



Arvand Pharmed



دانشگاه علوم پزشکی بابل

Choosing The Best Antiplatelet Case Based Discussion

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 **Venotica**
Ticagrelor

Case

Case Profile

- 53 years old Lady
- Previously using clopidogrel 75 mg/day
- Admitted in hospital with STEMI-ACS
- HG: 11 g/dl
- WBC: 16 g/dl
- CrCL: 65 ml/min
- Prior Bleeding: No

Question #1

Pre/Peri-PCI P2Y12 Loading

- Which Medicine for Loading?
 1. ASA 300 mg + Clopidogrel 600 mg
 2. ASA 300 mg + Ticagrelor 180 mg
 3. ASA 80 mg + Ticagrelor 180 mg
 4. Wait until we see the angiography

Pre-
Treatment

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graph TD; A[Pre-Treatment] --> B[STEMI]; A --> C[NSTE-ACS]
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STEMI

NSTE-ACS

STEMI



ESC

European Society
of Cardiology

European Heart Journal (2018) **39**, 119–177

doi:10.1093/eurheartj/ehx393

ESC GUIDELINES

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

The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC)

STEMI

Periprocedural and post-procedural antithrombotic therapy in patients undergoing primary percutaneous coronary intervention

Recommendations	Class ^b	Level ^c
Antiplatelet therapy		
A potent P2Y ₁₂ inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contraindicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding. ^{186,187}	I	A
Aspirin (oral or i.v. if unable to swallow) is recommended as soon as possible for all patients without contraindications. ^{213,214}	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. ^{192–194}	IIb	A

Switching Hospital Admission

Switching between oral P2Y₁₂ inhibitors

Recommendations	Class ^a	Level ^b
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 ^c of clopidogrel, unless contraindications to ticagrelor exist. ²⁰	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

ACS = acute coronary syndrome.

^aClass of recommendation.

^bLevel of evidence.

^cContraindications for ticagrelor: previous intracranial haemorrhage or ongoing bleeds.

- **ALL ACS Patients**
- **Early after hospital admission**
- **Irrespective of timing and loading dose of clopidogrel**
- **Unless ticagrelor contraindication**

NSTE-ACS



ESC

European Society
of Cardiology

European Heart Journal (2021) **42**, 1289–1367
doi:10.1093/eurheartj/ehaa575

ESC GUIDELINES

2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC)

NSTE-ACS

Pre-intervention



The NEW ENGLAND
JOURNAL of MEDICINE

September 12, 2013

N Engl J Med 2013; 369:999-1010

DOI: 10.1056/NEJMoa1308075

ACCOAST trial :

The randomized Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction

RESULT:

lack of any ischaemic benefit for pre-treatment in NSTE-ACS patients, but instead, a substantially higher bleeding risk with prasugrel pre-treatment.

NSTE-ACS

Pre-intervention

Open access

Original research

BMJ Open Nationwide observational study of incidence, management and outcome of spontaneous coronary artery dissection: a report from the Swedish Coronary Angiography and Angioplasty register

Henrik Wilander,¹ Christos Pagonis,¹ Dimitrios Venetsanos,² Eva Swahn ,¹ Christian Dworeck,³ Nina Johnston,⁴ Lena Jonasson,⁵ Thomas Kellerth,⁶ Per Tornvall,⁷ Troels Yndigejn,⁸ Sofia Sederholm Lawesson¹

SCAAR observational study:

Reported from the Swedish Coronary Angiography and Angioplasty Registry, data on pre-treatment with *ticagrelor*, *prasugrel*, and *clopidogrel* in **64 857 NSTE-ACS patients**.

RESULT:

The authors reported that P2Y12 receptor inhibitor pre-treatment in NSTE-ACS patients **was not associated with improved ischaemic outcomes, but instead, with a significantly increased risk of bleeding events.**

NSTE-ACS

Pre-intervention



The NEW ENGLAND
JOURNAL *of* MEDICINE

October 17, 2019

N Engl J Med 2019; 381:1524-1534

DOI: 10.1056/NEJMoa1908973

ISAR-REACT 5 trial

Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes

RESULT:

There was no apparent benefit of a pretreatment strategy in the study.

NSTE-ACS

Pre-intervention



ESC

European Society
of Cardiology

European Heart Journal (2021) 42, 1289–1367

doi:10.1093/eurheartj/ehaa575

RECOMENDATION

- **It is not recommended to administer routine pre-treatment with a P2Y12 receptor inhibitor in NSTE-ACS patients in whom coronary anatomy is not known** and an early invasive management is planned.
- For patients with a delayed invasive management, pre-treatment with a P2Y12 receptor inhibitor may be considered in selected cases and according to the bleeding risk of the patient.
- Fortunately, the recommended standard treatment with **potent P2Y12 receptor inhibitors (ticagrelor or prasugrel)** exhibits a fast onset of action, thereby allowing LD administration after diagnostic coronary angiography and directly before PCI.

Answer #1

Pre/Peri-PCI P2Y12 Loading

- Which Medicine for Loading?
 1. ASA 300 mg + Clopidogrel 600 mg
 2. ASA 300 mg + Ticagrelor 180 mg
 3. ASA 80 mg + Ticagrelor 180 mg
 4. Wait until we see the angiography

Question #2

Maintenance Therapy

- Which Medicine and What Duration for DAPT?
 1. Clopidogrel 75 mg/day + Aspirin 6 months
 2. Clopidogrel 75 mg/day + Aspirin 12 months
 3. Ticagrelor 90 mg BID + Aspirin 6 month
 4. Ticagrelor 90 mg BID + Aspirin 12 month

DAPT

Recommendations

Recommendations on P2Y₁₂ inhibitor selection and timing

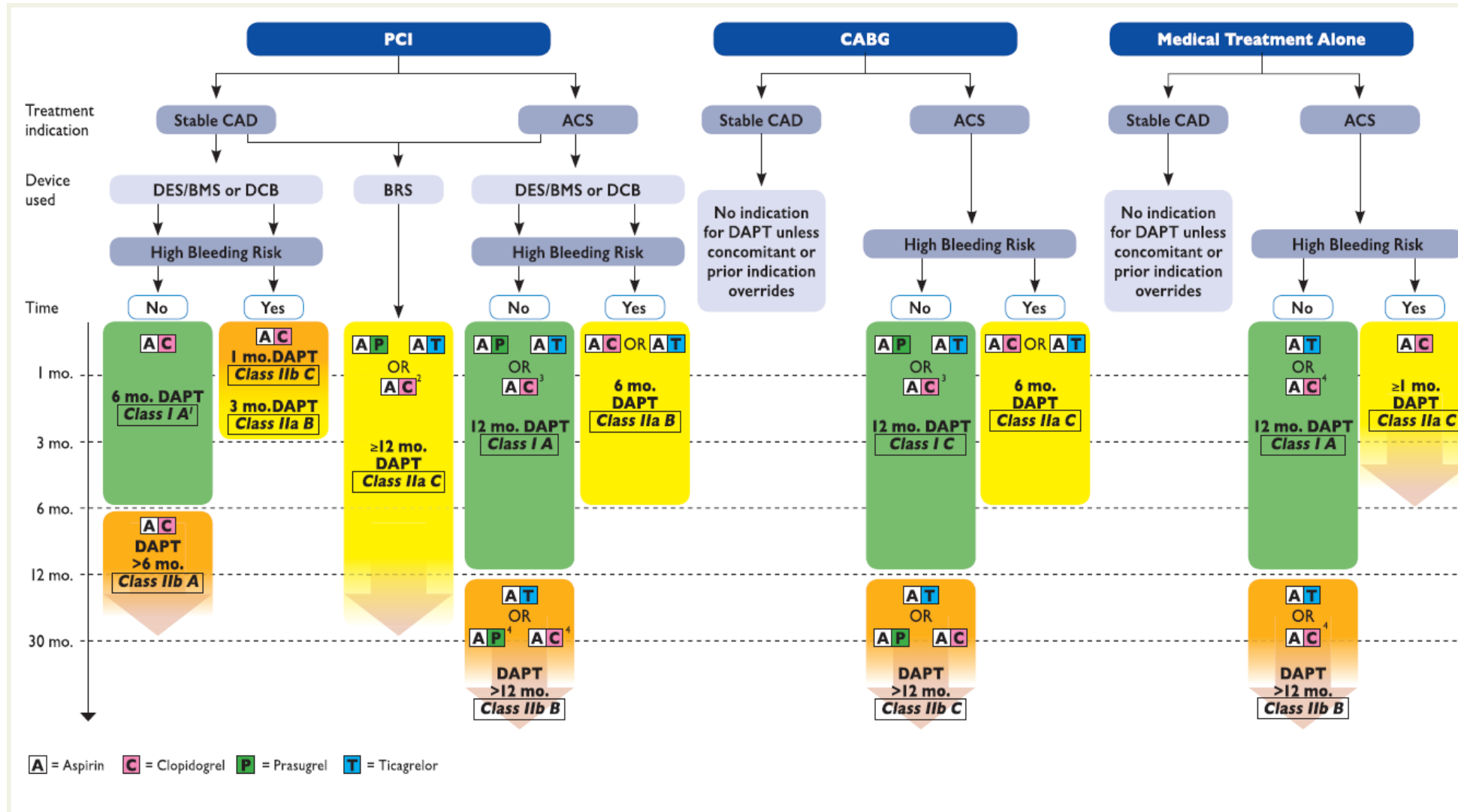
Recommendations	Class ^a	Level ^b
In patients with ACS, ticagrelor (180 mg loading dose, 90 mg twice daily) on top of aspirin ^c is recommended, regardless of initial treatment strategy, including patients pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced) unless there are contraindications. ²⁰	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 NSTEMI-ACS or initially conservatively managed STEMI if indication for PCI is established, or in STEMI patients undergoing immediate coronary catheterization ^c unless there is a high risk of life-threatening bleeding or other contraindications. ²³	I	B
Pre-treatment with a P2Y ₁₂ inhibitor is generally recommended in patients in whom coronary anatomy is known and the decision to proceed to PCI is made as well as in patients with STEMI. ^{20,23,38}	I	A
In patients with NSTEMI-ACS undergoing invasive management, ticagrelor administration (180 mg loading dose, 90 mg twice daily), or clopidogrel (600 mg loading dose, 75 mg daily dose) if ticagrelor is not an option, should be considered as soon as the diagnosis is established.	IIa	C

DAPT

Recommendations

In patients with stable CAD, pre-treatment with clopidogrel may be considered if the probability of PCI is high.	IIb	C
Clopidogrel (600 mg loading dose, 75 mg daily dose) on top of aspirin is recommended in stable CAD patients undergoing coronary stent implantation and in ACS patients who cannot receive ticagrelor or prasugrel, including those with prior intracranial bleeding or indication for OAC. ^{20,23,39,40}	I	A
Clopidogrel (300 mg loading dose in patients aged ≤ 75 , 75 mg daily dose) is recommended on top of aspirin in STEMI patients receiving thrombolysis. ^{31,32}	I	A
Ticagrelor or prasugrel on top of aspirin may be considered instead of clopidogrel in stable CAD patients undergoing PCI, taking into account the ischaemic (e.g. high SYNTAX score, prior stent thrombosis, location and number of implanted stents) and bleeding (e.g. according to PRECISE-DAPT score) risks.	IIb	C
In NSTEMI-ACS patients in whom coronary anatomy is not known, it is not recommended to administer prasugrel. ²⁵	III	B

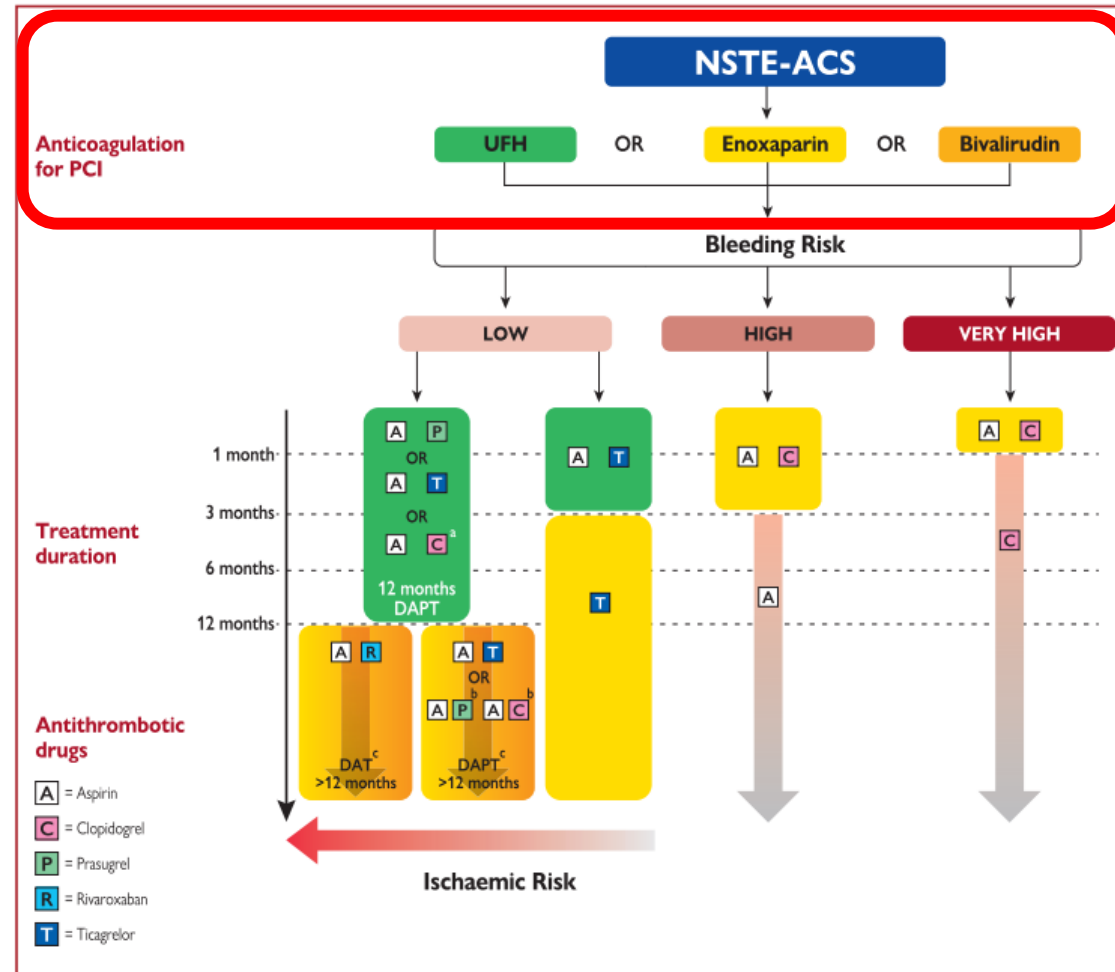
DAPT Algorithm



NSTE-ACS

Peri-intervention

USE
ANTICOAGULANTS



Risk Stratification

CLINICAL RESEARCH

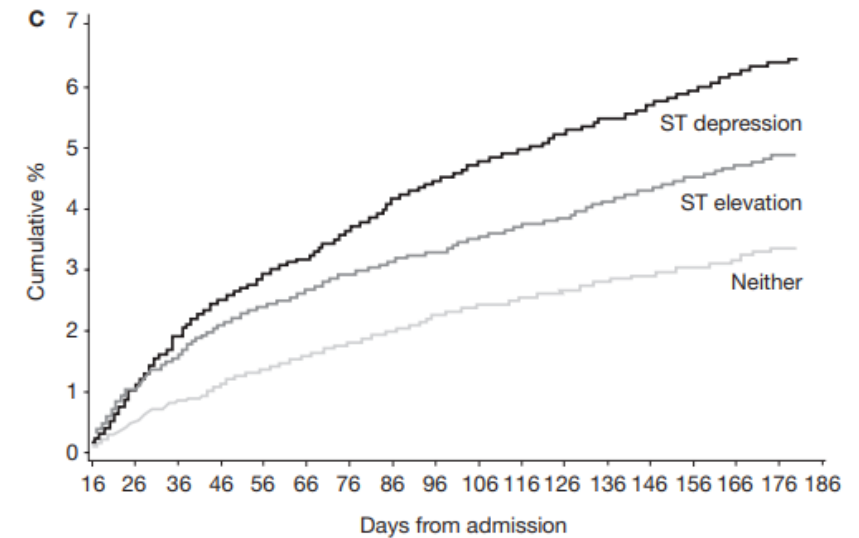
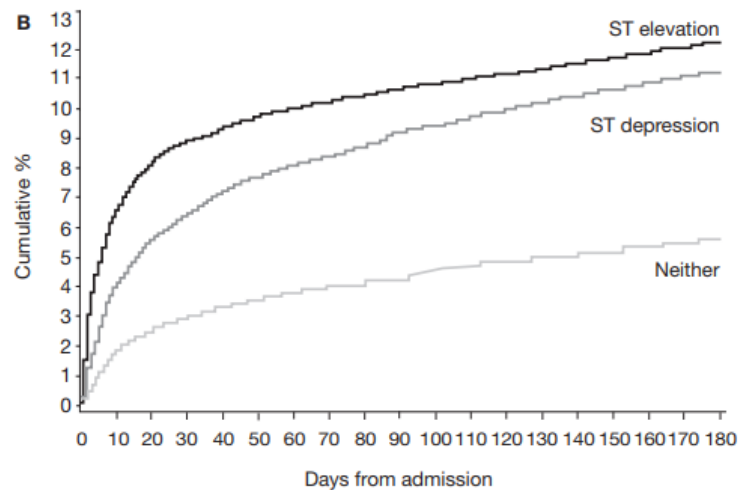
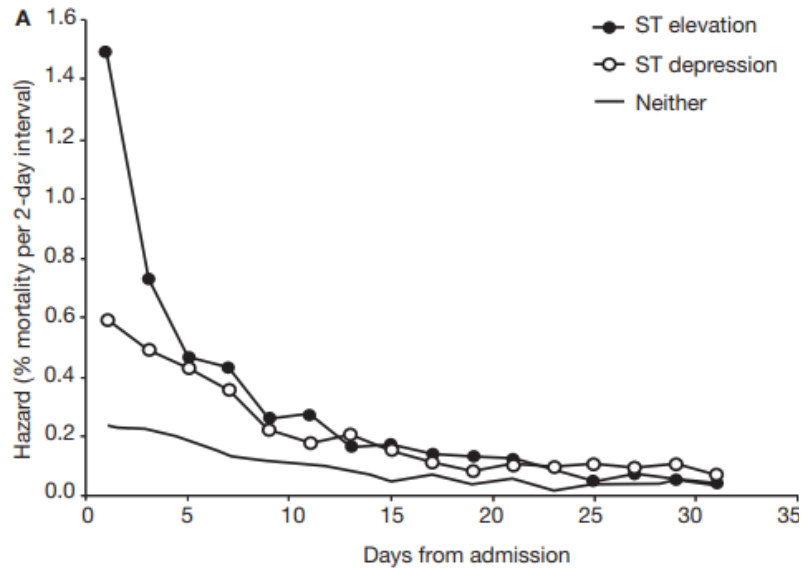
www.nature.com/clinicalpractice/cardio

Time course of events in acute coronary syndromes: implications for clinical practice from the GRACE registry

Keith AA Fox^{1*}, Frederick A Anderson Jr², Shaun G Goodman³, P Gabriel Steg⁴, Karen Pieper⁵, Ann Quill²
and Joel M Gore², for the GRACE Investigators

Risk Stratification

Empirical hazard function for mortality and Kaplan–Meier curves showing cumulative incidence of death in patients presenting with acute coronary syndromes



At First 30 days we have the most risk of death among ACS Patients

Table 11 Risk criteria for extended treatment with a second antithrombotic agent

High thrombotic risk (Class IIa)	Moderate thrombotic risk (Class IIb)
Complex CAD and at least 1 criterion	Non-complex CAD and at least 1 criterion
Risk enhancers	
Diabetes mellitus requiring medication	Diabetes mellitus requiring medication
History of recurrent MI	History of recurrent MI
Any multivessel CAD	Polyvascular disease (CAD plus PAD)
Polyvascular disease (CAD plus PAD)	CKD with eGFR 15–59 mL/min/1.73 m ²
Premature (<45 years) or accelerated (new lesion within a 2-year time frame) CAD	
Concomitant systemic inflammatory disease (e.g. human immunodeficiency virus, systemic lupus erythematosus, chronic arthritis)	
CKD with eGFR 15–59 mL/min/1.73 m ²	
Technical aspects	
At least 3 stents implanted	
At least 3 lesions treated	
Total stent length >60 mm	
History of complex revascularization (left main, bifurcation stenting with ≥ 2 stents implanted, chronic total occlusion, stenting of last patent vessel)	
History of stent thrombosis on antiplatelet treatment	

Thrombotic Risk

TABLE 62.2 Variables Associated with Stent Thrombosis

Clinical Variables

Acute myocardial infarction
Clopidogrel noncompliance and discontinuation
Clopidogrel bioavailability
Diabetes mellitus
Renal failure
Congestive heart failure
Previous brachytherapy

Anatomic Variables

Long lesions
Smaller vessels
Multivessel disease
Acute myocardial infarction
Bifurcation lesions

Procedural Factors

Stent underexpansion
Incomplete wall apposition
Residual inflow and outflow disease
Margin dissections

Risk Stratification

Table 3 Risk scores validated for dual antiplatelet therapy duration decision-making

	PRECISE-DAPT score ^{1B}	DAPT score ¹⁵
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	<p>HB ≥ 12 11.5 11 10.5 ≤ 10</p> <p>WBC ≤ 5 8 10 12 14 16 18 ≥ 20</p> <p>Age ≤ 50 60 70 80 ≥ 90</p> <p>CrCl ≥ 100 80 60 40 20 0</p> <p>Prior Bleeding No <input type="checkbox"/> Yes <input type="checkbox"/></p> <p>Score Points 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30</p>	<p>Age ≥ 75 -2 pt 65 to <75 -1 pt <65 0 pt</p> <p>Cigarette smoking +1 pt Diabetes mellitus +1 pt MI at presentation +1 pt Prior PCI or prior MI +1 pt Paclitaxel-eluting stent +1 pt Stent diameter <3 mm +1 pt CHF or LVEF <30% +2 pt Vein graft stent +2 pt</p>
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

GRACE score (for ACS)

Grace score									
Age	Points	HR	Points	SBP	Points	Cr	Points	Killip class	Points
<39	0	<70	0	<80	40	0.0–0.39	1	I	0
40–49	18	70–89	5	80–99	37	0.4–0.79	4	II	15
50–59	36	90–109	10	100–119	30	0.8–1.19	7	III	29
60–69	55	110–149	17	120–139	23	1.2–1.59	10	IV	44
70–79	73	150–199	26	140–159	17	1.6–1.99	13	Cardiac arrest	30
80–89	91	≥200	34	160–199	7	2.0–3.99	21	Elevated cardiac markers	13
>90	100	–	–	≥200	0	≥4	28	ST-segment deviation	17
Low risk								1–88	
Intermediate risk								89–118	
High risk								≥119	

Answer #2

Maintenance Therapy

- Which Medicine and What Duration for DAPT?
 1. Clopidogrel 75 mg/day + Aspirin 6 months
 2. Clopidogrel 75 mg/day + Aspirin 12 months
 3. Ticagrelor 90 mg BID + Aspirin 6 month
 4. Ticagrelor 90 mg BID + Aspirin 12 month

Risk Stratification



<http://www.precisedaptscore.com/predapt/webcalculator.html>

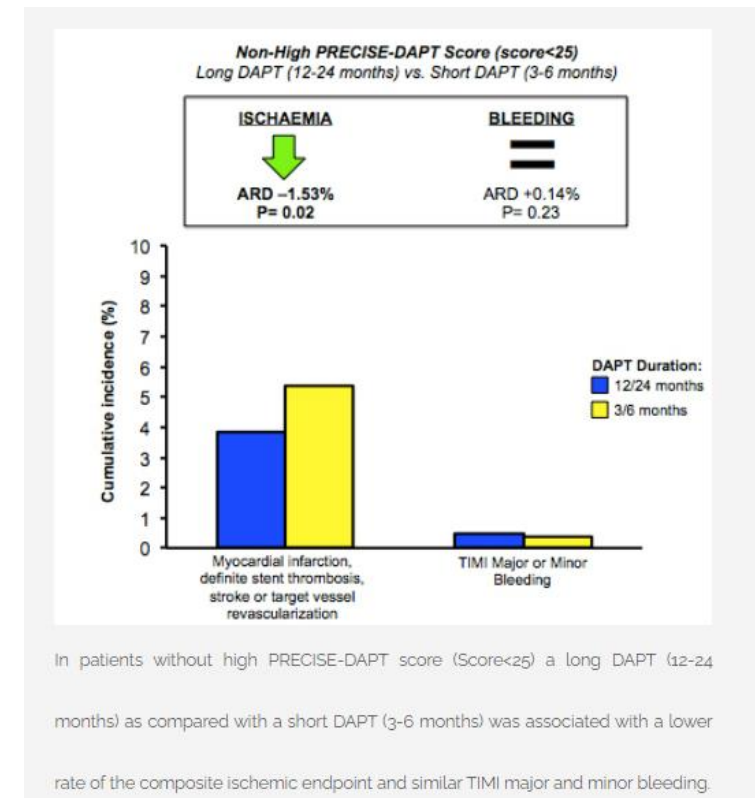
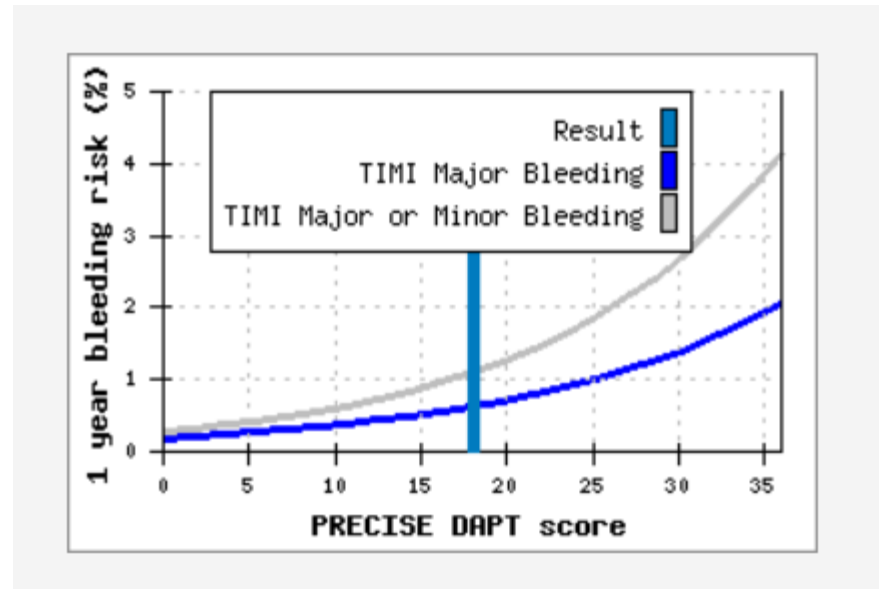
Haemoglobin i unit
 g/dl mmol/L

Age (years)

White blood cells i unit
 u/mcL $10^9/L$

Creatinine Clearance (mL/min) i

Prior Bleeding i



Risk Stratification

What if she was older?



<http://www.precisedaptscore.com/predapt/webcalculator.html>

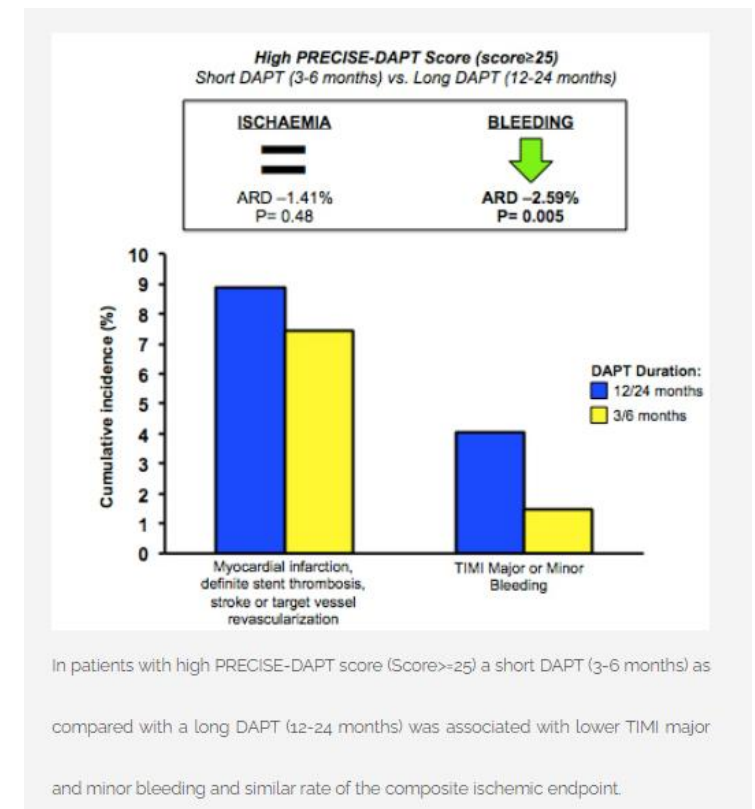
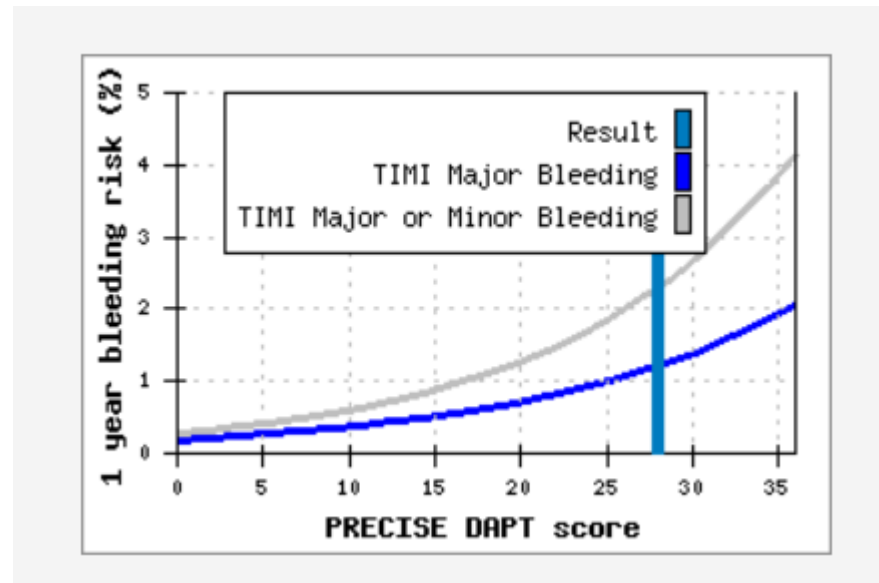
Haemoglobin i unit
11 g/dl mmol/L

Age (years)
75

White blood cells i unit
16 u/mcL 10⁹/L

Creatinine Clearance (mL/min) i
65

Prior Bleeding i



Risk Stratification

What if she had Prior Bleeding?



<http://www.precisedaptscore.com/predapt/webcalculator.html>

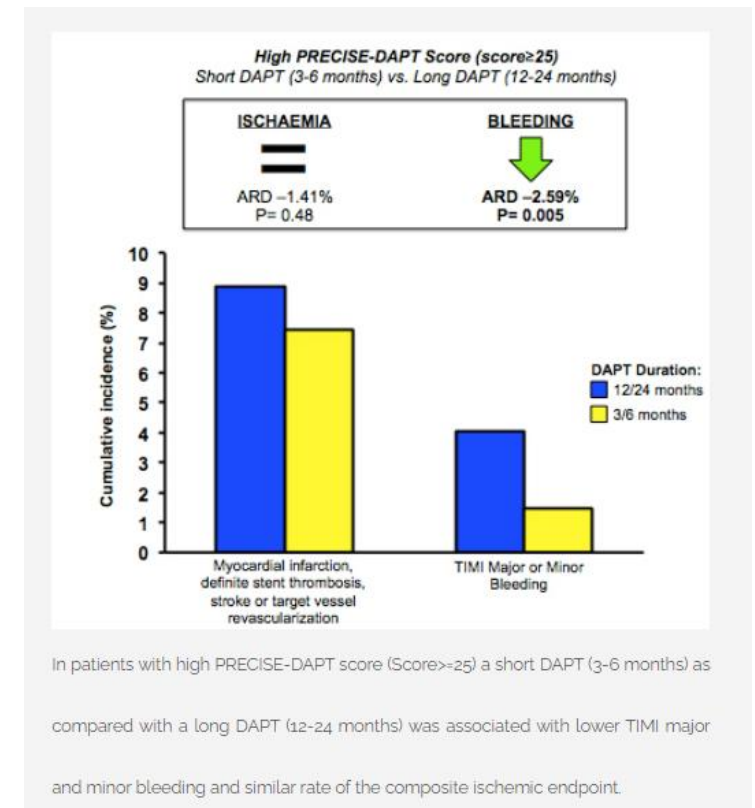
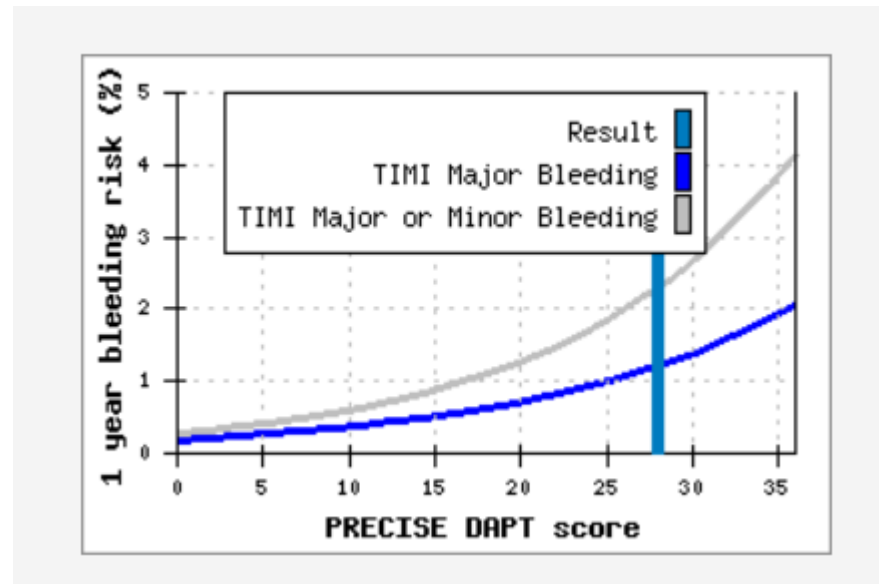
Haemoglobin ? unit
11 g/dl mmol/L

Age (years)
53

White blood cells ? unit
16 u/mcL 10⁹/L

Creatinine Clearance (mL/min) ?
65

Prior Bleeding ?



Can Ticagrelor Be Used Post Fibrinolytic Therapy?

2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization

A Report of the American College of Cardiology/American Heart Association
Joint Committee on Clinical Practice Guidelines

Can Ticagrelor Be Used Post Fibrinolytic Therapy?

COR	LOE	RECOMMENDATIONS
1	B-R	1. In patients undergoing PCI, a loading dose of aspirin, followed by daily dosing, is recommended to reduce ischemic events (1-4).*
1	B-R	2. In patients with ACS undergoing PCI, a loading dose of P2Y12 inhibitor, followed by daily dosing, is recommended to reduce ischemic events (5-15).
2a	B-R	5. In patients with ACS undergoing PCI, it is reasonable to use ticagrelor or prasugrel in preference to clopidogrel to reduce ischemic events, including stent thrombosis (6,14,20).
2b	B-R	6. In patients <75 years of age undergoing PCI within 24 hours after fibrinolytic therapy, ticagrelor may be a reasonable alternative to clopidogrel to reduce ischemic events (21).

Transfusions

Platelet transfusions:

- May be ***useful*** to treat serious bleeding complications in patients:
 - Taking **clopidogrel or prasugrel**
 - Which bind irreversibly to P2Y12
 - ***Not effective for ticagrelor reversal:***
 - ***It binds to the transfused platelets.***
- ***Bentracimab***
 - An antibody fragment that binds ticagrelor and its metabolite with high affinity and **rapidly reverses its inhibitory effects**
 - Is under development for ticagrelor reversal prior to urgent surgery or intervention or for patients with serious bleeding.

Dyspnea in PLATO

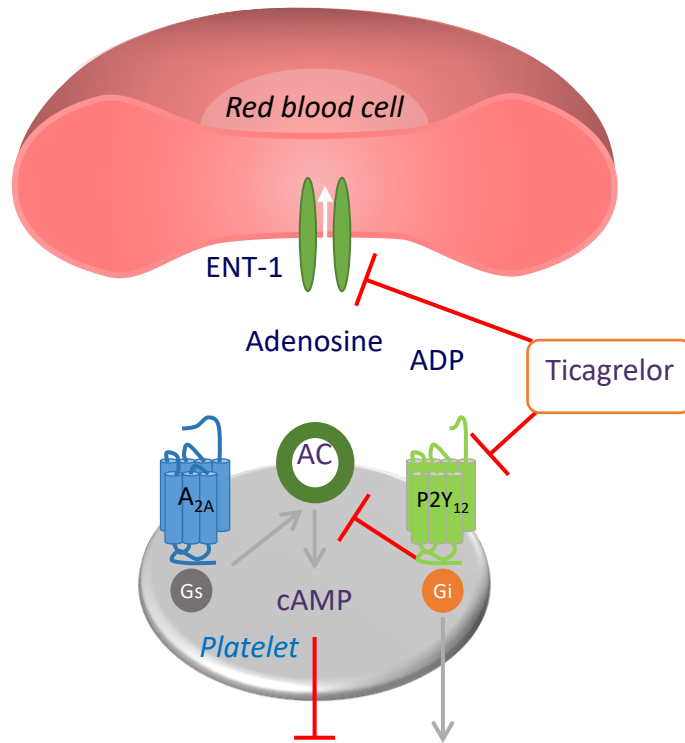
Category	Ticagrelor 90 mg bid N=9235	Clopidogrel 75 mg qd N=9186
Dyspnea AE	1270 (13.8%)	721 (7.8%)
Mild	890 (9.6%)	505 (5.5%)
Moderate	413 (4.5%)	218 (2.4%)
Severe	35 (0.4%)	18 (0.2%)
Dyspnea SAE	69 (0.7%)	39 (0.4%)
Death	1 (0.0%)	1 (0.0%)
Dyspnea AE leading to study drug discontinuation	79 (0.9%)	13 (0.1%)
Dyspnea SAE leading to study drug discontinuation	10 (0.1%)	1 (0.0%)

AE adverse event; bid Twice daily; qd Once daily; SAE Serious adverse event.

1. BRILIQUE SPC, 2011. 2. Wallentin L et al. *N Engl J Med.* 2009;361:1045-1057.

Dyspnea?

Is a result of Dual Mechanism of Action



- **Inhibition of P2Y₁₂ receptor**
 - Anti-platelet effect
- **Inhibition of ENT-1 transporter**
 - Enhanced local adenosine response may result in:
 - Additional inhibition of platelet aggregation/activation
 - Cardioprotection
 - Vasodilation
 - Modulation of inflammation
 - *Dyspnoea*

Dyspnea Characterization

Characterization:

- sudden and unexpected air hunger or unsatisfied inspiration.
- patient whether the identical symptom was present before starting ticagrelor?
- Its pattern may vary widely, from very brief episodes lasting minutes, generally starting in the first week of treatment, to sustained or intermittent episodes occurring over several weeks, with **most episodes being reported as mild.**
- Ticagrelor related dyspnoea is not associated with wheezing, orthopnoea, paroxysmal nocturnal dyspnoea, or chest tightness or pain.
- It usually occurs at rest, and is typically not related to exertion and does not limit exercise capacity.

Dyspnea Characterization

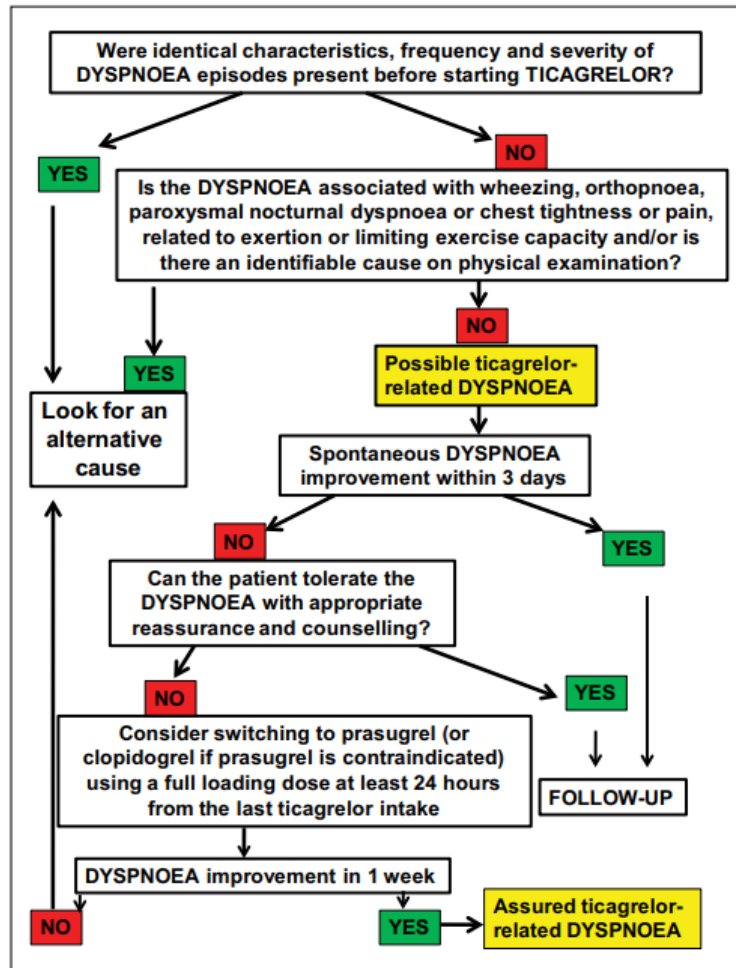


Figure 1. Dyspnoea diagnostic flow-chart.

- 1. Mostly lasts not for more than one week.
- 2. It can be fairly evaluated during hospitalization



Thanks for Your Attention



Arvand Pharmed