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RELEVANT EDUCATIONAL EXPERIENCE IN YOUR REGION

Evolving Concepts in Non-ST Elevation ACS

Antonio Jordan-Rios, MD

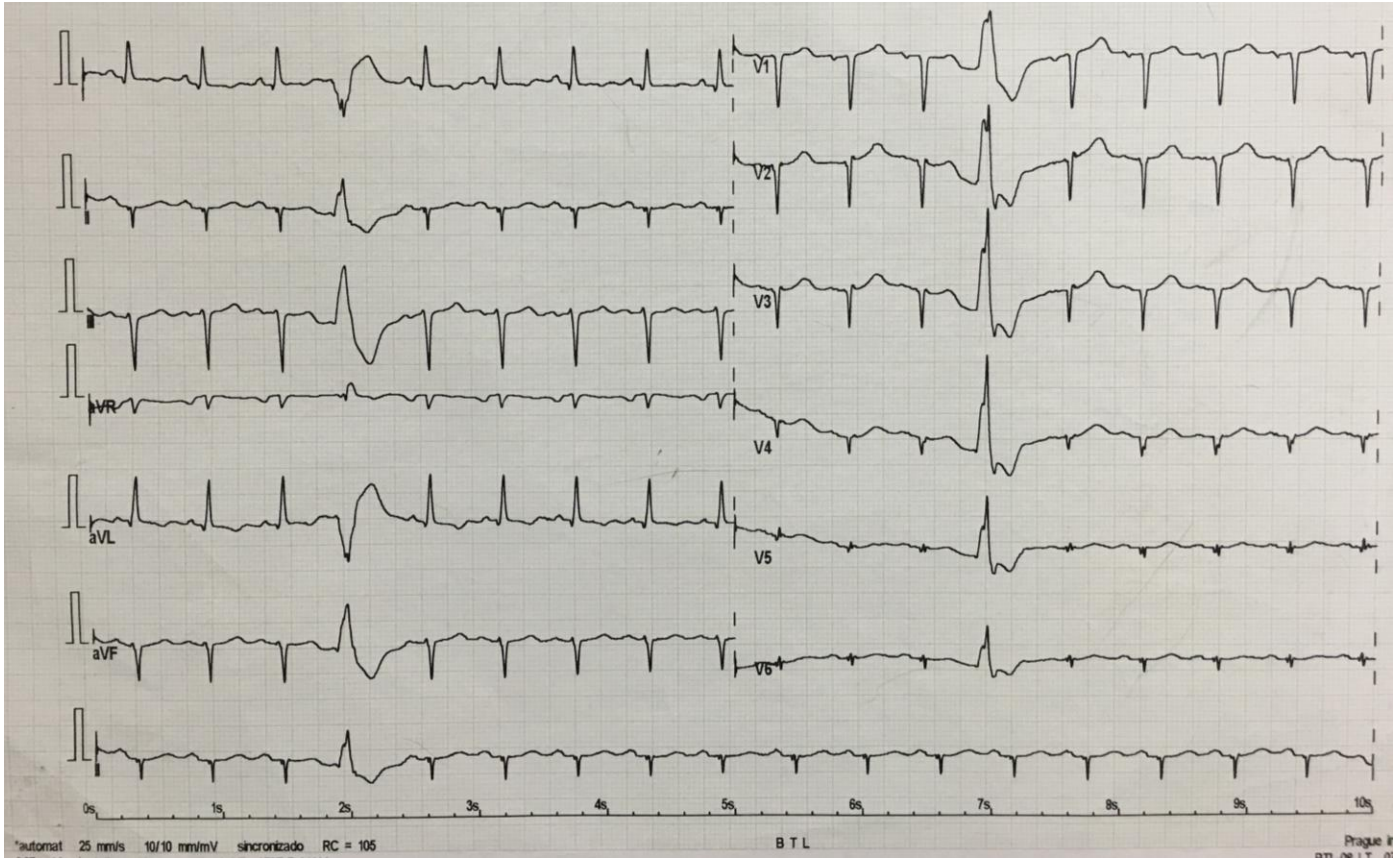
Instituto Nacional de Cardiología Ignacio Chávez

Case Presentation

- 72 year-old male
- Hypertension - ACE-inhibitor
- Ischemic Heart Disease - 1999 BMS Cx and RC - DAPT + standard therapy (full adherence)
- Diabetes - Insulin treatment
- Diverticular Disease - no prior gastrointestinal bleeding

Case Presentation

- Started with acute onset of chest pain after having his meals, 20 minutes length with diaphoresis
- He presented to ED of INCICh 80 minutes after onset of chest pain
- Physical exam revealed: BP 120/70mmHg, HR 100, SatO2p 91%. Lungs were clear. No murmurs. No abdominal pain
- EKG: negative T waves DI, aVL. Q waves V1-V4. Extrasystole
- LABS: Troponin 0.94 (+) Hemoglobin 13.4 g/L Hematocrit 40 Platelets 343,000


I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
0s
1s
2s
3s
4s
5s
6s
7s
8s
9s
10s
*automat 25 mm/s 10/10 mm/mV sincronizado RC = 105
B T L

Case Presentation

- LABS: Troponin 0.94 Hemoglobin 13.4 g/L Hematocrit 40 Platelets 343,000
  NT-proBNP 383 Creatinine 1.2 INR 0.99

- 3-hour later: Troponin 1.5

Case Presentation

- 72-year old male
- Cardiovascular Risk Factors
- Arrives ED acute chest pain
- EKG: Non-ST Elevation
- Troponin +

NSTE-ACS

TIMI-RS: 4 points (20%) GRACE: 145 points (3.7%) CRUSADE: 34 points (8.6%)

Early Invasive Strategy

Case Presentation

- Started on:

  - Aspirin 300mg
  - Clopidogrel 300mg
  - UFH 60 U/kg IVBolus 12U/kg/hr
  - Atorvastatin 80mg
  - Captopril 12.5mg tid
  - Metoprolol 25mg bid

Case Presentation

- 20 hours later started with lower gastrointestinal bleeding
- UFH and Aspirin were stopped
- Continued with:
    - Clopidogrel 75mg qd
    - Atorvastatin 80mg qd
    - Captopril 25mg tid
    - Metoprolol 25mg bid

Case Presentation

- 24 hours later continued with intermitent bleeding
- Hemodynamically stable. No angina. No EKG changes.
- Angiography was deferred and continued anti-ischemic treatment only with SAPT
- Hemoglobin control 12.1 g/dL
- Gastroenterologist was consulted
- Colonoscopy: active diverticular bleeding that was locally controlled

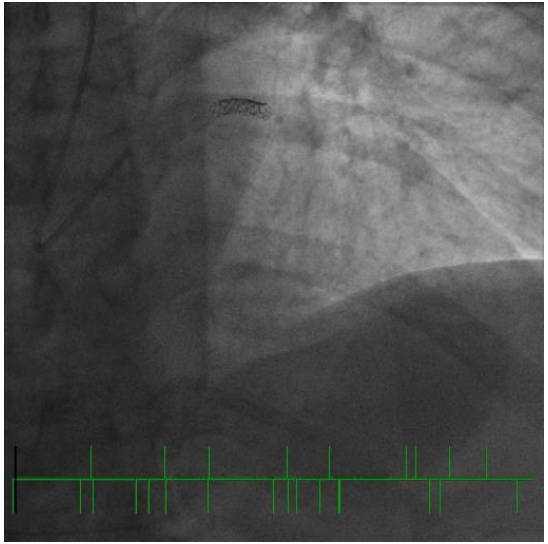
Case Presentation

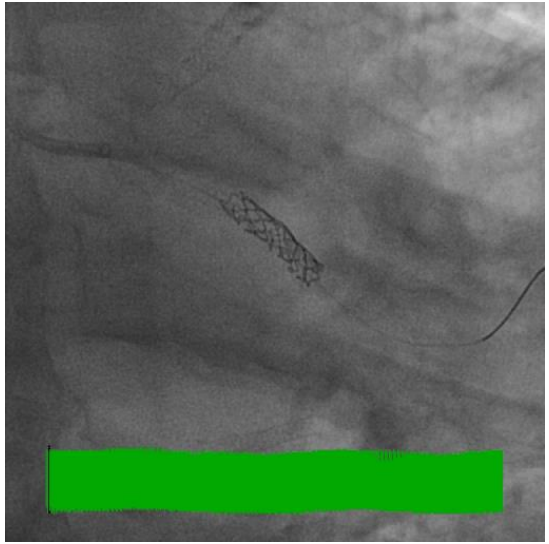
- 48 hours later GI bleeding was controlled
- Hemoglobin 11.5 g/dL Hematocrit 33.2
- Continued with DAPT // no heparin
- Angiography was performed 4 days after hospital admission

Case Presentation

- Angiography:

  -LAD: no significant lesions
  -First diagonal: 50% lesion
  -Cx – First marginal obtuse: 80% intrastent restenosis
  -RC – PD: permeable stent





Case Presentation

- Discharged 48 hours after angiography.
- No more bleeding during hospital stay
- Discharged with: aspirin + ticagrelor + standard anti-ischemic treatment + PPI
- Hemoglobin: 11.6 g/dL

Key points

- Stent thrombosis and strategies to manage it
- Ideal timming for delayed invasive strategy in bleeding patients
- Bleeding definitions & Risk factors associated with GI bleeding
- Duration of DAPT on patients with GI bleeding (guidelines & DAPT score)
- Final best treatment
- Unanswered questions

Key points – Stent thrombosis

- Uncommon but serious complication

- Very late stent thrombosis incidence 1.4%. Occurred median 4.7-6.1 years

- Risk factors (not well defined):
  - Vessel inflamation
  - Incomplete neointimal coverage
  - Mural red thrombi
  - Current smoking
  - Instent neoatherosclerosis

Keriakes, D. JACC 2015
Finn, J. Circ 2010

Key points – Stent thrombosis

- No RCT Platelet function testing, genetic testing or even switching P2Y12 inhibitors improves outcome (Class III: No Benefit)
- PPI's should be used in prior GI bleeding (Class I) + Increased risk patients (Class IIa – reasonable)
- PPI's not routine use in low risk patients

Keriakes, D. JACC 2015
Finn, J. Circ 2010
Glenn, H. JACC, 2015

Key points – Ideal timming

- Risk stratification is crucial
- Optimal timming has not been conclusively defined
- Low grade evidence for switching strategy from early to delayed in active bleeding patients

TABLE 8 Factors Associated With Appropriate Selection of Early Invasive Strategy or Ischemia-Guided Strategy in Patients With NSTE-ACS

mmediate invasive (within 2 h)	Refractory angina
	Signs or symptoms of HF or new or worsening mitral regurgitation
	Hemodynamic instability
	Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy
	Sustained VT or VF
schemia-guided strategy	Low-risk score (e.g., TIMI [0 or 1], GRACE [<109])
	Low-risk Tn-negative female patients
	Patient or clinician preference in the absence of high-risk features
arly invasive (within 24 h)	None of the above, but GRACE risk score >140
	Temporal change in Tn (Section 3.4)
	New or presumably new ST depression
elayed invasive (within 25–72 h)	None of the above but diabetes mellitus
	Renal insufficiency (GFR <60 mL/min/1.73 m^2)
	Reduced LV systolic function (EF <0.40)
	Early postinfarction angina
	PCI within 6 mo
	Prior CABG
	GRACE risk score 109–140; TIMI score ≥2

Amsterdam, et al. JACC 2014
Cannon J. NEJM 2001
Spacek, R. The VINO study. Eur Heart J 2002

Key points – Bleeding definitions & Risk Factors

- Several challenges in creating an universal bleeding deifinition
- Correlate closely with prognosis and MACE
- Heterogenity several trials: TIMI, GUSTO, ACCUITY, CURE

Mehran R. Circ 2012

Key points – Bleeding definitions

Table 3. Bleeding Academic Research Consortium Definition for Bleeding

Type 0: no bleeding

Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

Type 2: any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation

Type 3

- Type 3a
  - Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed)
  - Any transfusion with overt bleeding
- Type 3b
  - Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed)
  - Cardiac tamponade
  - Bleeding requiring surgical intervention for control (excluding
- Type 3c
  - Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
  - Subcategories confirmed by autopsy or imaging or lumbar puncture
  - Intraocular bleed compromising vision

Type 4: CABG-related bleeding

- Perioperative intracranial bleeding within 48 h
- Reoperation after closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period†
- Chest tube output ≥2L within a 24-h period

Type 5: fatal bleeding

- Type 5a
  - Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
- Type 5b
  - Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

Key points – Importance of bleeding

- All patients with NSTEMI should be evaluated for risk bleeding (Class I)
- Increases risk of MACE
- Antiplatelet and anticoagulant therapy has to be guided: age, CKD, risk bleeding (Class I)
- Restrictive blood transfusion improves outcome (>7 – 8 mg/dL)

Mehran R. ACUITY trial. Eur Heart J 2010

Key points – Risk Factors

- Some patients have both factors
- Difficult to establish acute and long term therapy
- Utility DAPT score

Levine G. et al. JACC 2016

TABLE 4 Clinical and Procedural Factors Associated W Increased Ischemic Risk (Including Stent Thrombosis) or Increased Bleeding Risk (62-

Increased Ischemic Risk/Risk of Stent Thrombosis (may favor longer-duration DAPT)	Increased Bleeding Risk (favor shorter-duration DA
Increased ischemic risk	History of prior bleeding
Advanced age	Oral anticoagulant therapy
ACS presentation	Female sex
Multiple prior MIs	Advanced age
Extensive CAD	Low body weight
Diabetes mellitus	CKD
CKD	Diabetes mellitus
Increased risk of stent thrombosis	Anemia
ACS presentation	Chronic steroid or NSAID thera
Diabetes mellitus	
Left ventricular ejection fraction <40%	
First-generation drug-eluting stent	
Stent undersizing	
Stent underdeployment	
Small stent diameter	
Greater stent length	
Bifurcation stents	
In-stent restenosis	

Key points – DAPT score

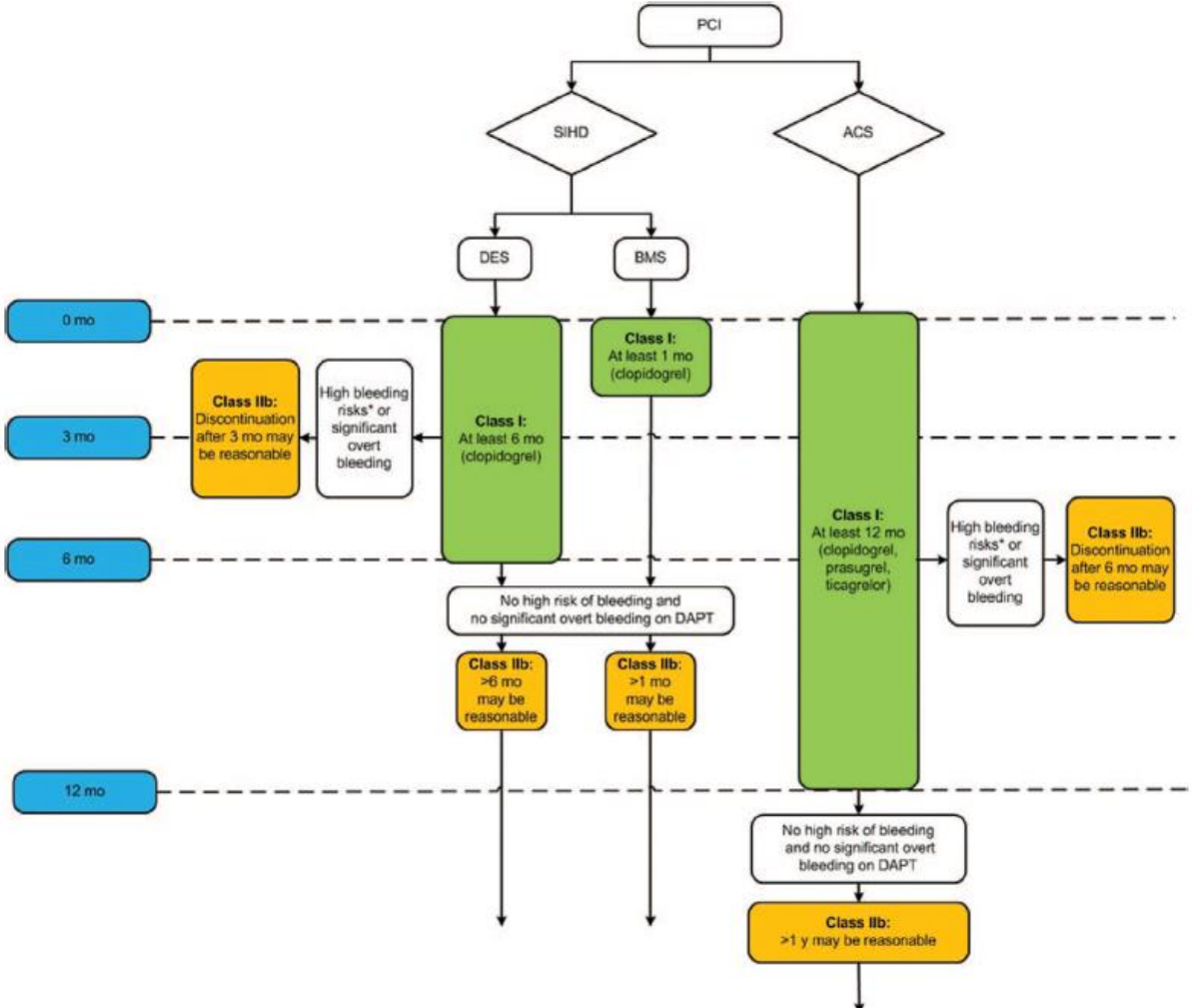
- Derived from the DAPT study
- Useful to decide whether to continue prolongued or extended DAPT
- DAPT score <2 // >2

TABLE 5 Factors Used to Calculate a "DAPT Score"

Variable	Points
Age ≥75 y	-2
Age 65 to <75 y	-1
Age <65 y	0
Current cigarette smoker	1
Diabetes mellitus	1
MI at presentation	1
Prior PCI or prior MI	1
Stent diameter <3 mm	1
Paclitaxel-eluting stent	1
CHF or LVEF <30%	2
Saphenous vein graft PCI	2

Levine G. et al. JACC 2016

FIGURE 2 Treatment Algorithm for Duration of $P2Y_{12}$ Inhibitor Therapy in Patients Treated With PCI



Key points – DAPT therapy

- Aspirin: mainstay of antiplatelet treatment

- Low dose aspirin = less major bleeding either monotherapy or combined P2Y12 (as low as 30-50mg). Not increasing ischemic events

- High aspirin doses decrease ticagrelor plasma activity

Levine G. et al. JACC 2016

Key points – DAPT therapy

- Prasugrel: effective at preventing stent thrombosis but high incidence of major bleeding events, spontaneous bleeding and fatal bleeding

- No benefit older patients (>75 y) (<60kg)

Levine G. et al. JACC 2016

Key points – DAPT therapy

- Ticagrelor: Reversible union. Short half-life. Faster platelet recovery

- Usefull in patients aspirin allergic or bleeding events

Levine G. et al. JACC 2016

Key points – DAPT therapy

Recommendations for 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 (53,71,72).
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 (54,55).
III: Harm	B-R	Prasugrel should not be administered to patients with a prior history of stroke or TIA (54).

Levine G. et al. JACC 2016

Key points – DAPT therapy

Recommendations for Duration of DAPT in Patients With ACS Treated With PCI

COR	LOE	RECOMMENDATIONS
I	B-R	In patients with ACS (NSTE-ACS or STEMI) treated with DAPT after BMS or DES implantation, $P2Y_{12}$ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) should be given for at least 12 months (16,50–55,72,96–98).
I	B-NR	In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended (56–60,75–78).
IIa	B-R	In patients with ACS (NSTE-ACS or STEMI) treated with DAPT after coronary stent implantation, it is reasonable to use ticagrelor in preference to clopidogrel for maintenance $P2Y_{12}$ inhibitor therapy (53,72).
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 (54,55).
IIb	A [SR]	In patients with ACS (NSTE-ACS or STEMI) treated with coronary stent implantation who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT (clopidogrel, prasugrel, or ticagrelor) for longer than 12 months may be reasonable (16,22–26,28,30,40,41,43,53,54,72).
IIb	C-LD	In patients with ACS treated with DAPT after DES implantation who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months may be reasonable (17–21,34,36,37).
III: Harm	B-R	Prasugrel should not be administered to patients with a prior history of stroke or TIA (54).

Key points – DAPT therapy

Recommendations for Duration of DAPT in Patients With ACS Treated With Medical Therapy Alone

COR	LOE	RECOMMENDATIONS
I	B-R	In patients with ACS who are managed with medical therapy alone (without revascularization or fibrinolytic therapy) and treated with DAPT, $P2Y_{12}$ inhibitor therapy (clopidogrel or ticagrelor) should be continued for at least 12 months (52,71,140,141).
I	B-NR	In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended (56-60,75-78).
IIa	B-R	In patients with NSTE-ACS who are managed with medical therapy alone (without revascularization or fibrinolytic therapy) and treated with DAPT, it is reasonable to use ticagrelor in preference to clopidogrel for maintenance $P2Y_{12}$ inhibitor therapy (53,71).
IIb	A ^{SR}	In patients with ACS treated with medical therapy alone (without revascularization or fibrinolytic therapy) who have tolerated DAPT without bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT for longer than 12 months may be reasonable (28,30,40,41,43,53,71,141).

Key points – Unanswered questions in NSTEMI - ACS

- What is the optimal timming of oral antiplatelet administration who are intended for invasive satrategy?
- What is the role of FFR-guided PCI in NSTEMI
- Optimal timming for blood transfusion?
- DAPT could be replaced for 1 single P2Y12 inhibitor?
- Role of PCSK9 in NSTEMI (acute phase)

Eisen, A. JAMA 2016

Thank you