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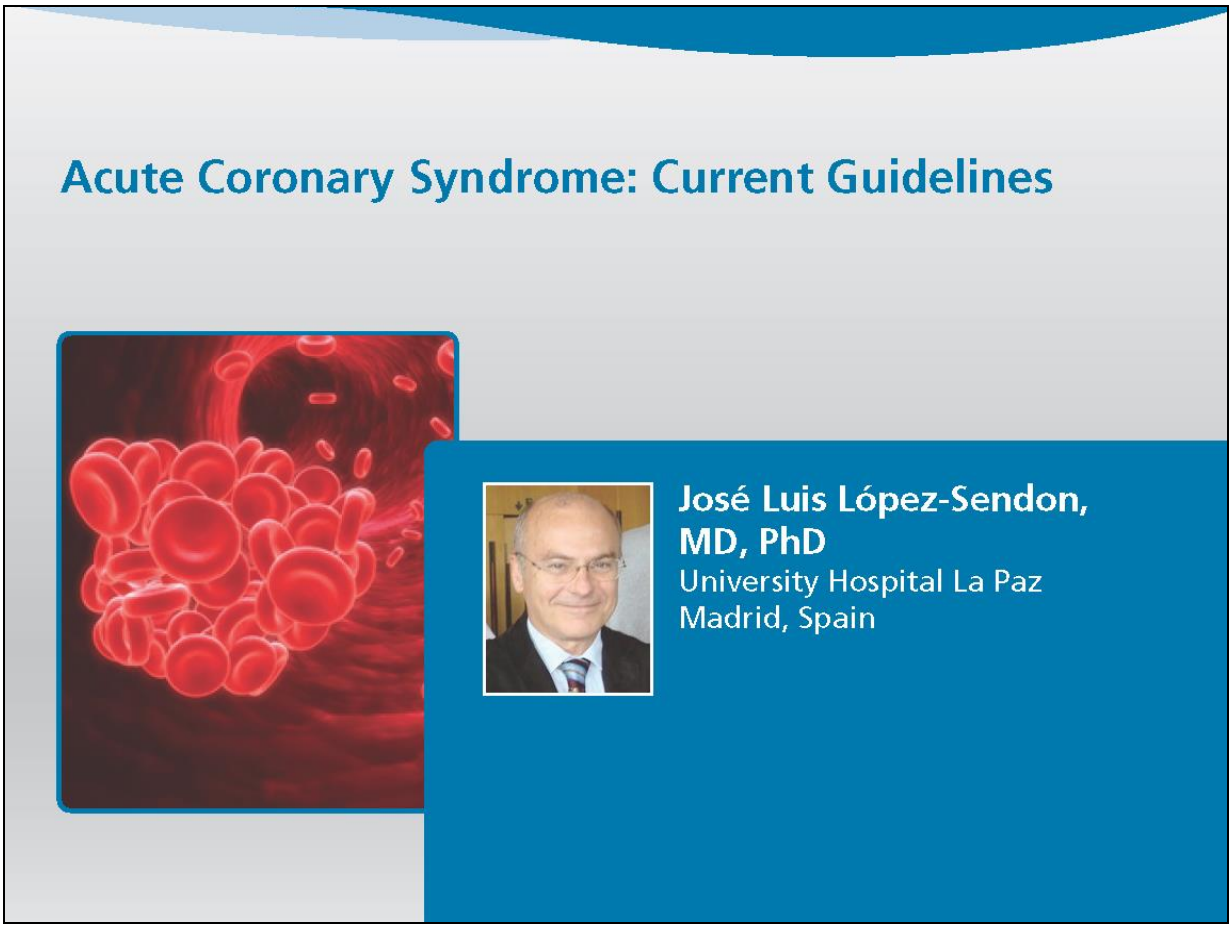
Content developed in concert with the faculty.

Narrator: Welcome to this PeerVoice activity on acute coronary syndrome. Please download the slides, transcript, and any other activity features that may interest you. To participate in the Ask the Faculty and/or Discussion Forum, click on the tabs below. For more information and resources on acute coronary syndrome, please access the series webpage at www.peervoice.com/ACS1.



Dr. López-Sendon: My name is José López-Sendon. I am a clinical cardiologist working in the University Hospital La Paz in Madrid. And I have the pleasure of introducing you [to] a programme focusing on best practices in acute coronary syndromes.

The first presentation 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.

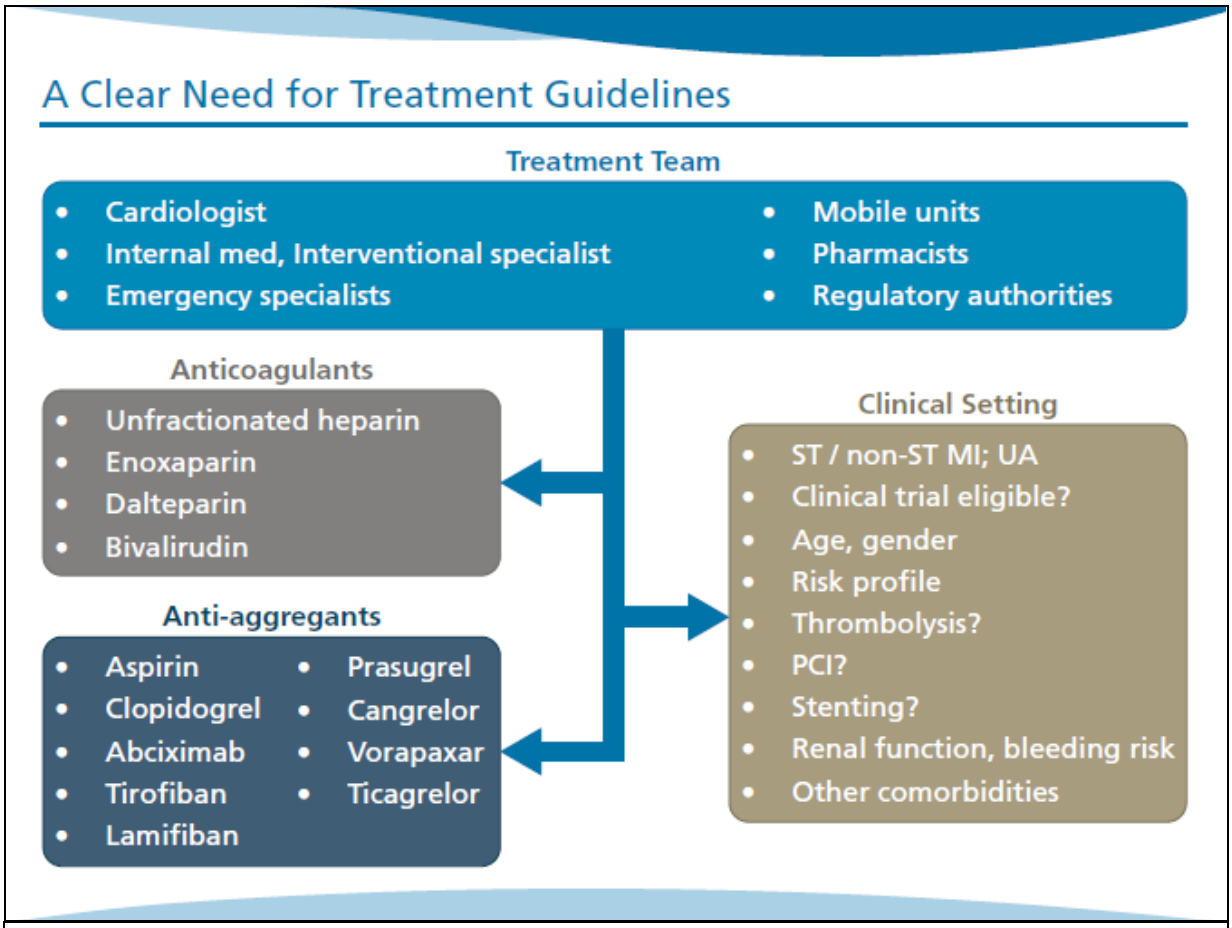
Advances in Antithrombotics for ACS

- **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

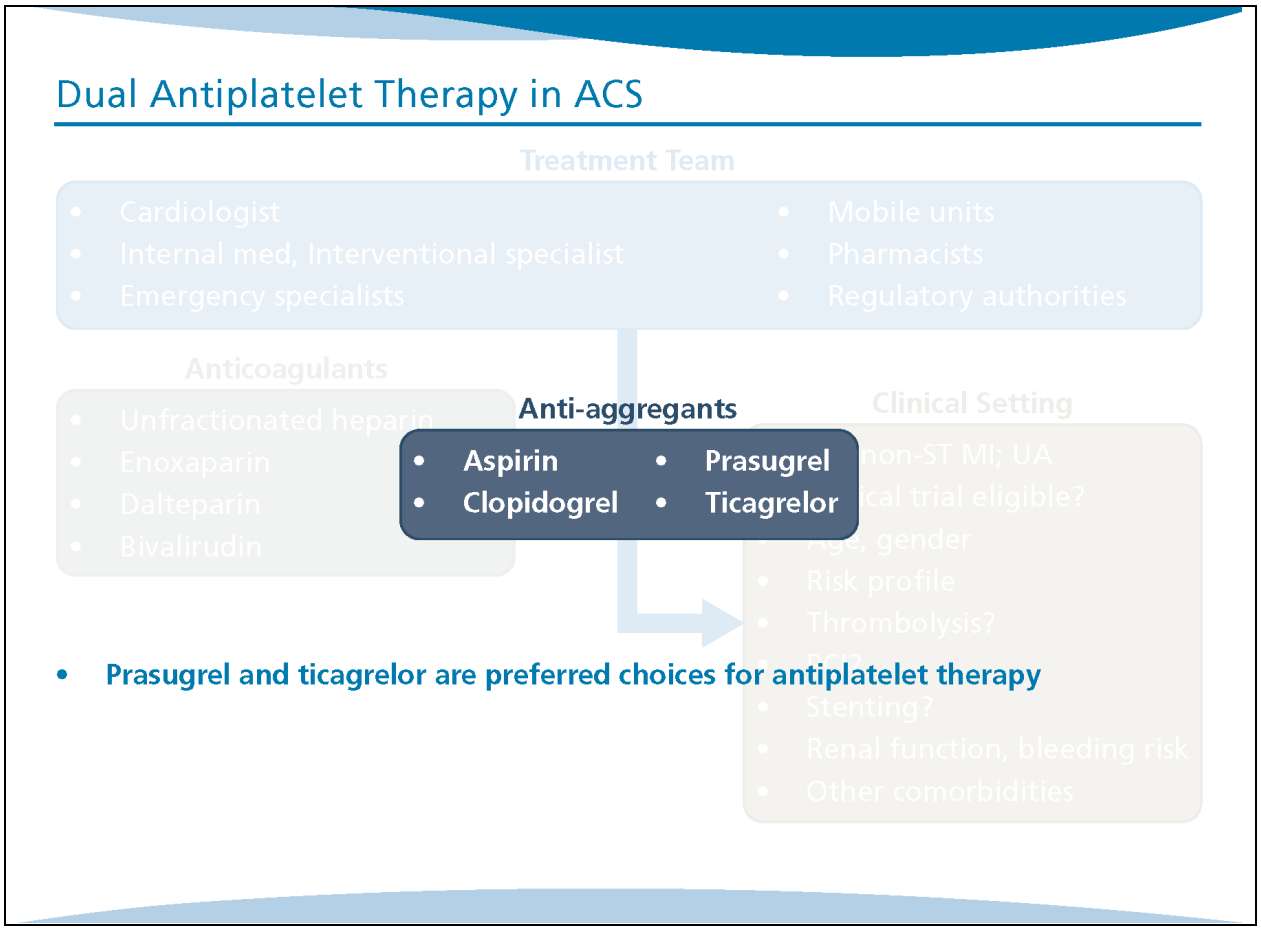
Dr. López-Sendon: In the good old days, we had only aspirin and heparin to treat patients with acute coronary syndromes and intracoronary thrombosis. And during the last 25 years, there was extraordinary research demonstrating that a number of new antiplatelet agents, as well as a number of new anticoagulant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



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

Dr. López-Sendon: And it is getting even more complicated because we have not only new anticoagulants and new anti-aggregants, but a setting where teamwork is important. 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. And we cannot be changing treatments every 2 hours according to the place where the patient is.

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.



Dr. López-Sendon: Now focusing on dual oral antiplatelet therapy, we have four options: that is aspirin, clopidogrel, prasugrel, and ticagrelor. There are two major trials that demonstrated the clear benefit of the new antiplatelet agents: the TRITON[-TIMI 38] and the PLATO trial. And 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.

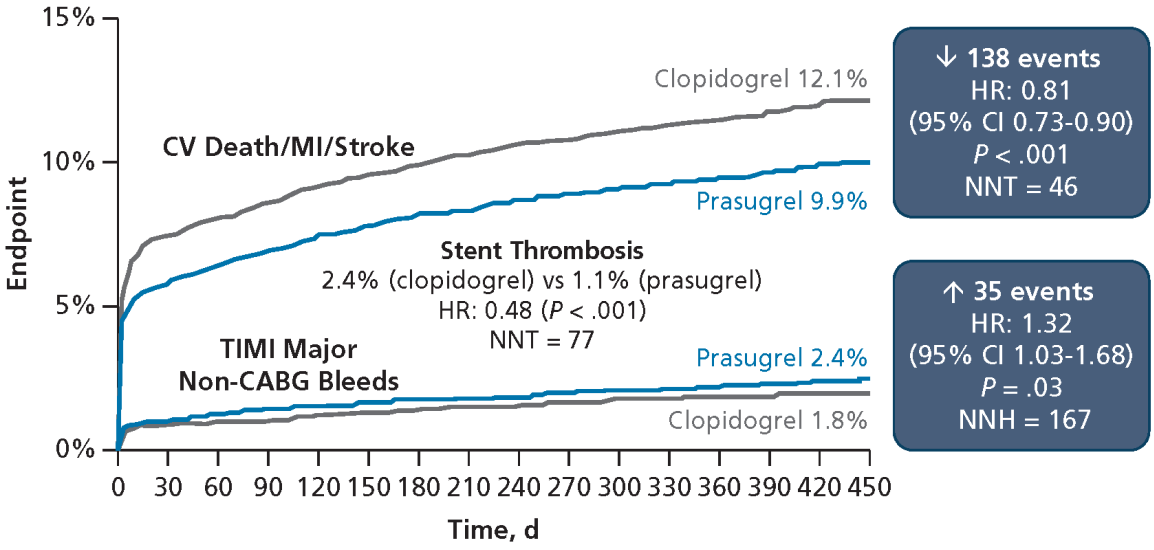
We don't have a head-to-head comparison trial, so we cannot state that one is better than the other. In general, both are better than clopidogrel and should be of choice, if possible. You should use prasugrel in a STEMI or in diabetic patients; and in patients that you think that are not going to go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

Challenge Question

Current European guidelines call for the use of prasugrel or ticagrelor therapy after PCI in patients with ACS. Which of the following studies provided the clinical evidence for these recommendations?

- CURE and ACCOAST
- TRILOGY and TRITON-TIMI 38
- TRITON-TIMI 38 and PLATO
- PLATO and ATLANTIC

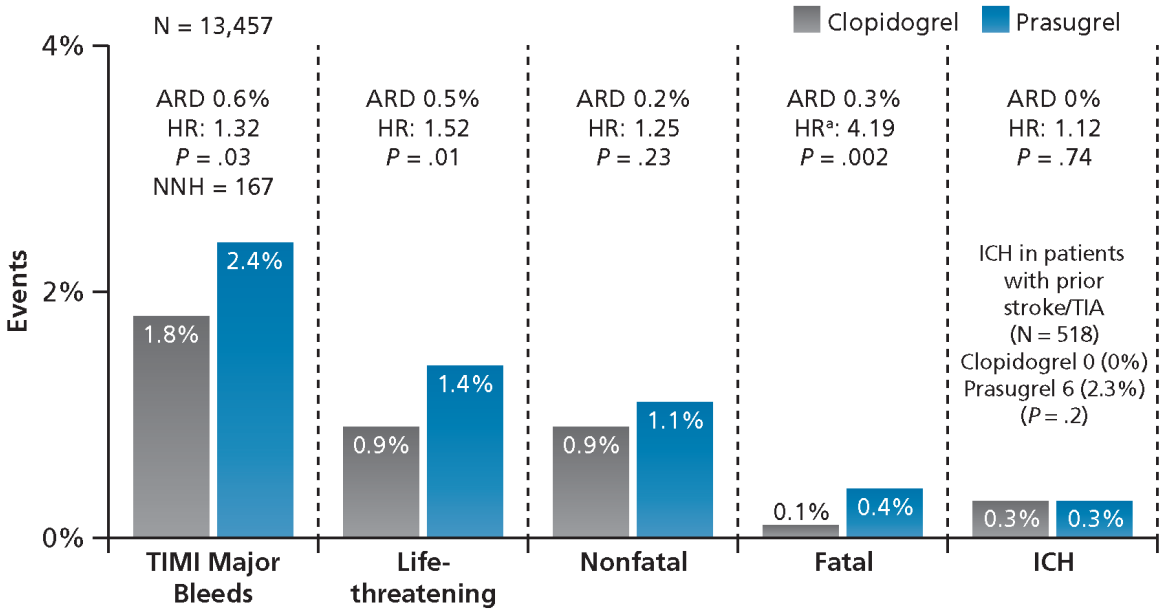
Go online to compare your answer with your peers' responses.



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.

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



ARD: absolute risk difference; ICH: intracranial haemorrhage; TIA: transient ischaemic attack.

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

Dr. López-Sendon: Major bleeding increased from 1.8% in the clopidogrel group to 2.4% in the prasugrel group. That was significant, so we should focus on the contraindications for using prasugrel because of the risk of bleeding in these patients.

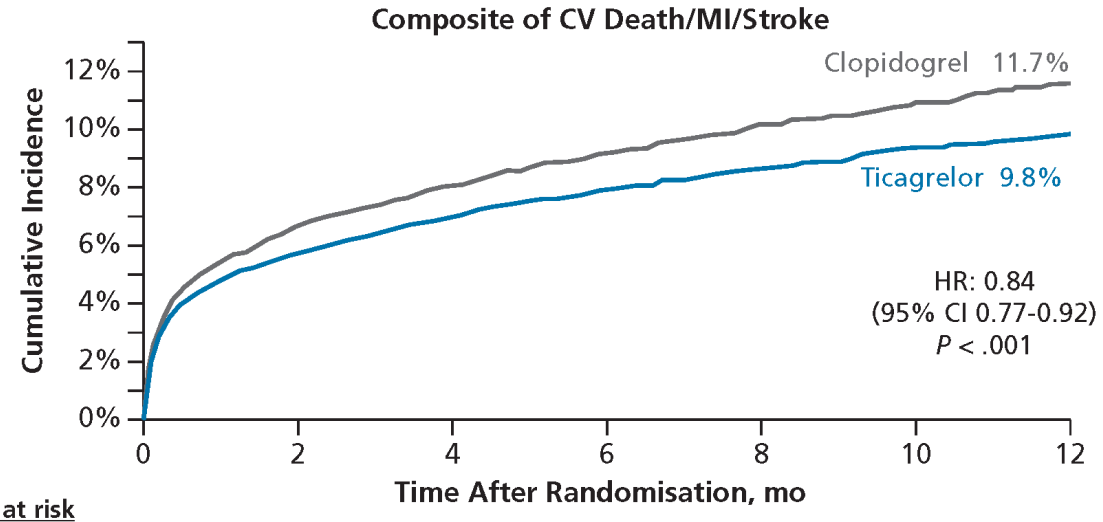
Challenge Question

Which of the following statements best describes the key findings of the TRITON-TIMI 38 trial, comparing prasugrel versus clopidogrel in patients with moderate-to-high risk ACS?

- Prasugrel demonstrated a significant reduction in the composite endpoint of cardiovascular death, myocardial infarction, and stroke versus clopidogrel
- Prasugrel demonstrated a comparable reduction in the composite endpoint and a significantly lower risk of major bleeding versus clopidogrel
- Clopidogrel demonstrated a significant reduction in the composite efficacy endpoint compared with prasugrel
- Clopidogrel demonstrated a higher incidence of all bleeding as well as increased risk of death from cardiovascular causes compared with prasugrel

Go online to compare your answer with your peers' responses.

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.

Dr. López-Sendon: In the PLATO trial, 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%.

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.

Dr. López-Sendon: There was also an excess in bleeding when excluding the patients that were submitted for a surgical revascularisation. 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

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

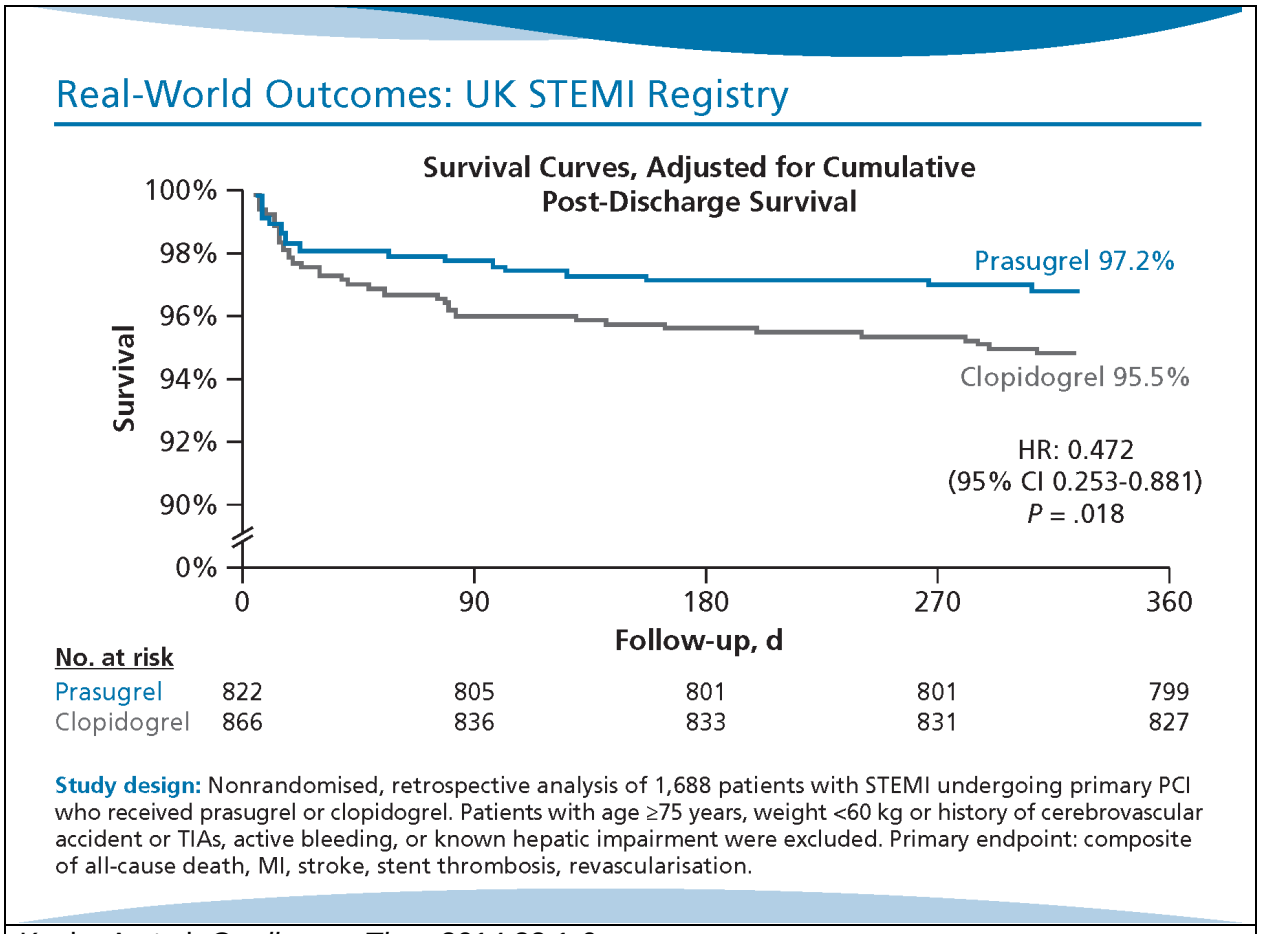
[a] Class of recommendation. [b] Level of evidence.

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.

Dr. López-Sendon: So accordingly, the new guidelines of the European Society of Cardiology reflect these results. And prasugrel and ticagrelor are the recommendation in the guidelines for patients with STEMI undergoing PCI. The recommendation is a Class I, Level of evidence B because there is only one trial for each drug. And 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 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.



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

Dr. López-Sendon: But if we move to real life, 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.

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. And 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

ATHRO Registry: Treatment for ACS with PCI 2013

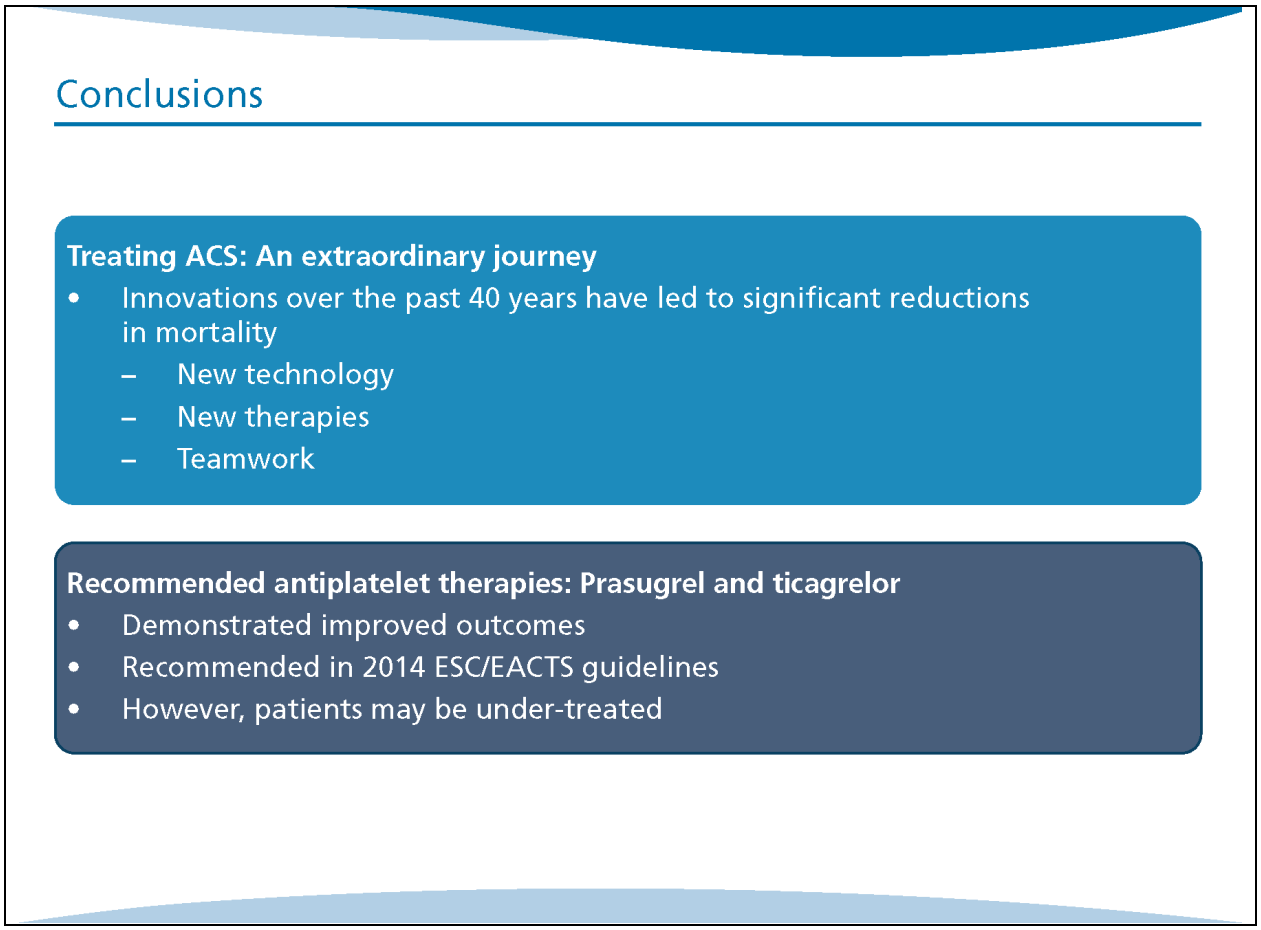
$P2Y_{12}$, %	Czech Republic	Slovakia
Clopidogrel	75.3	53.6
Ticagrelor	13.1	17.3
Prasugrel	2.6	23.1

- **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.

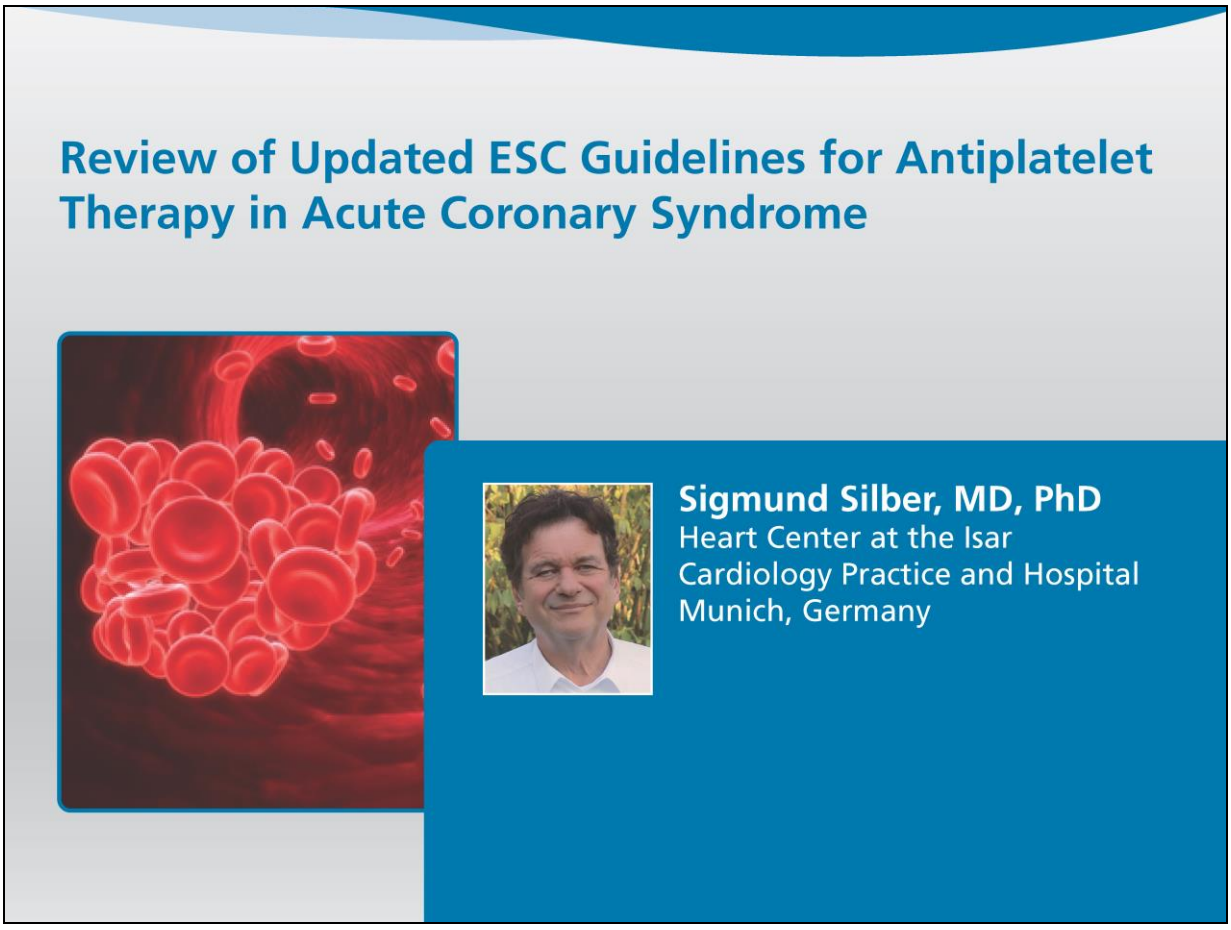
Dr. López-Sendon: So saying that, the next question is, are we incorporating this into clinical practice? In the Czech Republic, clopidogrel is [still] used in as many as 75% of the patients. And this figure changes from one country to another, but it is clear evidence that prasugrel and ticagrelor are 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. And it takes time to introduce innovation, and that is happening with new anti-aggregants. The second thing is cost.



Dr. López-Sendon: In acute coronary syndromes in the last 30 or 40 years, 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. And so this demonstrated that we could reduce the mortality from 30% to 5%.

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. And we have the evidence that these therapies are cost effective. And 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.



Prof. Silber: My name is Professor Silber. I'm a cardiologist in Munich, Germany. And what we should talk about is acute coronary syndrome in regards to the new European Society of Cardiology guidelines.

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.

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.

Prof. Silber: When we compare the guidelines for myocardial revascularisation, the number of experts to find consensus almost doubled between 2005 and 2010. And this is also reflected by the considerable increase [in the] of 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.

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?

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.

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

Prof. Silber: So one of the major changes is the recommendation for who should get PCI and who should get bypass surgery. 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

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.

Prof. Silber: But the main topic is acute coronary syndrome. And let's start with STEMI, [or] ST elevation myocardial infarction.

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. And for ticagrelor, it says 180 mg with 90 mg twice daily maintenance dose, again if no contraindication.

And actually the contraindications to prasugrel are only two: a previous stroke or transient ischaemic attack. And [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.

Challenge Question

A 68-year-old man has undergone emergency PCI and stenting after an ST segment elevation myocardial infarction (STEMI). Based on the 2014 ESC guidelines, what are his best options for antiplatelet therapy in addition to ASA?

- ○ Clopidogrel only
- ○ Prasugrel only
- ○ Ticagrelor only
- ○ Prasugrel or ticagrelor, if neither is contraindicated

Go online to compare your answer with your peers' responses.

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.

Prof. Silber: What about anticoagulation? 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

	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.

Prof. Silber: So in the first guidelines, we recommended after ACS a whole year of dual antiplatelet therapy. In 2010: again 1 year; and now in 2014: again 1 year.

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 it [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

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.

Prof. Silber: In patients with acute coronary syndrome with no ST segment elevation [NSTEMI or unstable angina], there's a new Class III recommendation—which means don't do it. 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.

Challenge Question

According to the 2014 ESC guidelines, which of the following patients with NSTE-ACS undergoing PCI can be considered a candidate for pretreatment with prasugrel?

- Patients with known coronary anatomy
- Patients who have no contraindications to therapy with prasugrel
- Patients with type 2 diabetes
- Patients who are ≤75 years of age

Go online to compare your answer with your peers' responses.

Anticoagulant Therapy in Patients With NSTE-ACS Undergoing PCI

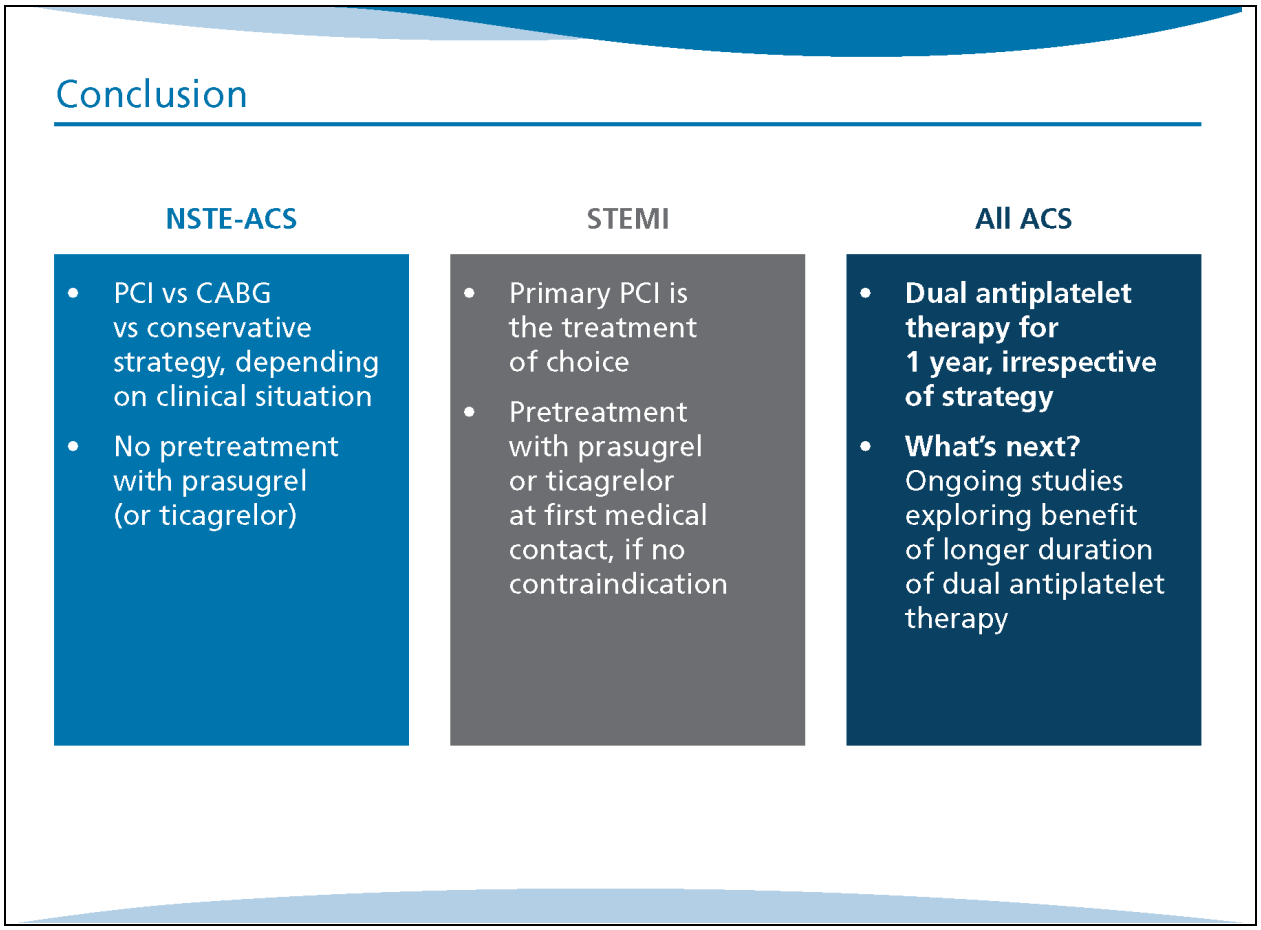
Recommendations	Class[a]	Level[b]
Anticoagulation is recommended for all patients in addition to antiplatelet therapy during PCI	I	A
The anticoagulation is selected according to both ischaemic and bleeding risks, and according to the efficacy-safety profile of the chosen agent	I	C
Bivalirudin (0.75 mg/kg 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.

Prof. Silber: What about bivalirudin anticoagulation? For NSTEMI, 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.



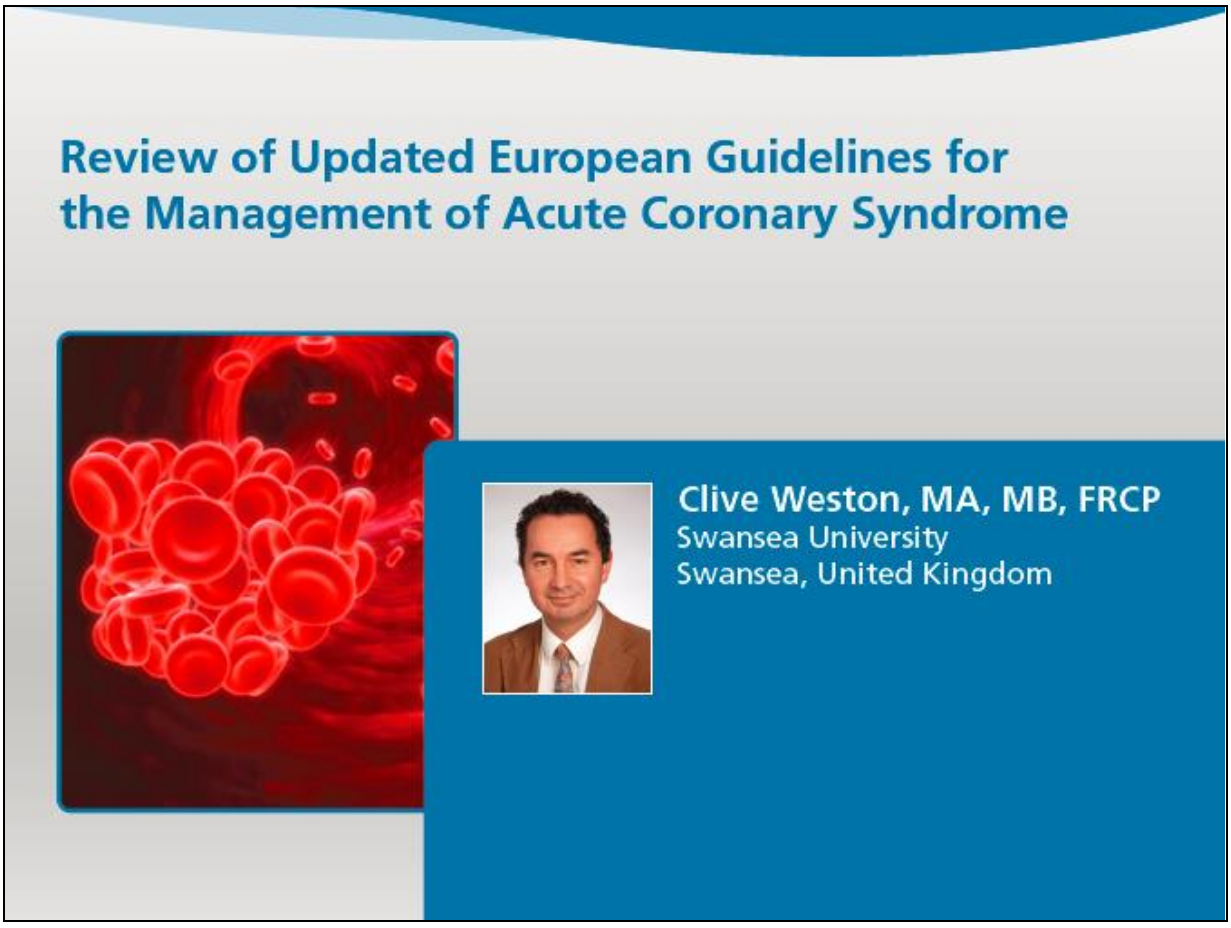
Prof. Silber: In NSTEMI, the overall bottom line is that you should not pretreat the patient—just give aspirin and heparin. The rest is decided in the cath lab after diagnostic angiography. And bivalirudin got a strong recommendation for prolonged infusion. IIb/IIIa inhibitors should not be given in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

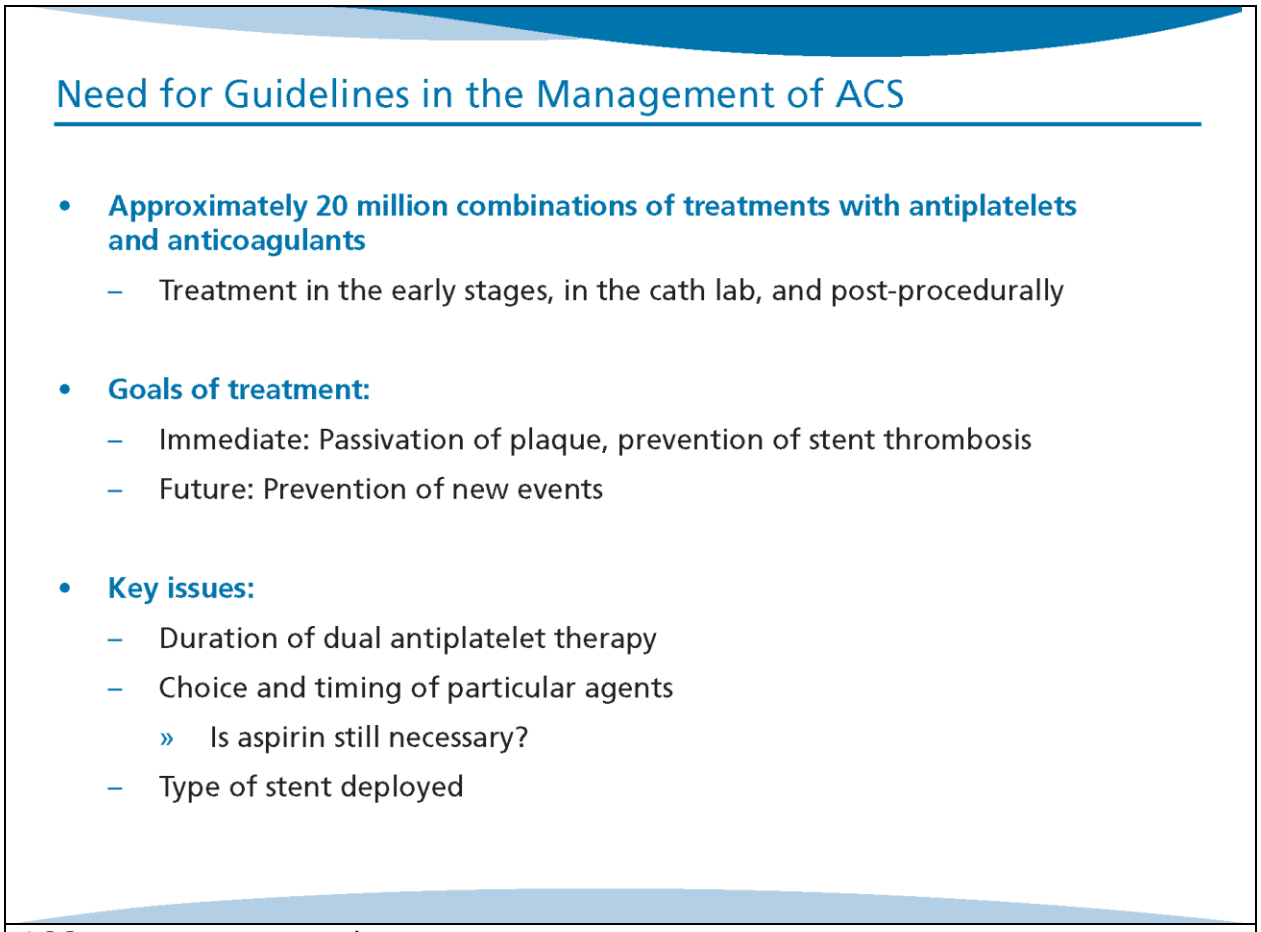
The ATLANTIC trial showed that if the transportation times are very short, there was no difference in the primary endpoints between pretreatment and no pretreatment [Montalescot G et al. *N Engl J Med*. 2014;371:1016-1027]. So does that mean you should not pretreat in STEMI also? I don't think so. If 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. And this will be actually investigated in the PEGASUS trial [Clinicaltrials.gov ID: NCT01225562]. And if this trial is positive, then this will change all our thoughts and concepts of how long to give dual antiplatelet therapy.

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. And 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.



Dr. Weston: Hello, I'm Clive Weston. I'm a cardiologist in South Wales in Swansea. I'm an associate professor at Swansea University in the College of Medicine. I'm going to talk to you about the management of acute coronary syndrome, and I'm going to focus on influential [European] guidelines.

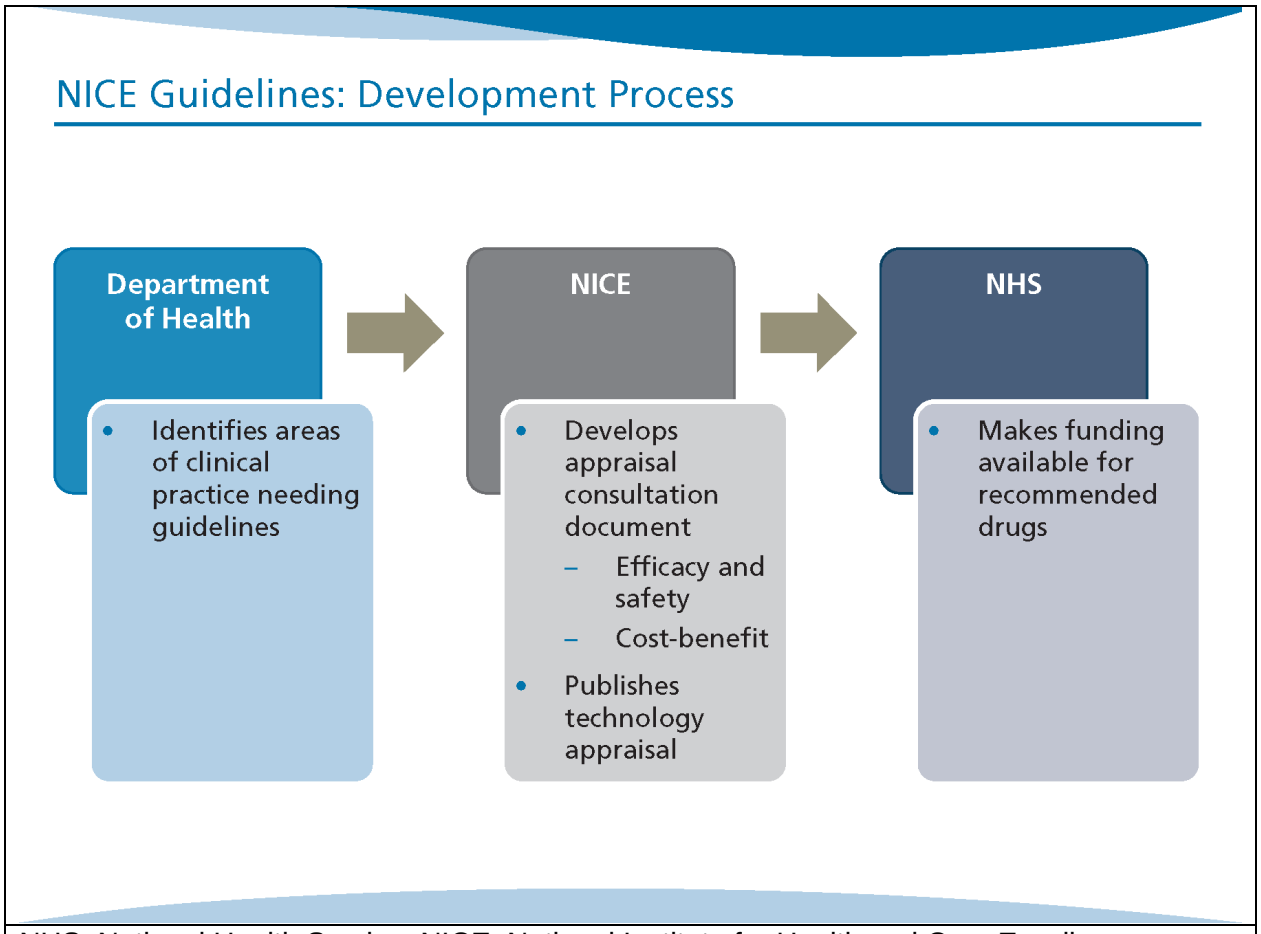


ACS: acute coronary syndrome.

Dr. Weston: Why do we need guidelines? 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, 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.



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

Dr. Weston: If we consider the NICE guidelines, the National Institute for Health and Care Excellence is a semi-independent body that is influenced by government. 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. And cost-benefit analyses of varying sorts are a necessary part of the NICE guideline development.

Based on these [appraisals], the National Health Service would make available funds for their clinicians to prescribe this particular drug.

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.

Dr. Weston: NICE decided to perform a second appraisal because of the publication of a substudy from the original TRITON-TIMI 38 trial. 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, and so this substudy was looked on by NICE as being more relevant to British practice. And 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 and ST elevation myocardial infarction.

And, 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”—in other words, those patients with non-ST elevation receiving PCI.

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.

Dr. Weston: Another important area of a NICE appraisal is the cost-effectiveness analysis. 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. And 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.

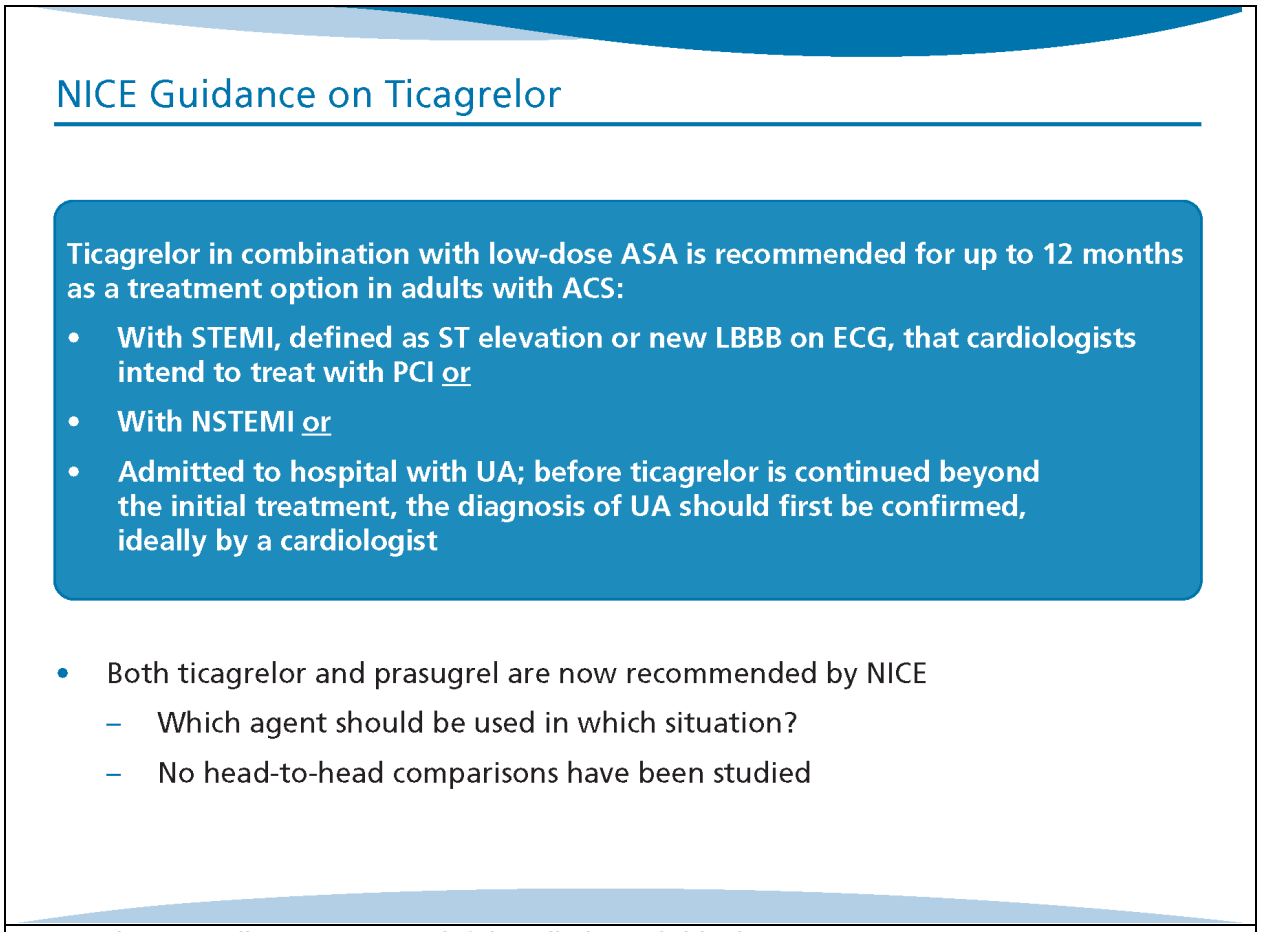
And it was only in the group of NSTEMI patients without diabetes that the cost of gaining extra life-years was in the region of £5,000. But these figures are well within the costs looked on as reasonable by the NICE institution itself and by government.

Challenge Question

Which of the following best describes a key difference between the 2014 ESC Guidelines on Myocardial Revascularisation and current NICE Guidelines?

- Recommendations for use of prasugrel for patients with STEMI or NSTEMI
- Recommendations for use of ticagrelor for patients with STEMI or NSTEMI
- Incorporation of cost-effectiveness analysis for prasugrel and ticagrelor for patients with ACS
- Incorporation of patient scenarios for use of prasugrel or ticagrelor

Go online to compare your answer with your peers' responses.

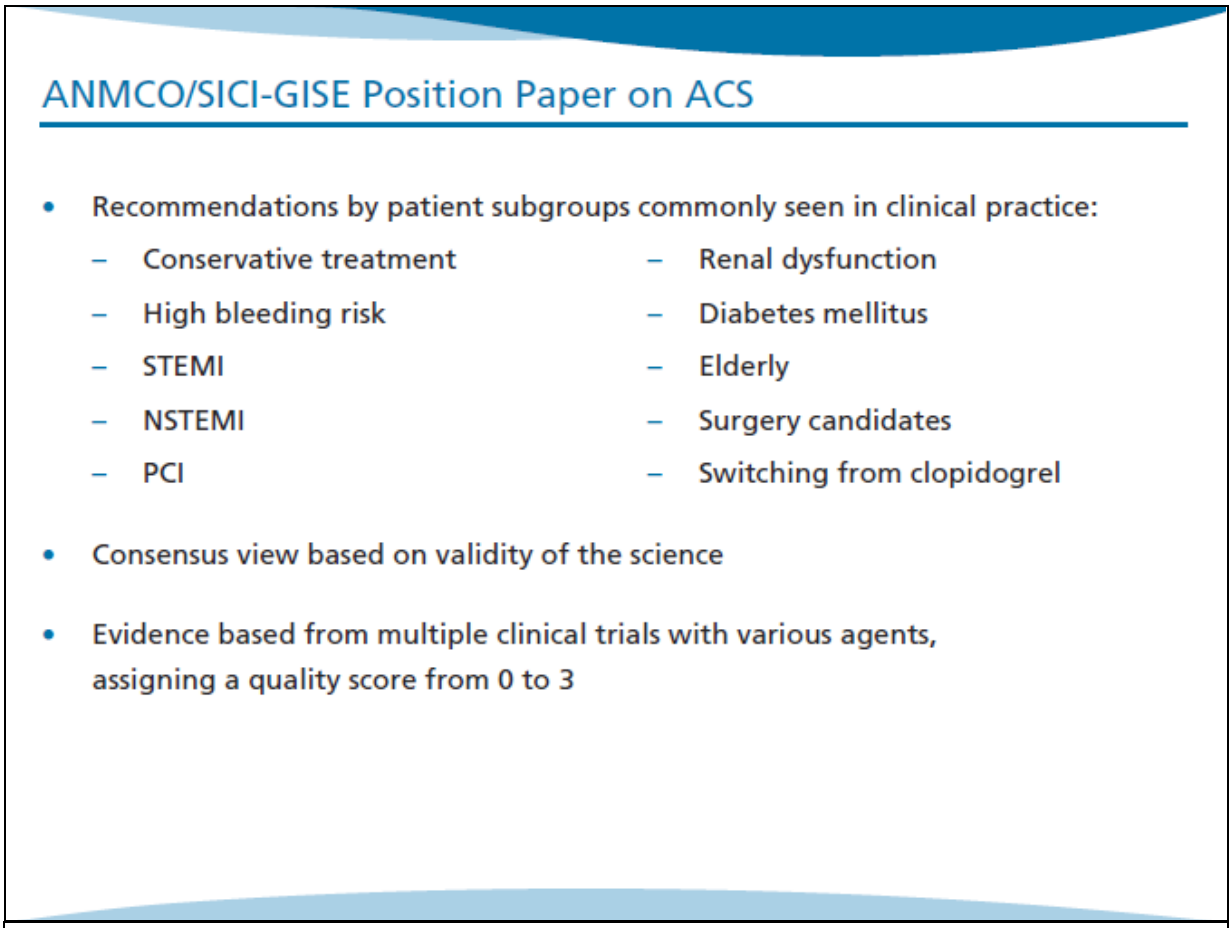


ECG: electrocardiogram; LBBB: left bundle branch block.

NICE technology appraisals 236. http://www.nice.org.uk/guidance/TA236. Accessed December 9, 2014.

Dr. Weston: The practising clinician can now look both at the technology appraisal of ticagrelor and of prasugrel and see that both are recommended. 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 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: 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.

Dr. Weston: Whilst many guideline groups, particularly the British NICE group, 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.

What they've tried to do is to look at individual subgroups of patients that 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.

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.

Dr. Weston: Looking at the subgroup of patients with ST elevation myocardial infarction, aspirin has a very high scientific quality [rating], similar to the use of oral prasugrel. Oral clopidogrel gains a quality rating of 1, and ticagrelor gets a quality rating of 2.

Challenge Question

Which of the following oral antiplatelet agents received the highest grading according to evidence base for management of patients with STEMI?

- ○ Clopidogrel
- ○ Prasugrel
- ○ Ticagrelor
- ○ All agents received the same grading

Go online to compare your answer with your peers' responses.

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.

Dr. Weston: Looking at the subgroup with non-ST elevation infarction, 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.

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.

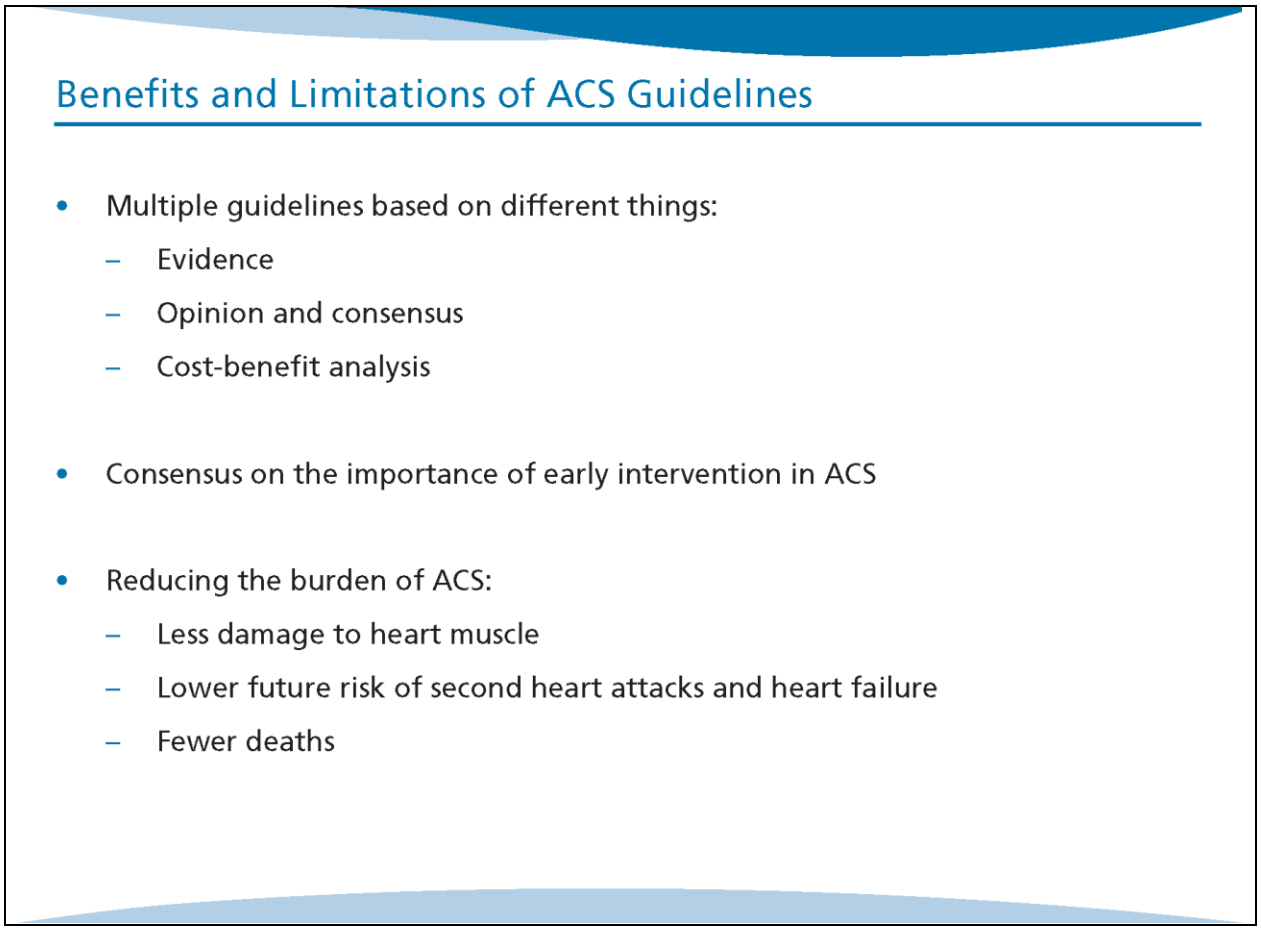
ANMCO/SICI-GISE Position Paper: Diabetes

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.

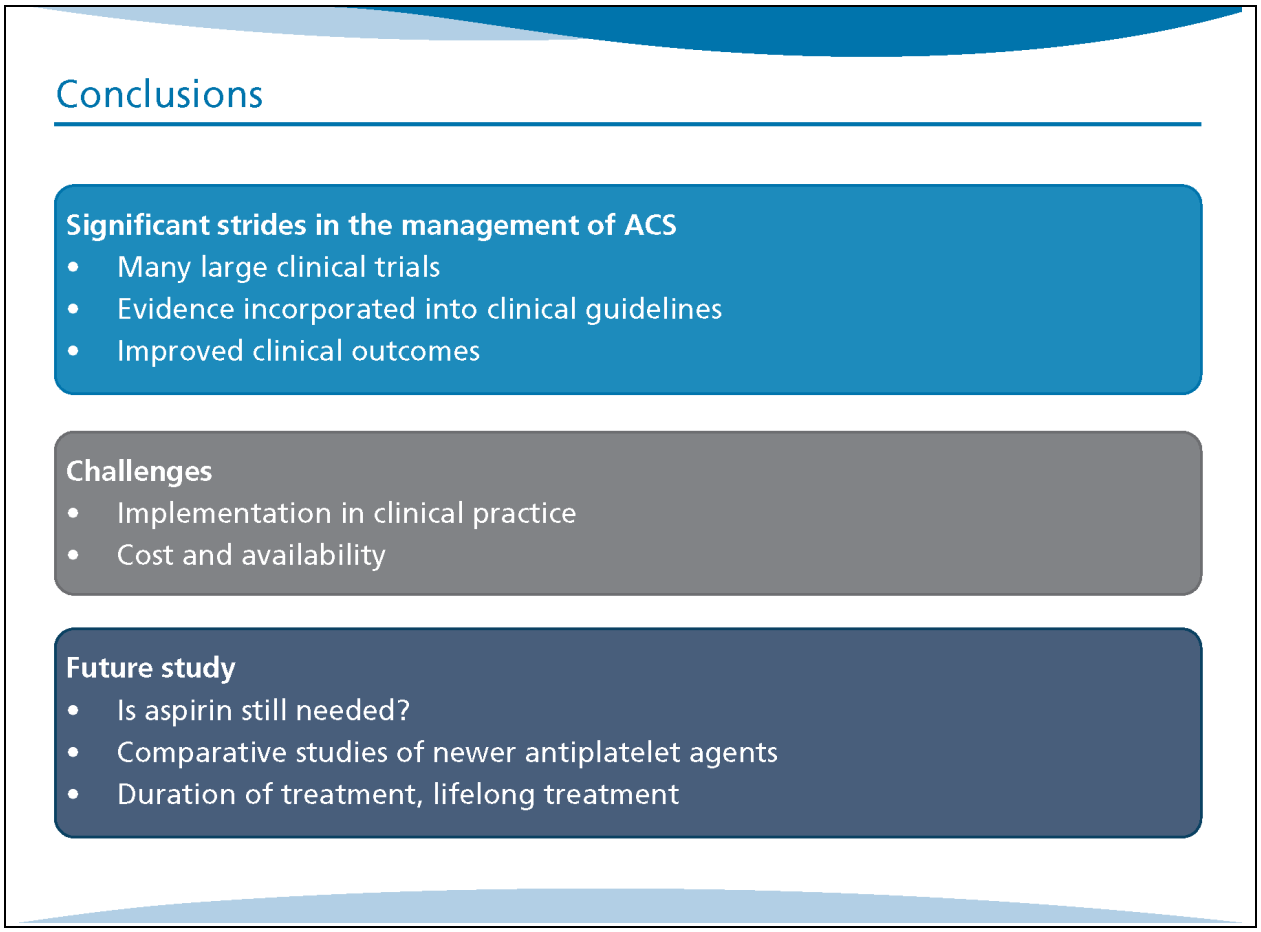
De Luca L et al. *G Ital Cardiol (Rome)*. 2013;14:839-866.

Dr. Weston: 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.



Dr. Weston: We have a number of guidelines, and there is [a] consensus. 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.

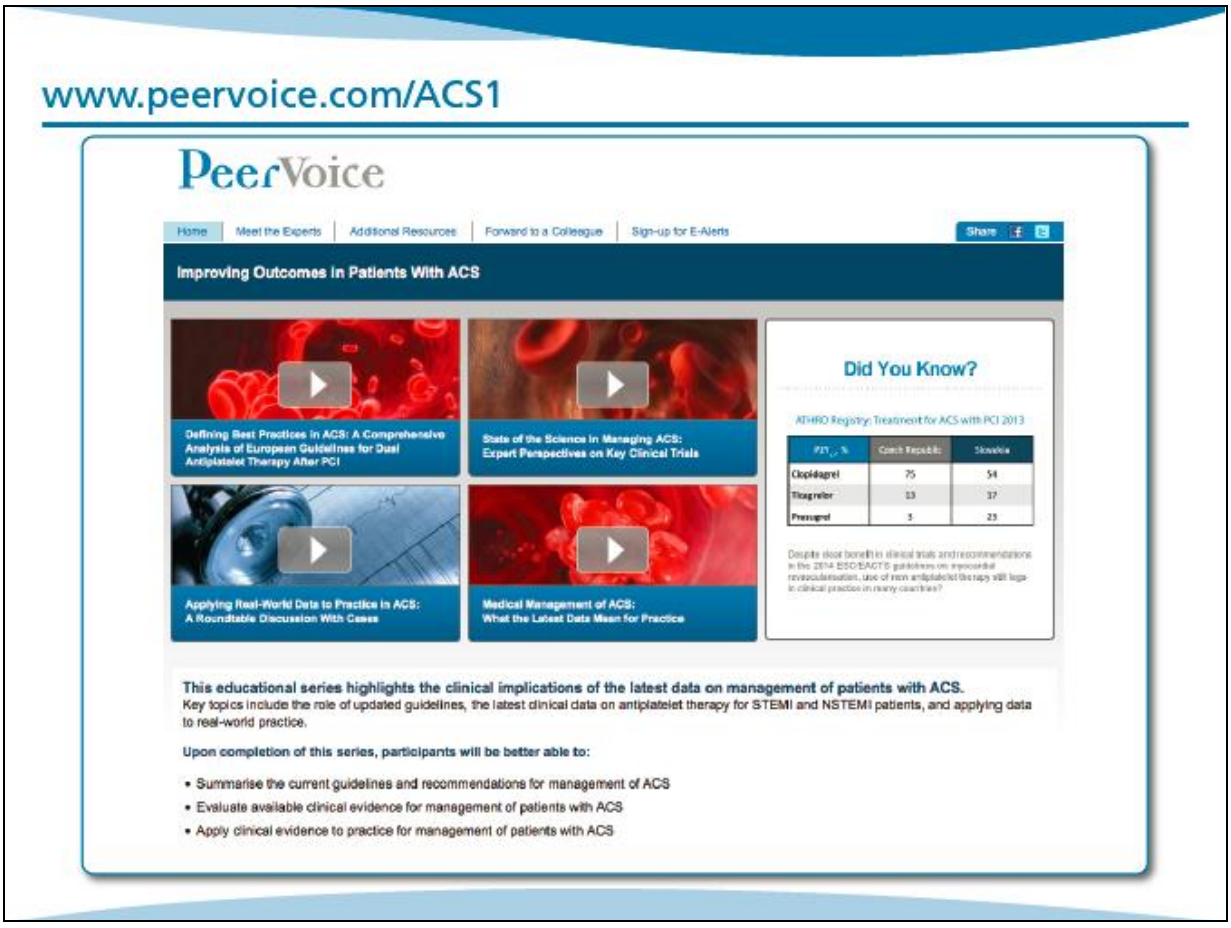
Will these guidelines reduce the burden of acute coronary syndrome in Europe? Well, they may not reduce the total number of patients admitted to hospitals, but they should reduce the amount of heart muscle damage suffered by individual patients, the likelihood that these individual patients will have 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.



Dr. Weston: 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. 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. 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, but other areas of the management of acute coronary syndrome in the hope of continuing to improve our treatments.



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

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