ACS Management
Bringing Guidelines to Practice

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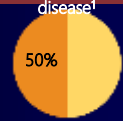
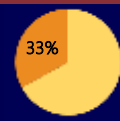
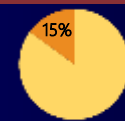
Acute Coronary Syndromes: High Burden of Mortality

ACS incidence and mortality rates

ACS (ST and non-ST elevation) are responsible for half of all deaths due to CV disease[1]	One third of STEMI patients die within 24 hours of onset of ischaemia2	15% of NSTE patients die or have a nonfatal MI within 30 days [3,4]
		
CV disease deaths due to ACS	Death in STEMI patients at 24 hours	Death or MI in NSTE patients within 30 days

1. Kolansky DM. *Am J Manag Care.* 2009;15:S36–S41.
2. Antman EM, et al. *Circulation.* 2004;110:e82–e292.
3. Braunwald E, et al. *Circulation.* 2002;106:1893–1900.
4. Boersma E, et al. *Circulation.* 2000;101:2557–2567.

Risk Of Death And Severity Of Acute Coronary Syndrome

Post discharge mortality among ACS patients who initially presented with ST elevation, ST depression, or no ST-segment deviation (GRACE registry)*

Fox KA, et al. *Nat Clin Pract Cardiovasc Med*. 2008;5:580-589

3

3/19/2018

ESC 2017 Guidelines updates

2017 ESC Focused Update on Dual Antiplatelet Therapy in Coronary Artery Disease developed in collaboration with the EACTS*

*: European Association for Cardio-Thoracic Surgery

ESC European Society of Cardiology

AMERICAN COLLEGE of CARDIOLOGY

American Heart Association. life is on

$P2Y_{12}$ inhibitor selection and timing

ESC European Society of Cardiology

Recommendations	Class	Level
In patients with ACS, ticagrelor (180 mg loading dose, 90 mg twice daily) on top of aspirin is recommended, regardless of initial treatment strategy, including patients pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced) unless there are contra-indications.	I	B
In patients with ACS undergoing PCI, prasugrel (60 mg loading dose, 10 mg daily dose) on top of aspirin is recommended for $P2Y_{12}$ inhibitor-naïve patients with NSTE-ACS or initially conservatively managed STEMI if indication for PCI is established, or in STEMI patients undergoing immediate coronary catheterization unless there is a high-risk of life-threatening bleeding or other contra-indications.	I	B

www.escardio.org/guidelines

2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419

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American Heart Association. life is on

Switching between oral $P2Y_{12}$ inhibitors

ESC European Society of Cardiology

Recommendations	Class	Level
In patients with ACS who were previously exposed to clopidogrel, switching from clopidogrel to ticagrelor is recommended early after hospital admission at a loading dose of 180 mg irrespective of timing and loading dose of clopidogrel, unless contra-indications to ticagrelor exist.	I	B
Additional switching between oral $P2Y_{12}$ inhibitors may be considered in cases of side effects/drug intolerance according to the proposed algorithms.	IIb	C

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2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

ESC European Society of Cardiology

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American Heart Association. life is why

Periprocedural and postprocedural antithrombotic therapyc in patients undergoing primary percutaneous coronary intervention

ESC European Society of Cardiology

Recommendations	Class	Level
Antiplatelet therapy		
A potent $P2Y_{12}$ inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contra-indicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months unless there are contra-indications such as excessive risk of bleeding.	I	A
Aspirin (oral or i.v, if unable to swallow) is recommended as soon as possible for all patients without contra-indications.	I	B
GP IIb/IIIa inhibitors should be considered for bailout if there is evidence of no-reflow or a thrombotic complication.	IIa	C
Cangrelor may be considered in patients who have not received $P2Y_{12}$ receptor inhibitors.	IIb	A

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American Heart Association. life is on

Maintenance antithrombotic strategy after ST-elevation myocardial infarction

ESC European Society of Cardiology

Recommendations	Class	Level
Antiplatelet therapy with low-dose aspirin (75–100 mg) is indicated.	I	A
DAPT in the form of aspirin plus ticagrelor or prasugrel (or clopidogrel if ticagrelor or prasugrel is not available or is contra-indicated) is recommended for 12 months after PCI unless there are contra-indications such as excessive risk of bleeding.	I	A
A PPI in combination with DAPT is recommended in patients at high risk of gastrointestinal bleeding.	I	B
In patients with an indication for oral anticoagulation, oral anti-coagulants are indicated in addition to antiplatelet therapy.	I	C

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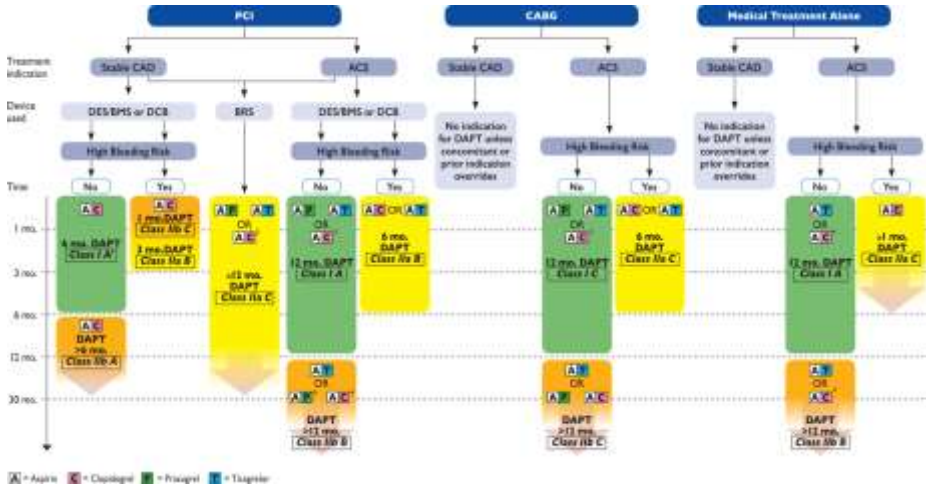
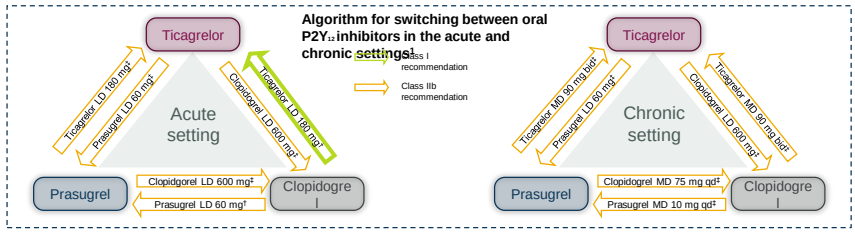


	PRECISE-DAPT score[10]	DAPT score[11]	
Time of use	At the time of coronary stenting	After 12 months of uneventful DAPT	
DAPT duration strategies assessed	Short DAPT (3–6 months) vs. Standard/long DAPT (12–24 months)	Standard DAPT (12 months) vs. Long DAPT (30 months)	
Score calculation[a]	HB ≥12 11-9 11 10-5 ≤10 WBC ≤5 8 10 12 14 16 18 ≥20 Age ≤50 60 70 80 ≥90 CrCl ≥100 80 60 40 20 0 Prior Bleeding No Yes Score Points 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30	Age ≥75 65 to <75 <65 Cigarette smoking Diabetes mellitus MI at presentation Prior PCI or prior MI Paclitaxel-eluting stent Stent diameter <3 mm CHF or LVEF <30% Vein graft stent	 –2 pt –1 pt 0 pt +1 pt +1 pt +1 pt +1 pt +1 pt +1 pt +2 pt +2 pt
Score range	0 to 100 points	–2 to 10 points	
Decision making cut-off suggested	Score ≥25 → Short DAPT Score <25 → Standard/long DAPT	Score ≥2 → Long DAPT Score <2 → Standard DAPT	
Calculator	www.precisedaptscore.com	www.daptstudy.org	

What guidance do the updated ESC Guidelines provide regarding switching of $P2Y_{12}$ inhibitors in the acute and long-term setting?

- **The ESC Focused Update on DAPT Guidelines recommend switching from clopidogrel to ticagrelor for ACS patients in the acute setting [*Class I recommendation*]*[1]**
  - **Switching from clopidogrel to ticagrelor is recommended early after hospitalisation irrespective of the timing and loading dose of clopidogrel*[1]**
- **Evidence for this recommendation is provided by the PLATO trial, in which 46% of patients randomized to ticagrelor 90 mg were administered clopidogrel before randomization[2]**



bid, twice daily; LD, loading dose; MD, maintenance dose; qd, daily
* Unless contraindications to ticagrelor exist; † irrespective of prior clopidogrel timing and dosing; ‡ 24 hr after last dose of previous drug
1. Valgimigli M *et al. Eur Heart J* 2017 doi:10.1093/eurheartj/ehx419; 2. Wallentin L *et al. N Engl J Med* 2009;361:1045–1057

2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease

Specific $P2Y_{12}$ Inhibitors

COR	LOE	Recommendations
IIa	B-R	In patients with ACS (NSTE-ACS or STEMI) treated with DAPT after coronary stent implantation and in patients with NSTE-ACS treated with medical therapy alone (without revascularization), it is reasonable to use ticagrelor in preference to clopidogrel for maintenance $P2Y_{12}$ inhibitor therapy.
IIa	B-R	In patients with ACS (NSTE-ACS or STEMI) treated with DAPT after coronary stent implantation who are not at high risk for bleeding complications and who do not have a history of stroke or TIA, it is reasonable to choose prasugrel over clopidogrel for maintenance $P2Y_{12}$ inhibitor therapy.
III: Harm	B-R	Prasugrel should not be administered to patients with a prior history of stroke or TIA.

6. Levine GN *et al. Circulation* 2016;134:e123–155

Evidence Behind

PLATO: Study design

ACS patients with UA/NSTEMI (moderate-to-high risk) or STEMI (if primary PCI)
All receiving ASA (75–100 mg daily); clopidogrel-treated or -naïve;
randomised within 24 hours of index event
(N=18,624)

Clopidogrel	Ticagrelor
300 mg or 600 mg loading dose (unless pretreated), then 75 mg QD maintenance	180 mg loading dose, then 90 mg BID maintenance

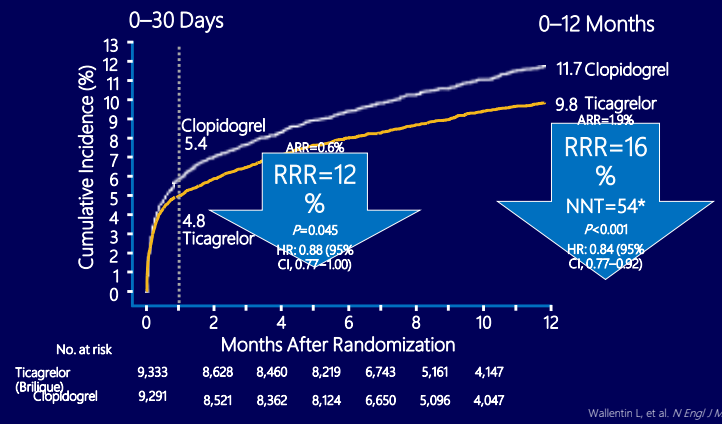
6–12-month exposure
Mean duration: 277 days

Primary endpoint	• Composite of CV death, MI or stroke
Primary safety endpoint	• Total major bleeding
Key secondary endpoints	• CV death, MI, stroke in patients intended for invasive management • Total mortality, MI or stroke • CV death, MI, stroke, recurrent ischaemia, TIA or arterial thrombotic events • Components of primary endpoint (CV death, MI and stroke) • Death from any cause

ACS, acute coronary syndromes; ASA, acetylsalicylic acid; BID, twice daily; CV, cardiovascular; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; QD, once daily; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischaemic attack; UA, unstable angina.

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

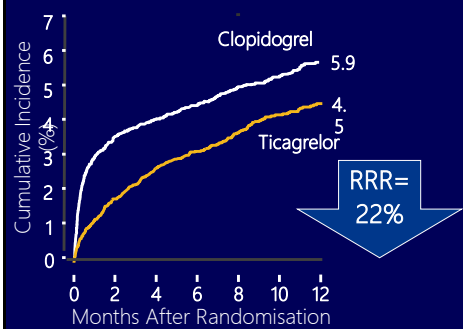
Primary Efficacy Endpoint
(Composite of CV Death, MI, or Stroke)



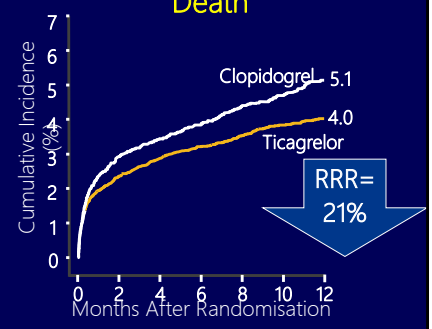
Wallentin L, et al. *N Engl J Med.* 2009;361:1045–1057.

PLATO Secondary Efficacy Endpoint:

All causes of death



Cardiovascular Death

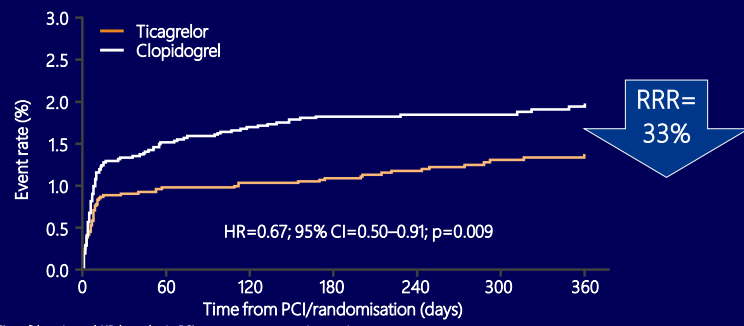


* All-cause mortality was a secondary endpoint of the PLATO study and was 4.5% with BRILIQUE vs 5.9% with clopidogrel (1.4% ARR 22% RRR; HR 0.78; 95% CI 0.69-0.89; nominal p<0.001)

Wallentin L et al. N Engl J Med 2009; 361: 1045-57.

PLATO: Stent Thrombosis

Ticagrelor was associated with a significant reduction in definite stent thrombosis compared with clopidogrel*



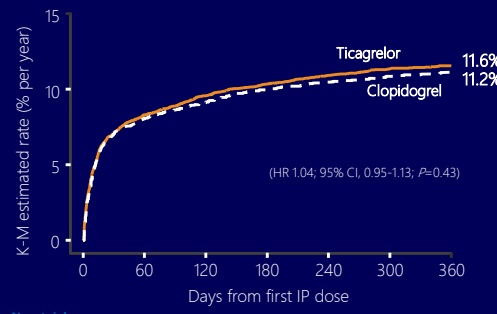
CI, confidence interval; HR, hazard ratio; PCI, percutaneous coronary intervention.
1- Steg PG, et al. *Circulation* 2013;128:1055–1065.

Ticagrelor was associated with a significant reduction in definite stent thrombosis compared with clopidogrel (1.4% vs. 1.9%; p=0.009)

Primary Safety Endpoint*

PLATO: Time to major bleeding

[Wallentin 2009:IJ]



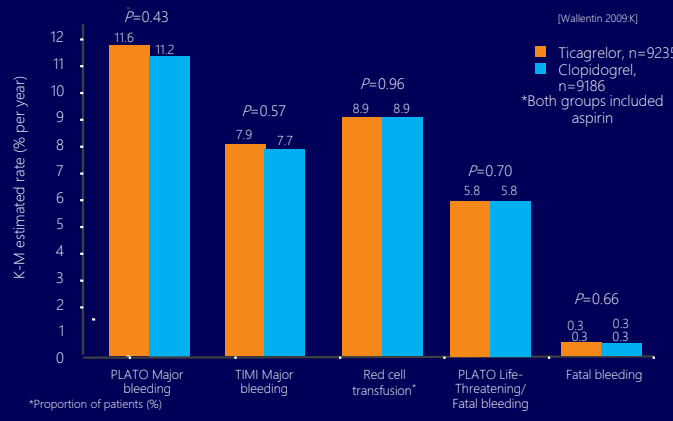
NS

No. at risk							
Ticagrelor	9235	7246	6826	6545	5129	3783	3433
Clopidogrel	9186	7305	6930	6670	5209	3841	3479

*Both groups included aspirin

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

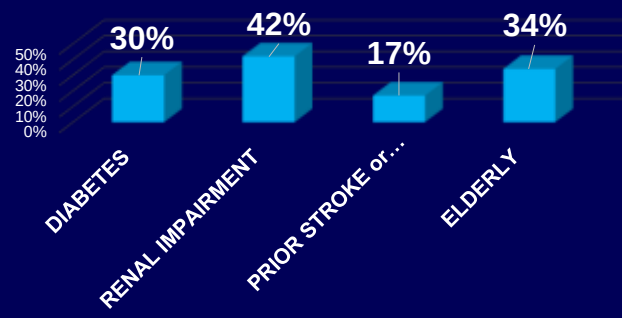
PLATO: Major bleeding



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

What about Ticagrelor in Special Patients Populations?

Prevalence of special populations among ACS patients (1-3)



JACC.vol.64No.24.2014
Circulation. 2013 Feb 12;127(6):730-8. doi: 10.1161/CIRCULATIONAHA.112.141572. Epub 2012 Dec 31
Doi:10.193/eurheartj/ehv320

PLATO: Study design

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300 mg or 600 mg loading dose
(unless pretreated), then 75 mg QD maintenance

Ticagrelor
180 mg loading dose,
then 90 mg BID maintenance

6–12-month exposure
Mean duration: 277 days

DIABETIC PATIENTS

RENAL IMPAIRMENT PATIENTS

PRIOR STROKE , TIA PATIENTS

ELDERLY PATIENTS

Special patient populations in PLATO

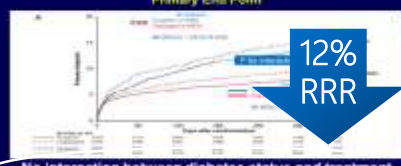
ACS, acute coronary syndromes; ASA, acetylsalicylic acid; BID, twice daily; CV, cardiovascular; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; QD, once daily; STEMI, ST-segment elevation myocardial infarction;TIA, transient ischaemic attack; UA, unstable angina.

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

PLATO: Primary End Points in special patient populations

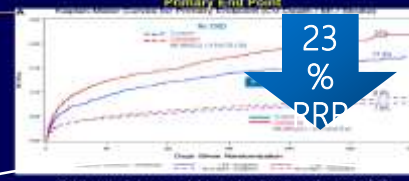
Consistent results among these special populations

PLATO: Diabetes
Primary End Point



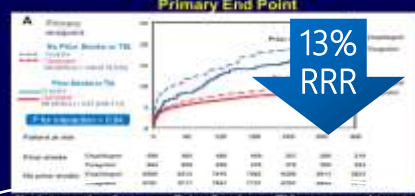
No interaction between diabetes status and treatment was observed p=0.49

PLATO: Renal
Primary End Point



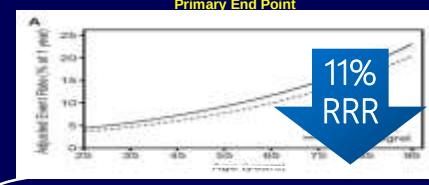
No interaction between renal status and treatment was observed p=0.13

PLATO: Prior Stroke or TIA
Primary End Point



No interaction between Prior Stroke or TIA status and treatment was observed p=0.84

PLATO: Elderly
Primary End Point



No interaction between Age status and treatment was observed p=0.56

PLATO: All Causes of Death in special patient populations

Consistent results among these special populations

PLATO: Diabetes
All Causes Of Death

No interaction between diabetes status and treatment was observed p=0.66

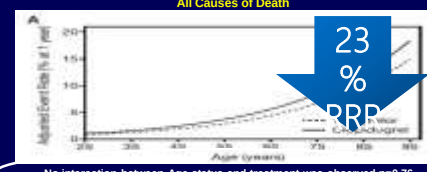
PLATO: Renal
All Causes of Death

No interaction between Renal status and treatment was observed p=0.16

PLATO: Prior Stroke or TIA
All Causes Of Death

No interaction between Prior Stroke or TIA status and treatment was observed p=0.19

PLATO: Elderly
All Causes of Death



No interaction between Age status and treatment was observed p=0.76

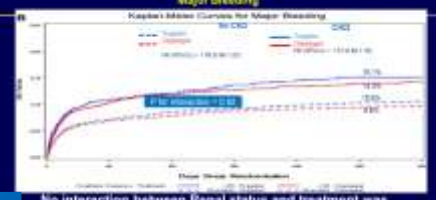
PLATO: Major Bleeding in special patient populations

Consistent results among these special populations

PLATO: Diabetes
Major Bleeding

No interaction between diabetes status and treatment was observed p=0.21

PLATO: Renal
Major Bleeding



No interaction between Renal status and treatment was observed p=0.92

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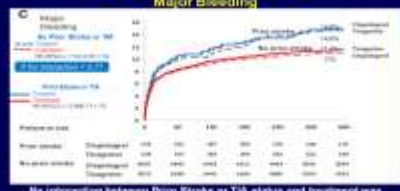
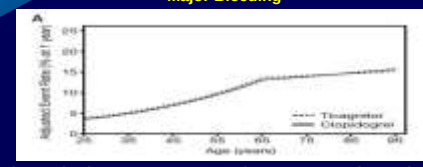
PLATO: Prior Stroke or TIA
Major Bleeding



No interaction between Prior Stroke or TIA status and treatment was observed p=0.77

PLATO: Elderly
Major Bleeding



No interaction between Age status and treatment was observed p=0.89

Circ cardiovasc qual outcomes 2012;5: 680-688

Dyspnea

All patients (%)	Ticagrelor (n=6732)	Clopidogrel (n=6676)	*P* value
Dyspnea			
Any dyspnea event	924 (13.9)	527 (8.0)	<0.0001
Requiring discontinuation of study treatment	51 (0.8)	10 (0.2)	

- Less than 1% of patients in the ticagrelor group (0.8%) and the clopidogrel group (0.2%) permanently discontinued the study drug because of dyspnea[

Cannon CP, et al. Lancet 2010;375:283

PLATO : Conclusion

- **In patients with an acute coronary syndrome with or without ST-segment elevation, treatment with ticagrelor compared with clopidogrel**
  - reduced the primary endpoint of death form vascular causes, myocardial infarction or stroke
  - reduced the rate of all cause mortality
  - without an increase in the rate of overall major bleeding (increase in nonCABG related major bleeding with ticagrelor)
- **Similar results were observed**
  - in patients identified by the investigator at randomisation as requiring invasive management via PCI/CABG (72% of the whole study cohort).
  - In patients with a diagnosis of STEMI (41% of the whole study cohort)
  - In patients identified by the investigator at randomisation as requiring non-invasive, medical management (28% of the whole study cohort).

Wallentin *et al*. *New Eng J Med* 2009; 361(11): 1045-1057
Note: Treatment with ticagrelor 90mg is the licenced recommendation for 12months in ACS patients

What about Real World Evidence?

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July 2016

Outcomes in Patients Treated With Ticagrelor or Clopidogrel After Acute Myocardial Infarction: Experiences From SWEDEHEART Registry

(The PRACTICAL study)

Anders Sahlén, Christoph Varenhorst, Bo Lagerqvist, Henrik Renlund, Elmir Omerovic, David Erlinge, Lars Wallentin, Stefan James, Tomas Jernberg

Eur Heart J 2016;dx.doi.org/10.1093/eurheartj/ehw284

Karolinska Institutet

AstraZeneca

Executive summary and presentation overview

SWEDEHEART

- A nationwide web-based registry including patients with MI at all Swedish acute cardiac care hospitals (n=71)
- Data accuracy is independently audited annually: 96% agreement between registry data and hospital records
- Baseline characteristics were enriched with diagnostic data available from the National Patient Registry (all diagnoses of all admissions to Swedish hospitals since 1987)

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Study design

- **Inclusion criteria:** Consecutive survivors of an acute MI, discharged on DAPT with ASA and either ticagrelor or clopidogrel, between 2010 and 2013
- **Exclusion criteria:** Previous admission for MI, discharged with OAC or CABG during hospitalization
- **Primary outcome**: Composite of death, readmission for MI or stroke within 2 years (NB: outcomes up to 2 years were measured, though DAPT may have been discontinued much earlier, ie 12 months or less)
- **Secondary outcome**: Individual components of the primary outcome
  - For MI analysis, a 28-day blanket period was applied at discharge to avoid index events being counted twice (through duplication between hospital transfers or attribution to index event for any early readmissions)
- **Bleeding outcomes:**
  - Readmission with bleeding
  - Bleeding in-hospital in those undergoing PCI

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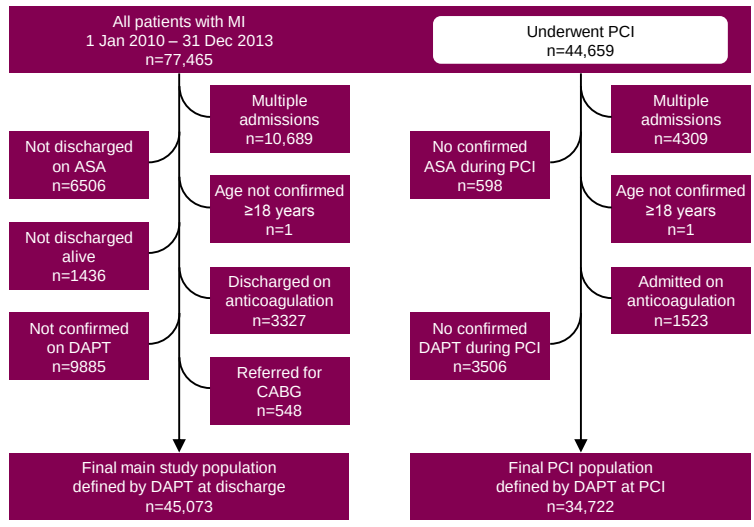
Patient flow diagram



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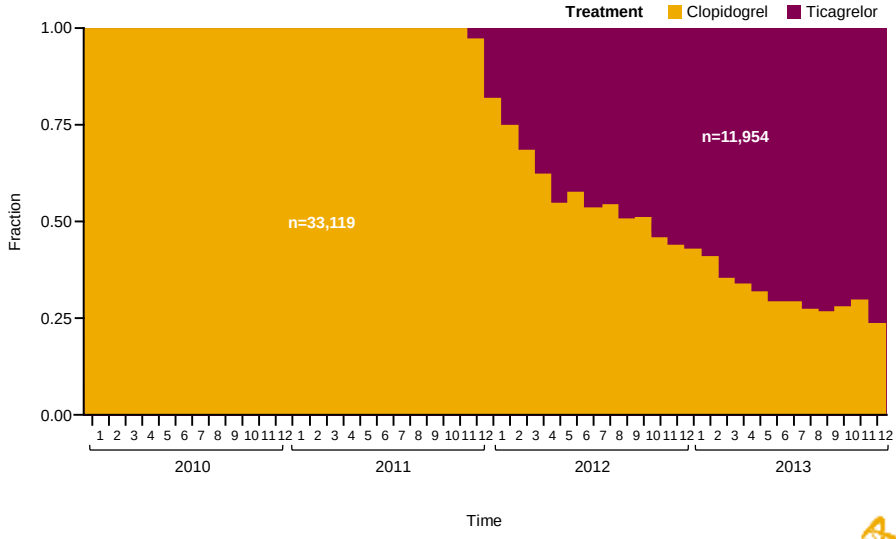
Introduction of ticagrelor

N = 45,073



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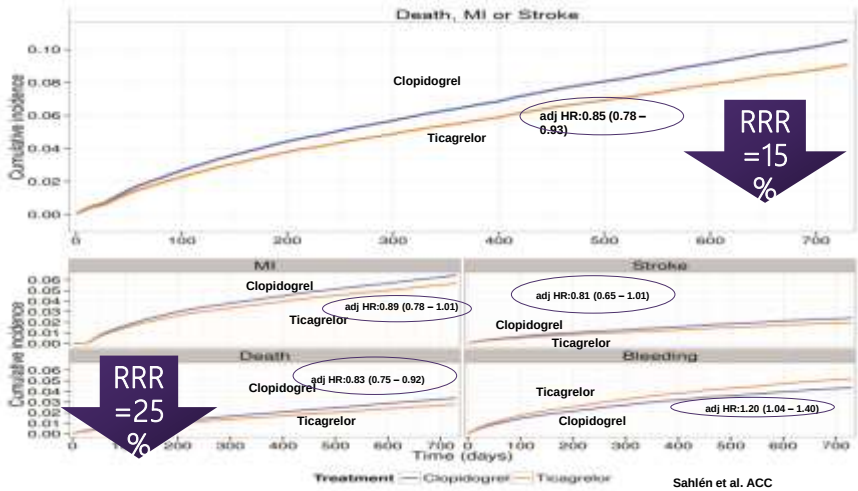
Adjusted Outcome



Sahlén et al. ACC 2016

Study interpretation

- PRACTICAL was derived from the world-renowned SWEDEHEART registry
- It was a high-quality observational study, conducted independently of AstraZeneca
  - AstraZeneca did not provide financial support for, nor had a role in, the design or conduct of the study, data analysis/interpretation or manuscript development
- PRACTICAL evaluated treatment outcomes in a large population of real-world ACS patients treated with ticagrelor or clopidogrel
- Benefits of ticagrelor 90 mg in PRACTICAL versus clopidogrel showed consistency with a PLATO secondary endpoint in a real-world setting at 12 months*
- PLATO remains the gold standard evidence for ticagrelor in ACS, and definitively demonstrated the superior benefit:risk profile of ticagrelor versus clopidogrel in a broad population of ACS patients

*PLATO primary endpoint was the composite of CV death, MI or stroke at 12 months; the composite of all-cause death, MI and stroke was a secondary endpoint in PLATO

Cardiovascular and Bleeding Risks in Acute Myocardial Infarction Newly Treated With Ticagrelor vs. Clopidogrel in Taiwan

Background:

- There are few data on ticagrelor in Asian patients. This study evaluated clinical outcomes with ticagrelor and clopidogrel in Taiwanese patients with acute myocardial infarction (AMI).

Methods and Results:

Taiwan National Health Insurance Research Database to identify 27,339 AMI patients aged ≥18 years between January 2012 and December 2014, and only patients who survived greater than or equal to 30 days after AMI and took dual antiplatelet therapy were included.

Cohorts of ticagrelor and clopidogrel were matched 1:8, based on propensity score matching, to balance baseline covariates.

The primary efficacy endpoints

- *Death from any cause, AMI, or stroke.*

The safety endpoints

- *consisted of major gastrointestinal bleeding or intracerebral hemorrhage*.

Lee, C. H., Cheng, C. L., Yang, Y. H. K., Chao, T. H., Chen, J. Y., & Li, Y. H. (2017). Cardiovascular and Bleeding Risks in Acute Myocardial Infarction Newly Treated With Ticagrelor vs. Clopidogrel in Taiwan. Circulation Journal, CJ-17.

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Cardiovascular and Bleeding Risks in Acute Myocardial Infarction Newly Treated With Ticagrelor vs. Clopidogrel in Taiwan

Results

- the primary efficacy endpoint rate was **22% lower in the ticagrelor** group than in the clopidogrel group (10.6% and 16.2%, respectively; adjusted HR, 0.779; 95% CI: 0.684–0.887).
- **The safety endpoint rate was similar between the ticagrelor and clopidogrel** groups (3.2% and 4.1% respectively; adjusted HR, 0.731; 95% CI: 0.522–1.026).

Conclusions:

- **In real-world AMI Taiwanese patients, ticagrelor seemed to offer better anti-ischemic protection than clopidogrel, without an increase in the rate of major bleeding.**
- A large-scale randomized trial is needed to assess the efficacy and safety of ticagrelor in East Asian AMI patients.

Lee, C. H., Cheng, C. L., Yang, Y. H. K., Chao, T. H., Chen, J. Y., & Li, Y. H. (2017). Cardiovascular and Bleeding Risks in Acute Myocardial Infarction Newly Treated With Ticagrelor vs. Clopidogrel in Taiwan. Circulation Journal, CJ-17.

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Conclusion

- ACS patients are at **high and persistent risk** of a recurrent ischaemic event;[1] it is therefore imperative that doctors practice evidence-based medicine and follow treatment guidelines
- **PLATO demonstrated superiority of ticagrelor** over clopidogrel, including a reduction in CV mortality, without a significant increase in overall major or fatal bleeding:[2]

1. Jernberg T *et al. Eur Heart J* 2015;136:1163–1170; 2. Wallentin L *et al. N Eng J Med* 2009;361:1045–1057;
3. Salhén A *et al. Eur Heart J* 2016;37:3335–3342; 4. Windecker S *et al. Eur Heart J* 2014;35:2541–2619;
5. Roffi M *et al. Eur Heart J* 2016;36:267–315; 6. Levine GN *et al. Circulation* 2016;134:e123–155

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Conclusion

- **Real World Evidence** is consistent with PLATO: in **>45,000 real-world ACS patients** (PRACTICAL), the benefit of ticagrelor over clopidogrel for the composite of all-cause death, MI or stroke at 12 months was consistent with the same endpoint in PLATO[3] and
- **In real-world AMI Taiwanese patients 27,339 ticagrelor seemed to offer better anti-ischemic protection than clopidogrel, without an increase in the rate of major bleeding.**

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Conclusion

- PLATO is reflected in **major international guidelines** (ACC/AHA, ESC), which prefer ticagrelor over clopidogrel for stented and non-stented patients with ACS
- The ESC Focused Update on DAPT Guidelines recommend **switching from clopidogrel to ticagrelor for ACS patients in the acute setting** [Class I recommendation]*

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Thank You