ACS MANAGEMENT (ANTIPLATLET)

Dr M.Pishgahi
Interventional Cardiologist
Factuality member of SBMU

CASE :

- 67 YEARS OLD MAN WITH TCP , WAS REFFERED TO YOUR HOSPITAL (NON PCI CAPABLE)
- **EKG** : ST ELEVATION IN ANTERIOR LEADS.

- TRANSFER TO PCI CAPABLE CENTER IN THE TIMELY MANNER IS NOT POSSIBLE

PASS THE TORCH

- CVRF: SMOKING
- DH: NEG
- VITAL SIGN : ACCEPTABLE

- YOU DECIDE TO ORDER RETEPLASE FOR HIM , (NO CONTRAINDICATION FOR FIBRINOLYTIC)

PASS THE TORCH

First Step

In emergency ward

STE MI

Pretreatment

Anti platlet

Anticoagulant

- YOU ARE GOINIG TO BE ASKED ABOUT SOME QUESTIONS BY YOUR ASSISSTANT

- WE START WITH ASPRIN

PASS THE TORCH

WHICH DOSE AND FORM OF ASA DO YOU RECOMMEND(CHEWABLE)?

1. 4*80mg
2. 3*100mg
3. 1*325 mg
4. No difference

PASS THE TORCH

PASS THE TORCH

IF HE EXPERINCED VF AND INTUBATED, WHAT DO YOU DO NOW?

I. Crush tablets , and use NGT
II. IV form of ASA
III. Solution of ASA
IV. All of above are correct

WHICH DOSE?

PASS THE TORCH

Which form of aspirin is the fastest to inhibit platelet aggregation in emergency department patients

chewable aspirin may be faster than soluble aspirin at decreasing the amount of time to achieve platelet inhibition in a patient.

Soluble aspirin is faster than whole solid aspirin, which is faster than enteric-coated aspirin

Emerg Med J 2015 32: 823-826

PASS THE TORCH

Adjunctive Antithrombotic Therapy to Support Reperfusion With Fibrinolytic Therapy

AHA guideline

	COR	LOE
Antiplatelet therapy		
Aspirin		
• 162- to 325-mg loading dose	I	A
• 81- to 325-mg daily maintenance dose (indefinite)	I	A
• 81 mg daily is the preferred maintenance dose	IIa	B
$P2Y_{12}$ receptor inhibitors		
• Clopidogrel:	I	A
• Age ≤75 y: 300-mg loading dose		
• Followed by 75 mg daily for at least 14 d and up to 1 y in absence of bleeding	I	A (14 d) C (up to 1 y)
• Age >75 y: no loading dose, give 75 mg	I	A
• Followed by 75 mg daily for at least 14 d and up to 1 y in absence of bleeding	I	A (14 d) C (up to 1 y)

PASS THE TORCH

Doses of antiplatelet co-therapies		
Aspirin	Starting dose of 150–300 mg orally (or 75–250 mg intravenously if oral ingestion is not possible), followed by a maintenance dose of 75–100 mg/day	
Clopidogrel	Loading dose of 300 mg orally, followed by a maintenance dose of 75 mg/day. In patients ≥75 years of age: loading dose of 75 mg, followed by a maintenance dose of 75 mg/day.	
Doses of anticoagulant co-therapies		
Enoxaparin	In patients <75 years of age: 30 mg i.v. bolus followed 15 min later by 1 mg/kg s.c. every 12 hours until revascularization or hospital discharge for a maximum of 8 days. The first two s.c. doses should not exceed 100 mg per injection. In patients ≥75 years of age: no i.v. bolus; start with first s.c. dose of 0.75 mg/kg with a maximum of 75 mg per injection for the first two s.c. doses. In patients with eGFR <30 mL/min/1.73 m^2, regardless of age, the s.c. doses are given once every 24 hours.	
UFH	60 IU/kg i.v. bolus with a maximum of 4000 IU followed by an i.v. infusion of 12 IU/kg with a maximum of 1000 IU/hour for 24–48 hours. Target aPTT: 50–70 s or 1.5 to 2.0 times that of control to be monitored at 3, 6, 12 and 24 hours.	
Fondaparinux (only with streptokinase)	2.5 mg i.v. bolus followed by a s.c. dose of 2.5 mg once daily up to 8 days or hospital discharge.	

IF HE WAS ON MAINTANANCE DOSE OF ASA DO YOU RELOAD ASA AGAIN

1. YES

2. NO

PASS THE TORCH

SCAI Expert Consensus Statement:

Evaluation,Management, and Special Considerations of Cardio-OncologyPatients in the Cardiac Catheterization Laboratory

Catheterization and Cardiovascular Interventions 87:E202–E223 (2016)

For platelet counts <30,000/mL, revascularization and DAPT should be decided after a preliminary multidisciplinary evaluation (interventional cardiology/oncology/hematology) and a risk/benefit analysis.

Aspirin administration may be used when platelet counts are >10,000/mL.

DAPT with clopidogrel may be used when platelet counts 30,000–50,000/mL. Prasugrel, ticagrelor and IIB-IIIA inhibitors should not be used in patients with platelet counts <50,000.

If platelet counts are <50,000, the duration of DAPT may be restricted to 2 weeks following PTCA alone, 4 weeks after bare-metal stent (BMS), and 6 months after second or third generation drug-eluting stents (DES) if optimal stent expansion was confirmed by IVUS or OCT .

There is no minimum platelet count to perform a diagnostic coronary angiogram.

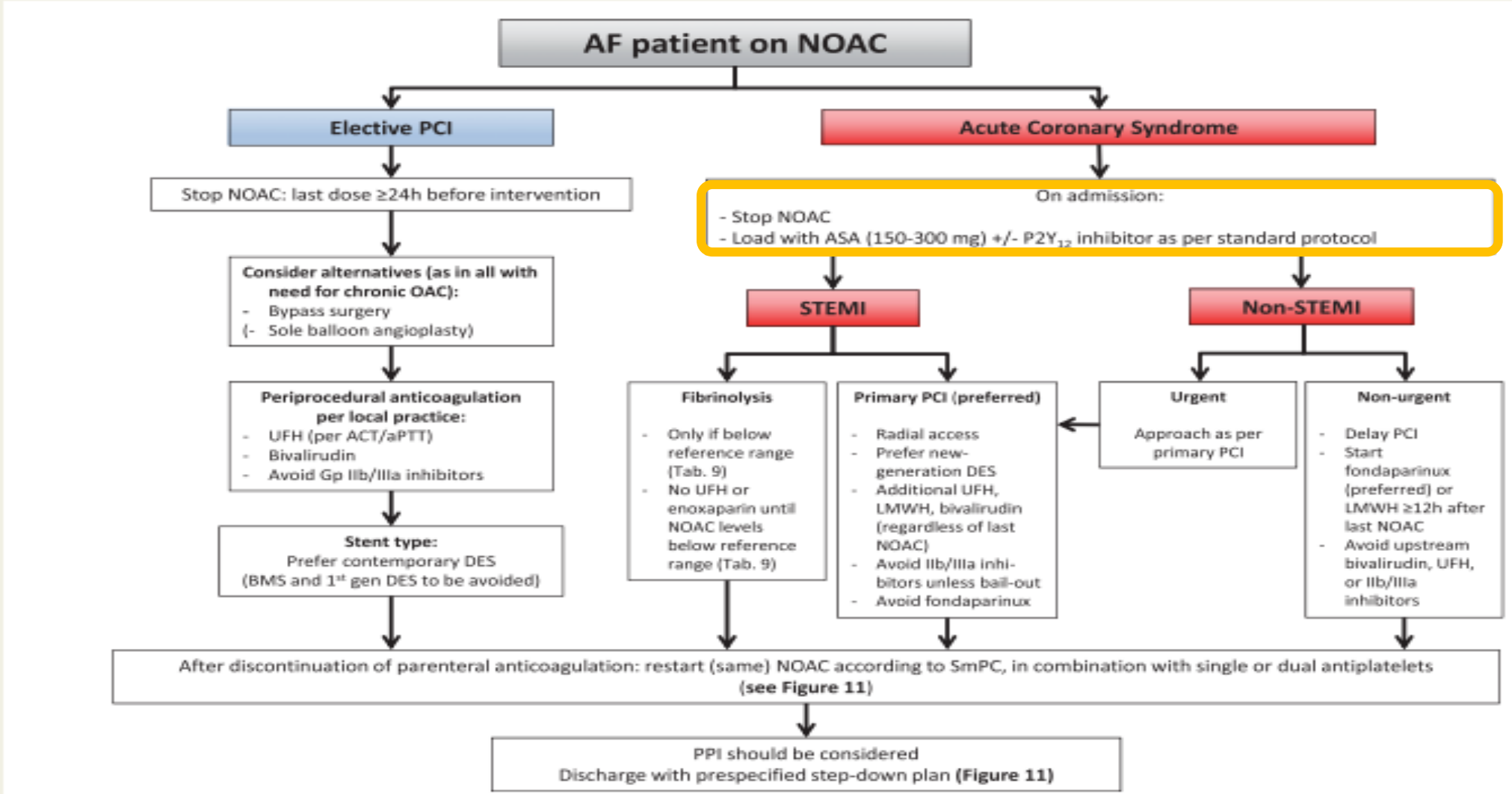
PASS THE TORCH

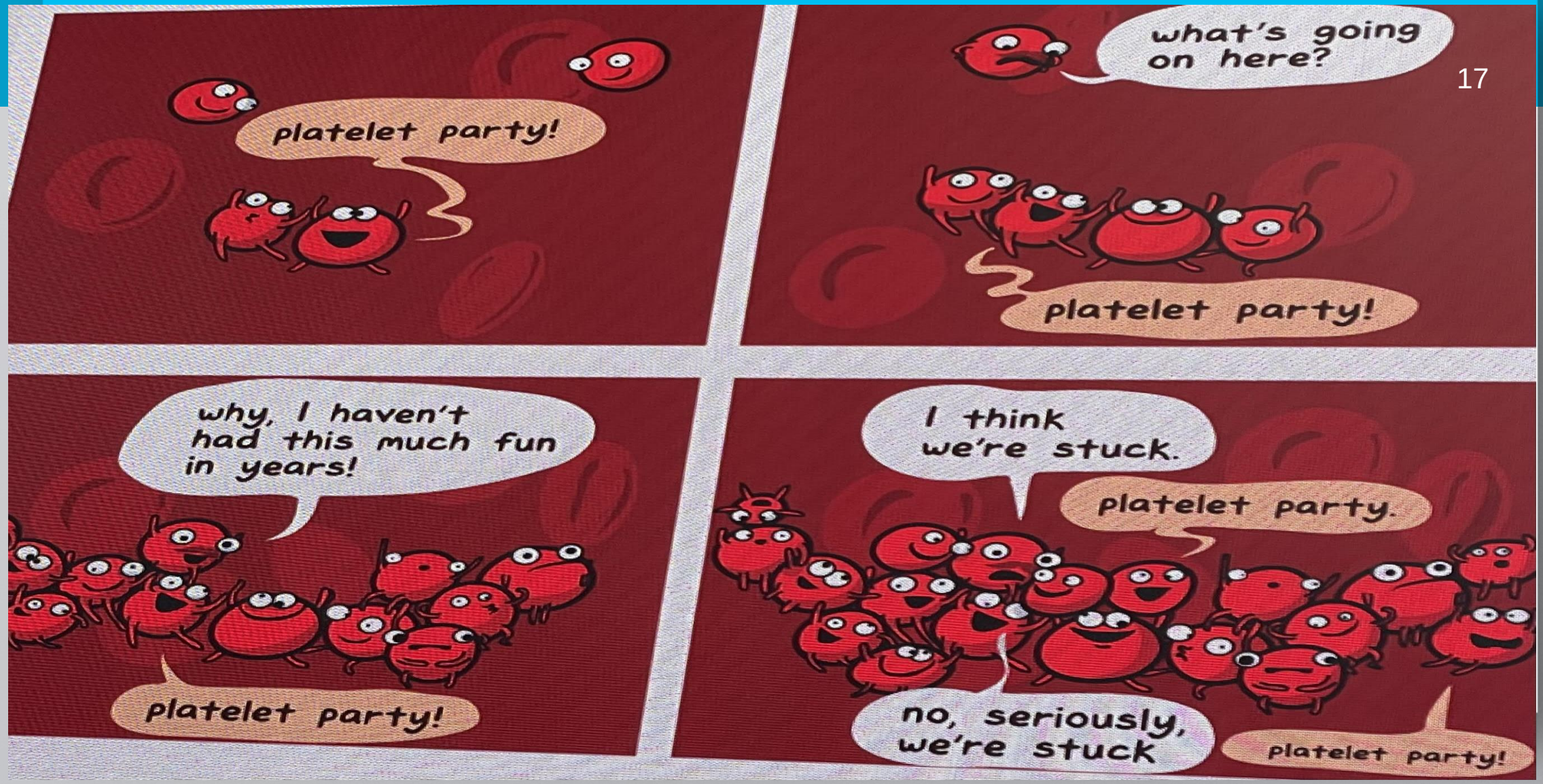
IF HE IS ON RIVAROXABAN 20mg ONCE DAILY BECAUSE OF TRANSIENT AF

WHAT IS YOUR PLAN FOR LOADING OF ANTI PLATLET ?

1. Load and then maintenance
2. Order with no loading dose
3. Wait for loading until 12 hours of last dose of RIVA

PASS THE TORCH




platelet party!
what's going on here?
platelet party!
why, I haven't had this much fun in years!
platelet party!
I think we're stuck.
platelet party.
no, seriously, we're stuck
platelet party!

GAMES OF THRONES

	COR	LOE
Antiplatelet therapy		
Aspirin		
• 162- to 325-mg loading dose	I	A
• 81- to 325-mg daily maintenance dose (indefinite)	I	A
• 81 mg daily is the preferred maintenance dose	IIa	B
With fibrinoltic		
$P2Y_{12}$ receptor inhibitors		
• Clopidogrel:	I	A
• Age ≤75 y: 300-mg loading dose	I	A (14 d)
• Followed by 75 mg daily for at least 14 d and up to 1 y in absence of bleeding		C (up to 1 y)
• Age >75 y: no loading dose, give 75 mg	I	A
• Followed by 75 mg daily for at least 14 d and up to 1 y in absence of bleeding	I	A (14 d)
		C (up to 1 y)

Table 6 Doses of antiplatelet and anticoagulant cotherapies in patients undergoing primary percutaneous coronary intervention or not reperfused

Doses of antiplatelet and parenteral anticoagulant co-therapies in primary PCI	
Antiplatelet therapies	
Aspirin	Loading dose of 150–300 mg orally or of 75–250 mg i.v. if oral ingestion is not possible, followed by a maintenance dose of 75–100 mg/day
Clopidogrel	Loading dose of 600 mg orally, followed by a maintenance dose of 75 mg/day
Prasugrel	Loading dose of 60 mg orally, followed by a maintenance dose of 10 mg/day In patients with body weight ≤60 kg, a maintenance dose of 5 mg/day is recommended Prasugrel is contra-indicated in patients with previous stroke. In patients ≥75 years, prasugrel is gen… not recommended, but a dose of 5 mg/day sh… used if treatment is deemed necessary
Ticagrelor	Loading dose of 180 mg orally, followed by a maintenance dose of 90 mg *b.i.d.*
Abciximab	Bolus of 0.25 mg/kg i.v. and 0.125 μg/kg/min infusion (maximum 10 μg/min) for 12 hours
Eptifibatide	Double bolus of 180 μg/kg i.v. (given at a 10-min interval) followed by an infusion of 2.0 μg/kg/min for up to 18 hours

https://ac… taryData/…

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

Anticoagulant therapy		
Anticoagulation is recommended for all patients in addition to antiplatelet therapy during primary PCI.	I	C
Routine use of UFH is recommended.	I	C
In patients with heparin-induced thrombocytopenia, bivalirudin is recommended as the anticoagulant agent during primary PCI.	I	C
Routine use of enoxaparin i.v. should be considered.[200–202]	IIa	A
Routine use of bivalirudin should be considered.[209,215]	IIa	A
Fondaparinux is not recommended for primary PCI.[199]	III	B

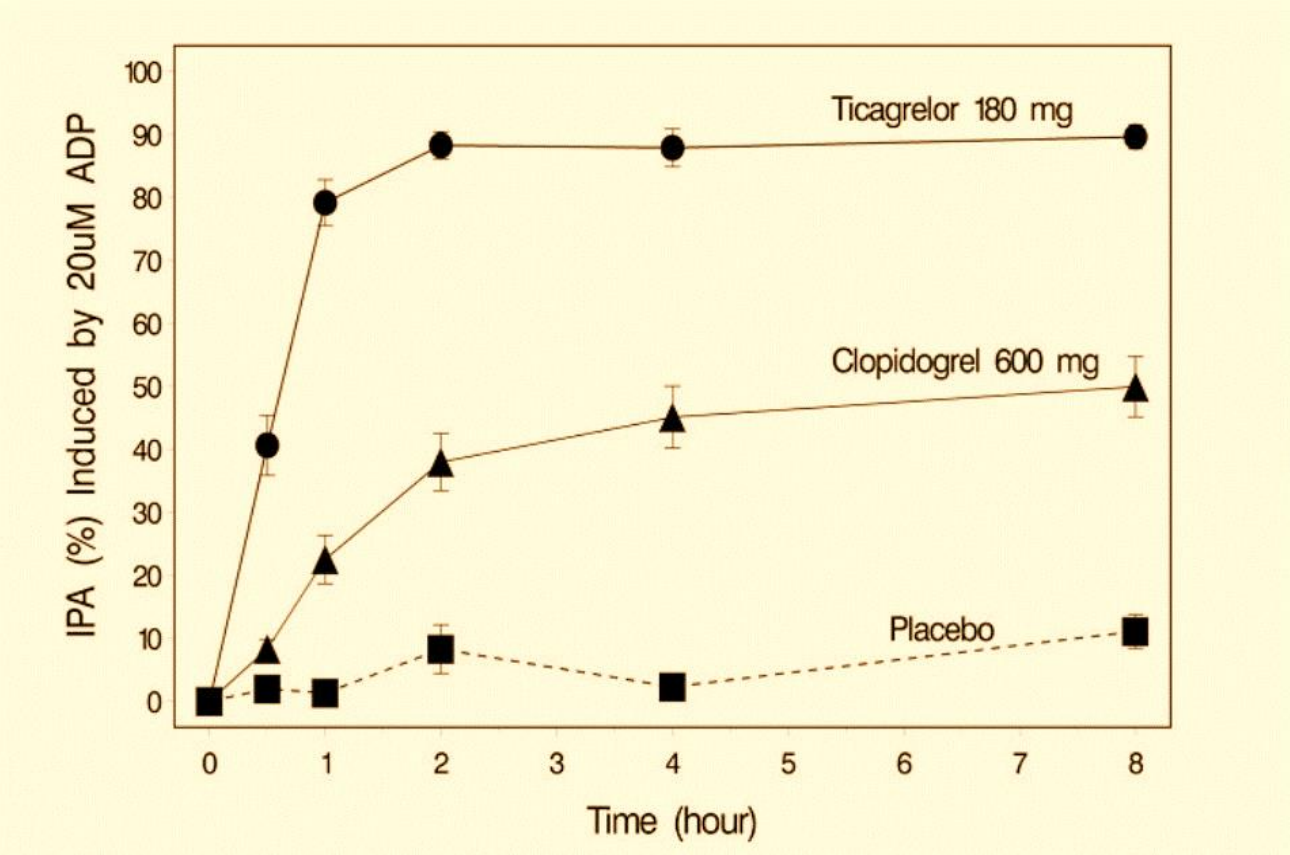
PULSE

Recommendations for antithrombotic treatment in non-ST-segment elevation acute coronary syndrome patients undergoing percutaneous coronary intervention (2)

Recommendations	Class	Level
Antiplatelet treatment (continued)		
• Ticagrelor irrespective of the planned treatment strategy (invasive or conservative) (180 mg LD, 90 mg b.i.d.).	I	B
• Clopidogrel (300–600 mg LD, 75 mg daily dose), only when prasugrel or ticagrelor are not available, cannot be tolerated, or are contraindicated.	I	C
Prasugrel should be considered in preference to ticagrelor for NSTE-ACS patients who proceed to PCI.	IIa	B
GP IIb/IIIa antagonists should be considered for bail-out if there is evidence of no-reflow or a thrombotic complication.	IIa	C

2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation (European Heart Journal 2020 - doi/10.1093/eurheartj/ehaa575)

Why Potent P2Y12i

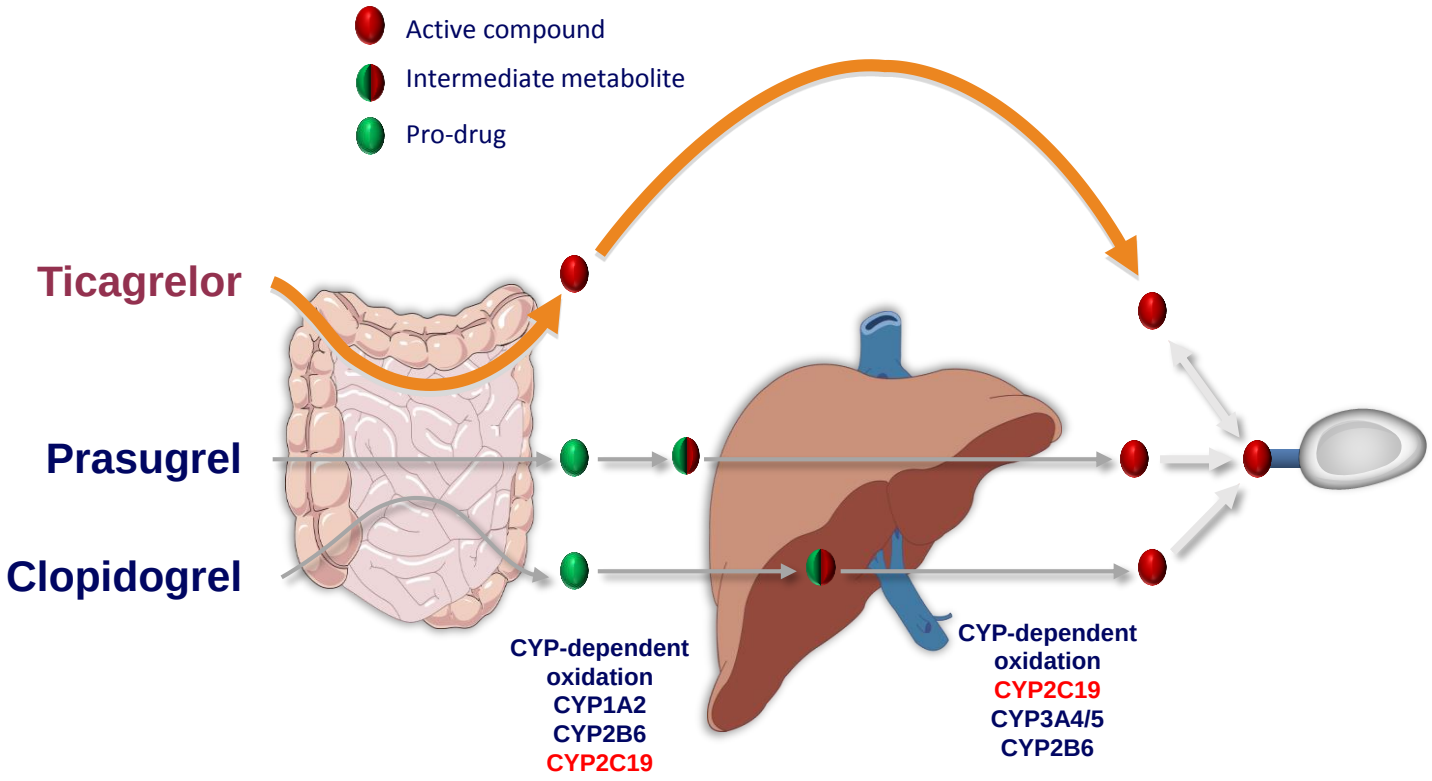


- ✓ **More Potent**
- ✓ **Faster Onset**

PULSE

Why Ticagrelor P2Y12i

No need for metabolic activation



PULSE

Why Ticagrelor P2Y12i

MOLECULAR MEDICINE REPORTS 17: 4195-4202, 2018

Prevalence of the CYP2C19*2 (681 G>A), *3 (636 G>A) and *17 (-806 C>T) alleles among an Iranian population of different ethnicities

A, CYP2C19*2

Ethnicity	CYP2C19*2 allele frequency (%)	Genotype frequency (%)			χ^2	P-value
		G/G	G/A	A/A		
Fars	15.3	72.8 (66.1-79.4)	23.9 (17.2-30.6)	3.3 (1.1-6.1)	137.4	<0.001[a]
Turk	25.0	58.2 (49.1-67.3)	33.6 (24.5-42.7)	8.2 (3.6-13.6)	41.2	<0.001[a]
Caspian	9.6	83.6 (74-91.8)	13.7 (5.5-21.9)	2.7 (0.0 -6.8)	84.1	<0.001[a]
Lure	35.0	41.3 (31.3-52.5)	47.5 (37.5-58.8)	11.3 (5.0 -18.8)	18.0	<0.001[a]
Kurd	26.3	55.8 (46.3-66.3)	35.8 (25.3-45.3)	8.4 (3.2-14.7)	32.2	<0.001[a]
Total population	21.4	63.6 (59.9-67.7)	30.1 (26-33.8)	6.3 (4.5-8.6)	269.0	<0.001[a]

PULSE

Switching
Hospital Admission

Switching between oral $P2Y_{12}$ 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.
[a]Class of recommendation.
[b]Level of evidence.
[c]Contraindications 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**

PULSE

Ticagrelor in ESC guidelines

- STEMI:
- NSTEMI:
- Stable angina:
  - **PCI** In specific high risk situations:

I

I

IIb

IF HE IS ON CLOPIDOGREL BECAUSE OF PCI ON RCA SINCE 6 MONTHS AGO, DO YOU **RELOAD** PLAVIX BEFORE FIBRINOLYTIC THERAPY?

1. **YES**
2. **NO**

PASS THE TORCH

Clopidogrel reloading for patients with acute myocardial infarction already on clopidogrel therapy

ACTION Registry-GWTG from 2009 to 2014.

Among the 12 366 patients on pre-admission clopidogrel therapy who were admitted with STEMI, 9369 (75.8%) received a loading dose. Of 39 158 patients with NSTEMI, 10 144 (25.9%) were reloaded. Reloaded patients were younger, had fewer comorbid conditions, and were more likely to be treated with primary PCI (STEMI) or an early invasive strategy (NSTEMI).

Risks of major bleeding were not significantly different between patients with and without reloading, whether presenting with STEMI (OR 0.98, 95% CI 0.85–1.13) or NSTEMI (OR 1.00, 95% CI 0.90–1.11).

Among STEMI patients, clopidogrel reloading was associated with lower risks of in-hospital mortality (OR 0.80, 95% CI 0.66–0.96), however no significant mortality difference was observed among NSTEMI patients (OR 1.13, 95% CI 0.93–1.37).

Conclusion

.We did not observe increased bleeding or mortality risk with clopidogrel reloading,

therefore reloading could be safe for most MI patients

European Heart Journal, Volume 39, Issue 3, 14 January 2018,

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PASS THE TORCH

3.

Antiplatelet therapy with fibrinolysis

$P2Y_{12}$ inhibitors after fibrinolysis

Recommendation Table 7 Recommendations for fibrinolytic therapy

Recommendations	Class[a]	Level[b]
Fibrinolytic therapy		
When fibrinolysis is the reperfusion strategy, it is recommended to initiate this treatment as soon as possible after diagnosis in the pre-hospital setting (aim for target of <10 min to lytic bolus).[206,353–355]	I	A
A fibrin-specific agent (i.e. tenecteplase, alteplase, or reteplase) is recommended.[356,357]	I	B
A half-dose of tenecteplase should be considered in patients > 75 years of age.[184]	IIa	B
Antiplatelet co-therapy with fibrinolysis		
Aspirin and clopidogrel are recommended.[340–342]	I	A

- Based on the available RCTs, there is ***insufficient evidence*** to support or refute improved outcomes with ***ticagrelor or prasugrel in patients with STEMI treated with thrombolytics***.

Ticagrelor Versus Clopidogrel in Patients With STEMI Treated With Fibrinolysis

TREAT Trial

Otavio Berwanger, MD, PhD,[a] Renato D. Lopes, MD, MHS, PhD,[b,c] Diogo D.F. Moia, PharmD,[a] Francisco A. Fonseca, MD, PhD,[c] Lixin Jiang, MD, PhD,[d] Shaun G. Goodman, MD, MSc,[e] Stephen J. Nicholls, MD, PhD,[f] Alexander Parkhomenko, MD, PhD,[g] Oleg Averkov, MD, PhD,[h] Carlos Tajer, MD, PhD,[i] Germán Malaga, MD,[j] Jose F.K. Saraiva, MD, PhD,[k] Helio P. Guimaraes, MD, PhD,[a] Pedro G.M. de Barros e Silva, MD, MHS, PhD,[a] Lucas P. Damiani, MSc,[a] Renato H.N. Santos, Stat,[a] Denise M. Paisani, PhD,[a] Tamiris A. Miranda, PharmD,[a] Nanci Valeis, Dr,[a] Leopoldo S. Piegas, MD, PhD,[l] Christopher B. Granger, MD, PhD,[b] Harvey D. White, MD, DSc,[m] Jose C. Nicolau, MD, PhD[n]

Guideline recommendations

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).

4.

Ticagrelor Considerations

Morphine, vomiting, and dyspnea

Ticagrelor and Morphine

Pain may be related to ***larger infarct*** .

- *severe pain also **delays** **gastric emptying** , which diminish the effect of p2y12 .*

*The most important **side effect of morphine** is **vasodilation** **especially in pulmonary vessels,** which is beneficial for ACS by reducing preload.*

- *But when morphine is washed out , **suddenly preload is increased and patient is still in critical moments** , when morphine is washing out , some other medication with pulmonary vessels vasodilation is administered .*

Impact of Morphine Treatment With and Without Metoclopramide Coadministration on Ticagrelor-Induced Platelet Inhibition in Acute Myocardial Infarction

The Randomized MonAMI Trial

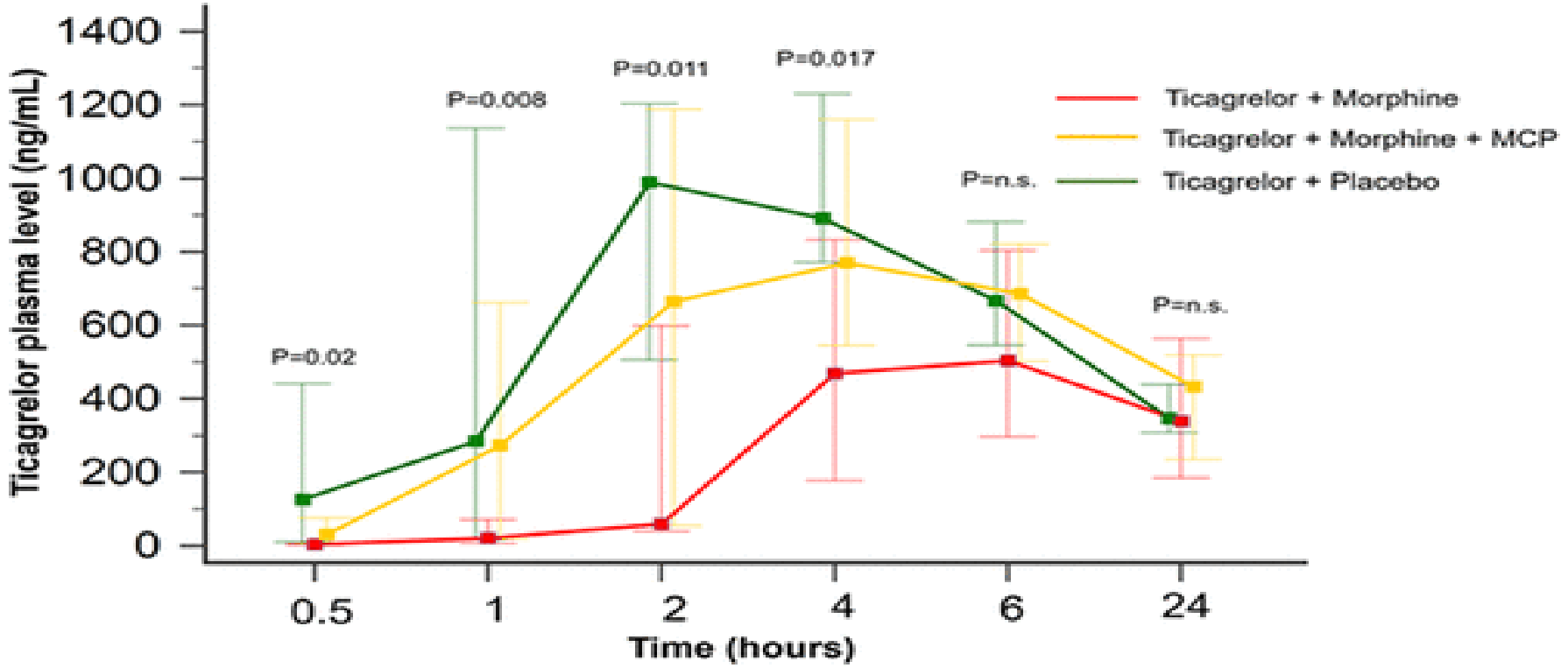
Mohammed Saad, Roza Meyer-Saraei, Suzanne de Waha-Thiele, Thomas Stiermaier, Tobias Graf, Georg Fuernau, Harald F. Langer, Thomas Kurz, Janine Pöss, Jörg Barkhausen, Steffen Desch, Ingo Eitel ✉ and **Holger Thiele** ✉

Originally published 20 Apr 2020 | https://doi.org/10.1161/CIRCULATIONAHA.119.042816 | Circulation. 2020;141:1354–1356

is corrected by

Other version(s) of this article

Plasma levels of ticagrelor 0.5, 1, 2, 4, 6, and 24 hours after the administration of a 180-mg loading dose of ticagrelor



Morphine and Ticagrelor

- *As **vomiting is a common adverse effect** of opioids, and moreover, opioids are associated with **reduced platelet inhibition**.*

- This analysis supports the search for ***alternative pain relievers for opioids*** in the acute phase of STEMI. ***Acetaminophen*** may be a suitable alternative, as presented in the main analysis of the ON-TIME 3 trial.

- ***If opioids are still being considered** (eg, persistent pain despite adequate treatment), use **of metoclopramide might help to limit** the adverse effects of opioids on platelet inhibition*.

Metoclopramide Administration as a Strategy to Overcome MORPHine-ticagrelOr Interaction in PatientS with Unstable Angina PectorIS-The METAMORPHOSIS Trial.

Conclusion:, the co-administration of metoclopramide in patients presenting with unstable angina and treated with morphine, has a *beneficial effect on the of ticagrelor* and its metabolite; however, its impact on ST-elevation myocardial infarction patients requires further investigation.

*** ***morphine +/- prokinetic and Paracetamol (acetaminophen)***

a GP IIb/IIa antagonist, or cangrelor, to cover an 8-hour delay in its onset of action when an opiate is given concurrently

Thromb Haemost. 2018 Dec;118(12):2126-2133.

Morphine and Ticagrelor Interaction in Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction: ATLANTIC-Morphine

Conclusions: Morphine-treatment was associated with ***increased GP IIb/IIIa inhibitor use, less pre-PCI TIMI 3 fow, and more bleeding***.

Judicious morphine use is advised with non-opioid analgesics preferred for non-severe acute pain.

Am J Cardiovasc Drugs. 2019 Apr;19(2):173-183.

TCT ۲۰۲۱

Lidocaine Less Likely Than Fentanyl to Blunt P2Y12 Inhibitors in the Cath Lab

LOCAL is the latest study to show that fentanyl affects ticagrelor absorption, making the case for lidocaine/lignocaine instead.

by L.A. McKeown | SEPTEMBER 07, 2021

If 40 min after loading, he has vomiting, what is your plan?

- 1. Need to reload
- 2. No need to reload

Is there any timetable cut-off?

Impact of vomiting on P2Y12 platelet inhibition in patients with ST-elevation myocardial infarction: A prespecified subanalysis of the ON-TIME 3 trial

Anne H. Tavenier, MD [a], Renicus S. Hermanides, MD, PhD [a], Jan Paul. Ottervanger, MD, PhD [a], Svetlana V. Belitser, MSc [b], Olaf. H. Klungel, PharmD, PhD [b], and Arnoud W.J. van 't Hof, MD, PhD [a,c,d], on behalf of the ON-TIME 3 investigators *Zwolle, The Netherlands*

Conclusions

- This analysis presented that **vomiting** in the **early hours of STEMI** was associated with lower plasma levels of ticagrelor and ***higher levels of platelet reactivity***.
- This analysis ***supports*** **reloading** with a ticagrelor loading dose and/or treatment with intravenous platelet inhibitors, such as cangrelor or GPIs, in STEMI patients who vomit.

- In ***vomiting patients***, it is necessary to record ***how much time*** has passed since the administration of oral drugs and to describe ***the possible presence of undissolved tablets in vomit*** . In such cases, ***DAPT re-loading should be considered individually.***

- *Moreover, **crushing ticagrelor tablets** or **simultaneous intravenous metoclopramide** administration may reduce this side effect. Both strategies have been proven to **increase the availability of the drug** and its antiplatelet effect .*
- *Recently **available ticagrelor in soluble tablets** could also be administered in vomiting or unconscious patients.*

NEWS - INTERVENTIONAL | TCT 2020

No Reperfusion Benefit From Crushed Prasugrel Prior to PCI: COMPARE CRUSH

The findings contrast with observations that early dosing with crushed pills improves platelet inhibition over integral tablets.

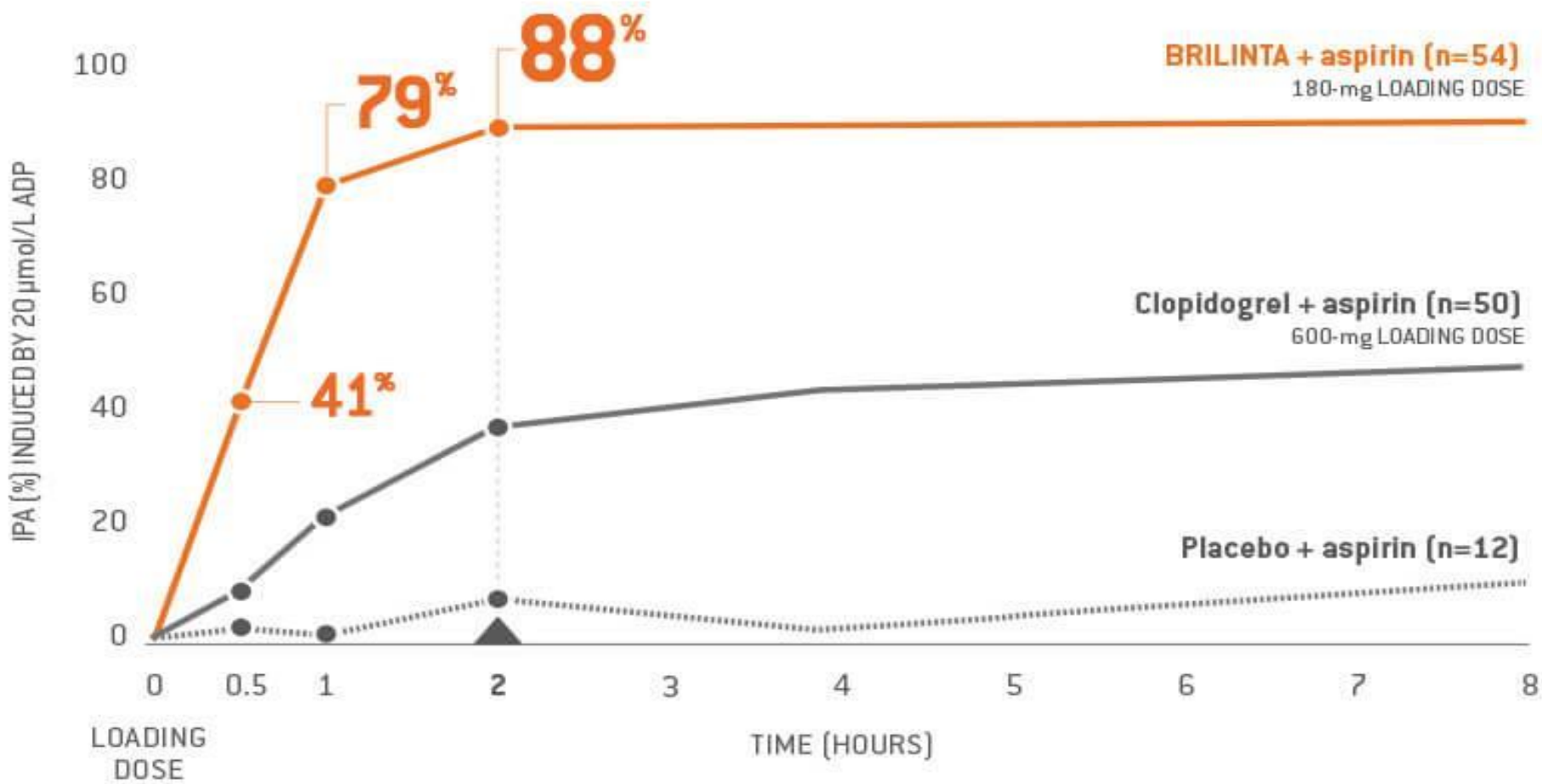
By L.A. McKeown | October 14, 2020

Giving ***crushed prasugrel tablets in the ambulance to STEMI patients with planned primary PCI*** does ***not improve*** reperfusion rates compared with giving the tablets whole, according to results of the COMPARE CRUSH trial.

No Differences in Clinical Endpoints

Table 1. Comparison of the pharmacokinetics of different antiplatelet therapy.

Drug	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor	Tirofiban	Eptifibatide	Abciximab	Voraxapar
Prodrug	Yes	Yes	No	No	No	No	No	No
Route	Oral	Oral	Oral	Intravenous	Intravenous	Intravenous	Intravenous	Oral
Mechanism of Action	$P2Y_{12}$ inhibition	$P2Y_{12}$ inhibition	$P2Y_{12}$ inhibition	$P2Y_{12}$ inhibition	GPIIb/IIIa inhibition[3]	GPIIb/IIIa inhibition[4]	GPIIb/IIIa inhibition[5]	PAR -1 inhibition
Onset of Action[2]	2–6 h	30 mins	30 mins	2 mins	<15 mins	<15 mins	<10 mins	1–2 h
Duration of Action	3–10 days	7–10 days	3–5 days	1–2 h	4–8 h	4–8 h	24–48 h	2–3 weeks[1]
Withdrawal before surgery	5 days	7 days	5 days	1 h	8 h	8 h	>48 h[6]	–
Loading Dose[7]	300–600 mg	60 mg	180 mg	30 µg/kg	25 µg/kg	180 mcg/kg	0.25 mg/kg	–
Regular Dose[7]	75 mg OD	10 mg OD	90 mg BD	4 µg/kg/min infusion	0.15 µg/kg/min infusion	2 µg/kg/min infusion	0.125 µg/kg/min infusion	2.5 mg OD


88%
79%
41%
BRILINTA + aspirin (n=54)
180-mg LOADING DOSE
Clopidogrel + aspirin (n=50)
600-mg LOADING DOSE
Placebo + aspirin (n=12)
IPA (%) INDUCED BY 20 µmol/L ADP
100
80
60
40
20
0
0
0.5
1
2
3
4
5
6
7
8
LOADING DOSE
TIME (HOURS)

Ticagrelor and Dyspnea

Dyspnea in PLATO

Dyspnoea in the PLATO trial	BRILIQUE	Clopidogrel	*P* Value
Incidence of dyspnoea adverse events (%)	13.8	7.8	<0.001
Patients who discontinued treatment due to dyspnoea (%)	0.9	0.1	<0.001

- BRILIQUE-associated dyspnoea was mostly mild to moderate in severity and did not reduce efficacy
- Most events were reported as single episode occurring early after starting treatment
- Not associated with new or worsening heart or lung disease
- In 2.2% of patients, investigators considered dyspnoea causally related to treatment with BRILIQUE
- *Label precautions and warnings: use with caution in patients with history of asthma and COPD*

Clopidogrel= 7.8%

- Discontinuation= 0.1%

Ticagrelor= 13.8%

- Discontinuation= 0.9%

Dyspnea

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.

Archives of Academic Emergency Medicine. 2020; 8(1): e42

BRIEF REPORT

One-Month Outcomes of Cases Receiving Ticagrelor after Percutaneous Coronary Intervention; a Case Series

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Received: January 2020; Accepted: February 2020; Published online: 30 March 2020

Our experience

Total case	108
Age	Mean:60 (37-78)
Male	65 (60%)
Female	43 (40%)
STEMI	45 (41%)
UA	27 (25%)
NSTEMI	36 (34%)
HTN	30 (28%)
DM	36 (34%)
Dyspnea	29 (27%)
Mild	20 (24%)
Severe	3 (2%)
Stent Thrombosis	0
Bleeding	
ICH	1 (0. 9%)
Hematuria	2 (1.8%)
Skin (rash)	1 (0. 9%)
BradyCardia	-
Discontinue	6 (5.5%)
ICH	1
SEVERE DYSPNEA	3
LV Clot	1
Skin rash(diffuse)	1

Ticagrelor-related dyspnea and altitude

Journal of International Medical Research

Impact Factor: **1.6** / 5-Year Impact Factor: **1.9**

JOURNAL HOMEPAGE

SUBMIT PAPER

Open access | Research article | First published online April 11, 2023

Effect of altitude on ticagrelor-induced dyspnea in patients with acute coronary syndrome

Gonenc Kocabay, Tarik Kivrak, [...], and Mehmet Birhan Yilmaz +6 View all authors and affiliations

All Articles | https://doi.org/10.1177/03000605211065932

Findings

- Patients with de novo ACS
- Admitted to two centers at a low altitude (18 and 25 m, n = 65) and two centers at a high altitude (1313 and 1041 m, n = 136).
- There were no significant differences in cardiac risk factors, concurrent medications, or procedural variables between the two groups.
- **Dyspnea developed during hospitalization in 53 (38%) patients from *high-altitude* centers and in 13 (20%) patients from *low-altitude* centers (66 patients represented 32% of the total ACS cohort).**

Diagnostic algori

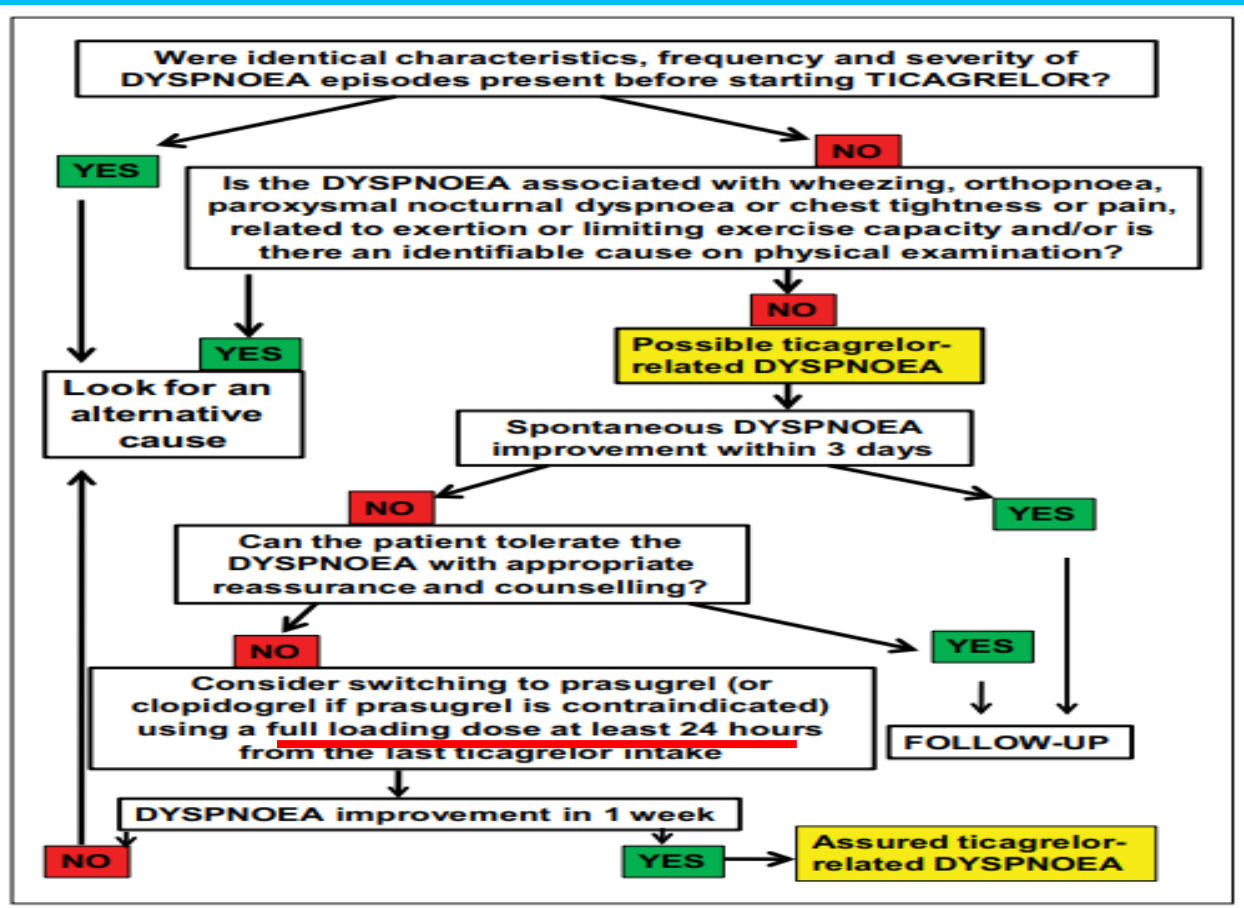


Figure 1. Dyspnoea diagnostic flow-chart.

Ticagrelor in patients with Pericarditis

- ***Probable symptoms of pericarditis***

ESC European Society of Cardiology
European Heart Journal (2017) **00**, 1–8
doi:10.1093/eurheartj/ehx393

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

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

Anti-inflammatory therapy is recommended in post-STEMI pericarditis as in post-cardiac injury pericardial syndromes for symptom relief and reduction of recurrences. Aspirin is recommended as first choice of anti-inflammatory therapy post-STEMI at a dose of 500–1000 mg every 6–8 h for 1–2 weeks, decreasing the total daily dose by 250–500 mg every 1–2 weeks in keeping with 2015 ESC Guidelines for the diagnosis and management of pericardial diseases.[57] Colchicine is recommended as first-line therapy as an adjunct to aspirin/non-steroidal anti-inflammatory drug therapy (3 months) and is also recommended for the recurrent forms (6 months).[57] Corticosteroids are not recommended due to the risk of scar thinning with aneurysm development or rupture.[57] Pericardiocentesis is rarely required, except for cases of haemodynamic compromise with signs of tamponade.

Coronary Heart Disease

Ticagrelor Compared With Clopidogrel by Geographic Region in the Platelet Inhibition and Patient Outcomes (PLATO) Trial

Kenneth W. Mahaffey, MD; Daniel M. Wojdyla, MS; Kevin Carroll, MS; Richard C. Becker, MD; Robert F. Storey, MD, DM; Dominick J. Angiolillo, MD, PhD; Claes Held, MD, PhD; Christopher P. Cannon, MD; Stefan James, MD, PhD; Karen S. Pieper, MS; Jay Horrow, MD; Robert A. Harrington, MD; Lars Wallentin, MD, PhD; on behalf of the PLATO Investigators

WARNING: (A) BLEEDING RISK, and (B) ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

See full prescribing information for complete boxed warning.

BLEEDING RISK

- **BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal bleeding. (5.1, 6.1)**
- **Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage. (4.1, 4.2)**
- **Do not start BRILINTA in patients undergoing urgent coronary artery bypass graft surgery (CABG). (5.1, 6.1)**
- **If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events. (5.4)**

ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

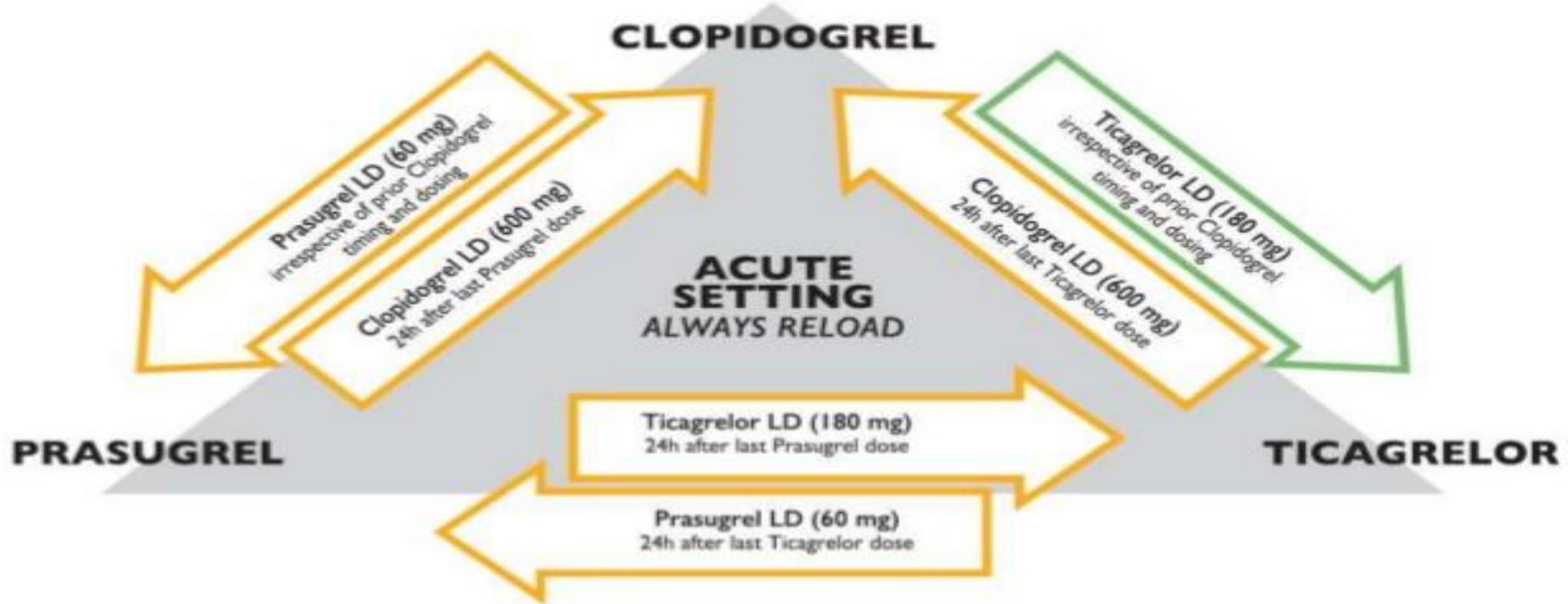
- **Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. (2.1, 5.2, 14.1)**

DESCALTE & LOAD CLOPIDOGREL

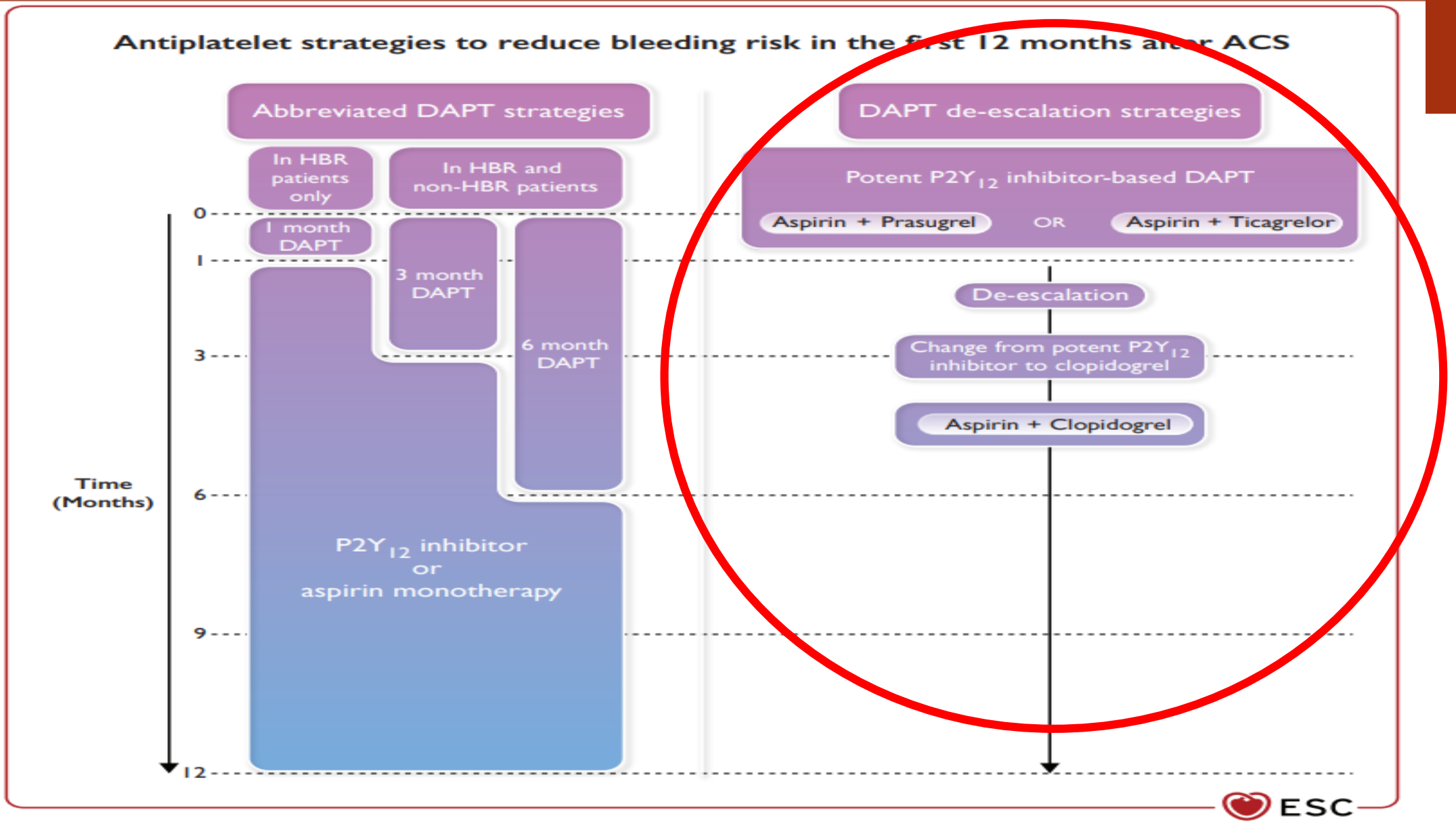
PLAN : High dose ASA + clopidogrel

Algorithm: Switching Between Oral P2Y12 Inhibitors In Acute Setting

ESC GUIDELINES

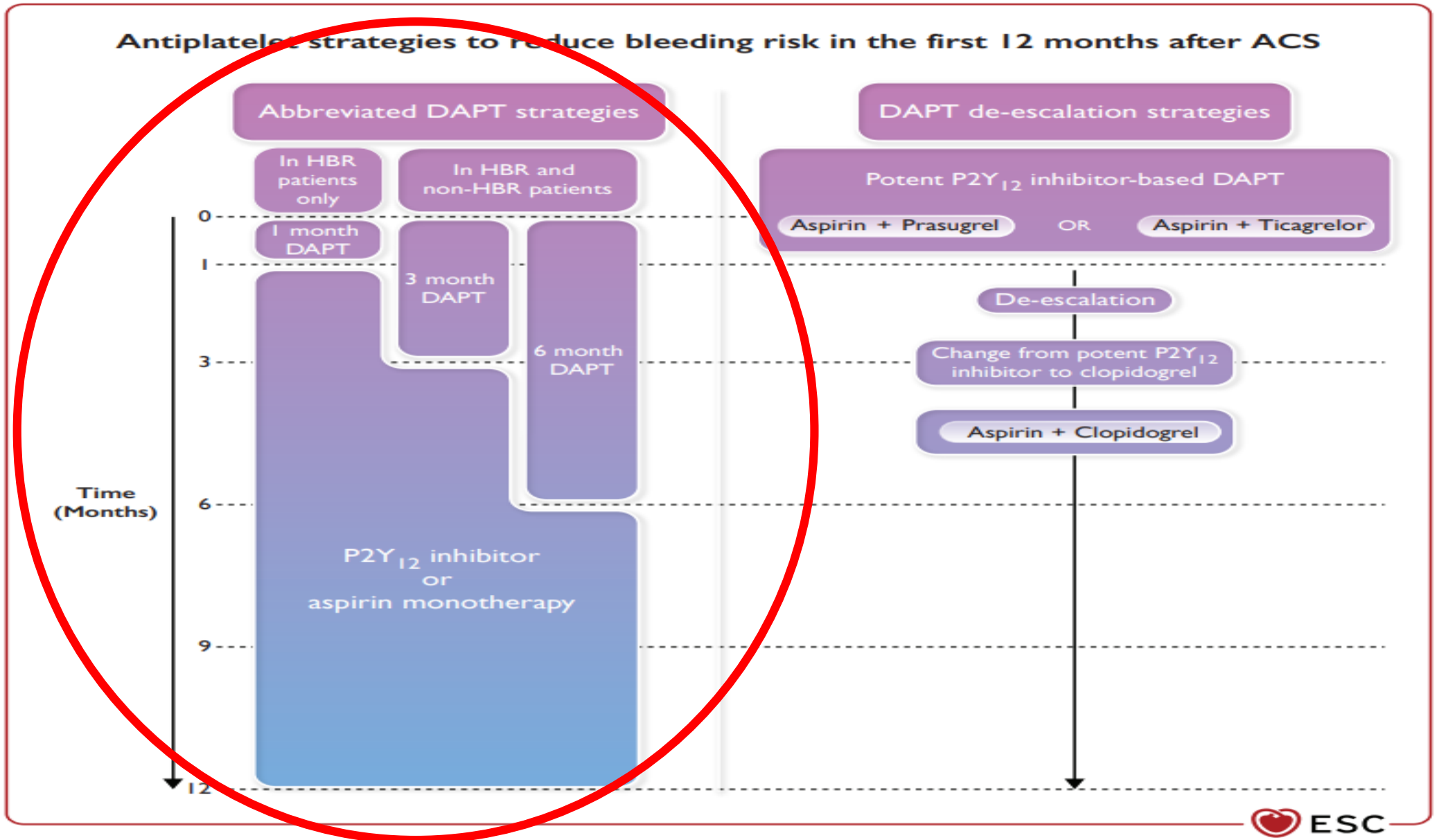


European Heart Journal (2017) 0, 1–48


Antiplatelet strategies to reduce bleeding risk in the first 12 months after ACS
Abbreviated DAPT strategies
In HBR patients only
In HBR and non-HBR patients
1 month DAPT
3 month DAPT
6 month DAPT
P2Y12 inhibitor or aspirin monotherapy
DAPT de-escalation strategies
Potent P2Y12 inhibitor-based DAPT
Aspirin + Prasugrel
OR
Aspirin + Ticagrelor
De-escalation
Change from potent P2Y12 inhibitor to clopidogrel
Aspirin + Clopidogrel
Time (Months)
0
1
3
6
9
12
ESC

Guideline recommendations

Recommendations	Class[a]	Level[b]
Shortening/de-escalation of antithrombotic therapy		
In patients who are event-free after 3–6 months of DAPT and who are not high ischaemic risk, single antiplatelet therapy (preferably with a $P2Y_{12}$ receptor inhibitor) should be considered.[264,268–271,273,274,276,313,320]	IIa	A
De-escalation of $P2Y_{12}$ receptor inhibitor treatment (e.g. with a switch from prasugrel/ticagrelor to clopidogrel) may be considered as an alternative DAPT strategy to reduce bleeding risk.[279–282,321,322]	IIb	A
In HBR patients, aspirin or $P2Y_{12}$ receptor inhibitor monotherapy after 1 month of DAPT may be considered.[276,313]	IIb	B
De-escalation of antiplatelet therapy in the first 30 days after an ACS event is not recommended.[238,323]	III	B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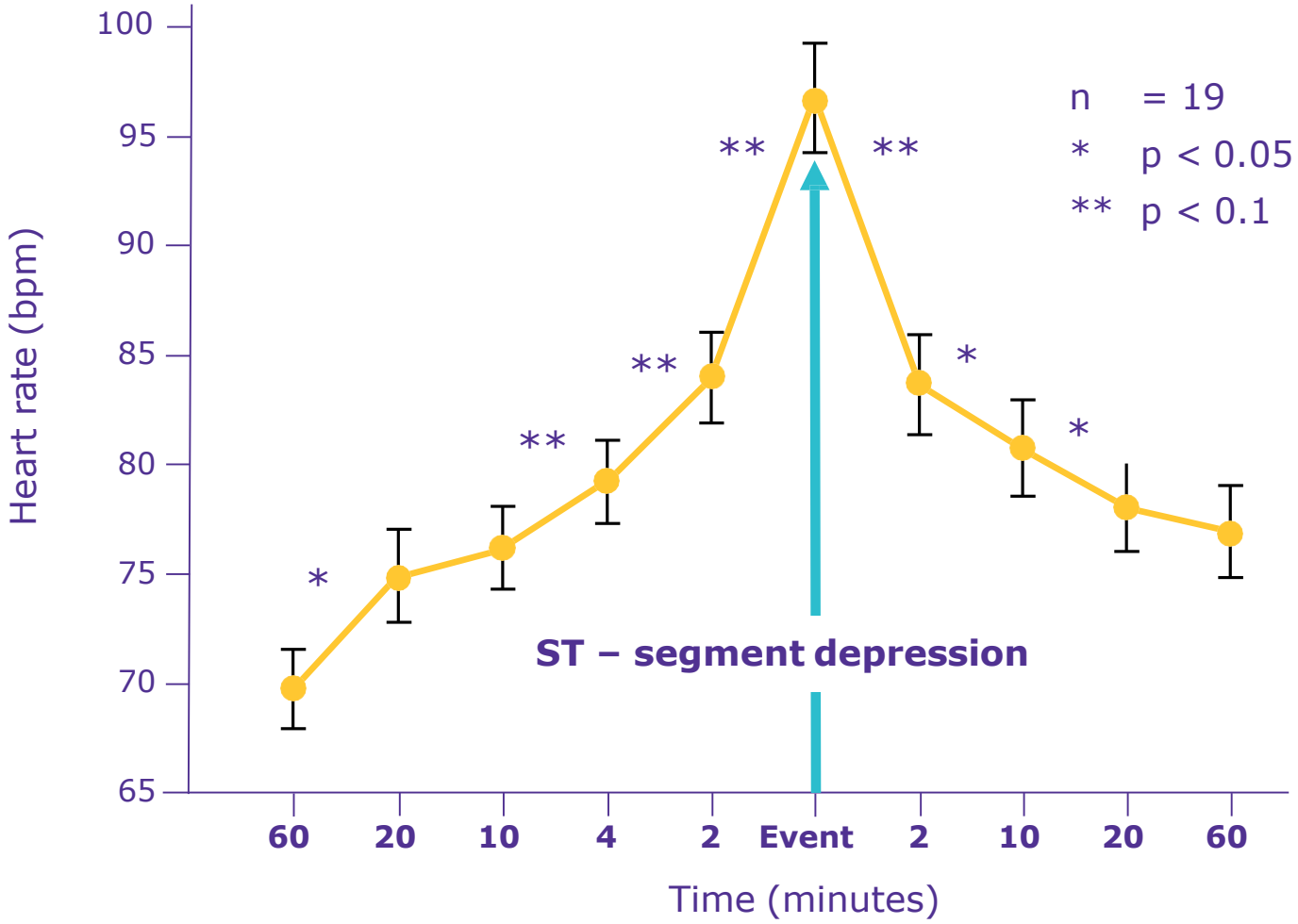
Change from potent P2Y12 inhibitor to clopidogrel
Aspirin + Clopidogrel
Time (Months)
0
1
3
6
9
12
ESC

BETA BLOCKERS

Elevated heart rate is associated with acute ischemic events in patients with CHD[1]



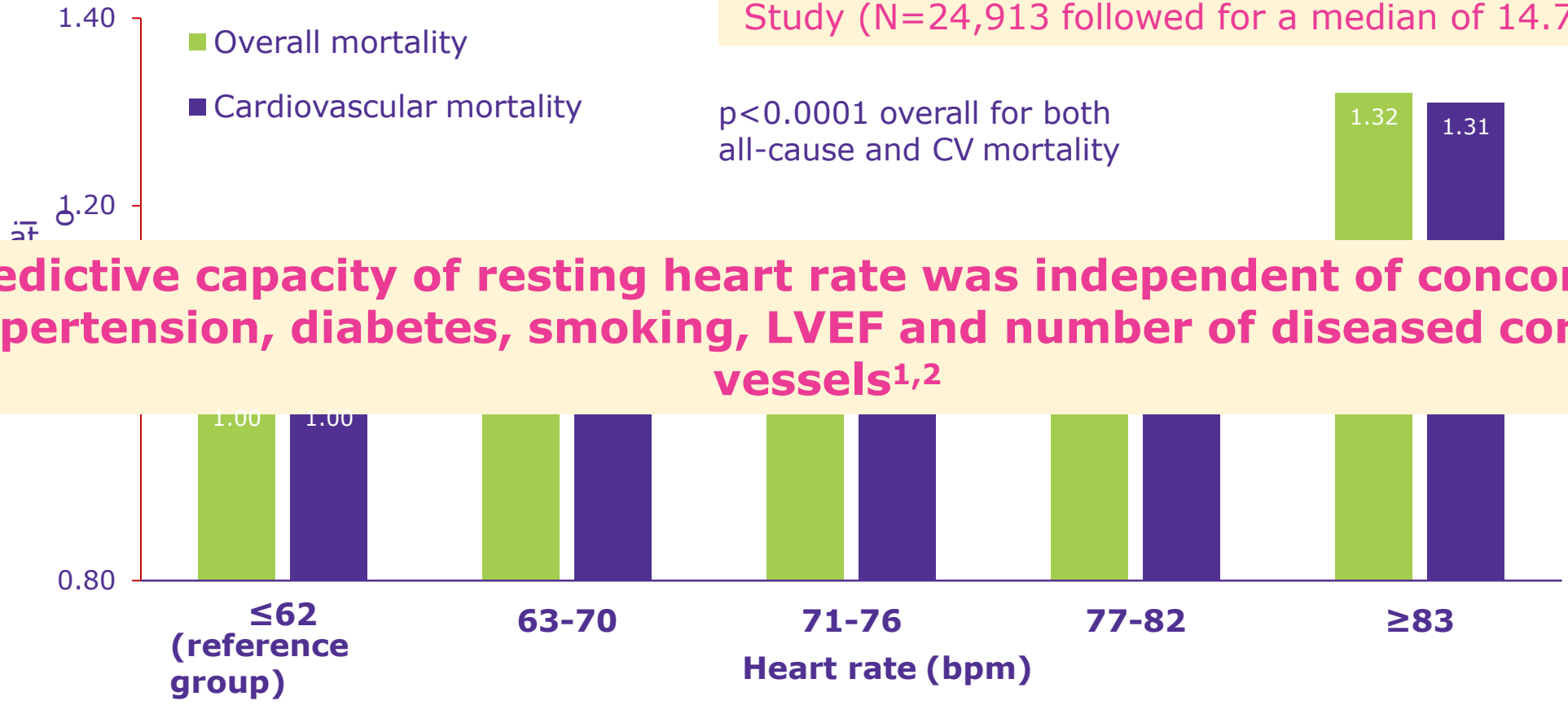
Observational study of 19 men with stable CHD undergoing 48-hour ambulatory ECG monitoring[1]

Heart rate was significantly elevated in the hour proceeding an acute ischemic event[1]

1. Kop WJ et al. J Am Coll Cardiol. 2001;38(3):742-9.

Sympathetic overdrive increases the risk of cardiovascular and all-cause mortality in patients with CHD[1,2]

Long-term follow-up of the Coronary Artery Surgery Study (N=24,913 followed for a median of 14.7 years)[2]



Predictive capacity of resting heart rate was independent of concomitant hypertension, diabetes, smoking, LVEF and number of diseased coronary vessels[1,2]

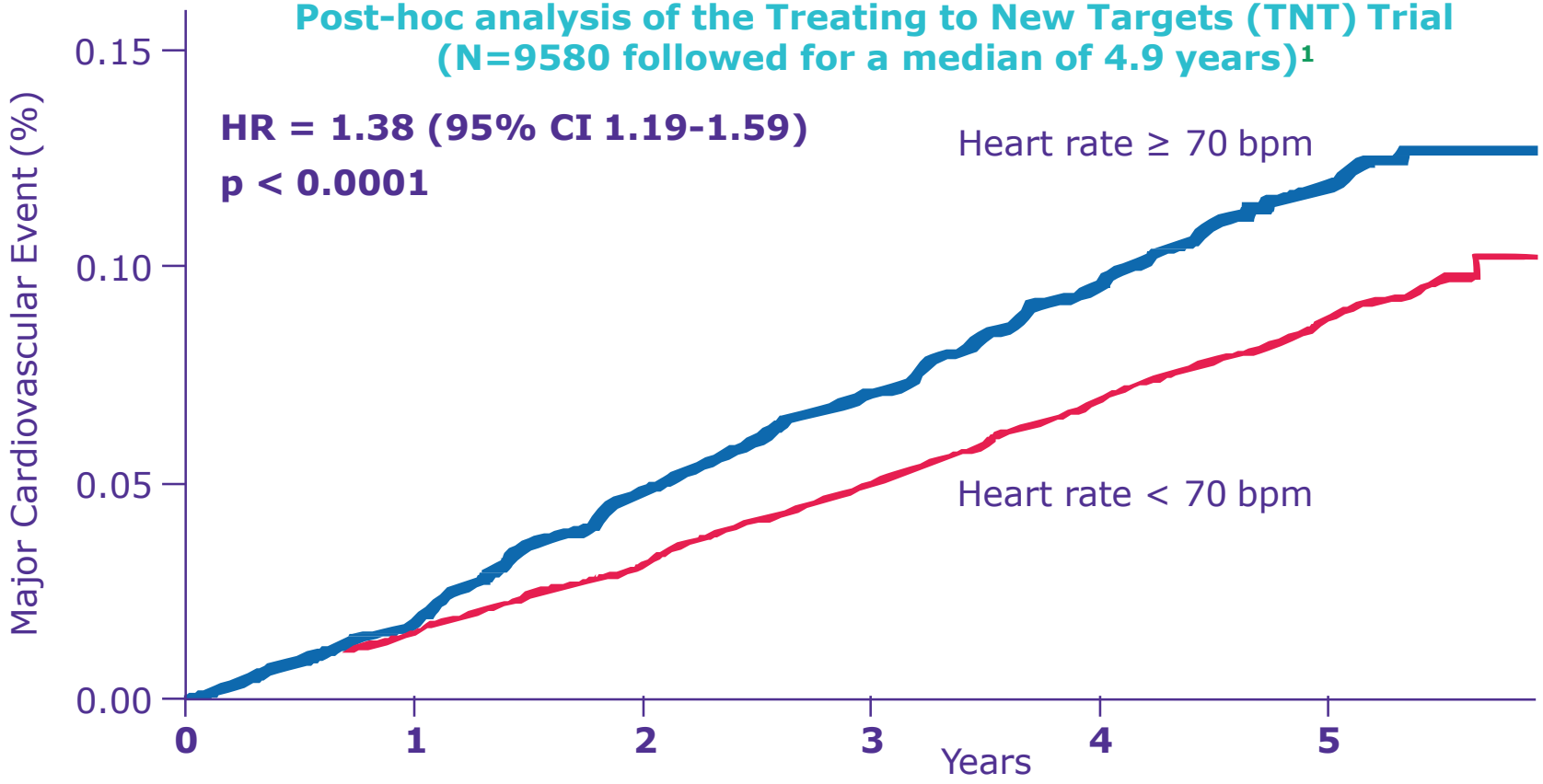
1. Fox K et al. J Am Coll Cardiol. 2007;50:823-30
2. Diaz A et al. Eur Heart J. 2005;26:967-74.

Sympathetic overdrive increases the risk of major cardiovascular events in patients with stable CHD[1]

- **A heart rate ≥70 beats/min was associated with a significantly higher incidence of major cardiovascular events during follow-up than a heart rate of <70 beats/min[1]**

Every 10-beats/min increase in heart rate increased the risk of a major cardiovascular event by 8%[1]

Post-hoc analysis of the Treating to New Targets (TNT) Trial (N=9580 followed for a median of 4.9 years)[1]



N at risk by baseline heart rate group

≥ 70 bpm	2007	1969	1901	1842	1778	966
< 70 bpm	7573	7450	7294	7110	6916	3533

1. Ho JE et al. Am J Cardiol. 2010;105:905-11.

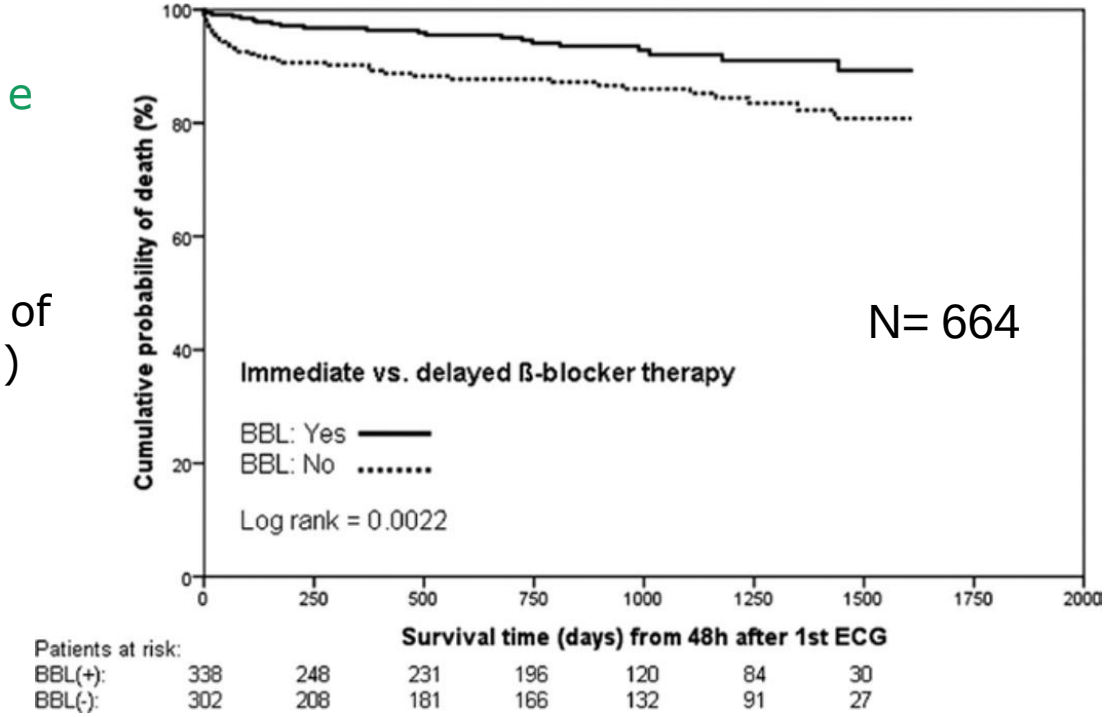
Benefit of immediate beta-blocker therapy on mortality in patients with ST-segment elevation myocardial infarction

30-Day & 1-Year All-Cause and CV Mortality in Patients with STEMI lower in the group of: immediate β-blockade

Analyzing all-cause mortality with regard to different reperfusion strategies, the decrease of mortality of the immediate β-blocker group was consistent in the group of patients who were treated with primary PCI (p = 0.009)

Interventions:
Oral administration of 2.5 mg bisoprolol:

- within 30 min after the first ECG: **immediate β-blockade** or
- 24 hours after acute myocardial infarction: **delayed β-blockade**



Conclusion: Immediate β-blocker administration with low-dose bisoprolol in the emergency setting is associated with a reduction of all-cause and cardiovascular mortality in patients with ST-segment elevation myocardial infarction and seems to be superior to a delayed β-blockade in our patient cohort

Hirschel MM et al. Crit Care Med 2013; 41:1396–1404

Effect of early bisoprolol administration on ventricular arrhythmia and cardiac death in patients with non-ST elevation myocardial infarction

Low-dose oral bisoprolol (1.25–2.5 mg)

- within 4 h: **Early Group**
- within 5–24 h: **Late Group**

N=399

The early group had significantly fewer ventricular arrhythmias cardiac deaths and consequently MACE than the late group

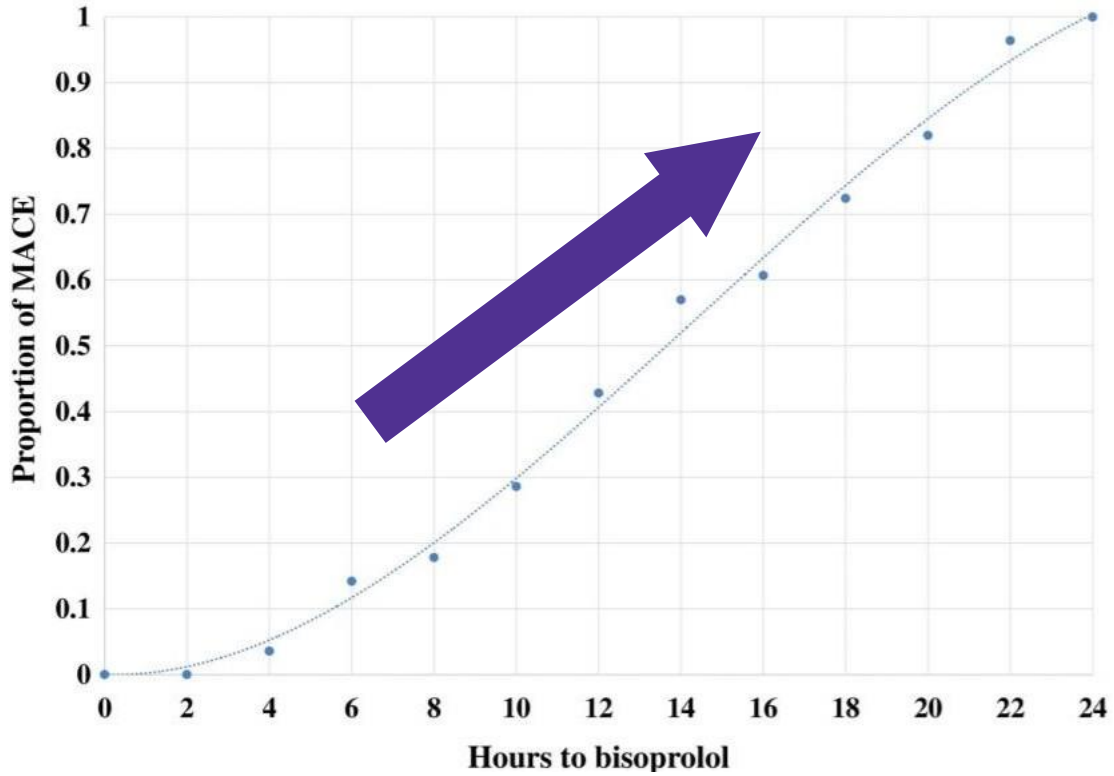
Patient outcome in early and late group

Outcome	Early group (n=99)	Late group (n=300)	p Value
Ventricular arrhythmia (%)	1.01	6.6	**0.036**
Cardiac death (%)	0	4.33	**0.044**
MACE (%)	1.01	9*	**0.005**
Death from other causes (%)	9.1	8	0.67
Death from all causes (%)	9.1	12.3	0.469
Adverse event (%)	0	1.01	1
Length of stay (days)	5 (3)	5 (3)	0.794

Significant p values are shown in bold typeface.
*Six ventricular arrhythmias were fatal and excluded from total MACE to prevent duplication.
MACE, major adverse cardiovascular events.

Maclean E, et al. Heart Asia 2015;7:46–51

Low-dose oral bisoprolol administered to patients with NSTEMI within 4 h of admission may be protective and lead to reduced inpatient MACE.



Regression plot showing hours to bisoprolol versus the proportion of subsequent inpatient major adverse cardiovascular events (MACE).

How might this impact on clinical practice?

This study suggests that low-dose oral bisoprolol should be considered in all patients presenting with a diagnosis of NSTEMI in the emergency department.

Maclean E, et al. Heart Asia 2015;7:46–51

β-blockers in CCS

- The dose of beta-blockers should be adjusted to limit the heart rate to 55 - 60 b.p.m. (beats per minute) at rest

Target heart rate to 55 - 60 b.p.m.

- Discontinuation should be tapered and not abrupt.
- β-blockers can be combined with DHP CCBs to reduce DHP-induced tachycardia, but with uncertain incremental clinical value
- Caution is warranted when a β-blocker is combined with verapamil or diltiazem due to the potential for developing worsening of HF, excessive bradycardia, and/or atrioventricular block
- Combination of a beta-blocker with a nitrate attenuates the reflex tachycardia of the latter

2019 ESC Guidelines for CCS, doi:10.1093/eurheartj/ehz425

Recommendations for event prevention in patients with CCS

Lipid-lowering drugs	Class[a]	Level[b]
Statins are recommended in all patients with CCS.[c] [341,342]	I	A
If a patient's goal[c] is not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended.[317,320]	I	B
For patients at very high risk who do not achieve their goal[c] on a maximum tolerated dose of statin and ezetimibe, combination with a PCSK9 inhibitor is recommended.[320,323]	I	A
ACE inhibitors		
ACE inhibitors (or ARBs) are recommended if a patient has other conditions (e.g. heart failure, hypertension, or diabetes).[328–330]	I	A
ACE inhibitors should be considered in CCS patients at very high risk of cardiovascular events.[331,332,335,336]	IIa	A
Other drugs		
Beta-blockers are recommended in patients with LV dysfunction or systolic HF.[211,212,214]	I	A
In patients with a previous STEMI, long-term oral treatment with a beta-blocker should be considered.[213,220–222,225,343]	IIa	B

2019 ESC Guidelines for CCS, doi:10.1093/eurheartj/ehz425

Beta-blockers and renin-angiotensin system inhibitors in acute myocardial infarction managed with inhospital coronary revascularization

Pivotal trials BB and ACEI/ARB in acute myocardial infarction (AMI) were largely conducted prior to the widespread adoption of early revascularization

A total of 15,073 patients with AMI who underwent in-hospital coronary revascularization from January 2007 to December 2013 were analyzed

At 12 months, BB was significantly associated with a lower incidence of:
- MACE (HR 0.80) and
- all-cause mortality (HR 0.69)

Combined BB and ACEI/ARB was associated with the lowest incidence of all-cause mortality and HF hospitalization

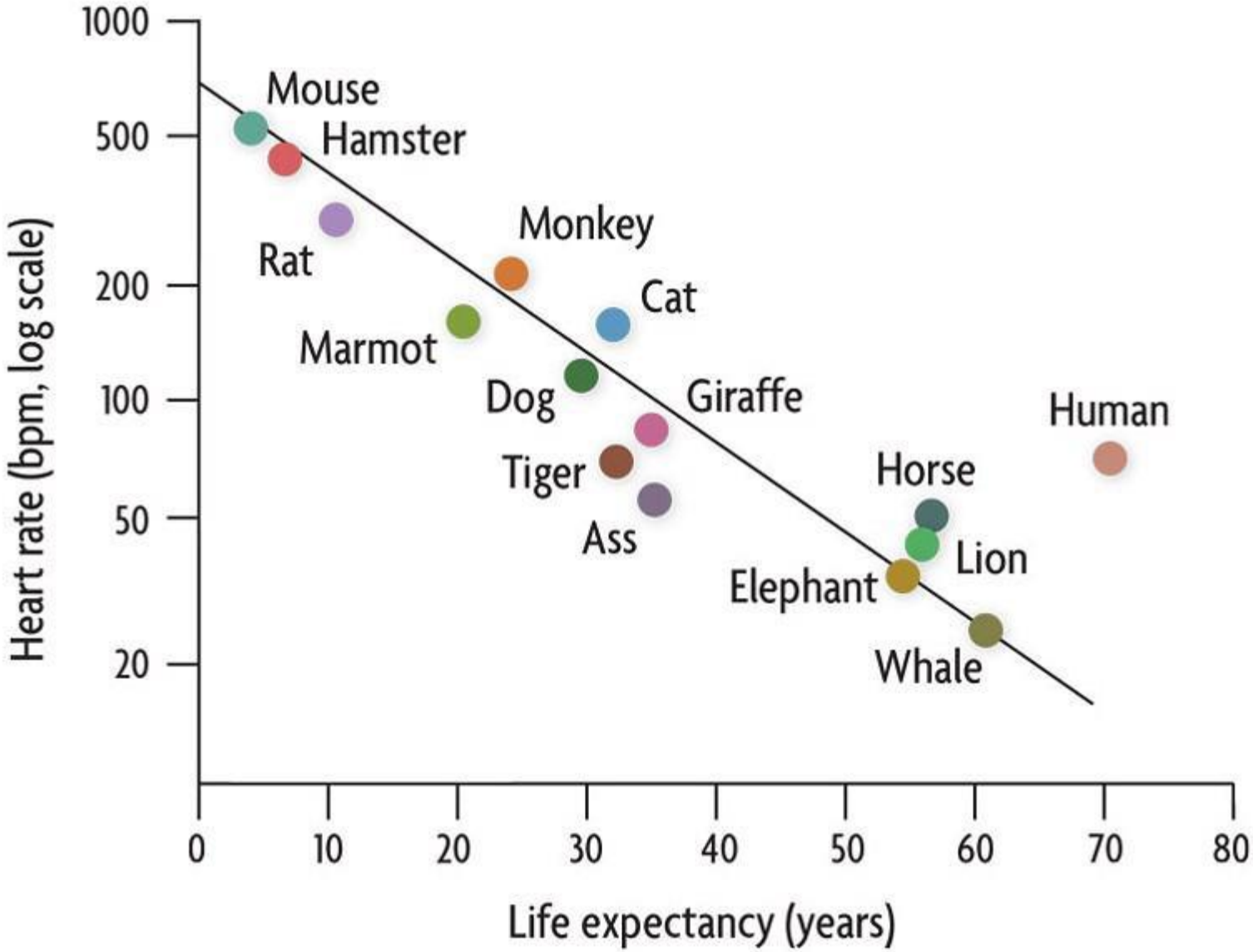
Sim HW et al. Scientific Reports 2020; 10:15184

Benefits of β-blockers in the post-MI period

1. myocardial ischemia
2. reinfarction and
3. the frequency of complex ventricular dysrhythmias

increase long-term survival

Ezra A. Amsterdam, et al. *Circulation*. 2014;130:e344-e426.


1000
500
200
100
50
20
Heart rate (bpm, log scale)
Mouse
Hamster
Rat
Monkey
Cat
Marmot
Dog
Giraffe
Tiger
Ass
Human
Horse
Lion
Elephant
Whale
0
10
20
30
40
50
60
70
80
Life expectancy (years)

Heart Rate and Survival

Survival (years)

200

80-90

60-70

4

0

Galapagos Turtle

Elite Athlete

Poorly conditioned

Rat

Humming Bird

<10 11-30 31-50 51-70 71-90 > 200

Resting Heart Rate (Beats / min)

In Humans average Heart Beats per LIFE TIME ~8×10^8. Reducing HR from 70 to 60 bpm would potentially increase life expectancy from 80 to 93.3 years!!!