

Stable CAD, NSTEMI-ACS, and STEMI: Three Challenging Patients and Antithrombotic Approaches



Glenn N. Levine, MD, FAHA, FACC

Professor of Medicine, Baylor College of Medicine

Director, Cardiac Care Unit, Michael E. DeBakey Medical Center

Chair, ACC/AHA Task Force on Clinical Practice Guidelines

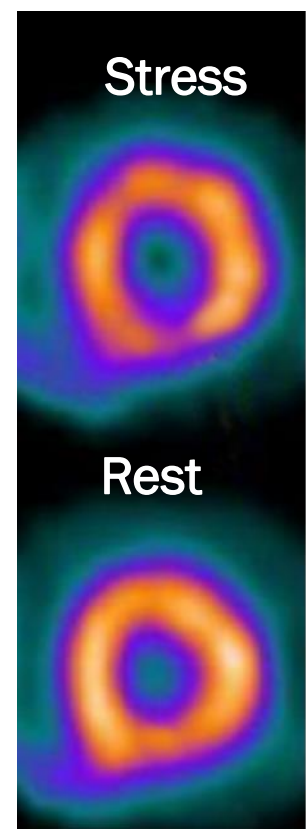
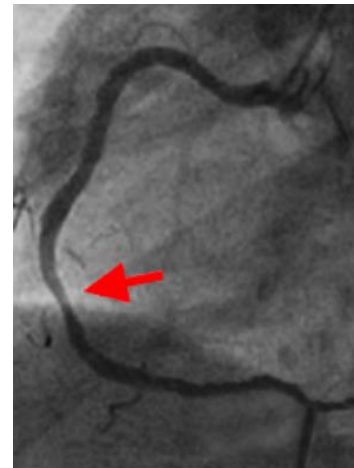


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A Patient With Stable CAD

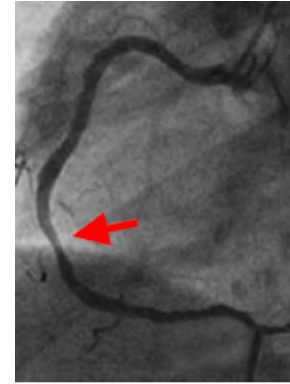
- 59 year old man living in Brooklyn. Smokes 2 PPD.
- Past medical history of stroke and subsequent complex seizures requiring multi-drug therapy
- Class II (mild exertional) angina
- HR 90 bpm and BP 140/90 on metoprolol 25 mg BID
- Nuclear stress test ordered by his primary physician showed mild (9%) inferior wall ischemia; referred for cardiac cath
- Diagnostic catheterization at a local hospital showed a 70% mid RCA lesion (and mild LAD and left circumflex disease). Elective stent implantation at a PCI-capable hospital scheduled in one week and he is prescribed clopidogrel to begin taking in preparation for the procedure



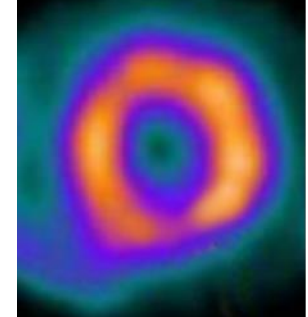


A Patient With Stable CAD

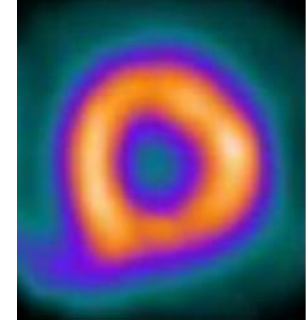
How would you treat this patient?



Stress



Rest



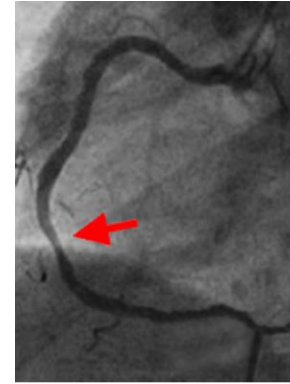
- 1) Placement of a bare metal stent (BMS)
- 2) Placement of a metallic drug-eluting stent (DES)
- 3) Placement of a bioresorbable scaffold DES
- 4) Intensify medical therapy





A Patient With Stable CAD

- Platelet function testing just before the stent implantation (one week after clopidogrel prescribed) revealed a PRU=242 (indicating high platelet reactivity)



How would you treat the patient ?

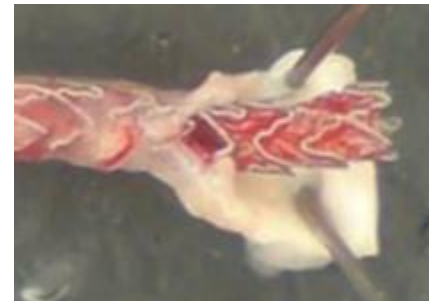
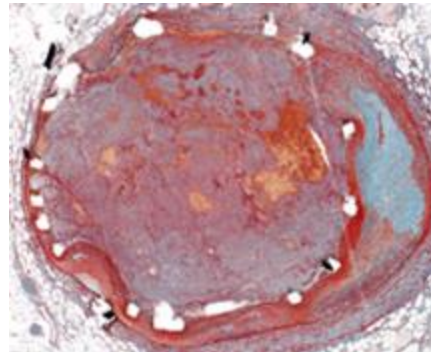
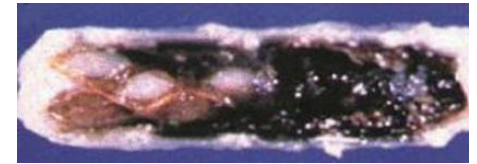
- 1) Continue clopidogrel
- 2) Change to ticagrelor
- 3) Change to prasugrel
- 4) Abort the planned stent procedure





A Patient With Stable CAD

- Patient undergoes stenting with a current generation metallic DES and is treated with clopidogrel 75 mg daily
- 43 days post-DES patient suffers sub-acute stent thrombosis
- Thrombectomy and IVUS-guided further stent dilation performed
- The patient is placed on ticagrelor 90 mg BID
- 37 days later the patient again presents with stent thrombosis





How Should The Patient Next Be Managed?

- 1) Try clopidogrel 150 mg bid
- 2) Continue ticagrelor 90 mg BID
- 3) Change to prasugrel 10 mg qD
- 4) Warfarin
- 5) Direct oral anticoagulant (DOAC)
- 6) Hypercoagulability workup





Does the patient have a hypercoagulable state?

Antiphospholipid Syndrome

- Antiphospholipid antibody (APA)
- Antibody to B2 glycoprotein-1
- Lupus anticoagulant
- Anticardiolipin antibody

Positive test on 2 or more occasions
at least 12 weeks apart

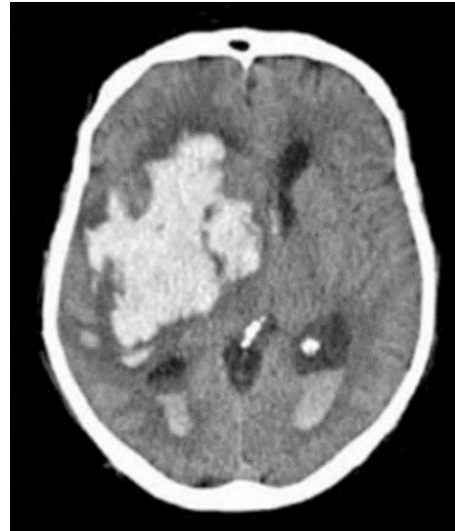
Inherited hypercoagulable disorders	Acquired hypercoagulable states
Factor V Leiden	Antiphospholipid syndrome
Prothrombin G20210A	Heparin-induced thrombocytopenia
Antithrombin deficiency	Myeloproliferative neoplasms
Protein C deficiency	Paroxysmal nocturnal hemoglobinuria
Protein S deficiency	Cancer



A Patient With Stable CAD

- Thrombectomy again performed and a bioresorbable polymer DES placed within the stent and aggressively dilated
- The patient is placed on prasugrel 10 mg qD

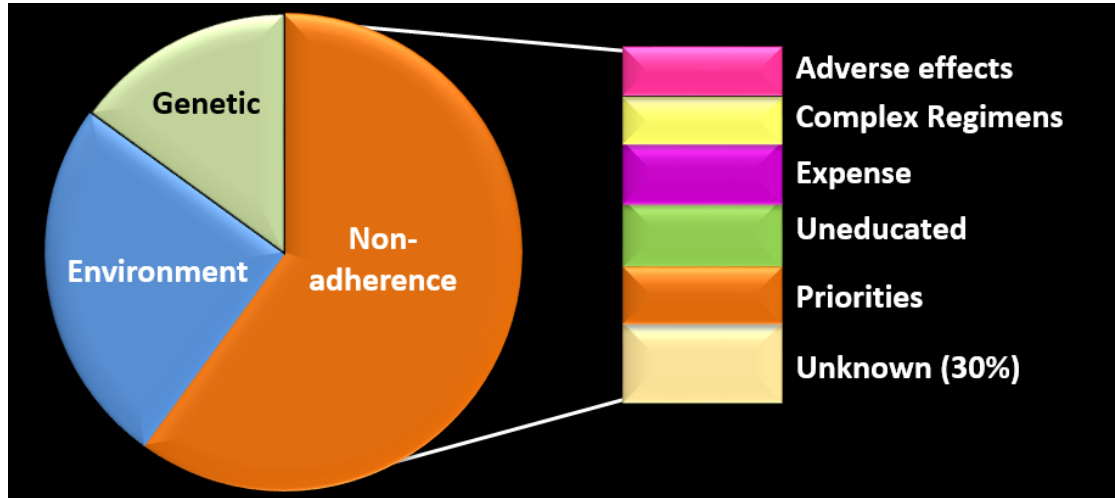
- 3 weeks later the patient presents with massive intracranial hemorrhage





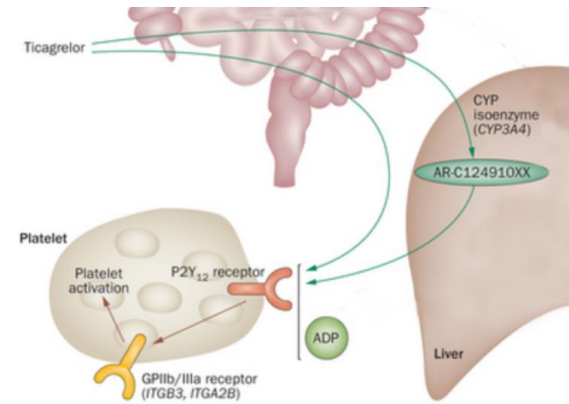
A Patient With Stable CAD

'Resistance' to Antiplatelet Therapy



Up to 28% of patients fail to fill their initial antiplatelet prescriptions

Metabolism of Ticagrelor



Strong CYP3A inhibitors (increase ticagrelor blood levels and risk of bleeding)	Potent inducers of CYP3A (decrease ticagrelor blood levels)
Clarithromycin	Rifampin
Itraconazole, Ketoconazole, Voriconazole	Dexamethasone
Atazanavir, indinavir	Phenytoin
Nefazodone	Carbamazepine
	Phenobarbital

Intracranial Hemorrhage in Patients with Prior Stroke/Transient Ischemic Attack:

Net (ischemic + bleeding) harm (↑37%) with prasugrel vs clopidogrel in those with prior stroke (CVA) or transient ischemic attack (TIA)

Clopidogrel: 0 (0%)
Prasugrel: 6 (2.3%)
(P=0.02)

Prasugrel Contraindications

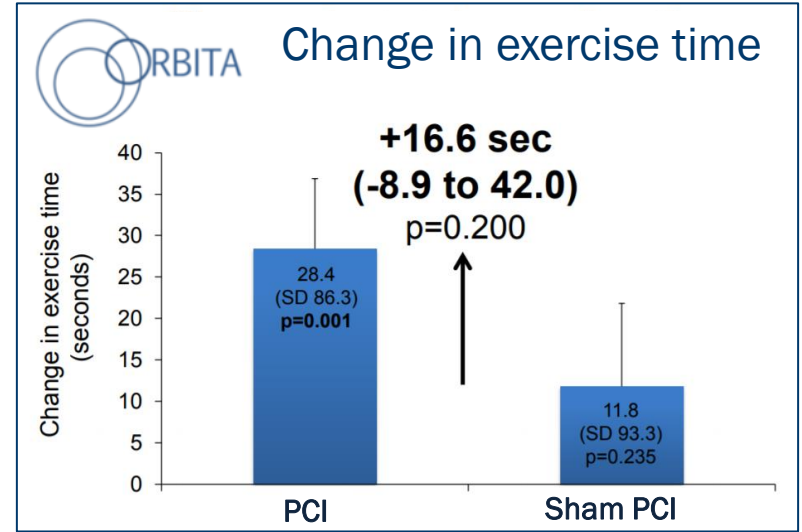
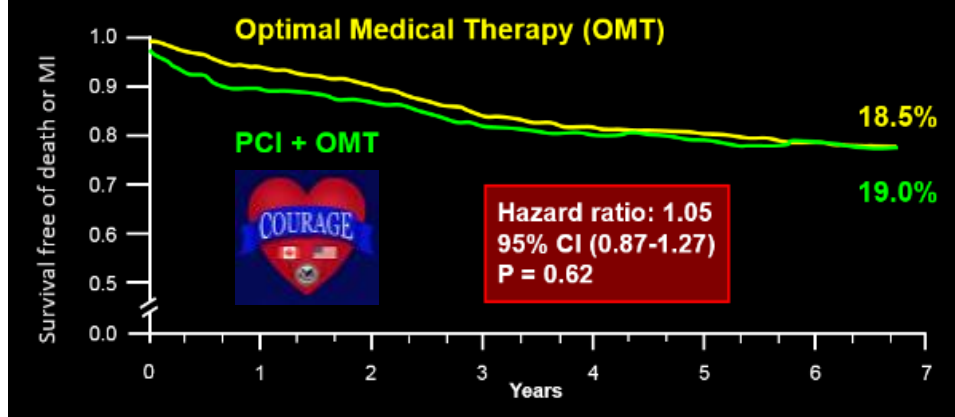
- Active bleeding
- History of prior CVA or TIA

COR	LOE	Recommendations
III: Harm	B-R	Prasugrel should not be administered to patients with a prior history of stroke or TIA.



A Patient With Stable CAD

- Class II (mild exertional) angina
- HR 90 bpm and BP 140/90 on metoprolol 25 mg BID



Great drugs, great tests, and great devices do not trump good clinical judgment !



The pen (prescribing medical therapy) is mightier
(or often at least as good as) the ~~sword~~ stent

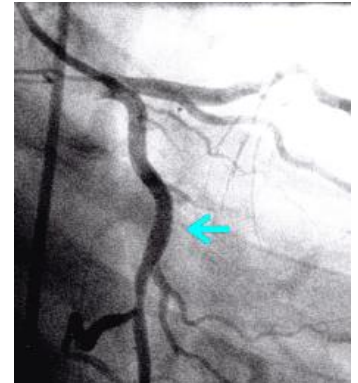
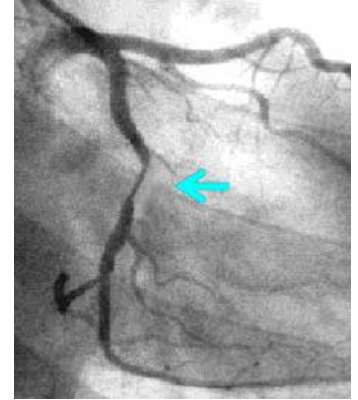




A Patient with NSTEMI-ACS

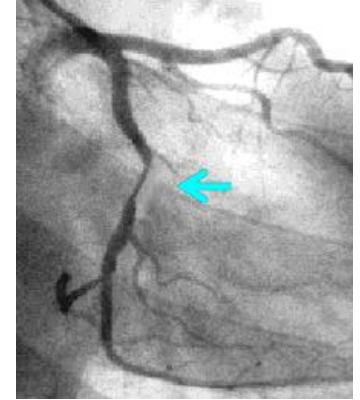
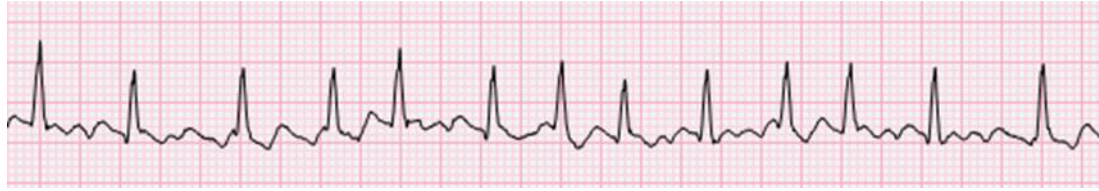


- 76 year old female with untreated hypertension (SBP=170 mmHg), diabetes and LDL=187
- She presents with atrial fibrillation and non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS) (troponin=1.3)
- Undergoes drug-eluting stent (DES) of a 90% left circumflex artery stenosis
- HAS-BLED Score = 3 (hypertension, age, antiplatelet therapy)



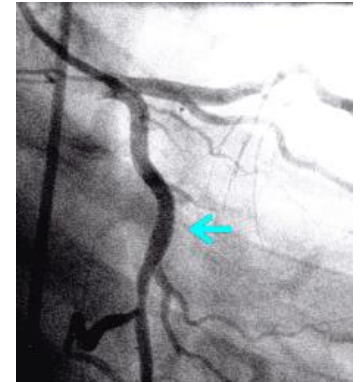


A Patient with NSTEMI-ACS



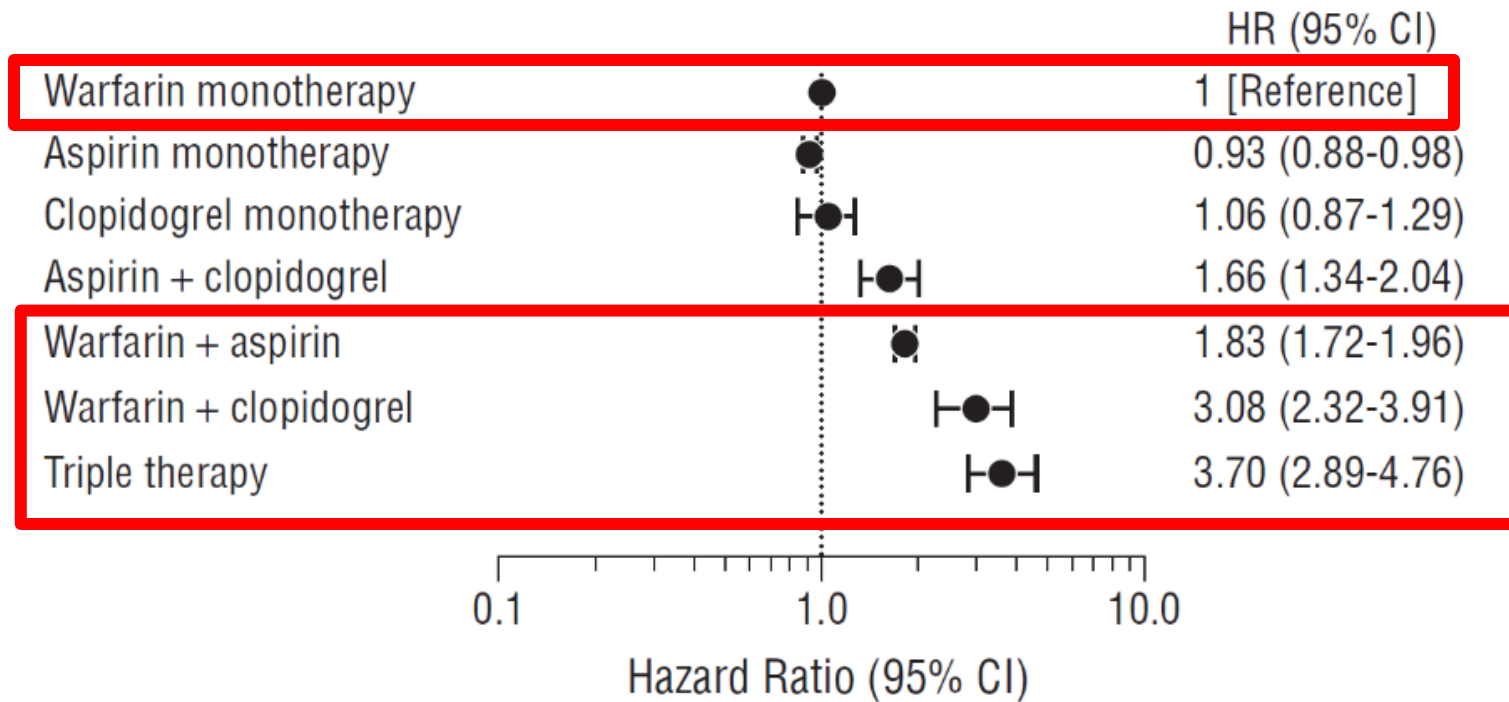
How would you treat this patient?

- 1) Dual antiplatelet therapy (DAPT) alone
- 2) Double therapy (oral anticoagulant + single antiplatelet therapy)
- 3) Triple therapy (oral anticoagulant + dual antiplatelet therapy)



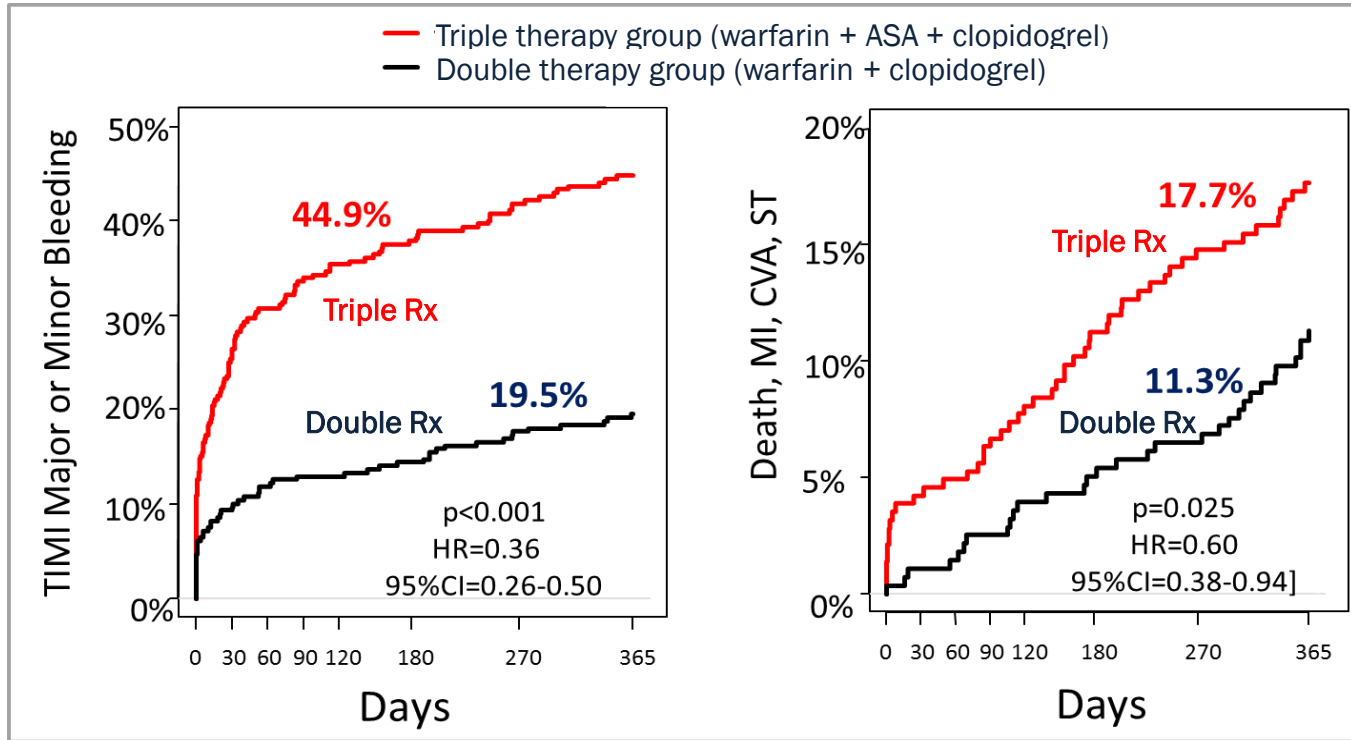
“Real World” Bleeding Risks

Adjusted HR in 82,854 patients with AF in a Nationwide Danish Registry



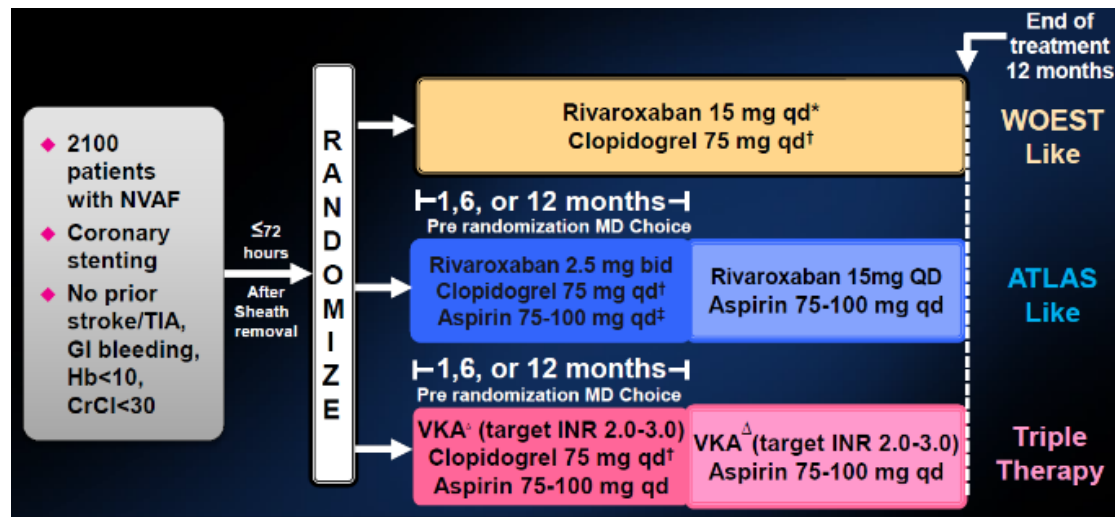
Triple vs Double Therapy Post-PCI

In patients with an indication for oral anticoagulant therapy



Dewilde WJM. Lancet 2013

Gibson CM et al., NEJM 2016;
Gibson CM et al. Circulation 2016

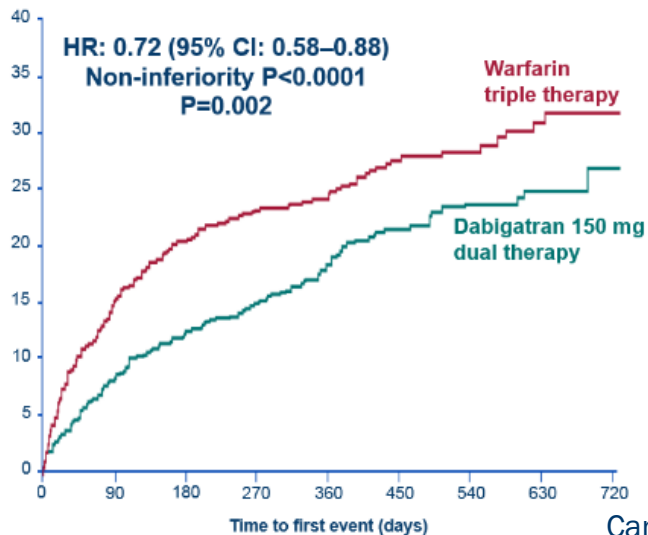


- Significant reductions in bleeding (TIMI major + TIMI minor + bleeding requiring medical attention) with both rivaroxaban arms (**16.8%**, **18.0%** vs **26.7%**)
- Reduction in all-cause hospitalization for an adverse event with both rivaroxaban regimens
- No difference in ischemic events (CV death, MI or stroke)
- Caveats:
 - Given study design, reductions in bleeding would be expected
 - No reduction in TIMI major or minor bleeding; results driven by reduction in “bleeding requiring medical attention”
 - Study not powered to detect significant differences in ischemic endpoints
 - 2.5 mg rivaroxaban not available in the US and cutting 10 mg tablet in quarters impractical

• 2725 patients with AF and either SIHD or ACS undergoing PCI randomized to:
(1) triple therapy (VKA+P2Y₁₂+ASA) **(2) dabigatran 150mg + P2Y₁₂** **(3) dabigatran 110mg + P2Y₁₂**

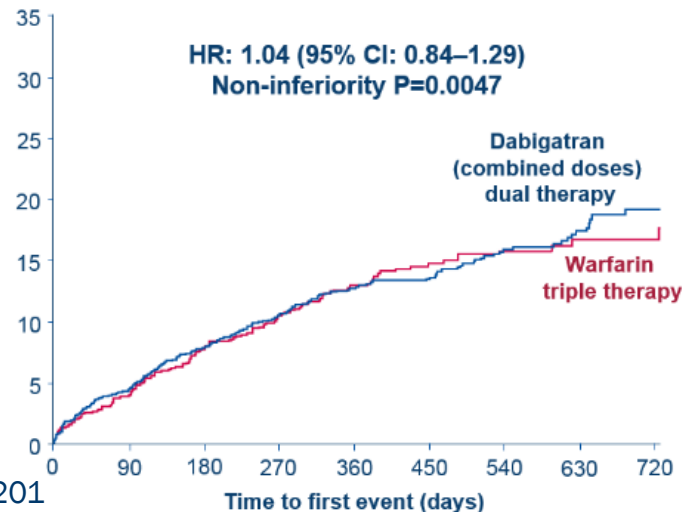
- In triple therapy group, ASA discontinued after 1 month (BMS) or 3 months (DES)
- 88% clopidogrel; 12% ticagrelor
- Mean duration of f/u = 14 months

ISTH major bleeding or clinically relevant non-major bleeding



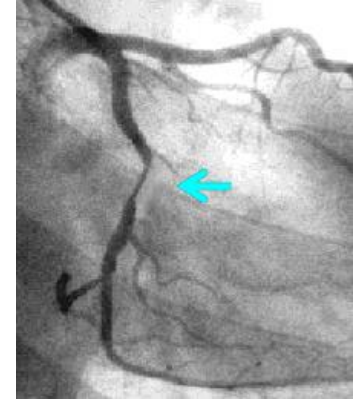
Cannon CP et al. NEJM 2011

Death, thrombotic event, or unplanned revascularization



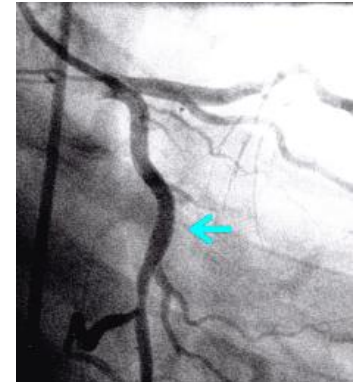


A Patient with NSTEMI-ACS



When, if ever, should ALL antiplatelet therapy be completely stopped?

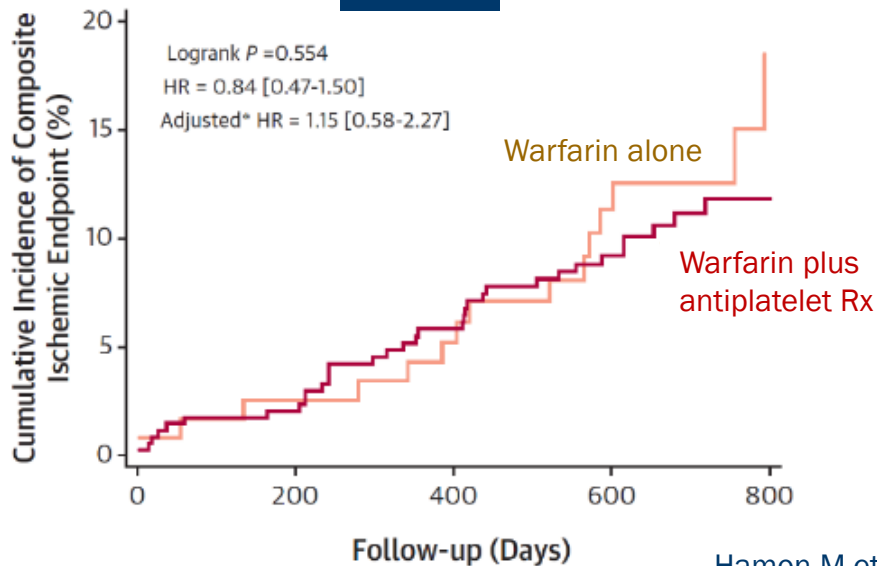
- 1) Never
- 2) At the latest 12 months after the coronary stent procedure



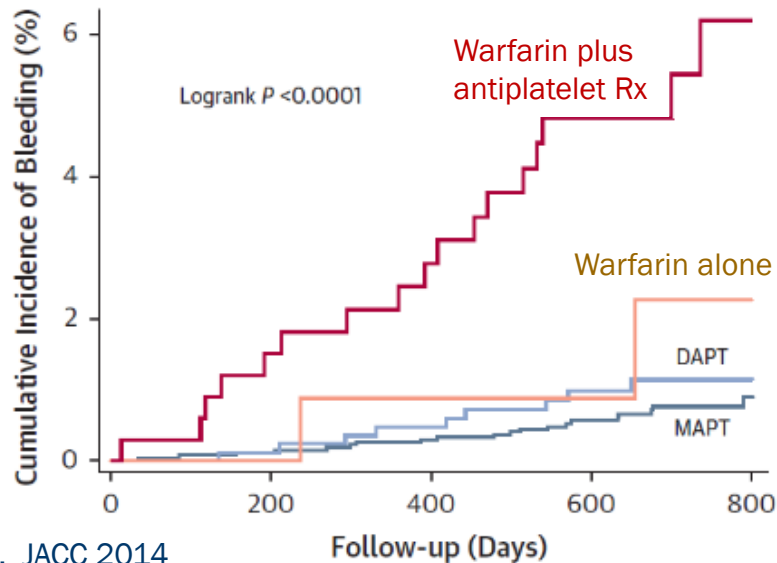
CORONOR

- French prospective multicenter observational study
- 4,184 patients with stable CAD, free from any prior MI (62%) or revasc (86%) >1 year
- 7% with AF, 11% treated with warfarin
- Antiplatelet therapy: ASA 77%; clopidogrel 21%; ASA+Clop 21%
- Major bleeding defined as BARC type ≥ 3 events

MACE



Major Bleeding



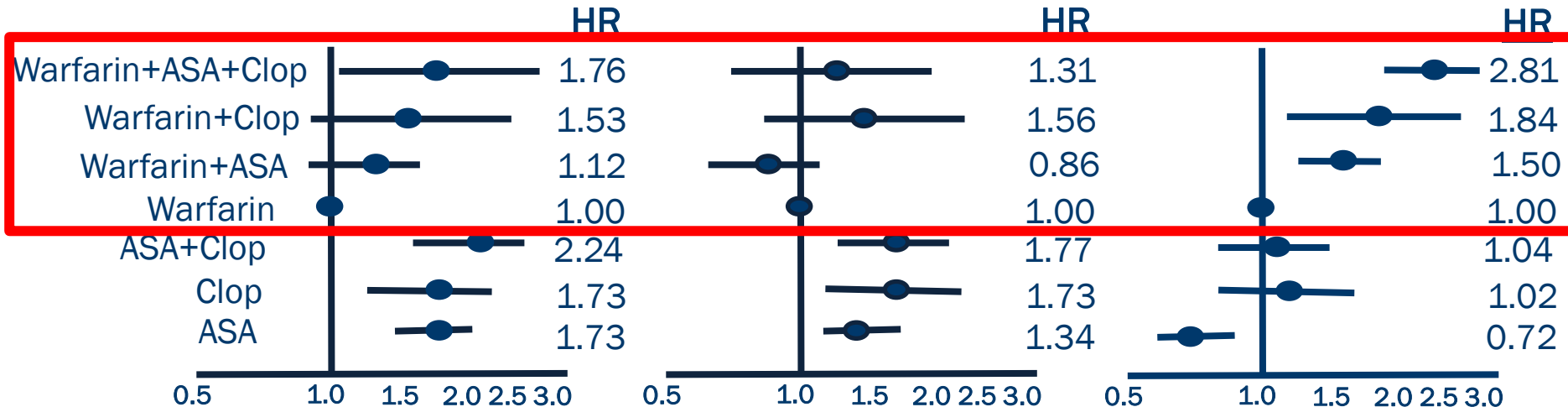
Antithrombotic Therapy in AF + Stable CAD: Danish Nationwide Cohort Study

Adjusted HR in 8700 stable CAD+AF patients, ≥1 year from MI or PCI

MI/Coronary Death

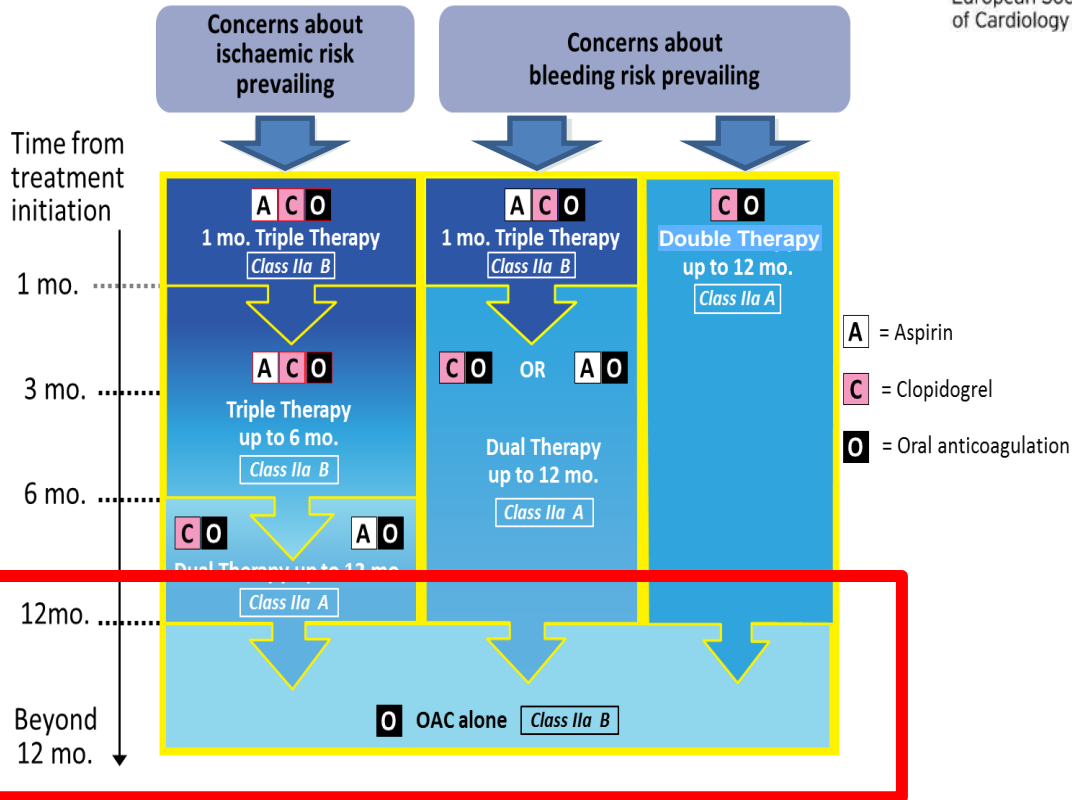
Thromboembolism

Serious Bleeding

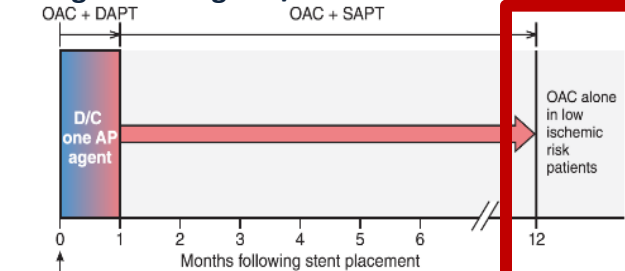


Adjusted HR for combined ischemic+bleeding events significantly lower for warfarin alone than any other therapy combinations

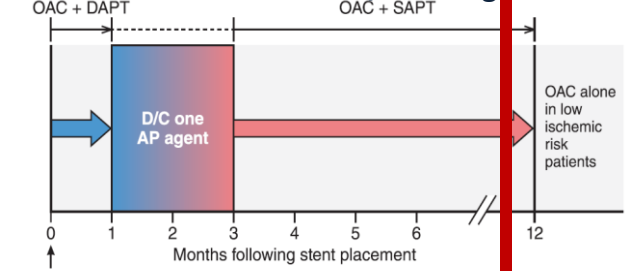
Patients with an indication for oral anticoagulation undergoing PCI



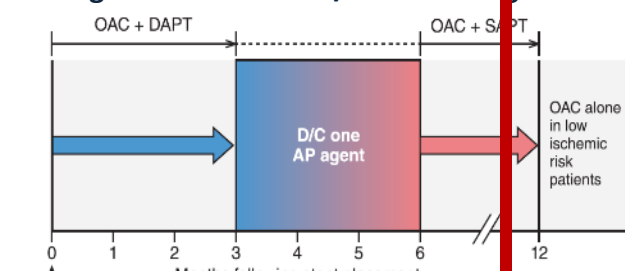
High bleeding risk/low ischemic risk



Balanced thrombotic/bleeding risk



High thrombotic risk/low bleeding risk



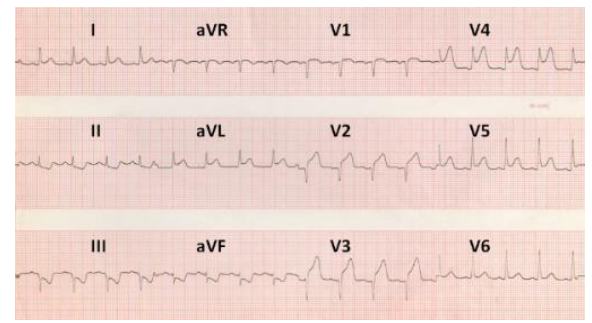
Take-home Messages So Far From Studies of Double and Triple Therapy in Patients with AF Undergoing PCI

- Not surprisingly, double therapy (oral anticoagulant + single antiplatelet therapy) leads to less bleeding than triple therapy
 - So far, in a total of 2,732 patients (WOEST, PIONEER, RE-DUAL) randomized to double therapy (oral anticoagulant + single antiplatelet therapy) post-PCI, no glaring signal of increased stent thrombosis or increased cardiac ischemic events
1. Keep triple therapy as short as possible (1-6 months)
 2. Double therapy (oral anticoagulant + single antiplatelet therapy) reasonable in high bleeding risk and perhaps average bleeding risk patients as well
 3. Strongly consider/routinely use PPI and other measures to decrease bleeding risk
 4. Strongly consider stopping all antiplatelet therapy after at most 1 year after ACS or PCI in many in not most patients

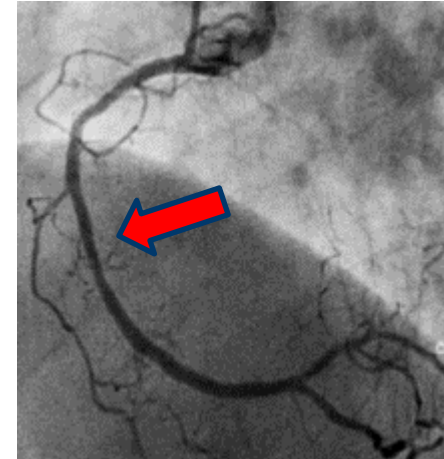
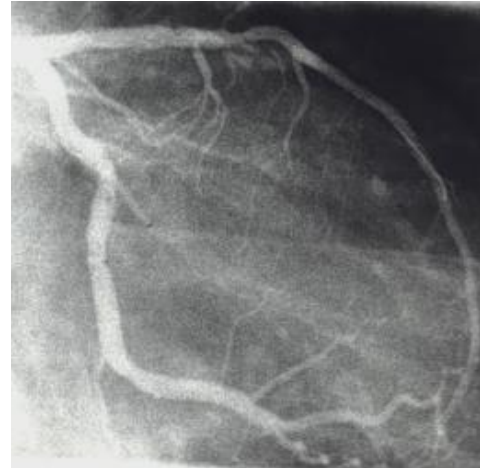




A Patient with STEMI

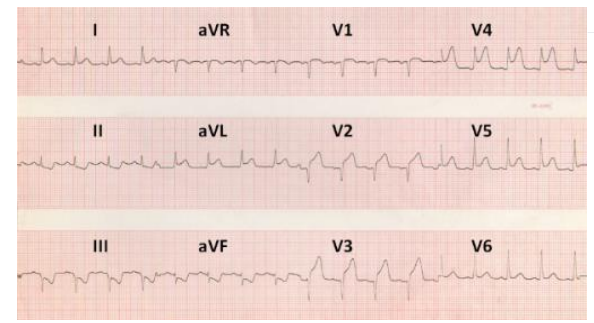


- 59 year old woman who smokes 3 PPD presents with extensive anterior wall STEMI.
- She undergoes primary PCI with placement of 2 DES in proximal and mid LAD
- Diagnostic catheterization at the time also reveals moderate RCA lesion; FFR two days later of the RCA is 0.93

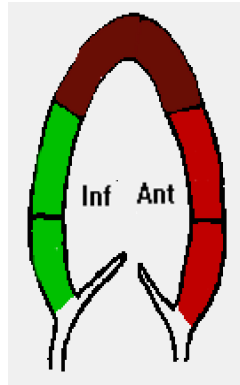
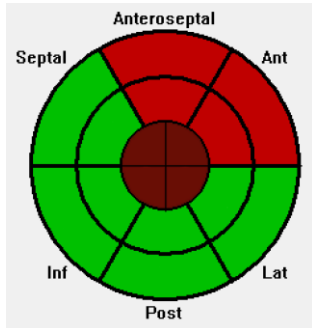




A Patient with STEMI

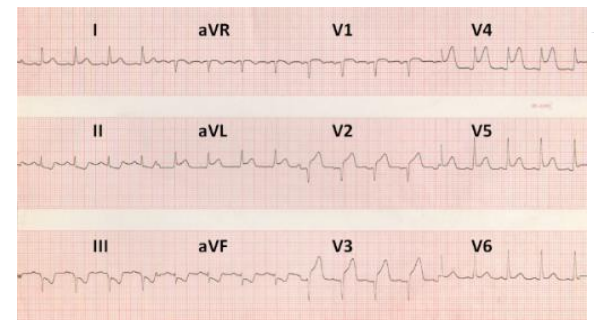


- Echocardiography done the following day reveals akinetic anterior wall and dyskinetic apex with EF=25%
- Her HAS-BLED score = 2 (assuming antiplatelet therapy)
- You weigh your concern about LV thrombus formation against her risk of bleeding



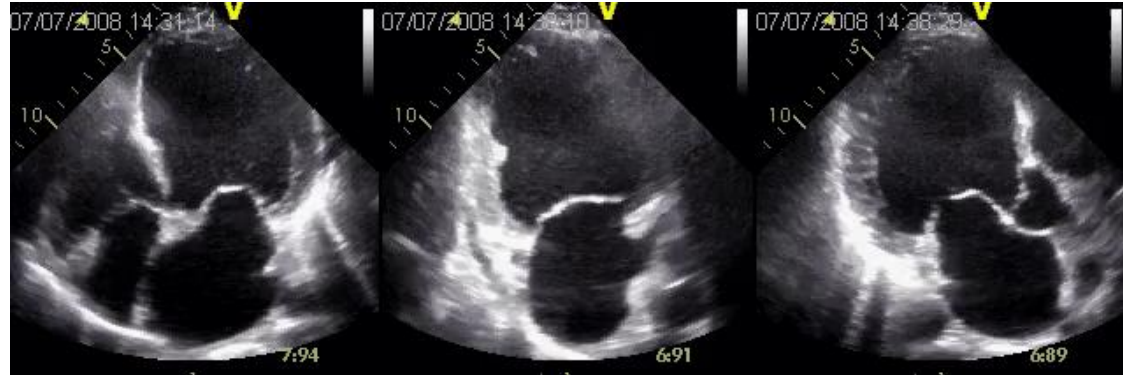
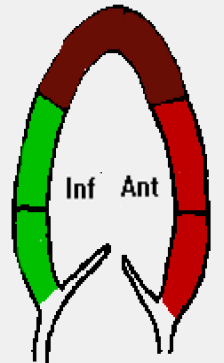
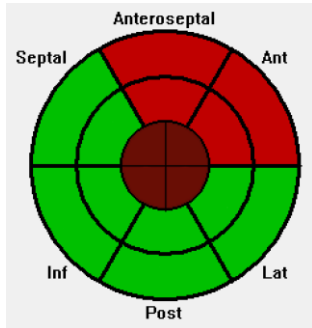


A Patient with STEMI



What antiplatelet and/or oral anticoagulant therapy (OAT) should she be treated with?

- 1) DAPT only
- 2) Double therapy (OAT + single antiplatelet Rx)
- 3) Triple therapy (OAT + DAPT)



Prevention of LV Mural Thrombus After STEMI: Current Guidelines

COR	LOE	ACC/AHA Recommendations
I ib	C	Anticoagulant therapy* may be considered for patients with STEMI and anterior apical akinesis or dyskinesis

*Text states therapy can be limited to 3 months

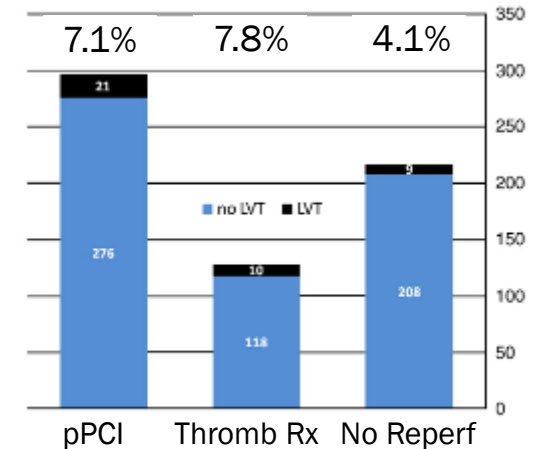
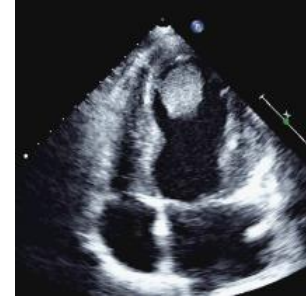
ESC 2012 STEMI Guideline Text (no formal recommendations)**

- Anticoagulation **should be considered** in patients with large anterior wall motion abnormalities, if they are at low risk of bleeding, to prevent the development of thrombi.

**No specific prevention recs or text in ESC 2017 STEMI guideline

LV Thrombus After Acute MI: Sobering Study Data

- In patients with anterior STEMI, reported LV thrombus rates detected by echo in most studies are in the range of 6-30%
- Up to 50% of LV thrombus are not identified on the initial echo but only on subsequent echo
- Compared to MRI for detection of thrombi, echo has a sensitivity of only 21-24%
- In patients with anterior STEMI treated with primary PCI and DAPT, reported LV thrombus rates detected by echo range from 4-22%



Incidence of LV Thrombus Among
Patients with Anterior STEMI

Osherov AB et al. Am Heart J 2009; Porter A et al. Cor Artery Disease 2005; Solheim S et al. Am J Cardiol 2010; Kalra A et al. J Thrombolysis 2000; Shacham Y et al. Am J Cardiol 2013; Delewi R et al. Eur J Radiol 2012; Porter A et al. Cor Artery Disease 2005

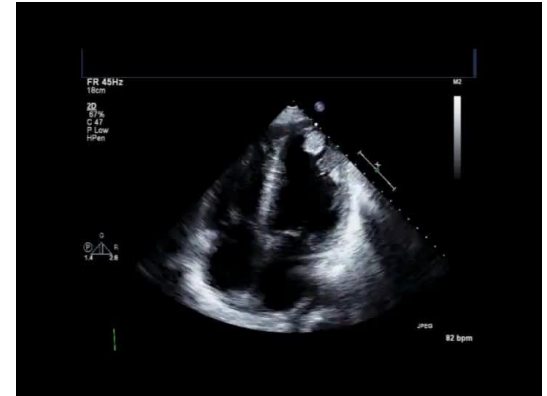
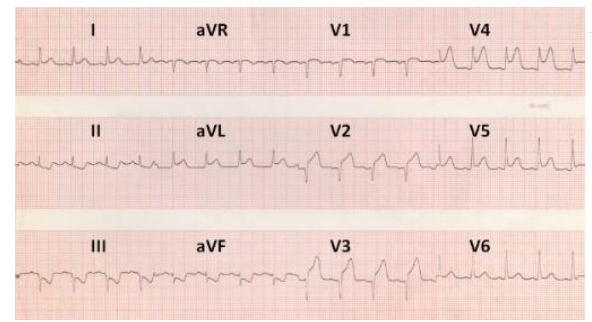


A Patient with STEMI

- You choose to treat the patient only with DAPT
- Follow-up echo 40 days later to re-assess left ventricular function reveals a mobile left ventricular thrombus

How would you treat the patient now?

- 1) Continue just DAPT
- 2) Add warfarin
- 3) Add a new/novel/direct) oral anticoagulant (NOAC/DOAC)



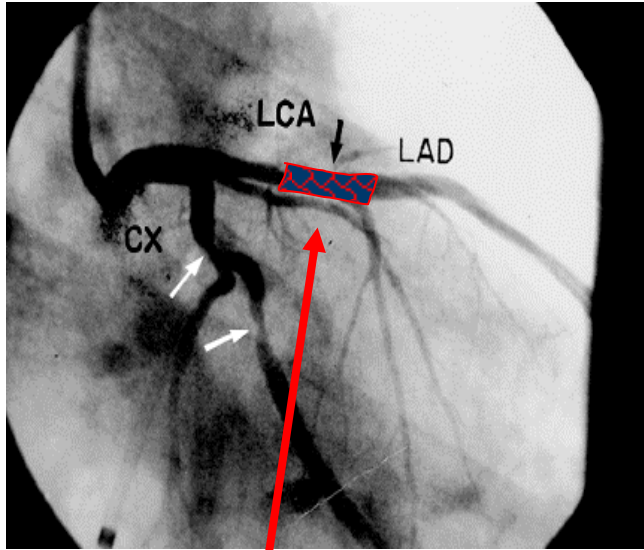
Direct Oral Anticoagulants (DOAC) vs Warfarin in Major Trials of Thromboembolic Prevention and Treatment

Study	Indication	DOAC	Efficacy Outcome with DOAC	Major Bleeding with DOAC
RE-LY	Atrial Fib	Dabigatran 150 mg BID	Superior	Similar
RE-LY	Atrial Fib	Dabigatran 110 mg BID	Similar	Less
ROCKET-AF	Atrial Fib	Rivaroxiban 20 mg qD	Similar	Similar
ARISTOTLE	Atrial Fib	Apixaban 5 mg BID	Superior	Less
ENGAGE-AF	Atrial Fib	Edoxaban 60 mg qD	Similar	Less
ENGAGE-AF	Atrial Fib	Edoxaban 30 mg qD	Similar	Less
RECOVER-I	VTE Rx	Dabigatran 150 BID	Similar	Similar
RECOVER-II	VTE Rx	Dabigatran 150 BID	Similar	Similar
RE-MEDY	VTE Rx	Dabigatran 150 BID	Similar	Similar
Hokusai-VTE	VTE Rx	Edoxaban 60 mg qD	Similar	Similar
EINSTEIN DVT	VTE Rx	Rivaroxiban 20 mg qD	Similar	Similar
EINSTEIN PE	PE Rx	Rivaroxiban 20 mg qD	Similar	Less

Challenging Patients With Atherothrombotic Disease



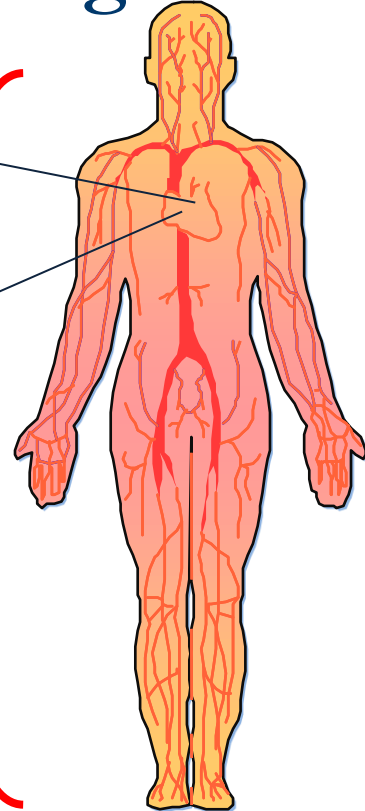
How Much of the ACS Patient Are We Really Treating With Coronary Stenting?



0.0002 m²

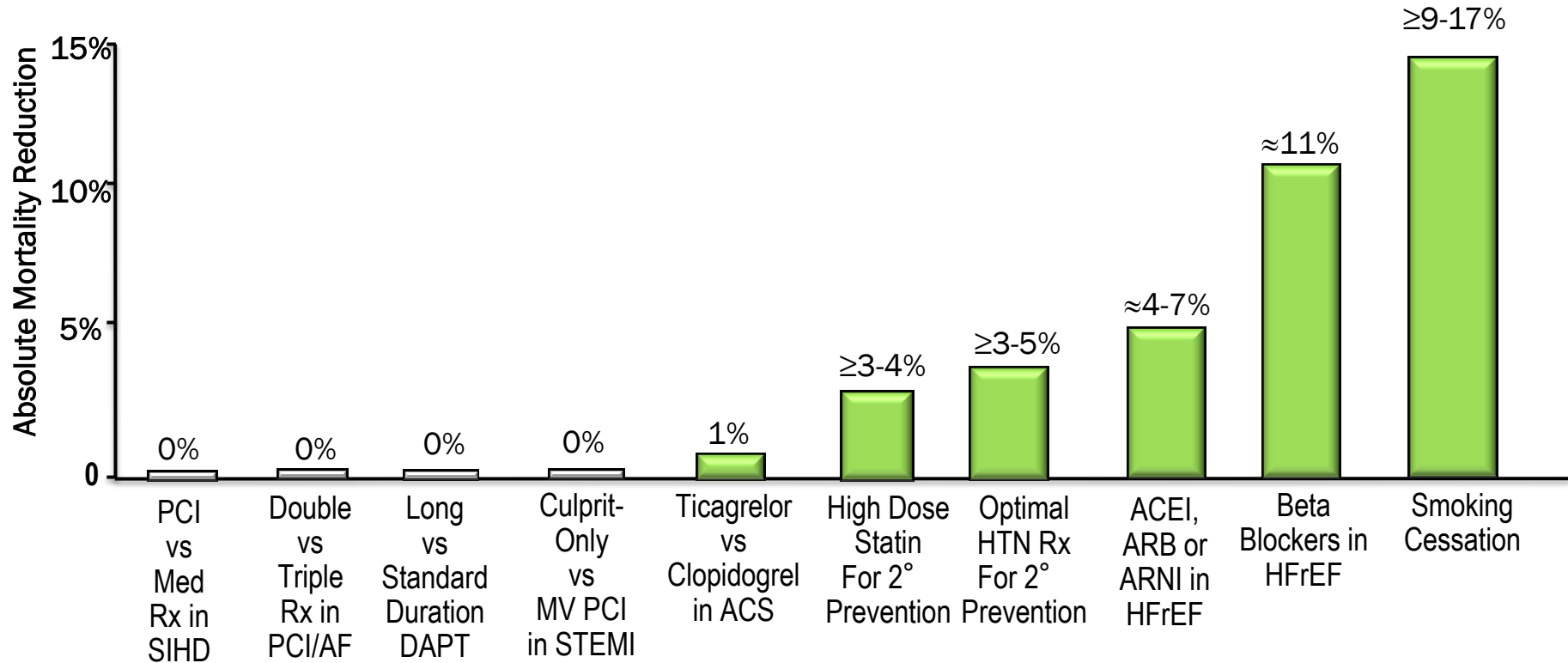
$$= 1 / 5,000,000$$

1,000 m²

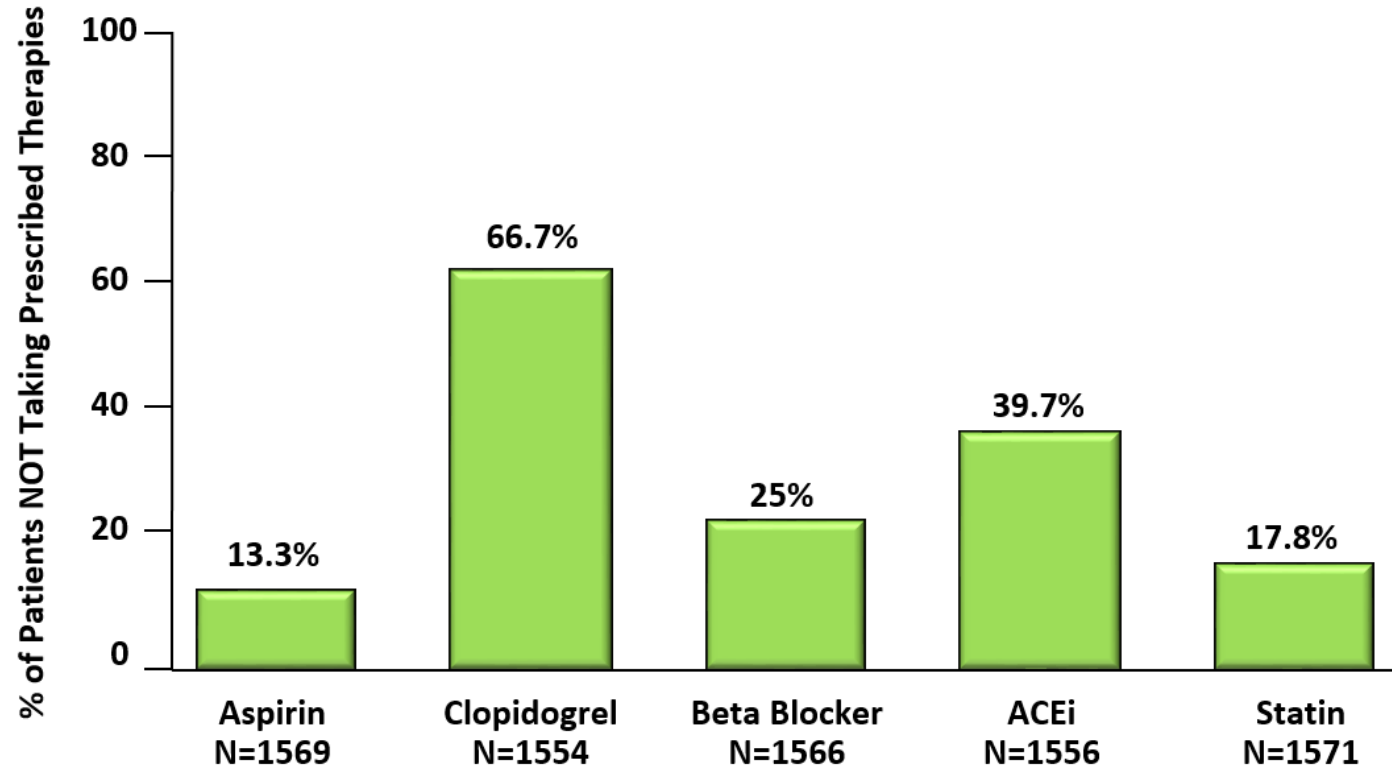


Slide courtesy of Steven Steinhubl

Approximate Absolute Mortality Reduction With Medicines and Interventions



Acute Coronary Syndrome (ACS) Patients **NOT** Taking Evidence-Based Therapy At 1-Year

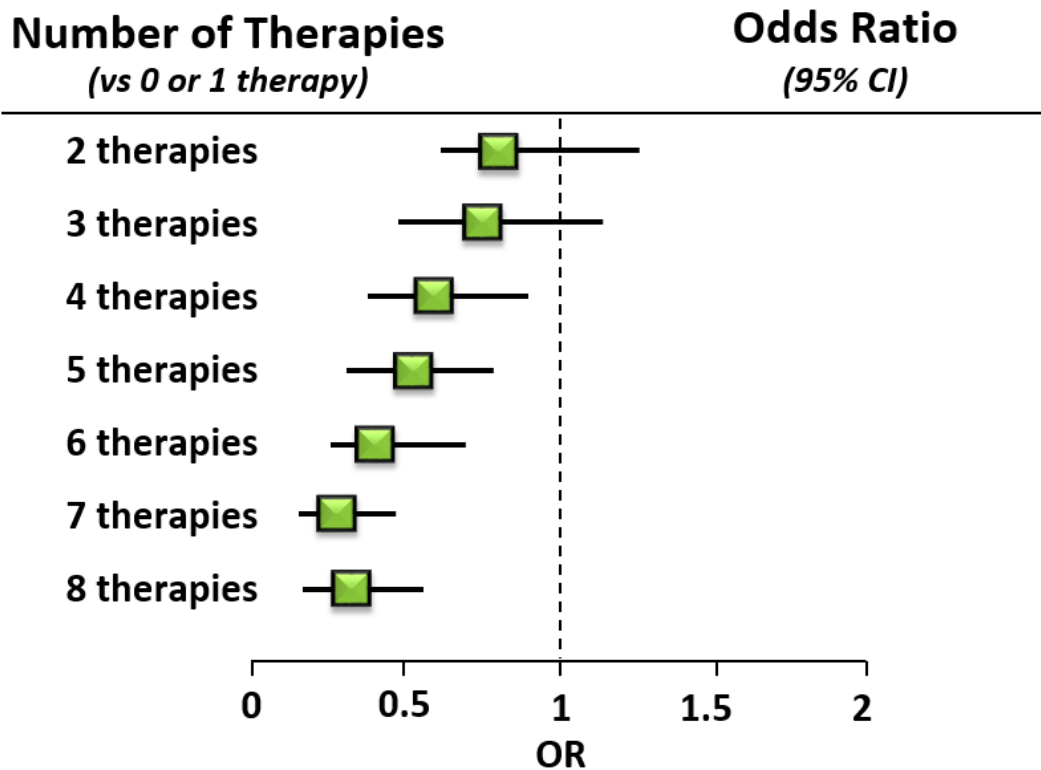


Medication Adherence

- One in three patients fail to fill their prescriptions
- Sixty percent of patients cannot correctly name their medications
- Approximately three of every four patients report they do not consistently take their medications as directed
- 20% of patients take other people's medications

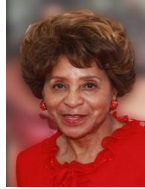
ADHERENCE MATTERS:

Impact of Adherence to Guideline-directed Therapies on 6-month Survival in the GRACE Registry of Patients with ACS



Odds Ratio for 6-month Mortality

Secondary Prevention



COR	LOE	Recommendations
I	A	Lipid management with lifestyle modification and lipid-lowering (primarily high dose, high potency statin) pharmacotherapy
I	A	Blood pressure control (<130/80)
I	A	Complete smoking cessation
I	B	Regular aerobic physical activity (30-60 minutes, 5-7 times/week)
I	A	ACEI/ARB/ARNI, beta blockers, and aldosterone in HFrEF



Smith S, et al. ACCF/AHA 2011 Secondary Prevention and Risk Reduction Update. Stone N, et al. ACC/AHA 2013 Cholesterol Guideline. Yancy C et al. ACC/AHA 2016 HF focused update.