Clopidogrel: Who, When, and How?

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Clopidogrel has demonstrated improved outcomes for patients with acute coronary syndromes in several large randomized controlled trials. However, some questions exist about the use of clopidogrel in practice. Who benefits from clopidogrel? When should clopidogrel treatment be initiated? How much clopidogrel should be administered and for how long? Reviewing the results from trials completed to date that have assessed clopidogrel in patients with acute coronary syndromes may help to answer some of these questions. Clinical trial results have demonstrated a reduction in the composite endpoint of death, myocardial infarction, or stroke for patients with acute coronary syndromes who received clopidogrel plus aspirin compared with aspirin alone. For this patient population, early treatment with clopidogrel more than 6 hours before percutaneous coronary intervention (PCI) was associated with a reduction in the risk of death or recurrent ischemic events. The benefits of initiating patients on a 600-mg loading dose of clopidogrel before PCI have been demonstrated in several clinical trials. Clinical trial results and current guidelines recommend long-term treatment with clopidogrel for up to 1 year after PCI.

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Clopidogrel, in addition to aspirin therapy, has demonstrated improvement in outcomes for patients with acute coronary syndromes (ACS) in several large well-controlled clinical trials. However, the optimal time to initiate clopidogrel treatment for patients with ACS or patients undergoing percutaneous coronary intervention (PCI) is still currently under debate. Another unresolved issue is determining the patients for whom the benefits of longer-term clopidogrel treatment outweigh the risks.

Who?

The first question to ask is which patients should be treated with clopidogrel? There are trials across the full spectrum of ACS, each showing benefit. For patients in the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial with unstable angina (UA) or non–ST-segment elevation myocardial infarction (NSTEMI), there was a 20% reduction in cardiovascular death, myocardial infarction (MI), or stroke seen when adding clopidogrel to aspirin.[1] This benefit was seen in patients treated medically, those who underwent PCI, or those who underwent coronary artery bypass grafting (CABG) surgery. Clopidogrel was beneficial in high-, medium-, and low-risk patients, and each subgroup assessed.

For patients with ST-segment elevation myocardial infarction (STEMI), the Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction (CLARITY–TIMI) 28 trial demonstrated that the addition of clopidogrel to a regimen of aspirin, heparin, and a thrombolytic agent improved infarct-related artery patency rates and reduced ischemic complications by 20%.[2] Bleeding rates were similar between the clopidogrel and placebo groups in this trial. Likewise, in the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) assessing 45,852 patients with MI (93% with STEMI), the addition of clopidogrel to aspirin was associated with a 7% reduction in mortality and a 9% reduction in major cardiovascular events, without an increase in intracranial hemorrhage or major bleeding.[3]

In the Clopidogrel for the Reduction of Events During Observation (CREDO) trial, patients scheduled to undergo elective PCI were randomized to pretreatment with either a 300-mg loading dose of clopidogrel or placebo. All patients received 28 days of clopidogrel at 75 mg/day after the procedure as well as 1 year of aspirin therapy. Patients assigned to the clopidogrel group continued on clopidogrel at 75 mg/day for 1 year.[4] At 1-year follow-up, long-term clopidogrel treatment was associated with a 27% reduction in the composite endpoint of death, MI, or stroke. Thus, the question of "who?" is relatively simple—all patients with ACS or undergoing PCI should receive clopidogrel (assuming no excessive bleeding risks), but issues of timing arise when factoring in the treatment strategy.

Patients presenting with ACS or undergoing PCI should receive clopidogrel.

When?

The timing of clopidogrel treatment is also a major issue and centers around the fact that clopidogrel is an irreversible inhibitor of the $P2Y_{12}$ receptor, a component of the adenosine diphosphate receptor. Thus, if clopidogrel is given, and a patient needs to proceed to CABG, the antiplatelet effect will still be evident, and the patient will face an increased risk of bleeding.[1] This issue is in the forefront of management of patients with ACS, where 2 approaches have evolved. One approach is to initiate treatment early (eg, in the emergency department) as in the clinical trials. The other approach is to wait until the patient undergoes cardiac catheterization, when the coronary anatomy can be defined. For the second approach, if the patient requires CABG, then clopidogrel is not initiated; however, if the planned treatment for the patient is PCI or medical therapy, then clopidogrel is initiated.[5]

When treatment with clopidogrel is started early, an advantage is the potential to reduce early ischemic events.[6] Pretreatment with clopidogrel is also beneficial for patients undergoing PCI[7]; however, a disadvantage of initiating clopidogrel pretreatment in patients prior to catheterization/PCI is the potential for increased bleeding in patients who go on to early CABG.[1] The approach of using clopidogrel only after cardiac catheterization avoids the increased bleeding risk for patients who undergo CABG; however, using this strategy results in loss of the early ischemic benefit, as well as the pretreatment benefit in patients undergoing PCI. Thus, the issue becomes a balance of the benefits and risks of early treatment with clopidogrel.

An advantage of early treatment with clopidogrel is the potential to reduce early ischemic events.

Early Initiation

The clinical outcomes of early initiation of clopidogrel in ACS,[6] as well as the benefits and risk in patients undergoing CABG from the CURE trial, have been published.[8] Over the first 24 hours, there is a 34% reduction in relative risk of death or recurring ischemic events.[6] Thus, by starting clopidogrel in the emergency department for patients with ACS, by the next day, for every 100 patients treated, 1 less patient will experience death, MI, stroke, or severe recurrent ischemia.

Pretreatment Before PCI

Another advantage of early treatment with clopidogrel is seen among patients who undergo PCI. In the Percutaneous Coronary Intervention–Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (PCI–CURE) study in the subgroup of patients undergoing PCI in the CURE trial, a clear benefit was seen for patients treated on average 6 to 10 days prior to PCI (thus, at a full, steady-state level). There was a 30% reduction in cardiovascular death, MI, or urgent revascularization.[7] A similar reduction of 30% was seen for just death or MI. It is worth noting that immediately after stent placement, patients in the placebo group of the PCI–CURE trial were treated with clopidogrel or ticlopidine (open label) for 1 month. Thus, during the first 30 days after PCI, when all patients were receiving active therapy, the benefit was clearly due to pretreatment.

Evaluation of more rapid timing of pretreatment before PCI was evaluated in the CREDO trial. Patients received a 300-mg loading dose of clopidogrel between 3 and 24 hours before undergoing PCI.[4] Overall, there was an 18.5% reduction in death, MI, or urgent target vessel revascularization at 28 days. However, in the time subgroup analysis, patients who received clopidogrel between 3 and 6 hours before PCI showed no benefit from pretreatment with a 300-mg loading dose. This would be akin to administering clopidogrel in the catheterization laboratory holding area in the morning before the procedure was carried out in the afternoon (and would represent a longer duration of pretreatment than the frequent practice of giving a loading dose in the cardiac catheterization laboratory minutes before PCI). However, for patients who received clopidogrel more than 6 hours before PCI (basically the day before), there was a 38.6% reduction in death, MI, or urgent target vessel revascularization. These results were similar to those seen in the PCI–CURE trial. Thus, it appears that clopidogrel dosing needs to be at the steady-state level to achieve the maximal benefit with pretreatment before PCI.

A third trial, the Percutaneous Coronary Intervention–Clopidogrel as Adjunctive Reperfusion Therapy (PCI–CLARITY) trial also found a dramatic and significant benefit of clopidogrel pretreatment (300 mg loading dose, then 75 mg once daily), with a 46% reduction in the odds of cardiovascular death, MI, or stroke within 30 days after PCI compared with "no pretreatment" that actually included loading of clopidogrel "on the table" before PCI.[9]

A meta-analysis of 3 trials showed that pretreatment with clopidogrel leads to a significant 29% reduction in cardiovascular death or MI (after PCI) compared with no pretreatment. Additionally, there was a 30% reduction in events before PCI.[9] Results from this meta-analysis led to a Class I, Grade A evidence recommendation for clopidogrel pretreatment in the 2005 American College of Cardiology/American Heart Association/Society for Cardiac Angiography and Interventions (ACC/AHA/SCAI) Guideline Update for Percutaneous Coronary Intervention.[10]

How Much?

As a means of attaining a steady-state level of antiplatelet effect more rapidly, interest in the use of a 600-mg loading dose of clopidogrel has grown. Müller and colleagues evaluated the level of platelet inhibition associated with clopidogrel use and found that a steady-state level of platelet inhibition could be achieved within 2 hours after administration of a 600-mg loading dose.[11] In contrast, a loading dose of 300-mg achieved approximately 75% of the steady-state level of platelet inhibition by the 2- to 4-hour time point.[11] This effect has been validated in several subsequent trials.[12-14] However, in these trials, the full steady-state level was not achieved until 6 to 8 hours after treatment with 300 mg.

Evidence of the clinical benefit of a 600-mg loading dose of clopidogrel has come from 2 sources. First, an indirect comparison of the results from the Intracoronary Stenting and Antithrombotic Regimen–Rapid Early Action for Coronary Treatment (ISAR–REACT) trial and prior trials of glycoprotein (GP) IIb/IIIa inhibitors suggested a benefit of pretreatment with clopidogrel. In ISAR–REACT, low-risk patients undergoing elective PCI were all given a 600-mg loading dose of clopidogrel at least 2 hours before PCI (average 7 hours) and 75 mg twice daily through the time of hospital discharge.[15] Patients were then randomized to either abciximab or placebo. There was no clinical benefit for the prevention of adverse cardiac events associated with abciximab treatment.[15]

This contrasts with the results from the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial and the Evaluation of Percutaneous Transluminal Coronary Angioplasty to Improve Long-term Outcome with Abciximab Glycoprotein IIb/IIIa Blockade (EPILOG) trial. In these trials, abciximab was seen (without pretreatment of clopidogrel) to reduce cardiovascular endpoints by 40% to 50%.[16,17] Thus, by comparing this ISAR–REACT trial to the other trials, it suggests that a large degree of the clinical benefits that can be achieved with the GP IIb/IIIa inhibitor could be accomplished with the high-dose clopidogrel pretreatment.

Kandzari and colleagues have analyzed the timing and found that pretreatment for 2 hours or more before PCI was associated with the same low event rates,[18] thus matching the platelet studies[11-13] that found that a 600-mg loading dose achieved a steady-state level within 2 hours. Pretreatment less than 2 hours before the procedure (eg, on the cardiac catheterization table, just minutes before PCI) has not been tested and would not be expected to confer the same benefit because there would not be sufficient time to achieve adequate platelet inhibition.

Two additional studies also suggested benefit from pretreatment with a 600-mg dose of clopidogrel. In a study of patients with ACS, all patients were pretreated with 600 mg of clopidogrel at least 2 hours before PCI and randomized to receive either abciximab or placebo. There was a 25% reduction in events in the abciximab group, and a 30% reduction in events seen in the troponin-positive patients.[19] This compares to a 70% reduction with abciximab seen when clopidogrel pretreatment is not used,[20] suggesting benefit of the clopidogrel pretreatment.

The beneficial effect of a 600-mg loading dose of clopidogrel is also supported by the results of the Antiplatelet Therapy for Reduction of Myocardial Damage During Angioplasty (ARMYDA-2) trial, which directly compared 300-mg and 600-mg doses of clopidogrel.[21] In this trial of 254 patients undergoing PCI, who received clopidogrel 4 to 8 hours before the procedure, the 600-mg loading dose of clopidogrel was associated with a significantly lower rate of major cardiovascular events.

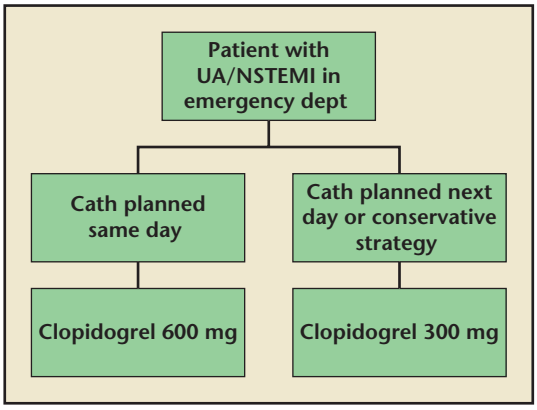


Figure 1. *An approach to choosing the initial loading dose of clopidogrel. Cath, catheterization; NSTEMI, non–ST-segment elevation myocardial infarction; UA, unstable angina. Reprinted with permission from Cannon CP.*[23]

The Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions (CURRENT/OASIS-7) trial to validate this benefit is currently under way. This trial has enrolled 14,000 patients with ACS undergoing early invasive strategy with intent for PCI.[22] Results from the CURRENT/OASIS-7 trial are expected in 2008.

Reduction in death or MI was seen out to 1 year in the CURE and CREDO trials.

An approach currently used by the author depends on the planned course of treatment. If the patient is admitted with UA/NSTEMI and cardiac catheterization is planned for the same day, a 600-mg loading dose of clopidogrel is administered (Figure 1).[23] However, if catheterization is planned for the next day, or a conservative strategy is planned a 300-mg loading dose of clopidogrel is administered (Figure 1).

How Long?

The long-term results of clopidogrel treatment after ACS and after PCI are remarkably similar—all showing benefit out to the duration of the trials—1 year. In the CURE trial, a 20% benefit was seen, in PCI–CURE, a 30% reduction in death or MI was also seen out to 1 year, and in CREDO, in elective PCI patients, there was a 27% relative risk reduction in death, MI, or stroke when treating patients with clopidogrel for 1 year after PCI when compared with treatment of 1 month. The number of patients needed to treat for 1 year after PCI, to prevent 1 patient from experiencing death, MI, or stroke, was 33 in the CREDO trial, and only 25 in the PCI–CURE trial. Thus, clopidogrel is quite an effective treatment in preventing major cardiovascular events in this PCI population.

The significant clinical benefit of clopidogrel is likely not isolated to the stented segment alone, but rather, long-term clopidogrel treatment may also prevent development of thrombus, and thus associated clinical events, at other plaques in the coronary tree. Several studies have looked at the diffuseness of disease and found that in patients with ACS, most have other vulnerable plaques in additional to the culprit lesion.[24] In a trial that used angioscopy and angiography to evaluate the coronary arteries of patients after MI, no apparent stenoses were seen in the nonculprit arteries; however, with angioscopy, multiple vulnerable plaques were seen in the coronary arteries.[24] Aggressive medical treatment after PCI is directed at these other vulnerable plaques,

which represent "hidden disease"—the target of long-term treatment with high-dose statins, aspirin, angiotensin-converting enzyme inhibitors, and now clopidogrel. Thus, in patients with stent placement, there are 2 simultaneous indications for the use of clopidogrel. One indication is to prevent stent thrombosis, and the other is to prevent clinical events, largely emerging from other vulnerable plaques. The optimal duration of clopidogrel to prevent clinical events has recently been debated, especially with the advent of drug-eluting stents, and this issue is discussed elsewhere in this supplement.

An analysis from the PCI–CURE trial further supports this idea, where event curves were evaluated based on whether a stent was used.[25] By comparing those who got a stent versus those who had no stent (ie, balloon angioplasty), researchers demonstrated an outstanding example of what is gained from preventing events in the vasculature beyond the stented segment. In patients who had no stent placed, there was a 44% reduction in cardiovascular death or MI out to 1 year, which was greater than the benefit seen in the patients who had stents placed (approximately 30%). This is a clear demonstration that much of the late benefits of clopidogrel in patients after PCI can be in coronary segments that are not the stented segment, which reemphasizes the importance of the long-term treatment for all the other blockages and vulnerable plaques throughout the coronary tree.

Balancing Benefit With Bleeding Risk

The benefit of adding an antithrombotic agent must be balanced with the risk of bleeding. As with the use of aspirin, heparin, low-molecular-weight heparin, or GP IIb/IIIa inhibitors, the addition of clopidogrel increases bleeding risk as compared with aspirin used alone (3.7% at 1 year vs 2.7%, respectively; relative risk, 1.38; 95% confidence interval; $P = .001$).[1] The good news is that the risk of bleeding can be reduced by lowering the dose of aspirin. When using low-dose aspirin (75-100 mg), the risk of bleeding is approximately half the risk as when using standard-dose aspirin (200-325 mg).[26] Interestingly, the relative risk of bleeding at 1 year was 3% for patients treated with low-dose aspirin plus clopidogrel, which was lower than the bleeding risk for patients treated with 325 mg of aspirin alone (3.75%).[26] Thus, as new therapies to protect against recurrent events are added, the safety profile and efficacy/safety balance can be improved by decreasing the dosages of other therapies.

Patients Undergoing CABG Surgery

The potential for increased bleeding among patients who must proceed to CABG has raised the question of timing for initiating clopidogrel treatment. Details on the patients in the CURE trial who underwent CABG were helpful in providing data on the risk and extent of bleeding—and of the benefit of early treatment with clopidogrel.[8] The initial data indicated that among patients treated with clopidogrel up until 5 days before CABG (which is recommended in the guidelines), the risk of major bleeding, as defined by the CURE trial, was increased from 6.3% for those treated with aspirin alone up to 9.6% for those treated with the combination of aspirin and clopidogrel (relative risk, 1.53; $P = .06$).[1] If patients waited more than 5 days after the last dose of clopidogrel before undergoing CABG, there was no excessive bleeding. In the more detailed analysis, which used the more stringent Thrombolysis in Myocardial Infarction (TIMI) or the Global Utilization of Streptokinase or Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) definitions for major bleeding, the incidence of major bleeding was not increased.[8] This indicates that the use of clopidogrel within 5 days before CABG is associated with more bleeding, but it falls into the mild to moderate category and is not a life-threatening degree of bleeding. Of note, a more recent analysis of CABG bleeding from the CLARITY–TIMI 28 trial showed no increase in TIMI major or minor bleeding even in patients receiving clopidogrel within 5 days of surgery, although the sample size of the cohort was small.[27]

The CABG analysis from the CURE trial also demonstrated the *benefits* of receiving clopidogrel both before and after CABG. The benefits were similar for patients undergoing CABG, patients undergoing PCI, and patients who were treated medically, with an approximately 20% reduction in events. For patients who underwent CABG during the initial hospitalization, the risk decreased from 16.7% for aspirin alone to 13.2% for aspirin plus clopidogrel for an absolute 3.5% reduction in the risk of cardiovascular death, MI, or stroke.[8] This matches the increase in (moderate) bleeding for the patients who received clopidogrel within 5 days of CABG. Thus, for the CABG patients themselves, it is an even trade between an increased risk of moderate bleeding and a decreased risk of death, MI, or stroke. This puts in perspective the benefit that is achieved for the increased risk in bleeding.

Interestingly, the CABG analysis of the CURE trial data shows that most of the benefit in patients receiving clopidogrel who underwent CABG during the initial hospitalization was achieved preoperatively. For every 1000 patients with ACS who underwent CABG, receipt of clopidogrel at

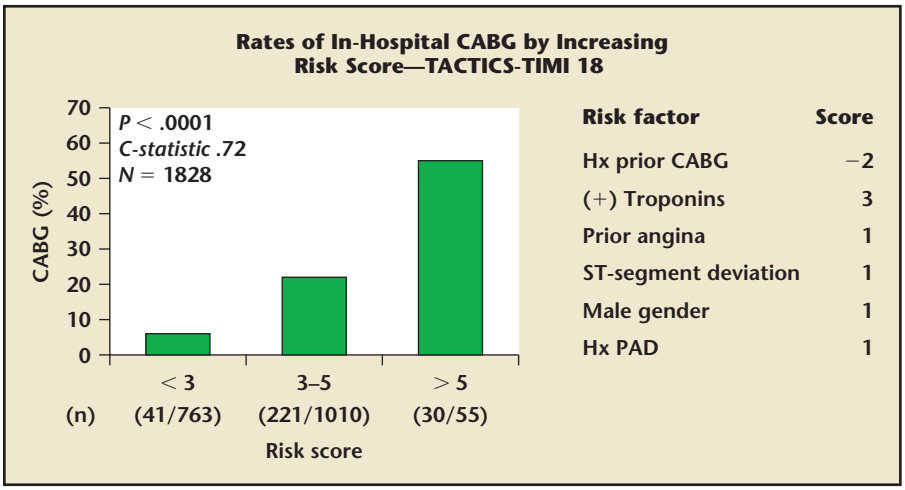


Figure 2. *A risk score to predict the need for CABG among patients presenting with acute coronary syndromes. CABG, coronary artery bypass grafting; Hx, history; PAD, peripheral arterial disease; TACTICS–TIMI 18, Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis in Myocardial Infarction trial. Adapted with permission from Sadanandan S et al.*[28]

hospital admission prevented 21 events of deaths, MI, or stroke.[8] This also appears to match clinical judgment. A patient with ACS, with diffuse 3-vessel disease, and who requires urgent CABG is one of the highest-risk patients and thus, it stands to reason that he or she will accrue the biggest benefit in terms of cardiovascular events prevented.

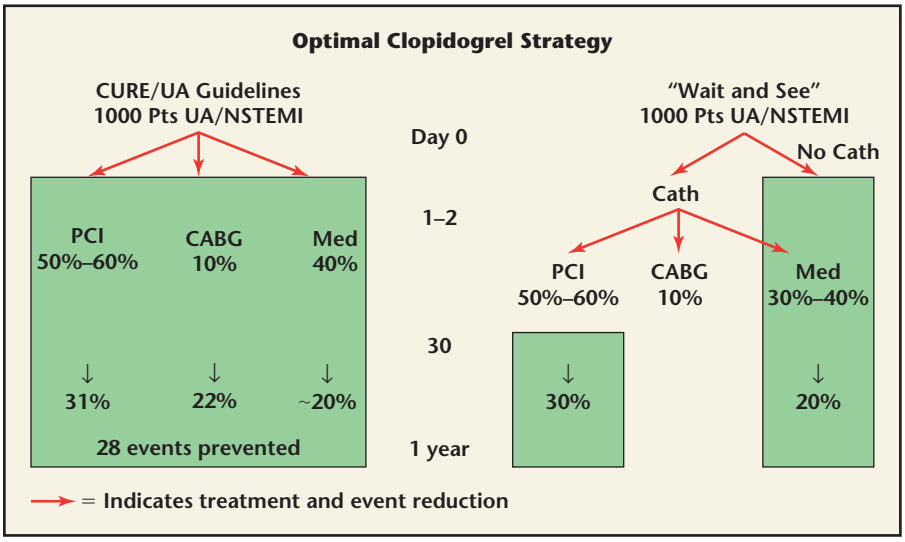
Clinicians might want to identify patients who may need urgent CABG and not treat those patients with clopidogrel. The TIMI Study Group developed a risk score to predict the need for early CABG. A history of prior CABG *decreases* a patient's risk of repeat CABG; therefore, these patients can usually be treated with early clopidogrel without fear of increased bleeding from CABG.[28] In addition, for patients who had a risk score of more than 5, the chance of needing early CABG was 55% (Figure 2). To avoid the excess bleeding risk, some clinicians may not want to treat these patients early with clopidogrel. On the other hand, given the benefits of early administration, some clinicians may choose to treat these patients with early clopidogrel despite the increased risk in order to get the benefit.

Conclusions

Data from the PCI–CURE and CREDO trials indicated that treatment with clopidogrel needs to be started at least 6 hours before the PCI procedure to obtain the post-PCI benefit. Using a 600-mg loading dose of clopidogrel may shorten this time period to 2 or 3 hours. However, this same benefit would not be likely when a loading dose was administered within minutes of the PCI. These results emphasize the need to administer clopidogrel before arrival to the catheterization laboratory to get the benefit of pretreatment. Benefit has also been seen for patients undergoing CABG who are treated with clopidogrel preoperatively.

Of the patients who present with ACS, approximately 50% to 60% will undergo PCI and between 8% and 20% (approximately 10% in current registries) will proceed to CABG (Figure 3). Thus, if 1 thousand patients are treated with clopidogrel in the emergency department, an additional 10 to 12 major cardiac events (death, MI, or stroke) would be prevented at the expense of causing 1 TIMI minor bleed in a patient who subsequently underwent CABG. The issue of timing comes down to weighing the benefits against the risks—the balance for which clinicians strive

Figure 3. *Benefit achieved by early (left) versus post-cardiac catheterization initiation of clopidogrel. CABG, coronary artery bypass grafting; cath, catheterization; CURE, Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events; med, medical therapy; NSTEMI, non–ST-segment elevation myocardial infarction; pt, patient; PCI, percutaneous coronary intervention; UA, unstable angina. Reprinted with permission from Cannon CP.*[23]



when making treatment management decisions. In this case, early treatment has a relatively small risk but a large benefit in terms of preventing major cardiac events. Thus, this balance emphasizes the importance of early antiplatelet therapy with clopidogrel to maximize the benefit in patients with ACS. ■

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Main Points

- Clopidogrel has demonstrated improvement in outcomes for patients with acute coronary syndromes (ACS) in several large randomized controlled trials.
- In clinical trials, clopidogrel was associated with a reduction in the composite endpoint of death, myocardial infarction, or stroke for patients with ACS.
- Treatment with clopidogrel more than 6 hours before percutaneous coronary intervention (PCI) was associated with a reduction in the risk of death or recurrent ischemic events.
- Initiating clopidogrel at a loading dose of 600 mg for patients scheduled to undergo PCI was associated with a significantly lower rate of major cardiovascular events.
- Clinical trial results support guidelines recommending clopidogrel treatment for up to 9 months after PCI, and in fact indicate that patients might benefit from daily treatment with clopidogrel for up to 1 year post procedure.
- To avoid the risk of major bleeding, clinicians might elect not to initiate clopidogrel for patients who might require urgent coronary artery bypass grafting surgery; however, these risks need to weighed against the potential benefits from initiating clopidogrel before intervention.
- As with all decisions related to treatment management, clinicians must find the balance between the benefits and risks of treating an individual patient with clopidogrel.

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