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Aspirin + clopidogrel therapy: How does your care compare to the evidence?

Did you know that patients with drug-eluting stents should receive dual therapy for at least a year, and that dual therapy for stroke prevention may put patients at risk?

Practice recommendations

- Patients with drug-eluting stents should receive dual therapy (aspirin + clopidogrel) for at least 12 months (**B**).
- For patients who have had an ischemic stroke or transient ischemic attack, adding aspirin to clopidogrel increases the risk of hemorrhage and is not routinely recommended (**A**).
- Adding clopidogrel to aspirin is not more effective than aspirin alone in the primary prevention of coronary artery disease in patients with multiple risk factors. In fact, it may actually cause harm in patients without established cardiovascular disease (**B**).

Strength of recommendation (SOR)
A Good-quality patient-oriented evidence
B Inconsistent or limited-quality patient-oriented evidence
C Consensus, usual practice, opinion, disease-oriented evidence, case series

Jessica is 72 years old and a new patient of yours, having recently moved to the area. She has a history of non-ST elevation myocardial infarction (NSTEMI) 8 months ago, hypertension, and hyperlipidemia. Her NSTEMI did not require stent placement. Upon reviewing her medications, you see she is taking aspirin 81 mg, clopidogrel 75 mg, simvastatin 80 mg, and metoprolol XL 100 mg. The patient isn't sure how long she has been on clopidogrel and wants to know if she still needs to take it because she has a high co-pay.

What would you tell her?

John is a 60-year-old patient of yours with a history of coronary artery disease, who had an elective catheterization 18 months ago at which time a sirolimus drug-eluting stent was placed. Also at that time, he was placed on aspirin 325 mg daily and clopidogrel 75 mg daily. The patient says he has a friend at work who also has a coronary stent, but his friend stopped taking clopidogrel 12 months after his stent was placed. The patient wants to know why he is still taking clopidogrel and when he can stop it.

What would you tell him?

Anna is a 68-year-old patient of yours who has uncontrolled type 2 diabetes. She still smokes a pack a day, as she has done for the last 53 years, her BMI

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is 43, and her LDL is 103 on 80 mg of simvastatin. Her additional meds include lisinopril, 70/30 insulin, and a daily aspirin. Despite her inability to quit smoking or lose weight, she is compliant with her medications. You are both very concerned about her future risk of cardiovascular disease. You consider whether she would benefit from adding clopidogrel to aspirin in order to prevent future coronary events.

Do you write a prescription for clopidogrel, 75 mg/day?

In your conversation with Jessica, you should have told her that she needs to take the clopidogrel for another 4 months (making it 1 year of therapy following her NSTEMI). 2007 guidelines from the American Heart Association and the American College of Cardiology support this approach.[1]

In your discussion with John, you should have told him that for drug-eluting stents, recent studies have shown an additional benefit to continuing dual therapy longer than 1 year, and that consideration should be given to continuing clopidogrel indefinitely.[1,2]

In the case of Anna, your patient with multiple atherothrombotic risk factors, you should have opted against writing her a prescription for clopidogrel. The evidence suggests that putting her on clopidogrel might actually increase her risk of cardiovascular death.[3]

These 3 cases demonstrate how much our understanding of dual antiplatelet therapy (aspirin + clopidogrel) has evolved over the past few years—and even months. Given the volume of information we must sift through daily, it is easy to occasionally miss a study or update. The result? You may be underutilizing combination antiplatelet therapy when treatment is indicated. Or, you may be combining aspirin and clopidogrel in situations where there is insufficient data to support its use—and possibly, in situations where it is associated with an increased incidence of adverse events.

This review can help.

Here we have summarized the latest trials and recommendations on dual antiplatelet therapy as they pertain to:

- acute coronary syndrome (ACS)
- coronary stents
- stroke
- the primary prevention and secondary prevention of distant cardiovascular events.

Should you need a quick reference tool for your office, we have also included an at-a-glance summary of current recommendations (**TABLE**).

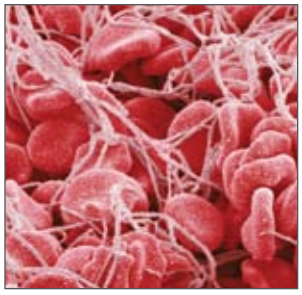
Dual therapy reduces future MI risk in ACS

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial in 2001 was one of the first combination trials published; it looked at combination antiplatelet therapy in ACS.[4] CURE enrolled patients with NSTEMI and randomized them to receive aspirin plus clopidogrel or aspirin plus placebo for 3 to 12 months. Out of the total number of patients, 9.3% of the dual therapy group reached the endpoint of cardiovascular death, MI, or stroke, compared with 11.4% of the aspirin-only group (relative risk [RR]=0.80 for dual therapy). Further, the rate of each component of the composite outcome tended to be lower in the combination-therapy group.

In particular, there was an RR of 0.77 for MI and, more specifically, an RR of 0.60 for Q-wave MI in the dual therapy group. There was, however, a 1.38 RR for major bleeding (defined as bleeding resulting in disability, vision loss, or transfusion of at least 2 units of blood) in the combination-therapy group vs the aspirin-only group (3.7% to 2.7%). However, neither rates of life-threatening bleeding nor hemorrhagic stroke were significantly different between the 2 groups.

Overall, the CURE trial showed that combining clopidogrel and aspirin was superior to aspirin alone in preventing repeat ischemic events in patients with NSTEMI for up to 12 months, and this

Colored scanning electron micrograph of a blood clot.



FAST TRACK

Combining aspirin and clopidogrel is superior to aspirin alone in preventing repeat MI for up to 12 months

conclusion was supported by a 2007 Cochrane review.[5]

The Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)-Thrombolysis in Myocardial Infarction (TIMI) trial studied the short-term (30 days) effect of clopidogrel combined with aspirin and fibrinolytic therapy in patients with ST elevation MI (STEMI).[6] The study showed that the addition of clopidogrel improved the patency rate of infarct-related arteries and reduced short-term ischemic complications.

There are, however, no trials looking at combination antiplatelet therapy for STEMI patients beyond 30 days.

GUIDELINE RECOMMENDATIONS

Unstable angina/non-ST elevation MI/acute coronary syndrome

The American Heart Association/American College of Cardiology Guidelines recommend that patients with unstable angina (UA)/NSTEMI or ACS receive both clopidogrel 75 mg and aspirin (75 to 162 mg/day) for at least a month, and preferably, up to 12 months (**TABLE**).[1,7]

FAST TRACK

Drug-eluting stents may require protracted—and possibly indefinite—dual therapy

Prolonged therapy needed with drug-eluting stents

The Clopidogrel for the Reduction of Events During Observation (CREDO) trial, published in 2002, enrolled patients referred for percutaneous coronary intervention (PCI), about 89% of whom received at least 1 cardiac stent, and followed them for 12 months.[8] All patients received aspirin and clopidogrel up to day 28. From day 29 to 1 year, half the patients continued dual antiplatelet therapy and the other half received aspirin plus placebo.

The primary outcome measure was death, MI, or stroke. The combination therapy group showed a relative risk reduction of 37.4% (RR=0.73) in the combined endpoint, compared with the aspirin/placebo group. CREDO did not show a significant difference in risk for major bleeding between the 2 groups.

Further data from the CURE trial was released in 2004. Researchers conducted a subgroup analysis to see if there was a benefit to combination antiplatelet therapy for patients with NSTEMI who underwent PCI or coronary artery bypass grafting (CABG). This further analysis revealed an RR of 0.72 for the outcome of CV death, MI, or stroke with the addition of long-term (3 to 12 months) clopidogrel to aspirin in the PCI group and an RR of 0.89 for the CABG group with combination therapy. These findings led researchers to conclude that combination antiplatelet therapy is beneficial for high-risk patients undergoing revascularization for NSTEMI regardless of the type of revascularization.[9]

A 2007 observational study conducted at the Duke Heart Center investigated the addition of long-term clopidogrel to aspirin for both drug-eluting stents (DES) and bare-metal stents (BMS).[2] The study population was split into 4 groups:

- combination antiplatelet therapy in patients with DES,
- aspirin alone with DES,
- combination therapy with BMS, and
- aspirin alone with BMS.

Follow-up was conducted at 6, 12, and 24 months. For patients with DES, continuing clopidogrel with aspirin therapy was associated with a significant decrease in death or MI at 24 months (3.1% vs 7.2%, RR=0.43). For patients with BMS, researchers found no significant benefit for those who continued dual antiplatelet therapy longer than 6 months compared with aspirin alone.

The data from this study led the authors to speculate that drug-eluting stents may require protracted—and possibly indefinite—dual antiplatelet therapy with clopidogrel and aspirin. Additional research with a large clinical trial is necessary to assess the appropriate length of treatment with combination antiplatelet therapy after DES, as

TABLE

Dual antiplatelet therapy: The recommendations at a glance

Unstable angina/ non-ST elevation MI/ acute coronary syndrome (without stenting)	**American Heart Association/American College of Cardiology** Low dose aspirin (75 to 162 mg per day) indefinitely (Strength of Recommendation [SOR]: **A**), and clopidogrel 75 mg per day for at least 1 month (SOR: **A**) and ideally up to 1 year (SOR: **B**)[1,7]
Cardiac stent placement	**American Heart Association/American College of Cardiology** ***Bare metal stent*** • Full dose aspirin (162 - 325 mg per day) for 1 month (SOR: **B**) after implantation, then continued indefinitely at low dose (SOR: **A**)[1] • Clopidogrel 75 mg per day added to aspirin for a minimum of 1 month, and ideally up to 1 year (SOR: **B**)[1] ***Drug-elutingstent (DES)*** • Full dose aspirin for at least 3 months after sirolimus DES implantation, and 6 months after paclitaxel DES implantation, then continued indefinitely at low dose (SOR: **B**)[1] • Clopidogrel 75 mg per day should be added to aspirin for a minimum of 12 months (SOR: **B**)[1]
Stroke	**American Heart Association/American Stroke Association** • Combination of aspirin (50 - 325 mg per day) and extended-release dipyridamole is suggested instead of aspirin alone (SOR: **A**), and clopidogrel may be considered instead of aspirin alone (SOR: **B**)[17] • The addition of aspirin to clopidogrel increases the risk of hemorrhage and is not routinely recommended for ischemic stroke or TIA patients (SOR: **A**)[17]
Primary prevention/ secondary prevention of distant cardiovascular events	• There is no evidence or guidelines supporting combination therapy for the prevention of cardiovascular events in high-risk patients with multiple risk factors • Adding clopidogrel to aspirin is not more effective than aspirin alone and may cause harm in patients without established cardiovascular disease (SOR: **B**) [3]

it may extend even longer than current recommendations suggest.

An analysis of the Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER) registry illustrates the catastrophic consequences of premature discontinuation of dual antiplatelet therapy.[10] This study of 500 patients with acute MI treated with DES revealed a striking increase in mortality rate related to discontinuation of dual antiplatelet therapy within 3 months of their initial MI. Patients who prematurely stopped dual therapy had a mortality rate of 7.5% over the next 11 months compared to 0.7% in patients who continued dual antiplatelet therapy for a minimum of 3 months.

Of note: Researchers say that patients who self-discontinued the dual therapy were less likely to have been given instructions about their medication at discharge. In addition, these patients were less likely to have completed high school and more likely to avoid health care because of cost.

Finally, a recent study that evaluated the safety of off-label use of drug-eluting stents revealed further data in support of prolonged use of dual antiplatelet therapy in this group.[11] (Off-label use included, among other things, using sirolimus- and paclitaxel eluting stents on lesions that were longer than specified in the stent manufacturer's "information for use.") Forty-seven percent of patients who received DES were for off-label indications.

Among the off-label patients, the 1-year rate of death, MI, or stent thrombosis was 7.7% for standard dual therapy duration (3 months for sirolimus-eluting stents and 6 months for paclitaxel-eluting stents) compared with 6.0% (RR=0.78) for prolonged duration (defined as beyond standard duration).

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Patients who self-discontinued dual therapy were less likely to have been given instructions about their medication at discharge

CONTINUED

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Combination aspirin and clopidogrel therapy is not routinely recommended in stroke patients

GUIDELINE RECOMMENDATIONS

Cardiac stent placement

Current American Heart Association/American College of Cardiology recommendations state that full-dose aspirin (162–325 mg/day) should be used for 1 month after BMS implantation, at least 3 months after sirolimus DES implantation, and 6 months after paclitaxel DES implantation, then continued indefinitely at low dose (75 to 162 mg/day).[1]

Clopidogrel 75 mg/day should be added to aspirin for a minimum of 1 month, and ideally up to a year for BMS; and for a minimum of 12 months for all DES regardless of type.[1] In addition to the duration and type of therapy, the American Heart Association states it is not appropriate to withhold dual therapy in stent patients for minor surgery or dental procedures within their recommended treatment period.[12]

Of note: The American Heart Association and American College of Cardiology guidelines, cited above, are an August 2007 revision to the groups' 2002 guidelines.[1] Although specifically written for UA/NSTEMI, the revision states that clopidogrel should be added to aspirin for at least 12 months in "all post-PCI patients receiving DES." A revised AHA/ACC PCI guideline, however, has not yet been published to reflect these new data and recommendations.

Bleeding rates offset stroke prevention benefits

The Management of ATherothrombosis with Clopidogrel in High-risk patients (MATCH) trial is the only major trial that has evaluated combination clopidogrel and aspirin therapy for secondary prevention of stroke.[13] The MATCH trial, first published in 2004, differed from the cardiovascular antiplatelet trials in that it used clopidogrel in its control group instead of aspirin.

Patients who'd had a recent ischemic stroke or transient ischemic attack (TIA) and at least 1 additional vascular risk factor were randomized to receive clopidogrel plus aspirin therapy or clopidogrel plus placebo for 18 months. Primary outcome measure was a composite of ischemic stroke, MI, vascular death, or rehospitalization for acute ischemia. Although researchers observed a consistent reduction of vascular events in the combination therapy group, the differences did not reach statistical significance. In addition, higher bleeding rates "offset any beneficial effect" of combination therapy.

Overall, treatment with aspirin and clopidogrel compared with aspirin alone might prevent 10 ischemic events per 1000 treated (not statistically significant) at a cost of 13 life-threatening hemorrhages per 1000 treated. The researchers concluded that there was no demonstrable benefit of adding aspirin to clopidogrel for secondary prevention of stroke.

A major limitation of this study was that the majority of patients enrolled had lacunar strokes, a stroke subtype that is not believed to be of pure atherothrombotic origin and that has the lowest recurrence rates.[13] Future studies on secondary stroke prevention will address issues of stroke subtype and location.[14]

Other trials that did not specifically look at clopidogrel + aspirin therapy for noncardioembolic stroke but examined relevant issues also warrant mention:

- **The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events—W (ACTIVE W) trial** compared an aspirin + clopidogrel combination to warfarin in patients with atrial fibrillation.[15] ACTIVE W showed warfarin to be superior to combination antiplatelet therapy for prevention of vascular events including stroke, non-central nervous system emboli, MI, or vascular death (RR=1.44 for combination therapy).
- **The Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial** investigated combination antiplatelet therapy in patients with recently symptomatic carotid artery stenosis.[16] Researchers in this small study used doppler ultrasound to see if combination therapy would lead to a reduction in asymptomatic microembolism from the carotid plaques. Pa-

tients received clopidogrel plus aspirin or aspirin alone for 7 days. The patients in the combination group had a 40% relative reduction in microembolism.

Clearly, the CARESS trial opens the door for further study into clinically important outcomes for carotid artery stenosis and dual antiplatelet therapy.

GUIDELINE RECOMMENDATIONS

Stroke

The current American Heart Association/American Stroke Association guidelines recommend aspirin plus extended-release dipyridamole or clopidogrel alone for the secondary prevention of noncardioembolic stroke. The guidelines state that the "addition of aspirin to clopidogrel increases risk of hemorrhage and is not routinely recommended." However, aspirin + clopidogrel combination therapy may be appropriate in stroke patients with recent ACS or vascular stents.[17]

When prevention efforts can harm patients

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial studied the value of using aspirin + clopidogrel combination therapy for primary or secondary prevention of distant coronary events (longer than 12 months).[3] CHARISMA researchers studied patients with either multiple cardiac risk factors (termed "asymptomatic") or clinically evident cardiovascular disease (termed "symptomatic") who did not have a current indication for dual antiplatelet therapy (ie, recent MI or coronary stent).

The patients were randomized to receive aspirin plus clopidogrel or aspirin plus placebo and were followed for a median length of 28 months. The primary outcome measure was a combination of MI, stroke, or cardiovascular death. Overall, there was no significant difference in the primary endpoint, which occurred in 6.8% of the combination group and in 7.3% of the aspirin-only group (RR=0.93).

Subgroup analysis revealed that asymptomatic patients actually had a 20% increase in primary events with the addition of clopidogrel to aspirin (6.6% vs 5.5%, RR=1.20), and an increase in death (3.9% vs 2.2%, RR=1.77). In the symptomatic group, however, there was a "marginally significant" reduction in primary events, with 6.9% of patients in the combination group and 7.9% of patients in the aspirin-only group experiencing primary events (RR=0.88). The rate of severe bleeding in the combination group was 1.7% compared with 1.3% in the placebo group (RR=1.25).

The authors of CHARISMA propose a hypothesis to explain the seemingly paradoxical effect of an increase of primary endpoints in the asymptomatic group. They suggest that established vascular disease could be a proxy for hyperactive platelets. Thereby, the action of combination therapy may be more effective in patients with established vascular disease and less effective in patients with normal platelets.

GUIDELINE RECOMMENDATIONS

Primary prevention/secondary prevention of distant cardiovascular events

No evidence or recommendations currently exist to support using dual antiplatelet therapy for primary prevention or secondary prevention of cardiovascular events in patients not covered under current American Heart Association/American College of Cardiology guidelines for recent ACS or stent/PCI. Adding clopidogrel to aspirin may cause harm in patients without established cardiovascular disease.[3]

Ongoing studies explore stroke subtypes, CABG

Because of insufficient or conflicting data, it is unclear whether dual therapy is advisable for a number of disease states, including specific stroke subtypes,

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Adding clopidogrel to aspirin may cause harm in patients without established cardiovascular disease

peripheral artery disease, and CABG.[18] The following ongoing dual therapy studies may provide some answers:[14]

- **The Secondary Prevention of Small Subcortical Strokes (SPS3) trial** is investigating secondary prevention of subcortical stroke.
- **The Fast Assessment of Stroke and Transient ischemic attack to prevent Early Recurrence (FASTER) trial** is also investigating secondary prevention of stroke.
- **The Aortic arch Related Cerebral Hazard (ARCH) trial** is investigating aortic plaques and stroke.
- **The Effects of Physical Training, ASA and Clopidogrel on the Walking Capacity of Patients with Stage II PAD trial** is investigating walking capacity in patients with peripheral artery disease. ■

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Ongoing trials are investigating dual therapy in specific stroke subtypes