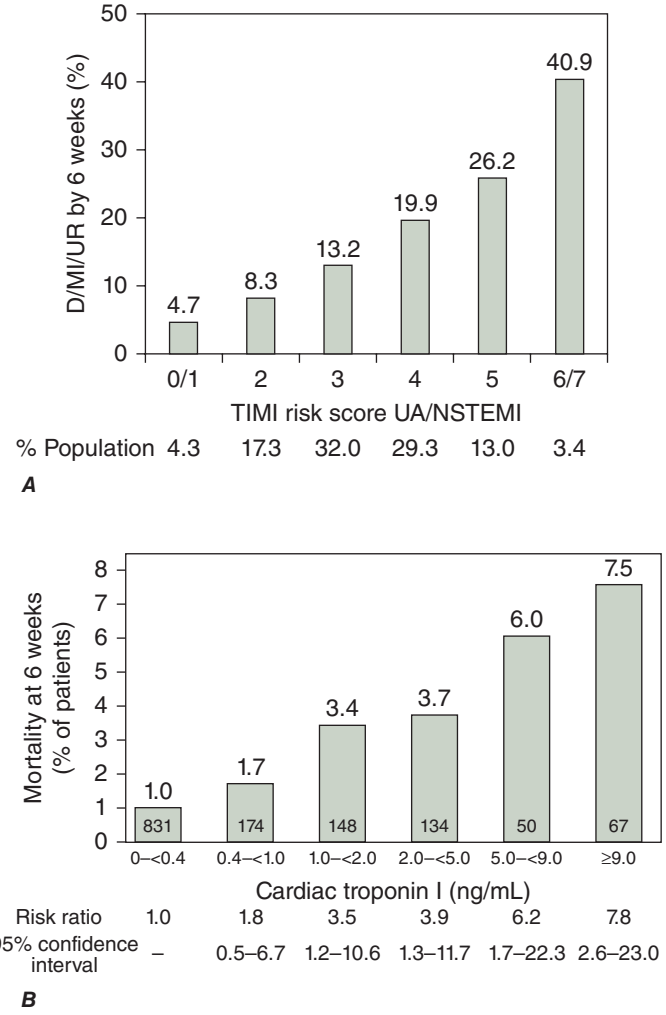

FIGURE 294-4 ***A.*** Death (D), myocardial infarction (MI), or need for urgent revascularization (UR) through 6 weeks by Thrombolysis in Myocardial Infarction (TIMI) Risk Score in the unfractionated heparin arm of the TIMI 11B trial. (*From EM Antman et al: JAMA 284:835, 2000.*) ***B.*** Mortality rate at 42 days by baseline cardiac troponin I levels in the TIMI 3B trial. *(From EM Antman et al: N Engl J Med 335:1342, 1996.)*

<100 mmHg, or the dose reaches 200 μg/min. Topical or oral nitrates **(Chap. 293)** can be used when the pain has resolved, or they may replace intravenous nitroglycerin when the patient has been pain-free for 12–24 h. The only absolute contraindications to the use of nitrates are hypotension or the use of sildenafil or other phosphodiesterase-5 inhibitors within the previous 24–48 h.

Beta Adrenergic Blockers and Other Agents Beta blockers are the other mainstay of anti-ischemic treatment. They may be started by the intravenous route in patients with severe ischemia, but this is contraindicated in the presence of heart failure. Ordinarily, oral beta blockade targeted to a heart rate of 50–60 beats/min is recommended. Heart rate–slowing calcium channel blockers, e.g., verapamil or diltiazem, are recommended for patients who have persistent symptoms or ECG signs of ischemia after treatment with full-dose nitrates and beta blockers and in patients with contraindications to either class of these agents. Additional medical therapy includes angiotensin-converting enzyme (ACE) inhibitors or, if these are not tolerated, angiotensin receptor blockers. Early administration of intensive HMG-CoA reductase inhibitors (statins), such as atorvastatin 80 mg/d, prior to percutaneous coronary intervention (PCI), and continued thereafter, has been shown to reduce complications of the procedure and recurrences of ACS.

ANTITHROMBOTIC THERAPY (TABLE 294-2)

This is the second major cornerstone of treatment. There are two components of antithrombotic therapy: antiplatelet drugs and anticoagulants.

Antiplatelet Drugs (See Chap. 143) Initial treatment should begin with the platelet cyclooxygenase inhibitor aspirin. The typical initial dose is 325 mg/d, with lower doses (75–100 mg/d) recommended thereafter. Contraindications are active bleeding or aspirin intolerance. "Aspirin resistance" has been noted in 2–8% of patients but frequently has been related to noncompliance.

In the absence of a high risk for bleeding, patients with NSTE-ACS, irrespective of whether an invasive or conservative strategy (see below) is selected, should receive a platelet $P2Y_{12}$ receptor blocker to inhibit platelet activation. The thienopyridine clopidogrel is an inactive prodrug that is converted into an active metabolite that causes irreversible blockade of the platelet $P2Y_{12}$ receptor. When added to aspirin, so-called dual antiplatelet therapy, it has been shown to confer a 20% relative reduction in cardiovascular death, MI, or stroke, compared to aspirin alone, but to be associated with a moderate (absolute 1%) increase in major bleeding.

Continued benefit of treatment with the combination of aspirin and clopidogrel has been observed both in patients treated conservatively and in those who underwent PCI. This regimen should continue for at least 1 year in patients with NSTE-ACS, especially those with a drug-eluting stent, to prevent stent thrombosis. Up to one-third of patients have an inadequate response to clopidogrel, and a substantial proportion of these cases are related to a genetic variant of the cytochrome P450 system. A variant of the 2C19 gene leads to reduced conversion of clopidogrel into its active metabolite, which, in turn, reduces platelet inhibition and is associated with increases in the incidence of adverse cardiovascular events. Alternate $P2Y_{12}$ blockers, such as prasugrel or ticagrelor (see below) used with aspirin, should be considered in patients with NSTE-ACS who develop a coronary event while receiving clopidogrel and aspirin or who are hyporesponsive to clopidogrel as identified by platelet and/or genetic testing, although such testing is not yet widespread.

A second $P2Y_{12}$ blocker, prasugrel, also a thienopyridine, achieves a more rapid onset and higher level of platelet inhibition than clopidogrel. It has been approved for ACS patients following angiography in whom PCI is planned. It should be administered at a loading dose of 60 mg followed by 10 mg/d for up to 15 months. The TRITON-TIMI 38 trial showed that relative to clopidogrel, prasugrel reduced the risk of cardiovascular death, MI, or stroke significantly, albeit with an increase in major bleeding. Stent thrombosis was reduced by half. This agent is contraindicated in patients with prior stroke or transient ischemic attack or at high risk for bleeding. It has not been found to be effective in patients treated by a conservative strategy (see below).

Ticagrelor is a novel, potent, *reversible* platelet $P2Y_{12}$ inhibitor. It has been shown in the PLATO trial to reduce the risk of cardiovascular death, MI, or stroke compared with clopidogrel in ACS patients who are treated by either an invasive or a conservative strategy. This agent reduced mortality but increased the risk of bleeding not associated with coronary artery bypass grafting. After a loading dose of 180 mg, 90 mg bid is administered as maintenance.

Prior to the development of the oral $P2Y_{12}$ receptor blockers, many trials had shown the benefit of intravenous glycoprotein IIb/IIIa inhibitors. Their benefit, however, has been small (i.e., only a 10% reduction in death or MI, with a significant increase in major bleeding). Two recent studies failed to show a benefit of routine early initiation of a drug in this class compared with their use only in patients who undergo PCI. The addition of these agents to aspirin and a $P2Y_{12}$ inhibitor (i.e., triple antiplatelet therapy) should be reserved for unstable patients with recurrent rest pain, elevated cTn, and ECG changes, as well as those who have a coronary thrombus evident on angiography when they undergo PCI.