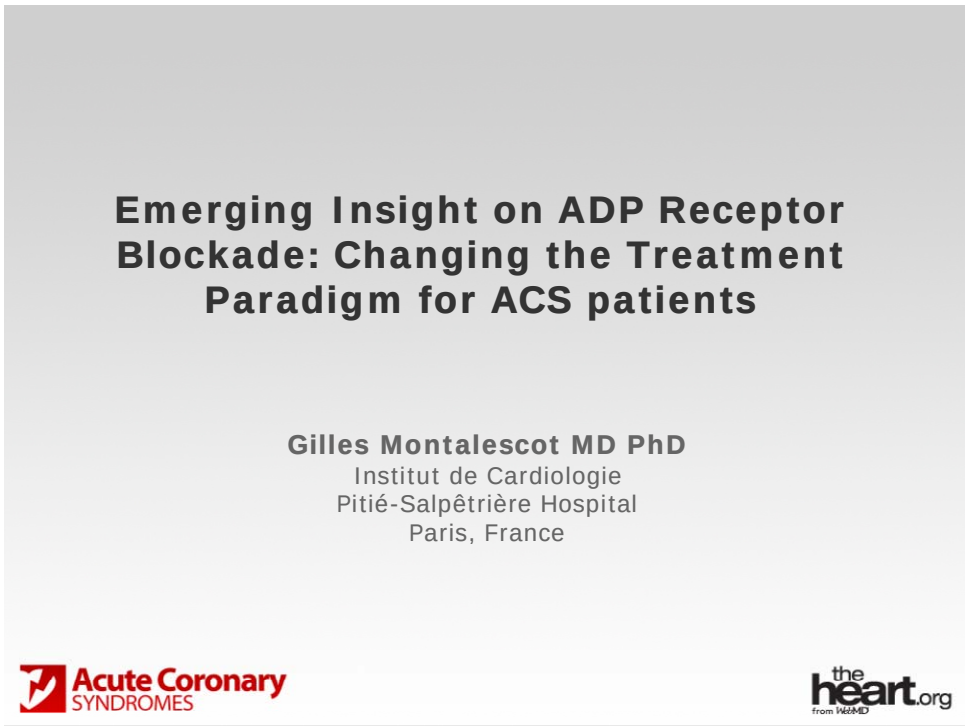
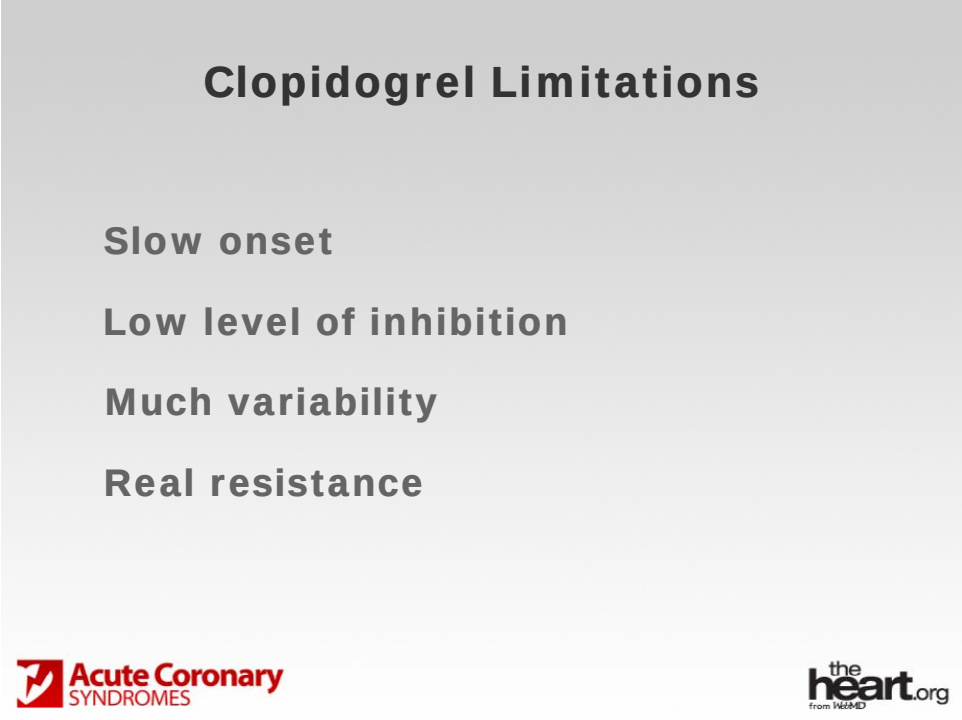


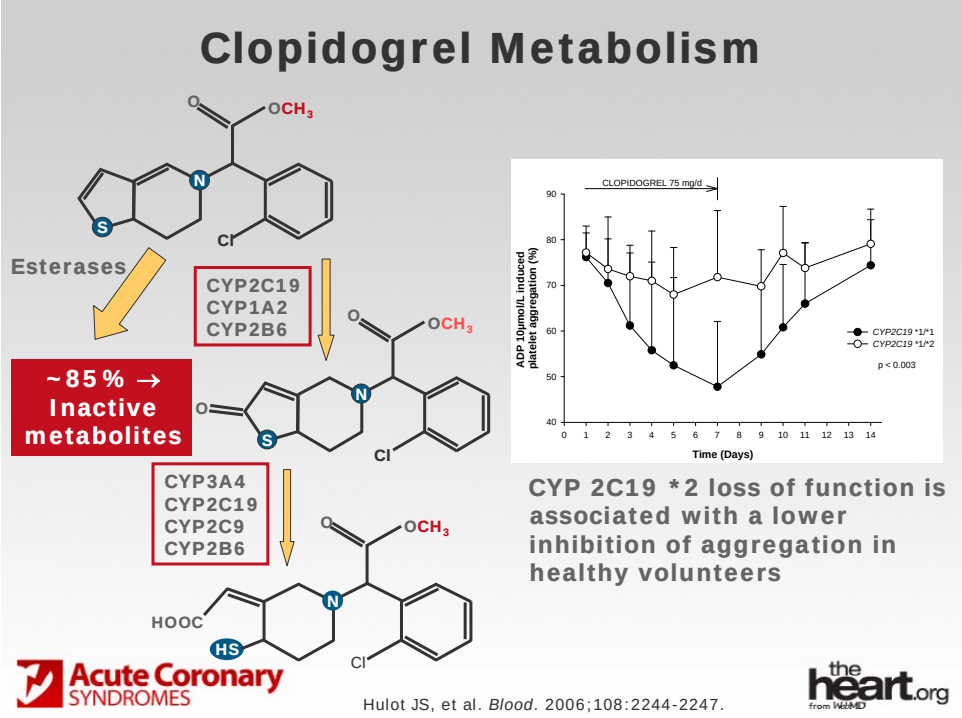
Slide 1

Gilles Montalescot, MD: Hello I am Dr. Montalescot. I work in Paris, France at Pitié-Salpêtrière Hospital and we are going to discuss today new information about ADP [adenosine diphosphate] receptor blockade, and we have important new information from new studies.



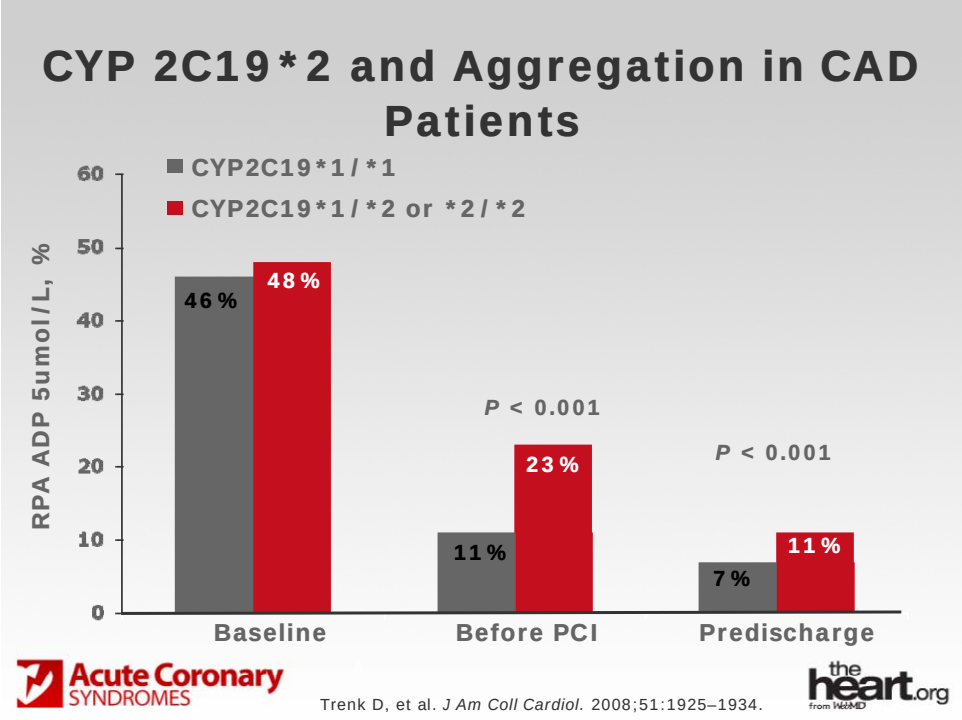
Slide 2

As you know, there are a couple of limitations for clopidogrel, there is a slow onset of action, a low level of inhibition, there's also much variability in reference to this drug, and some patients even have real resistance to the drug; this may well be associated to specific genotypes.



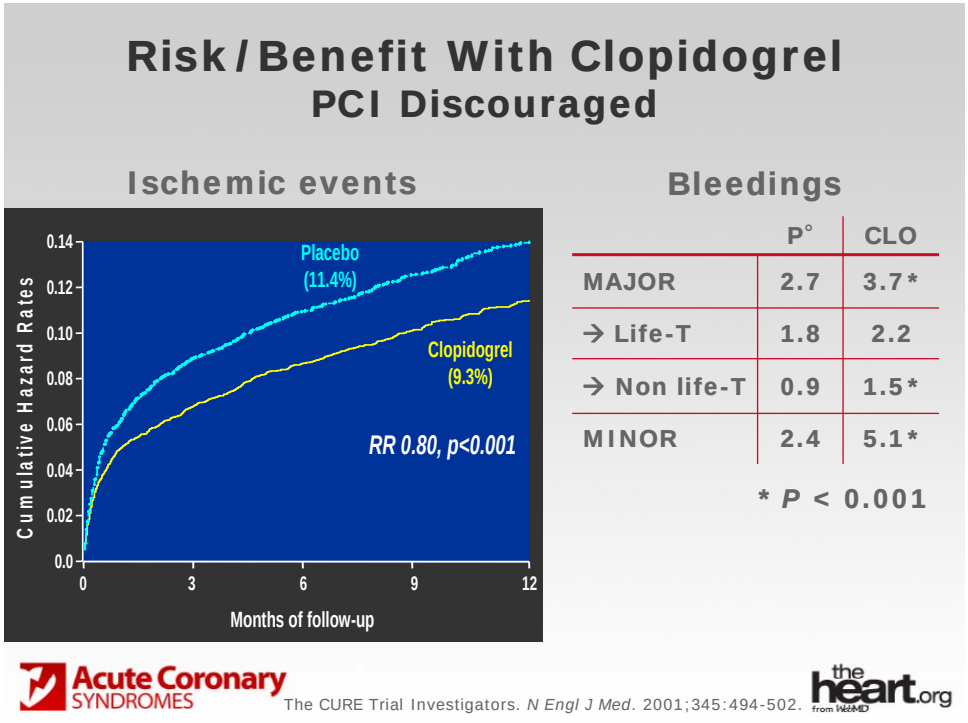
Slide 3

As you know, clopidogrel is a prodrug and it needs to be conformed in an active metabolite. It goes through different pathways, numerous pathways, the CYP 2C19 pathway is very important and there are genetic variance on these pathways. On this slide you have the impact of this 2C19 start of loss-of- function variant associated with low inhibition of aggregation in healthy volunteers receiving clopidogrel. This is a study performed in healthy volunteers but we now have had studies performed in coronary patients.



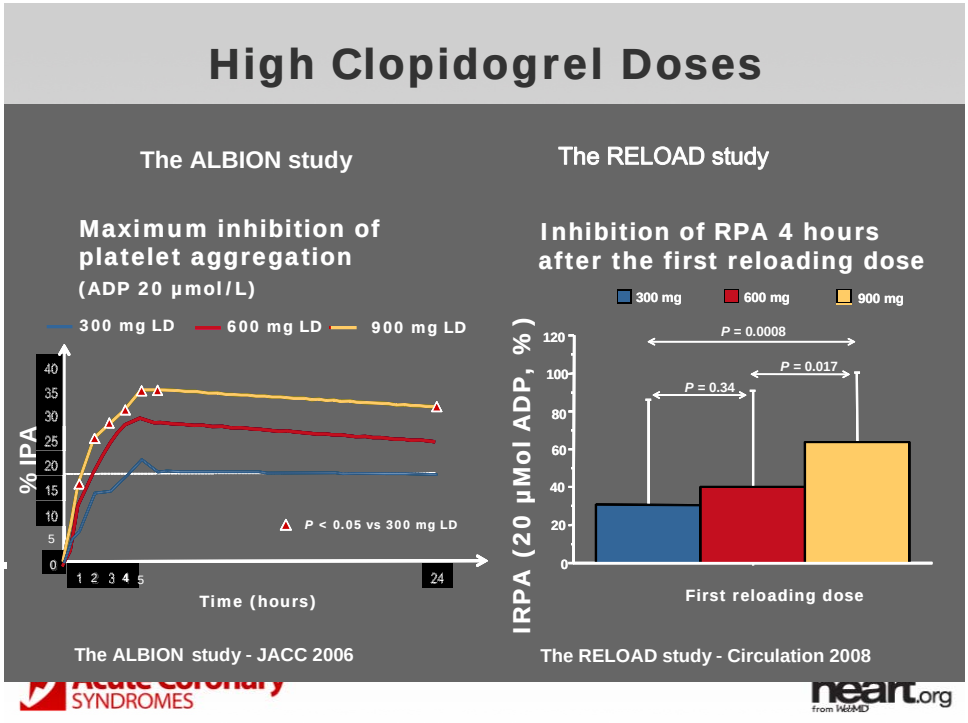
Slide 4

This is another study coming from Germany and demonstrating, I think, quite clearly the link that we have between this variant 2C19 and the level of aggregation on clopidogrel. You can see that just before PCI [percutaneous coronary intervention], when platelet aggregation was measured there was a big difference, a significant difference between the 2 types of patients: a wild type for CYP2C19 and a genetic variant for 2C19. These patients with the genetic variant had less inhibition of platelet aggregation with clopidogrel. But what we miss is of course studies showing that there is a link between this genotype and clinical outcome but we will see in the next few weeks several of these studies demonstrating a link between this genetic variance, this polymorphism, and clinical outcome measured by hard ischemic events. So this is an important finding and we would have probably have to think about genotyping patients with post-stenotic ischemic events or may have poor response to clopidogrel.



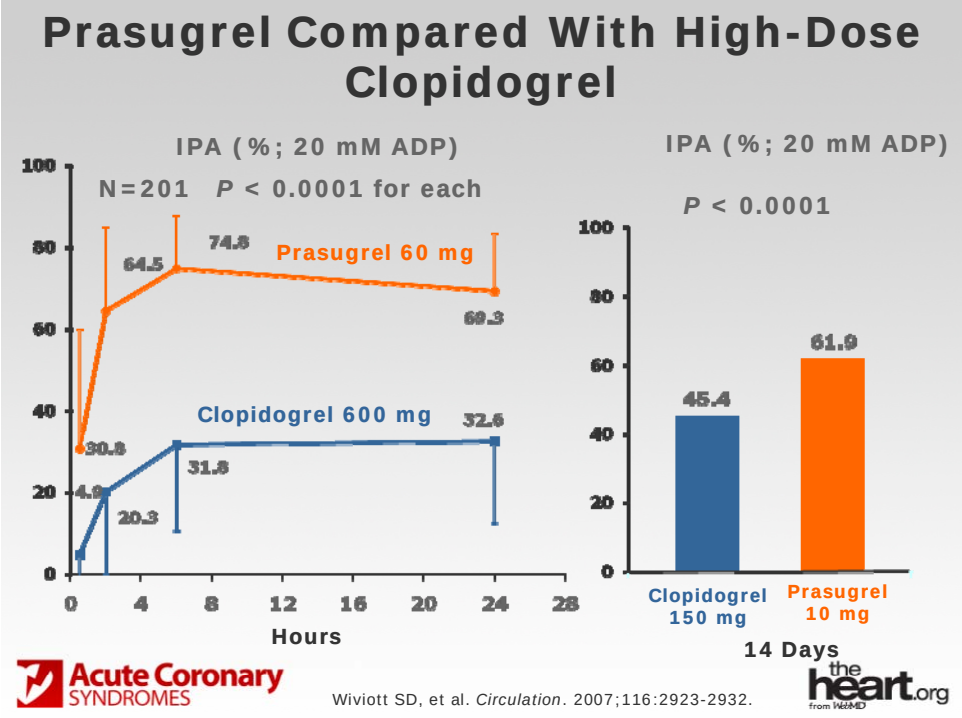
Slide 5

What we know from the clopidogrel story is that this drug has been very effective in acute coronary syndrome [ACS] patients starting with the CURE study, a study where PCI was discouraged. It was really a study looking at a conservative approach of treatment for these ACS patients and there was a real impact on the ischemic side with reduction of ischemic events by 20%, but there was also a price to pay at the time against a placebo arm. There was a price to pay in terms of bleeding, more major bleeding, more minor bleeding, and we discussed at that time, the real risk/benefit of clopidogrel on top of everything else, but we started using this drug in ACS.



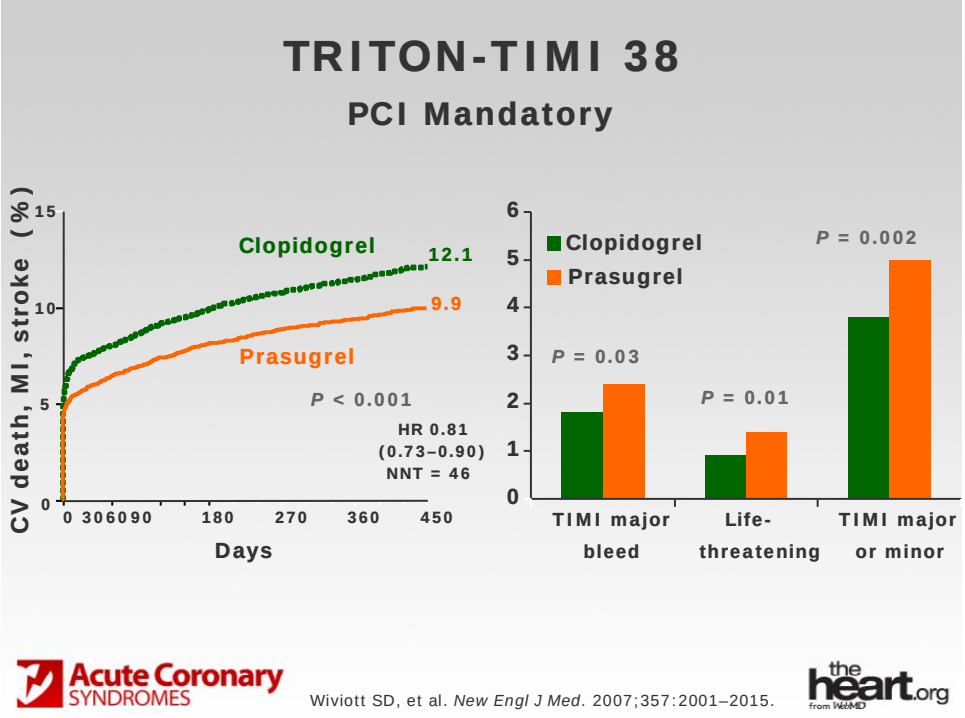
Slide 6

It has been then recommended by the guidelines -- and we have started seeing patients not responding well to clopidogrel and we have seen the studies like these 2 studies that tried to increase the dose of clopidogrel -- to increase the dose of loading with clopidogrel to 300, 600, 900 mg, and even studies with doses now higher than 900 mg. On the left-hand side of this slide is the ALBION [Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation, and Ongoing Necrosis] study that was in clopidogrel-naïve patients that were recruited at the time of presentation for an ACS. On the right side is the RELOAD study [Reload With Clopidogrel Before Coronary Angioplasty in Subjects Treated Long Term With Dual Antiplatelet Therapy], this is again ACS patients but they were on clopidogrel treatment with 75 mg a day and again there is a dose effect relationship into the 2 situations for the dose of clopidogrel. So this is probably a way to overcome poor response and sometimes resistance to clopidogrel.



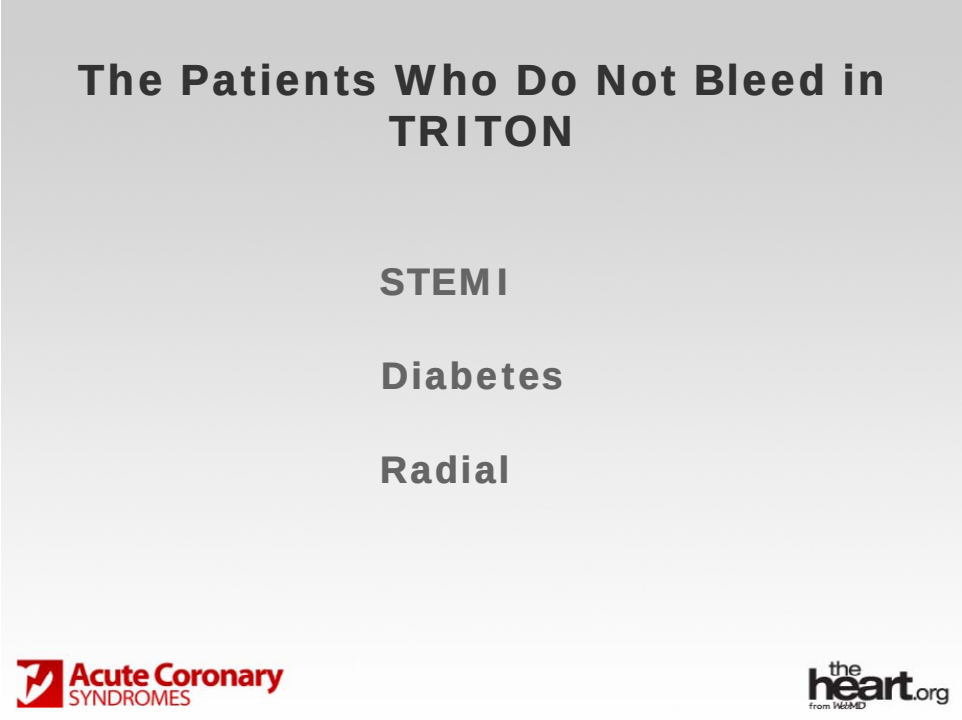
Slide 7

But what we have seen more recently are data coming from studies performed with prasugrel -- a new agent which has a fast onset of action and which is also more potent than clopidogrel. Here you have the data from the PRINCIPLE [Prasugrel In Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation] study showing prasugrel either with loading or with a maintenance dose is more effective in terms of platelet inhibition than clopidogrel, and clopidogrel in this study has been used at high doses, 600 mg to the patients and 150 mg chronically as a maintenance dose so we have a new alternative here for more efficacy on the platelet function.



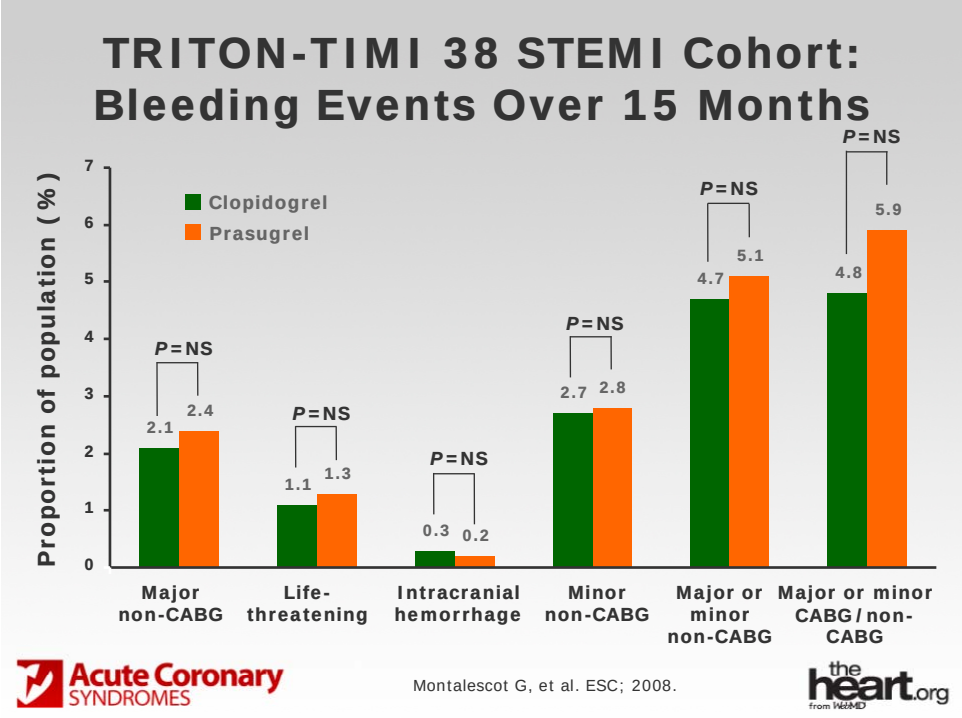
Slide 8

Of course the pivotal trial is the TRITON-TIMI 38 [Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel] study; it's very interesting to see the results we produced with that we had seen years ago in the CURE [Clopidogrel in Unstable Angina to Prevent Recurrent Events] study but this time this is with prasugrel against clopidogrel and not against a placebo arm. You can see that we have the same reduction, risk reduction for ischemic events, a 20% reduction for death, MI [myocardial infarction], and stroke, and again there is a price to pay in terms of bleeding, small major bleeding, small minor bleeding. Clearly we have to reevaluate again the risk-benefit ratio of this work compared with the standard of care which is now clopidogrel on top of course, of aspirin and anticoagulation.



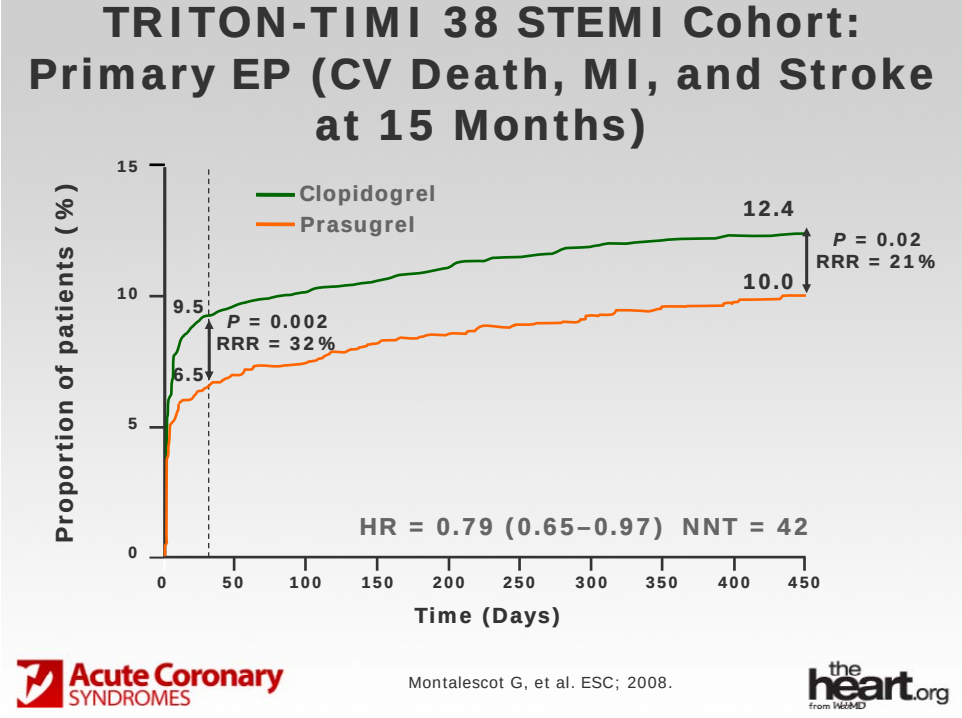
Slide 9

What we know from the TRITON study is that specific subgroups where we do not see this excess of bleeding, for example, the STEMI [ST-elevated myocardial infarction] patients. These are patients that are presenting with STEMI for a primary angioplasty, or sometimes as treatment arises, and come to the lab a few days later for an angioplasty but most of them were primary angioplasty patients. So diabetic patients were also patients with a high level of platelet activation and there was no difference between clopidogrel and prasugrel for bleeding; also for the patients that had a radial access for PCI, they didn't have an excess of bleeding.



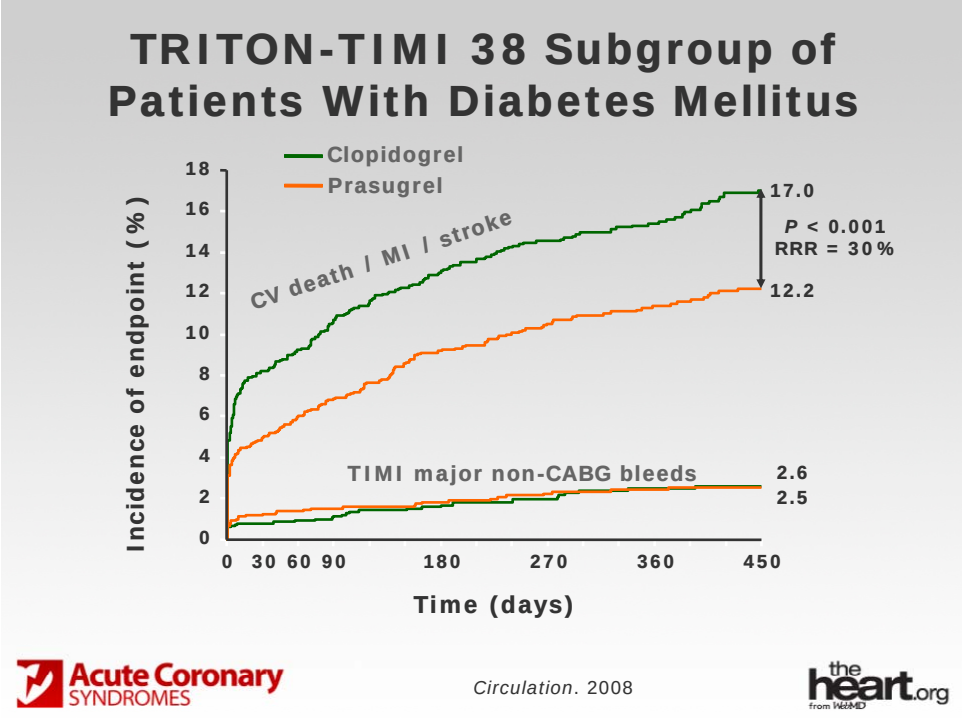
Slide 10

We see these results on the slides that I show now. This here's the bleeding risk in the STEMI cohort of the TRITON study. As you can see whatever you look at there is major bleeding, life-threatening bleeding, minor bleeding, or the combination of these different types of bleeding.



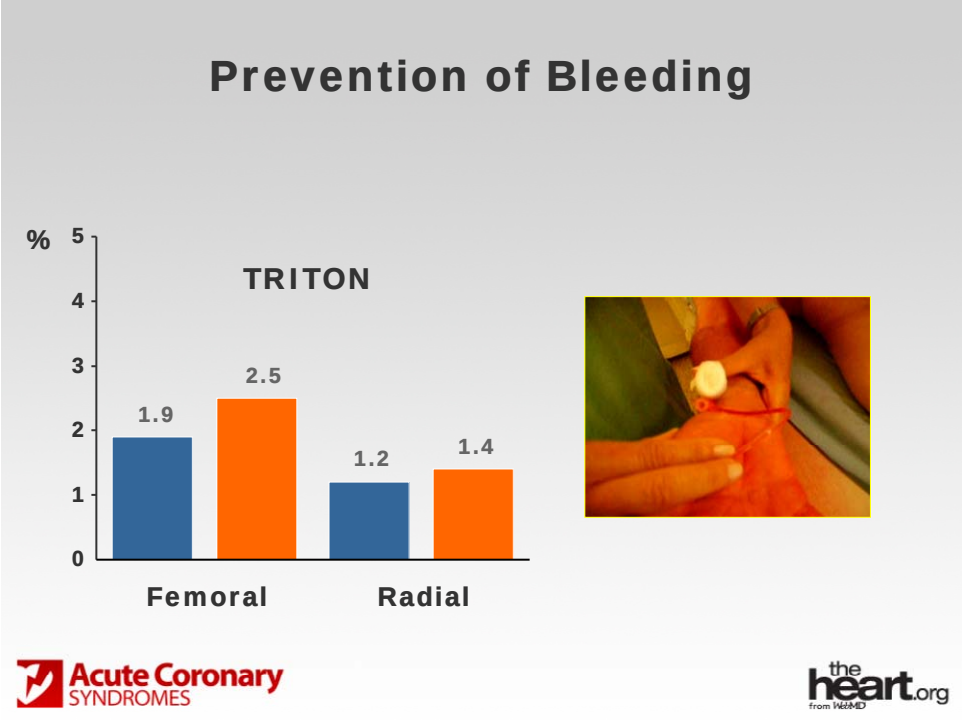
Slide 11

There is no difference between clopidogrel and prasugrel and still there is a real impact on the ischemic side as shown here for the primary endpoint cardiovascular death, MI, and stroke -- at 15 months a 21% reduction of this primary endpoint in the STEMI cohort so the whole benefit was obtained on the ischemic side and there was no excessive bleeding which is good news of course on these types of patients.



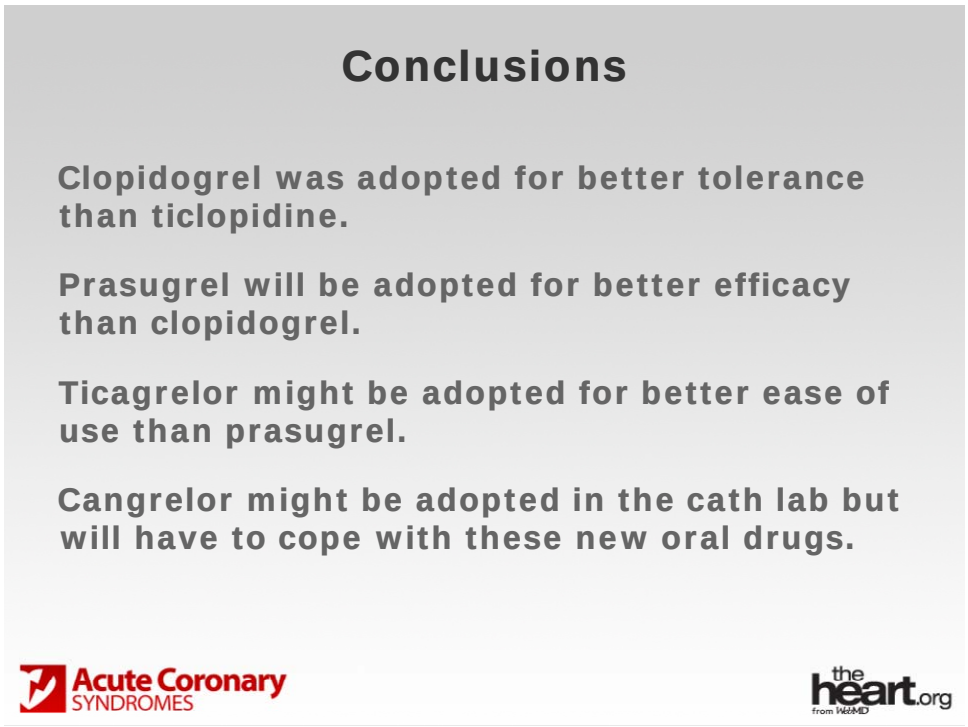
Slide 12

And the diabetic patients have a similar profile – a significant reduction of the primary endpoint with prasugrel compared with clopidogrel, and we know that clopidogrel in diabetics is not very effective and we have a lot of resistant patients among the diabetic patients for clopidogrel. At the bottom of this slide you see the 2 curves for TIMI major bleedings and they are superimposed. There are no differences for bleedings in this cohort of patients that presented with a status of diabetes.



Slide 13

This slide shows what was obtained with this subset in HORIZONS [Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction] for femoral vs radial access, and clearly radial access was seen with less bleeding, so we know what are the subgroups of patients that can have a whole benefit on the ischemic side without an excess of bleedings.



Slide 14

So in conclusion what can we say? Probably that clopidogrel was adopted in the past for better tolerance than ticlopidine, and you remember this serious hematological effect that we had with ticlopidine and that disappeared with clopidogrel. Prasugrel probably will be adopted for better efficacy than clopidogrel, and we have also it looks like ticagrelor [AZD 6140] which has been developed by AstraZeneca and this drug is reversible and is being tested against clopidogrel. It might be adopted for better ease of use because it's a reversible agent so you can get rid of the effect, in case of cardiac surgery for example. And cangrelor is an IV drug that might be adopted into the cath lab for PCI so we'll have to cope with these new oral agents that will be available at the time that cangrelor is being put on the market. So I hope you found this information interesting with this presentation. Thank you very much.