent thrombosis.<sup>10</sup> Furthermore, patients receiving clopidogrel plus aspirin for 1 year after a percutaneous coronary intervention (PCI) had a combined incidence of death, myocardial infarction, or stroke of 8.5%, compared with 11.5% in patients receiving combination therapy for 28 days followed by aspirin alone.<sup>11</sup> This corroborated and extended a substudy of the aforementioned unstable angina trial.<sup>12</sup> Patients in that trial undergoing PCI received combination therapy for 1 month and then resumed their randomized therapy for an average of 8 months. This resulted in a combined incidence of cardiovascular death or myocardial infarction of 8.8% at the end of follow-up in those receiving combination therapy compared with 12.6% in those receiving aspirin alone.

These trials were conducted before the advent of drug-eluting stents. Sirolimus-eluting stents were

introduced in the United States in 2003, with paclitaxel-eluting stents following in 2004. Their use was then very quickly and extensively adopted. This has complicated the debate about the appropriate duration of combination antiplatelet therapy considerably because the same mechanism that underlies the drug-eluting stents' benefits also imparts long-term complications.

Originally, stents were developed to reduce the incidence of acute and subacute reocclusion at the site of balloon angioplasty. This is different from the acute and subacute thrombosis that dual antiplatelet therapy helps to prevent. Thrombosis is mediated by disruption of the plaque and exposing the necrotic core, the contents of which stimulate platelet activation. Reocclusion occurs because of both elastic recoil of the artery and vascular thickening and contraction caused by scar formation. The permanent solid structure of the stent minimizes these complications. However, bare metal stents allow the intima to regrow through the structure. If this neointimal growth is excessive it can result in restenosis at the site. Restenosis does not generally result in acute events, but can cause the return of anginal symptoms and impact quality of life to the point where a repeat procedure must be performed.

Drug-eluting stents address this problem by excluding chemicals that inhibit neointimal growth, thus significantly reducing restenosis and subsequent revascularization procedures. However, that neointimal growth helps provide stability to the underlying plaque. Without it, the window for thrombosis caused by exposed plaque extends beyond the 1-month period typical for bare metal stents to at least 3 to 6 months. Failure to comply with dual antiplatelet therapy for at least this period of time is one of the largest risk factors for in-stent thrombosis in those receiving drug-eluting stents. Estimates of the hazard ratio from premature discontinuation of dual antiplatelet therapy range from 13.74<sup>13</sup> to 89.78.<sup>14</sup> Furthermore, postmortem pathology studies have shown re-endothelialization of the vessel may be incomplete even years after the insertion of a drug-eluting stent.<sup>15</sup> This may or may not reflect a direct effect of the eluted drug. The drugs are lipophilic and thus may be retained for some time at the site. However, it also may reflect an inflammatory response to the nonadsorbable polymer. Either way, it does present a theoretical rationale for indefinite use of dual antiplate-

let therapy in patients receiving drug-eluting stents.

Recently, a large number of publications have addressed the incidence of very late (>1 year after procedure) stent thrombosis with drug-eluting stents. They range from single registry data<sup>16</sup> to large meta-analyses of clinical trials.<sup>17</sup> Although the results are not entirely concordant, there seems to be a small excess of very late events when compared with bare metal stents. Interestingly, given the medically acute and serious nature of thromboses, there is not a clear trend toward increased myocardial infarction or death, although a few studies have reported this. In response to this data, the Food and Drug Administration<sup>4</sup> and the American College of Cardiology/American Heart Association<sup>18</sup> both issued guidance suggesting the use of dual antiplatelet therapy for "at least 1 year" in patients receiving drug-eluting stents. They stopped short of recommending indefinite therapy, in large part because it is not known if longer-term therapy will reduce the incidence of very late thromboses or myocardial infarctions.

### **Benefits of Long-Term Use of Combination Therapy**

What scant literature there is on the use of clopidogrel and aspirin for longer than 1 year has yielded inconsistent findings. Results supporting long-term use of combination therapy for patients receiving drug-eluting stents were reported in a study from Duke Medical Center.<sup>19</sup> In this observational trial, patients who took combination therapy for at least 12 months, most of whom continued therapy thereafter, had no deaths or nonfatal myocardial infarctions in the subsequent 12 months. Another group who stopped clopidogrel before 12 months but continued aspirin had a 4.5% adjusted rate of this composite endpoint between 12 and 24 months after their stent placement. There was no difference in second-year event rates in patients who received bare metal stents (4.7% with an initial 12 months of clopidogrel vs 3.6% without). In opposition to these findings, 2 large-scale registries of drug-eluting stent patients suggested that late use or discontinuation of clopidogrel did not effect late stent thrombosis. Twenty-three percent<sup>20</sup> to 50%<sup>13</sup> of late thromboses occurred in the presence of combined antiplatelet therapy. Thus, although there is a theoretical

**Table 2. Bleeding Rates with Long-Term Combination Therapy in Selected Clinical Trials**

Trial	Patient Population	Duration (months)	Major and Minor Bleeds	
			Combination Therapy (%)	Monotherapy (%)
CURE (9)	NSTEMI	9	8.8	5.1
CREDO (11)	PCI	12	14.1	12.3
CHARISMA (3)	CAD	28	3.8	2.6
MATCH (5)	CVA	18	5.1	1.6*
TRITON (2)	ACS with PCI	15	5.0 <sup>†</sup> /3.8	NA

\*Clopidogrel monotherapy.

<sup>†</sup>Prasugrel plus aspirin.

CURE, Clopidogrel in Unstable Angina to Prevent Recurrent Events; CREDO, Clopidogrel for the Reduction of Events During Observation; CHARISMA, Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance; MATCH, Management of Atherothrombosis with Clopidogrel in High-Risk Patients; TRITON, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel; NSTEMI, non-ST-segment elevation myocardial infarction; CAD, coronary artery disease; CVA, cardiovascular accident; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention.

rationale, there are no clear trends in the published evidence to support long-term dual antiplatelet therapy in the drug-eluting stent patient.

Data regarding long-term use in a broader population of patients are also somewhat conflicting. As noted earlier, the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance trial<sup>3</sup> showed no benefit from long-term use (28 months) of combination therapy in a high-risk cardiovascular patient population. However, an interesting contrast was reported in a secondary analysis of the data.<sup>21</sup> Patients with stable cardiovascular disease but without a documented thrombotic event derived no benefit from reducing the combined endpoint of cardiovascular death, myocardial infarction, or stroke over receiving aspirin alone, with even a suggestion of harm (event rate, 6.3% vs 5.7%). Conversely, if patients had a previous myocardial infarction, combination therapy did seem to reduce the subsequent incidence of events relative to aspirin monotherapy (6.6% vs 8.3%). Both groups had significant numbers of patients with a prior PCI, although neither time from PCI nor proportion of stent type was reported.

### Bleeding Risks with Combination Therapy

Although there is no consensus as to the benefit of long-term dual antiplatelet therapy, there is a general conclusion that it does pose bleeding risk. For instance, a case-control study evaluating patients with serious gastrointestinal bleeding suggested adjusted hazard ratios of 1.1 for clopidogrel mono-

therapy, 1.8 for aspirin monotherapy, and 7.4 for their combination when compared with no treatment.<sup>22</sup> A second similarly designed study reported adjusted hazard ratios of 1.67, 1.39, and 3.90, for clopidogrel, aspirin, and their combination, respectively.<sup>23</sup> In terms of absolute numbers, a study including 4 major combination therapy trials yielded an aggregate rate of severe bleeds of 1.8%.<sup>24</sup> A review of those trials also yields additional minor bleeding with a range of 2.1% to 5.3%. The total aggregate event rates for selected trials has been provided in Table 2. As mentioned earlier, a new thienopyridine, prasugrel, could prove even more problematic.<sup>2</sup> In the TRITON study, prasugrel plus aspirin for 15 months yielded a 2.4% rate of major bleeds and 2.6% rate of additional minor bleeds. In the same study, clopidogrel plus aspirin caused a 1.8% rate of major bleeds and a 2.0% rate of minor bleeds. Unfortunately, the time course of the bleeding events in any of these trials was not clearly reported. Possibly, a subset of sensitive patients was selected out fairly early on with the remainder having little increased risk.<sup>21</sup> However, this remains conjecture in the absence of well-designed trials.

### Conclusions

Based on these data, there are some logical recommendations that can be offered (Table 3). Patients treated for acute coronary syndromes without the use of a stent should receive combination clopidogrel and aspirin for at least 1 month, and it is reasonable to lengthen that up to 1 year. Patients

**Table 3. Recommendations for the Use of Clopidogrel with Aspirin**

Indication	Duration	SORT
Primary prevention of cardiovascular events	Avoid	B
Secondary prevention of stroke	Avoid	B
ACS, without stent	1–12 months	A
Bare-metal stent	1–12 months	A
Drug-eluting stent	12 months	C

SORT, strength of recommendation taxonomy;<sup>25</sup> ACS, acute coronary syndrome.

who receive stents, either electively or emergently, are not as clear-cut. Given the recent controversies, the use of bare metal stents may increase. This is probably appropriate but means that general assumptions as to the type of stent placed cannot be made. Although the primary care physician is not usually involved in choosing the type of stent to be placed, it is vital that the PCP find out this information. For patients receiving bare metal stents, combination therapy should be strongly recommended for the first month. Continued therapy out to 1 year may be helpful, but durations longer than that are not supported. For patients receiving drug-eluting stents, 1 year of combination therapy should be encouraged. However, longer term therapy from that point may best be reserved for those with a clear prothrombotic history (ie, previous myocardial infarction) and a relatively low risk of bleeding.

Unfortunately, there is no standard definition as to who is at low risk of bleeding. There are certain patients who are clearly at high risk. These include patients with a personal history of significant bleed, advanced age, thrombocytopenia, recent stroke or transient ischemic attack, or those taking chronic anticoagulants or nonsteroidal anti-inflammatory drugs. Other factors that may contribute to bleeding include low body weight, alcoholism, poorly controlled hypertension, and impaired renal function.

Indefinite use of the combination of clopidogrel and aspirin should not be the rule at this time. The data in patients receiving drug-eluting stents sometimes show benefit but are far from compelling. For patients not receiving these stents, data are sparse and suggest little, if any, benefit. Long-term trials are needed to ascertain if any reduction in cardiovascular events is of sufficient magnitude to offset

increases in the risk of bleeding. Until such time, PCPs should feel comfortable discontinuing clopidogrel after 1 year in many, if not most, instances.

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