5. Peterson JC, Adler S, Burkart JM, et al. Blood pressure control, proteinuria, and the progression of renal disease: the Modification of Diet in Renal Disease Study. Ann Intern Med 1995; 123:754-62.
6. The ESCAPE Trial Group. Strict blood-pressure control and progression of renal failure in children. N Engl J Med 2009;361: 1639-50.
7. Bianchi S, Bigazzi R, Campese VM. Intensive versus conventional therapy to slow the progression of idiopathic glomerular diseases. Am J Kidney Dis 2010;55:671-81.
8. Jafar TH, Stark PC, Schmid CH, et al. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. Ann Intern Med 2003;139:244-52.
9. National Kidney Foundation. K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. (Accessed July 27, 2010, at http://www.kidney.org/professionals/kdoqi/guidelines_bp/guide_9.htm.)
10. Jolly SE, Burrows NR, Chen SC, et al. Racial and ethnic differences in albuminuria in individuals with estimated GFR greater than 60 mL/min/1.73 m(2): results from the Kidney Early Evaluation Program (KEEP). Am J Kidney Dis 2010;55:Suppl 2: S15-S22.

Fine-Tuning Therapy for Acute Coronary Syndromes

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Aspirin and clopidogrel are mainstays of therapy for patients presenting with an acute coronary syndrome. National guidelines dictate that at the time of the patient's presentation to an emergency department, these therapies should be given expeditiously, whether or not percutaneous coronary intervention is planned. In this issue of the *Journal*, Mehta et al. report on the results of the Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events–Seventh Organization to Assess Strategies in Ischemic Syndromes (CURRENT–OASIS 7) trial, which evaluated alternative dosing regimens for both of these agents.[1]

In this trial, in contrast to other recent acute coronary syndrome trials,[2,3] patients with an acute coronary syndrome were randomly assigned before their planned coronary angiographic assessment rather than after it. The trial had a 2-by-2 randomized design with comparisons of double-dose clopidogrel (a 600-mg loading dose on day 1 and 150 mg daily for 6 days, followed by 75 mg daily) with standard-dose clopidogrel (a 300-mg loading dose, followed by 75 mg daily) and of higher-dose aspirin (300 to 325 mg daily) with lower-dose aspirin (75 to 100 mg daily). At 30 days, there were no significant differences in the primary outcome measure of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in either of the comparisons. The rates of major bleeding were higher in the double-dose clopidogrel group than in the single-dose clopidogrel group. In contrast, only the rates of minor bleeding were increased in the higher-dose aspirin group as compared with the lower-dose aspirin group. Complete follow-up of patients was outstanding at 99.9%.

On the basis of this robust trial, one could readily conclude that no change in practice is warranted and close the books. However, there are at least three important insights arising from these data that I believe should guide clinical practice in the years to come.

First, when the dosing regimens of aspirin were evaluated on a risk–benefit basis, the lower-dose regimen emerged the winner, with equivalent efficacy but lower rates of minor bleeding than the higher-dose regimen. The lower rate of minor bleeding may not impress clinical trialists, but it certainly has relevance for our patients and their clinicians. It is time for the proponents of higher-dose aspirin to concede defeat and modify clinical practice.

Second, there were two components of the double-dose clopidogrel group: a 600-mg loading dose (as compared with the standard 300-mg dose) and an additional 6 days of the double dose at 150 mg (as compared with 75 mg) per day. A well-conducted meta-analysis has demonstrated that the 600-mg loading dose is effective and safe, and I concur with many of my colleagues who have adopted this dosing in clinical practice.[4] However, there appears to be no role for the routine double dosing of clopidogrel in the subsequent 6 days, particularly in light of the higher rates of major bleeding. The question of whether a longer duration of double-dose clopidogrel might have proved to be effective was beyond the scope of the CURRENT–OASIS 7 trial, but it is compelling and deserves further consideration. Although promising reductions in the rate of stent thrombosis were noted, double-dose clopidogrel did not meet prespecified criteria for superiority in the subgroup of patients who underwent percutaneous coronary intervention. Clinically significant stent-thrombosis events leading to cardiovascular death or

myocardial infarction would have been accounted for in the primary outcome measure.

Third, subgroup analyses in this trial showed a remarkably consistent treatment effect in the comparison groups for both the aspirin dose comparison and the clopidogrel dose comparison. A lack of power to detect differences in important subgroups such as patients with diabetes prompts the question of whether targeting high-risk subpopulations for higher-dose regimens may be more optimal than a wholesale approach of treating all comers in the same way.[5] This issue is at the heart of a major ongoing debate in the clinical-trials world. Figure 1 summarizes my fine-tuned therapy recommendations for acute coronary syndromes. These recommendations are based on previous guidelines and the present data.

One development that is of concern in the interpretation of the results of the CURRENT–OASIS 7 trial arises from apparent discrepancies between the reporting of the trial at the annual meeting of the European Society of Cardiology in 2009[6] and the publication of the trial findings 1 year later in the *Journal.* During the hotline presentation at the meeting, it was concluded that the use of double-dose clopidogrel significantly reduced major cardiovascular events in patients undergoing percutaneous coronary intervention. It is clear that this conclusion differs from that of the current article, which reports that the trial failed to demonstrate superiority of double-dose clopidogrel over standard dosing for the reduction of cardiovascular events in the interventional subgroup. The conclusions reported at the meeting led many cardiologists to adopt the double-dose clopidogrel strategy, thus leading to more clopidogrel being prescribed. This outcome underscores the need for simultaneous publication of high-impact clinical trials when they are presented at international meetings.

From the CURRENT–OASIS 7 trial, we have learned not only about the optimal dosing of aspirin and clopidogrel in acute coronary syndromes but also valuable lessons regarding the design, interpretation, and reporting of pivotal and definitive clinical trials.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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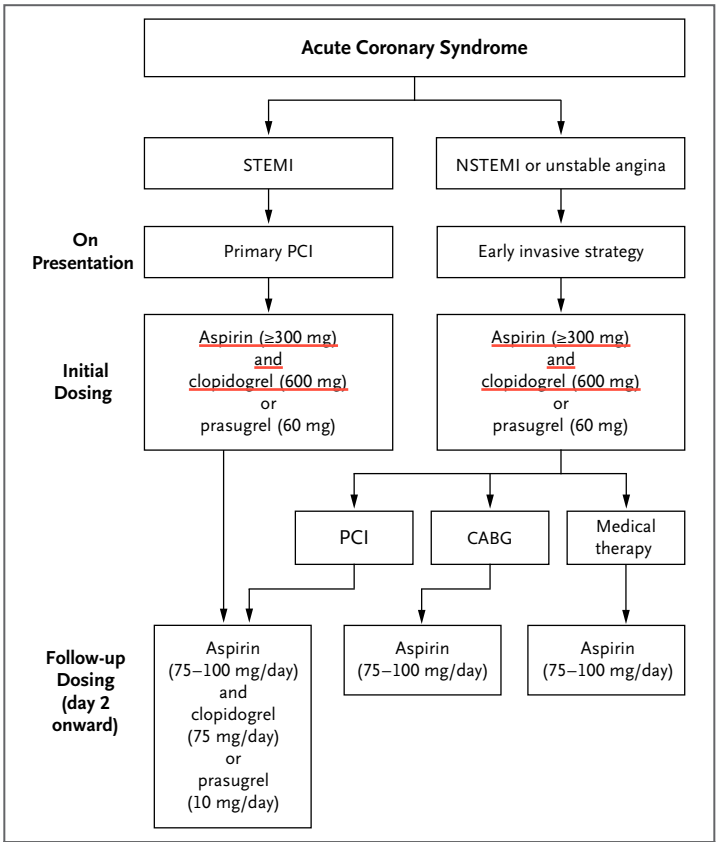

Figure 1. Recommended Therapy in a Patient with a Suspected Acute Coronary Syndrome Referred for an Early Invasive Strategy.

CABG denotes coronary-artery bypass surgery, NSTEMI non–ST-segment elevation myocardial infarction, PCI percutaneous coronary intervention, and STEMI ST-segment elevation myocardial infarction.

1. The CURRENT–OASIS 7 Investigators. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. N Engl J Med 2010;363:930-42.
2. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001-15.
3. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045-57.
4. Lotrionte M, Biondi-Zoccai GG, Agostoni P, et al. Meta-analysis appraising high clopidogrel loading in patients undergoing percutaneous coronary intervention. Am J Cardiol 2007;100:1199-206.
5. Fuster V, Farkouh ME. Acute coronary syndromes and diabetes mellitus: a winning ticket for prasugrel. Circulation 2008;118:1607-8.
6. Mehta SR. A randomized comparison of a clopidogrel high loading and maintenance dose regimen versus standard dose and high versus low dose aspirin in 25,000 patients with acute coronary syndromes: results of the CURRENT OASIS 7 Trial. Presented at the Hotline Session of the European Society of Cardiology Congress, Barcelona, August 30, 2009. abstract.