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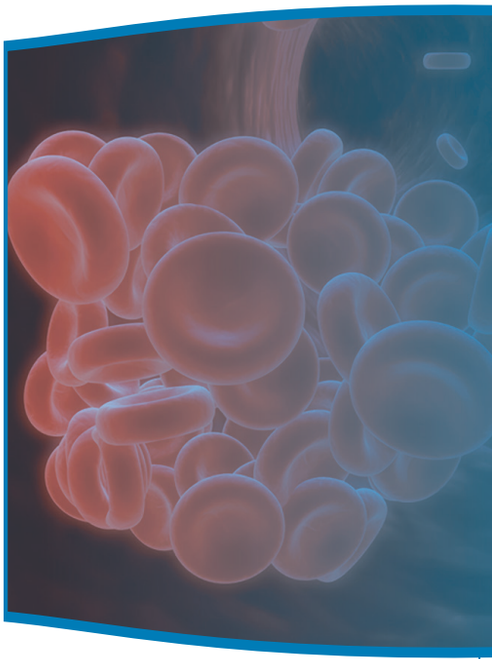

Defining Best Practices in ACS: A Comprehensive Analysis of European Guidelines for Dual Antiplatelet Therapy After PCI

For more information and resources on acute coronary syndrome, please access the series webpage at **www.peervoice.com/ACS1.**

Acute Coronary Syndrome: Current Guidelines

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In this activity, José Luis López-Sendon, MD, PhD, outlines the best practices for management of patients with acute coronary syndrome (ACS) "The first presentation," states Dr. López-Sendon, "is focusing on the guidelines for antiplatelet therapy in acute coronary syndromes. Intracoronary thrombosis plays a key role in the physiopathology of acute coronary syndromes; one opportunity for treating these patients is antithrombotic therapy."

Advances in Antithrombotics for ACS

"In the good old days," notes Dr. López-Sendon, "we had only aspirin and heparin to treat patients with acute coronary syndromes and intracoronary thrombosis [Slide 1.1]. During the last 25 years, there was extraordinary research demonstrating that a number of new antiplatelet agents, as well as a number of new anticoagulant agents, could be of use in patients with acute coronary

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syndromes. So we have now a very complex picture of antithrombotic treatment, and that is one of the reasons why the guidelines are really needed for good clinical practice."

A Clear Need for Treatment Guidelines

"It is getting even more complicated because we have not only new anticoagulants and new anti-aggregants, but a setting where teamwork is important [Slide 1.2]. The patient during the first 24 hours goes from a mobile coronary care unit to the emergency department, then to the coronary care unit, then to the cath lab. We cannot be changing treatments every 2 hours according to the place where the patient is.

"Intracoronary thrombosis plays a key role in the physiopathology of acute coronary syndromes; one opportunity for treating these patients is antithrombotic therapy."

"So we have a really complex picture of different people working together, and we have a lot of options for using different agents. So there is clear evidence that we need the guidelines."

Dual Antiplatelet Therapy in ACS

"Now," says Dr. López-Sendon, "focusing on dual oral antiplatelet therapy (DAPT), we have four options: that is aspirin, clopidogrel, prasugrel, and ticagrelor [Slide 1.3]. There are two major trials that demonstrated the clear benefit of the new antiplatelet agents: the TRITON-TIMI 38 and the PLATO trial. These two trials demonstrated the superiority of prasugrel and ticagrelor in patients with acute coronary syndromes, as compared with the use of aspirin associated with clopidogrel.

"We have now a very complex picture of antithrombotic treatment, and that is one of the reasons why the guidelines are really needed for good clinical practice."

"We don't have a head-to-head comparison trial, so we cannot state that one is better than the other. In general, both are better than clopidogrel and should be of choice, if possible. You should use prasugrel in a ST elevation myocardial infarction (STEMI) or in diabetic patients; and in patients who you think are not going to go through the cath lab, ticagrelor should be the choice according to the evidence we have."

TRITON-TIMI 38:

"In the TRITON-TIMI 38 trial," outlines Dr. López-Sendon, "what was demonstrated is a 19% reduction in the composite endpoint of cardiovascular death, myocardial infarction, and stroke in favour of prasugrel [Slide 1.4].

"Major bleeding increased from 1.8% in the clopidogrel group to 2.4% in the prasugrel group [Slide 1.5]. That was significant, so we should focus on the contraindications for using prasugrel because of the risk of bleeding in these patients."

PLATO:

"In the PLATO trial," points out Dr. López-Sendon, "ticagrelor was also better than clopidogrel in relation to the composite endpoint of cardiovascular death, myocardial infarction, or a stroke; overall there was a reduction of about 16% [Slide 1.6].

"There was also an excess in bleeding when excluding the patients who were submitted for a surgical revascularisation [Slide 1.7]. There was a significant increase in bleeding and some other minor complications according to the TIMI criteria or the PLATO criteria—not very relevant from the clinical point of view.

"So it looks like a better anti-aggregation is somehow also associated with a small, but significant, increase in bleeding. But altogether, I want to make it very clear that both in the PLATO and in the TRITON-TIMI 38 study, the net clinical benefit was clearly in favour of the new therapies ticagrelor and prasugrel."

2014 ESC/EACTS Guidelines on Myocardial Revascularisation: Antiplatelet Therapy

"So accordingly," observes Dr. López-Sendon, "the new guidelines of the European Society of Cardiology reflect these results [Slide 1.8]. Prasugrel and ticagrelor are the recommendation in the guidelines for patients with STEMI undergoing percutaneous coronary intervention (PCI). The recommendation is a Class I, Level of evidence B because there is only one trial for each drug. The interesting thing is that it is clear that clopidogrel is second choice to be used only when prasugrel or ticagrelor are not available or are contraindicated.

"In patients with non-STEMI (NSTEMI) acute coronary syndromes, the recommendation is the same. Most of the European countries that belong

to the European Society of Cardiology have endorsed the guidelines to avoid confusion."

Real-World Outcomes: UK STEMI Regsitry

"But if we move to real life," adds Dr. López-Sendon, "we have to go to registries: There are an important number of registries that focus on the treatments we are using in patients with acute coronary syndromes and the impact on the outcomes of patients with acute coronary syndromes in real life [Slide 1.9].

"The United Kingdom STEMI registry, where prasugrel is compared with clopidogrel, demonstrated that there is better outcome with prasugrel, including all-cause death, myocardial infarctions, stroke, and stent thrombosis. After adjusting for covariate and confounding factors, there is an improvement in postdischarge survival when using the new therapies. This was also observed in other registries—it is only one example—but it tells us that we should follow the guidelines and incorporate the set-ups."

Incorporating Guidelines Into Clinical Practice

"So saying that," notes Dr. López-Sendon, "the next question is, are we incorporating this into clinical practice [Slide 1.10]? In the Czech Republic, clopidogrel is still used in as many as 75% of the patients. This figure changes from one country to another, but it is clear evidence that prasugrel and ticagrelor are not being used as much as we should in clinical practice.

"I think the two major barriers are that the clinical cardiologists are cautious; we are conservative. It takes time to introduce innovation, and that is happening with new anti-aggregants. The second thing is cost."

Conclusions

"In acute coronary syndromes in the last 30 or 40 years," concludes Dr. López-Sendon, "we went through an extraordinary journey from the creation of the coronary care units with fast ECG monitoring, training of the nurses, defibrillation, then the introduction of beta blockers, thrombolysis, aspirin, primary PCI, the statins, then the new anticoagulation and new antithrombotic therapy [Slide 1.11]. So this demonstrated that we could reduce the mortality from 30% to 5%.

"Most of the European countries that belong to the European Society of Cardiology have endorsed the guidelines."

"We have the evidence of the benefit in clinical trials, and we have the evidence in real life—in registries not only in the United Kingdom STEMI registry, but also in many others. We have the evidence that these therapies are cost effective. So I think that we have all the ingredients for taking advantage of this opportunity to improve the benefits and the outcomes of patients with acute coronary syndromes. Thank you." ■

Review of Updated ESC Guidelines for Antiplatelet Therapy in Acute Coronary Syndrome

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Next, Sigmund Silber, MD, PhD, highlights the latest European Society of Cardiology guidelines for the management of acute coronary syndrome (ACS).

Evolution of the ESC Guidelines for Myocardial Revascularisation

As Prof. Silber notes, "when we compare the guidelines for myocardial revascularisation, the number of experts to find consensus almost doubled between 2005 and 2010 [Slide 2.1]. This is also reflected by the considerable increase in the number of pages. This shows you that things have become more and more complicated.

"So what's important to know is that the definition of '*recommendation*' is fortunately the same. So the Class of recommendation and the Level of evidence have not changed.

"So the Class of recommendation and the Level of evidence have not changed."

"For those who say I don't want to read 100 pages, look at the tables; look for the red colour, which means Class III recommendations. Because you should, at least, know what is not recommended by the guidelines."

2014 Update: Who Should Undergo PCI?

"So one of the major changes," points out Prof. Silber, "is the recommendation for who should get percutaneous coronary intervention (PCI) and who should get bypass surgery [Slide 2.2]. There are now more indications for PCI like left main disease, at least with lower SYNTAX scores."

Antiplatelet Therapy in Patients With STEMI Undergoing Primary PCI

"But the main topic," states Prof. Silber, "is acute coronary syndrome. Let's start with STEMI, or ST elevation myocardial infarction [Slide 2.3].

"There's a slight change of the wording in the guidelines. For example, the $P2Y_{12}$ inhibitor should be given as soon as possible. Even paramedics could decide whether to give a $P2Y_{12}$ inhibitor or not. The new wording says prasugrel 60 mg loading dose, 10 mg daily if no contraindication. For ticagrelor, it says 180 mg with 90 mg twice daily maintenance dose, again if no contraindication.

"Actually the contraindications to prasugrel are only two: a previous stroke or transient ischaemic attack. For ticagrelor, the major contraindication is haemorrhagic stroke. So there should be an increase in usage of prasugrel and ticagrelor. If there's no contraindication, there is no place for clopidogrel anymore.

"Regarding intravenous or intercoronary antithrombotic treatment, the use of IIb/IIIa inhibitor actually is a Class IIb, Level B recommendation. Upstream use of glycoprotein IIb/IIIa inhibitor versus in-lab use may be considered in high-risk patients undergoing transfer for primary PCI."

Anticoagulant Therapy in Patients With STEMI Undergoing Primary PCI and DAPT Following PCI in ACS

"What about anticoagulation [Slide 2.4]?" Prof. Silber asks. "For primary PCI and STEMI, enoxaparin received intermediate recommendation Class IIa, Level B for STEMI patients. It was not recommended in the previous guidelines. What's also new is the recommendation of bivalirudin for STEMI patients, with a recommendation of prolonging the infusion after PCI because there might an increased risk of stent thrombosis. So it is now recommended to keep up the infusion rate for up to 4 hours after the procedure."

ESC Guidelines: 1 Year of Dual Antiplatelet Therapy After ACS

"So in the first guidelines," explains Prof. Silber, "we recommended after ACS a whole year of dual antiplatelet therapy (DAPT). In 2010: again 1 year; and now in 2014: again 1 year [Slide 2.5].

"Now, this is interesting because actually we do not have many trials of monotherapy versus dual antiplatelet therapy. So all the recommendations of 1 year are derived from the old CURE trial [Yusef S et al. *N Engl J Med*. 2001;345:494-502]. But what I see as the major problem is that many patients discontinue the dual antiplatelet therapy after 6 months.

"But for acute coronary syndrome, patients should have dual antiplatelet therapy for at least 1 year, independent of a bare stent or drug-eluting stent—even if they had no stent. We have to make more emphasis that ACS is not over when the patient gets home; ACS goes on and has a higher risk than patients with stable angina."

Antiplatelet Therapy in Patients With NSTE-ACS Undergoing PCI

"In patients with acute coronary syndrome with no ST segment elevation, NSTEMI or unstable angina," adds Prof. Silber, "there's a new Class III recommendation—which means don't do it [Slide 2.6]. Pretreatment with prasugrel in patients in whom coronary anatomy is not known is not recommended. This comes from the ACCOAST trial [Montalescot G et al. *N Engl J Med*. 2013;369:999-1010]. For the first time, it was tested whether pretreatment with prasugrel versus no pretreatment in these patients is helpful or not. It had only negative effects, which means more bleeding but not preventing ischaemic events.

"There are two questions with this: The first question is, should and could this recommendation be extrapolated also to ticagrelor? We do not have any data for ticagrelor in NSTEMI pretreatment versus no pretreatment. In our institution, we say this recommendation is the same for both drugs. So we do not do any pretreatment with DAPT.

"The second thing is, if you withhold prasugrel or ticagrelor and you give only aspirin and heparin before coronary angiography, then patients usually should not wait longer than 4 hours or 8 hours for the cath.

"So what about pretreatment with a IIb/IIIa inhibitor? There is no change in the guidelines. You should not pretreat NSTEMIs with a IIb/IIIa antagonist before the cath lab and before you see a lot of thrombus."

Anticoagulant Therapy in Patients With NSTE-ACS Undergoing PCI

"What about bivalirudin anticoagulation [Slide 2.7]? For NSTEMI," notes Prof. Silber, "there's a new recommendation which says bivalirudin should be used in these patients as an alternative to unfractionated heparin plus IIb/IIIa inhibition. But also—and that's important to emphasise—do not reduce the rate of infusion after PCI; go with the same dose for the next 4 hours."

Conclusion

"In NSTEMI," concludes Prof. Silber, "the overall bottom line is that you should not pretreat the patient—just give aspirin and heparin [Slide 2.8]. The rest is decided in the cath lab after diagnostic angiography. Bivalirudin got a strong recommendation for prolonged infusion. IIb/IIIa inhibitors should not be given in NSTEMI upstream.

"The recommendation in STEMI has not changed. The most important thing in STEMI is go to the next hospital with a cath lab. Of course, these hospitals should have 24 hours/7 days a week service. Pretreatment should be given at first medical contact. That is a challenge.

"So one of the major changes is the recommendation for who should get percutaneous coronary intervention (PCI) and who should get bypass surgery."

"The ATLANTIC trial showed that if the transportation times are very short, there was no difference in the primary endpoints between pretreatment and no pretreatment [Montalescot G et al. *N Engl J Med*. 2014;371:1016-1027]. So does that mean you should not pretreat in STEMI also? I don't think so. If you have longer transportation times, prasugrel or ticagrelor should be on board of the emergency cars.

"What is to be expected in the future? Regarding ACS, how long should dual antiplatelet therapy really be performed? Well usually we say 1 year and that's it, but if you continue dual antiplatelet therapy for 2 or 3 years or even 4 years there might be some signs of a benefit. This will be actually investigated in the PEGASUS trial [Clinicaltrials.gov ID: NCT01225562]. If this trial is positive, then this will change all our thoughts and concepts of how long to give dual antiplatelet therapy.

"We have to make more emphasis that ACS is not over when the patient gets home; ACS goes on and has a higher risk than patients with stable angina."

"So I think this is the most important thing in the next years to decide. For the patients with stable coronary disease, dual antiplatelet treatment duration is limited to the stent and not to the patient, but ACS is different. This is one thing in the future we have to emphasise: ACS is not over when ACS is

over. Many people think I got my heart attack, the doctor fixed it, and that's it. No, it is a dangerous disease with still an increased mortality, and we need more drugs to treat in the following years after ACS." ■

Review of Updated European Guidelines for the Management of Acute Coronary Syndrome

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In this activity Clive Weston, MA, MB, FRCP, discusses the management of acute coronary syndrome (ACS), by focusing on influential European guidelines, including NICE and ANMCO/SICI-GISE.

Need for Guidelines in the Management of ACS

Dr. Weston begins by asking, "why do we need guidelines [Slide 3.1]? There are close to 20 million combinations of treatments, simply looking at the various combinations of antiplatelets and anticoagulant treatments available in the early stages, in the cath lab, and post-procedurally.

"Patients with acute coronary syndromes remain at risk of vascular events in the future," explains Dr. Weston, "and so whilst the earliest treatment probably does focus on the passivation of plaque and the prevention of stent thrombosis, our later treatments are really based on prevention of new events.

"The major areas in the field of antiplatelet and anticoagulant therapy relate to the duration of dual antiplatelet therapy; which particular antiplatelet agents should be used and when; whether it's possible to switch; whether aspirin necessarily needs to be part of the duo of antiplatelet agents; and whether the type of stent deployed matters."

NICE Guidelines:

Development Process

"If we consider the NICE guidelines, the National Institute for Health and Care Excellence is a semi-independent body that is influenced by government [Slide 3.2]. The Department of Health in the United Kingdom agrees which particular areas of clinical practice require a guideline, and an independent appraisal committee and an assessment group develop an appraisal consultation document that should take into account various aspects not

only of effectiveness and benefit, but also safety and cost. Cost-benefit analyses of varying sorts are a necessary part of the NICE guideline development.

"Based on these appraisals," says Dr. Weston, "the National Health Service would make available funds for their clinicians to prescribe this particular drug."

NICE Updated Guidance on Prasugrel

"NICE decided to perform a second appraisal because of the publication of a substudy from the original TRITON-TIMI 38 trial **[Slide 3.3]**. This particular substudy looked at that group of patients within the original trial who were younger than 75 years of age, weighed 60 kg or more, and had no history of prior stroke or transient ischaemic attack.

"These are the sorts of patients for which prasugrel is advised," notes Dr. Weston, "and so this substudy was looked on by NICE as being more relevant to British practice. It allowed the NICE technology appraisal to recommend that prasugrel 10 mg was, indeed, an option for preventing further events with acute coronary syndrome in both non-ST (NSTEMI) and ST elevation myocardial infarction (STEMI).

"Interestingly, they gave this recommendation both for those patients having a primary percutaneous intervention for the ST elevation group, but also what they describe as '*delayed percutaneous coronary intervention (PCI)*'—in other words, those patients with non-ST elevation receiving PCI."

Cost Effectiveness

"Another important area of a NICE appraisal," points out Dr. Weston, "is the cost-effectiveness analysis **[Slide 3.4]**. The assessment group were able to demonstrate a better cost effectiveness for prasugrel—in other words, extra cost to gain extra benefit for patients with ST elevation, both in patients with and without diabetes. When they looked at unstable angina or non-ST elevation myocardial infarction, then in those patients with diabetes the cost-effectiveness model suggested that not only was there greater benefit, but that the overall cost was actually lower.

"It was only in the group of NSTEMI patients without diabetes that the cost of gaining extra life-years was in the region of £5,000. But these figures are well within the costs looked on as reasonable by the NICE institution itself and by government."

NICE Guidance on Ticagrelor

"The practising clinician can now look both at the technology appraisal of ticagrelor and of prasugrel and see that both are recommended **[Slide 3.5]**. This actually leads on to the potential for increased confusion in clinical practice. Neither the manufacturers nor their own independent assessment group have attempted to undertake any comparison between prasugrel and ticagrelor. It leaves us, as practicing clinicians, very much in the dark as to which particular agents should be used in each of the different indications.

"The difference in my interpretation of these two technology appraisals," explains Dr. Weston, "is that prasugrel is being recommended for patients in both STEMI and NSTEMI groups in whom a PCI is planned to be performed, whereas the recommendation allows the use of ticagrelor in those patients in whom a decision to perform percutaneous coronary intervention has not yet been made."

ANMCO/SICI-GISE Position Paper on ACS

"Whilst many guideline groups, particularly the British NICE group," observes Dr. Weston, "have tended to look very much at a single technology and build a guideline, the Italian group in their position paper have tried to translate into practice a consensus view of experts on the validity of the science behind the use of various antiplatelet agents **[Slide 3.6]**.

"The earliest treatment probably does focus on the passivation of plaque and the prevention of stent thrombosis, our later treatments are really based on prevention of new events."

"What they've tried to do is to look at individual subgroups of patients who clinicians might be asked to manage. They've tried to look within the evidence base for clinical trials into which that particular patient might have been entered. They've then assigned a score to those clinical trials and to each individual agent used in a particular subgroup, ranging from 0 to 3 based on scientific quality."

STEMI

"Looking at the subgroup of patients with ST elevation myocardial infarction," notes Dr. Weston, "aspirin has a very high scientific quality rating, similar to the use of oral prasugrel **[Slide 3.7]**.

Oral clopidogrel gains a quality rating of 1, and ticagrelor gets a quality rating of 2."

NSTEMI

"Looking at the subgroup with non-ST elevation infarction," adds Dr. Weston, "we can see that there is a slightly more complex nature to their interpretation because they've been looking for evidence of benefits of early pre-procedural, or upstream, treatments with antiplatelet agents, and then at the time of or soon after procedures, so-called downstream treatment [Slide 3.8].

"The major areas in the field of antiplatelet and anticoagulant therapy relate to the duration of dual antiplatelet therapy; which particular antiplatelet agents should be used and when."

"Looking at upstream treatment, then management with aspirin and ticagrelor gains high quality scientific scores, whereas for prasugrel, the evidence for benefit is really only in downstream treatment."

Diabetes

"Looking at the diabetes subsets, high levels of quality were assigned by the Italian group for aspirin, prasugrel, and for glycoprotein inhibitors; and slightly lower levels of quality for ticagrelor; and lower levels still for clopidogrel [Slide 3.9]."

Benefits and Limitations of ACS Guidelines

"We have a number of guidelines," states Dr. Weston, "and there is a consensus [Slide 3.10]. Early interventional treatment seems to be something upon which we are all agreed, though there are still subgroups of patients in whom early treatment may carry more hazard than benefit.

"It would be good to have comparative studies of the newer antiplatelet agents, one versus another."

"Will these guidelines reduce the burden of acute coronary syndrome in Europe? Well, they may not reduce the total number of patients admitted to hospitals, but they should reduce the amount of heart muscle damage suffered by individual patients, the likelihood that these individual patients will have second heart attacks, and the likelihood that these patients will develop heart failure in the future. And with vigorous and early treatment, they should reduce the number of patients admitted who fail to leave hospital alive."

Conclusions

"If we look back over the last 10 to 20 years, there have been large strides in improving the management of patients with acute coronary syndrome [Slide 3.11]. Large, expansive, multicentre, randomised trials have been performed, interpreted, and incorporated into clinical guidelines, and hopefully now implemented into clinical practice.

"There are many areas that still require further study," observes Dr. Weston. "We'll need to decide whether aspirin is a required member of dual antiplatelet therapy. It would be good to have comparative studies of the newer antiplatelet agents, one versus another. And until it is studied, then we have to choose one agent over another, and that comes down to availability, familiarity with one drug versus another, and consensus in groups of clinicians. Newer studies should guide us to determine how long these treatments should be given and whether they should be given lifelong in the absence of bleeding risk.

"So we should continue to research not only the field of antiplatelet agents," concludes Dr. Weston, "but other areas of the management of acute coronary syndrome in the hope of continuing to improve our treatments." ■

Defining Best Practices in ACS: A Comprehensive Analysis of European Guidelines for Dual Antiplatelet Therapy After PCI

Acute Coronary Syndrome: Current Guidelines

José Luis López-Sendon, MD, PhD

Slide 1.1

Advances in Antithrombotics for ACS

- **Historically, aspirin and heparin were used to treat ACS**

- **Today:**
  - Dozens of clinical studies with hundreds of thousands of patients evaluating many new antiplatelet and anticoagulant agents
  - Complex picture of treatment reinforces the need for guidelines

ACS: acute coronary syndrome.

Slide 1.2

A Clear Need for Treatment Guidelines

Treatment Team

- Cardiologist
- Internal med, Interventional specialist
- Emergency specialists
- Mobile units
- Pharmacists
- Regulatory authorities

Anticoagulants

- Unfractionated heparin
- Enoxaparin
- Dalteparin
- Bivalirudin

Anti-aggregants

- Aspirin
- Clopidogrel
- Abciximab
- Tirofiban
- Lamifiban
- Prasugrel
- Cangrelor
- Vorapaxar
- Ticagrelor

Clinical Setting

- ST / non-ST MI; UA
- Clinical trial eligible?
- Age, gender
- Risk profile
- Thrombolysis?
- PCI?
- Stenting?
- Renal function, bleeding risk
- Other comorbidities

MI: myocardial infarction; PCI: percutaneous coronary intervention; UA: unstable angina.

Slide 1.3

Dual Antiplatelet Therapy in ACS

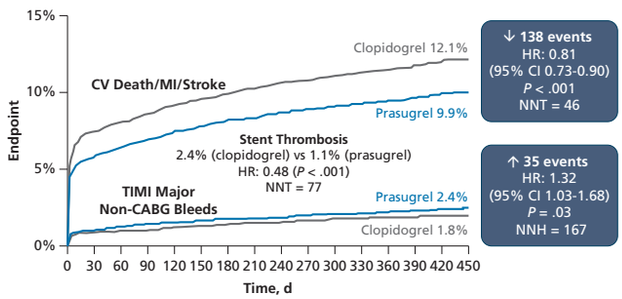
Anti-aggregants

- Aspirin
- Clopidogrel
- Prasugrel
- Ticagrelor

- **Prasugrel and ticagrelor are preferred choices for antiplatelet therapy**

Slide 1.4

TRITON-TIMI 38: Efficacy and Safety



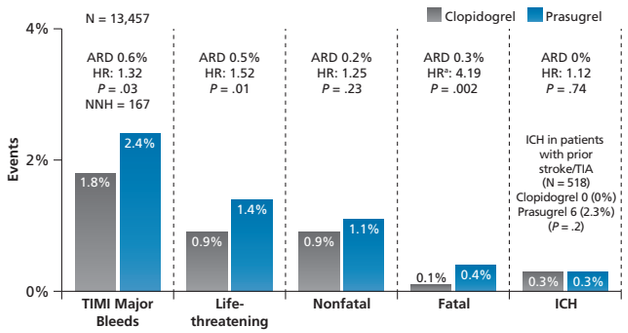
Study design: 13,608 patients with moderate- to high-risk ACS with scheduled PCI were randomly assigned to receive prasugrel (60 mg loading dose + 10 mg daily maintenance dose) or clopidogrel (300 mg loading dose + 75 mg daily maintenance dose) for 6 to 15 months. Primary efficacy endpoint: death from cardiovascular causes, nonfatal MI, or nonfatal stroke. Key safety endpoint: major bleeding.

CABG: coronary artery bypass graft; CI: confidence interval; CV: cardiovascular; HR: hazard ratio; NNH: number needed to harm; NNT: number needed to treat; TIMI: thrombolysis in myocardial infarction.

Wiviott SD et al. *N Engl J Med*. 2007;357:2001-2015.

Slide 1.5

TRITON-TIMI 38: Bleeding Events

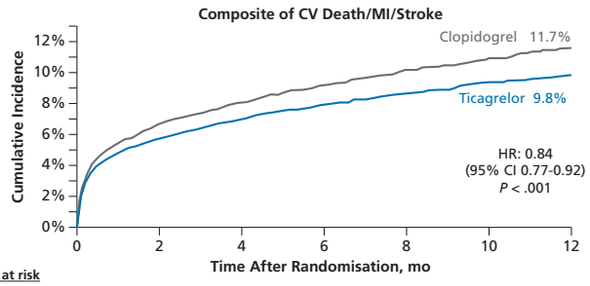


[a] One patient in the clopidogrel group had a fatal gastrointestinal haemorrhage while receiving the study medication, but haemoglobin testing was not performed. Therefore, the criteria for TIMI major bleeding (including life-threatening and fatal bleeding) could not be applied, and the data do not appear in this graph.

ARD: absolute risk difference; ICH: intracranial haemorrhage; TIA: transient ischaemic attack.
Wiviott SD et al. *N Engl J Med*. 2007;357:2001-2015.

Slide 1.6

PLATO: Primary Efficacy



No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,650	5,096	4,047

Study design: 18,624 patients with ACS with or without ST-segment elevation were randomly assigned to receive ticagrelor (180 mg loading dose + 90 mg twice daily maintenance dose) or clopidogrel (300 or 600 mg loading dose + 75 mg daily maintenance dose) for 12 months. Primary efficacy endpoint: composite of death from vascular causes, MI, or stroke.

Wallentin L et al. *N Engl J Med*. 2009;361:1045-1057.

Slide 1.7

PLATO: Major Bleeding and Related Events

Event, %	Ticagrelor	Clopidogrel	*P*
Bleeding	(n = 9,235)	(n = 9,186)	
Total Major – PLATO criteria	11.6	11.2	.43
Total Major – TIMI criteria	7.9	7.7	.57
Non-CABG Major – Plato criteria	4.5	3.8	.03
Non-CABG Major – TIMI criteria	2.8	2.2	.03
Holter Monitoring at First Week	(n = 1,451)	(n = 1,415)	*P*
Ventricular pauses ≥3 sec	5.8	3.6	.01
Ventricular pauses ≥5 sec	2.0	1.2	.10
All Patients	(n = 9,235)	(n = 9,186)	*P**
Dyspnoea			
Any	13.8	7.8	< .001
With discontinuation of study treatment	0.9	0.1	< .001
Bradycardia-Related Event	(n = 9,235)	(n = 9,186)	*P*
Syncope	1.1	0.8	.08
Bradycardia	4.4	4.0	.21

* *P* values were calculated using Fischer's exact test.

TIMI: Thrombosis in Myocardial Infarction.
Wallentin L et al. *N Engl J Med*. 2009;361:1045-1057.

Slide 1.8

2014 ESC/EACTS Guidelines on Myocardial Revascularisation: Antiplatelet Therapy

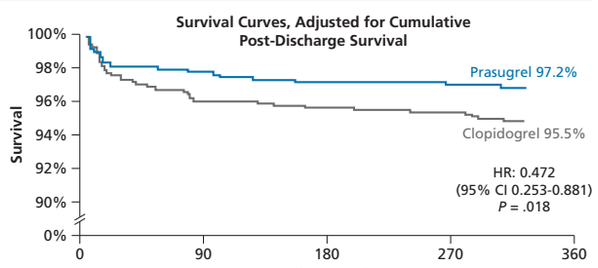
Recommendations	Class[a]	Level[b]
Patients With STEMI Undergoing Primary PCI		
ASA is recommended for all patients without contraindications at an initial oral loading dose of 150-300 mg (or 80-150 mg IV) and at a maintenance dose of 75-100 mg daily long-term regardless of treatment strategy	I	A
A $P2Y_{12}$ inhibitor is recommended in addition to ASA and maintained over 12 months unless there are contraindications such as excessive risk of bleeding. Options are:	I	A
• Prasugrel (60 mg loading dose, 10 mg daily dose) if no contraindication	I	B
• Ticagrelor (180 mg loading dose, 90 mg twice daily) if no contraindication	I	B
• Clopidogrel (600 mg loading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated	I	B
Patients With NSTE-ACS Undergoing PCI		
Pretreatment with prasugrel in patients in whom coronary anatomy not known is not recommended	III	B
• Prasugrel (60 mg loading dose, 10 mg daily dose) in patients in whom coronary anatomy is known and who are proceeding to PCI if no contraindication	I	B
• Ticagrelor (180 mg loading dose, 90 mg twice daily) for patients at moderate-to-high risk of ischaemic events, regardless of initial treatment strategy including those pretreated with clopidogrel if no contraindication	I	B
• Clopidogrel (600 mg loading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated	I	B

[a] Class of recommendation. [b] Level of evidence.

ASA: acetylsalicylic acid; EACTS: European Association for Cardio-Thoracic Surgery; ESC: European Society of Cardiology; IV: intravenous; NSTE-ACS: non-ST elevation acute coronary syndrome; STEMI: ST elevation myocardial infarction.
Windecker S et al. *Eur Heart J*. 2014;35:2541-2619.

Slide 1.9

Real-World Outcomes: UK STEMI Registry



No. at risk					
Prasugrel	822	805	801	801	799
Clopidogrel	866	836	833	831	827

Study design: Nonrandomised, retrospective analysis of 1,688 patients with STEMI undergoing primary PCI who received prasugrel or clopidogrel. Patients with age ≥75 years, weight <60 kg or history of cerebrovascular accident or TIAs, active bleeding, or known hepatic impairment were excluded. Primary endpoint: composite of all-cause death, MI, stroke, stent thrombosis, revascularisation.

Koshy A et al. *Cardiovasc Ther*. 2014;32:1-6.

Slide 1.10

Incorporating Guidelines Into Clinical Practice

ATHRO Registry: Treatment for ACS with PCI 2013

$P2Y_{12}$, %	Czech Republic	Slovakia
Clopidogrel	75.3	53.6
Ticagrelor	13.1	17.3
Prasugrel	2.6	23.1

- **Barriers to adoption in clinical practice:**
  - Clinicians are conservative with new treatments
  - New therapies are more expensive than clopidogrel

Widimský P et al. *Cor et Vasa*. 2014;56:e320-e324.

Please tear along perforation

Slide 1.11

Conclusions

Treating ACS: An extraordinary journey
- Innovations over the past 40 years have led to significant reductions in mortality
  - New technology
  - New therapies
  - Teamwork

Recommended antiplatelet therapies: Prasugrel and ticagrelor
- Demonstrated improved outcomes
- Recommended in 2014 ESC/EACTS guidelines
- However, patients may be under-treated

Review of Updated ESC Guidelines for Antiplatelet Therapy in Acute Coronary Syndrome

Sigmund Silber, MD, PhD

Slide 2.1

Evolution of the ESC Guidelines for Myocardial Revascularisation

	2005[1]	2010[2]	2014[3]
Experts for consensus	44	57	78
Printed pages	44	55	100
Tables	19	41	50
References	404	1,126[a]	961

- New guidelines replace the ESC guidelines on myocardial revascularisation from 2010, which replaced the ESC PCI guidelines from 2005
- **2014 guidelines do not replace: 2013 ESC guidelines for stable CAD, STEMI from 2012, or NSTEMI from 2011**

[a] 270 references in the document, plus an additional 856 online references.

CAD: coronary artery disease; ESC: European Society of Cardiology; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction.

Slide 2.2

2014 Update: Who Should Undergo PCI?

Recommendations According to Extent of CAD	CABG		PCI	
	Class[a]	Level[b]	Class[a]	Level[b]
One- or two-vessel disease without proximal LAD stenosis	IIb	C	I	C
One-vessel disease with proximal LAD stenosis	I	A	I	A
Two-vessel disease with proximal LAD stenosis	I	B	I	C
Left main disease with a SYNTAX score ≤22	I	B	I	B
Left main disease with a SYNTAX score 23-32	I	B	IIa	B
Left main disease with a SYNTAX score >32	I	B	III	B
Three-vessel disease with a SYNTAX score ≤22	I	A	I	B
Three-vessel disease with a SYNTAX score 23-32	I	A	III	B
Three-vessel disease with a SYNTAX score >32	I	A	III	B

Class	Description	Recommendation
I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective	Is recommended/indicated
IIa	Weight of evidence/opinion is in favour of usefulness/efficacy	Should be considered
IIb	Usefulness/efficacy is less well established by evidence/opinion	May be considered
III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful	Is not recommended

[a] Class of recommendation. [b] Level of evidence.

CABG: coronary artery bypass graft; LAD: left anterior descending artery.

1. Silber S et al. *Eur Heart J*. 2005;26:804-847.
2. Wijns W et al. *Eur Heart J*. 2010;31:2501-2555.
3. Windecker S et al. *Eur Heart J*. 2014;35:2541-2619.

Slide 2.3

Antiplatelet Therapy in Patients With STEMI Undergoing Primary PCI

Recommendations	Class[a]	Level[b]
ASA is recommended for all patients without contraindications at an initial oral loading dose of 150-300 mg (or 80-150 mg IV) and at a maintenance dose of 75-100 mg daily long-term regardless of treatment strategy	I	A
A $P2Y_{12}$ inhibitor is recommended in addition to ASA and maintained over 12 months unless there are contraindications such as excessive risk of bleeding. Options are:	I	A
• Prasugrel (60 mg loading dose, 10 mg daily dose) if no contraindication	I	B
• Ticagrelor (180 mg loading dose, 90 mg twice daily) if no contraindication	I	B
• Clopidogrel (600 mg loading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated	I	B
It is recommended to give $P2Y_{12}$ inhibitors at the time of first medical contact	I	B
GP IIb/IIIa inhibitors should be considered for bail-out or evidence of no reflow or a thrombotic complication	IIa	C
Upstream use of a GP IIb/IIIa inhibitor (vs in-lab use) may be considered in high-risk patients undergoing transfer for primary PCI	IIb	B

[a] Class of recommendation. [b] Level of evidence.

ASA: acetylsalicylic acid; GP: glycoprotein; IV: intravenous; TIA: transient ischaemic attack.
Windecker S et al. *Eur Heart J*. 2014;35:2541-2619.

Slide 2.4

Anticoagulant Therapy in Patients With STEMI Undergoing Primary PCI and DAPT Following PCI in ACS

Recommendations	Class[a]	Level[b]
Anticoagulation is recommended for all patients in addition to antiplatelet therapy during PCI	I	A
The anticoagulation is selected according to both ischaemic and bleeding risks, and according to the efficacy-safety profile of the chosen agent	I	C
Unfractionated heparin: 70-100 U/kg IV bolus when no GP IIb/IIIa inhibitor is planned, 50-70 U/kg IV bolus with GP IIb/IIIa inhibitor	I	C
Bivalirudin 0.75 mg/kg IV bolus followed by IV infusion of 1.75 mg/kg/h for up to 4 hours after the procedure	IIa	A
Enoxaparin IV 0.5 mg/kg with or without GP IIb/IIIa inhibitor	IIb	B

In patients undergoing myocardial revascularisation for high-risk ACS, DAPT is recommended for 1 year, irrespective of stent type

- After stenting for ACS, particularly STEMI, extended DAPT reduces the risk of:
  - Stent thrombosis
  - Re-infarction
  - Cardiovascular mortality
- It is important to inform patients and their physicians about the need to avoid premature discontinuation of DAPT

[a] Class of recommendation. [b] Level of evidence.

DAPT: dual antiplatelet therapy.
Windecker S et al. *Eur Heart J*. 2014;35:2541-2619.

Slide 2.5

ESC Guidelines: 1 Year of Dual Antiplatelet Therapy After ACS

	2005[1]	2010[2]	2014[3]
Duration	12 months irrespective of revascularisation strategy	12 months irrespective of revascularisation strategy	12 months irrespective of revascularisation strategy
ASA	+	+	+
Clopidogrel	+	(+)	Only if prasugrel or ticagrelor are not available or contraindicated
Prasugrel *or* Ticagrelor	N/A	Preferred depending on approval and availability	Definitively preferred

N/A: not available.
1. Silber S et al. *Eur Heart J*. 2005;26:804-847.
2. Wijns W et al. *Eur Heart J*. 2010;31:2501-2555.
3. Windecker S et al. *Eur Heart J*. 2014;35:2541-2619.

Slide 2.6

Antiplatelet Therapy in Patients With NSTE-ACS Undergoing PCI

Recommendations	Class[a]	Level[b]
ASA is recommended for all patients without contraindications at an initial oral loading dose of 150-300 mg (or 80-150 mg IV) and at a maintenance dose of 75-100 mg daily long-term regardless of treatment strategy	I	A
A $P2Y_{12}$ inhibitor is recommended in addition to ASA and maintained over 12 months unless there are contraindications such as excessive risk of bleeding. Options are:	I	A
• Prasugrel (60 mg loading dose, 10 mg daily dose) in patients in whom coronary anatomy is known and who are proceeding to PCI if no contraindication	I	B
• Ticagrelor (180 mg loading dose, 90 mg twice daily) for patients at moderate-to-high risk of ischaemic events, regardless of initial treatment strategy including those pretreated with clopidogrel if no contraindications	I	B
• Clopidogrel (600 mg loading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated	I	B
GP IIb/IIIa antagonists should be considered for bail-out situation or thrombotic complications	IIa	C
Pretreatment with prasugrel in patients in whom coronary anatomy not known is not recommended	III	B
Pretreatment with GP IIb/IIIa antagonists in patients in whom coronary anatomy is not known is not recommended	III	A

[a] Class of recommendation. [b] Level of evidence.

NSTE-ACS: non-ST-elevation acute coronary syndrome.
Windecker S et al. *Eur Heart J*. 2014;35:2541-2619.

Slide 2.7

Anticoagulant Therapy in Patients With NSTE-ACS Undergoing PCI

Recommendations	Class[a]	Level[b]
Anticoagulation is recommended for all patients in addition to antiplatelet therapy during PCI	I	A
The anticoagulation is selected according to both ischaemic and bleeding risks, and according to the efficacy-safety profile of the chosen agent	I	C
Bivalirudin (0.75 mg/kg bolus, followed by 1.75 mg/kg/h for up to 4 hours after the procedure) is recommended as alternative to UFH plus GP IIb/IIIa receptor inhibitor during PCI	I	A
UFH is recommended as anticoagulant for PCI if patients cannot receive bivalirudin	I	C
In patients on fondaparinux (2.5 mg daily SC), a single bolus UFH (85 IU/kg, or 60 IU/kg in the case of concomitant use of GP IIb/IIIa receptor inhibitors) is indicated during PCI	I	B
Enoxaparin should be considered as anticoagulant for PCI in patients pre-treated with subcutaneous enoxaparin	IIa	B
Discontinuation of anticoagulation should be considered after an invasive procedure unless otherwise indicated	IIa	C
Crossover of UFH and LMWH is not recommended	III	B

[a] Class of recommendation. [b] Level of evidence.

LMWH: low-molecular-weight heparin; SC: subcutaneous; UFH: unfractionated heparin.
Windecker S et al. *Eur Heart J*. 2014;35:2541-2619.

Slide 2.8

Conclusion

NSTE-ACS	STEMI	All ACS
• PCI vs CABG vs conservative strategy, depending on clinical situation • No pretreatment with prasugrel (or ticagrelor)	• Primary PCI is the treatment of choice • Pretreatment with prasugrel or ticagrelor at first medical contact, if no contraindication	• **Dual antiplatelet therapy for 1 year, irrespective of strategy** • **What's next?** Ongoing studies exploring benefit of longer duration of dual antiplatelet therapy

Please tear along perforation

Review of Updated European Guidelines for the Management of Acute Coronary Syndrome

Clive Weston, MA, MB, FRCP

Slide 3.1

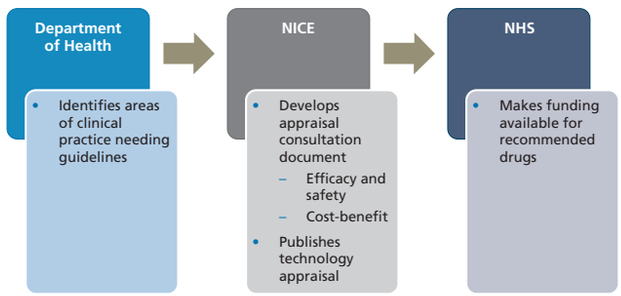
Need for Guidelines in the Management of ACS

- **Approximately 20 million combinations of treatments with antiplatelets and anticoagulants**
  - Treatment in the early stages, in the cath lab, and post-procedurally
- **Goals of treatment:**
  - Immediate: Passivation of plaque, prevention of stent thrombosis
  - Future: Prevention of new events
- **Key issues:**
  - Duration of dual antiplatelet therapy
  - Choice and timing of particular agents
    - » Is aspirin still necessary?
  - Type of stent deployed

ACS: acute coronary syndrome.

Slide 3.2

NICE Guidelines: Development Process



NHS: National Health Service; NICE: National Institute for Health and Care Excellence.

Slide 3.3

NICE Updated Guidance on Prasugrel[1]

Prasugrel 10 mg in combination with ASA is recommended as an option within its marketing authorisation, that is, for preventing atherothrombotic events in adults with ACS (UA, NSTEMI, or STEMI) having primary or delayed PCI

- Updated appraisal published July 2014; replaces previous guidance
- Based on a substudy from the TRITON-TIMI 38 trial[2]
  - Compared efficacy of prasugrel with clopidogrel
  - Patient characteristics: age <75 y, weight ≥60 kg, no history of prior stroke or TIA
  - Seen as more relevant to practice in UK

ASA: acetylsalicylic acid; NSTEMI: non-ST segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST segment elevation myocardial infarction; TIA: transient ischaemic attack; UA: unstable angina; UK: United Kingdom.

1. NICE technology appraisals 317. http://www.nice.org.uk/guidance/TA317. Accessed December 9, 2014.
2. Wiviott SD et al. *Am J Cardiol*. 2011;108:905-911.

Slide 3.4

NICE Updated Guidance on Prasugrel: Cost Effectiveness

Patient Group[a]	Incremental cost-effectiveness ratio (cost per QALY gained compared with clopidogrel)		
	Former appraisal	Current appraisal	
	Evidence Review Group's exploratory analyses	Manufacturer's model	Assessment Group's model
Core clinical cohort	£20,247	£11,796	—
STEMI with diabetes	£1,805	—	£1,640
STEMI without diabetes	£6,616	—	£6,626
Unstable angina or NSTEMI with diabetes	£3,005	—	Dominant[b]
Unstable angina or NSTEMI without diabetes	£136,888	—	£4,667

[a] Excluding prior stroke or transient ischaemic attack, those aged 75 years or older, and those weighing less than 60 kg.
[b] Dominant = less costly and more effective.

QALY: quality-adjusted life year.

NICE technology appraisals 317. https://www.nice.org.uk/guidance/ta317/chapter/4-evidence-and-interpretation. Accessed December 9, 2014.

Slide 3.5

NICE Guidance on Ticagrelor

Ticagrelor in combination with low-dose ASA is recommended for up to 12 months as a treatment option in adults with ACS:

- **With STEMI, defined as ST elevation or new LBBB on ECG, that cardiologists intend to treat with PCI or**
- **With NSTEMI or**
- **Admitted to hospital with UA; before ticagrelor is continued beyond the initial treatment, the diagnosis of UA should first be confirmed, ideally by a cardiologist**

- Both ticagrelor and prasugrel are now recommended by NICE
  - Which agent should be used in which situation?
  - No head-to-head comparisons have been studied

ECG: electrocardiogram; LBBB: left bundle branch block.
NICE technology appraisals 236. http://www.nice.org.uk/guidance/TA236. Accessed December 9, 2014.

Slide 3.6

ANMCO/SICI-GISE Position Paper on ACS

- Recommendations by patient subgroups commonly seen in clinical practice:
  - Conservative treatment
  - High bleeding risk
  - STEMI
  - NSTEMI
  - PCI
  - Renal dysfunction
  - Diabetes mellitus
  - Elderly
  - Surgery candidates
  - Switching from clopidogrel
- Consensus view based on validity of the science
- Evidence based from multiple clinical trials with various agents, assigning a quality score from 0 to 3

ANMCO: National Association of the Hospital Cardiologists; SICI-GISE: Italian Society of Invasive Cardiology.
De Luca L et al. *G Ital Cardiol (Rome)*. 2013;14:839-866.

Slide 3.7

ANMCO/SICI-GISE Position Paper: STEMI

Agent	Grading	Evidence Discussed
ASA	3	
GPI		
Abciximab	3	RCTs, observational registries, meta-analyses
Eptifibatide	1	
Tirofiban	2	
Oral APLT		
Clopidogrel	1	Retrospective analyses
Prasugrel	3	TRITON-TIMI 38 cohort, primary vs secondary PCI, mortality curves
Ticagrelor	2	PLATO subgroup, mortality in early presenters, mortality curves, side effects

APLT: antiplatelet; GPI: glycoprotein IIb/IIIa inhibitor; RCT: randomised controlled trial.
De Luca L et al. *G Ital Cardiol (Rome)*. 2013;14:839-866.

Slide 3.8

ANMCO/SICI-GISE Position Paper: NSTEMI

Agent	Grading		Evidence Discussed
	Upstream	Downstream	
ASA	3		
GPI	1 (3 in $P2Y_{12}$-naïve or CABG likely pts)	1 (3 in $P2Y_{12}$-naïve or CABG likely pts)	RCTs, observational registries, meta-analyses
Cangrelor ($P2Y_{12}$-naïve)	0	2	CHAMPION studies
Oral APLT			
Clopidogrel	2	0	RCTs, observational registries, meta-analyses
Prasugrel (clopidogrel-naïve)	0	3 (PCI)	TRITON-TIMI 38 design, subgroup, survival curves, ACCOAST (?)
Ticagrelor	3	3	PLATO design, subgroup, survival curves

CABG: coronary artery bypass graft.
De Luca L et al. *G Ital Cardiol (Rome)*. 2013;14:839-866.

Slide 3.9

ANMCO/SICI-GISE Position Paper: Diabetes

Agent	Grading	Evidence Discussed
ASA	3	
GPI	3	RCTs, post-hoc analyses, registries, meta-analyses
Oral APLT		
Clopidogrel	1	Post-hoc analyses
Prasugrel (PCI pts, clopidogrel-naïve)	3	TRITON-TIMI 38 subanalysis, RR in death and MI
Ticagrelor	2	PLATO subanalysis, diabetic status

MI: myocardial infarction; RR: risk reduction.
De Luca L et al. *G Ital Cardiol (Rome)*. 2013;14:839-866.

Slide 3.10

Benefits and Limitations of ACS Guidelines

- Multiple guidelines based on different things:
  - Evidence
  - Opinion and consensus
  - Cost-benefit analysis
- Consensus on the importance of early intervention in ACS
- Reducing the burden of ACS:
  - Less damage to heart muscle
  - Lower future risk of second heart attacks and heart failure
  - Fewer deaths

Slide 3.11

Conclusions

Significant strides in the management of ACS
- Many large clinical trials
- Evidence incorporated into clinical guidelines
- Improved clinical outcomes

Challenges
- Implementation in clinical practice
- Cost and availability

Future study
- Is aspirin still needed?
- Comparative studies of newer antiplatelet agents
- Duration of treatment, lifelong treatment

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PeerVoice

Defining Best Practices in ACS: A Comprehensive Analysis of European Guidelines for Dual Antiplatelet Therapy After PCI

For more information and resources on acute coronary syndrome, please access the series webpage at **www.peervoice.com/ACS1.**

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