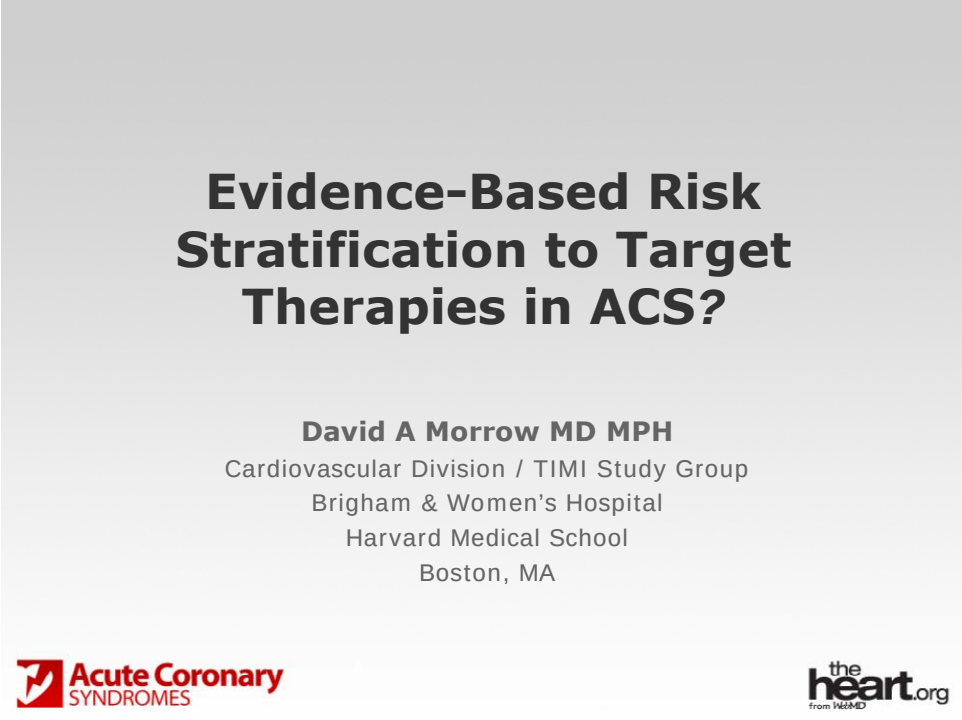
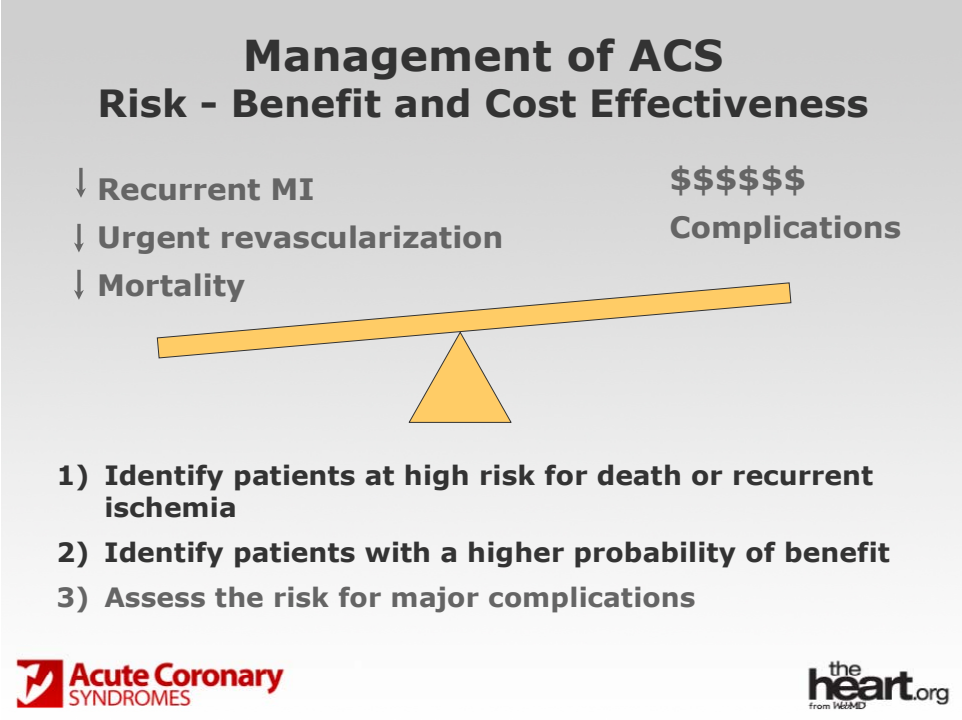


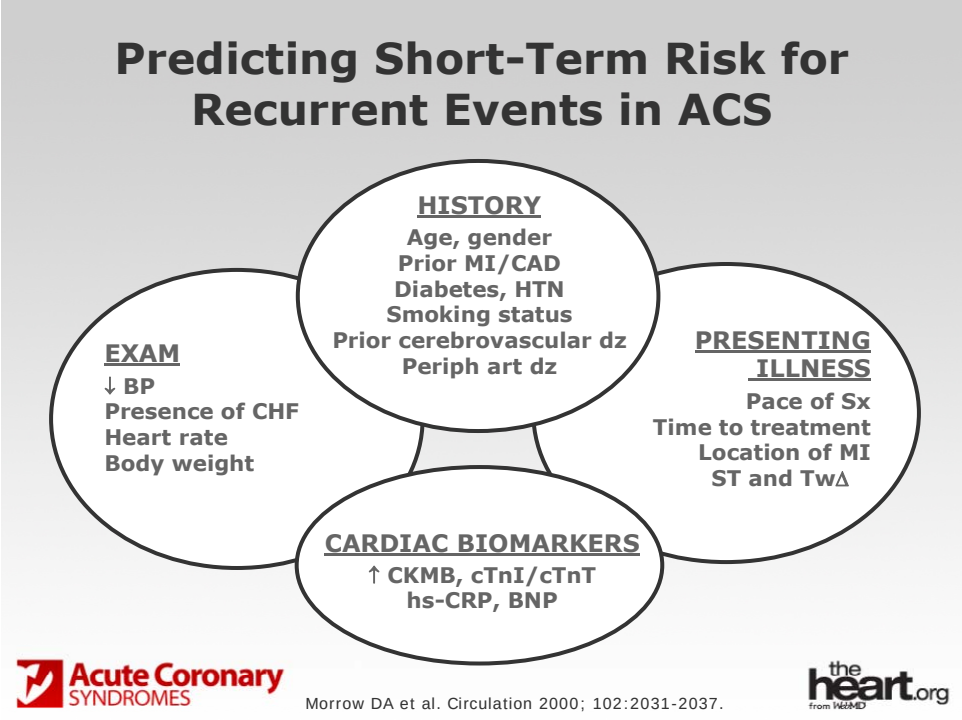
Slide 1

David Morrow, MD: Hi, I'm Dr. David Morrow from the TIMI Study Group in Brigham & Women's Hospital. I'm going to address the important topic of whether evidence-based risk stratification can be used to target our potent antithrombotic therapies for patients with acute coronary syndromes [ACS].



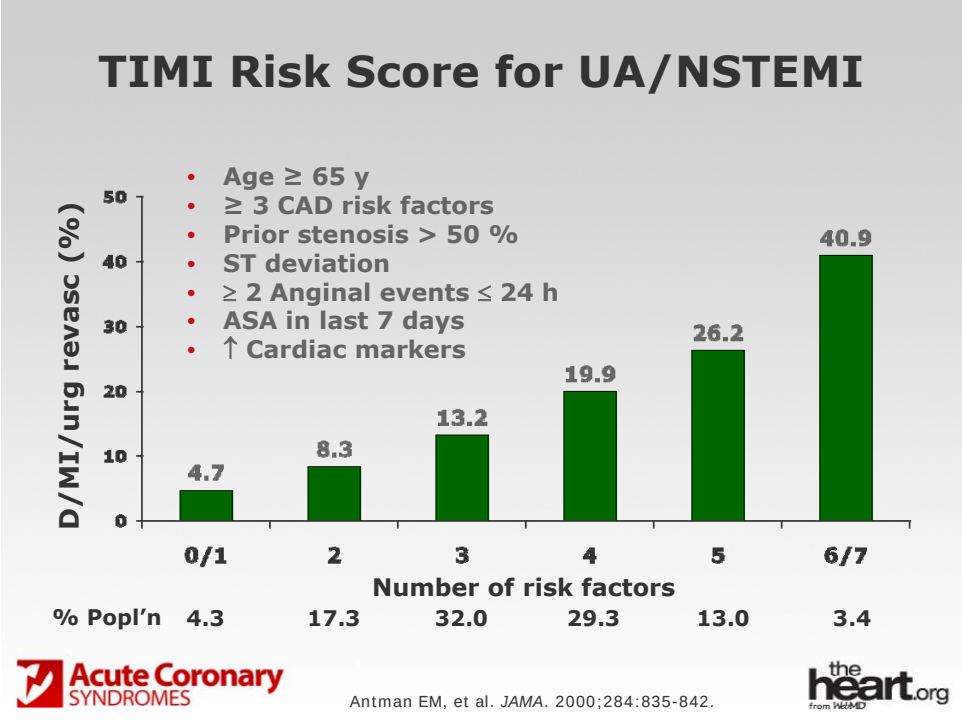
Slide 2

A pivotal question every time we make a decision about clinical care for a patient is to weigh the potential benefits or reduction in recurrent myocardial infarction [MI], urgent revascularization, and cardiovascular death, vs the potential complications and perhaps increased costs of the therapy. So our goal of risk stratification is to identify patients who are at highest risk for death and recurrent ischemic events, and also to identify those patients who are most likely to benefit from a particular therapy. At the same time we're weighing their risk for complications and Professor Gabriel Steg will deal with that in the next presentation.



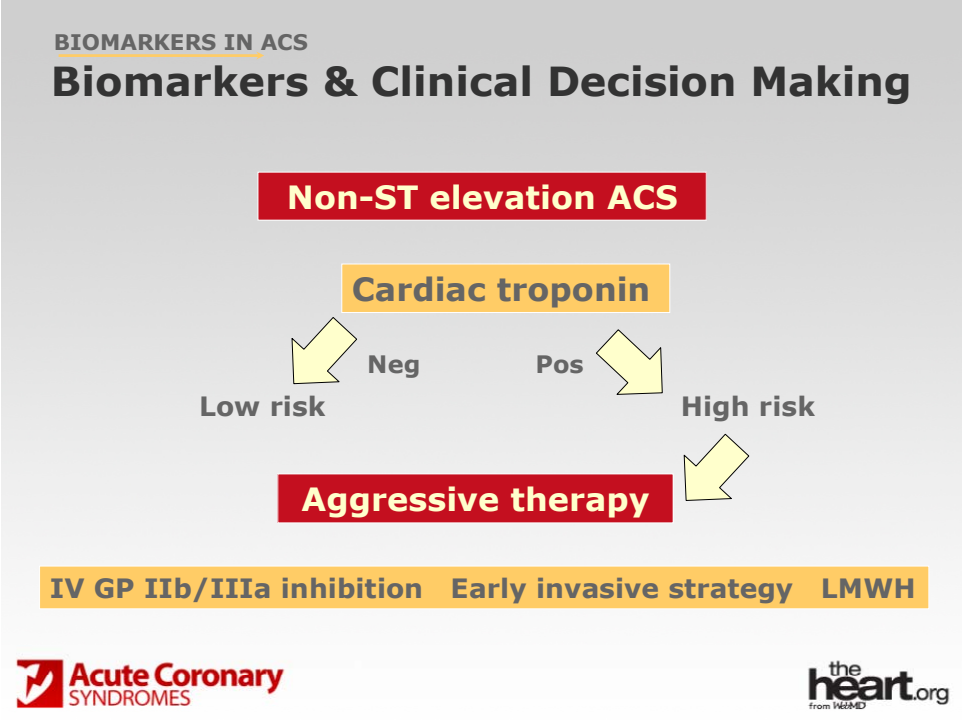
Slide 3

There are a variety of risk indicators that we can use. We use the clinical history, for example a history of diabetes mellitus or prior stroke. We use their physical exam, the assessment for heart failure, their body weight, along with elements of their presenting illness such as the ECG, and cardiovascular biomarkers, in particular cardiac troponin. All of these together help us assess the risk of the patient as well as the potential benefit for therapy.



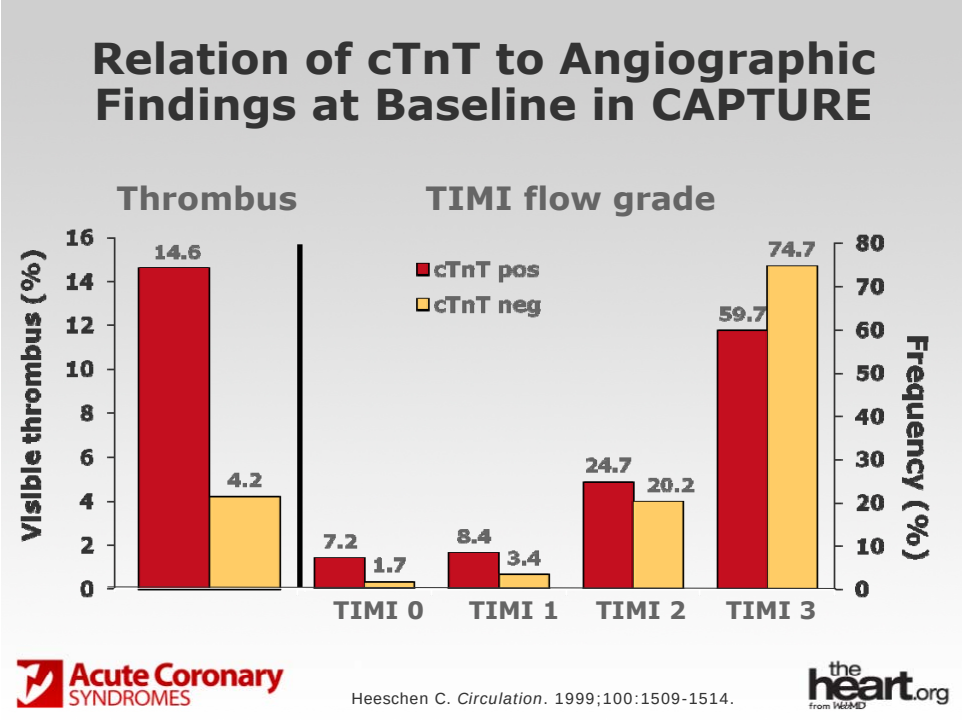
Slide 4

Here you see the application of the TIMI risk score which pulls each of these together in a very simple way. We use the age of the patient, the prevalence of risk factors which underlie the probability of coronary disease, ST-segment deviation, the pace of their anginal symptoms, and also refractoriness to prior antiplatelet therapy or resistance to aspirin administered in the previous 7 days. Together each of these as you can see establishes a strong graded relationship with a risk for death and recurrent ischemic events allowing us to effectively risk stratify the patient. The key question is whether we can translate that into specific therapy.



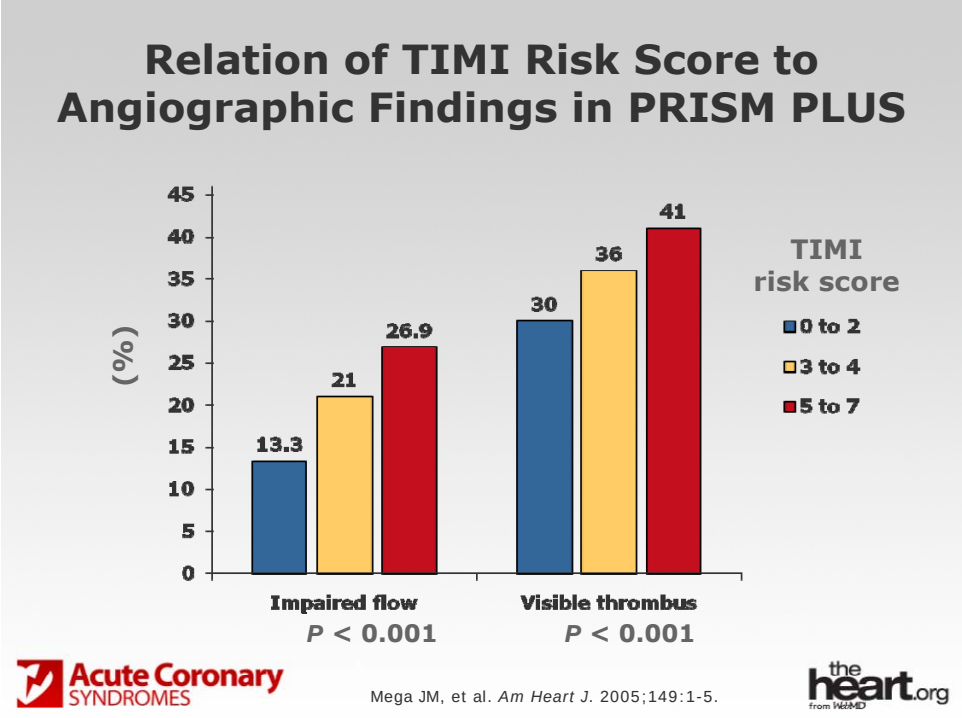
Slide 5

Here troponin has really been the paradigm among the broad spectrum of patients with ACS who are heterogeneous with respect to risk. Troponin helps us identify those high-risk patients reliably and then also those patients who gained particular benefit from aggressive therapy. So let's look at these data specifically. And first, there's important pathobiologic insight that we gain from this risk marker.



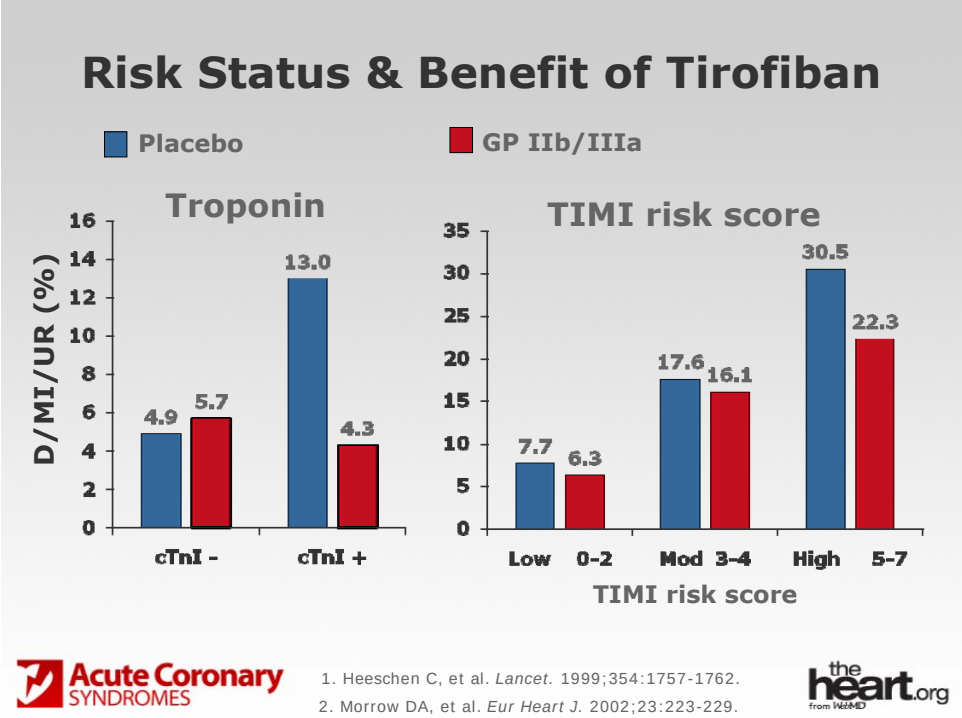
Slide 6

You can see that patients with elevated troponin in red are substantially more likely to have intracoronary thrombus as shown on the left of the slide. Then on the right-hand side you see those patients in red are shifted toward lower TIMI flow grades with slower intracoronary flow, a pathobiologic correlate of this risk marker. We also see that that's the case for the TIMI risk score.



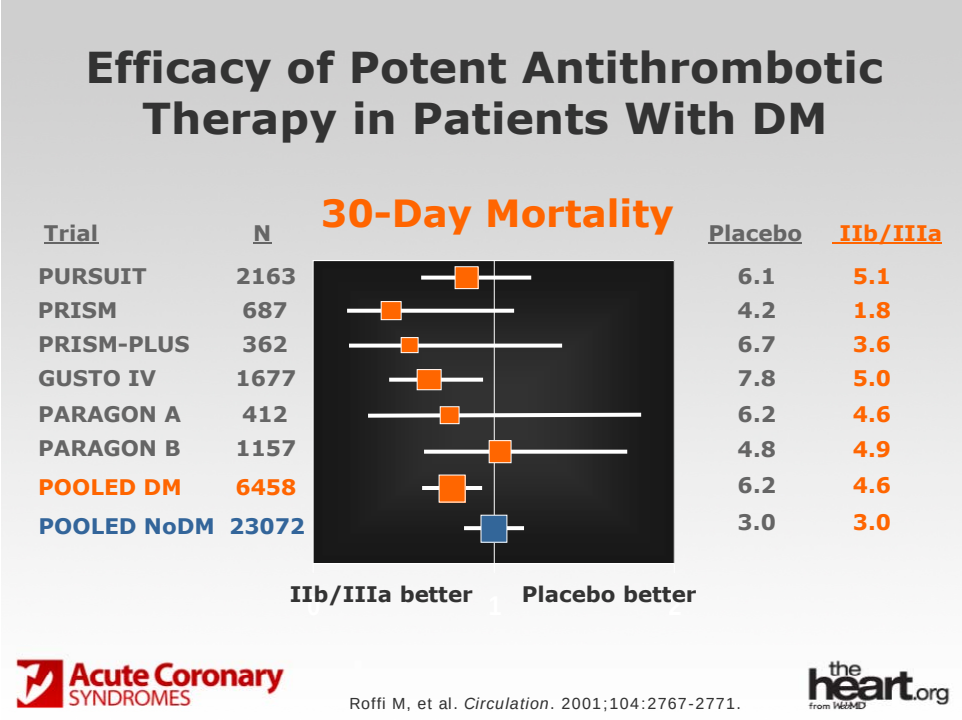
Slide 7

So here you see patients stratified by the TIMI risk score into low-, medium-, and high-risk groups using a TIMI risk score of: 0 to 2, 3 to 4, and 5 to 7. And what you can see is that there's a strong relationship between risk assessed with the risk score and impaired coronary flow, and also the likelihood of visible thrombus in the coronary artery within patients with ACS enrolled in the PRISM PLUS [Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms] trial. So you might hypothesize based on this and the previous slide that these are patients who are not only at high risk but also have the greatest potential to benefit from a more potent antithrombotic therapy.



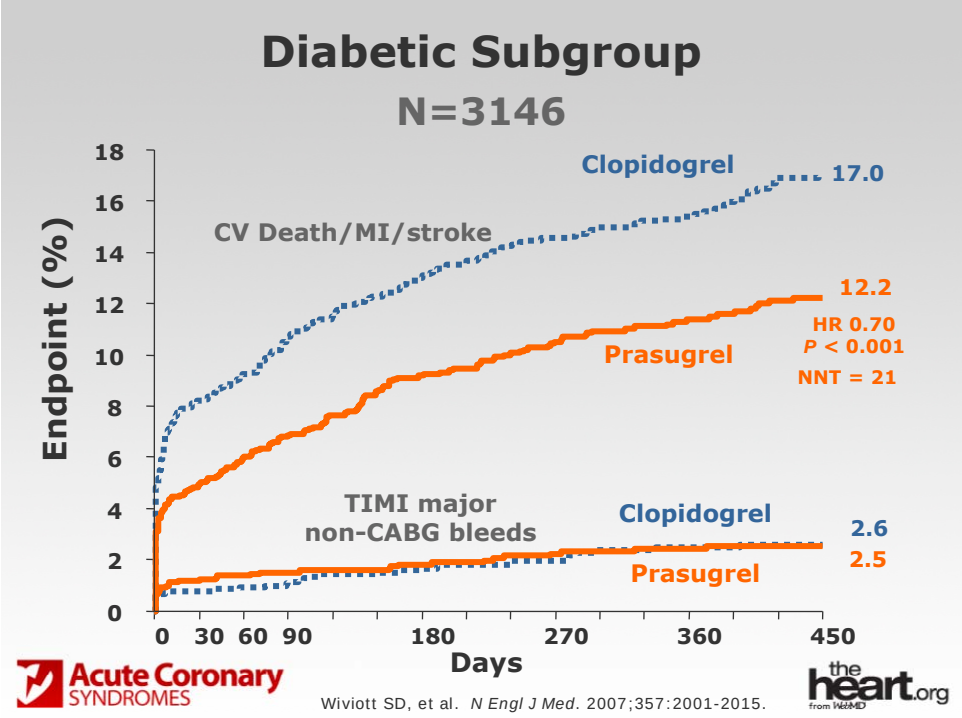
Slide 8

So let's look first at the effect of the [glycoprotein] IIb/IIIa inhibitors as an example. And what you can see is on the left-hand side of the slide patients with an elevated troponin (troponin positive) had a significant more than 50% reduction in the risk for death and recurrent ischemic events when treated with a potent inhibitor of platelets with tirofiban in this example. In contrast, those patients without an elevated troponin, troponin-negative patients, had no demonstrable benefit from this more potent antiplatelet therapy. Now on the right-hand side of this slide you see the TIMI risk score and you see again the exact same qualitative message that those patients in the highest-risk group with the TIMI risk score of 5 to 7 accrued the greatest benefit for more potent platelet inhibition with tirofiban compared with heparin alone in this study.



Slide 9

Now we also know that diabetes is an important risk indicator and if we look at the advantages of the glycoprotein IIb/IIIa inhibitors among patients with diabetes, we see that in nearly 6500 patients included in this meta-analysis, that there was actually a mortality benefit from treatment with more potent antiplatelet therapy compared with placebo along with heparin in these studies of patients with ACS. Now when we look at those patients without diabetes there was no reduction in mortality although there still was a reduction in MI.



Slide 10

Now if we look in another example with our most recently studied oral antiplatelet therapy with more potent antiplatelet activity with prasugrel compared with clopidogrel in the TRITON-TIMI 38 trial, here in the more than 3000 patients with diabetes, you see a significant reduction in the primary endpoint of cardiovascular death, MI, and stroke, with a number needed to treat of only 21 patients with a 30% relative risk reduction. Now in this particular cohort, there was no increase in TIMI major non-CABG [coronary artery bypass graft] bleeding with prasugrel compared with clopidogrel, so overall in those patients there was a significant benefit weighed against a lower risk at least as evident in this cohort.

Slide 11

So in summary, our goal in risk stratification is to identify modifiable risk -- those patients who have the most to gain from effective therapies but also in whom that therapy can provide a favorable outcome. Many of our risk indicators such as cardiac troponin and the TIMI risk score may give information not only about risk but also pathobiology that can lead us to specific treatments, and in fact, I think these data have shown that those patients with high risk for recurrent ischemic events have the most to gain from more potent antithrombotic therapies. Thank you very much for your attention.