Antiplatelet Therapy in Early Management of Non-ST-segment Elevation Acute Coronary Syndrome: The 2002 and 2007 Guidelines From North America and Europe

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Abstract: The American College of Cardiology, American Heart Association, and the European Society of Cardiology published updated guidelines in 2007 for patients with non-ST elevation acute coronary syndrome. In this article, we review the recommendations for antiplatelet therapy and supporting data, highlight new changes, and describe differences between the European and North American guidelines. The new guidelines provide more details regarding the selection of an early conservative versus an early invasive approach based on the patient's profile and balance between ischemic and bleeding risks. Important new recommendations include wider endorsement for low-dose aspirin maintenance therapy, longer duration of clopidogrel following percutaneous coronary intervention, additional guidance regarding surgery in selected patients on clopidogrel, identification of patients most likely to benefit from glycoprotein IIb/IIIa inhibitors (with appropriate dose modification in patients with renal failure), and the option to use early clopidogrel with bivalirudin in patients managed invasively who are at increased risk of bleeding. The new guidelines also discourage the concomitant use of nonsteroidal anti-inflammatory drugs and delineate indications for adding warfarin to antiplatelet therapy. Because antiplatelet therapy is the cornerstone of management of patients with non-ST elevation acute coronary syndrome, health care providers should make themselves familiar with the new data and latest guideline recommendations.

Key Words: non-ST elevation acute coronary syndrome, guidelines, glycoprotein IIb/IIIa inhibitors, percutaneous coronary intervention, myocardial infarction

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The American College of Cardiology (ACC) and the American Heart Association (AHA),[1] as well as the European Society of Cardiology (ESC)[2] published updated guidelines, in 2007 for patients with non-ST elevation (NSTE) acute coronary syndrome (ACS). These guidelines cover a broad range of topics, including diagnosis, risk stratification, early evaluation and management, and postdischarge therapy.

Antiplatelet therapy is one of the key initial therapeutic interventions in patients with NSTE-ACS. New clinical data for old and new agents continue to accrue, resulting in further refinement of the guidelines. The guidelines describe two management strategies in patients with NSTE-ACS, known as the "early invasive" and "early conservative" approaches. In the early invasive approach, the treating physician intends to perform coronary angiography within the first 48 hours, whereas in the early conservative approach, medical management is implemented and coronary angiography is performed only if patients fail medical stabilization or have an abnormal noninvasive test for ischemia.

In this article, we review the recommendations for antiplatelet therapy and their supporting data, highlight new changes since the 2002 versions,[3,4] and describe differences between the European and North American guidelines. In doing so, the standard definitions for class of recommendation and level of evidence as described in the guidelines will be used. Class I recommendations are supported by evidence and/or agreement for benefit, utility, and effectiveness. Conflicting evidence and opinions regarding a procedure or treatment's efficacy leads to a class II recommendation, a category that is further divided into classes IIa and IIb, in which, respectively, the weight of evidence either supports usefulness and efficacy (IIa) or is less well established (IIb). A treatment with lack of effectiveness or usefulness, or harmfulness, receives a class III recommendation. The levels of evidence supporting these recommendations are indicated by the letters A (derived from multiple randomized clinical trials [RCT] or meta-analyses); B (from a single RCT or large, nonrandomized studies); and C (consensus of expert opinion, small studies, retrospective studies, registries).

PATIENTS WITH NSTE-ACS SELECTED FOR INITIAL CONSERVATIVE MANAGEMENT

Aspirin

All four guidelines from 2002[3,4] and 2007[1,2] emphasize that aspirin should be administered to all patients with NSTE-ACS at presentation, unless there is a contraindication to its use.

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The initial recommended dose is 162 to 325 mg (class I-A) and the nonenteric coated formulation is preferred because of the faster buccal absorption. Thereafter, lower doses may be used. The 2007 ESC guidelines recommend (class I-A) continuation of a maintenance dose of 75 to 100 mg. The 2007 ACC/AHA guidelines do not have a similar recommendation, but they support the use of 75 to 162 mg aspirin per day, a change from the 2002 guidelines[3] support of the use of up to 325 mg aspirin indefinitely. We believe that lower dosages over the long term are preferable because gastrointestinal side effects such as dyspepsia and nausea occur less often with lower dosages.[5–9] while there remains no good evidence that higher dosages are more effective in the long-term secondary prevention of cardiovascular complications following acute coronary syndrome (ACS).[7,10]

Thienopyridines

The thienopyridines ticlopidine and clopidogrel are the two currently available drugs that irreversibly block the adenosine diphosphate (ADP)-induced pathway of platelet activation by specific inhibition of the $P2Y_{12}$ ADP receptor. Ticlopidine is less frequently used in current clinical practice because of its potential for side effects (primarily rash and nausea, with rare cases of neutropenia and thrombocytopenic thrombotic purpura).[11]

The 2007 guidelines[1,2] continue to recommend (class 1) that clopidogrel (loading dose followed by daily maintenance dose) be administered to patients with NSTE-ACS who are unable to take acetylsalicylic acid (ASA) secondary to major gastrointestinal contraindications such as peptic ulcer bleeding or allergy (primarily manifested as asthma with nasal polyps). The ACC/AHA 2007 guidelines consider the level of evidence supporting the use of clopidogrel instead of aspirin in such patients to be "A," while the ESC guidelines assign it a level of evidence "B." There are no new large studies since the from the Clopidogrel vs. Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial[12] that clopidogrel was slightly more effective than aspirin in reducing cardiovascular complications. The CAPRIE trial compared clopidogrel with aspirin in reducing the risk of vascular events in 19,185 patients with clinical manifestations of atherosclerosis. Event rates for the primary composite endpoint of myocardial infarction (MI), ischemic stroke, and vascular death were 5.32% and 5.83% with clopidogrel and aspirin therapy, respectively, over the treatment period of 1 to 3 years. Clopidogrel therapy resulted in a relative risk reduction (RRR) of 8.7% [95% confidence interval (CI), 0.3 to 16.5%] compared with aspirin therapy alone ($P = 0.043$).

For patients with NSTE-ACS in whom an initial conservative strategy is selected, clopidogrel (loading dose 300 mg followed by daily maintenance 75 mg) should be added to ASA and anticoagulant therapy as soon as possible after admission and administered for at least 1 month (class I-A)[1–4] and, ideally, for up to 1 year (class I-B, ACC/AHA; class I-A, ESC).[1,2] The duration of therapy has been lengthened compared with 2002 (when the recommendations were 9 months, ACC/AHA[3]; 9 to 12 months, ESC[4]), based on the additional long-term clopidogrel data that have been published in the interim (see below).[13]

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE trial), conducted in 12,500 patients with NSTE-ACS, demonstrated a significant reduction in recurrent MI in patients taking aspirin and clopidogrel for 3 to 12 months (average duration, 9 months) compared with patients taking aspirin alone within the first 30 days after randomization (RR, 0.79; 95% CI, 0.67 to 0.92; $P = 0.003$).[14,15] New longer term data confirming these results are now available from the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial,[13] which randomly assigned 15,603 patients to receive a combination of ASA with clopidogrel versus aspirin and placebo and followed them for a median duration of 28 months. The rates of primary efficacy endpoint, a composite of myocardial infarction, stroke, or death from cardiovascular causes, were 6.8% with clopidogrel plus aspirin and 7.3% with placebo plus aspirin (relative risk, 0.93; 95% confidence interval, 0.83 to 1.05; $P = 0.22$). In the subgroup of patients with clinically evident atherothrombosis, the rate of the primary composite endpoint were 6.9% with clopidogrel and 7.9% with placebo (RR, 0.88; 95% CI, 0.77 to 0.998; $P = 0.046$).

Additional Considerations Regarding Aspirin and Clopidogrel

In patients with a history of gastrointestinal bleeding, when ASA and clopidogrel are administered alone or in combination, the ACC/AHA, in a new class I-B recommendation in the 2007 guidelines,[1] endorses the concomitant administration of drugs (eg, proton-pump inhibitors) to minimize the risk of recurrent gastrointestinal bleeding. The ESC does not have a similar recommendation but does support the use of proton-pump inhibitors before introduction of antiplatelet therapy in patients with a history of gastrointestinal bleeding during an earlier treatment with antithrombotic or anticoagulant therapy.[2] In a more general recommendation, the ESC endorses (class I-B) the use of drugs, combination of drugs, and nonpharmacologic procedures known to carry a reduced risk of bleeding in patients at high risk of bleeding undergoing treatment for NSTE-ACS.

Routine assessment of platelet aggregation inhibition in patients receiving aspirin or clopidogrel, or both, is recommended by the ESC 2007 guidelines (class IIb-C),[2] while the current ACC/AHA guidelines[1] are silent on this issue. Widespread clinical application of testing for aspirin or clopidogrel resistance awaits studies with large populations using consistent definitions and reproducible assays that correlate with clinical outcomes, which then can be improved by alterations in antiplatelet strategy (eg, increasing the dosage of antiplatelet agent, adding or substituting a second antiplatelet agent), given the existing limitations of current methods.[16,17] Ongoing studies are evaluating the effectiveness of such alternative strategies in patients with aspirin and/or clopidogrel resistance. One such trial, the Aspirin Nonresponsiveness and Clopidogrel Endpoint Trial (ASCET),[18] is evaluating whether switching to clopidogrel will be superior to continued aspirin therapy in improving clinical outcomes in aspirin-resistant patients with angiographically documented coronary artery disease (CAD).

A new Class III-C recommendation by the ESC in 2007[2] discourages the use of nonselective nonsteroidal

anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors in combination with either aspirin or clopidogrel. Coadministration of nonselective NSAIDs with aspirin may impair the inactivation of COX-1 and decrease the antiplatelet effect of aspirin.[19] A retrospective analysis of a large cohort of patients discharged from hospital after MI showed that the use of selective COX-2 inhibitors and nonselective NSAIDs in the post-MI period led to a higher risk of death. Clopidogrel metabolites can inhibit the enzymatic activity of cytochrome P4502C9 and increase plasma levels of NSAIDs.[20] This could increase the risks of gastrointestinal bleeding as well as impair the antiplatelet action of aspirin. The ACC/AHA guidelines recommend discontinuation of any NSAID other than aspirin at the time of initial presentation (class I-C) because of the increased risks of mortality, reinfarction, hypertension, heart failure, and myocardial rupture associated with their use. A multivariable proportional hazards model and case-crossover analysis from the Danish administrative registry of all patients with first-time MI and NSAIDs use revealed that selective COX-2 inhibitors in all dosages and nonselective NSAIDs in high dosages increase mortality (hazard ratio [HR], rofecoxib, 2.80; 95% CI, 2.41 to 3.25; ibuprofen, 1.50; 95% CI, 1.36 to 1.67) in patients with previous MI.[21]

Glycoprotein (GP) IIb/IIIa Antagonists

Three GP IIb/IIIa antagonists have been approved for clinical use: abciximab, eptifibatide, and tirofiban. They block the final common pathway of platelet activation binding to fibrinogen and, under high shear conditions, von Willebrand factor, and thus inhibit bridging between activated platelets. Experimental and clinical studies have suggested that occupancy of at least 80% of the GP IIb/IIIa receptor population and inhibition of platelet aggregation by at least 80% to ADP results in potent antithrombotic effects.[22,23] This level of platelet inhibition is much greater than the median effect reported for clopidogrel (30% to 40%) using similar techniques, regardless of the dosage of clopidogrel.[24]

The 2007 ACC/AHA guidelines[1] state that it may be reasonable to add eptifibatide or tirofiban to anticoagulant and oral antiplatelet therapy (Class IIb-B) in high-risk patients without evidence of continuing ischemia who are being managed conservatively. The ACC/AHA[1] and ESC[2] agree that abciximab should not be used if percutaneous coronary intervention (PCI) is not planned (Class III-A). If patients managed with an initial conservative strategy develop recurrent symptoms or ischemia, heart failure, or serious arrhythmias, they should undergo diagnostic angiography (class I-A, ACC/AHA; class I-C, ESC). Per the ACC/AHA, *either* an intravenous GP IIb/IIIa inhibitor (eptifibatide or tirofiban; Class I-A) *or* clopidogrel (loading dose followed by daily maintenance dose; class I-A) should be added to ASA and anticoagulant therapy before diagnostic angiography (upstream) (class I-C). The addition of GP IIb/IIIa inhibitor in these unstable patients who are *already* on clopidogrel, ASA, and anticoagulant therapy prior to angiography is a class IIa-C recommendation by the ACC/AHA, as less data are available on this quadruple antithrombotic regimen. Details of the ESC 2007 recommendations in patients proceeding to angiography and PCI are described below.

Both the ACC/AHA and ESC 2007 guidelines[1,2] recognize that patients at higher risk for cardiovascular complications are more likely to benefit from a GP IIb/IIIa antagonist. The ESC guidelines advise that for patients at intermediate- to high-risk—particularly those with elevated troponin levels, ST-segment depression, or diabetes—either eptifibatide or tirofiban for initial early treatment should be administered in addition to oral antiplatelet agents (class IIa-A). Meanwhile the ACC/AHA guidelines note that the benefit of GP IIb/IIIa inhibition may be enhanced in patients with diabetes (class I-B). No new large-scale trials have evaluated GP IIb/IIIa inhibitors in medically managed patients; instead, the ACC/AHA and ESC tend to use different risk assessment scores (Thrombolysis in Myocardial Infarction [TIMI],[25] Global Registry of Acute Coronary Events [GRACE][26]) and to have slightly different interpretations of the results seen in patient subgroups of the prior trials.

The most comprehensive review of the use of GP IIb/IIIa inhibitors in NSTE-ACS is a meta-analysis by Boersma and colleagues[27] of the Platelet Receptor Inhibition in Ischaemic Syndrome Management (PRISM), Platelet Receptor Inhibition in Ischaemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS), Platelet IIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON-A), Platelet Glycoprotein IIb/IIIa in Unstable Angina; Receptor Suppression Using Integrilin Therapy (PURSUIT), PARAGON-B, and Global Utilization of Strategies To open Occluded Coronary Arteries Trial IV in Acute Coronary Syndromes (GUSTO-IV ACS) trials. These six randomized placebo-controlled trials enrolled a total of 31,402 patients. The meta-analysis revealed a 10.8% event rate in the GP IIb/IIIa inhibitor group (n = 18,297) versus 11.8% in the placebo group (n = 13,105)—a 9% reduction in the odds of death or MI ($P = 0.015$). Glycoprotein IIb/IIIa inhibitors were associated with a significant reduction in death or MI (HR, 0.92; $P = 0.030$) until PCI or at 30-day follow-up. The benefits of GP IIb/IIIa inhibitors were consistent across various subgroups as defined by age, history of diabetes mellitus, cardiac disease, and condition on admission. Differences in outcomes dependent upon gender were apparent, with a treatment benefit in men (two thirds of the study population) but not in women. However, no sex difference in treatment effect was seen in a selected subgroup of patients with raised cardiac troponin concentrations (Fig. 1).[27] This finding of consistent benefit between men and women at higher risk was similarly seen in the Treat Angina with Aggrastat and Determine Cost of Therapy with Invasive or Conservative Strategy (TACTICS)–TIMI 18 trial, which largely enrolled troponin-positive or otherwise high-risk patients with unstable angina.[28]

Because the risk of bleeding increases when warfarin is added to dual antiplatelet therapy[29,30] (so-called triple therapy), the current guidelines are cautious about this combination. The 2007 ACC/AHA guidelines[1] cautiously recommend (class IIb-B) addition of warfarin to aspirin and clopidogrel in patients with unstable angina/NSTEMI if there is another indication for anticoagulation, such as atrial fibrillation, mechanical valves, left ventricular thrombus, or cerebral, venous, or pulmonary emboli. When warfarin is added to aspirin plus clopidogrel, an

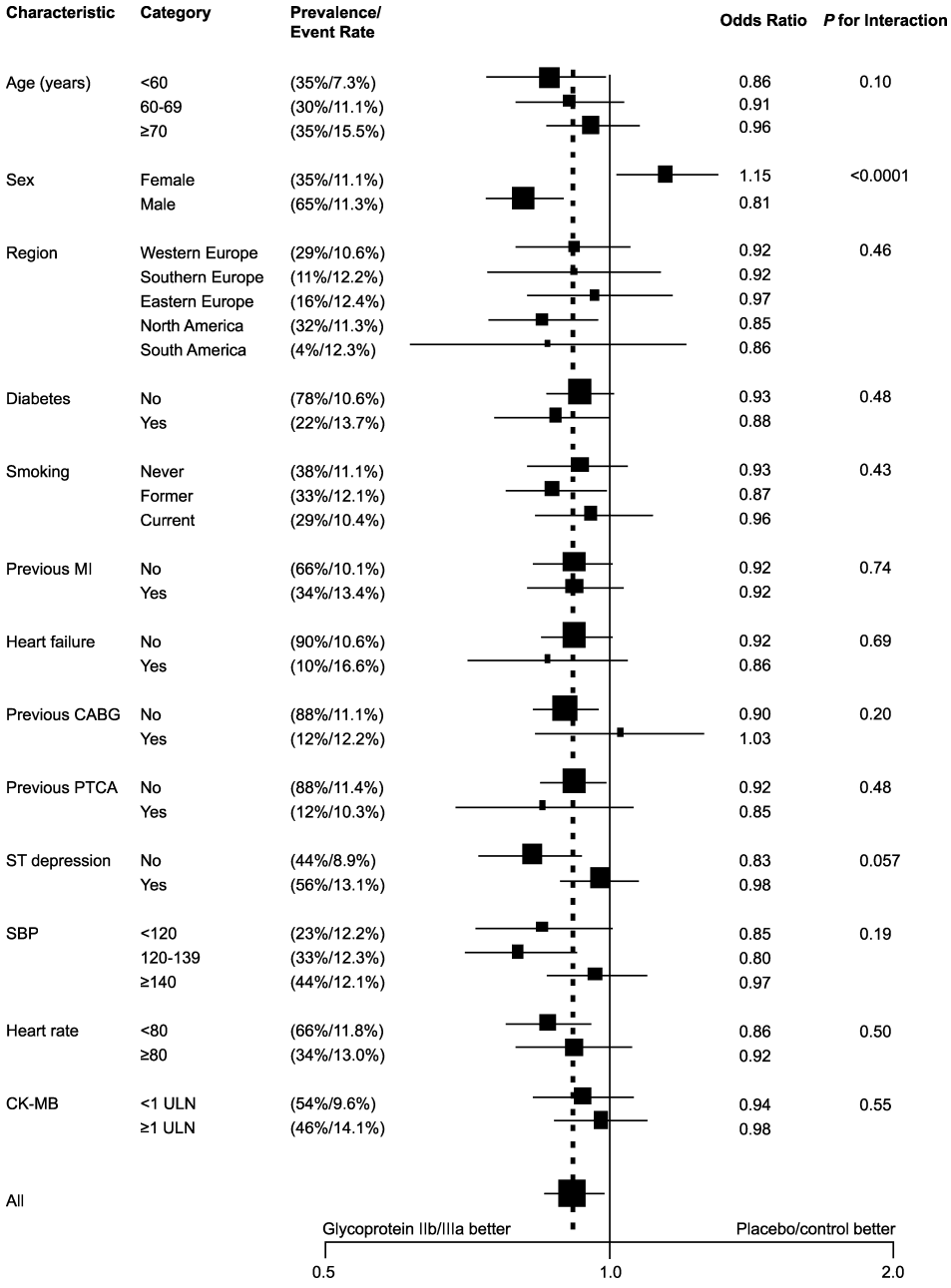

FIGURE 1. Odds ratio of 30-day death or MI in subgroups of patients according to important clinical baseline characteristics from a metanalysis of 6 trials involving 31,402 patients. MI, myocardial infarction; CABG, coronary artery bypass graft; PTCA, percutaneous coronary angioplasty; SBP, systolic blood pressure; CK, creatine kinase. Reprinted from Boersma et al,[27] with permission from Elsevier.

international normalized ratio (INR) of 2.0 to 2.5 is recommended. It also recommends the administration of warfarin and low-dose aspirin (75 to 81 mg/day) in patients who cannot tolerate clopidogrel (class IIb-B). The ESC 2007 guidelines[2] emphasize that the choice of combination of antiplatelet agents and anticoagulants should be made in relation to risk of ischemic and bleeding events (class I-B), and that triple therapy should only be given if a compelling indication exists, in which case the lowest efficacious INR and shortest duration for the triple association should be targeted (class IIa-C).

There are no prospective trials and limited observational data to establish the benefit and risk of such triple antithrombotic therapy.[31] Stenestrand and colleagues performed a prospective cohort study on the data of 6182 patients discharged from the hospital with a diagnosis of atrial fibrillation and acute MI, obtained from the Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKS-HIA).[31] Patients in the registry were discharged from the hospital on combined antiplatelet and anticoagulant therapy (n = 1848) or antiplatelet therapy alone (n = 4934). The study found that at 1 year, the unadjusted mortality rate was 31% (1183/4934) in the antiplatelet-only group and 22% (414/1848) in the combined treatment group (RR, 0.73; $P < 0.001$). There was no significant difference in fatal (0.5% vs 0.5%) or in nonfatal bleeding (1.5% vs 1.3%) in patients treated with combination anticoagulant plus antiplatelet vs antiplatelet therapy alone.

NSTE-ACS PATIENTS SELECTED FOR INITIAL INVASIVE MANAGEMENT

Antiplatelet Therapy in Addition to Aspirin

According to the 2007 ACC/AHA guidelines,[1] in patients with NSTE-ACS in whom an initial invasive strategy is selected, antiplatelet therapy in addition to aspirin should be initiated before diagnostic angiography with *either* clopidogrel (300 mg loading dose followed by 75 mg daily maintenance dose for 12 months) or an intravenous GP IIb/IIIa inhibitor (class I-A). The importance of a 300 mg loading dose (compared with no loading dose) prior to PCI was evaluated by the Clopidogrel for the Reduction of Events During Observation (CREDO trial),[32] which randomly assigned 2116 patients to either a 300 mg clopidogrel loading dose 3 to 24 hours prior to PCI followed by clopidogrel 75 mg/day for 12 months (n = 1053) or placebo followed by clopidogrel for 1 month post-PCI (n = 1063). At 1 year, long-term clopidogrel therapy was associated with a 26.9% relative reduction in the combined risk of death, MI, or stroke ($P = 0.02$); administration of a loading dose at least 6 hours prior to PCI was associated with a relative reduction of 38.6% ($P = 0.051$) in the above endpoints. The PCI-CURE study, a nonrandomized subset analysis of the 2658 patients in the CURE trial who underwent PCI, demonstrated that patients with NSTE-ACS receiving ASA plus clopidogrel experienced a 20% relative reduction in the primary composite outcome of cardiovascular death, MI, and stroke at the end of 1 year (9.3% vs 11.4%; $P < 0.001$), compared with patients receiving aspirin plus placebo.[33]

In both guidelines, abciximab as the choice for upstream IV GP IIb/IIIa therapy is indicated only if there is no appreciable delay to angiography and PCI is likely to be performed (class I-B, ACC/AHA;[1] class I-A, ESC[2]). The ESC further states that abciximab has the strongest evidence of benefit (class IIa-B) if PCI is scheduled to be performed within 24 hours of presentation. In cases in which intervention is likely to be delayed, eptifibatide or tirofiban is the preferred choice of GP IIb/IIIa inhibitor (class I-B). The old and the new ACC/AHA guidelines[1,3] advise that it is reasonable to administer both clopidogrel and an intravenous GP IIb/IIIa inhibitor to patients in whom PCI is planned (class IIa-B). The choice of the particular GP IIb/IIIa inhibitor is again determined by the expected time to angiography/PCI. For patients with NSTE-ACS in whom PCI has been selected as a postangiography management strategy, a loading dose of clopidogrel (see details below), if it has not been started before diagnostic angiography (class I-A), and an intravenous GP IIb/IIIa inhibitor, if the patient is at high risk or has an elevated troponin level (class I-A), are both recommended.

Dosing of Clopidogrel

The 2007 ESC guidelines[2] recommend an immediate loading dose of clopidogrel 300 mg followed by 75 mg daily (class I-A) for 12 months, unless there is an excessive risk of bleeding (class I-A). If a more rapid antiplatelet effect is required (eg, time to PCI is anticipated to be less than 6 hours), a 600 mg loading dose may be used (class IIa-B). Both European and United States 2007 guidelines[1] note that no large-scale randomized trials evaluating clinical outcomes have been completed comparing 300 versus 600 mg loading doses of clopidogrel, and the 2007 ACC/AHA guidelines in particular do not give a formal recommendation for a loading dose other than 300 mg. Several small studies have shown that in the absence of a GP IIb/IIIa inhibitor, 600 mg clopidogrel provides better platelet inhibition than the standard 300 mg dose. The Antiplatelet Therapy for Reduction of Myocardial Damage during Angioplasty (ARMYDA-2) study randomly assigned 255 patients scheduled to undergo PCI to a 600 mg (n = 126) or 300 mg (n = 129) loading regimen of clopidogrel given 4 to 8 hours before the procedure.[34] The primary endpoint of 30-day occurrence of death, MI, or target vessel revascularization (TVR) occurred in 4% of patients receiving the high loading dose versus 12% of those receiving the conventional loading dose ($P = 0.041$), driven by reduction in periprocedural MI.[34] The Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation, and Ongoing Necrosis (ALBION) trial found that a 900-mg loading dose achieved little more platelet inhibition beyond 600 mg; thus neither guideline endorses a dose greater than 600 mg.[24] The Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Optimal Antiplatelet Strategy for Interventions (CURRENT-OASIS) 7 trial is an ongoing prospective study[35] that will randomly assign 14,000 patients undergoing an early invasive strategy to either 600-mg loading dose of clopidogrel followed by 150 mg for 1 week and then 75 mg daily *or* to the standard regimen of a 300-mg loading dose followed by 75 mg daily. Patients will also be randomly assigned to high- ($\geq$300 mg) versus low-dose of aspirin ($\leq$100 mg) for 30 days. The primary outcome of the study will be 30-day cardiovascular death, MI, or recurrent ischemia. This trial is expected to clarify the optimal dosing regimen of both clopidogrel and aspirin in patients undergoing an early invasive strategy.

GP IIb/IIIa Inhibitors: General Recommendations

Administration of GP IIb/IIIa inhibitors in patients with NSTE-ACS undergoing PCI is widely recommended in both 2007 guidelines. Patients who receive initial treatment with eptifibatide or tirofiban prior to angiography should be maintained on the same drug during and after PCI (class IIa-B, ESC[2]). In high-risk patients not pretreated with GP IIb/IIIa inhibitors who proceed to PCI, abciximab is recommended immediately following angiography (class I-A, ESC). The ESC considers the use of eptifibatide or tirofiban in this setting less well established (class IIa-B). Both guidelines caution that GP IIb/IIIa inhibitors should not be given alone and must be combined with an anticoagulant, and the ESC also specifically recommends the combination (class I-A). Supporting these recommendations, the use of a GP IIb/IIIa inhibitor without an anticoagulant was associated with a higher short-term mortality rate in the PRISM-PLUS trial,[36] compared with a GP IIb/IIIa inhibitor plus unfractionated heparin (4.6% vs 1.1%; RR = 4.11; $P = 0.012$).

GP IIb/IIIa Inhibitors in Addition to Aspirin and Clopidogrel

In high-risk patients with NSTE-ACS undergoing PCI, GP IIb/IIIa inhibitors appear to be beneficial regardless of

whether clopidogrel has been previously administered. Initial insight from the Clopidogrel Loading With Eptifibatide to Arrest the Reactivity of Platelets (CLEAR PLATELETS) study of patients undergoing elective stenting without clopidogrel pretreatment demonstrated that GP IIb/IIIa inhibition produced superior platelet inhibition and reduced myocardial necrosis compared with high- (600 mg) or standard-dose (300 mg) clopidogrel loading alone.[37] Important new data from Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 2 (ISAR-REACT 2)[38] trial that supported the use of GP IIb/IIIa inhibitors in patients with NSTE-ACS undergoing PCI are discussed below. In this trial, 2022 patients were treated with aspirin and 600 mg clopidogrel at least 2 hours before PCI and were randomly assigned to receive either abciximab or placebo. Abciximab was associated with a 25% reduction in risk of the primary endpoint of death, MI, or urgent TVR at 30 days (RR, 0.75; 95% CI, 0.58 to 0.97; $P = 0.03$)[38]; however, all the early benefits were observed in patients with elevated troponin levels at baseline (13.1% vs. 18.3%; RRR, 29%; $P = 0.02$ treatment-subgroup interaction, $P = 0.07$). The rates of major bleeding (1.4%) were the same whether or not patients were randomized to abciximab. One-year follow up from ISAR-REACT 2[39] demonstrated a 20% risk reduction of the primary endpoint in the total population (23.3% vs. 28.0%; $P = 0.012$). Long-term follow up through 1 year showed a beneficial effect of abciximab across several subgroups, including analysis by age, gender, diabetes status, and clopidogrel interval (>3 hours or <3 hours). Interestingly, abciximab led to a decrease of the primary endpoint not only in patients with elevated troponin (28.6% vs. 33.3%; RR, 0.82; 95% CI, 0.66 to 1.02), as was evident at 30 days,[38] but also in patients *without* elevated troponin (17.8% vs. 22.0%; RR, 0.79; 95% CI, 0.59 to 1.05), as a trend toward reduction in TVR was seen even among patients with normal preprocedure troponin levels (17.1% vs. 13.2%, in favor of patients who received abciximab). The apparent discrepancy in outcomes in the troponin-negative subgroup through 30 days (identical outcomes with or without abciximab) compared with 1 year (strongly favorable trend with abciximab) remains to be fully explained and deserves prospective re-evaluation in an adequately powered study.

Timing of Initiation of GP IIb/IIIa Inhibitors

The 2007 ACC/AHA and ESC[1,2] guidelines recommend the use of GP IIb/IIIa inhibitors in patients undergoing early invasive management but permit flexibility regarding the timing of initiation (upon presentation or "upstream" versus in the catheterization laboratory after diagnostic angiography but before PCI; ie, "downstream").[40] A second controversy regarding the use of GP IIb/IIIa antagonists centers on the need for them and clopidogrel. The current ACC/AHA guidelines strongly recommend either clopidogrel *or* GP IIb/IIIa antagonists (class I-A), while the administration of both medications in patients undergoing early intervention is considered a class IIa-B recommendation. No large, well-designed study has compared clopidogrel with placebo in patients with NSTE-ACS who are being managed with aspirin, GP IIb-IIIa antagonist, and an early invasive strategy. However, both these issues are being investigated by the ongoing Early Glycoprotein IIb/IIIa Inhibition in patients with Non-ST-segment Elevation Acute Coronary Syndromes (EARLY ACS) trial,[41] a prospective, randomized, double-blinded, placebo-controlled trial of 10,500 patients with high-risk unstable angina or NSTE-ACS treated with an early invasive approach and assigned to receive either early eptifibatide (double bolus plus infusion) or initial placebo therapy, with provisional eptifibatide administered in the catheterization laboratory. Randomization is stratified by the early administration of clopidogrel, a decision left to the treating physician's discretion.

Bivalirudin Without GP IIb/IIIa Inhibiton

Based upon the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial results,[42] the 2007 ACC/AHA and ESC[1,2] guidelines recommend that in patients selected for an initial invasive strategy, it is reasonable to omit upstream intravenous GP IIb/IIIa inhibition if bivalirudin is selected as the anticoagulant and at least 300 mg clopidogrel has been administered at least 6 hours before planned catheterization or PCI (class IIa-B) (Table 1). In ACUITY, 13,819 patients with moderate- or high-risk ACS managed with angiography within 72 hours were randomly assigned to heparin with GP IIb/IIIa inhibitor, bivalirudin with GP IIb/IIIa inhibitor, or bivalirudin

TABLE 1. Main Results of the ACUITY Trial at 30 Days

Anticoagulant	UFH/Enoxaparin	Bivalirudin		No Bivalirudin	
GP IIb/IIIa inhibitor	Yes	Rate, RR [95% CI]	*P* value	Rate, RR [95% CI]	*P* value
Net clinical benefit†	11.7%	11.8%, 1.01 [0.90, 1.12]	<0.001¶	10.1%, 0.86 [0.77, 0.97]	<0.001¶
			0.93		0.015
Ischemic composite‡	7.3%	7.7%, 1.07 [0.92, 1.23]	0.007¶	7.8%, 1.08 [0.93, 1.24]	0.01¶
			0.39		0.32
Major non-CABG bleeding§	5.7%	5.3%, 0.93 [0.78, 1.10]	<0.001¶	3.0%, 0.53 [0.43, 0.65]	<0.001¶
			0.38		<0.001

Risk ratios (RR) are compared with the UFH/enoxaparin + GP IIb/IIIa inhibitor arm. All *P*-values are for superiority, unless otherwise noted.[39]

*Provisional use (9%) during angiography/PCI was permitted, the majority of which was to treat procedural complications (6.5%).

†Ischemic composite or major non-CABG bleeding.

‡Death, MI, or urgent revascularization.

§Intracranial or intraocular bleeding, access site hemorrhage requiring intervention, hematoma ≥ 5 cm, hemoglobin drop ≥ 4 g/dL without an overt bleeding source or ≥ 3 g/dL with such a source, reoperation for bleeding, or transfusion ≤30 days.

¶*P* values are for noninferiority compared to UFH/enoxaparin + GP IIb/IIIa inhibitor.

Adapted with permission from Stone et al.[42]

monotherapy. The three major outcomes of interest were an ischemic composite (death, MI, urgent revascularization), major bleeding (intracranial or intraocular bleeding, hemorrhage at the access site requiring intervention, hematoma with a diameter of at least 5 cm, reduction in hemoglobin levels of at least 4 g/dL without an overt bleeding source or at least 3 g/dL with such a source, reoperation for bleeding, or transfusion of a blood product within 25 to 35 days after randomization), or net clinical benefit (ischemic composite or major bleeding). Bivalirudin monotherapy (compared with heparin with GP IIb/IIIa inhibitor) was noninferior with respect to the ischemic composite (7.8% vs. 7.3%, $P = 0.32$) but reduced major bleeding (3.0% vs. 5.7%, $P < 0.001$) and thereby improved net clinical benefit (10.1% vs. 11.7%, $P = 0.02$). However, bivalirudin monotherapy was associated with a trend toward more ischemic complications compared with heparin plus a GP IIb/IIIa inhibitor among patients who did not receive clopidogrel before angiography (9.1% and 7.1%; RR, 1.29; 95% CI, 1.03 to 1.63, $P = 0.054$).

The results of the 1-year follow up of ACUITY[43] demonstrated that in patients treated with an early invasive strategy, treatment with bivalirudin alone resulted in comparable mortality at 1 year versus heparin [either unfractionated heparin (UFH) or enoxaparin] plus GP IIb/IIIa therapy (3.8% bilvalirudin vs. 4.4% heparin + GP IIb/IIIa, P = NS), regardless of whether patients were treated medically (3.8% vs. 4.0%, P = NS) or with PCI (3.2% vs. 4.0%, P = NS). The data from the 30-day and 1-year follow-up of the ACUITY trial support the use of bivalirudin monotherapy in NSTE-ACS patients at moderate risk of ischemic complications undergoing PCI and high risk for bleeding, provided they are pretreated with clopidogrel. No recent data are available (and hence no recommendation) for the use of bivalirudin in NSTE-ACS patients who are selected for conservative management.

Efforts to Minimize Bleeding Complications

The 2007 ACC/AHA and ESC[1,2] guidelines advise dosage adjustment of GP IIb/IIIa inhibitors in patients with chronic kidney disease, as excess dosing has been associated with increased bleeding.[44,45] The ESC specifically recommends adjustment for eptifibatide and tirofiban (class I-B) in patients with renal insufficiency, but not for abciximab (since it is not renally cleared). Both the 2002 and the 2007 ACC/AHA guidelines[1,3] recommend discontinuation of clopidogrel 5 to 7 days prior to elective coronary artery bypass graft (CABG; class I-B). A new recommendation in the 2007 ACC/AHA guidelines states that in patients receiving clopidogrel 5 to 7 days prior to surgery, more urgent surgery may be performed by experienced surgeons if the incremental bleeding risk is considered acceptable (class I-C). In contrast, the ESC guidelines suggest postponement of CABG by at least 5 days in patients pretreated with clopidogrel if feasible (class IIa-C).

SUMMARY

The 2007 ACC/AHA and the ESC recommendations for initial antiplatelet therapy in the management of NSTE-ACS are consonant except for a few subtle differences. They contain a number of new recommendations compared with those released in 2002 (Table 2). Aspirin and clopidogrel remain the mainstays of antiplatelet therapy in patients being managed with an initial conservative approach. Use of NSAID drugs is discouraged because they may interfere with the action of aspirin and can increase the risk of bleeding. Prophylactic agents that prevent gastrointestinal bleeding are recommended, particularly in patients at increased risk for bleeding. For patients being managed invasively, administration of a GP IIb/IIIa inhibitor is recommended (particularly for those at

TABLE 2. Major New Recommendations in the 2007 ACC/AHA and ESC Guidelines for Antiplatelet Therapy in Management of Unstable Angina and NSTE-ACS

Either Conservative or Early Invasive Strategy
• For UA/NSTE-ACS patients, clopidogrel maintenance dose should be administered for at least 1 month (ACC/AHA class I-A) and ideally up to 1 year (ACC/AHA class I-B; ESC class I-A)
• Routine assessment of platelet aggregation inhibition in patients submitted to either aspirin or clopidogrel therapy, or both, is not recommended (ESC class IIb-C)
• In patients with UA/NSTE ACS, NSAIDs should be discontinued at the time of initial presentation (ACC/AHA class I-C). NSAIDs should not be administered in combination with aspirin and clopidogrel (ESC class III-C)
• In UA/NSTE ACS patients with a history of gastrointestinal bleeding, when ASA and clopidogrel are administered alone or in combination, drugs to minimize the risk of recurrent gastrointestinal bleeding (eg, proton-pump inhibitors) should be prescribed concomitantly. (ACC/AHA class I-B)
• GP IIb/IIIa inhibitors must be combined with an anticoagulant (ESC class I-A)
• In patients with renal failure, dosage adaptation is needed when eptifibatide and tirofiban are administered (ESC class I-B)
• Warfarin may be combined with low-dose aspirin (75-100 mg) in patients who cannot tolerate clopidogrel (ACC/AHA class IIb-B)
Early Invasive Strategy
• In patients considered for an invasive procedure/PCI, a loading dose of 600 mg of clopidogrel may be used to achieve more rapid inhibition of platelet function (ESC class IIa-B)
• If clopidogrel cannot be discontinued for 5-7 days, urgent CABG, if necessary, may be performed by experienced surgeons if the incremental bleeding risk is considered acceptable (ACC/AHA class I-C)
• For UA/NSTE ACS patients in whom an initial invasive strategy is selected, it is reasonable to omit upstream administration of an intravenous GP IIb/IIIa antagonist before diagnostic angiography if bivalirudin is selected as the anticoagulant and at least 300 mg clopidogrel was administered at least 6 h earlier than planned catheterization or PCI (ACC/AHA and ESC class IIa-B)

UA/NSTE-ACS, unstable angina/non-ST elevation acute coronary syndrome.

high risk), although bivalirudin, as long as early upstream clopidogrel was administered, is a new alternative.

The 2007 guidelines from the ACC/AHA and ESC recommend addition of warfarin to dual antiplatelet therapy with aspirin and clopidogrel only in patients with compelling indication for the triple therapy. The lowest efficacious INR (2 to 2.5) and shortest duration of triple therapy should be targeted in these patients.

Given the importance of antiplatelet therapy in the management of patients with NSTE-ACS and the wealth of new data that have become available in the last 5 years since the prior guidelines were published, health care providers who care for these patients should become familiar with the important new recommendations regarding antiplatelet therapy in the 2007 guidelines. These evidence based guidelines represent the most comprehensive and authoritative recommendations for the management of NSTE-ACS and are a critical tool for providers as they strive to provide optimal and evidence-based therapy for their patients.

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