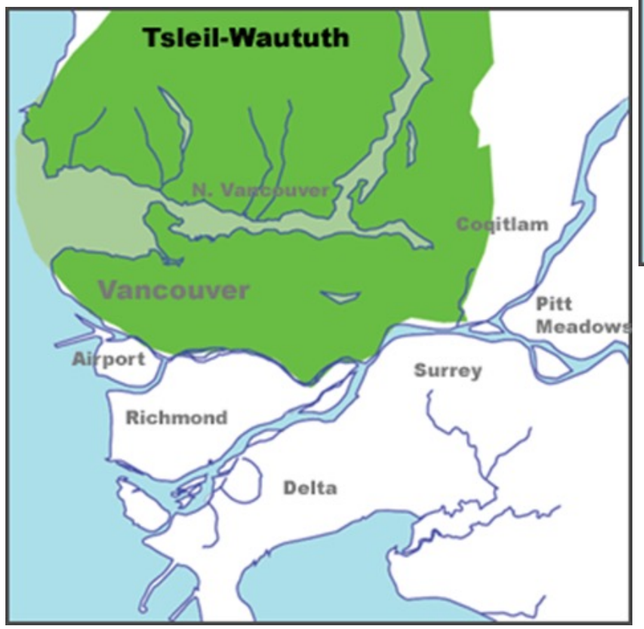
The Treatment of the Acute Coronary Syndromes (ACS)

GRAHAM WONG MD MPH FRCPC FACC FCCS FAHA
DIRECTOR, UBC CARDIOL0GY TRAINING PROGRAM
ASSOCIATE DIRECTOR, VGH CARDIAC INTENSIVE CARE UNIT
CLINICAL PROFESSOR, UNIVERSITY OF BRITISH COLUMBIA

We would like to acknowledge that we are gathered today on the traditional territories of the Musqueam, Squamish and Tsleil-Waututh peoples.

Source: www.johomaps.net/na/canada/bc/vancouver/firstnations/firstnations.html



Outline

- Review the physiology of unstable coronary syndromes
- Pharmacology of ACS management
  - Antithrombotic/antiplatelet agents
  - Cardioprotective agents
  - Anti-inflammatory/cholesterol lowering agents

Atherosclerosis: The Scourge of Affluence

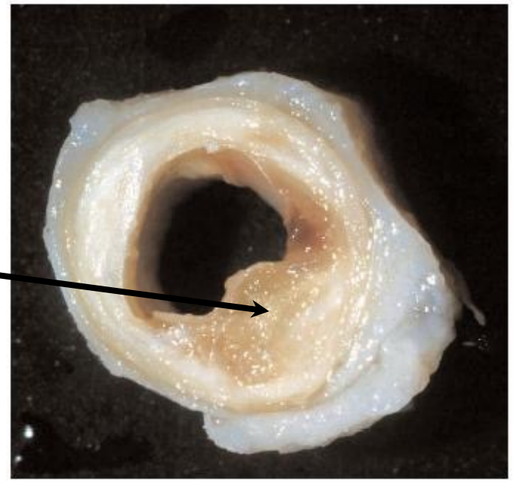
AT RISK

NOT SO MUCH...

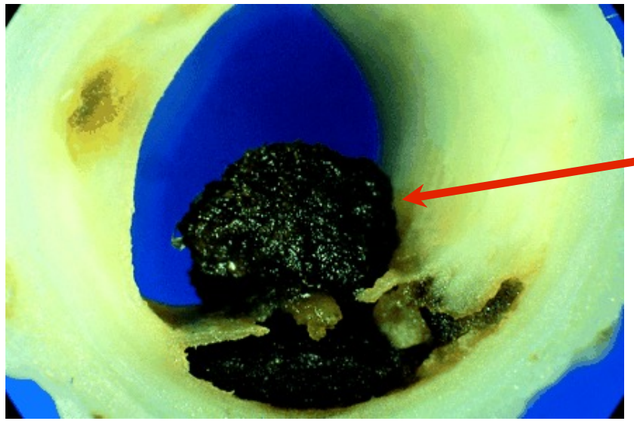
Two presentations of CAD

	STABLE CAD	UNSTABLE CAD
Predictable?	Yes	No
Mortality	Relatively low	Relatively high

Obstructive plaque



Lifestyle disease



Occlusive thrombus

Mortal and morbid disease

Atherothrombosis for laypersons

STABLE CAD (>70% LESION)

Fibrous cap

Soft gooey cholesterol center

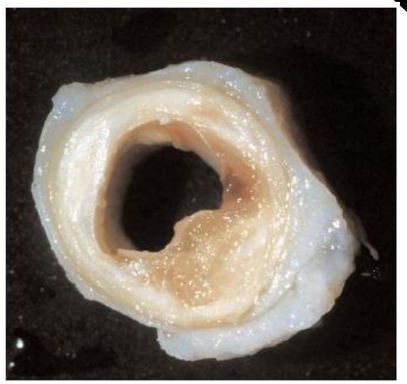
UNSTABLE CAD (ANY SIZE)

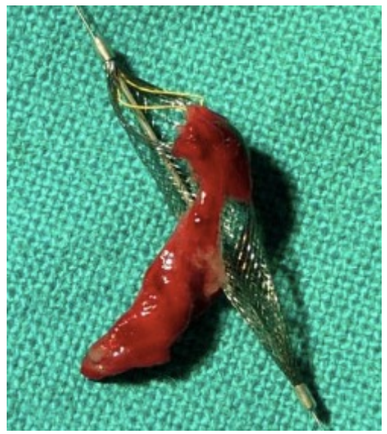
Causes of Instability

Inflammation

Shear stress

Oxidative stress

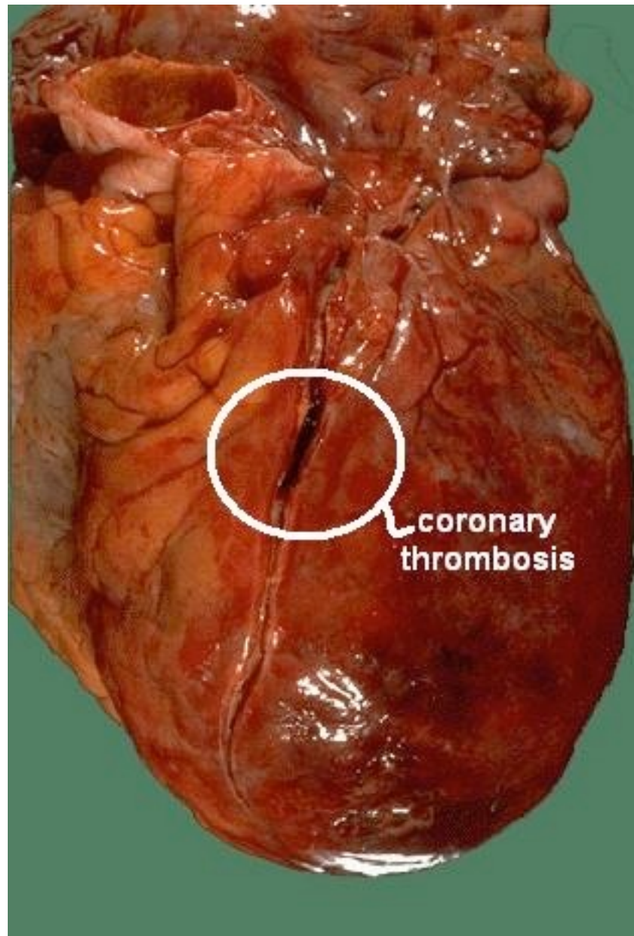




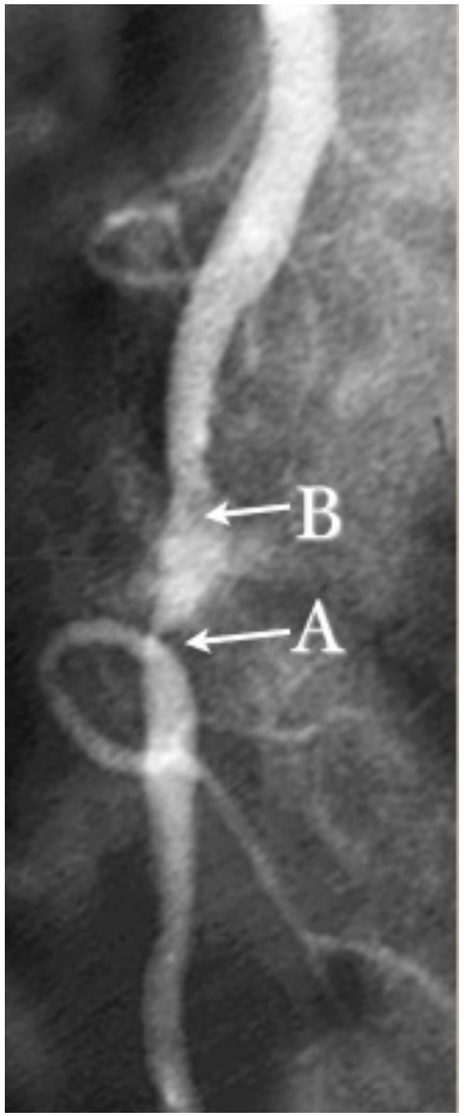
ATHEROSCLEROTIC PLAQUE

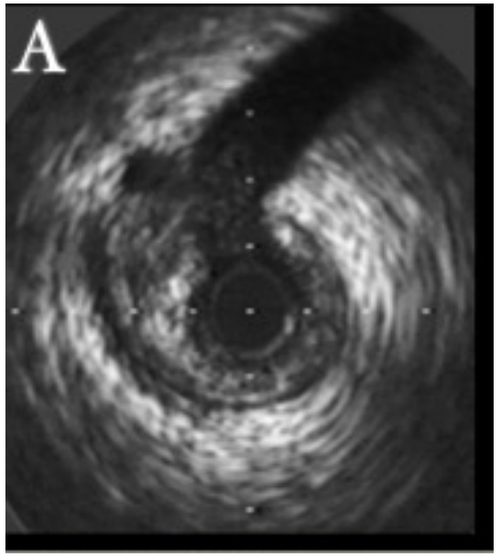
THROMBUS

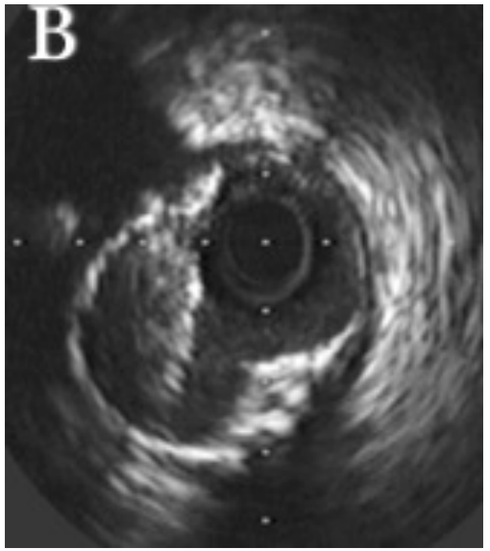
“ATHEROTHROMBOSIS”

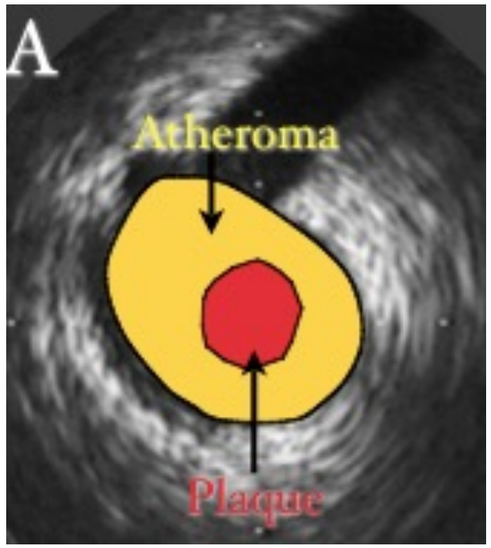


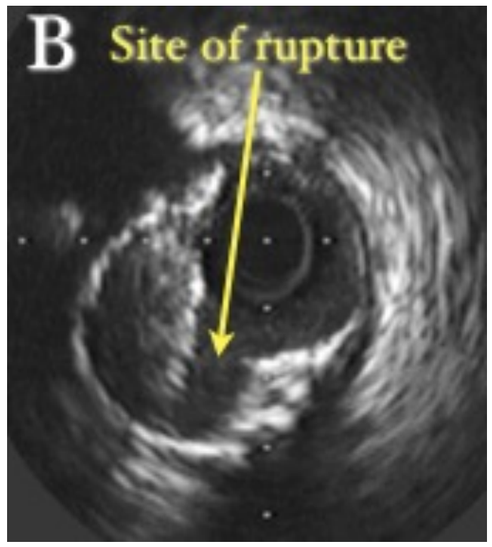
The Active Lesion is Not Always the Tight Lesion: Implications for Therapy











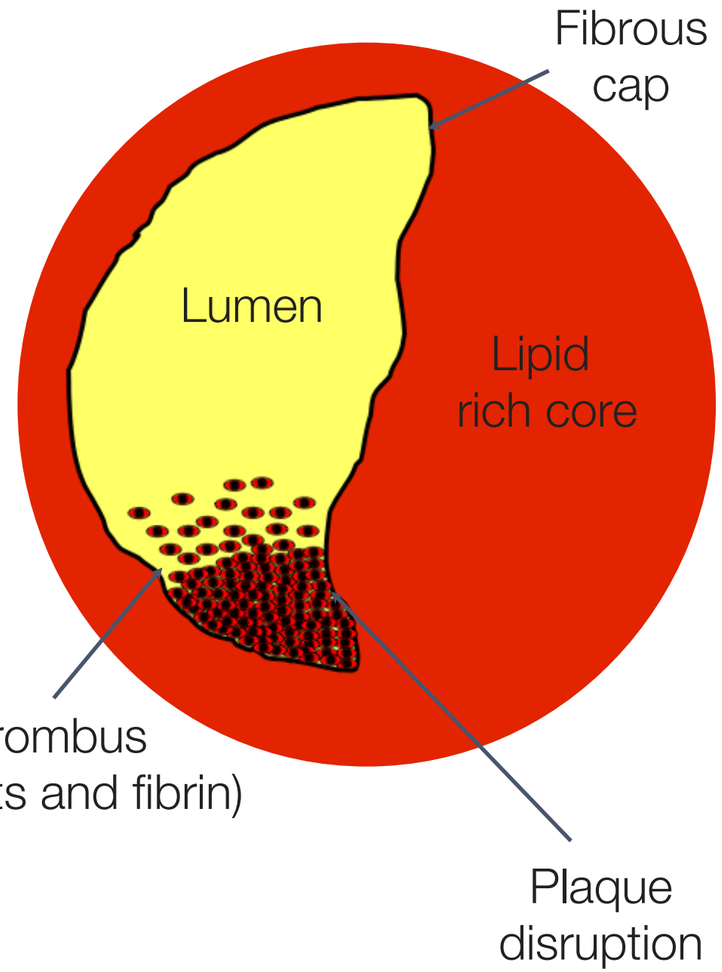
Acute Coronary Syndromes: From Stable to Unstable

MYONECROSIS

Unstable angina

Non ST elevation myocardial infarction

ST elevation myocardial infarction



MECHANISMS OF MORTALITY POST MI

MECHANISM	TIME FRAME	PREVENTION	INTERVENTION
MECHANICAL COMPLICATION (VSD, MR)	SHORT TERM	BETA BLOCKER	EMERGENT CV SURGERY
HEART FAILURE	LONG TERM	USUAL LV ENHANCING RX	TRANSPLANT
RECURRENT MI	LONG TERM	REDUCE/ELIMINATE CV RISK FACTORS (LIPIDS, HTN, DM, SMOKING)	REVASCULARIZATION
VENTRICULAR ARRYHTHMIAS	RANDOM BADNESS	BETA BLOCKER LVEF PRESERVATION	ICD

WARNING:
BORING SCIENCE COMING UP

ACS Causing Ischemia: Its All Economics

SUPPLY

Thrombotic luminal obstruction

DEMAND

Preload
Afterload
Contractility
Heart rate

“MVO_2”

Rebalancing the Economic Imbalance

SUPPLY ⟷ DEMAND

Antithrombotic agents

Antiplatelet agents

Anti-ischemic agents

CARDIOPROTECTION

Anti arrhythmic

Anti inflammatory

Goals of Therapy for any Acute Coronary Syndrome

REPERFUSION OF CULPRIT VESSEL

Preventing re-occlusion	Preventing mechanical complications	Preventing recurrent infarction	Preventing sudden cardiac death
Antiplatelets Antithrombins	Beta blockers ACE-I/ARBs Aldosterone antagonists	Statins Beta blockers Cardiac rehab	AICD Beta blockers

Why We Use The Drugs We Use: Rationale for Drugs in the Treatment of ACS

ANTITHROMBIN ANTIPLATELET	PLAQUE STABILIZATION	CARDIOPROTECTION	SYMPTOM RELIEF
ANTIPLATELET AGENTS ANTITHROMBINS	CHOLESTEROL LOWERING DRUGS (“STATINS”)	BETA BLOCKER STATINS	NITROGLYGERIN ANALGESICS
IMPROVES BLOOD SUPPLY	REDUCES RECURRENT THROMBOSIS	PREVENTS ISCHEMIC RELATED COMPLICATIONS	MAKES PATIENT FEEL BETTER

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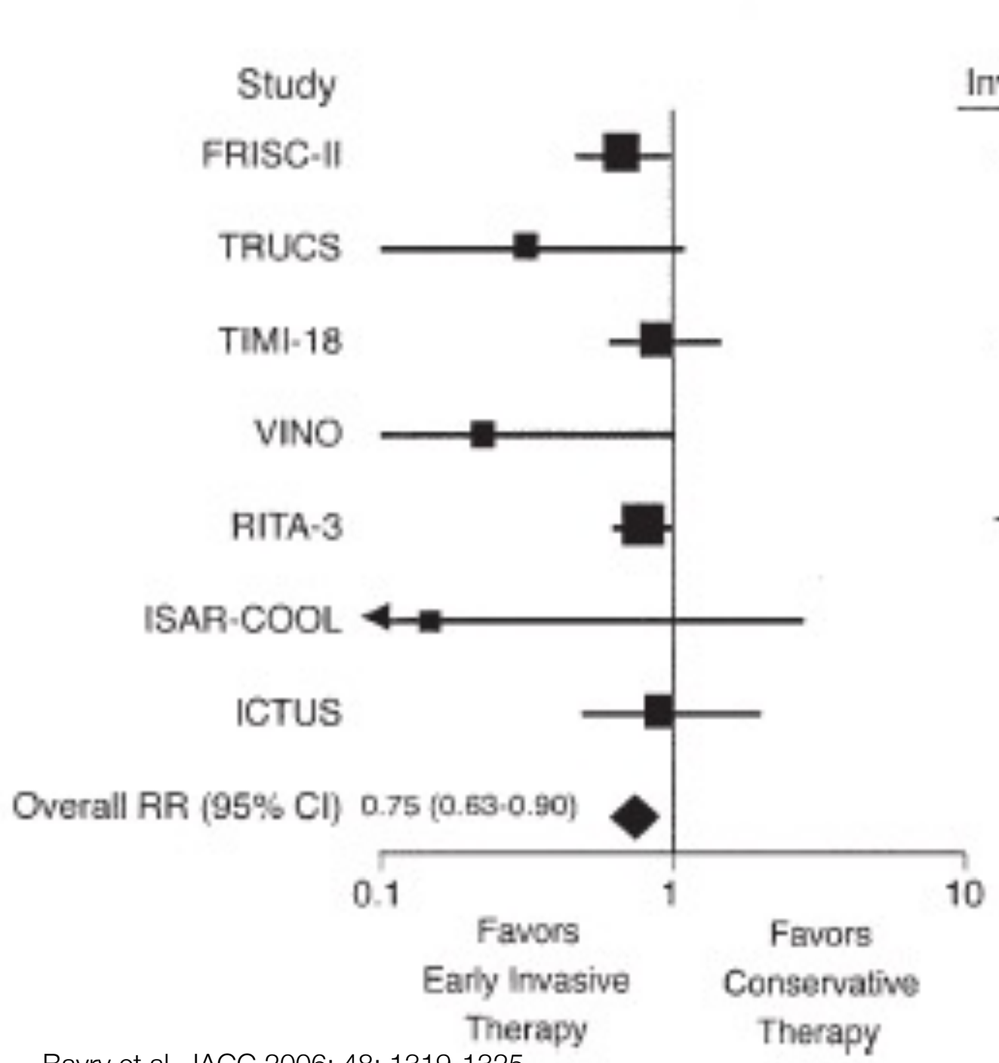
Benefit of Revascularization in ACS



Study	Deaths, n: Invasive	Deaths, n: Conservative	Follow-up, Months
FRISC-II	45	67	24
TRUCS	3	9	12
TIMI-18	37	39	6
VINO	2	9	6
RITA-3	102	132	60
ISAR-COOL	0	3	1
ICTUS	15	15	12

Endpoint	NNT
All cause mortality	62
Myocardial infarction	66
Rehospitalization for ACS	11

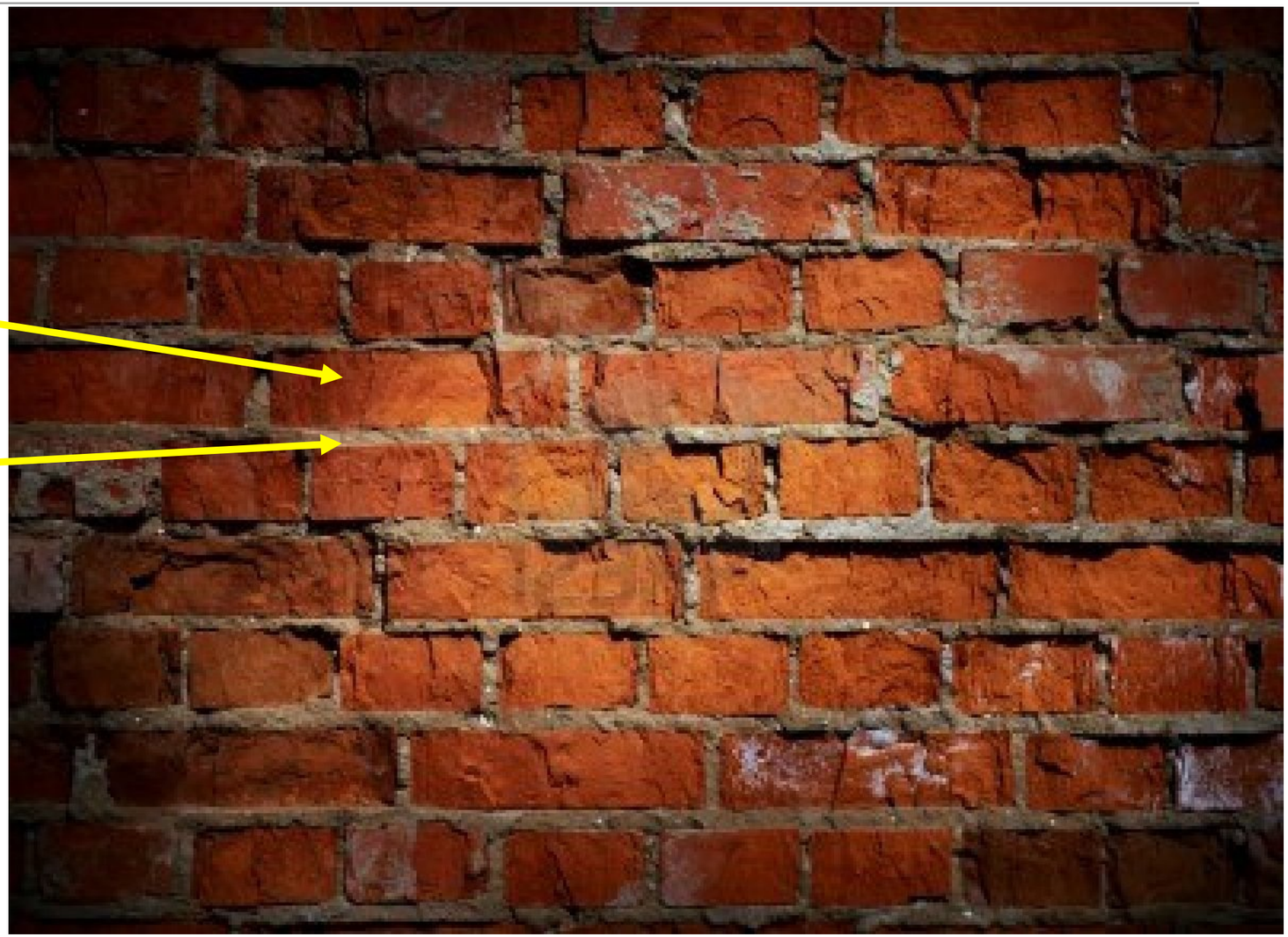
Mean Followup 2 years

Bavry et al. JACC 2006; 48: 1319-1325

Targets For Antithrombotic therapy

PLATELETS

FIBRIN



STANDARD THERAPY FOR ACS:

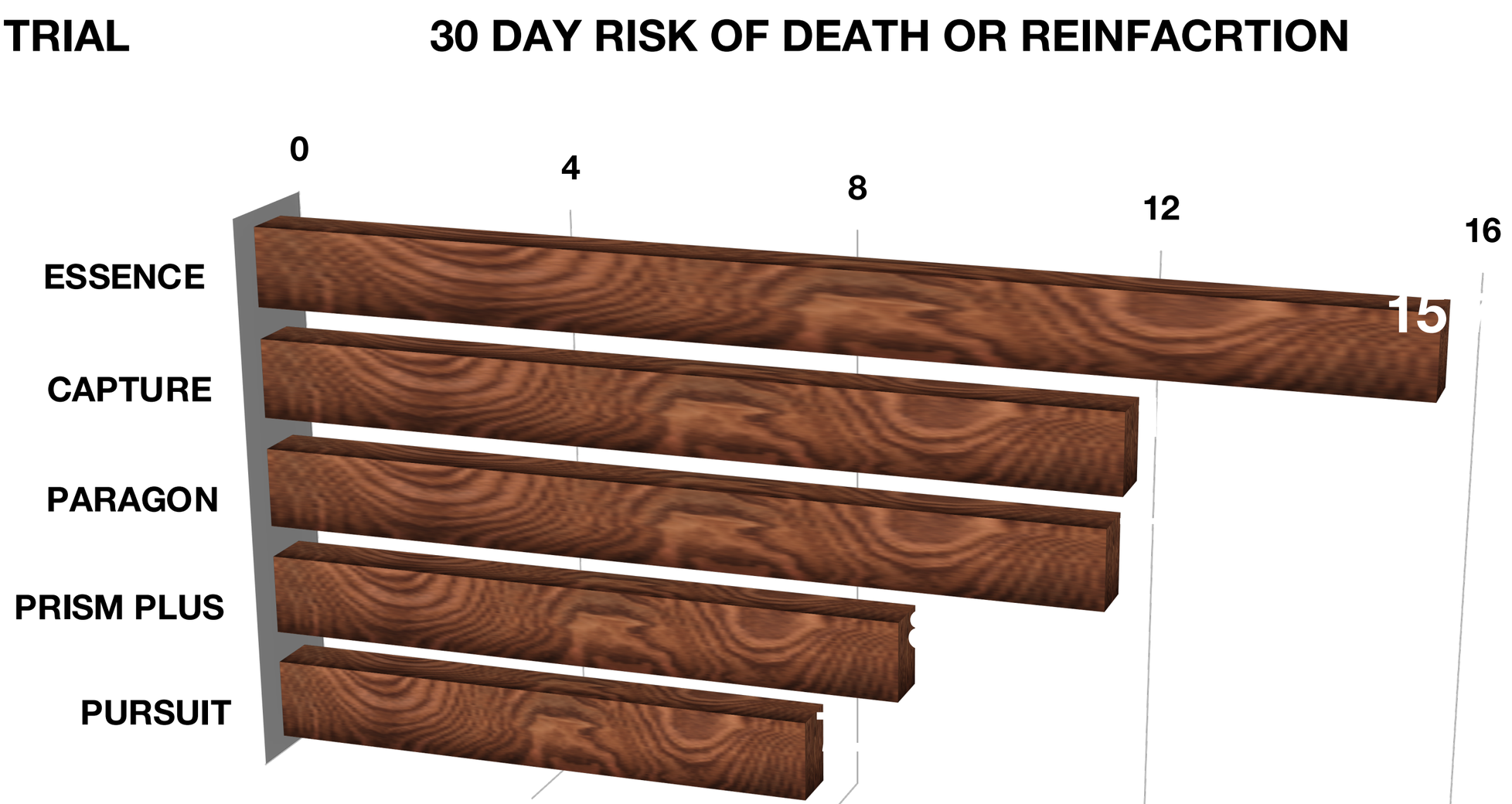
ANTITHROMBIN + ANTIPLATELET

↓ ↓

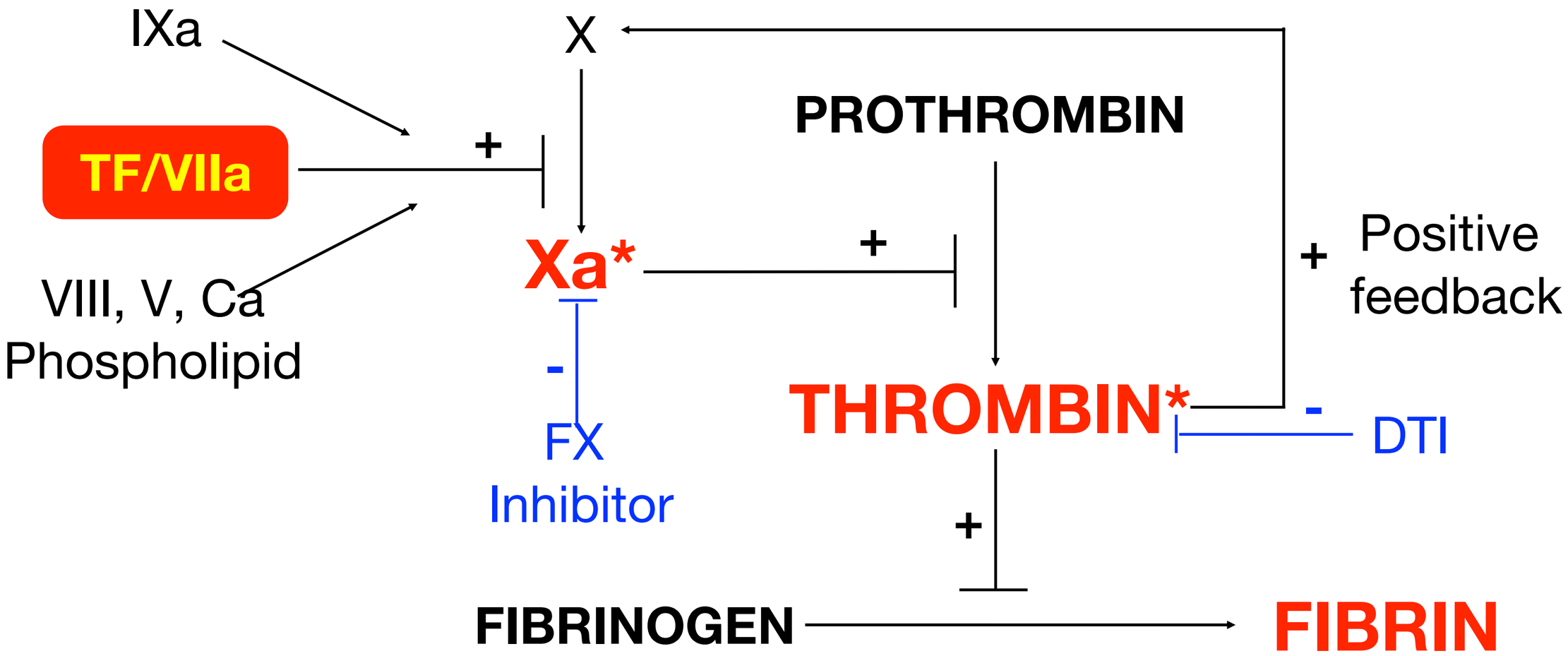
UNFRACTIONATED HEPARIN (UFH)

ASPIRIN (ASA)

UFH and ASA:
How “Good” is Standard Therapy?



The Coagulation Cascade: How to Block Thrombin (and therefore fibrin)



* Blockade with UFH or LMWH via AT

ASA: What Does It Do?

ASA — | Thromboxane A2

Serotonin

Epinephrine

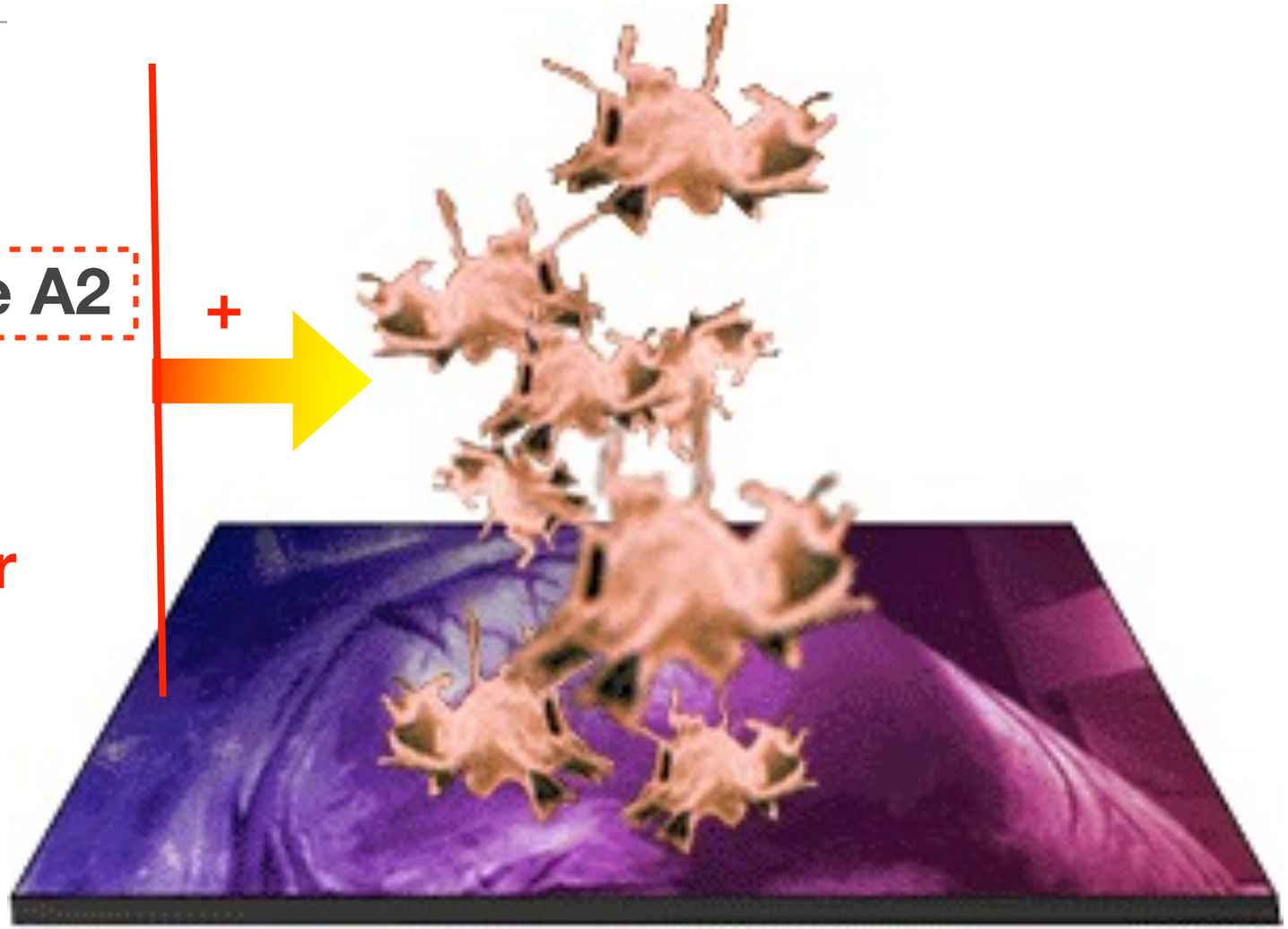
Thromboxane A2

ADP

Collagen

Tissue factor

Thrombin



ACTIVATION

AGGREGATION

Your Options Beyond the Usual.....

ANTIPLATELET

(Aspirin)

Thienopyridine
- -Clopidogrel
- -Prasugrel

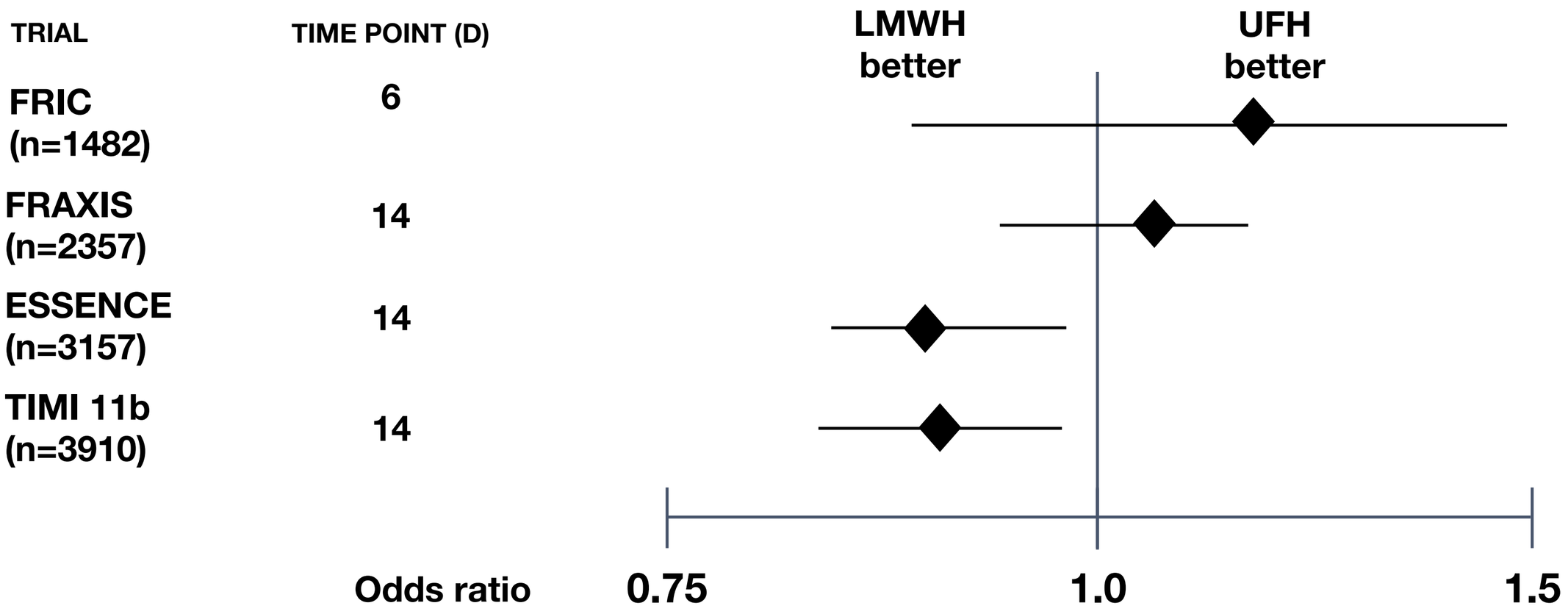
Ticagrelor
GP IIb/IIIa inhibitor (GP2b3a)
Vorapaxar

ANTITHROMBIN

[Unfractionated heparin (UFH)]

Low molecular weight heparin (LWMH)
Fondaparinux (Pure Factor X inhibitor)
Bivalirudin (Direct thrombin inhibitor)
Dabigatran
Rivaroxaban
Apixaban

LMWH vs UFH: Impact on recurrent events (Death, recurrent infarction, recurrent ischemia)



Overall, ~20% improvement seen with enoxaparin vs. UFH; no improvement seen with nadroparin or dalteparin

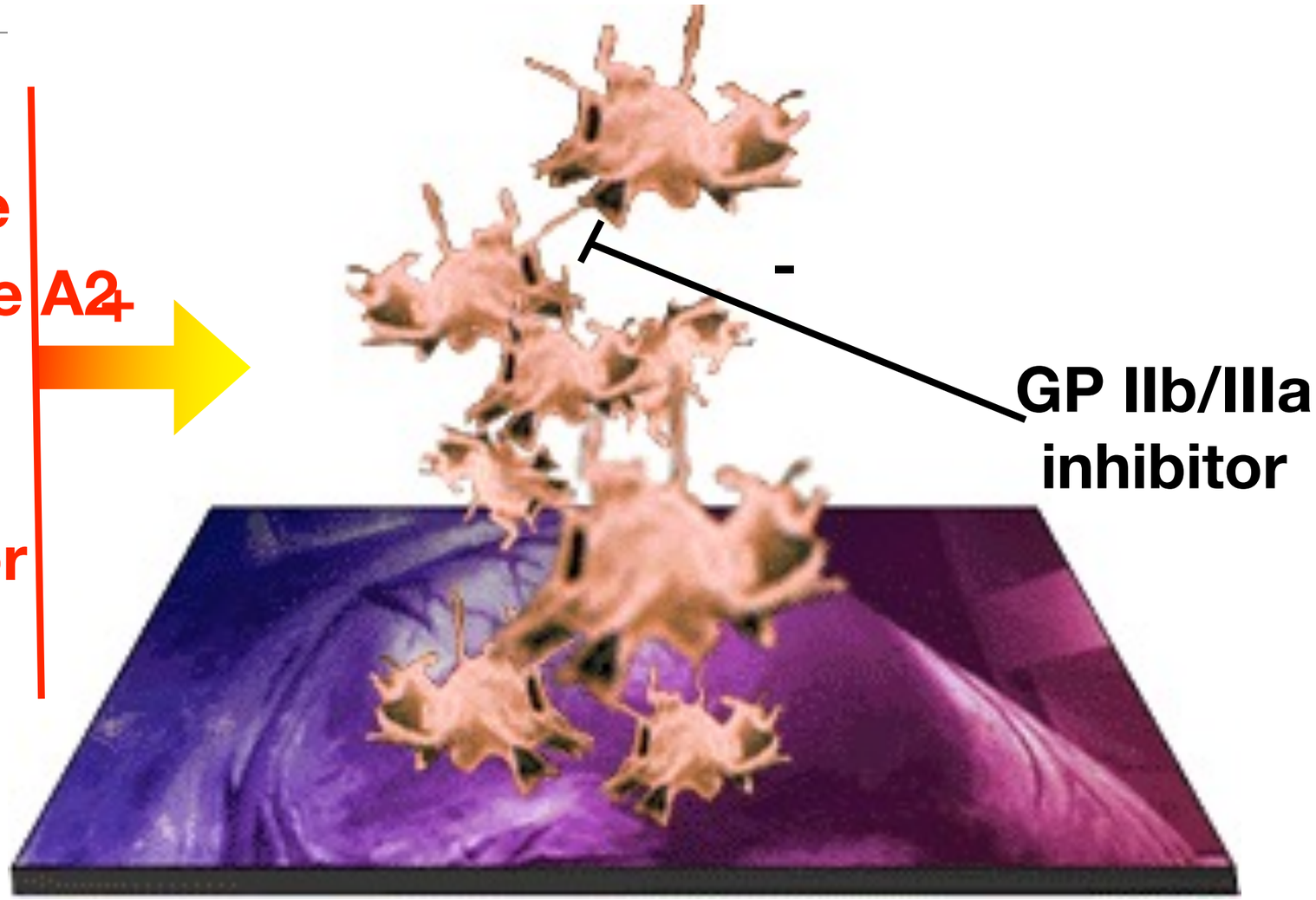
Other Anticoagulants

Drug	MOA	Trial	Works?
Fondaparinux	SC Factor X inhibitor	OASIS 5 FUTURA/OASIS 8	YES
Bivalirudin	IV Direct Thrombin Inhibitor	ACUITY	YES
Rivaroxaban	Oral Factor X Inhibitor	ATLAS ACS TIMI 46	NO (BLEEDS YOU OUT)
Apixaban	Oral Factor X Inhibitor	APPRAISE	NO (BLEEDS YOU OUT)
Dabigatran	Oral Direct Thrombin Inhibitor	RE-DEEM	NO (BLEEDS YOU OUT)
Ximelagatran*	Oral Direct Thrombin Inhibitor	ESTEEM	NO (SMOKES YOUR LIVER)

*Removed from the market

Antiplatelet options beyond ASA…

Serotonin
Epinephrine
ASA — Thromboxane A2
Thienopyridine — ADP
Collagen
Ticagrelor
Tissue factor
Vorapaxar — Thrombin



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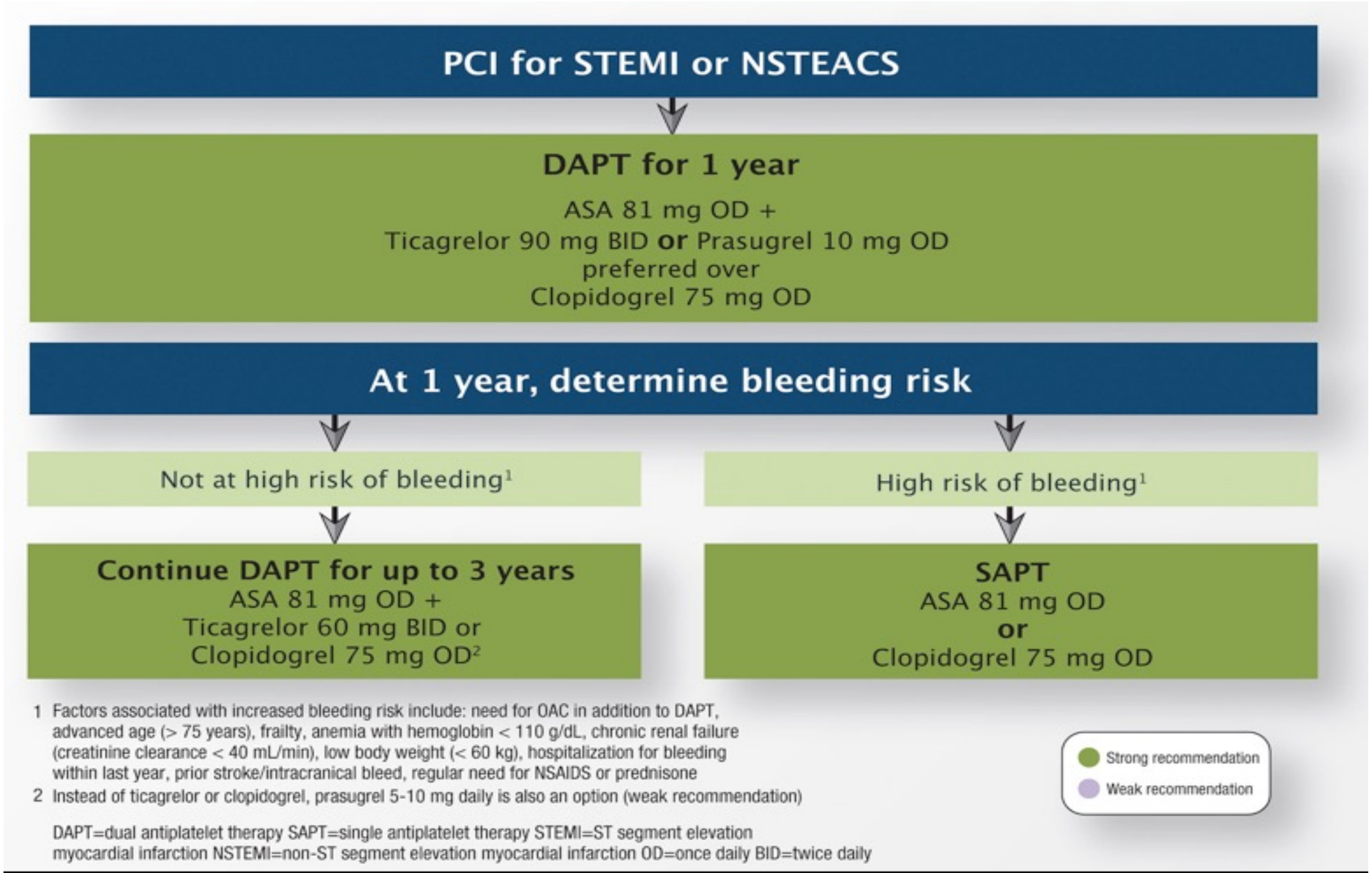
AGGREGATION


PCI for STEMI or NSTEACS
DAPT for 1 year
ASA 81 mg OD +
Ticagrelor 90 mg BID or Prasugrel 10 mg OD
preferred over
Clopidogrel 75 mg OD
At 1 year, determine bleeding risk
Not at high risk of bleeding1
High risk of bleeding1
Continue DAPT for up to 3 years
ASA 81 mg OD +
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SAPT
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1 Factors associated with increased bleeding risk include: need for OAC in addition to DAPT, advanced age (> 75 years), frailty, anemia with hemoglobin < 110 g/dL, chronic renal failure (creatinine clearance < 40 mL/min), low body weight (< 60 kg), hospitalization for bleeding within last year, prior stroke/intracranical bleed, regular need for NSAIDS or prednisone
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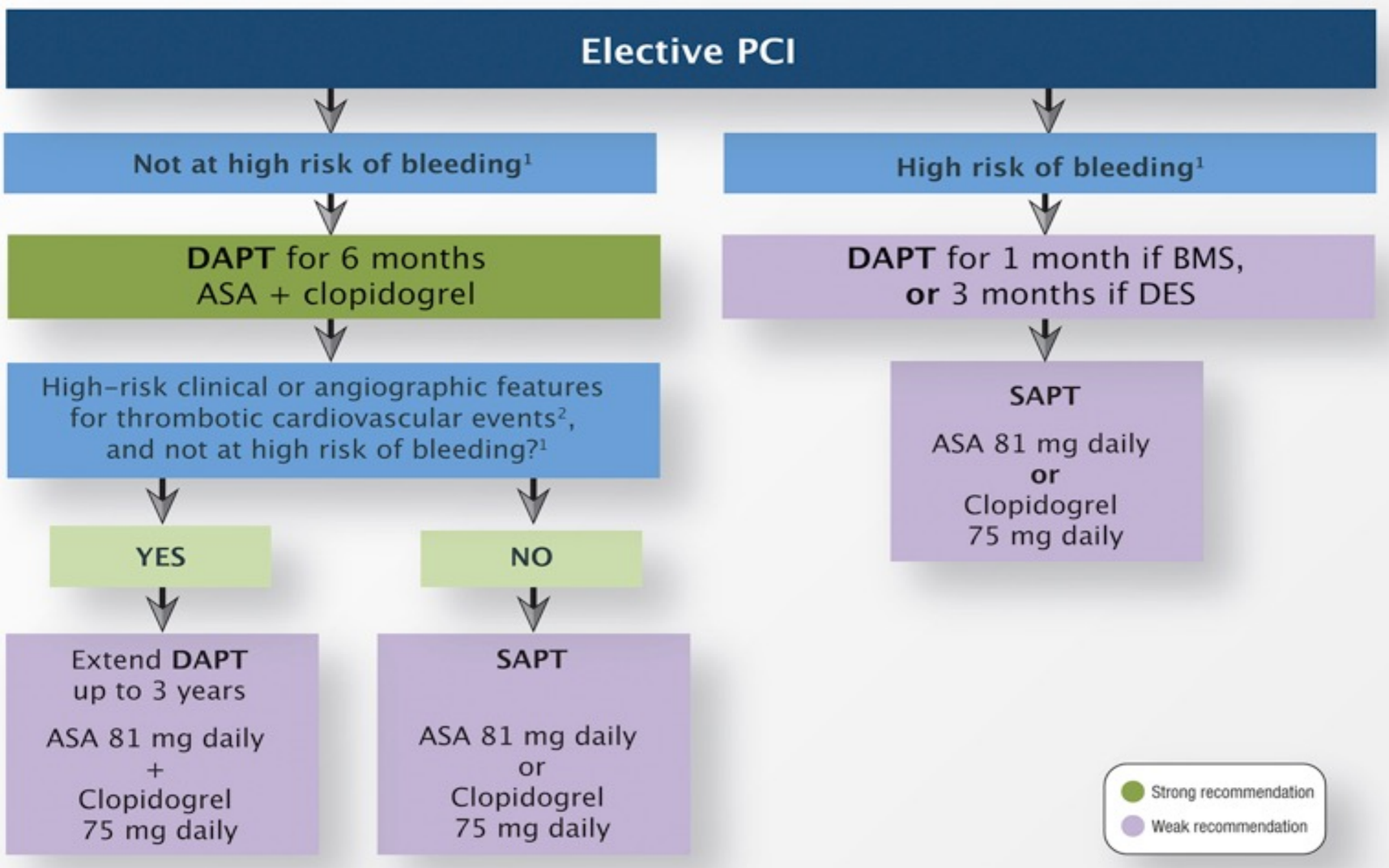
Strong recommendation
Weak recommendation



1 Factors associated with increased bleeding risk include: need for OAC in addition to DAPT, advanced age (> 75 years), frailty, anemia with hemoglobin < 110 g/dL, chronic renal failure (creatinine clearance < 40 mL/min), low body weight (< 60 kg), hospitalization for bleeding within last year, prior stroke/intracranical bleed, regular need for NSAIDS or prednisone

2 Clinical and angiographic features associated with increased risk of thrombotic events include: age > 65, diabetes mellitus, prior myocardial infarction, chronic renal dysfunction (creatinine clearance < 60 mL/min), multi-vessel disease, multiple stents implanted, complex bifurcation lesion, total stent length > 60 mm, chronic total occlusion intervention or bioabsorbable vascular scaffold (BVS) implantation.

DAPT=dual antiplatelet therapy SAPT=single antiplatelet therapy BMS=bare metal stent DES=drug eluting stent

High Risk Features

THROMBOSIS

Clinical	Angiographic
Prior myocardial infarction or troponin positive acute coronary syndrome	Multiple stents (≥ 3 stents implanted, ≥ 3 lesions stented)
Diabetes Mellitus treated with oral hypoglycemics or insulin+	Long lesion length (> 60 mm total stent length)
Chronic kidney disease (creatinine clearance ≤ 60 ml/min)	Complex lesions (birfurcation treated with 2 stents, stenting of chronic occlusion)
Prior stent thrombosis	Left main or proximal LAD stenting
	Multivessel PCI

BLEEDING

1.	Need for OAC in addition to DAPT
2.	Advanced age (> 75 years)
3.	Frailty
4.	Anemia with hemoglobin < 110 g/dL
5.	Chronic renal failure (creatinine clearance < 40 mL/min)
6.	Low Body Weight (< 60 kg)
7.	Hospitalization for bleeding within last year
8.	Prior stroke/intracranical bleed
9.	Regular need for NSAIDS or prednisone

OMG: Which Drugs Do I Choose?

STEP 1 Define your patient

↓

STEP 2 Define the risk category

↓

STEP 3 Define the treatment strategy

↓

STEP 4 Choose your drugs

CATEGORY	CLINICAL	BIOCHEMICAL	ECG

VERY HIGH RISK	• Medically refractory angina or recurrent angina despite intense medical therapy ***AND***
	  ○ New ST depression 2 mm in 2 or more leads ***OR***
	  ○ New deep negative T waves in 2 or more leads
	• Clinical symptoms of cardiogenic shock or advanced heart failure
	• Life threatening arrhythmias (ventricular fibrillation or tachycardia)		

HIGH RISK GRACE RISK SCORE above 140	• N/A	• At least 1 elevated troponin	• New ST depression 2 mm in 2 or more contiguous leads or T wave changes as above ***OR*** • New T wave inversion 2 mm in 2 or more contiguous leads
INTERMEDIATE RISK GRACE RISK SCORE 109 to 140	• Presence of diabetes or renal insufficiency (GFR below 60 mL/min) ***OR*** • Known EF below 40%***OR*** • PCI, ACS or CABG in past 6 months	• Toponin negative	• New ST depression below 1mm or any ST depression but less than 2 leads ***OR*** • New T wave inversion below 1mm or in less than 2 leads
LOW RISK: GRACE RISK SCORE below 109	• No heart failure ***OR*** • No arrhythmias ***OR*** • No recurrent chest pain	• Troponin negative	• Normal

Vancouver CoastalHealth

Providence HEALTH CARE

DRAFT

Feb 25, 2013

ORDERS

COMPLETE OR REVIEW ALLERGY STATUS PRIOR TO WRITING ORDERS

NON ST-ELEVATION MYOCARDIAL INFARCTION (NSTEMI) AND UNSTABLE ANGINA MANAGEMENT ALGORITHM (REGIONAL)

Step 3: ASSIGN PATIENT TO TREATMENT STRATEGY

CATEGORY	MANAGEMENT STRATEGY	TIMELINE TARGET
VERY HIGH RISK	Urgent Invasive	Consult Interventional Cardiologist urgently; angiography to be performed as soon as possible and within 24 hours.
HIGH RISK	Early Invasive	Consult local cardiac specialist; angiography to be performed by end of next business day
INTERMEDIATE RISK	Invasive	Consult local cardiac specialist; non-emergent angiography within 72 hours (pre-discharge)
LOW RISK	Primary Conservative	Refer for angiography only if ischemia recurs prior to discharge or is provocable on follow-up inpatient functional exam

Step 4: DETERMINE ANTI-PLATELET AND ANTICOAGULANT THERAPY

- If possible, calculate patient's CRUSADE Bleeding Risk Score using online calculator available at:
  http://www.crusadebleedingscore.org Crusade Bleeding Score: _____

OR Use anti-platelet guide below to assist with selection of anti-platelet and anticoagulant agents

<table>
<tr><th>STRATEGY</th><th colspan="2">INITIAL ANTIPLATELET</th><th>INITIAL ANTICOAGULANT</th></tr>
<tr><td rowspan="5">Invasive</td><td colspan="2">ASA and clopidogrel</td><td rowspan="5">heparin IV (preferred)
OR
enoxaparin (may be used in patients requiring inter-facility transfer *AND* if eGFR above 30 mL/min)</td></tr>
<tr><td colspan="2">clopidogrel Loading Dose</td></tr>
<tr><td>PCI planned within 6 hours</td><td>600 mg</td></tr>
<tr><td>PCI planned beyond 6 hours</td><td>300 mg</td></tr>
<tr><td>On clopidogrel for past 7 consecutive days</td><td>NO load</td></tr>
<tr><td colspan="3">Avoid clopidogrel in patients at high risk for bleeding</td></tr>
<tr><td rowspan="5">Conservative</td><td colspan="2">ASA and clopidogrel
(AVOID in patients at high risk for bleeding)</td><td rowspan="5">If eGFR above 30 mL/min:
fondaparinux (Preferred agent)
AVOID if patient may undergo PCI in the next 7 days
OR
enoxaparin
OR
Heparin IV
If eGFR is 30 mL/min or below:
heparin IV</td></tr>
<tr><td colspan="2">clopidogrel Loading Dose</td></tr>
<tr><td>clopidogrel-naïve or on clopidogrel for less than 7 days</td><td>300 mg</td></tr>
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ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Hamm et al., EHJ (2011) 32, 2999-3054

What's New Since the CCS Antiplatelet Guidelines in 2018?

- Duration of dual antiplatelet therapy (was longer than 1 year, now probably shorter than 1 year)

- Need for "upstream" P2Y12 inihibitor prior to angiography (Probably don't need it)

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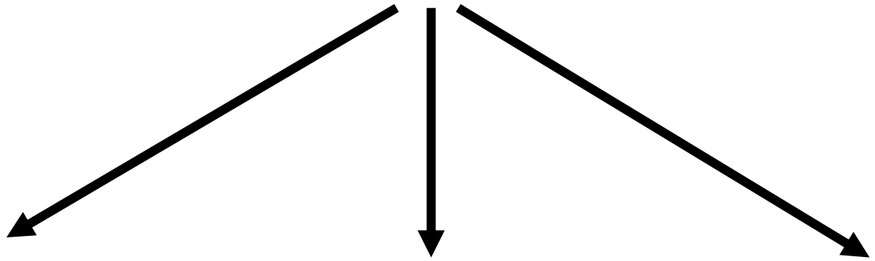
REASONS FOR DAPT POST ACS



TREAT THE INDEX EVENT

PREVENT FUTURE EVENTS

TREAT COMPLICATIONS FROM PCI

RECURRENT THROMBOSIS

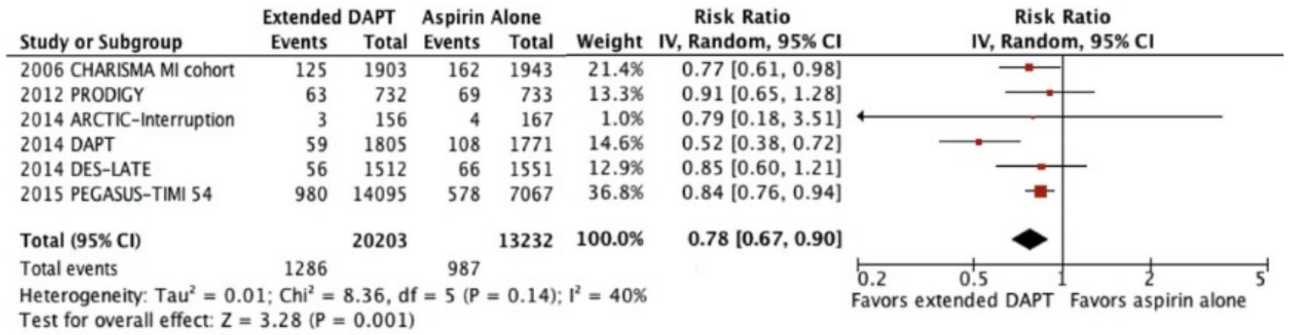
N=33435 post MI pts
Mean F/U 31 months

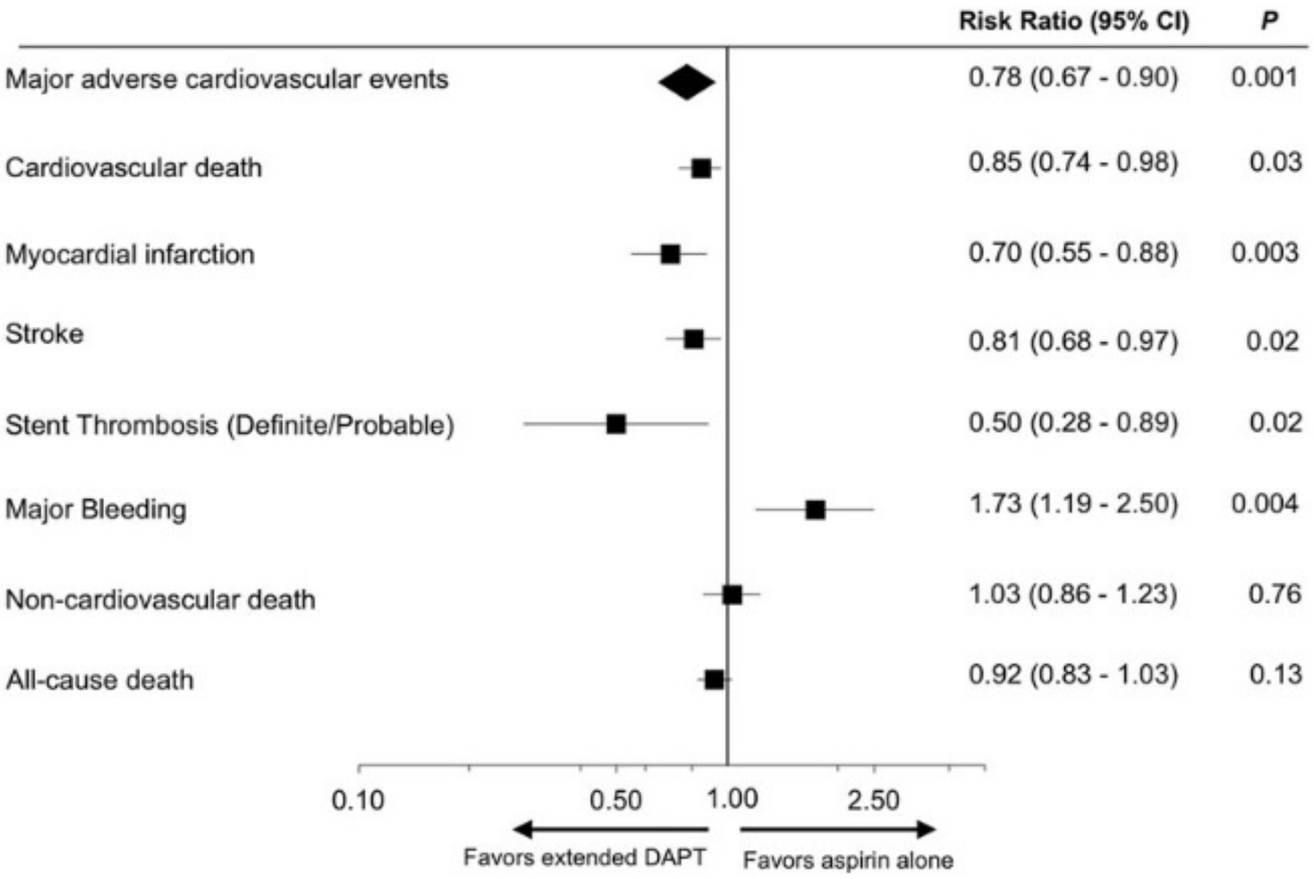
Extended DAPT Post MI:

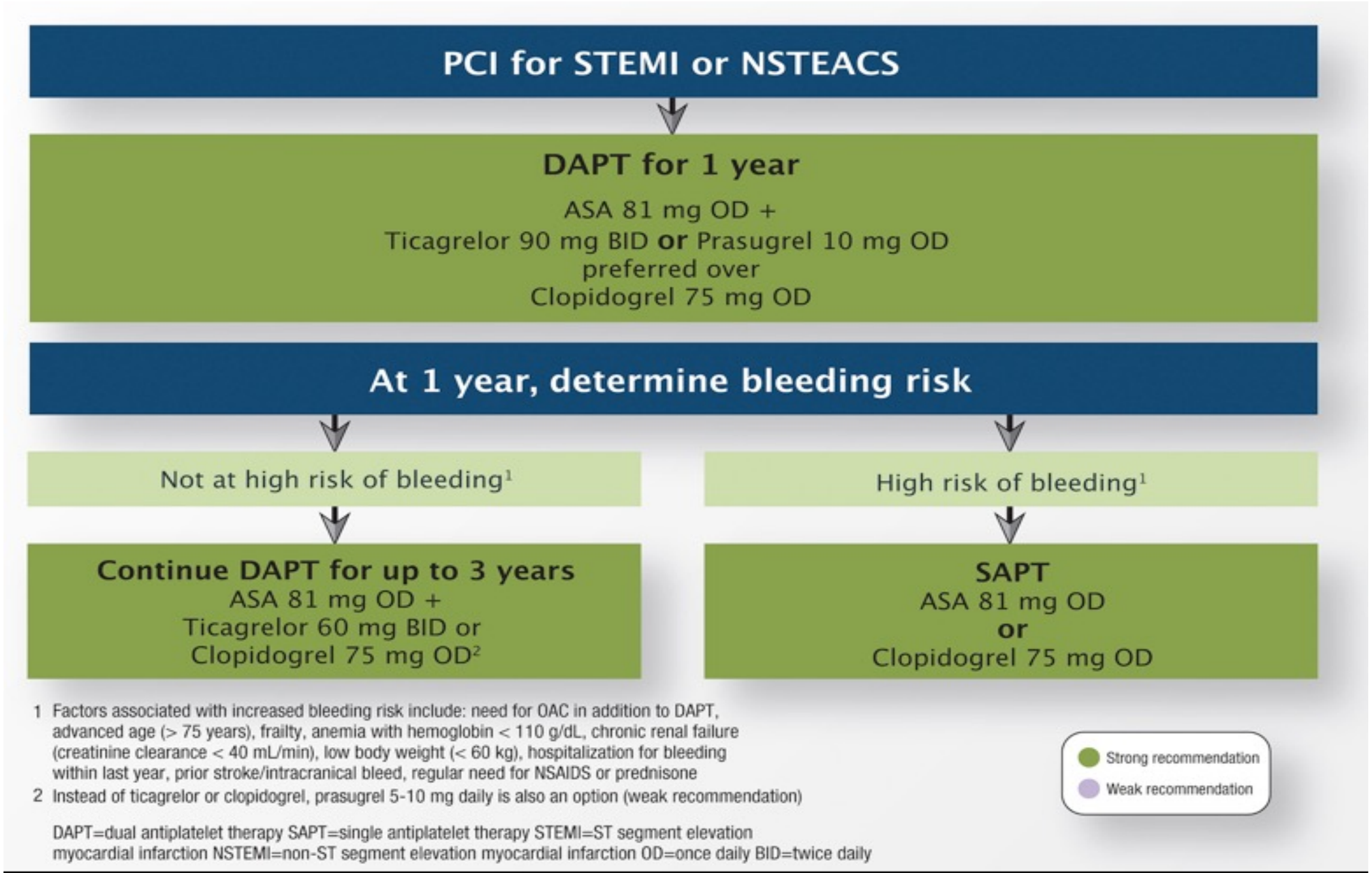
1.1% ARR in MACE
0.3% ARR in CV death
0.76% ARI in major bleeding

No sig difference in all cause mortality
(RR 0.92, 95% C.I. 0.83-1.03)
nor fatal bleeding
(RR 0.91 95% C.I. 0.53-1.5)

Udell et al Eur Heart J 2016; 37: 390-399



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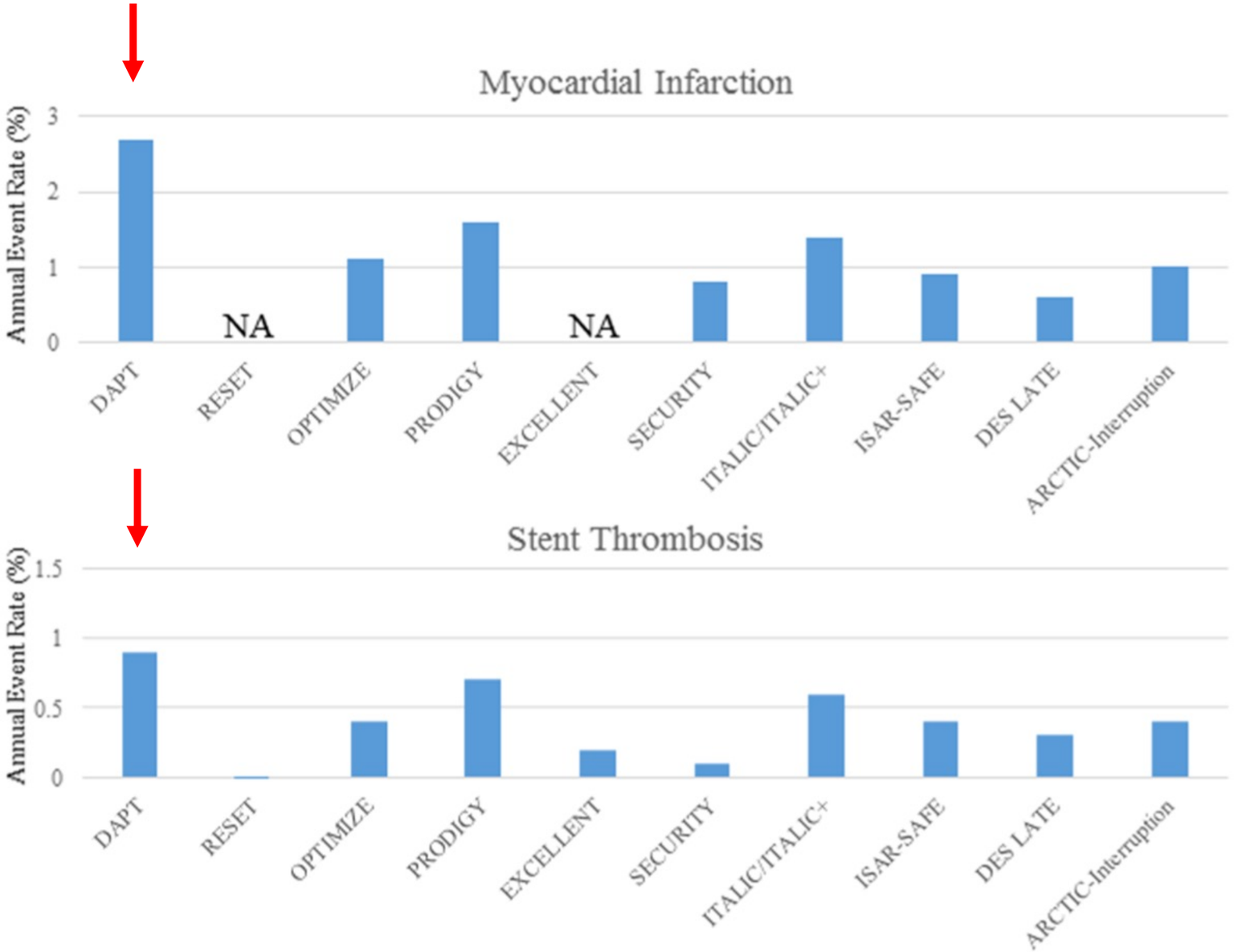
Weak recommendation

IF THE RISK OF RECURRENT THROMBOSIS IS LOW
EXTENDED DAPT MAY NOT BE NECESSARY



DAPT

OR 0.48 (95% C.I. 0.32-0.68)

P<0.001

OR 0.88 (95% C.I. 0.67-1.15)

OTHER STUDIES

DAPT

OR 0.29 (95% C.I. 0.17-0.48)

P<0.03

OR 0.63 (95% C.I. 0.38-1.03)

OTHER STUDIES

Toyota et al. PLoS ONE; 2017; 12: 1-13

Post PCI DAPT Duration: ?CCS Update

Trial	% ACS	P2Y12 Agent	Control	Comparator	Primary Efficacy Endpoint	Primary Safety Endpoint
SMART DATE[1]	100	80% clopidogrel	12M DAPT	6M DAPT	18M MACE (D/MI/CVA)	18M BARC 2-5 bleeding
STOP DAPT2[2]	38	60% clopidogrel 40% prasugrel	12M DAPT	1M DAPT then clopidogrel monotherapy	12M MACE (CV death /MI/CVA/ST/major & minor bleeding)	12M major and minor bleeding
SMART CHOICE[3]	58	76.9% clopidogrel	12M DAPT	3M DAPT then P2Y12 monotherapy	12M MACE (All cause death/MI/CVA)	12M BARC 2-5 bleeding
GLOBAL LEADERS[4]	47	Ticagrelor	12M DAPT 12M ASA	1M DAPT then 23M P2Y12	24M D/MI	24M BARC 3 or 5 bleeding
TWILIGHT[5]	63	Ticagrelor	12M DAPT after 3 month run-in	Ticagrelor monotherapy after 3 month run-in	12M MACE (All cause death/MI/CVA)	12M BARC 2, 3, 5 bleeding

1. Lancet 2018; 391: 1274-84. 2. JAMA 2019; 321: 2414-27 3. JAMA 2019; 321: 2428-37. 4. Lancet 2018; 392:940-9 5. NEJM 2019; DOI: 10.1056/NEJMoa1908419

FACTOR	MASTER DAPT	STOP DAPT2	STOP DAPT2 ACS
POPULATION	STABLE AND UNSTABLE CAD	STABLE AND UNSTABLE CAD	UNSTABLE CAD (1161 FROM STOPDAPT 2 AND 3008 FROM STOPDAPT2 ACS)
N	4434	3009	4169
MEAN AGE (YRS)	76	69	67
% FEMALE	31	22	21
% ACS	48	38	100
% STEMI	12	18	56
% ON OAC	37	0 (OAC USE AN EXCLUSION)	0 (OAC USE AN EXCLUSION)
TYPE OF MONOTHERAPY P2Y12	CLOPIDOGREL (56%)	CLOPIDOGREL (100%)	CLOPIDOGREL (100%)
TYPE OF STENT	ULIMASTER BIODEGRADABLE STENT	COBALT CHROMIUM EES (XIENCE)	COBALT CHROMIUM EES (XIENCE)
BARC 3/5 BLEEDING(%) (STANDARD THERAPY)	2.5	1.81	1.31

My Take

- If you use a inherently less thrombogenic stent you don't need always prolonged DAPT
- Clinical factors such as indication for stenting may increase thrombogenic risk and mandate longer DAPT
- If you choose SAPT you should go with a P2Y12 instead of ASA
- Optimal duration of DAPT post PCI still unclear and is NOT a "one size fit all"
  - Probably less than 1 year, probably more than 1 month

The “Duh” Slide

- If you are high risk for bleeding and not at very high risk for an ischemic event: a truncated course of DAPT makes sense
- If you are at high risk for an ischemic event and not at very high risk for bleeding: a truncated course of DAPT may not make sense

What's New Since the CCS Antiplatelet Guidelines in 2018?

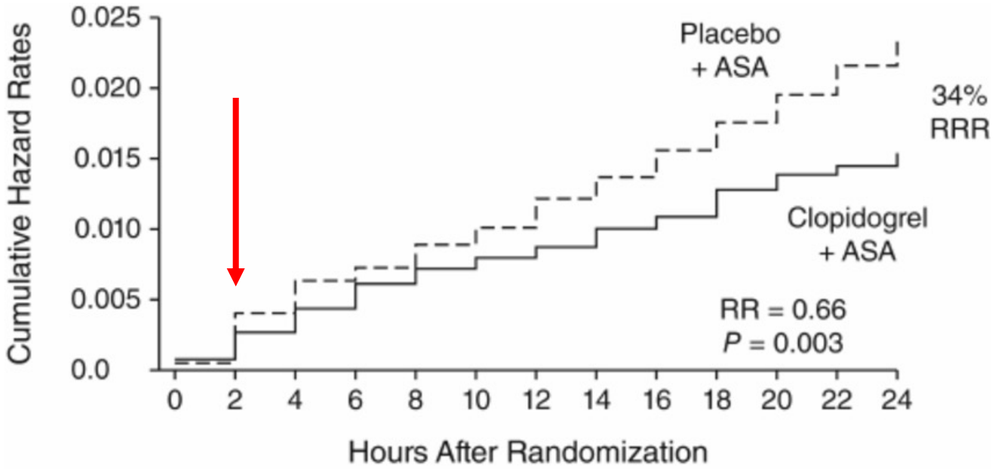
- Duration of dual antiplatelet therapy (was longer than 1 year, now probably shorter than 1 year)

- Need for "upstream" P2Y12 inhibitor prior to angiography (Probably don't need it)

WHY PRETREAT?

PRO

- Biological plausibility for reduced thrombotic burden
- Early benefit seen (<2hrs) in CURE



CON

- Biological plausibility for increased bleeding
- Classic trials for DAPT not designed to evaluate pretreatment and the only RCT to assess this was negative
- Increase in surgical bleeding
- Benefit of pretreatment may be negated by earlier and more predictable onset of action of more potent direct acting P2Y12 inhibitors
- Potential for delay in surgical revascularization

The main issue that has come up regionally is the impact of the finding of surgical disease for ACS patients who may require emergent/urgent surgical revascularization and the impact of P2Y12 preloading on the timing and bleeding risk of cardiac surgery

Left Main Disease in ACS

- Found in 2-17.8% of patients presenting with ACS (NSTEMI and STEMI) (Boden et al NEJM 1998)
- No clinical predictors are useful at identifying LM disease in ACS patients
- ST elevation in aVR provides ~80% sensitivity and specificity for the identification of LM disease (Yamaji et al. JACC 2001)

How long does it take to block platelets with P2Y12 inhibitors?

AGENT	DOSE (LOAD)	METABOLISM	TIME TO MAXIMUM PLATELET INHIBITION
CLOPIDOGREL	300mg	2 step	6 hours
CLOPIDOGREL	600mg		3 hours
PRASUGREL	60mg	1 step	2-3 hours
TICAGRELOR	180mg	No metabolism needed	1-2 hours

Wallentin. Eur Heart J. 2009; 30: 1964-1977

How long dose it take for the effects of P2Y12 inhibition to wear off?

Recommendations

11. We recommend continuation of ASA in all patients with ACS who require CABG surgery (Strong Recommendation; Moderate-Quality Evidence).
12. To minimize the risk of bleeding, for patients with an ACS who are receiving ticagrelor and need semi-urgent CABG, we suggest a minimum interruption of ticagrelor for 48-72 hours before CABG (Weak Recommendation; Low-Quality Evidence) and recommend an ideal interruption period of 5 days before elective CABG (Strong Recommendation; Moderate-Quality Evidence).
13. To minimize the risk of bleeding, for patients with an ACS who are receiving clopidogrel and need semi-urgent CABG, we suggest a minimum interruption of clopidogrel for 48-72 hours before CABG (Weak Recommendation; Low-Quality Evidence) and recommend an ideal interruption period of 5 days before elective CABG (Strong Recommendation; Moderate-Quality Evidence).
14. To minimize the risk of bleeding, for patients with an ACS who are receiving prasugrel and need semiurgent CABG, we suggest a minimum interruption of prasugrel for 5 days before CABG (Weak Recommendation; Very Low-Quality Evidence) and recommend an ideal interruption period of 7 days before elective CABG (Strong Recommendation; Moderate-Quality Evidence).

AGENT	MINIMUM PERIOD OF INTERRUPTION	IDEAL PERIOD OF INTERRUPION
CLOPIDOGREL	2-3 DAYS	5 DAYS
TICAGRELOR	2-3 DAYS	5 DAYS
PRASUGREL	2-3 DAYS	5 DAYS

Mehta et al. Can J Cardiol 2018; 34; 214-233

EVIDENCE FOR PRELOADING P2Y12 INHIBITORS IN ACS

Timing of Angiography and Pretreatment in the 3 Classic DAPT Trials

TRIAL	TRIAL POPULATION	AGENT	TIMING OF DOSE	TIME TO PCI AFTER RANDOMIZATION
PCI CURE[1]	UA/NSTEMI	CLOPIDOGREL	14 HRS FROM ON SET OF PAIN	10 d
TRITON[2]	NSTEMI/STEMI	PRASUGREL	CATH LAB TABLE	Not stated
PLATO[3]	NSTEMI/STEMI	TICAGRELOR	11 HRS FROM ONSET OF PAIN	41 min

1. Mehta et al. Lancet 2001; 358:527-533 2. Price et al. JACC Cardiovasc Int 2010; 8:806-811 3. Kunadian et al. JACC Cardiovasc In t2013; 6:67

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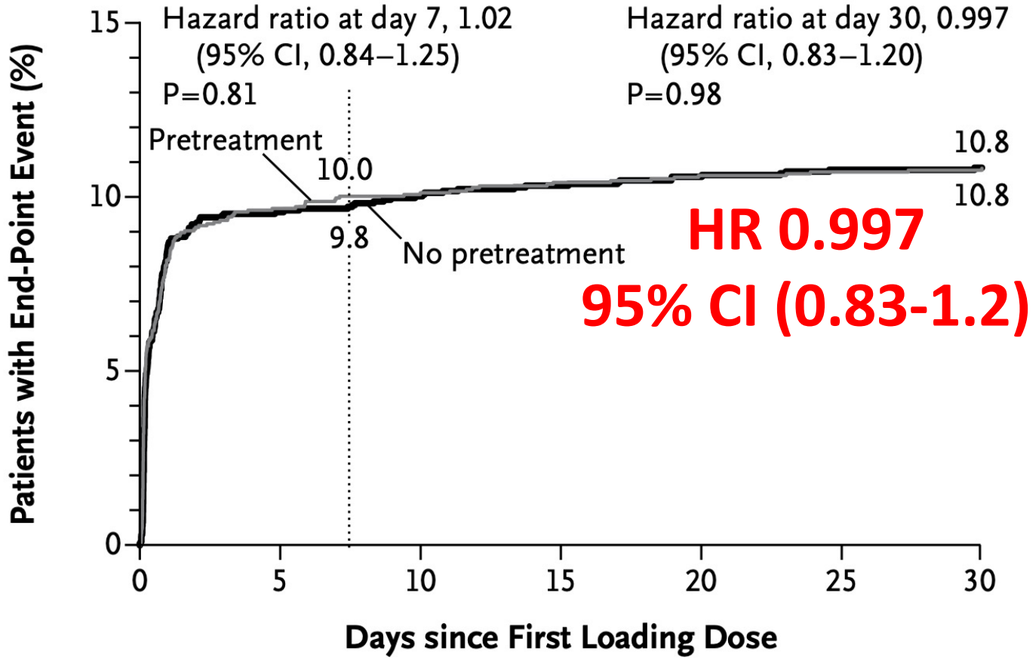
ACCOAST

N=4033 NSTEACS
SCHEDULED FOR ANGIOGRAPHY

PRASUGREL 30mg PRELOAD — **PLACEBO**

ANGIOGRAPHY WITHIN 2-48hrs

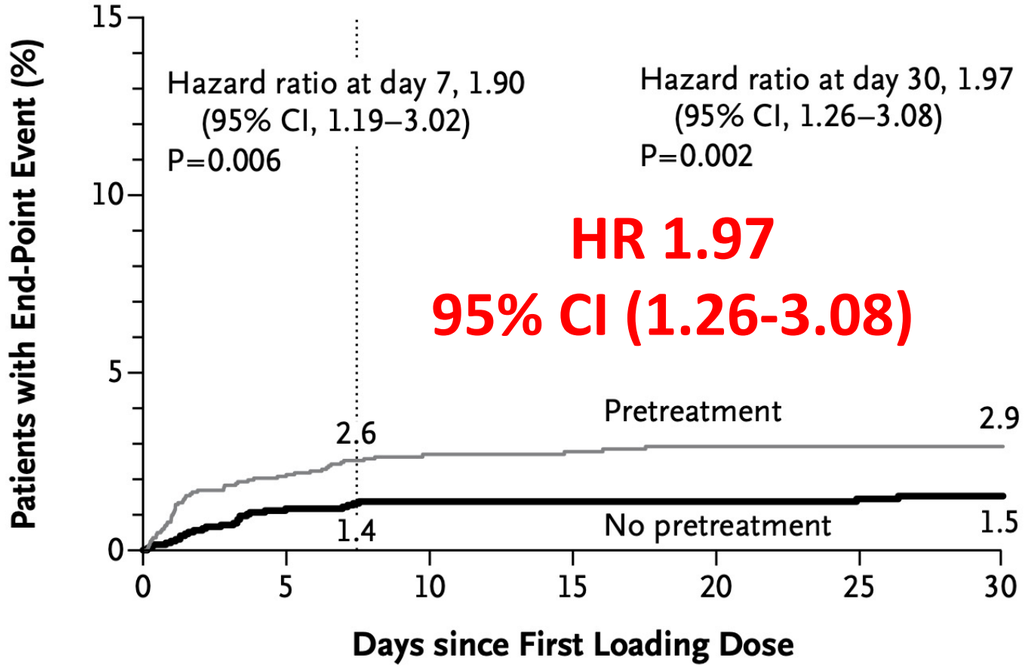
A Primary Efficacy End Point



No. at Risk

No pretreatment	1996	1788	1775	1769	1762	1752	1621
Pretreatment	2037	1821	1809	1802	1797	1791	1616

B All TIMI Major Bleeding

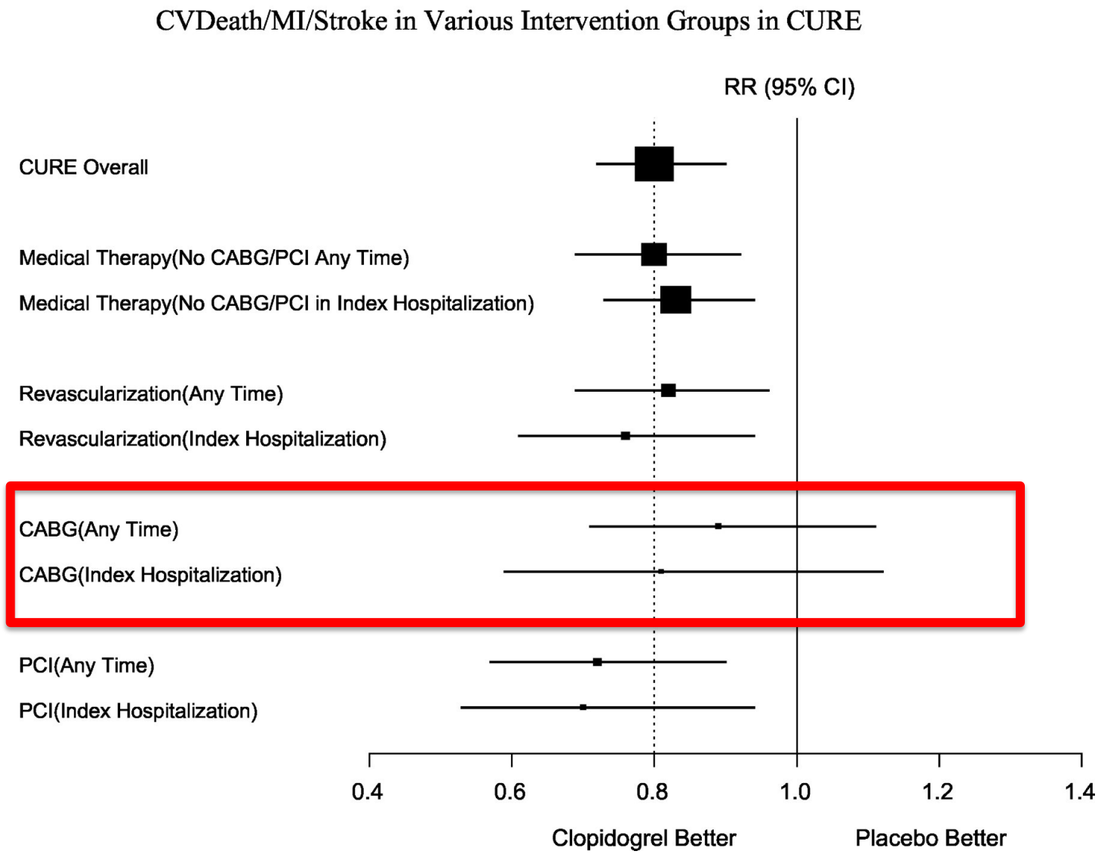


No. at Risk

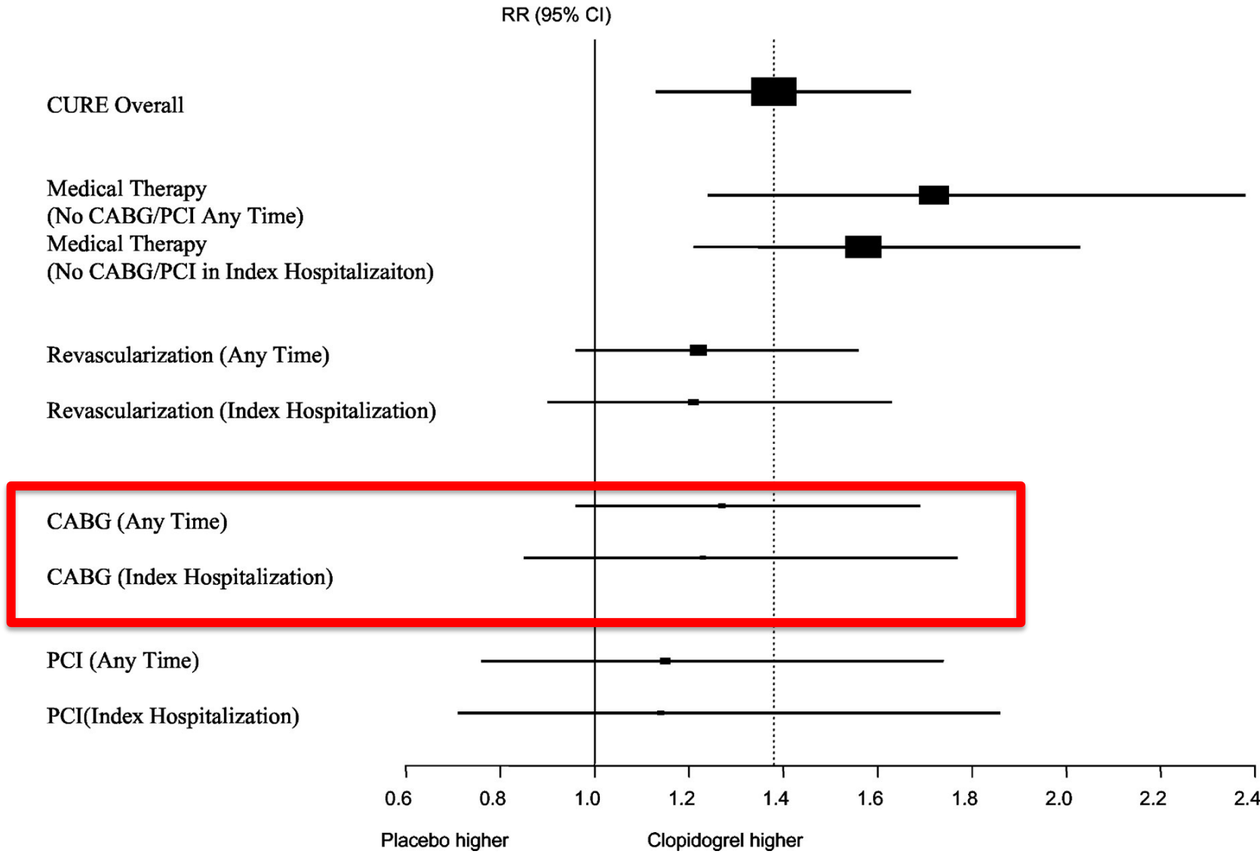
No pretreatment	1996	1947	1328	1297	1288	1284	1263
Pretreatment	2037	1972	1339	1310	1299	1297	1280

Montalescot et al. NEJM 203: 369:999-1010

CURE: Impact of clopidogrel in CABG treated patients with UA/NSTEMI



EFFICACY



SAFETY/MAJOR BLEEDING

Fox et al. Circ 2004: 110:1202-1208

WHAT DO THE GUIDELINES SAY RE: DAPT PRETREATMENT PRIOR TO ANGIOGRAPHY FOR ACS?

- CCS Antiplatelet Guidelines (2011, 2013 and 2018):

  No specific recommendation nor wording. Acknowledged (2013) that DAPT increases CABG related bleeding and discontinuation requires careful calculation of risk/benefit ratio
- AHA/ACC NSTEMI Guidelines (2014):

  Ticagrelor and clopidogrel loading doses given a Ib recommendation. No mention of timing relative to angiography. ASA recommended to be given "as soon as possible".
- ESC NSTE-ACS Guidelines (2020):

  "It is not recommended to administer routine pre-treatment with a P2Y12 receptor inhibitor in patients in whom coronary anatomy is not known and an early invasive management is planned."

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NSTEMI - PCI

Date: _____ Time: _____

MEDICATIONS: (ANTIPLATELETS continued)

Routine pre-treatment with a $P2Y_{12}$ receptor inhibitor in ACS patients, in whom an early invasive management is planned and coronary anatomy is not known, is NOT RECOMMENDED given the lack of established benefit. However, for patients with a planned delayed invasive management strategy (>24 hours), $P2Y_{12}$ receptor inhibitor may be considered based on thrombotic and bleed risk; AND likelihood of requiring urgent cardiac surgery in the next 5 days.

☐ **No ticagrelor or clopidogrel until angiogram performed - *PREFERRED***

Ticagrelor:
- ☐ 180 mg PO STAT, then 90 mg PO BID ***OR***
- ☐ 90 mg PO BID (on ticagrelor for the past 7 days) ***OR***

Clopidogrel:
- ☐ 300 mg PO STAT, then 75 mg PO daily ***OR***
- ☐ 600 mg PO STAT, then 75 mg PO daily ~~(PCI planned within 6 hours)~~ ***OR***
- ☐ 75 mg PO daily(on clopidogrel for past 7 consecutive days)
- ☐ Refer to completed GP IIb/IIIa INHIBITOR FOR ACS ORDERS (REGIONAL) PPO #259

ROUTINE PRETREATMENT WITH A P2Y12 INHIBITOR IN ACS PATIENTS, IN WHOM AN EARLY INVASIVE MANAGEMENT STRATEGY IS PLANNED AND CORONARY ANATOMY IS NOT KNOWN, IS NOT RECOMMENDED GIVEN THE LACK OF ESTABLISHED BENEFIT. HOWEVER FOR PATIENTS WITH A PLANNED DELAYED INVASIVE MANAGEMENT STRATEGY (>24HRS) P2Y12 RECEPTOR INHIBITOR MAY BE CONSIDERED BASED ON THROMBOTIC AND BLEEDING RISK; AND LIKELIHOOD OF REQUIRING URGENT CARDIAC SURGERY IN THE NEXT 5 DAYS

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ORDERS

ADDRESSOGRAPH

COMPLETE OR REVIEW ALLERGY STATUS PRIOR TO WRITING ORDERS

ST-ELEVATION MYOCARDIAL INFARCTION (STEMI): Primary PCI ORDERS (Regional)

(items with check boxes must be selected to be ordered) **(Page 1 of 4)**

Time Processed
RN/LPN Initials
Comments

Date: _____ **Time:** _____ **Weight:** _____ **kg** ☐ **Actual** ☐ **Estimate**

Primary Percutaneous Coronary Intervention (PCI)

Activate Cardiac Cath Lab

VGH: call ext. 55000 and activate Code Hot STEMI

UBC: call Patient Transfer Network (PTN) and activate Code Hot STEMI

MEDICATIONS: heparin (60 units/kg rounded to the nearest 500 units to a maximum of 5000 units)
_____ units IV bolus x 1 dose **(NO MAINTENANCE INFUSION)**

ASA 160 mg chewed and swallowed STAT (ensure patient has received a total dose of 160 mg in the past 12 hours), then ASA enteric coated 81 mg PO daily

Considerations when initiating and choosing a P2Y12 Receptor Blocker

1. **Consider withholding P2Y12 Receptor Blocker when urgent cardiac surgery is anticipated (within 5 days), as in cases of previously discerned coronary anatomy, clinically significant valvular disease, those suffering mechanical complications of MI, or hemodynamic compromise and/or shock suggestive of multi-vessel CAD that may require urgent open heart surgery**
2. **For patients requiring long-term oral anticoagulation, clopidogrel is preferred**
3. **Avoid ticagrelor in patients with severe bradycardia (HR less than 50 bpm)**

☐ **No ticagrelor or clopidogrel until angiogram performed - *PREFERRED***

☐ ticagrelor 180 mg PO STAT (first choice, unless contraindicated), then 90 mg PO BID

∗OR∗

☐ clopidogrel 600 mg PO STAT, then 75 mg PO daily

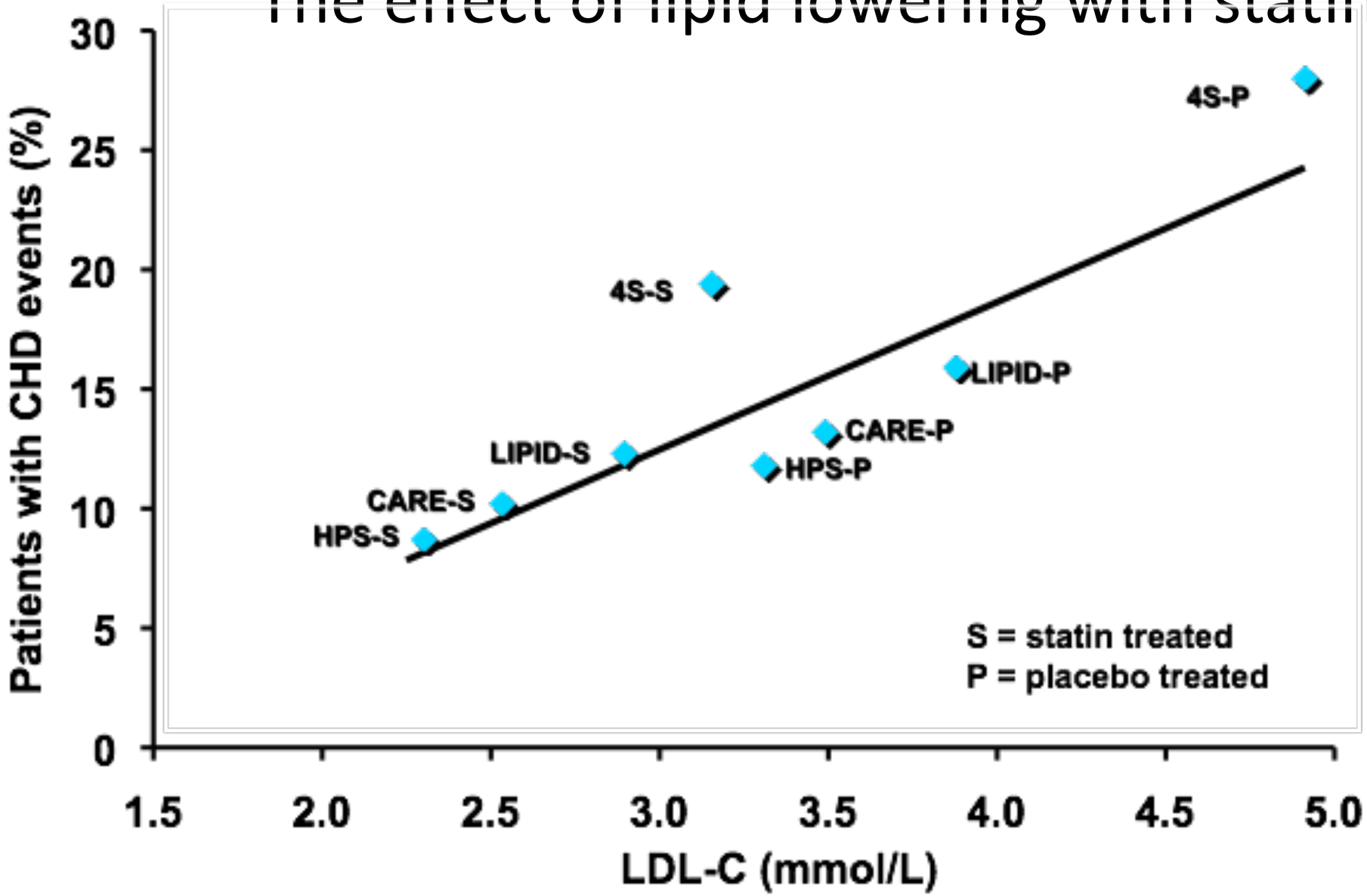
STEMI - PCI

CONSIDER WITHHOLDING P2Y12 RECEPTOR BLOCKER WHEN URGENT CARDIAC SURGERY IS ANTICIPATED (WITHIN 5 DAYS), AS IN CASES OF PREVIOUSLY DISCERNED CORONARY ANATOMY, CLINICALLY SIGNIFICANT VALVULAR DISEASE, THOSE SUFFERING MECHANICAL COMPLICATIONS OF MI OR HEMODYNAMIC COMPROMISE AND/OR SHORT SUGGESTIVE OF MULTIVESSEL CAD THAT MAY REQUIRE URGENT OPEN HEART SURGERY

Why We Use The Drugs We Use: Rationale for Drugs in the Treatment of ACS

ANTITHROMBIN ANTIPLATELET	PLAQUE STABILIZATION	CARDIOPROTECTION	SYMPTOM RELIEF
ANTIPLATELET AGENTS ANTITHROMBINS	CHOLESTEROL LOWERING DRUGS ("STATINS")	BETA BLOCKER CALCIUM BLOCKERS RAS BLOCKERS ?STATINS	NITROGLYGERIN ANALGESICS
IMPROVES BLOOD SUPPLY	REDUCES RECURRENT THROMBOSIS	PREVENTS ISCHEMIC RELATED COMPLICATIONS	MAKES PATIENT FEEL BETTER

The effect of lipid lowering with statins



Modified from Kastelein JJP. *Atherosclerosis.* 1999;143(suppl 1):S17-S21

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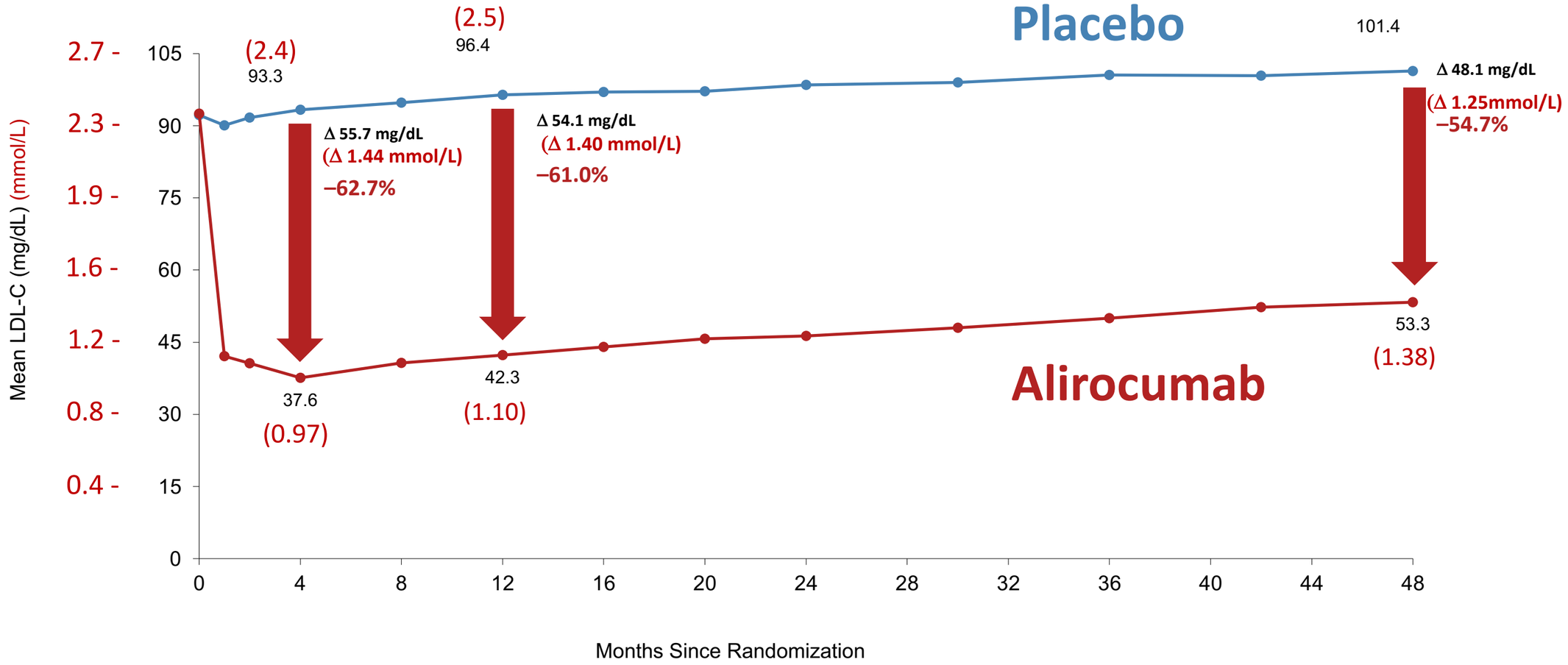
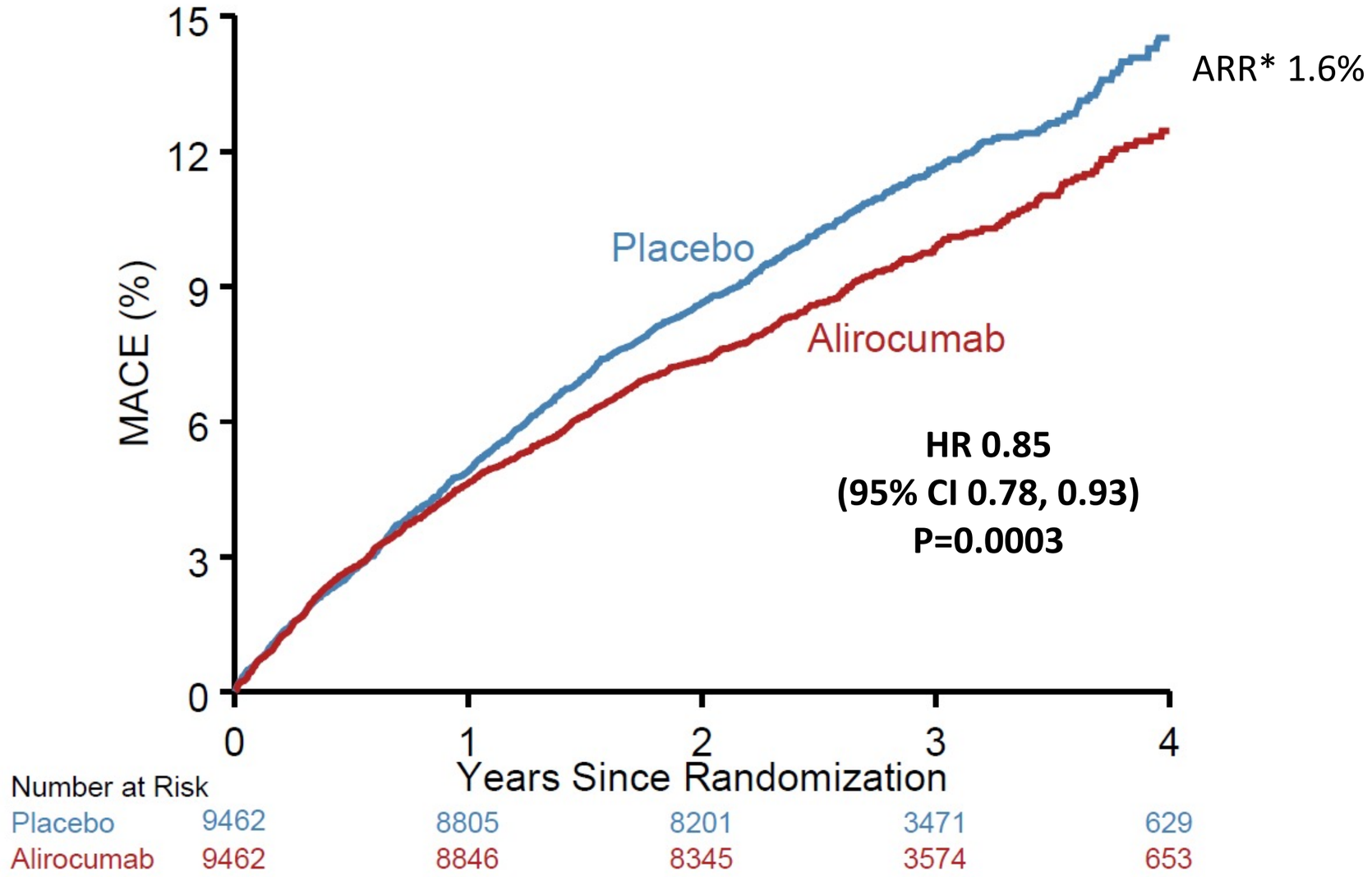
Benefit of Lipid Lowering: Impact on Inflammation

ODYSSEY OUTCOMES: LDL-C: On-Treatment Analysis



Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo
Approximately 75% of months of active treatment were at the 75 mg dose

Primary Efficacy Endpoint: MACE



MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

*Based on cumulative incidence

Why We Use The Drugs We Use: Rationale for Drugs in the Treatment of ACS

ANTITHROMBIN ANTIPLATELET	PLAQUE STABILIZATION	CARDIOPROTECTION	SYMPTOM RELIEF
ANTIPLATELET AGENTS ANTITHROMBINS	CHOLESTEROL LOWERING DRUGS ("STATINS")	BETA BLOCKER CALCIUM BLOCKERS RAS BLOCKERS ?STATINS	NITROGLYGERIN ANALGESICS
IMPROVES BLOOD SUPPLY	REDUCES RECURRENT THROMBOSIS	PREVENTS ISCHEMIC RELATED COMPLICATIONS	MAKES PATIENT FEEL BETTER

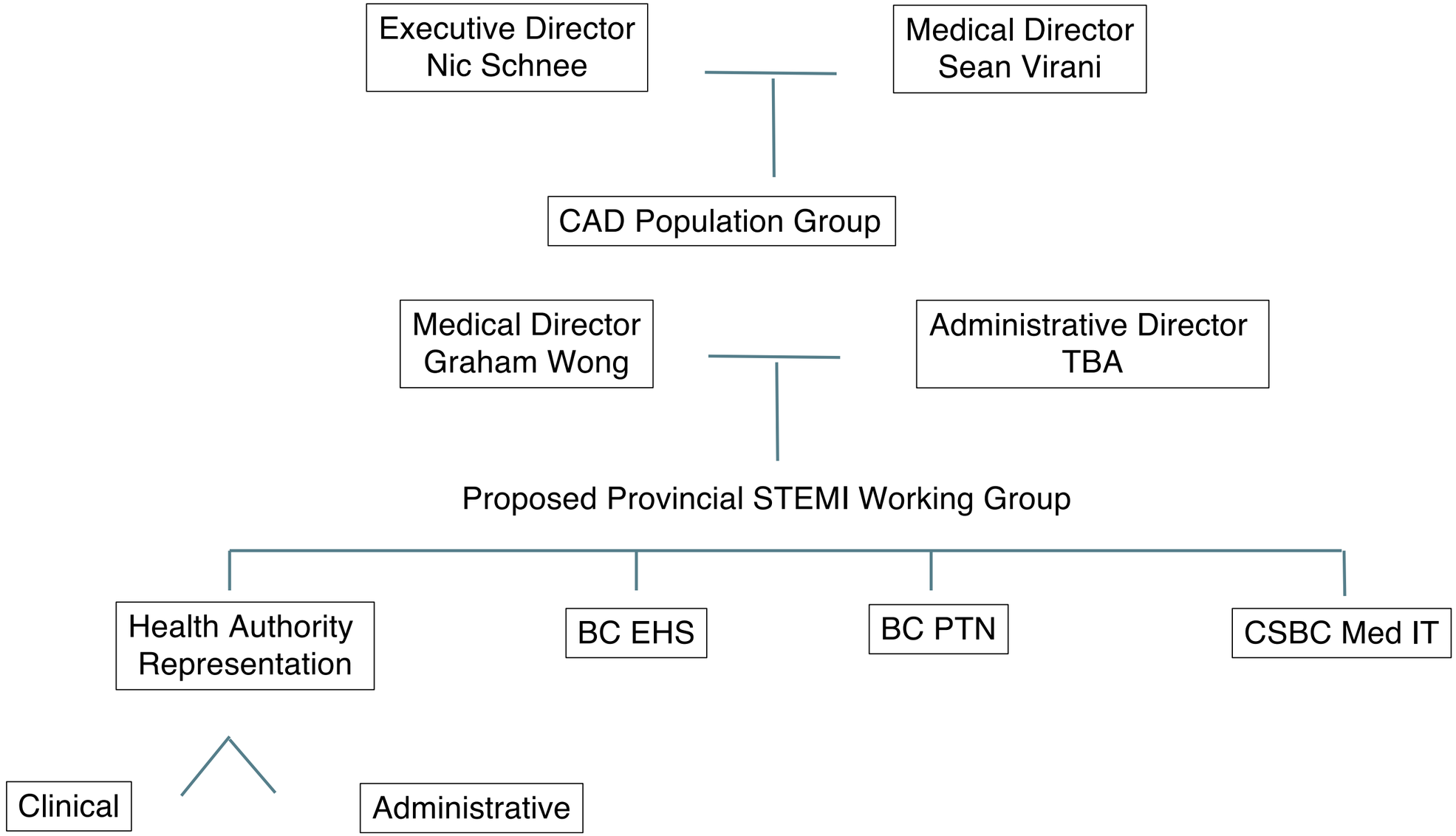
PHARMACOLOGICAL WAYS TO REDUCE MVO2 REQUIREMENTS THAT WOULD BE BENEFICIAL IN ACS

DESIRED EFFECT	HOW TO ACHIEVE IT	DRUG(S) TO DO IT	NOTES
REDUCTION IN AFTERLOAD	VASODILATE	CALCIUM BLOCKER BETA BLOCKER* RAS ANTAGONISM	*VIA BETA BLOCKER MEDIATED REDUCTION IN RENIN RELEASE
REDUCTION IN CONTRACTILITY	BETA 1 BLOCKADE CALCIUM BLOCKADE	BETA BLOCKER CALCIUM BLOCKER	AVOID IN ACUTE HEART FAILURE
REDUCTION IN HEART RATE	BETA 1 BLOCKADE CALCIUM BLOCKADE	BETA BLOCKER CALCIUM BLOCKER	AVOID IN CLINICALLY SIGNIFICANT BRADYCARDIA
REDUCTION IN PRELOAD	VENODILATE	DIURETIC NITROGLYCERIN	AVOID IF PRELOAD DEPENDENT
INCREASE IN FIBRILLATORY THRESHOLD	BETA 1 BLOCKADE	BETA BLOCKER	PROBABLY THE MECHANISM OF GREATEST BENEFIT OF BB THERAPY

Putting it All Together

- Acute coronary syndromes are caused by coronary thrombosis superimposed upon an unstable plaque
- Resultant luminal occlusion causes supply/demand mismatch and ischemia/necrosis
- Pharmacological and mechanical treatment is directed towards:
  - Relieving coronary obstruction by treating thrombosis
  - Reduction in inflammation to reduce recurrent events
  - Reduction in myocardial oxygen demand to reduce demand

Provincial Initiatives: CSBC


Executive Director
Nic Schnee
Medical Director
Sean Virani
CAD Population Group
Medical Director
Graham Wong
Administrative Director
TBA
Proposed Provincial STEMI Working Group
Health Authority
Representation
BC EHS
BC PTN
CSBC Med IT
Clinical
Administrative

Proposed Clinical Representation

- **Health Authorities:**
  - VCHA: Graham Wong
  - FHA: Josh Wenner
  - VIHA: Chris Franco
  - IHA: Frank Halperin
  - NHA: Firas Mansour
  - Community Hospitals: Denise Jaworsky
- **BC EHS**: Anders Ganstal/Jon Deakin/Phillip Yoon

2019 CCS STEMI Guidelines: Recommendation on Regionalization of STEMI Care

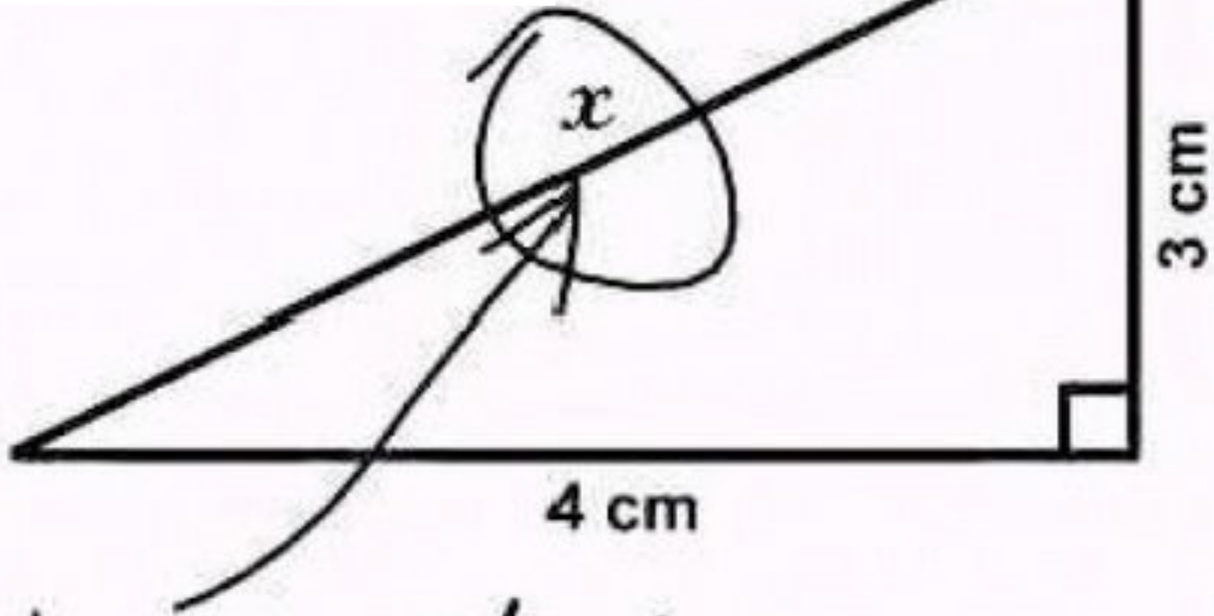
Evidence suggests that STEMI care is best performed using an organized STEMI network with a primary PCI centre[s] (the ‘hub[s]’) receiving referrals from surrounding hospitals (the ‘spokes’) and a defined catchment area from the field via emergency medical services (EMS).

Wong GC et al. Can J Cardiol 2019; 35:102-137

Elements of a Regional STEMI Network

A pre-planned default initial reperfusion strategy (PPCI or fibrinolysis) for each hospital within the network based on geographic and transport considerations.
The ability to deliver appropriate adjunctive PCI following fibrinolysis.
The capability of emergency medical service (EMS) and emergency department teams to rapidly diagnose and treat STEMI.
For PPCI, the ability for EMS and emergency departments to activate the STEMI team for reperfusion therapy through a ‘single call’ mechanism immediately from the point of first medical contact (FMC) with the patient.
The implementation of a “no-refusal” policy at PCI centres for STEMI patients who are deemed appropriate for PPCI.
The ability for EMS teams that diagnose STEMI patients in the field to bypass non-PCI centres and transport patients directly to a PCI centre.
The ability for appropriately selected patients to bypass the emergency department (ED) of a PCI centre and proceed directly to the cardiac catheterization laboratory.

3. Find X.



Here it is

SIMPLICITY

The simplest solutions are often the cleverest
They are also usually wrong

Questions?

“If I know the answer, I’ll tell you the answer. If I don’t know the answer, I’ll respond, cleverly.”

Former US Secretary of Defense Donald Rumsfeld

gcwong@mail.ubc.ca