2016 Pharmacotherapy Specialty Examination Review Course: Cardiovascular Disease: Secondary Prevention Case #1

Snehal H. Bhatt, Pharm.D., BCPS
Associate Professor of Pharmacy Practice
Massachusetts College of Pharmacy and Health Sciences
Clinical Pharmacist
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Learning Objectives:

At the conclusion of this session, given a patient case, the participant should be able to

1. Select the appropriate treatment and monitoring of a complex patient-case with multiple conditions, including acute decompensated heart failure/electrolyte disturbances, acute coronary syndromes (ACS), and gastroesophageal reflux disease (GERD).
2. Develop a plan to address continuity of care issues.
3. Formulate a medication therapy plan for smoking cessation.
4. Determine how to manage drug-drug and drug-disease interactions in a patient with ischemic heart disease.
5. Discuss quality of life in this population
6. Discuss national benchmarking standards and implications for patient care.
7. Identify and recommend appropriate resource organizations/groups to assist a specific patient.

Format: Today's session will be a highly interactive discussion of the attached case studies.

Premise: You are a clinical pharmacy specialist working in a large tertiary care academic medical center. Your job is to recommend and critically evaluate the response to cardiovascular medications prescribed for these patients for acute coronary syndromes and related cardiovascular diseases that require admission to the hospital. You are also responsible for assisting in optimizing medication therapies to ensure safe and effective transition of care from the hospital to home.

Initials	DOB/Age	Sex	Race/Ethnicity	Source
BA	63 years old	M	Caucasian	Patient and medical records

Chief Complaint/History of Present Illness (CC/HPI) (including symptom analysis for CC):
"Sharp, shooting chest pain"

BA is a 63-year-old man who was awakened from sleep at 5 am with what he describes as 9/10 sharp, shooting substernal chest pain that radiates up to his jaw. He has never experienced anything like this and immediately called 911. While being transported in the ambulance, he was given two 0.3-mg sublingual nitroglycerin tablets and four baby aspirin (81-mg chewable tablets) as a single dose.

Upon arrival at the emergency department at his local hospital, he was stable, but still complained of 2/10 chest pain. An ECG was immediately performed and a blood sample was sent to the laboratory for urgent assay of cardiac enzymes. The ECG revealed > 1 mm ST-segment depressions in the anterior leads. Minutes later, cardiac enzymes were noted to be positive. BA was deemed a candidate for early revascularization via cardiac catheterization, and a decision was made to transfer BA to a hospital with those capabilities. Immediately prior to transfer, he was given a single 300-mg oral clopidogrel dose.

Past Medical History (major illnesses and surgeries)
From Medical Record
Hypertension
Dyslipidemia
Type 2 diabetes mellitus
Coronary artery disease, s/p balloon angioplasty many years ago
Osteoarthritis

Current Prescription/OTC Medications

Start Date	Drug Name/Strength/Regimen	Indication
	Aspirin 81 mg orally once daily	ASCVD Prevention
	Ibuprofen 600 mg orally three times a day	Osteoarthritis
	Lisinopril 20 mg orally once daily	Hypertension, Diabetes
	Amlodipine 5 mg orally once daily	Hypertension
	Atorvastatin 20 mg orally once daily	Dyslipidemia
	Metformin 500 mg orally twice a day	Type 2 diabetes mellitus
Vaccinations: Influenza vaccine: Fall annually		Pharmacy(ies) Used: Neighborhood Pharmacy

RX Payment: Private Insurance (prefers generic medications, unsure of what his copays are)		Meds Admin by: Self
Drug Allergies/Adverse Effects: NKDA		
Family Medical History: Non-contributory		
Social History	Residence: lives at home w/ wife	Occupation: Engineer
Smoking: Smokes cigarettes 1 ppd x 20 years		EtOH: He drinks 2-3 beers most days of the week
Illicit Drugs: Never		Diet: Reports eating 3 meals per day mostly whatever his wife cooks. Has not really kept track of how much salt he consumes daily.
Education: College graduate		Family/Social Environment: Lives with wife; has one son and one daughter)
Review of Systems: Per HPI:		

Objective Data (observations/vital signs/physical examination/labs)
BP= 157/78 mm Hg Pulse= 77 bpm, regular RR = 20/min T = 97.6 °F

Height = 5' 11" Weight = 215 lb BMI =30 kg/m^2 Waist Circumference: 38 inches

Remarkable physical exam findings:
Gen: Pleasant male in acute distress from chest pain
Chest: 2/10 radiating substernal chest pain
Lungs: Mild inspiratory and expiratory crackles ¼ of the way up both lung fields bilaterally
Extremities: Trace bilateral edema of both lower extremities

Laboratory Tests

Chem Panel
Na = 138 mEq/L
K = 4.4 mEq/L
Cl = 100 mEq/L
CO_3 = 20 mg/dL
BUN = 17 mg/dL
SCr = 0.8 mg/dL
Glucose = 134 mg/dL
Ca = 9.4 mg/dL
Mg: 1.6 mg/dL

CBC
WBC = 7.8 x 10^9/L
Hgb = 12.0 g/dL
Hct = 37.2%
Platelets = 175 x 10^9/L

Miscellaneous (obtained in the emergency department)
Troponin T: 1.85 ng/mL
CK-MB: 28 ng/mL
CK: 210 ng/mL
ECG: > 1 mm ST-depresssion in V2-V4

Summary of 2014 ACC/AHA NSTE-ACS Pharmacotherapy Recommendations:

Antiplatelet Therapy to Support Primary Percutaneous Coronary Intervention (PCI) for Non-ST-Elevation Acute Coronary Syndromes (NSTE-ACS)

Class I

1. Non–enteric-coated, chewable aspirin (162 mg to 325 mg) should be given to *all* patients with NSTE-ACS without contraindications as soon as possible after presentation. (Level of Evidence: A).
2. A maintenance daily dose of aspirin (81–162 mg/day) should be continued indefinitely. (Level of Evidence: B).
3. A loading dose of a $P2Y_{12}$ receptor inhibitor should be given to all patients with NSTE-ACS without contraindications who are treated with either an early invasive or ischemia-guided strategy. Options include:
    a. Clopidogrel 600 mg orally (Level of Evidence: B)
    b. Ticagrelor 180 mg orally (Level of Evidence: B)
4. Oral $P2Y_{12}$ inhibitor therapy should be given for 1 year to patients with NSTE-ACS who receive a stent (bare-metal or drug-eluting), using the following maintenance doses:
    a. Clopidogrel 75 mg daily (Level of Evidence: B)
    b. Prasugrel 10 mg daily (Level of Evidence: B)
    c. Ticagrelor 90 mg twice a day (Level of Evidence: B) (Note: aspirin should be dosed at 81 mg daily when used with ticagrelor)

Class IIa

1. It is reasonable to use 81 mg/day of aspirin in preference to larger maintenance doses (Level of Evidence: B).
2. It is reasonable to start treatment with an intravenous glycoprotein (GP) IIb/IIIa receptor antagonist in selected patients with NSTE-ACS who are receiving unfractionated heparin (UFH). Examples include:
    a. Abciximab: 0.25-mg/kg IV bolus, then 0.125 mcg/kg/min (maximum 10 mcg/min) IV (Level of Evidence: A)
    b. High bolus-dose tirofiban: 25-mcg/kg IV bolus, then 0.15 mcg/kg/min IV (Level of Evidence: B). In patients with CrCl <30 mL/min, reduce infusion rate by 50%
    c. Double-bolus eptifibatide: 180-mcg/kg IV bolus, then 2 mcg/kg/min IV; a second 180-mcg/kg bolus is administered 10 min after the first bolus (Level of Evidence: B). In patients with CrCl <30 mL/min, reduce infusion rate by 50%

Class III: Harm

Prasugrel should not be administered to patients with a history of prior stroke or transient ischemic attack. (Level of Evidence: B).

Anticoagulant Therapy to Support Primary PCI for NSTE-ACS

Class I

1. For patients with NSTEMI, the following supportive anticoagulant regimens are recommended:

    a. UFH, with additional boluses administered as needed to maintain a therapeutic activated clotting time (ACT), taking into account whether a GP IIb/IIIa receptor antagonist has been administered. (Level of Evidence: C).
    Dosing: 50–70 units/kg IV bolus (with GP IIb/IIIa antagonist), or 70–100 units/kg IV bolus (without GP IIb/IIIa antagonist). Repeat UFH bolus doses as needed to achieve a therapeutic ACT (200–250 seconds with GP IIb/IIIa antagonist, 250–300 seconds without GP IIb/IIIa antagonist).

    b. Bivalirudin with or without prior treatment with UFH. (Level of Evidence: B).
    Dosing: 0.75 mg/kg IV bolus, followed by 1.75 mg/kg/hr IV infusion.

Class III: Harm

Fondaparinux should not be used as the sole anticoagulant because of the risk of catheter thrombosis. (Level of Evidence: B).

Summary of routine pharmacotherapy medications after NSTE-ACS:

Beta Blockers

Class I

1. Oral beta blockers should be initiated within the first 24 hours in patients who do not have any of the following: signs of heart failure (HF), evidence of a low-output state, increased risk for cardiogenic shock, or other contraindications to use of oral beta blockers (PR interval more than 0.24 seconds, second- or third-degree heart block, active asthma, or reactive airways disease). (Level of Evidence: A).

2. Patients with initial contraindications to the use of beta blockers within the first 24 hours should be reevaluated to determine their subsequent eligibility. (Level of Evidence: C)

Class IIa

1. It is reasonable to administer intravenous beta blockers at the time of presentation to patients with NSTEMI and no contraindications to use of the drugs who are hypertensive or have ongoing ischemia. (Level of Evidence: B).

Class III (harm)

1. Administration of intravenous beta blockers is potentially harmful in patients with NSTE-ACS who have risk factors for shock. (Level of Evidence: B)

Renin-Angiotensin-Aldosterone System Inhibitors

Class I

1. Angiotensin converting-enzyme (ACE) inhibitors should be started and continued indefinitely in all patients with a left ventricular ejection fraction (LVEF) less than 0.40 and in those with hypertension, diabetes mellitus, or stable chronic kidney disease (CKD) (Section 7.6), unless contraindicated. (Level of Evidence: A).

2. Angiotensin receptor blockers (ARBs) are recommended in patients with HF or myocardial infarction (MI) with a LVEF less than 0.40 who are ACE inhibitor intolerant. . (Level of Evidence: A).

3. Aldosterone blockade is recommended in patients post–MI without significant renal dysfunction (creatinine >2.5 mg/dL in men or >2.0 mg/dL in women) or hyperkalemia (K >5.0 mEq/L) who are receiving therapeutic ACE inhibitor and beta blocker doses and have a LVEF 0.40 or less, diabetes mellitus, or HF. (Level of Evidence: A).

Lipid Management

Class I

1. High-intensity statin therapy should be initiated or continued in all patients with NSTEMI and no contraindications to its use. (Level of Evidence: A).

2. Examples of high-intensity and moderate-intensity statins, as defined in the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol:

High Intensity Statin	Moderate Intensity Statin
Atorvastatin 40–80 mg daily	Atorvastatin 10–20 mg daily
Rosuvastatin 20–40 mg daily	Rosuvastatin 5–10 mg daily
	Pravastatin 40–80 mg daily
	Fluvastatin 40 mg twice daily Fluvastatin XL 80 mg daily
	Lovastatin 40 mg daily
	Pitavastatin 2–4 mg daily
	Simvastatin 20–40 mg daily

Adapted from: Stone NJ, Robinson J, Lichtenstein AH et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014; 129(25 Suppl 2):S1-45. http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a.citation

Presentation Questions

1. Which of the following represents the best initial anticoagulant pharmacotherapy?
    a. Unfractionated heparin
    b. Enoxaparin
    c. Fondaparinux
    d. Bivalirudin

2. Based on clinical trial data, which of the following medications probably is responsible for BA's thrombocytopenia?
    a. UFH
    b. Eptifibatide
    c. Clopidogrel
    d. Aspirin

3. Based on clinical trial data, which of the following $P2Y_{12}$ inhibitors is associated with a reduction in all-cause mortality when given in combination with aspirin for the treatment of ACS?
    a. Ticagrelor
    b. Prasugrel
    c. Clopidogrel
    d. Ticlopidine

4. Based on current clinical data, which of the following represents the optimal dose of aspirin for BA?
    a. Enteric-coated aspirin 81 mg daily indefinitely
    b. Enteric-coated aspirin 325 mg daily for 6 months followed by 81 mg daily indefinitely
    c. Aspirin 81 mg daily indefinitely
    d. Aspirin 325 mg daily indefinitely

5. Which of the following represents the most appropriate duration of dual antiplatelet therapy (DAPT)?
    a. 1 month
    b. 6 months
    c. 12 months
    d. 30 months

6. Which of the following therapies should be initiated to reduce all-cause mortality?
    a. Valsartan/sacubitril
    b. Eplerenone
    c. Losartan
    d. Furosemide

7. Which of the following represents the best outpatient monitoring regimen to minimize the risk of hyperkalemia?
    a. Check serum potassium 4 weeks after hospital discharge
    b. Check serum creatinine and serum potassium within 1 week after hospital discharge and again 4 weeks later
    c. Check serum potassium and serum creatinine within 4 weeks after hospital discharge
    d. Check serum creatinine 4 weeks after hospital discharge

8. BA is encouraged to stop smoking. Which of the following changes in his quality of life (QOL) are likely since BA experienced an MI?
    a. It will worsen if he continues to smoke cigarettes
    b. It will not change if he continues to smoke cigarettes
    c. It will improve if he changes to smoking e-cigarettes
    d. It will not change if he switches to smoking e-cigarettes

9. Which of the following NSAIDs is most appropriate for BA's osteoarthritis?
    a. Ibuprofen 600 mg po three times daily
    b. Naproxen 220 mg po twice daily
    c. Celecoxib 200 mg po twice daily
    d. Diclofenac 75 mg po twice daily

10. Which of the following represents the best acid suppressive therapy recommendation to minimize both bleeding risk and interactions with dual antiplatelet therapy (DAPT) in this patient?
    a. Pantoprazole 40 mg daily
    b. Esomeprazole 20 mg daily
    c. Omeprazole 20 mg daily
    d. Ranitidine 150 mg twice daily

11. If BA was interested in a support group that allowed him to meet with other MI survivors, which of the following would be the best to recommend?
    a. American Heart Association Support Network
    b. Ironheart Foundation
    c. American College of Cardiology
    d. Mended Hearts

12. Which of the following represents the most appropriate beta-blocker therapy at this time?
    a. Continue carvedilol 6.25 mg po twice daily
    b. Decrease carvedilol to 3.125 mg po twice daily
    c. Increase carvedilol to 12.5 mg po twice daily
    d. Withhold carvedilol while BA is volume overloaded

13. In addition to diuretic therapy, which of the following represents the best approach to managing hyponatremia in this patient?
    a. Start oral tolvaptan
    b. Give 3% sodium chloride IV
    c. Give 0.9% sodium chloride IV
    d. Use fluid restriction

References and Recommended Reading:

Acute Coronary Syndromes:

Amsterdam EA, Wenger NK, Brindis RG et al. 2014 ACCF/AHA guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014; 64:2645-87.

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Stone NJ, Robinson J, Lichtenstein AH et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014; 129(25 Suppl 2):S1-45. http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a.citation

Stone GW, McLaurin BT, Cox DA et al. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med.* 2006; 355:2203-16.

Mauri L, Kereiakes DJ, Yeh RW et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med.* 2014; 371:2155-66.

Cannon CP, Harrington RA, James S et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndrome (PLATO): a randomized double-blind study. *Lancet.* 2010; 375:283-93.

Cannon CP, Braunwald E, McCabe CH et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004; 350:1495-504.

O'Gara PT, Kushner FG, Ascheim DD et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013; 127:529-55.

U.S. Food and Drug Administration. Information for healthcare professionals: update to the labeling of clopidogrel bisulfate (marketed as Plavix) to alert healthcare professionals about a drug interaction with omeprazole (marketed as Prilosec and Prilosec OTC). November 17, 2009. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm190787.htm.

Heart Failure:

Yancy CW, Jessup M, Bozkurt B et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013; 62:e147-239

Heart Failure Society of America. HFSA 2010 comprehensive heart failure practice guideline. *J Card Fail.* 2010; 16(6):e1-e194.

Jondeau G, Neuder Y, Eicher JC et al. B-convinced: beta-blocker continuation vs. interruption in patients with congestive heart failure hospitalized for decompensation episode. *Eur Heart J.* 2009; 30:1-7.

Hyponatremia:

Verbalis JG, Goldsmith SR, Greenberg A et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. *Am J Med*. 2013; 126(10 Suppl 1):S1-S42.

U.S. Food and Drug Administration. Samsca (tolvaptan): drug warning—potential risk of liver injury. January 25, 2013. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm336669.htm.

Smoking Cessation:
Cahill K, Stevens S, Perera R et al. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev.* 2013; 5:CD009329.

University of California San Francisco Center for Tobacco Control Research and Education. Smoking cessation leadership center. http://tobacco.ucsf.edu/content/rx-change-clinician-assisted-tobacco-cessation

Patient resource organizations:

Mended Hearts: a national and community non-profit support group for patients and families with heart disease. http://mendedhearts.org

American Heart Association patient tools and resources for cardiovascular diseases. http://www.heart.org/HEARTORG/Conditions/Conditions_UCM_001087_SubHomePage.jsp

Drug-induced thrombocytopenia:

Kenney B, Stack G. Drug-induced thrombocytopenia. *Arch Pathol Lab Med.* 2009; 133:309-14.

George JN, Raskob GE, Rizvi S et al. Drug-induced thrombocytopenia: a systematic review of published case reports. *Ann Intern Med.* 1998; 129:886-90.

Warkentin TE. Drug-induced immune mediated thrombocytopenia – from purpura to thrombosis. *N Engl J Med.* 2007; 356:891-3.

Cardiovascular Disease: Secondary Prevention Case # 1

Snehal H. Bhatt, Pharm.D., BCPS
Associate Professor of Pharmacy Practice
Massachusetts College of Pharmacy and Health Sciences
Clinical Pharmacist
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Disclosure

- I declare that I have served on the advisory board and speaker's bureau for Janssen Pharmaceuticals, Inc.

Learning Objectives

- Select the appropriate treatment and monitoring of a complex patient with multiple conditions, including, acute decompensated heart failure/electrolyte disturbances, acute coronary syndromes (ACS), and gastroesophageal reflux disease (GERD).
- Develop a plan to address continuity of care issues.
- Formulate a medication therapy plan for smoking cessation.
- Determine how to manage drug – drug and drug-disease interactions in a patient with ischemic heart disease.
- Discuss quality of life in this population.
- Discuss national benchmarking standards and implications to patient care.
- Identify and recommend appropriate resource organizations/groups to assist a specific patient.

Premise

- You are a clinical pharmacy specialist working in a tertiary care academic medical center.
- Your job is to recommend and critically evaluate the response to cardiovascular medications prescribed for this patient for ACS management, along with optimizing his medication regimen after hospital discharge.
- The medical team will rely on your expertise to optimize drug therapy for multiple chronic cardiovascular conditions

Case

- BA: 63 year-old Caucasian man
  - Presents with crushing sub-sternal chest pain radiating to his jaw
  - Awakened from sleep with 9/10 pain
  - Called 911 who quickly arrived to his home:
- At an outside hospital:
  - Nitroglycerin 0.3 mg SL x 2 dose
  - Aspirin 324 mg (4 x 81mg tablets) chewed po x 1 dose
  - Clopidogrel 300 mg po x 1 dose
- ECG: ST-depressions suggestive of ischemia
- Transfer to hospital with catheterization laboratory arranged.

Case

- Past Medical History:
  - Hypertension
  - Osteoarthritis
  - Dyslipidemia
  - Diabetes
  - Coronary artery disease (CAD)
    - History of prior Percutaneous Coronary Intervention (PCI) with balloon angioplasty
- Social history:
  - (+) smoking 1 pack per day
- Current Medications:
  - Aspirin 81 mg once daily
  - Lisinopril 20 mg once daily
  - Amlodipine 5 mg once daily
  - Atorvastatin 20 mg once daily
  - Metformin 500 mg twice a day
  - Ibuprofen 600 mg three times a day

Case: NSTEMI

- Physical Exam:
  - Mild inspiratory and expiratory crackles ¼ of the way up both lung fields bilaterally
  - Trace bilateral edema of both lower extremities
- ECG: > 1 mm ST-depressions V1-V4
- Laboratory Data:
  - Troponin T: 1.85 ng/mL
  - CK-MB: 28 ng/mL
  - CK: 210 ng/mL
  - Calcium: 9.4 mg/dL
  - Magnesium: 1.6 mEq/dL

138	100	17	134
4.4	20	0.8	

Question # 1

Which of the following represents the best initial anticoagulant pharmacotherapy?

A. Unfractionated heparin
B. Enoxaparin
C. Fondaparinux
D. Bivalirudin

Initial Parenteral Anticoagulant Therapy in Patients With Definite NSTE-ACS

Anticoagulation, in addition to antiplatelet therapy, is recommended for all patients irrespective of initial treatment strategy. Treatment options include:

- UFH, with additional boluses administered as needed to maintain therapeutic activated clotting time levels, taking into account whether a glycoprotein (GP) IIb/IIIa inhibitor has been administered; or

- Bivalirudin: 0.10 mg/kg loading dose followed by 0.25 mg/kg per hour (only in patients managed with an early invasive strategy), continued until diagnostic angiography or PCI, with only provisional use of GP IIb/IIIa inhibitor (GPI), provided the patient is also treated with dual antiplatelet therapy (DAPT).

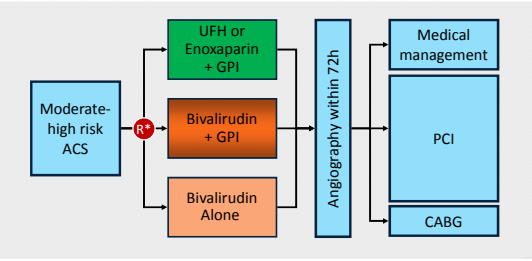
Amsterdam EA et al. J Am Coll Cardiol. 2014; 64:2645-2687.

Initial Parenteral Anticoagulant Therapy in Patients With Definite NSTE-ACS

Recommendations	COR	LOE
• Enoxaparin: 1 mg/kg subcutaneously (SC) every 12 hours (reduce dose to 1 mg/kg SC once daily in patients with creatinine clearance [CrCl] <30 mL/min), continued for the duration of hospitalization or until PCI is performed. An initial intravenous loading dose is 30 mg. • Fondaparinux: 2.5 mg SC daily, continued for the duration of hospitalization or until PCI is performed.	I	A B

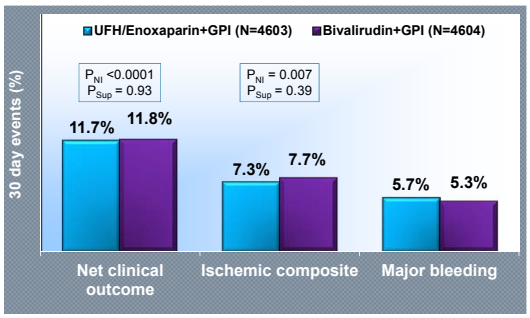
Amsterdam EA et al. J Am Coll Cardiol. 2014; 64:2645-2687.

ACUITY: Study Design



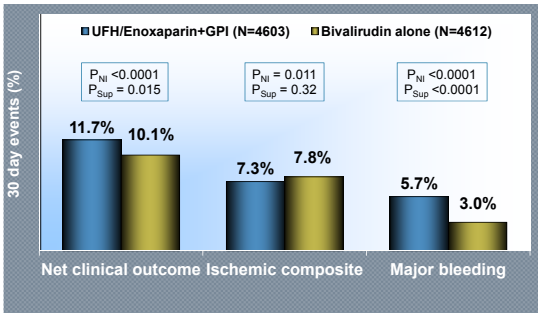
Stone GW et al. N Engl J Med 2006;355:2203-16.

Results: UFH/enox + GPI vs. Bival + GPI



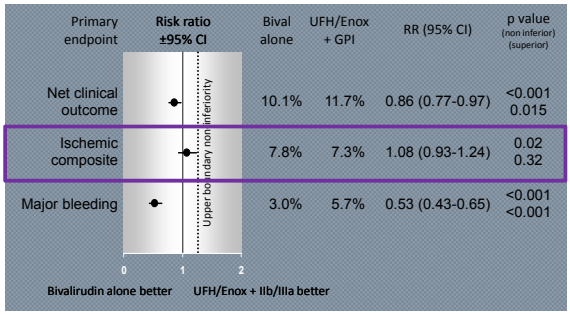
Stone GW et al. N Engl J Med 2006;355:2203-16.

Results: UFH/enox + GPI vs. Bival Alone



Stone GW et al. N Engl J Med 2006;355:2203-16.

UFH/Enoxaparin + GPI vs. Bivalirudin Alone



Stone GW et al. N Engl J Med 2006;355:2203-16.

Bivalirudin: Conflicting data!

Study	UFH Dose	Ischemic Endpoints	Major Bleeding	Stent Thrombosis
HEAT – PPCI	70 units/kg	UFH: 5.7% Bival: 8.7%	UFH: 3.1% Bival: 3.5% (no significant difference)	UFH: 0.9% Bival: 3.4%
BRIGHT	100 units/kg	UFH: 13.2% Bival: 8.8%	UFH: 7.5% Bival: 4.1%	UFH: 0.9% Bival: 0.6% (no significant difference)

Shazad A et al. Lancet 2014;384:1849-58.
Han Y et al. JAMA 2015;313:1336-46.

Incidence of major Bleeding

Study	Bivalirudin	Heparin (UFH)
HORIZONS-AMI	89/1800 (5%)	149/1802 (8%)
EUROMAX	28/1089 (3%)	67/1109 (6%)
BRIGHT	4/729 (1%)	14/724 (2%)
HEAT PPCI	32/905 (4%)	28/907 (3%)
OVERALL	308/10 600 (3%)	593/10 900 (5%)

Cavendar MA. Lancet 2014;384:599-606.

Incidence of acute stent thrombosis

Study	Bivalirudin	Heparin (UFH)
HORIZONS-AMI	21/1571 (1.3%)	4/1553 (0.2%)
EUROMAX	12/1089 (1.1%)	2/1109 (0.2%)
HEAT PPCI	20/697 (2.8%)	6/682 (0.8%)
OVERALL	53/3357 (1.5%)	12/3344 (0.3%)

Cavendar MA. Lancet 2014;384:599-606.

Dosing of Anticoagulants: NSTEMI with Primary PCI

Drug	In Patients Who Have Received Prior Anticoagulant Therapy	In Patients Who Have Not Received Prior Anticoagulant Therapy
Enoxaparin	• For prior treatment with enoxaparin, if last SC dose was administered 8–12 hr earlier or if <2 therapeutic SC doses of enoxaparin have been administered, an IV dose of enoxaparin 0.3 mg/kg should be given • If the last SC dose was administered within prior 8 hr, no additional enoxaparin should be given	• 0.5 mg/kg–0.75 mg/kg IV loading dose
Bivalirudin	• For patients who have received UFH, wait 30 min, then give 0.75 mg/kg IV loading dose, then 1.75 mg/kg/hr IV infusion • For patients already receiving bivalirudin infusion, give additional loading dose 0.5 mg/kg and increase infusion to 1.75 mg/kg/hr during PCI	• 0.75 mg/kg loading dose, 1.75 mg/kg/hr IV infusion

Amsterdam EA et al. J Am Coll Cardiol. 2014; 64:2645-2687

Dosing of Parenteral Anticoagulants During PCI

Drug	In Patients Who Have Received Prior Anticoagulant Therapy	In Patients Who Have Not Received Prior Anticoagulant Therapy
Fondaparinux	• For prior treatment with fondaparinux, administer additional IV treatment with anticoagulant possessing anti-factor IIa activity, considering whether GPI have been administered	N/A
UFH	• IV GPI planned: additional UFH as needed (e.g., 2,000–5,000 units) to achieve ACT of 200–250 s • No IV GPI planned: additional UFH as needed (e.g., 2,000–5,000 units) to achieve ACT of 250–300 s for HemoTec, 300–350 s for Hemochron	• IV GPI planned: 50–70 units/kg loading dose to achieve ACT of 200–250 s • No IV GPI planned: 70–100 unit/kg loading dose to achieve target ACT of 250–300 s for HemoTec, 300–350 s for Hemochron

Amsterdam EA et al. J Am Coll Cardiol. 2014; 64:2645-2687.

Antiplatelet and Anticoagulant Therapy: GP IIb/IIIa Inhibitors (GPI)

Recommendations	COR	LOE
In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) and not adequately pretreated with clopidogrel or ticagrelor, it is useful to administer a GPI (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI.	I	A
In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) treated with UFH and adequately pretreated with clopidogrel, it is reasonable to administer a GPI (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI.	IIa	B

Amsterdam EA et al. J Am Coll Cardiol. 2014; 64:2645-2687.

Case Continues

- While in the lab, BA receives UFH and eptifibatide.
- After PCI, UFH is discontinued, and the plan is to continue eptifibatide for a total of 18 hours.
- Team to decide about additional antiplatelet therapy tomorrow morning on rounds.

Case Continues: Platelet count drop

- The next morning while on rounds, the team raises concerns about BA's platelet count:
  - 10×10^9/L
  - down from baseline of 175×10^9/L
  - Hematocrit/Hemoglobin are stable from admission (Hgb 12 g/dL, HCT: 35%)
- No evidence of bleeding or thrombosis is noted during physical exam

Question # 2

Based on clinical trial data, which of the following medications probably is responsible for BA's thrombocytopenia?

A. UFH
B. Eptifibatide
C. Clopidogrel
D. Aspirin

Thrombocytopenia

- Can be broken down into 3 categories
  - Underproduction
    - —Bone marrow disorders (so other cell lines also affected)
  - Destruction/Consumption
    - —Antibody mediated clearance
    - —Consumption within thrombi
  - Redistribution

Kenney B et al. Arch Pathol Lab Med 2009;133:309-14.

Thrombocytopenia

Underproduction	Destruction/consumption	Redistribution
Nutrient deficiencies	Primary ITP	Splenomegaly
Myelodysplastic syndromes	Secondary ITP	
Infections	Drug-induced	
	TTP	
	DIC	

ITP: Immune thrombocytopenic purpura TTP: Thrombotic thrombocytopenic purpura DIC: Disseminated intravascular coagulation

Kenney B et al. Arch Pathol Lab Med 2009;133:309-14.

Mechanisms of Drug-induced thrombocytopenia

Mechanism	Description	Clinical Consequence	Prototype Drug
Hapten-dependent	Binds to plt membrane = neo-epitope recognized by antibody	**Hemorrhage**	Penicillins, Cephalosporins
Drug-glycoprotein complex	Noncovalent interaction with plt membrane	**Hemorrhage**	Quinine, Quinidine, NSAIDs
Ligand-induced binding site	Binds to GP IIb/IIIa complex = antibody recognition	**Hemorrhage**	Eptifibatide, Tirofiban
Drug-specific antibody	Chimeric Fab fragments against GP IIIa with murine component	**Hemorrhage**	Abciximab
Autoantibody	Autoantibody that reacts with plt surface in the absence of drug	**Hemorrhage**	Gold Salts, Procainamide
Immune complex	PF4 complex to produce antigenic complex	**Thrombosis**	Heparin, low-molecular-weight heparin

Kenney B et al. Arch Pathol Lab Med 2009;133:309-14.

TTP

- Most commonly presents with:
  - Abdominal pain, weakness, nausea, vomiting
- Can also present with:
  - Hemolytic anemia
  - Neurologic changes
  - Renal injury
- Laboratory abnormalities:
  - Anemia, thrombocytopenia (with leukopenia)
  - ↑ lactate dehydrogenase (LDH), indirect bilirubin
  - Negative Coombs test

George JN. N Engl J Med 2006;354:1927-35.

Clopidogrel-induced TTP

- Time-course: usually 2-3 weeks after starting therapy (range 3 – 21 days)
- Platelet count < 20 x 10^9/L
- Hematocrit < 27%

Bennett CL et al. N Engl J Med 2000;342:1773-7.

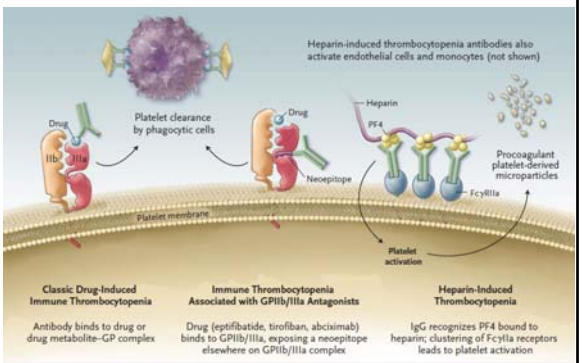
Heparin-induced thrombocytopenia

4Ts	Score = 2 points	Score = 1 point	Score = 0
Thrombocytopenia	Platelet count fall > 50 % from baseline **AND** nadir > 20,000	Platelet count fall 30 – 50% **OR** platelet nadir 10 – 19,000	Platelet count fall < 30% **OR** platelet nadir 10,000 x 10^9/L
Timing	Clear onset between days 5-10 of heparin exposure OR platelet count fall at ≤1 day with prior heparin exposure within 30 days	Consistent with fall in platelet count at 5-10 days, but not clear (e.g., missing platelet counts) OR onset after day 10 OR fall ≤1 day with prior heparin exposure 30-100 days ago	Platelet count fall < 4 days without prior heparin exposure in past 100 days
Thrombosis	New thrombosis (confirmed); Skin necrosis at heparin injection site; Anaphylactoid reaction after IV unfractionated heparin bolus	Progressive or recurrent thrombosis; Non-necrotizing (erythematous) skin lesions; Suspected thrombosis (not confirmed)	None evident
oTher causes	None evident	Possible	Definite • Sepsis or Severe Infection • Severe DIC • New medication known to cause thrombocytopenia • Cardiopulmonary bypass within previous 96 hr • Indwelling arterial device (e.g. IABP, VAD, ECMO)

Pre-test probability: High (score 6-8), Intermediate (score 4-5), Low (score 0-3)

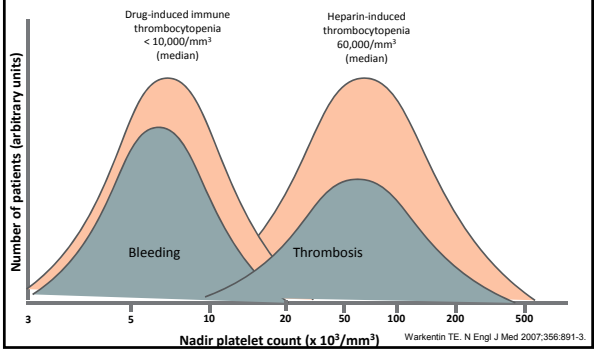
IABP: Intra-aortic balloon pump; DIC: Disseminated Intravascular Coagulation; ECMO: Extracorporeal Membrane Oxygenation; VAD: Ventricular Assist Device

Lo GK et al. J Thromb Haemost 2006;4:759-65.



From N Engl J Med, Drug-induced immune-mediated thrombocytopenia – from purpura to thrombosis. Warkentin TE, 356,891-3. Copyright 2007 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Drug-induced immune thrombocytopenia vs. HIT



Warkentin TE. N Engl J Med 2007;356:891-3.

Question # 3

Based on clinical trial data, which of the following $P2Y_{12}$ inhibitors is associated with a reduction in all-cause mortality when given in combination with aspirin for the treatment of ACS?

A. Ticagrelor
B. Prasugrel
C. Clopidogrel
D. Ticlopidine

Antiplatelet and Anticoagulant Therapy: Oral Antiplatelet Agents

Recommendations	COR	LOE
In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) not adequately pretreated with clopidogrel or ticagrelor, it is useful to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI.	I	A

Amsterdam EA et al. J Am Coll Cardiol. 2014; 64:2645-2687.

Antiplatelet and Anticoagulant Therapy: Oral Antiplatelet Agents

Recommendations	COR	LOE
It is reasonable to choose ticagrelor over clopidogrel for $P2Y_{12}$ inhibition treatment in patients with NSTE-ACS treated with an early invasive strategy and/or coronary stenting.	IIa	B
It is reasonable to choose prasugrel over clopidogrel for $P2Y_{12}$ treatment in patients with NSTE-ACS who undergo PCI who are not at high risk of bleeding complications.	IIa	B

Amsterdam EA et al. J Am Coll Cardiol. 2014; 64:2645-2687.

PLATO Study Design

NSTE-ACS (moderate-to-high risk) or STEMI (if primary PCI)
Clopidogrel-treated or -naive;
randomized within 24 hours of index event
(N=18,624)

Clopidogrel
If pre-treated, no additional loading dose;
if naive, standard 300 mg loading dose,
then 75 mg daily maintenance;
(additional 300 mg allowed pre PCI)

Ticagrelor
180 mg loading dose, then
90 mg twice daily maintenance;
(additional 90 mg pre-PCI)

6–12-month exposure

Primary endpoint: CV death + MI + Stroke
Primary safety endpoint: Total major bleeding

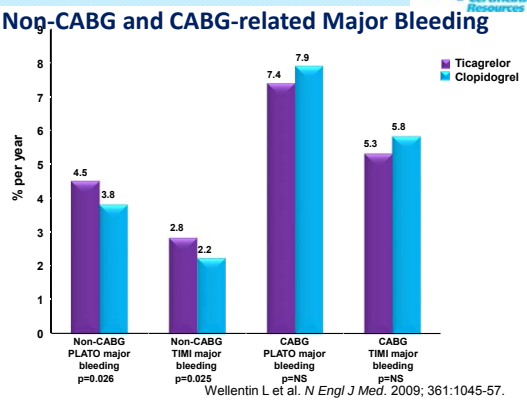
Wellentin L et al. *N Engl J Med*. 2009; 361:1045-57.

Results: Primary and Secondary Endpoints

All patients	Ticagrelor (n=9,333)	Clopidogrel (n=9,291)	HR for (95% CI)	p value
Primary objective, n (%)				
CV death + MI + stroke	864 (9.8)	1,014 (11.7)	0.84 (0.77–0.92)	<0.001
Secondary objectives, n (%)				
Total death + MI + stroke	901 (10.2)	1,065 (12.3)	0.84 (0.77–0.92)	<0.001
CV death + MI + stroke + ischemia + TIA + arterial thrombotic events	1,290 (14.6)	1,456 (16.7)	0.88 (0.81–0.95)	<0.001
Myocardial infarction	504 (5.8)	593 (6.9)	0.84 (0.75–0.95)	0.005
CV death	353 (4.0)	442 (5.1)	0.79 (0.69–0.91)	0.001
Stroke	125 (1.5)	106 (1.3)	1.17 (0.91–1.52)	0.22
All-cause mortality	399 (4.5)	506 (5.9)	0.78 (0.69–0.89)	<0.001

Wellentin L et al. *N Engl J Med*. 2009; 361:1045-57.

Non-CABG and CABG-related Major Bleeding



Wellentin L et al. *N Engl J Med*. 2009; 361:1045-57.

Case Continues

- Offending drug was discontinued, and BA's platelet count recovers within 48 hours
  - Platelet count: 10 x 10^9/L ⟶ 124 x 10^9/L

Question # 4

Based on current clinical data, which of the following represents the optimal dose of aspirin for BA?

A. Enteric-coated aspirin 81 mg daily indefinitely
B. Enteric-coated aspirin 325 mg daily for 6 months followed by 81 mg daily indefinitely
C. Aspirin 81 mg daily indefinitely
D. Aspirin 325 mg daily indefinitely

2014 ACC/AHA NSTEMI Guidelines: Aspirin

Recommendations	COR	LOE
Aspirin should be continued indefinitely. The maintenance dose should be 81 mg daily in patients treated with ticagrelor and 81 mg to 325 mg daily in all other patients.	I	A
It is reasonable to use an aspirin maintenance dose of 81 mg per day in preference to higher maintenance doses in patients with NSTE-ACS treated either invasively or with coronary stent implantation.	IIa	B

[ll]The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.

Amsterdam EA et al. J Am Coll Cardiol. 2014; 64:2645-2687.

Enteric-Coated Aspirin

- 400 healthy volunteers screened for response to 325 mg x 1 dose
  - Either enteric-coated or plain aspirin
- All patients in plain aspirin group responded pharmacologically
- 17-49% were non-responders in the enteric-coated aspirin group
  - Required multiple doses to convert non-responders.

Grosser T. *Circulation*. 2013; 127:377-85.

Question # 5

Which of the following represents the most appropriate duration of dual antiplatelet therapy (DAPT)?

A. 1 month
B. 6 months
C. 12 months
D. 30 months

2014 ACC/AHA NSTEMI Guidelines

Recommendations	COR	LOE
In patients receiving a stent (bare-metal stent or drug-eluting stent [DES]) during PCI for NSTE-ACS, $P2Y_{12}$ inhibitor therapy should be given for at least 12 months. Options include:	I	B
a.Clopidogrel: 75 mg daily *(Level of Evidence: B)* or		B
b.Prasugrel[#]: 10 mg daily *(Level of Evidence: B)* or		B
c.Ticagrelor[‖]: 90 mg twice daily *(Level of Evidence: B)*		B

[#]Patients should receive a loading dose of prasugrel, provided that they were not pretreated with another $P2Y_{12}$ receptor inhibitor.
[‖]The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.

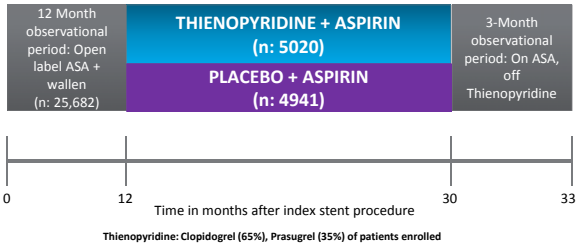
Amsterdam EA et al. J Am Coll Cardiol. 2014; 64:2645-2687.

Dual antiplatelet therapy (DAPT) Study

- Objectives:
  - In patients with DES: whether DAPT beyond 12 months is associated with:
    - —reduction in stent thrombosis and/or
    - —major adverse cardiovascular and cerebrovascular events (MACCE)
      - Defined as a composite of: Death, MI, stroke
  - To determine the impact of prolonged DAPT on moderate or severe bleeding

Mauri L et al. N Engl J Med 2014;371:2155-66.

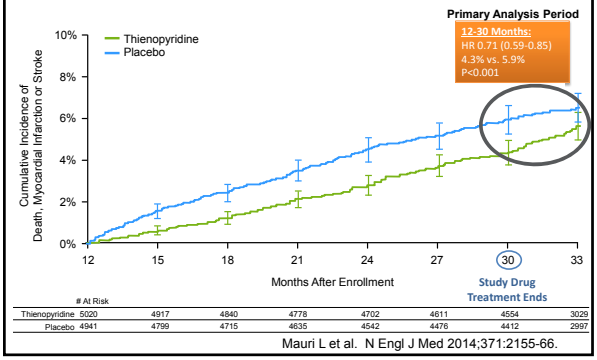
DAPT Study Design



Thienopyridine: Clopidogrel (65%), Prasugrel (35%) of patients enrolled

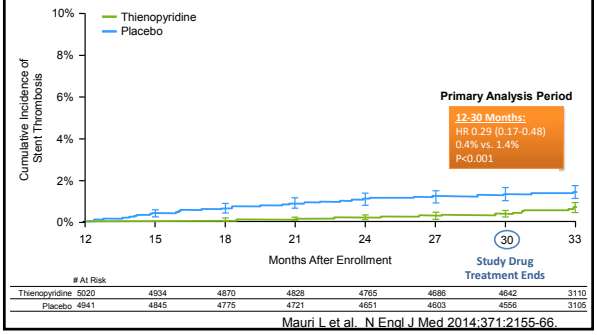
Mauri L et al. N Engl J Med 2014;371:2155-66.

Results: MACCE Endpoint



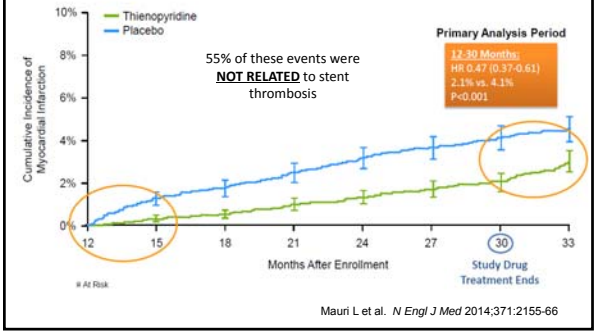
Mauri L et al. N Engl J Med 2014;371:2155-66.

Results: Stent Thrombosis



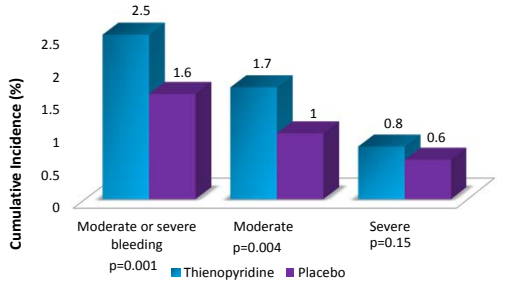
Mauri L et al. N Engl J Med 2014;371:2155-66.

Results: Myocardial Infarction



Mauri L et al. *N Engl J Med* 2014;371:2155-66

DAPT: Safety results



Mauri L et al. N Engl J Med 2014;371:2155-66.

DAPT Score: New risk tool to help?

- Objective:
  - To develop a decision tool to identify whether a patient is more or less likely to benefit from prolonged DAPT beyond 1 year
  - Account for risks of recurrent ischemia and bleeding simultaneously
- Derived from patients in DAPT trial
  - Those who tolerated DAPT for at least 1 year
  - Remember DAPT exclusion criteria
    - The risk scoring system would not apply to these patients

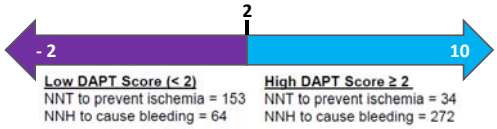
www.daptstudy.org

DAPT Score

Variable	Points
Patient Characteristics	
Age:	
≥ 75 years-old	- 2
65 – 74	- 1
≤ 64	0
Diabetes	1
Current cigarette smoker	1
Prior PCI or prior MI	1
CHF or LVEF < 30%	2
Index Procedure Characteristic	
MI at presentation	1
Vein graft PCI	2
Stent Diameter < 3 mm	1
TOTAL SCORE	**-2 – 10 points**

www.daptstudy.org

DAPT Score



- DAPT score may help identify patients where:
  - Ischemic benefits outweigh the risks of bleeding
  - Bleeding risk outweighs ischemic benefits

For BA: DAPT Score = 4

www.daptstudy.org

P2Y$_{12}$ Inhibitors: Clinical Pearls

- Prasugrel:
  - **should not be administered** to patients with a history of prior stroke or transient ischemic attack.
  - Generally not recommended in patients with age ≥ 75 years old
- Ticagrelor:
  - the recommended maintenance dose of aspirin to be used with is **81 mg daily.**

Brilinta (ticagrelor) prescribing information. Wilmington, DE: AstraZeneca, LP; 2013 Dec.
Effient (prasugrel) prescribing information. Indianapolis, IN: Eli Lilly and Company; 2013 Nov.

2014 ACC/AHA NSTEMI Guidelines: Cholesterol Management

Recommendations	COR	LOE
High-intensity statin therapy should be initiated or continued in all patients with NSTE-ACS and no contraindications to its use.	I	A
It is reasonable to obtain a fasting lipid profile in patients with NSTE-ACS, preferably within 24 hours of presentation.	IIa	C

Amsterdam EA et al. J Am Coll Cardiol. 2014; 64:2645-2687.

2013 ACC/AHA Cholesterol Guidelines

- **Statin therapy** recommended in 4 groups:
  1. Adults with **clinical** atherosclerotic cardiovascular disease (ASCVD)
  2. Adults with LDL-C ≥190 mg/dL
  3. Adults 40 to 75 years of age with diabetes
  4. Adults with ≥ 7.5% estimated 10-year risk of ASCVD
- ASCVD:
  - Inclusion criteria for secondary prevention statin trials:
    - Acute Coronary Syndromes, hx MI, unstable angina
    - Stroke/transient ischemic attack (TIA)
    - Peripheral artery disease

Stone NJ et al. *Circulation* 2014; 129(25 Suppl 2):S1-45. .

2013 ACC/AHA Cholesterol Guidelines

- High-Intensity statins: (reduce LDL ≥ 50%)
  - Atorvastatin 80 mg daily
  - Atorvastatin 40 mg daily
    - Down-titration in the IDEAL trial
  - Rosuvastatin 20 mg (40mg) daily

Stone NJ et al. *Circulation* 2014; 129(25 Suppl 2):S1-45. .

PROVE IT - TIMI 22: Study Design

4,162 patients with an Acute Coronary Syndrome < 10 days

ASA + Standard Medical Therapy

Double-blind

"Standard Therapy" Pravastatin 40 mg daily

"Intensive Therapy" Atorvastatin 80 mg daily

2x2 Factorial: Gatifloxacin vs. placebo

Duration: Mean 2 year follow-up (>925 events)

Primary Endpoint: Death, MI, Documented unstable angina requiring hospitalization, Stroke

Cannon CP et al. *N Engl J Med.* 2004; 350:1495-504.

Components of the Primary Endpoint

	Atorvastatin	Pravastatin	p value
Death due to CHD, MI, or revasculazation*			0.029
Death, MI or urgent revasculaization*			<0.001
Death from any cause (%)	2.2	3.2	NS p=0.07
Death from CHD (%)	1.1	1.4	NS
MI (%)	6.6	7.4	NS
Stroke (%)	1.0	1.0	NS
Revascularization (%)	16.3	18.8	< 0.05
Unstable angina requiring hospitalization (%)	3.8	5.1	< 0.05

Cannon CP et al. *N Engl J Med.* 2004; 350:1495-504.

Improve-It

Patients stabilized post ACS ≤ 10 days:
LDL-C 50–125*mg/dL (or 50–100**mg/dL if prior lipid-lowering Rx)

N=18,144

Standard Medical & Interventional Therapy

Simvastatin 40 mg

Uptitrated to Simva 80 mg if LDL-C > 79 (adapted per FDA label 2011)

Ezetimibe / Simvastatin 10 / 40 mg

Follow-up Visit Day 30, every 4 months

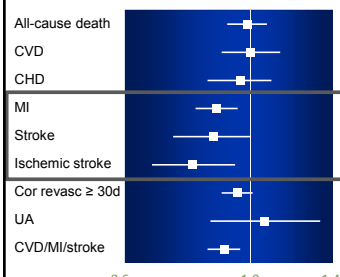
90% power to detect ~9% difference

Duration: Minimum 2 ½-year follow-up **(at least 5250 events)**

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

Cannon CP et al. N Engl J Med 2015; 372:2387-2397.

Improve-It: Results



	HR	Simva*	EZ/Simva*	p-value
All-cause death	0.99	15.3	15.4	0.782
CVD	1.00	6.8	6.9	0.997
CHD	0.96	5.8	5.7	0.499
MI	0.87	14.8	13.1	0.002
Stroke	0.86	4.8	4.2	0.052
Ischemic stroke	0.79	4.1	3.4	0.008
Cor revasc ≥ 30d	0.95	23.4	21.8	0.107
UA	1.06	1.9	2.1	0.618
CVD/MI/stroke	0.90	22.2	20.4	0.003

**7-year event rates (%)*

Cannon CP et al. N Engl J Med 2015; 372:2387-2397.

Case Continues:

- Patient experiences worsening shortness of breath post PCI, attributed to volume overload
- ECHO:
  - Ejection Fraction (EF): 30 – 35%
  - Global LV hypokinesis

Current Medications

- Aspirin 81 mg po daily
- Clopidogrel 75 mg po once daily
- Lisinopril 20 mg po daily
- Atorvastatin 80 mg po daily
- Carvedilol 3.125 mg po twice daily
- Docusate 100 mg po twice daily PRN constipation
- Nitroglycerin 0.3mg SL PRN chest pain
- Acetaminophen 500 mg po four times daily PRN pain

- Medication changes:
  - D/C Amlodipine – to allow for the addition of Carvedilol
  - Ticagrelor switched to clopidogrel due to cost concerns
  - Temporarily withholding Metformin and Ibuprofen, contrast dye exposure during PCI

Question # 6
Which of the following therapies should be initiated to reduce all-cause mortality?

A. Valsartan/Sacubitril
B. Eplerenone
C. Losartan
D. Furosemide

2014 ACC/AHA NSTEMI Guidelines:

Inhibitors of Renin-Angiotensin-Aldosterone System

Recommendations	COR	LOE
ACE inhibitors should be started and continued indefinitely in all patients with LVEF less than 0.40 and in those with hypertension, diabetes mellitus, or stable CKD (Section 7.6), unless contraindicated.	I	A
ARBs are recommended in patients with HF or MI with LVEF less than 0.40 who are ACE inhibitor intolerant.	I	A
Aldosterone blockade is recommended in patients post–MI without significant renal dysfunction (creatinine >2.5 mg/dL in men or >2.0 mg/dL in women) or hyperkalemia (K >5.0 mEq/L) who are receiving therapeutic doses of ACE inhibitor and beta blocker and have a LVEF 0.40 or less, diabetes mellitus, or HF.	I	A

Amsterdam EA et al. J Am Coll Cardiol. 2014; 64:2645-2687.

EPHESUS Trial

6,632 patients with acute MI complicated by heart failure and systolic left ventricular dysfunction

- Acute MI in prior 3-14 days
- Left ventricular dysfunction (EF ≤40%)
- Heart failure (in non-diabetics but not required for diabetics)

Optimal medical therapy
(ACE inhibitors, angiotensin-receptor blockers, diuretics, and beta-blockers, coronary reperfusion therapy)

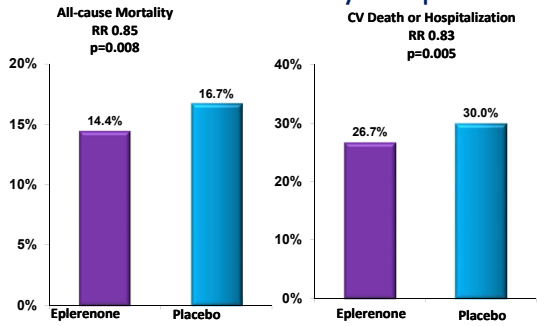
Eplerenone (n = 3,313) | Placebo (n = 3,319)

Endpoints (at mean of 16 month follow-up):

- Primary – 1) death from any cause and 2) death or hospitalization from CV causes

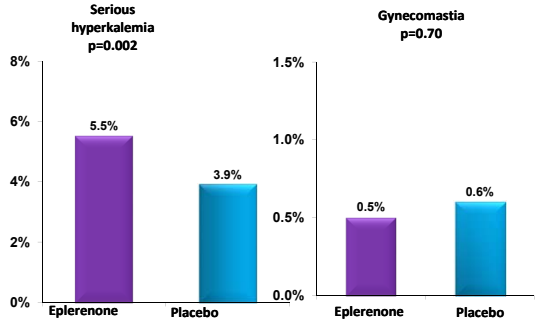
Pitt B. N *Engl J Med*. 2003; 348:1309-21.

EPHESUS Trial: Primary Endpoints



Pitt B. *N Engl J Med*. 2003; 348:1309-21.

EPHESUS Trial: Serious Adverse Events



Pitt B. *N Engl J Med*. 2003; 348:1309-21.

Question # 7

Which of the following represents the best outpatient monitoring regimen to minimize the risk of hyperkalemia?

A. Check serum potassium 4 weeks after hospital discharge
B. Check serum creatinine and serum potassium within 1 week after hospital discharge and again 4 weeks later
C. Check serum potassium and serum creatinine within 4 weeks after hospital discharge
D. Check serum creatinine 4 weeks after hospital discharge

Outpatient Potassium Monitoring

- Heart Failure Society of America (HFSA) Guidelines:
  - It is recommended that serum potassium concentration be monitored frequently following initiation or change in an aldosterone antagonist.
  - Monitoring should reflect protocols followed in clinical trials (Strength of Evidence: A)

Heart Failure Society of America. HFSA 2010 comprehensive heart failure practice guideline. *J Card Fail*. 2010; 16(6):e1-e194.

Potassium Monitoring: Clinical Trials

- Clinical trials of aldosterone antagonists
  - EPHESUS:
    - The serum potassium concentration was measured 48 hours after the initiation of treatment, at 1, 4, and 5weeks, at all scheduled study visits, and within 1week after any change of dose
  - EMPHASIS-HF
    - Similar recommendations

Pitt B. *N Engl J Med*. 2003; 348:1309-21.
Zannad F. *N Engl J Med*. 2011;364:11-21.

Question # 8

BA is encouraged to stop smoking. Which of the following changes in his quality of life (QOL) are likely since BA experienced an MI?

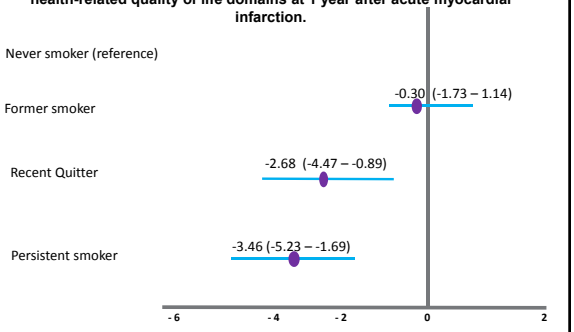
A. It will worsen if he continues to smoke cigarettes
B. It will not change if he continues to smoke cigarettes
C. It will improve if he changes to smoking e-cigarettes
D. It will not change if he switches to smoking e-cigarettes

Post Hospitalization Plan of Care

Encouragement and advice to stop smoking and to avoid secondhand smoke should be provided to patients with STEMI.

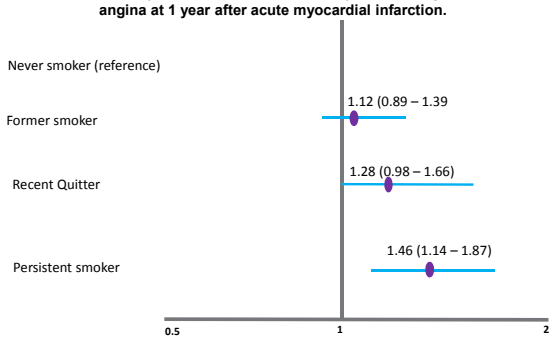
O'Gara PT et al. *Circulation*. 2013; 127:529–55.

Multivariable analyses of the association of 1-year smoking status with health-related quality of life domains at 1 year after acute myocardial infarction.



Buchanan DM et al. Circ Cardiovasc Qual Outcomes 2015;8:493-500

Multivariable analyses of the association of 1-year smoking status with angina at 1 year after acute myocardial infarction.



Buchanan DM et al. Circ Cardiovasc Qual Outcomes 2015;8:493-500

Smoking Cessation Counseling

- The 5 A's
  - Ask patient if they smoke
  - Advise tobacco users to quit
  - Assess the patient's readiness to quit
  - Assist the patient with quitting
  - Arrange follow-up care

Fiore MC, Jaén CR, Baker TB et al. Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. May 2008.
Smith SC et al. *Circulation*. 2011; 124:2458-73.

Smoking Cessation Pharmacotherapy

- First-line therapy: Many options!
  - Nicotine replacement therapies (NRT)
    - Patch
    - Gum
    - Lozenge
    - SL Tablets
    - Sprays
    - Inhaler
  - Bupropion SR
  - Varenicline
- Second-line options: many more!
  - Tricyclic antidepressants (TCAs)
  - Clonidine
  - Anxiolytics: Buspirone, Benzodiazepines, Beta-Blockers

Tailoring Pharmacotherapy: Long + Short Acting

Long Acting

- Pick 1 or 2 from here
  - Nicotine patch
  - Bupropion

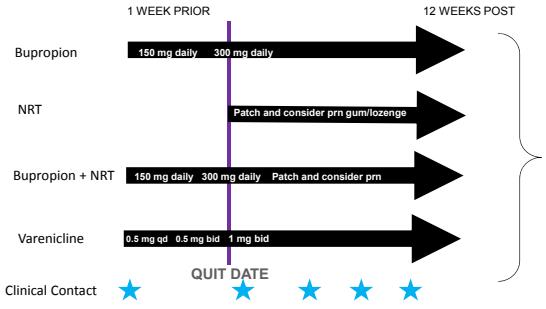
Short Acting

- Plus 1 or 2 from here
  - Nicotine gum
  - Nicotine inhaler
  - Nicotine lozenge
  - Nicotine nasal spray

*Combination of varenicline and NRT is exploratory, no trials to support its efficacy to date but initial evidence indicates well tolerated

University of California San Francisco Center for Tobacco Control Research and Education. Smoking cessation leadership center. URL in ref list.

Treatment Timelines



University of California San Francisco Center for Tobacco Control Research and Education. Smoking cessation leadership center. URL in ref list.

Smoking Cessation Resources

Internet based Resources:
- Smoking cessation leadership center
  - http://smokingcessationleadership.uscf.edu
- Treatobacco.net

Nonpharmaceutical Cessation Support
- ASPIRE: MD Anderson Cancer Center
- Become an Ex
  - http://www.becomeanex.com
- Quit Key – handheld device for gradual reduction
- Quit Net – online comprehensive support program
  - http://www.quitnet.com

Pharmaceutical Company Aids:
- Nicorette: http://www.nicorette.com
- NicoDerm CQ: http://www.nicodermcq.com
- Chantix: http://www.chantix.com
- Nicotrol: http://www.nicotrol.com

University of California San Francisco Center for Tobacco Control Research and Education. Smoking cessation leadership center. URL in ref list.

Question # 9

Which of the following NSAIDs is most appropriate for BA's osteoarthritis?

A. Ibuprofen 600 three times daily
B. Naproxen 220 mg twice daily
C. Celecoxib 200 mg twice daily
D. Diclofenac 75 mg twice daily

2014 ACC/AHA Guidelines: NSAIDs

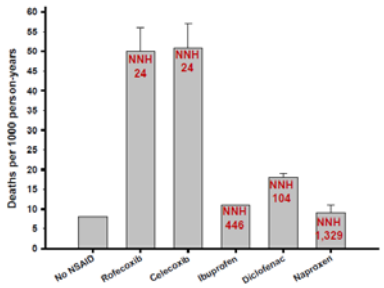
Recommendations	COR	LOE
Before hospital discharge, the patient's need for treatment of chronic musculoskeletal discomfort should be assessed, and a stepped-care approach should be used for selection of treatments. Pain treatment before consideration of NSAIDs should begin with acetaminophen, nonacetylated salicylates, tramadol, or small doses of narcotics if these medications are not adequate.	I	C
It is reasonable to use nonselective NSAIDs, **such as naproxen**, if initial therapy with acetaminophen, nonacetylated salicylates, tramadol, or small doses of narcotics is insufficient.	IIa	C
NSAIDs with increasing degrees of relative cyclooxygenase-2 selectivity should not be administered to patients with NSTE-ACS and chronic musculoskeletal discomfort when therapy with acetaminophen, nonacetylated salicylates, tramadol, small doses of narcotics, or nonselective NSAIDs provide acceptable pain relief.	III: Harm	B

Amsterdam EA et al. J Am Coll Cardiol. 2014; 64:2645-2687.

NSAIDs and Cardiovascular Risk

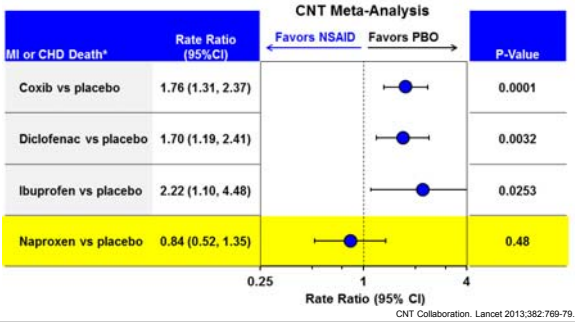
- All NSAIDs appear to increase risk for:
  - MI
  - Heart Failure
  - Gastrointestinal Bleeding
- Are all NSAIDs equal in terms of risk?

NSAIDs and risk of MI/Death



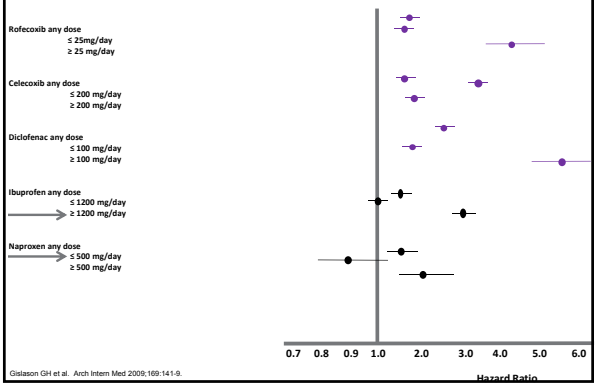
Fosbol EL et al. Clin Pharmacol Ther 2009;85:190-7

Type of NSAID: Death/MI events



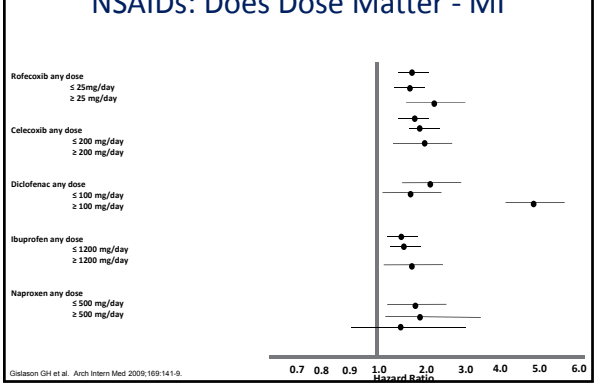
CNT Collaboration. Lancet 2013;382:769-79.

NSAIDs: Does Dose Matter - Death



Gislason GH et al. Arch Intern Med 2009;169:141-9.

NSAIDs: Does Dose Matter - MI



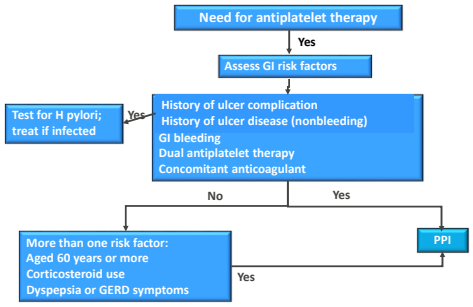
Gislason GH et al. Arch Intern Med 2009;169:141-9.

Question # 10

Which of the following represents the best acid suppressive therapy recommendation to minimize both bleeding risk and interactions potential dual antiplatelet therapy (DAPT) in this patient?

A. Pantoprazole 40 mg daily
B. Esomeprazole 20 mg daily
C. Omeprazole 20 mg daily
D. Ranitidine 150 mg twice daily

Algorithm to Assess GI Risk With Antiplatelet Therapy



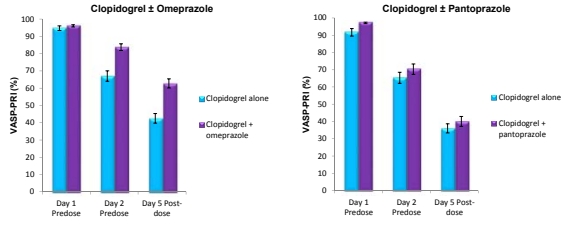
Bhatt DL et al. *J Am Coll Cardiol.* 2008; 52:1502–17.

Clopidogrel – PPI Drug Interaction

- VERY controversial!!!
- Studies associated with interaction:
  - Case-control, cohort studies (retrospective)
  - Platelet reactivity studies
- Studies that suggest no interaction exists
  - Case-control, cohort studies (retrospective)
  - COGENT trial

Standard-Dose Clopidogrel + Omeprazole Versus Standard-Dose Clopidogrel + Pantoprazole: Crossover Comparison

Mean ± SEM of Vasodilator-Stimulated Phosphoprotein Phosphorylation-Platelet Reactivity Index (%)



- After coadministering omeprazole (left panel) or pantoprazole (right panel) with clopidogrel (300-mg LD/75-mg/day MD), the estimated treatment differences (90% CIs) at Day 5 were:
  - 20.7% (90% CI, 14.1% to 27.2%; *P*<0.0001) for omeprazole and
  - 3.9% (–2.7% to 10.4%; *P*=0.3319) for pantoprazole.

LD, loading dose; MD, maintenance dose; SEM, standard error of the mean; VASP-PRI, vasodilator-stimulated phosphoprotein phosphorylation-platelet reactivity index.

Angiolillo DA et al. *Clin Pharmacol Ther*. 2011; 89:65-74.

COGENT Trial: Methods

- Multicenter, international, randomized, double-blind, double-dummy, placebo-controlled, parallel group, phase 3 efficacy and safety study of CGT-2168, a fixed-dose combination of clopidogrel (75 mg) and omeprazole (20 mg), compared with clopidogrel.
- Patients were stratified based on two baseline factors: *H. pylori* serology (positive or negative) and concomitant use of any NSAID.
- All patients were to receive enteric coated aspirin at a dose of 75 to 325 mg/day.

Bhatt DL et al. *N Engl J Med.* 2010; 363:1909-17.

COGENT Trial: Endpoints

- The GI endpoint:
  - Upper GI bleeding,
  - Bleeding of presumed occult GI origin with decrease in hemoglobin of ≥ 2 g/dL or decrease in hematocrit ≥ 10%,
  - Asymptomatic gastroduodenal ulcer confirmed by endoscopy or radiography,
  - Pain of presumed GI origin with underlying multiple erosive disease confirmed by endoscopy, obstruction, or perforation.
- The cardiovascular endpoint:
  - composite of cardiovascular death, non-fatal MI, CABG or PCI, or ischemic stroke.
- The initial planned sample size was 3200 patients, an accrual period of 1 year, and maximum follow up of 2 years. Because a low rate of gastrointestinal events was observed as the trial was ongoing, the sample size target was increased to 4200 and then ~5000 (143 GI events). The study ended when the sponsor declared bankruptcy.

Bhatt DL et al. *N Engl J Med.* 2010; 363:1909-17.

COGENT Trial: Enrollment and Results

- Enrollment:
  - 3873 patients (Below the modified target of 4200, and then 5000)
  - Median follow-up 106 days (essentially 3.5 months)
  - 109 adjudicated cardiovascular events
  - 55 adjudicated GI events (below the 143 that had been planned)
- Cardiovascular endpoint results:
  - 55 events: (clopidogrel + PPI group) vs. 54 events (p=0.98)
  - 180 day event rate: 4.9% (clopidogrel + PPI) vs. 5.7%
    - HR: 0.99 (95% CI: 0.68 – 1.44, p=0.96)

Bhatt DL et al. *N Engl J Med.* 2010; 363:1909-17.

FDA Label Change: Clopidogrel

- Avoid clopidogrel + omeprazole
  - Separating the time of administration will not avoid the interaction
- Additional medications that should be avoided with clopidogrel:
  - Esomeprazole
  - Cimetidine
  - Fluconazole, Ketoconazole, Voriconazole
  - Etravirine
  - Felbamate
  - Fluoxetine, Fluvoxamine
  - Ticlopidine

U.S. Food and Drug Administration. Information for healthcare professionals: update to the labeling of clopidogrel bisulfate (marketed as Plavix) to alert healthcare professionals about a drug interaction with omeprazole (marketed as Prilosec and Prilosec OTC). November 17, 2009. URL in ref list.

Question # 11

If BA was interested in a support group that allowed him to meet with other MI survivors, which of the following would be the best to recommend?

A. American Heart Association Support Network
B. Ironheart Foundation
C. American College of Cardiology
D. Mended Hearts

Additional Patient Resources

- Mended Hearts: National and community nonprofit support group for patients and families with heart disease. http://mendedhearts.org
- American Heart Association patient tools and resources for cardiovascular diseases. http://www.heart.org/HEARTORG/Conditions/Conditions_UCM_001087_SubHomePage.jsp

Additional Patient Resources

- Ironheart Foundation
  - http://www.ironheartfoundation.org/
  - On-line community for multiple heart disease patients
  - Hold many athletic events for disease awareness

Case Continues

- 2 years later, patient is now admitted for acute decompensated heart failure
- Past Medical History:
  - Hypertension
  - Dyslipidemia
  - NSTEMI
  - CAD
  - Diabetes
  - GERD (diagnosed 6 months ago, after he did not respond to over-the-counter options)
  - s/p Total Knee Replacement 18 months ago
- Current Medications:
  - Aspirin 81 mg po daily
  - Clopidogrel 75 mg po daily
  - Lisinopril 20 mg po daily
  - Eplerenone 25 mg po daily
  - Atorvastatin 80 mg po daily
  - Carvedilol 6.25 mg po twice daily
  - Metformin 1000 mg po twice daily
  - Pantoprazole 40 mg po daily
  - Nitroglycerin 0.3 mg SL PRN chest pain

Case Continues

- Pertinent Laboratory data:
  - Na: 130 mEq/L
  - K: 4.8 mEq/L
  - Serum creatinine: 1.4 mg/dL
- ECG: no ischemic changes
- ECHO: EF 30 – 35%
- Physical exam:
  - 3 + pitting edema up to the calves
  - Crackles: ½ way up lung fields bilaterally
  - Weight: increased 15 lb over past week
- Chest X-Ray: Pulmonary edema
- NT-pro-BNP: 5800 ng/mL

Question # 12:
Which of the following represents the most appropriate beta-blocker therapy at this time?

A. Continue carvedilol 6.25 mg po twice daily
B. Decrease carvedilol to 3.125 mg po twice daily
C. Increase carvedilol to 12.5 mg po twice daily
D. Withhold carvedilol while BA is volume overloaded

Beta blockers during acute hospitalization: Continue therapy or not?

- One randomized trial
  - 147 patients with systolic dysfunction heart failure
  - Hospitalized for acute heart failure based on:
    - Pulmonary edema
    - Dyspnea
    - Radiologic evidence of edema
  - Randomized to:
    - Continue current Beta blocker therapy uninterrupted
    - Stop Beta blocker for a minimum of 3 days

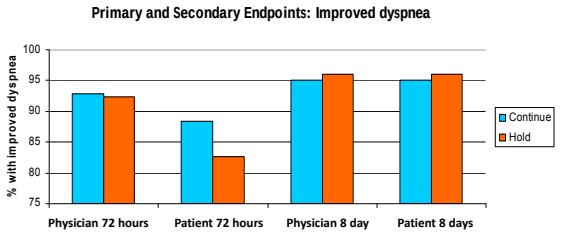
Jondeau G et al. *Eur Heart J.* 2009;30:1-7.

Endpoints

- Primary:
  - % patients whose well being and dyspnea improved at 72 hours and 8 days
    - As determined by a physician blinded to treatment assignment
- Secondary:
  - % patients whose well being and dyspnea improved at 72 hours
    - As determined by the patient
  - Plasma BNP levels at 72 hours
  - Duration of hospitalization
  - Re-hospitalization rate at 3 months
  - Proportion of patients receiving a Beta Blocker at 3 months

Jondeau G et al. *Eur Heart J.* 2009;30:1-7.

Results



Jondeau G et al. *Eur Heart J.* 2009;30:1-7.

	Continue Group N = 69	Hold Group N = 78	p value
Death during hospitalization	1	2	p= NS
BNP Levels at 72 hours	882 ± 950 pg/mL	876 ± 1382 pg/mL	p= NS
Hospitalization for heart failure: 3 mos	22%	32%	p= NS
Receiving Beta Blocker: 3 mos*	90%	76%	p= 0.04
Target dose*	26%	11%	p= 0.03
At least half target dose*	60%	38%	p= 0.03

* = significant difference

NS = not significant

Jondeau G et al. *Eur Heart J.* 2009;30:1-7.

Beta blocker management

- HFSA Guidelines:
  - It is recommended that beta blocker therapy be continued in most patients experiencing a symptomatic exacerbation of HF during chronic maintenance treatment. (Strength of Evidence: C)
- Exceptions: (Strength of Evidence: C)
  - Development of cardiogenic shock
  - Refractory volume overload
  - Symptomatic bradycardia

Heart Failure Society of America. *J Card Fail.* 2010; 16:e1-194

Question # 13

In addition to diuretic therapy, which of the following represents the best approach to managing hyponatremia?

A. Start oral tolvaptan
B. Give 3 % sodium chloride IV
C. 0.9% sodium chloride IV
D. Use fluid restriction

Hyponatremia Expert Panel Recommendations: Heart Failure

- For patients with mild to moderate hyponatremia symptoms, begin with fluid restriction (1 L/day total):
  - If signs of volume overload are present, administer loop diuretics.
- For severely symptomatic patients with very low or rapidly falling sodium:
  - treatment should consist of hypertonic saline (3%) combined with loop diuretics to prevent fluid overload;
- If the serum sodium does not correct to the desired level:
  - lift the fluid restriction and start either conivaptan or tolvaptan

Verbalis JG et al. *Am J Med.* 2013; 126 (10 suppl 1):S1-S42.

HFSA Guidelines: Hyponatremia

- Fluid restriction (2 L/day) is recommended in patients with moderate hyponatremia (serum sodium < 130 mEq/L) and should be considered to assist in treatment of fluid overload in other patients.
  - Strength of Evidence: C

Heart Failure Society of America. HFSA 2010 comprehensive heart failure practice guideline. *J Card Fail.* 2010; 16(6):e1-e194.

Arginine Vasopressin Antagonists (AVP)

In patients hospitalized with volume overload, including HF, **who have persistent severe hyponatremia** and are at risk for or having active cognitive symptoms despite water restriction and maximization of guideline-directed medical therapy (GDMT), vasopressin antagonists may be considered in the short term to improve serum sodium concentration in hypervolemic, hyponatremic states with either a V_2 receptor selective or a nonselective vasopressin antagonist.

Yancy CW et al. *J Am Coll Cardiol.* 2013; 62:e147-239.

Recent Tolvaptan Warning

- Risk of liver injury has been described in those with preexisting liver disease when exposed to AVP antagonists

U.S. Food and Drug Administration. Samsca (tolvaptan): drug warning—potential risk of liver injury. January 25, 2013. URL in ref list.

Inpatient and Transitions of Care

Throughout the hospitalization as appropriate, before hospital discharge, at the first post discharge visit, and in subsequent follow-up visits, the following should be addressed:

a. initiation of GDMT if not previously established and not contraindicated
b. precipitant causes of HF, barriers to optimal care transitions, and limitations in post-discharge support
c. assessment of volume status and supine/upright hypotension with adjustment of HF therapy, as appropriate
d. titration and optimization of chronic oral HF therapy
e. assessment of renal function and electrolytes, where appropriate
f. assessment and management of comorbid conditions
g. reinforcement of HF education, self-care, emergency plans, and need for adherence
h. consideration for palliative care or hospice care in selected patients.

Yancy CW et al. *J Am Coll Cardiol.* 2013; 62:e147-239.