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Controversies in non-ST-elevation acute coronary syndromes and percutaneous coronary interventions

ABSTRACT

Non-ST-elevation myocardial infarction (MI) and unstable angina represent the majority of acute coronary syndromes. Recent studies have helped clarify treatment strategies. Drug-eluting stents have reduced the problem of restenosis, but questions remain about the length of time patients need dual antiplatelet therapy.

KEY POINTS

The data favor an aggressive strategy of routine catheterization, rather than a conservative strategy of catheterization only if a patient develops recurrent, spontaneous, or stress-induced ischemia.

Early percutaneous intervention (within 24 hours) may be beneficial in patients at higher risk, but not necessarily in those at lower risk.

Drug-eluting stents appear safe, assuming dual antiplatelet therapy is used. It is unclear how long this therapy needs to be continued.

The choice of revascularization strategy—bypass surgery, bare-metal stent, or drug-eluting stent—should be individualized based on the risk of restenosis, thrombosis, and other factors.

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Despite all the attention paid to ST-segment-elevation myocardial infarction (MI), in terms of sheer numbers, non-ST-elevation MI and unstable angina are where the action is. Acute coronary syndromes account for 2.43 million hospital discharges per year. Of these, 0.46 million are for ST-elevation MI and 1.97 million are for non-ST-elevation MI and unstable angina.[1,2]

A number of recent studies have begun to answer some of the pressing questions about treating these types of acute coronary syndromes. In this article, I update the reader on these studies, along with recent findings regarding stenting and antiplatelet agents. As you will see, they are all interconnected.

TO CATHETERIZE IS BETTER THAN NOT TO CATHETERIZE

In the 1990s, a topic of debate was whether patients presenting with unstable angina or non-ST-elevation MI should routinely undergo catheterization or whether they would do just as well with a conservative approach, ie, undergoing catheterization only if they developed recurrent, spontaneous, or stress-induced ischemia. Now, the data are reasonably clear and favor an aggressive strategy.[3]

Mehta et al[4] performed a meta-analysis of seven randomized controlled trials (N = 9,212 patients) of aggressive vs conservative angiography and revascularization for non-ST-elevation MI or unstable angina. The results favored the aggressive strategy. At 17 months of follow-up, death or MI had occurred in 7.4% of patients who received the aggressive therapy compared with 11.0% of those who

received the conservative therapy, for an odds ratio of 0.82 (P = .001).

The CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implemention of the ACC/AHA Guidelines?) Quality Improvement Initiative[5] analyzed data from a registry of 17,926 patients with non-ST-elevation acute coronary syndrome who were at high risk because of positive cardiac markers or ischemic electrocardiographic changes. Overall, 2.0% of patients who received early invasive care (catheterization within the first 48 hours) died in the hospital compared with 6.2% of those who got no early invasive care, for an adjusted odds ratio of 0.63 (95% confidence interval [CI] 0.52–0.77).

The investigators also stratified the patients into those at low, medium, and high risk, using the criteria of the PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin [eptifibatide] Therapy) risk score. There were fewer deaths with early invasive therapy in each risk group, and the risk reduction was greatest in the high-risk group.[5]

In a retrospective study, fewer repeat revascularizations were needed with multivessel intervention than with culprit-vessel intervention

Bavry et al[6] performed an updated meta-analysis of randomized trials. At a mean follow-up of 24 months, the relative risk of death from any cause was 0.75 in patients who received early invasive therapy.

In another meta-analysis, O'Donoghue et al[7] found that the odds ratio of death, MI, or rehospitalization with acute coronary syndromes was 0.73 (95% CI 0.55–0.98) in men who received invasive vs conservative therapy; in women it was 0.81 (95% CI 0.65–1.01). In women, the benefit was statistically significant in those who had elevations of creatine kinase MB or troponin but not in those who did not, though the benefit in men appeared to be less dependent on the presence of biomarker abnormalities.

MUST ANGIOGRAPHY BE DONE IN THE FIRST 24 HOURS?

Although a number of trials showed that a routine invasive strategy leads to better outcomes than a conservative strategy, until recently we had no information as to whether the catheterization needed to be done early (eg, within the first 24 hours) or if it could be delayed a day or two while the patient received medical therapy.

Mehta et al[8] conducted a trial to find out: the Timing of Intervention in Acute Coronary Syndrome (TIMACS) trial. Patients were included if they had unstable angina or non-ST-elevation MI, presented to a hospital within 24 hours of the onset of symptoms, and had two of three high-risk features: age 60 years or older, elevated cardiac biomarkers, or electrocardiographic findings compatible with ischemia. All received standard medical therapy, and 3,031 were randomly assigned to undergo angiography either within 24 hours after randomization or 36 or more hours after randomization.

At 6 months, the primary outcome of death, new MI, or stroke had occurred in 9.6% of the patients in the early-intervention group and in 11.3% of those in the delayed-intervention group, but the difference was not statistically significant. However, the difference in the rate of a secondary end point, death, MI, or refractory ischemia, was statistically significant: 9.5% vs 12.9%, P = .003, owing mainly to less refractory ischemia with early intervention.

The patients were also stratified into two groups by baseline risk. The rate of the primary outcome was significantly lower with early intervention in high-risk patients, but not in those at intermediate or low risk. Thus, early intervention may be beneficial in patients at high risk, such as those with ongoing chest pain, but not necessarily in those at low risk.

LEAVE NO LESION BEHIND?

Coronary artery disease often affects more than one segment. Until recently, it was not known whether we should stent all stenotic segments in patients presenting with non-ST-elevation MI or unstable angina, or only the "culprit lesion."

Shishehbor et al[9] examined data from a Cleveland Clinic registry of 1,240 patients with acute coronary syndrome and multivessel coronary artery disease who underwent bare-metal stenting. The median follow-up was 2.3 years. Using a propensity model to match patients in the two groups with similar baseline character-

istics, they found that the rate of repeat revascularization was less with multivessel intervention than with culprit-only stenting, as was the rate of the combined end point of death, MI, or revascularization, but not that of all-cause mortality or the composite of death or MI.

BARE-METAL VS DRUG-ELUTING STENTS: BALANCING THE RISKS AND BENEFITS

After a patient receives a stent, two bad things can happen: the artery can close up again either gradually, in a process called restenosis, or suddenly, via thrombosis.

Drug-eluting stents were invented to solve the problem of restenosis, and they work very well. Stone et al[10] pooled the data from four double-blind trials of sirolimus (Rapamune) stents and five double-blind trials of paclitaxel (Taxol) stents and found that, at 4 years, the rates of target-lesion revascularization (for restenosis) were 7.8% with sirolimus stents vs 23.6% with bare-metal stents ($P < .001$), and 10.1% with paclitaxel stents vs 20.0% with bare-metal stents ($P < .001$).

Thrombosis was much less common in these studies, occurring in 1.2% of the sirolimus stent groups vs 0.6% of the bare-metal stent groups ($P = .20$), and in 1.3% of the paclitaxel stent groups vs 0.9% of the bare-metal stent groups ($P = .30$).[10]

However, drug-eluting stents appear to increase the risk of thrombosis later on, ie, after 1 year. Bavry et al,[11] in a meta-analysis, calculated that when stent thrombosis occurred, the median time after implantation was 15.5 months with sirolimus stents vs 4 months with bare-metal stents ($P = .0052$), and 18 months with paclitaxel stents vs 3.5 months with bare-metal stents ($P = .04$). The absolute risk of very late stent thrombosis after 1 year was very low, with five events per 1,000 patients with drug-eluting stents vs no events with bare-metal stents ($P = .02$). Nevertheless, this finding has practical implications. How long must patients continue dual antiplatelet therapy? And what if a patient needs surgery a year later?

Restenosis is not always so gradual

Although stent thrombosis is serious and often fatal, bare-metal stent restenosis is not always benign either, despite the classic view that stent restenosis is a gradual process that results in exertional angina. Reviewing 1,186 cases of bare-metal stent restenosis in 984 patients at Cleveland Clinic, Chen et al[12] reported that 9.5% of cases presented as acute MI (2.2% as ST-elevation MI and 7.3% as non-ST-elevation MI), and 26.4% as unstable angina requiring hospitalization.

A Mayo Clinic study[13] corroborated these findings. The 10-year incidence of clinical bare-metal stent restenosis was 18.1%, and the incidence of MI was 2.1%. The 10-year rate of bare-metal stent thrombosis was 2%. Off-label use, primarily in saphenous vein grafts, increased the incidence; other correlates were prior MI, peripheral arterial disease, and ulcerated lesions.

Furthermore, bare-metal stent thrombosis can also occur later. We saw a case that occurred 13 years after the procedure, 3 days after the patient stopped taking aspirin because he was experiencing flu-like symptoms, ran out of aspirin, and felt too sick to go out and buy more. The presentation was with ST-elevation MI. The patient recovered after treatment with intracoronary abciximab (ReoPro), percutaneous thrombectomy, balloon angioplasty, and, eventually, bypass surgery.[14]

About 10% of cases of restenosis with bare-metal stents present as acute coronary syndromes

No difference in risk of death with drug-eluting vs bare-metal stents

Even though drug-eluting stents pose a slightly higher risk of thrombosis than bare-metal stents, the risk of death is no higher.[15]

I believe the reason is that there are competing risks, and that the higher risk of thrombosis with first-generation drug-eluting stents and the higher risk of restenosis with bare-metal stents essentially cancel each other out. For most patients, there is an absolute benefit with drug-eluting stents, which reduce the need for revascularization with no effect in terms of either increasing or decreasing the risk of MI or death. Second-generation drug-eluting stents may have advantages in reducing rates of death or MI compared with first-generation drug-eluting stents, though this remains to be proven conclusively.

The right revascularization for the right patient

Bavry and I[16] developed an algorithm for de-

ciding on revascularization, posing a series of questions:

- Does the patient need any form of revascularization?
- Is he or she at higher risk of both stent thrombosis and restenosis, as in patients with diabetes, diffuse multivessel disease with bifurcation lesions, or chronic total occlusions? If so, coronary artery bypass grafting remains an excellent option.
- Does he or she have a low risk of restenosis, as in patients without diabetes with focal lesions in large vessels? If so, one could consider a bare-metal stent, which would probably be more cost-effective than a drug-eluting stent in this situation.
- Does the patient have relative contraindications to drug-eluting stents? Examples are a history of noncompliance with medical therapy, financial issues such as lack of insurance that would make buying clopidogrel (Plavix) a problem, long-term anticoagulation, or anticipated need for surgery in the next few years.

If a drug-eluting stent is used, certain measures can help ensure that it is used optimally. It should often be placed under high pressure with a noncompliant balloon so that it achieves contact with the artery wall all around. One should consider intravascular ultrasonographic guidance to make sure the stent is well opposed if it is in a very calcified lesion. Dual antiplatelet therapy with clopidogrel and aspirin should be given for at least 1 year, and if there is no bleeding, perhaps longer, pending further data.[16]

With drug-eluting stents, dual antiplatelet therapy should be given for at least 1 year

LEAVE NO PLATELET ACTIVATED?

Platelets have several types of receptors that, when bound by their respective ligands, lead to platelet activation and aggregation and, ultimately, thrombus formation. Antagonists to some of these receptors are available or are being developed.[17]

For long-term therapy, blocking the process "upstream," ie, preventing platelet activation, is better than blocking it "downstream," ie, preventing aggregation. For example, clopidogrel, ticlopipine (Ticlid), and prasugrel (Effient) have active metabolites that bind to a subtype of the adenosine diphosphate receptor and prevent platelet activation, whereas the glycoprotein IIb/IIIa inhibitors such as abciximab work downstream, binding to a different receptor and preventing aggregation.[18]

Dual therapy for 1 year is the standard of care after acute coronary syndromes

The evidence for using dual antiplatelet therapy (ie, aspirin plus clopidogrel) in patients with acute coronary syndromes without ST-elevation is very well established.

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial,[19] published in 2001, found a 20% relative risk reduction and a 2% absolute risk reduction in the incidence of MI, stroke, or cardiovascular death in patients randomly assigned to receive clopidogrel plus aspirin for 1 year vs aspirin alone for 1 year ($P < .001$). In the subgroup of patients who underwent percutaneous coronary intervention, the relative risk reduction in the incidence of MI or cardiovascular death at 1 year of follow-up was 31% ($P = .002$).[20]

As a result of these findings, the cardiology society guidelines[21] recommend a year of dual antiplatelet therapy after acute coronary syndromes, regardless of whether the patient is treated medically, percutaneously, or surgically.

But what happens after clopidogrel is withdrawn? Ho et al[22] retrospectively analyzed data from Veterans Affairs hospitals and found a spike in the incidence of death or MI in the first 90 days after stopping clopidogrel treatment. This was true in medically treated patients as well as in those treated with percutaneous coronary interventions, in those with or without diabetes mellitus, in those who received a drug-eluting stent or a bare-metal stent, and in those treated longer than 9 months.

The investigators concluded that there might be a "clopidogrel rebound effect." However, I believe that a true rebound effect, such as after withdrawal of heparin or warfarin, is biologically unlikely with clopidogrel, since clopidogrel irreversibly binds to its receptor for the 7- to 10-day life span of the platelet. Rather, I believe the phenomenon must be due to withdrawal of protection in patients at risk.

In stable patients, dual therapy is not as beneficial

Would dual antiplatelet therapy with clopid-

ogrel and aspirin also benefit patients at risk of atherothrombotic events but without acute coronary syndromes?

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial[23] included 15,603 patients with either clinically evident but stable cardiovascular disease or multiple risk factors for atherothrombosis. They were randomly assigned to receive either clopidogrel 75 mg/day plus aspirin 75 to 162 mg/day or placebo plus aspirin. At a median of 28 months, the groups did not differ significantly in the rate of MI, stroke, or death from cardiovascular causes.

However, the subgroup of patients who had documented prior MI, ischemic stroke, or symptomatic peripheral arterial disease did appear to derive significant benefit from dual therapy.[24] In this subgroup, the rate of MI, stroke, or cardiovascular death at a median follow-up of 27.6 months was 8.8% with placebo plus aspirin compared with 7.3% with clopidogrel plus aspirin, for a hazard ratio of 0.83 (95% CI 0.72–0.96, $P = .01$). Unstented patients with stable coronary artery disease but without prior MI derived no benefit.

Bleeding and thrombosis: The Scylla and Charybdis of antiplatelet therapy

However, with dual antiplatelet therapy, we steer between the Scylla of bleeding and the Charybdis of thrombosis.[25]

In the CHARISMA subgroup who had prior MI, ischemic stroke, or symptomatic peripheral arterial disease, the incidence of moderate or severe bleeding was higher with dual therapy than with aspirin alone, but the rates converged after about 1 year of treatment.[24] Further, there was no difference in fatal bleeding or intracranial bleeding, although the rate of moderate bleeding (defined as the need for transfusion) was higher with dual therapy (2.0% vs 1.3%, $P = .004$).

I believe the data indicate that if a patient can tolerate dual antiplatelet therapy for 9 to 12 months without any bleeding issues, he or she is unlikely to have a major bleeding episode if dual therapy is continued beyond this time.

About half of bleeding events in patients on chronic antiplatelet therapy are gastrointestinal. To address this risk, in 2008 an expert committee from the American College of Cardiology, American College of Gastroenterology, and American Heart Association issued a consensus document[26] in which they recommended assessing gastrointestinal risk factors in patients on antiplatelet therapy, such as history of ulcers (and testing for and treating *Helicobacter pylori* infection if present), history of gastrointestinal bleeding, concomitant anticoagulant therapy, and dual antiplatelet therapy. If any of these were present, the committee recommended considering a proton pump inhibitor. The committee also recommended a proton pump inhibitor for patients on antiplatelet therapy who have more than one of the following: age 60 years or more, corticosteroid use, or dyspepsia or gastroesophageal reflux symptoms.

Some ex vivo platelet studies and observational analyses have suggested that there might be an adverse interaction between clopidogrel and proton pump inhibitors due to a blunting of clopidogrel's antiplatelet effect. A large randomized clinical trial was designed and launched to determine if a single-pill combination of the proton pump inhibitor omeprazole (Prilosec) and clopidogrel would be safer than clopidogrel alone when added to aspirin. Called COGENT-1 (Clopidogrel and the Optimization of GI Events Trial), it was halted early in 2009 when it lost its funding. However, preliminary data did not show an adverse interaction between clopidogrel and omeprazole.

About half of bleeding events in patients on chronic antiplatelet therapy are gastrointestinal

What is the right dose of aspirin?

Steinhubl et al[27] performed a post hoc observational analysis of data from the CHARISMA trial. Their findings suggested that higher doses of aspirin are not more effective than lower doses for chronic therapy. Furthermore, in the group receiving clopidogrel plus aspirin, the incidence of severe or life-threatening bleeding was significantly greater with aspirin doses higher than 100 mg than with doses lower than 100 mg, 2.6% vs 1.7%, $P = .040$.

A randomized, controlled trial called Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions (CURRENT/OASIS 7)[28] recently reported that higher-dose aspirin (ie, 325 mg) may be better than lower

dose aspirin (ie, 81 mg) in patients with acute coronary syndromes undergoing percutaneous coronary intervention and receiving clopidogrel. During this 30-day study, there was no increase in overall bleeding with the higher dose of aspirin, though gastrointestinal bleeding was slightly increased.[29] In a factorial design, the second part of this trial found that a higher-dose clopidogrel regimen reduced stent thrombosis.[29]

Should nonresponders get higher doses of clopidogrel?

In vitro, response to clopidogrel shows a normal bell-shaped distribution.[30] In theory, therefore, patients who are hyperresponders may be at higher risk of bleeding, and those who are hyporesponders may be at risk of ischemic events.

A clinical trial is under way to examine whether hyporesponders should get higher doses. Called GRAVITAS (Gauging Responsiveness With a VerifyNow Assay Impact on Thrombosis and Safety), it will use a point-of-care platelet assay and then allocate patients to receive either standard therapy or double the dose of clopidogrel. The primary end point will be the rate of cardiovascular death, nonfatal MI, or stent thrombosis at 6 months.

In a randomized trial, there were fewer end point events with prasugrel than with clopidogrel, but more bleeding

Is prasugrel better than clopidogrel?

Prasugrel (Effient) is a new drug of the same class as clopidogrel, ie, a thienopyridine, with its active metabolite binding to the same platelet receptor as clopidogrel and inhibiting platelet aggregation more rapidly, more consistently, and to a greater extent than clopidogrel. Prasugrel was recently approved by the Food and Drug Administration. But is it better?[31]

The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction (TRITON-TIMI 38) compared prasugrel and clopidogrel in 13,608 patients with moderate- to high-risk acute coronary syndromes who were scheduled to undergo percutaneous coronary intervention.[32]

Overall, prasugrel was better. At 15 months, the incidence of the primary end point (death from cardiovascular causes, nonfatal MI, or nonfatal stroke) was significantly lower with prasugrel therapy than with clopidogrel in the entire cohort (9.9% vs 12.1%, hazard ratio 0.81, 95% CI 0.73–0.90, $P < .001$), in the subgroup with ST-segment elevation MI, and in the subgroup with unstable angina or non-ST-elevation MI.

However, there was a price to pay. The rate of major bleeding was higher with prasugrel (2.4% vs 1.8%, hazard ratio 1.32, 95% CI 1.03–1.68, $P = .03$). Assessing the balance between the risk and the benefit, the investigators identified three subgroups who did not derive a net clinical benefit from prasugrel: patients who had had a previous stroke or transient ischemic attack (this group actually had a net harm from prasugrel), patients 75 years of age or older, and patients weighing less than 60 kg (132 pounds).

More work is needed to determine which patients are best served by standard-dose clopidogrel, higher doses of clopidogrel, platelet-assay-guided dosing of clopidogrel, or prasugrel.[24]

Short-acting, potent intravenous platelet blockade with an agent such as cangrelor is theoretically appealing, but further research is necessary.[33,34] Ticagrelor, a reversible adenosine diphosphate receptor antagonist, provides yet another potential option in antiplatelet therapy for acute coronary syndromes. In the recent PLATO trial (Study of Platelet Inhibition and Patient Outcomes), compared with clopidogrel, ticagrelor reduced the risk of ischemic events, including death.[35,36] Here, too, there was more major bleeding (unrelated to coronary artery bypass grafting) with ticagrelor.

Thus, clinical assessment of an individual patient's ischemic and bleeding risks will continue to be critical as therapeutic strategies evolve.

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