Cases in Antithrombotics: Management in the Inpatient Setting

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Disclosure Statement

- Drs. Jessie Dunne and Gregory Tallman have no relevant financial relationship(s) with ineligible companies to disclose.

Learning Objectives

- Design an antithrombotic regimen for patients on dual antiplatelet therapy requiring surgical procedures.
- Implement and monitor an antithrombotic regimen for patients with valvular heart disease undergoing surgery.

Pre-Test Question #1

Which of these antithrombotic regimens are an option for patients who have had coronary stenting receiving dual antiplatelet therapy after an acute coronary syndrome event in the last 30 days?

A. Continue dual antiplatelet therapy without interruption
B. Stop P2Y12 inhibitor 5-7 days preoperatively, continue ASA, no other antiplatelet therapy needed
C. Stop P2Y12 inhibitor and ASA. Start Cangrelor infusion until 1-6 hrs prior to surgery
D. Stop P2Y12 inhibitor, continue ASA, start eptifibatide infusion until 4-10 hours prior to surgery

Case 1: Stent maintenance during cardiac surgery

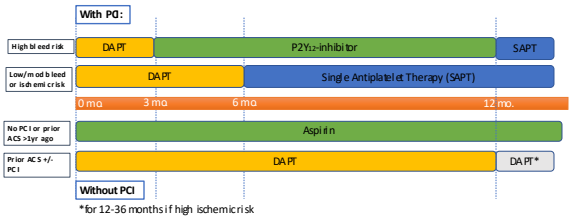
- RF is a 62 yo gentleman who presented to the ED after having ~35 minutes of acute onset of crushing chest pain that radiates to his left arm and neck. EKG showed ST-elevation in leads II, III, & aVF. He was given ASA 325 mg and UFH 4000 units IV x1 and taken to the cath lab. A DES x2 was placed in the RCA. As the left coronary was visualized, it was found 60% occlusion of LM and 80% in mid-LAD.
- Cardiothoracic surgery was consulted. Coronary artery bypass grafting (CABG) is now being planned.

- RF has no pertinent PMH
- All labs WNL
- Patient started on evidence-based post-ACS cardiac regimen

What antithrombotic agent(s) should be started to prevent acute stent thrombosis in the newly implanted stent?

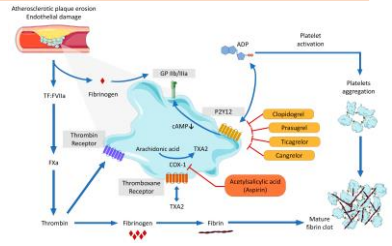
How does the upcoming CABG alter this plan?

Guideline Recommended Antiplatelet Therapy for CCD



JA CC. 2 023; 8 2(9) :833-955

Antiplatelet Agents: Site of Action



Int. J Mol Sci, 2024 ; 25(7):3981

Case 1: Stent Management with STEMI

Usual PCI Care:

ASA load, UFH bolus → PCI with P2Y12i load → DAPT (ASA + P2Y12i)

RF's Care:

ASA load, UFH load → Coronary angiogram, RCA PCI → ???

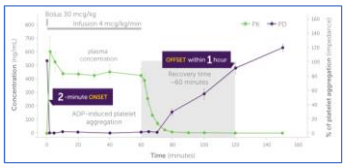
Antiplatelet Therapy Prior to CABG: Guideline Recommendations

	COR	LOE	RECOMMENDATIONS
➡	1	B-R	In patients undergoing CABG who are already taking daily aspirin preoperatively, it is recommended that they continue taking aspirin until the time of surgery to reduce ischemic events
	1	B-NR	In patients referred for urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours before surgery to reduce major bleeding complications
➡	1	B-NR	In patients undergoing CABG, discontinuation of short-acting glycoprotein IIb/IIIa inhibitors (eptifibatide and tirofiban) for 4 hours and abciximab for 12 hours before surgery is recommended to reduce the risk of bleeding and transfusion
➡	2a	B-NR	In patients undergoing elective CABG who receive P2Y12 receptor inhibitors before surgery, it is reasonable to discontinue clopidogrel for 5 days, ticagrelor for 3 days, and prasugrel for 7 days before CABG to reduce risk of major bleeding and blood product transfusion
	3: No benefit	B-R	In patients undergoing elective CABG who are not already taking aspirin, the initiation of aspirin (100–300 mg daily) in the immediate preoperative period

JACC, 2022; 79(2): e21–e129

Cangrelor

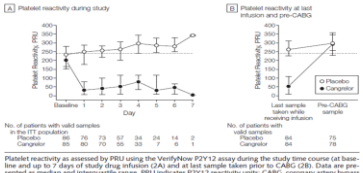
- Reversible, direct-acting P2Y12 inhibitor with a chemical structure similar to ATP
  - Onset of action: 2 minutes
  - Quickly metabolized to a nucleoside via active dephosphorylation



Kengreal® [package insert]. Parsippany, NJ: The Medicines Company; 2024.

Bridging Antiplatelet Therapy with Cangrelor in Patients Undergoing Cardiac Surgery (BRIDGE Trial)

Figure 2. Distribution of Platelet Reactivity During The Overall Study



Platelet reactivity as assessed by PRU using the VerifyNow P2Y12 assay during the study time course (at baseline and up to 7 days of study drug infusion (2A) and at last sample taken prior to CABG (2B). Data are presented as median and interquartile range. PRU indicates P2Y12 reactivity units; CABG, coronary artery bypass grafting; dotted line, cut-off level of 240 PRU; ITT, intention to treat.

- RCT, cangrelor vs placebo as bridge between irreversible $P2Y_{12}$ inhibitors to open heart surgery
  - 1° endpoint: proportion of patients with PRU<240

Angiolillo, et al. JAMA. 2012; 307(3): 265-274

Table 3. CABG-Related and Preoperative Bleeding Events in the Safety Population

Excessive Bleeding, Primary End Point, During the CABG Period, Through Hospital Discharge	No. of Patients/Total (%)		Relative Risk (95% CI)	P Value
	Cangrelor (n = 106)	Placebo (n = 101)		
Protocol-defined	10/102 (11.8)	10/96 (10.4)	1.1 (0.5-2.5)	.76
Surgical resuscitation	2/102 (2.0)	2/96 (2.1)	0.9 (0.1-6.5)	.95
24-h chest tube output, >1.5 L	8/102 (7.8)	5/96 (5.2)	1.5 (0.5-4.4)	.46
Incidence of PRBC transfusions >4 units	6/102 (5.9)	8/96 (8.3)	0.7 (0.3-2.0)	.50
BARC -defined	10/102 (9.8)	10/96 (10.4)	0.9 (0.4-2.2)	.89
Fatal bleeding	0/102 (0.0)	0/96 (0.0)	NA	NA
Preoperative intracranial bleeding within 48 h	0/102 (0.0)	0/96 (0.0)	NA	NA
Reoperation following closure of sternotomy for the purpose of controlling bleeding	2/102 (2.0)	2/96 (2.1)	0.9 (0.1-6.5)	.95
Transfusion of >=5 units of whole blood or PRBC within a 48-h period	7/102 (6.9)	8/96 (8.3)	0.8 (0.3-2.2)	.70
Chest tube output >=2 L within a 24-h period	3/102 (2.9)	4/96 (4.2)	0.7 (0.2-3.1)	.64
Preoperative-related bleeding, from randomization until surgical incision				
ACUITY				
Major	3/106 (2.8)	1/101 (1.0)	2.9 (0.3-27.9)	.36
Minor	18/106 (17.0)	10/101 (9.9)	1.8 (0.9-3.7)	.10
GUSTO				
Severe/life threatening	0/106 (0.0)	0/101 (0.0)	NA	NA
Moderate	2/106 (1.9)	1/101 (1.0)	1.9 (0.2-20.7)	.60
Mild	19/106 (17.9)	10/101 (9.9)	1.8 (0.9-3.7)	.10
TIM				
Major	1/106 (0.9)	0/101 (0.0)	NA	NA
Minor	1/106 (0.9)	0/101 (0.0)	NA	NA

Abbreviations: ACUITY, acute catheterization and urgent intervention triage strategy; BARC, Bleeding Academic Research Consortium; CABG, coronary artery bypass graft; GUSTO, Global Use of Strategies To Open coronary arteries; NA, not applicable; PRBC, packed red blood cell; TIM, Thrombolysis in Myocardial Infarction.

BRIDGE Trial

No significant CABG-related or pre-operative bleeding event differences in those receiving Cangrelor vs placebo.

FDA Approved Labeling:
- 0.75 mcg/kg/min (no bolus) following thienopyridine discontinuation for up to 7 days prior to surgery
- Stop 1-6 hours prior to surgical incision (based upon thrombotic risk)

Angiolillo, et al. JAMA. 2012; 307(3): 265-274
Kengreal® [PI]. Parsippany, NJ: The Medicines Company; 2024

Glycoprotein IIb/IIIa Inhibitors

- MOA: inhibits IIb/IIIa receptor, which binds activated platelets to fibrin, thereby preventing thrombosis formalization and propagation

	Onset	Half-life	Renal dosing adjustments	Bolus dose	Infusion Rate	Post PCI duration	Pre-op Stop Time
Eptifibatide	Immediate	2.5 hrs	<50 ml/min: same bolus but ½ rate; Avoid in HD; Dialyzable	180 mcg/kg	2 mcg/kg/min	18-24 hrs	2-4 hrs
Tirofiban	72-96% inhibition within 5min	90-180 min	<60ml/min: give same boluses but ½ rate; <30 ml/min: no bolus and ½ rate infusion; Dialyzable	25 mcg/kg	0.15 mcg/kg/min	18 hrs	2-4 hrs

High Blood Press Cardiovasc Prev, 2023; 30(2):93-107

Bridging with GP IIb/IIIa Inhibitors for Periprocedural Management of DES

- Retrospective analysis of 3 major cardiovascular centers
  - Use of GP IIb/IIIa inhibitors
  - Recent DES implantation
  - Required procedures where oral APT are usually held

Primary Outcome:
Stent Thrombosis

Secondary Outcomes:
Major bleeding
Minor bleeding
Acute coronary syndrome
Death

- Population (19 patients)
  - 6 non-cardiac surgery
  - 13 cardiac surgery
- All received eptifibatide:
  - Started median 2 days after clopidogrel stop
  - Infused for median 54h prior to surgery
  - Stopped ~10 hours before surgery
- 13 of 19 continued ASA throughout

Catheter Cardiovasc Interv, 2012; 79(4):575-82

Bridging with GP IIb/IIIa Inhibitors for Periprocedural Management of DES

	Non-Cardiac	Cardiac Surgery
Major Bleeding	0	7
>2 PRBC		5
Pericardial bleed		1
Reoperation		1
Minor Bleeding	1	1
No bleeding	5	5

NO patients in either group experienced:
Stent thrombosis
Acute coronary syndrome
Death

Days to Clopidogrel re-start
- If bled: 4.2 days
- No bleed: 1.6 days

Catheter Cardiovasc Interv, 2012; 79(4):575-82

Case 1: Stent maintenance during cardiac surgery

- Since RF has very new stents with high risk of stent thrombosis, he should receive parenteral antiplatelet therapy in the perioperative setting. He has NOT been loaded with P2Y12 inhibitor yet, so there is no delay needed to allow that therapy to wear off.
- In addition to continuing Aspirin, other options for APT:
  - Cangrelor 0.75 mcg/kg/min continuous infusion. Stop 1-6 hours prior to surgery
  - Eptifibatide 180 mcg/kg bolus followed by 2 mcg/kg/min continuous infusion, stopped at least 4 hours prior to surgery
  - Tirofiban 25 mcg/kg bolus followed by 0.15 mcg/kg/min continuous infusion, stopped at least 4 hours prior to surgery.
- P2Y12 inhibitor may be initiated 1-4 days postoperatively based upon post-op bleeding occurrence. If using clopidogrel and desiring loading dose, do not exceed 300 mg x1 dose.

Pre-Test Question #1

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Pre-Test Question #2

Which perioperative anticoagulant plan is most appropriate?

A. 66 yo male with history of papillary muscle rupture after AMI s/p CABG & mechanical MRV (bileaflet) c/b valve thrombosis s/p tPa – no bridge therapy needed
B. 78 yo female with history of rheumatic heart disease s/p mechanical MVR (tilting-disc) – bridge with LMWH (adjusted for renal function)
C. 53 yo male with heart failure d/t bicuspid aortic valve s/p mechanical AVR (bileaflet) – bridge with LMWH (adjusted for renal function)
D. 47 yo female with marphan's syndrome s/p mechanical AVR (bileaflet) and antiphospholipid syndrome; no bridge therapy needed

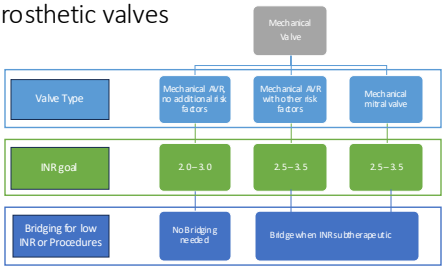
Case 2: Antithrombotic management perioperatively for prosthetic valves

Mr. Johnson is a 62-year-old man with a mechanical aortic valve replacement who was admitted with acute symptomatic gallstones. He is now being scheduled for a cholecystectomy. INR today is 2.4.

What kind of perioperative anticoagulation management is required?

- PMH:
  - Bicuspid aortic valves/p mechanical AVR (St Jude, 2010)
  - Dyslipidemia
  - Diabetes
  - Hypertension
- Home medications:
  - Warfarin 5 mg MWF, 7.5 mg AOD
  - Aspirin 81 mg daily
  - Rosuvastatin 20 mg daily
  - Metformin ER 500mg twice daily
  - Empagliflozin 25 mg daily
  - Lisinopril 5 mg daily

Antithrombotic therapy for mechanical prosthetic valves



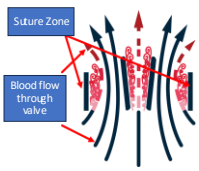
Aspirin 75-100 mg daily if additional antiplatelet therapy is needed

JACC. 2 021; 7 7(4) :e25 -197

Valve flow and thrombogenesis

Thrombosis formation is influenced by:

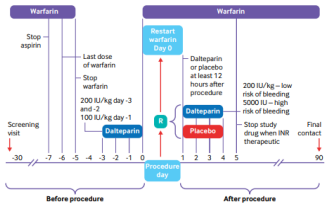
- Blood turbulence
- Force of blood passing through valve
- Material of valve
- Time since implantation



A = Bileaflet valve
B = Monoleaflet / tilting-disc valve
C = Caged ball valve

Circulatio n, 200 9; 119(7):1 034-104 8

PERIOP2 Trial: Bridging for patients at high risk of arterial thromboembolism



Patients included:
- Mechanical valve implanted
- Atrial fibrillation or flutter with CHADS$_2$ ≥1

Outcomes:
- 1°: Major thromboembolism @90 days; bleeding events
- 2°: type of thromboembolism; thromboembolism and bleeding events

BMJ. 2 021;3 73:n1 205

PERIOP2 Trial: Anticoagulant Use

Warfarin Data
- Pre-Procedure:
  - Stopped ~5 days preoperatively
  - INR >1.7 (day T-1): ~1.35%
  - INR 1.5-1.7 (day T-1): 5.2%
  - Received Vit K: ~6.45%
- Post-Procedure:
  - Resumed day 0: 87.4% & 92.4%
    - Higher in those bridged (p=0.001)
    - Non-significant on day +1

Dalteparin vs Placebo
- Pre-Procedure:
  - All patients received day T-1
- Post-Procedure:
  - No dose given: ~1.6%
  - Started postop day 1: ~96.5%
  - Number of doses given: ~5.5

Antiplatelet Use
- Baseline antiplatelet in ~24.4% patients
- Held ≥7 days pre-op: ~25.6%
- Resumed postop: 85.6%
- Postop days resumed: 9-10 days

BMJ. 2 021;3 73:n1 205

PERIOP2 Trial: Results

Table 3 | Study outcomes for whole population and subgroups of patients with atrial fibrillation and mechanical valves at 90 days. Data are numbers (%) unless indicated otherwise

Outcomes	Whole study population				Atrial fibrillation				Mechanical valve†			
	No bridging (n=1310)	Bridging (n=1220)	P value	Risk difference (95% CI)	No bridging (n=696)	Bridging (n=670)	P value	Risk difference (95% CI)	No bridging (n=154)	Bridging (n=150)	P value	Risk difference (95% CI)
Primary												
Major thromboembolism*	8 (1.2)	8 (1.0)	0.64	+0.2 (−0.3 to 0.8)	8 (1.6)	7 (1.0)	0.39	+0.7 (−0.9 to 0.9)	0	1 (0.7)	0.49	0.7 (−0.4 to 2.0)
Secondary												
Ischaemic stroke	3 (0.5)	1 (0.1)	0.33	—	3 (0.6)	1 (0.2)	0.32	—	—	—	—	—
Transient ischaemic attack	0	1 (0.1)	1	—	—	—	—	—	0	1 (0.7)	0.49	—
Symptomatic myocardial infarction	3 (0.4)	3 (0.5)	1	—	3 (0.4)	3 (0.5)	0.70	—	—	—	—	—
Peripheral embolism	—	—	—	—	—	—	—	—	—	—	—	—
Valve thrombosis	—	—	—	—	—	—	—	—	—	—	—	—
Venous thromboembolism	2 (0.3)	3 (0.4)	1	—	2 (0.4)	3 (0.5)	1	—	—	—	—	—
Vascular death	3 (0.5)	0	0.08	—	3 (0.4)	0	0.08	—	—	—	—	—
All deaths	4 (0.3)	4 (0.7)	0.33	−0.5 (−1.5 to 0.5)	4 (1.2)	5 (0.8)	0.54	+0.5 (−1.6 to 0.7)	2 (1.3)	1 (0.7)	1	+0.6 (−2.8 to 1.6)
Major bleeding	13 (2.0)	11 (1.3)	0.33	+0.7 (−1.0 to 0.7)	10 (2.0)	10 (1.5)	0.49	+0.5 (−2.1 to 1.0)	3 (2.0)	1 (0.7)	0.62	+1.3 (−1.8 to 1.3)
Clinically relevant non-major bleeding	25 (3.9)	50 (6.1)	0.05	2.2 (0.1 to 4.5)	20 (4.0)	42 (6.3)	0.09	2.2 (−0.3 to 4.8)	5 (3.3)	8 (5.3)	0.57	2.1 (−2.5 to 6.4)
Total bleeding	36 (5.5)	57 (7.0)	0.29	—	31 (5.8)	50 (7.7)	0.09	—	7 (5.3)	9 (5.7)	0.44	—
Major thromboembolism or major bleeding	21 (3.2)	19 (2.3)	0.28	+0.9 (−0.6 to 0.8)	18 (3.4)	17 (2.5)	0.28	+1.1 (−1.1 to 0.9)	3 (2.0)	2 (1.3)	1	+0.6 (−3.5 to 2.2)
Major thromboembolism or major bleeding, or death	35 (5.9)	34 (2.9)	0.33	+0.9 (−0.8 to 1)	29 (4.4)	21 (3.1)	0.41	+0.9 (−1.1 to 1.3)	5 (3.3)	3 (2.0)	0.72	+1.3 (−4.4 to 2.3)

*Major thromboembolism—any one of first seven secondary outcomes: ischaemic stroke, transient ischaemic attack, symptomatic myocardial infarction, peripheral embolism, valve thrombosis, venous thromboembolism (pulmonary embolism or deep vein thrombosis), or vascular death.
†With or without atrial fibrillation.

- Significant increase in clinically relevant non-major bleeding in overall population
- No other statistically significant findings

BMJ. 2 021;3 73:n1 205

Assessing perioperative risk of thrombosis

Risk Category	Mechanical Heart Valve	Atrial Fibrillation	VTE
HIGH (>10% per year risk of ATE or >10 % per month of VTE)	Mitral valve *with* major stroke risk factors* Caged ball or tilting-disc valve in mitral or aortic valve position Recent (< 3 mo) stroke or TIA	CHADS2/CHA2DS2-VASc score ≥ 7 or CHADS2 score of 5 or 6 Recent (< 3 mo) stroke or TIA Rheumatic valvular heart disease	Recent (< 3 mo & especially 1 mo) VTE Severe thrombophilia (deficiency of protein C, protein S, or AT; homozygous factor V leiden or prothrombin gene G20210A mutation, or double heterozygous for each mutation; multiple thrombophilias Antiphospholipid Antibodies Active cancer with high VTE risk
MODERATE (4-10% per year risk of ATE or 4-10% per month of VTE)	Mitral valve *without* major risk factors for stroke Bileaflet AVR *with* major risk factors for stroke*	CHADS2/CHA2DS2-VASc score 5 or 6 or CHADS2 score of 3 or 4	VTE within past 3-12 mo Recurrent VTE Non-severe thrombophilia (heterozygous factor V leiden or prothrombin gene G20210A mutation) Active or recent cancer
LOW (<4 % per year risk of ATE or <4% per month of VTE)	Bileaflet AVR *without* major risk factors for stroke	CHADS2/CHA2DS2-VASc score of 1 – 4 or CHADS2 score of 0 – 2 (and no prior stroke or TIA)	VTE >12 months ago

*Major risk factors for stroke: prior stroke/TIA during anticoagulant interruption or other prior stroke/TIA, prior valve thrombosis, rheumatic heart disease, hypertension, diabetes, heart failure, age 75 or higher

CHEST 2022; 162 (5): e207-e243

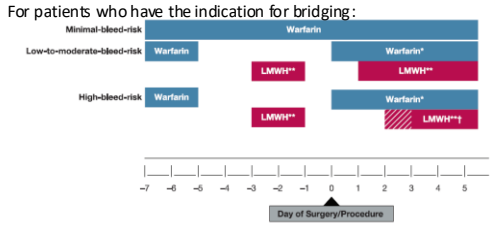
Assessing procedural bleed risk:

High (30d risk ≥2%)	Moderate (30d risk 0-2%)	Low (30d risk ~0%)
• Cardiac, intracranial, or spinal surgery • Major surgery w/extensive tissue injury • Cancer surgery (solid tumor) • Reconstructive plastics surgery • Major thoracic surgery • Urologic or GI surgery (especially anastomotic) • Transurethral prostate, bladder, or tumor resection • Nephrectomy, kidney biopsy • Bowel resection • PEG placement • Endoscopic retrograde cholangiopancreatography • Surgery of highly vascular organs • Major surgeries > 45 min • Neuraxial anesthesia • Epidural injections	• Arthroscopy • Cutaneous/lymph-node biopsies • Food/hand surgery • Coronary angiogram • GI endoscopy ± biopsy • Colonoscopy ± biopsy • Abdominal hysterectomy • Laparoscopic cholecystectomy • Abdominal hernia repair • Hemorrhoidal Surgery • Bronchoscopy ± biopsy	• Minor derm procedures • Ophthalmologic procedures • Minor dental procedures • Pacemaker/AICD implantation

CHEST 2022; 162 (5): e207-e243

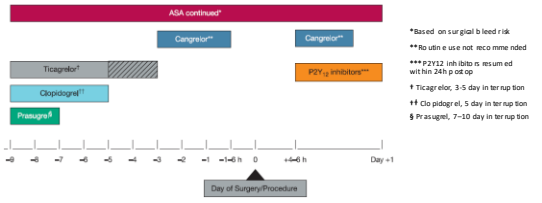
Guideline recommendations for bridging warfarin:

For patients who have the indication for bridging:



CHEST 2022; 162 (5): e207-e243

Guideline recommendations for perioperative antiplatelet use:



*Based on surgical bleed risk
**Routine use not recommended
***P2Y12 inhibitors resumed within 24h post op
† Ticagrelor, 3-5 day interruption
†† Clopidogrel, 5 day interruption
§ Prasugrel, 7–10 day interruption

CHEST 2022; 162 (5): e207-e243

Case 2: Antithrombotic management perioperatively for prosthetic valves

Mr. Johnson is a 62-year-old man with a mechanical aortic valve replacement who was admitted with acute symptomatic gallstones. He is now being scheduled for a cholecystectomy.

PMH:
- Bicuspid aortic valve s/p mechanical AVR (St Jude, 2010)
- Dyslipidemia
- Diabetes
- Hypertension

Risk of thrombosis:
- Low (bileaflet AVR; no risk factors)

Procedure bleed risk:
- Laparoscopic – moderate risk
- Open – high risk

Stop Warfarin 5 days prior to surgery
Continue Aspirin throughout
NO BRIDGE THERAPY NECESSARY

Resume Warfarin POD0

Pre-Test Question #2

Which perioperative anticoagulant plan is most appropriate?

A. 66 yo male with history of papillary muscle rupture after AMI s/p CABG & mechanical MRV (bileaflet) c/b valve thrombosis s/p tPa – no bridge therapy needed

B. 78 yo female with history of rheumatic heart disease s/p mechanical MVR (tilting-disc) – bridge with LMWH (adjusted for renal function)

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D. 47 yo female with marphan's syndrome s/p mechanical AVR (bileaflet) and antiphospholipid syndrome; no bridge therapy needed