Stable ischemic heart disease

Ali Elfandi, MD, FACC

Chronic Ischemic Heart Disease: Epidemiology

- 17 million Americans have CAD
- 10 million Americans have angina
- Age 60-79 @25% of men, 16% of women
- <code>MD -37% of men, 23% of women</code>



Fihn SD, et al. JACC 2012; 60:2564-2603.

Grading Angina Pectoris: Canadian Cardiovascular Society Classification

Class I:

- Ordinary activity []
- Walking, climbing stairs
- Class II: "Slight limitation"
 - Walking rapidly
 - Activity after meal
 - Walk in cold, wind, AM
 - Climb stairs fast

<u>*Can:*</u> walk 2 blocks or one flight of stairs without angina.

JACC 2003;41:158-68.

A N G I N A





Pathobiology

Inflammation

Platelets and coagulation

Vasospasm

Microvascular dysfunction

Endothelial dysfunction

Critical coronary stenosis







ATHEROSCLEROSIS





1. NORMAL ARTERY

2. ENDOTHELIAL DISFUNCTION

AL FATTY

3. FATTY STREAK FORMATION P

4. 5. STABLE (FIBROUS) UNSTABLE LAQUE FORMATION PLAQUE FORMATION

+A/56-year-old man is seen in cardiology clinic for evaluation of intermittent chest discomfort that has been occurring over the preceding 3 months. He recently lost his job and describes a "squeezing pressure" deep within his chest when thinking about his family's financial situation. The pain is improved by deep breathing and attempts at relaxation. He has no significant past medical history and reports a sedentary lifestyle. He takes no medications. Physical examination reveals male-pattern balding but is otherwise unremarkable. His electrocardiogram is normal.

Which of the following labels best describes this patient's chest pain?

- a) Atypical angina.
- b) Noncardiac chest pain.
- c) Typical angina.
- d) Unstable angina.

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Spectrum of IHD



A 58-year-old man is seen in the emergency department for the evaluation of sharp, stabbing chest pain. He has had multiple similar episodes lasting 3-5 minutes over the past 2 weeks while mowing his lawn, carrying boxes up the stairs, and climbing uphill and always relieved by rest. On the day of presentation, he was sitting at his desk at work when an episode occurred. He took a coworker's sublingual nitroglycerin with eventual resolution of the discomfort. He is currently chest pain-free. His past medical history includes gout, type 2 diabetes mellitus, dyslipidemia, and gastroesophageal reflux disease. He takes metformin 500 mg twice daily, allopurinol 100 mg daily, pravastatin 40 mg daily, and an over-the-counter antacid as needed. He smokes 1/2 pack of cigarettes daily. His physical examination is unremarkable. His electrocardiogram and initial troponin I are normal.

Which of the following is the best description of his clinical presentation?

- a) Unstable angina
- b) Non cardiac chest pain
- c) NSTEMI
- d) Typical angina
- e) Stable angina

Which of the following is the best description of his clinical presentation?

a) Unstable angina

b) Non cardiac chest pain

c) NSTEMI

- d) Typical angina
- e) Stable angina

NonInvasive Risk Stratification



NonInvasive Risk Stratification



NonInvasive Risk Stratification



Myocardial Stunning VS Hibernation





- A 55-year-old man who has a history of hypertension , hypercholesterolemia, and a 35-year history of active cigarette smoking is referred to you for evaluation of a month long history of a stabbing pain in his chest that becomes worse with climbing stairs. The pain is described as "knife-like", lasts 30 seconds, and is located on the right side of his chest in a 3 cm area just below his nipple. The pain occurs with climbing stairs, walking a block or more (his most strenuous activities), and is relieved with rest. There are no other associated symptoms.
- + He has been treated by his primary care physician with metoprolol succinate 200 mg daily and atorvastatin 40 mg for several years. His physical examination is benign except for obesity, a blood pressure of 136/87 mm Hg, and heart rate of 54 bpm. His electrocardiogram (ECG) demonstrates sinus bradycardia.

In addition to counseling for weight loss, which of the following is the next most appropriate step in the management of this patient?

- a) A transthoracic echocardiogram
- b) Prescription of an exercise regimen.
- c) An exercise nuclear stress test.
- d) Coronary calcium score.
- e) An ambulatory ECG monitor.

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Comprehensive management of SIHD

Treatment of disease that can precipitate angina/ischemia

Coronary risk factor reduction

Lifestyle changes

Pharmacologic management of angina

Revascularization

Guideline-Directed Medical Therapy for Patients with SIHD



Guideline-Directed Medical Therapy for Patients with SIHD



Guideline-Directed Medical Therapy for Patients with SIHD



Case 1:

A 62 yr. old retired PE teacher asks for your opinion about management of his stable ischemic heart disease. Because of a (+) family history (Father – fatal MI age 45) he underwent an exercise stress echo 3 months ago. He exercised to 14 MET's and had no symptoms. At 8 MET's, he developed 1 mm STD in the inferior leads. After exercise, he had 3-4 mm of STD in both inferior and anterior leads. Echo showed normal LV function at rest. During stress, he had inferior and lateral mild hypokinesis.

Diet: Healthy *Exercise*: He works out 1-2 hrs/day. **Risk Factors:** Hypertension, hyperlipidemia, family history. Meds: ACE inhibitor, β-blocker, aspirin, calcium channel blocker. He developed muscle cramps on atorvastatin. Exam: Looks healthy. BP-160/80. Pulse-54. CV exam and lung exam is totally normal.

- To exclude left main disease, he underwent a cardiac cath. This revealed:
 - Normal LV pressures
 - Normal left main
 - Long 60-70% mid to distal LAD stenosis
 - Occluded but small left circumflex
 - Distal 70% RCA stenosis
 - Large clear ramus



His local cardiologist wants to "fix" his blockages. What will you recommend?

- A. Offer him multivessel CABG for survival advantage.
- B. Offer multivessel PCI to reduce silent ischemia.
- C. Maximize medical treatment: add statin, increase BP meds.
- D. Offer hybrid treatment LIMA to LAD, stent to RCA.E. Order a PET study to further characterize his risk.



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 E. Order a PET study to further characterize his risk.



Medical Management of Patients with Stable Coronary Artery Disease



Indications for

coronary revascularization



COURAGE: Death or MI by Residual Ischemia at 1 Year



Global Strategy of Intervention in Stable Coronary Artery Disease Patients with Demonstrated Ischemia



Syntax Score



Farooq V, et al. Heart 2014;100:276-287.



Courage: Rates of Major Adverse Cardiac or Cerebrovascular Events Among the Study Patients, According to Treatment Group and SYNTAX Score Category



AMERICAN COLLEGE of CARDIOLOGY

Serruys PW et al. N Engl J Med 2009;360:961-972.

CAD SYNTAX 5 Year Results



OLLEGE 0

CARDIOLOGY

Lancet 2013;381:629-38.

PCI or CABG in Stable Coronary Artery Disease without Left Main Coronary Artery Involvement



Montalescot G, et al. Eur Heart J 2013;296:11-62.
PCI or CABG in Stable Coronary Artery Disease with Left Main Coronary Artery Involvement



Case 2: A 67 yr. old woman is referred to you for a second opinion regarding "stable" ischemic heart disease. She has diabetes, hypertension, and hyperlipidemia. All are currently well controlled. She recently was evaluated for an episode of chest pressure at rest, and a subsequent echocardiogram revealed a fall in her LVEF from 58% to 42%. A local cardiologist performed coronary angiography. This revealed 3 vessel disease. It included 85% proximal LAD stenosis, 74% proximal RCA stenosis, and an occluded left circumflex artery with right to left collaterals.

FFR was performed on the LAD& RCA lesions and was 0.74

And 0.79 respectively The patient's meds include:

- Aspirin 81 QD
- Metoprolol tartrate 50mg BID
- Lisinoril 10mg QD
- Atorvastatin 80mg QD
- Isosorbide mononitrate 60mg QD



Physical Exam:

Well appearing woman. BP 129/75, pulse 59. Estimate RA pressure 7 cm of H2O. Carotids brisk without bruit. Lungs clear. Heart – normal distal LV apical impulse S1 normal. S2 slightly loud. S4 I-1I/VI mid peaking systolic murmur left sternal area to base, not neck. Abdomen and extremities unremarkable.



Physical Exam:

Well appearing woman. BP 129/75, pulse 59. Estimate RA pressure 7 cm of H2O. Carotids brisk without bruit. Lungs clear. Heart – normal distal LV apical impulse S1 normal. S2 slightly loud. S4 I-11/VI mid peaking systolic murmur left sternal area to base, not neck. Abdomen and extremities unremarkable.



Her cardiologist had recommend staged PCI – he'd do the circumflex marginal CTO first, then later come back and stent the LAD and RCA. Which option below is most supported by clinical trials and current guidelines?

- A. PCI of all 3 lesions in a staged approach to allow her to avoid CABG.
- B. Hybrid PCI/CABG-LIMA-LAD and SVG to the left circumflex marginal; PCI of RCA.
- C. Advance her medical treatment; increase nitrates. Add amlodipine; add ezetimide.
- D. 3-vessel CABG including LIMA to LAD.
- E. Hybrid CABG/PCI: LIMA to LAD, PCI the RCA and the marginal CTO.



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CAD FREEDOM Trial Revascularization



CARDIOLOGY

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NEJM 2012;367:2675-84.

DM + Left Main Disease: PCI vs. CABG

DM + MVD: PCI vs. CABG

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Head SJ, et al. Lancet 2018;391:939-948.

Hybrid Coronary Revascularization: Recommendations

Class IIa

- 1. Hybrid coronary revascularization defined as the planned combination of LIMA-to LAD artery Mathematical Coronary arteries is reasonable in patients with 1 or more of the following. *(Level of Evidence: B)*
 - a. Limitations to traditional CABG, such as heavily calcified proximal aorta or poor target vessels for CABG (but amenable to PCI):
 - b. Lack of suitable graft conduits;
 - c. Unfavorable LAD artery for PCI (i.e.; excessive vessel tortuosity or chronic total occlusion).

Class IIb

1. Hybrid coronary revascularization (defined as the planned combination of LIMA-LAD artery Market Market Coronary arteries) may be reasonable as an alternative to multivessel PCI or CABG in an attempt to improve the overall risk-benefit ratio of the procedures. *(Level of Evidence: C)*



Fihn SD, et al. JACC 2012;60:2654-2603.

Use of Fractional Flow Reserve, Intravascular Ultrasound, and Optical Coherence Tomography in SCAD

Recommendations	Class
FFR is recommended to identify hemodynamically relevant coronary lesion(s) when evidence of ischemia is not available	I
Revascularization of stenoses with FFR <0.80 is recommended in patients with angina symptoms or a positive stress test	Ι
IVUS or OCT may be considered to characterize lesions	IIb
IVUS or OCT may be considered to improve stent deployment	IIb
Revascularization of an angiographically intermediate stenosis without related ischemia or without FFR <0.80 is not recommended	Ш

Montalescot G, et al. Eur Heart J 2013;296:11-62.



FAME Trial: Fractional Flow Reserve (FFR) vs. Angiography for Guiding Multi-Vessel PCI

Study Enrollment and Randomization



FAME Trial: Fractional Flow Reserve (FFR) vs. Angiography for Guiding Multi-vessel PCI

Primary and Secondary Points at 2-Year Follow-Up



CardioSource Interventional News 2012; Sept/Oct. Pijls N et al. JACC 2010;56:177.

FAME Trial: "Downgrading" MV Disease with FFR



FAME 2



Primary end point (a composite of death from any cause, nonfatal myocardial infarction, or urgent revascularization)

De Bruyne B et al. N Engl J Med 2014;371:1208-1217

Ongoing Follow-Up

Annual Check-Up

- Sx, Function?
- HF, Arrhythmia?
- Risk Factors
- Adequacy of Rx

Assess LVEF and Segmental WMA in Patients with New or Worsening HF, New MI

Class I



Follow-up of Revascularized Stable Coronary Artery Disease Patients

Recommendations	
General measures	
It is recommended that all revascularized patients receive secondary prevention and be scheduled for follow-up visit	I
It is recommended to instruct patients before discharge about return to work and reuptake of full activities. Patients have to be advised to seek immediate medical contact if symptoms (re-) occur	I
Antiplatelet therapy	
SAPT, usually aspirin, is recommended indefinitely	Ι
DAPT is indicated after BMS for at least one month	Ι
DAPT is indicated for 6 to 12 months after 2 nd generation DES	I
DAPT may be used for more than one year in patients with high ischemic risk (e.g. stent thrombosis, recurrent ACS on DAPT, post MI/diffuse CAD)and low bleeding risk	IIb
DAPT for 1 to 3 months may be used in patients at high bleeding risk or with undeferable surgery or concomitant anticoagulant treatment	IIb



Montalescot G, et al. Eur Heart J 2013;296:11-62.

Oral Antiplatlet Therapy

Ali Elfandi, MD, FACC

Platelet-Mediated Thrombosis Targets



GP = glycoprotein; vWF = von Willebrand factor; ADP = adenosine diphosphate; TX = throm boxane.



Meadows et al. Circulation Res. 2007;100:1261-1275

Metabolism of P2Y12 Receptor Blockers



Summary: Oral P2Y₁₂ Inhibitor Pharmacology

	Clopidogrel	Prasugrel	Ticagrelor
Class	Thienopyridine	Thienopyridine	Triazolopyrimidine
Reversibility	Irreversible	Irreversible	Reversible
Activation	Prodrug, limited by metabolism	Prodrug, not limited by metabolism	Active drug
Onset of Effect*	2-4 hours	30 minutes	30 minutes
Duration of Effect	3-10 days	5-10 days	3-4 days
Withdrawal before major surgery	5 days	7 days	5 days

* 50% inhibition of platelet aggregation



Consensus recommendations on switching between oral P2Y12 inhibitors.

Switching Between Oral P2Y₁₂ Inhibitors

A Acute/Early phase



Dominick J. Angiolillo et al. Circulation. 2017;136:1955-1975



Does PCI Complexity Favor Longer-Term DAPT?

Complex Features:

3 vessels treated

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Effect of ≥12 Months Versus 3 or 6 Months DAPT on the Risk of Major Adverse Cardiac Events According to Procedural Complexity



Giustino, G. et al. J Am Coll Cardiol. 2016;68(17):1851-64.

COLUMBIA UNIVERSITY MEDICAL CENTER



Question

-68 YO M with PMH of CAD and MI s/p mid LAD DES, HTN, HLD and DM2 who presents to your office for routine follow up. It has been about 1 year since his MI. He is currently maintained on ASA 81mg, Prasugrel 10mg, Atorvastatin 80mg, Metoprolol XL 50mg and Lisinopril 20mg. He exercises twice weekly and describes no limiting symptoms. His examination reveals normal vitals and controlled BP. Otherwise unremarkable. +Which of the following is the best step in managing this patient?

- a) Stop his ASA.
- b) Stop his metoprolol.
- c) Discuss risks/benefits of continuation vs discontinuation of second antiplatelet therapy.
- d) Perform an exercise treadmill stress test.

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ACC/AHA FOCUSED UPDATE



2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/ PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction,

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

COR	LOE	RECOMMENDATIONS
1.	A	In patients with SIHD treated with DAPT after BMS implantation, P2Y ₁₂ inhibitor therapy (clopidogrel) should be given for a minimum of 1 month (94,95).
ĩ	B-R ^{sr}	In patients with SIHD treated with DAPT after DES implantation, P2Y ₁₂ inhibitor therapy (clopidogrel) should be given for at least 6 months (17,18,21,30,96,97).
T	B-NR	In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended (56-60,75-78).
lib	A ^{SR}	In patients with SIHD treated with DAPT after BMS or DES implantation who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT with clopidogrel for longer than 1 month in patients treated with BMS or longer than 6 months in patients treated with DES may be reasonable (16,22,24–26,30,50).
llb	C-LD	In patients with SIHD treated with DAPT after DES implantation who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, discontinuation of P2Y ₁₂ inhibitor therapy after 3 months may be reasonable (19,20,34,36,37).

SR indicates systematic review.

Recommendations for Duration of DAPT in Patients Undergoing CABG

COR	LOE	RECOMMENDATIONS
ļ	C-EO	In patients treated with DAPT after coronary stent implantation who subsequently undergo CABG, P2Y ₁₂ inhibitor therapy should be resumed postoperatively so that DAPT continues until the recommended duration of therapy is completed.
Û	C-LD	In patients with ACS (NSTE-ACS or STEMI) being treated with DAPT who undergo CABG, P2Y ₁₂ inhibitor therapy should be resumed after CABG to complete 12 months of DAPT therapy after ACS (52–54,118–120).
ļ	B-NR	In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended (56-60,75-78).
lib	B-NR	In patients with SIHD, DAPT (with clopidogrel initiated early postoperatively) for 12 months after CABG may be reasonable to improve vein graft patency (121-125).

Recommendations for Duration of DAPT in Patients With SIHD

COR	LOE	RECOMMENDATIONS
4	A	In patients with SIHD treated with DAPT after BMS implantation, P2Y ₁₂ inhibitor therapy (clopidogrel) should be given for a minimum of 1 month (94,95).
1	B-R ^{SR}	In patients with SIHD treated with DAPT after DES implantation, P2Y ₁₂ inhibitor therapy (clopidogrel) should be given for at least 6 months (17,18,21,30,96,97).
a -	B-NR	In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended (56-60,75-78).
lib	A ^{SR}	In patients with SIHD being treated with DAPT for an MI that occurred 1 to 3 years earlier who have tolerated DAP without a bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy oral anticoagulant use), further continuation of DAPT may be reasonable (28,30,40,41,44).
IIb	A ^{sr}	In patients with SIHD treated with BMS or DES implantation who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, oral anticoagulan use), continuation of DAPT with clopidogrel for longer than 1 month in patients treated with BMS or longer than months in patients treated with DES may be reasonable (16,22,24–26,30,50).
lib	C-LD	In patients with SIHD treated with DAPT after DES implantation who develop a high risk of bleeding (e.g., treatmen with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery) or develop significant overt bleeding, discontinuation of P2Y ₁₂ inhibitor therapy after 3 months may be reasonabl (19,20,34,36,37).
lib	B-NR	In patients with SIHD, treatment with DAPT (with clopidogrel initiated early postoperatively) for 12 months after CABG may be reasonable to improve vein graft patency (121–125).
III: No Benefit	B-R	In patients with SIHD without prior history of ACS, coronary stent implantation, or recent (within 12 months) CABG treatment with DAPT is not beneficial (28,40-42).

SR indicates systematic review.

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Recommendations for Perioperative Management-Timing of Elective Noncardiac Surgery in Patients Treated With PCI and DAPT

COR	LOE	RECOMMENDATIONS
Ì	B-NR	Elective noncardiac surgery should be delayed 30 days after BMS implantation and optimally 6 months after DES implantation (101-103,143-146).
ţ	C-EO	In patients treated with DAPT after coronary stent implantation who must undergo surgical procedures that mandate the discontinuation of P2Y ₁₂ inhibitor therapy, it is recommended that aspirin be continued if possible and the P2Y ₁₂ platelet receptor inhibitor be restarted as soon as possible after surgery.
lla	C-EO	When noncardiac surgery is required in patients currently taking a P2Y ₁₂ inhibitor, a consensus decision among treating clinicians as to the relative risks of surgery and discontinuation or continuation of antiplatelet therapy can be useful.
lib	C-EO	Elective noncardiac surgery after DES implantation in patients for whom P2Y ₁₂ inhibitor therapy will need to be discontinued may be considered after 3 months if the risk of further delay of surgery is greater than the expected risks of stent thrombosis.
III: Harm	B-NR	Elective noncardiac surgery should not be performed within 30 days after BMS implantation or within 3 months after DES implantation in patients in whom DAPT will need to be discontinued perioperatively (101-103,143-146).

472 YO female with PMH of paroxysmal afib, HTN and HLD who was recently admitted to the hospital for a Non-STEMI and received a proximal RCA DES. She was initiated on ASA 81mg and Ticagrelor 90mg BID on top of her home medications which include: Rivoroxaban 20mg, Rosuvastatin 20mg and Valsartan 40mg.

+Upon discharging this patient, which of the following would be the most appropriate antiplatelet and antithrombotic therapy?

Question

- (a) /ASA 81 + Brilinta 90mg BID + Xarelto 20mg.
- b) Stop ASA and continue with Brilinta 90mg BID + Xarelto 20mg
- c) Stop ASA. Switch Brilinta to Plavix 75mg + Xarelto 20mg.
- d) ASA 81mg + Brilinta 90mg BID + Xarelto 15mg.
- e) Brilinta 60mg BID + Xarelto 20mg.

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- b) Stop ASA and continue with Brilinta 90mg BID + Xarelto 20mg.
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EXPERT CONSENSUS DECISION PATHWAY

2020 ACC Expert Consensus Decision Pathway for Anticoagulant and Antiplatelet Therapy in Patients With Atrial Fibrillation or Venous Thromboembolism Undergoing Percutaneous Coronary Intervention or With Atherosclerotic Cardiovascular Disease

A Report of the American College of Cardiology Solution Set Oversight Committee

VOL. 77, NO. 5, 2021

Potential Clinical Situations (1) Prior AF on anticoagulation and the need for PCI

(2) New-onset AF requiring anticoagulation in a patient already on antiplatelet therapy for coronary artery disease (CAD)

(3) Prior VTE on anticoagulation and the need for PCI

(4) New or recurrent VTE requiring anticoagulation in a patient already on antiplatelet therapy for CAD. In general, the use of "triple therapy" (dual antiplatelet therapy plus anticoagulation) is not recommended for most patients due to an increased risk of bleeding. If triple therapy is needed, a short duration (e.g., no more than 30 days) is recommended.

When combined with an anticoagulant, clopidogrel is the recommended antiplatelet agent for most patients.

If aspirin is being used, it should be limited to <100 mg daily dosing.

Rule Of Thumb

Dharam J. Kumbhani et al. J Am Coll Cardiol 2021; 77:629-658.
Patients with AF on anticoagulation who need a PCI

- +Use of a direct oral anticoagulant (DOAC) is preferred over a vitamin K antagonist (VKA) when appropriate.
- +Oral anticoagulation plus P2Y₁₂ antiplatelet combination is recommended for the first 6-12 months (potentially switching P2Y₁₂ to aspirin for months 6-12 if PCI for stable ischemic heart disease), followed by anticoagulation monotherapy after 12 months.





For patients on antiplatelet therapy who develop new AF

- 4 For primary cardiovascular prevention, switch to anticoagulation __monotherapy is recommended.
- + For PCI with stable ischemic heart disease or acute coronary syndrome, use of oral anticoagulant plus a P2Y₁₂ inhibitor for no more than 12 months is recommended, followed by oral anticoagulation alone.
- + For patients with cerebrovascular disease without carotid stenting, oral anticoagulation monotherapy is recommended.
- + For patients with carotid stenting or peripheral artery disease, a short course of anticoagulation plus P2Y₁₂ inhibitor may be recommended, followed by oral anticoagulation alone.

Dharam J. Kumbhani et al. J Am Coll Cardiol 2021; 77:629-658.

Management of patients with prior VTE

- +If the VTE was associated with strongly provoking, reversible risk factors, then delaying a PCI may be beneficial so that anticoagulation therapy can be discontinued.
- +If long-term/indefinite anticoagulation is required, then use of standard treatment doses of anticoagulation plus P2Y₁₂ inhibitor antiplatelet therapy are recommended following PCI.
- +If the dose of anticoagulation is reduced (e.g., "half-dose DOAC" for VTE secondary prevention), then continued use of a single antiplatelet medication (e.g., aspirin) is indicated long-term

Dharam J. Kumbhani et al. J Am Coll Cardiol 2021; 77:629-658.

Patients on antiplatelet therapy who develop a new VTE event

- +Use of anticoagulation plus single antiplatelet medication is generally recommended.
- +Patients using antiplatelet therapy for primary cardiovascular disease prevention or >12 months from the most recent PCI or acute coronary syndrome can be treated with anticoagulation monotherapy.

Patients on DOAC pre-PCI

+For patients taking DOAC medications who require PCI, most DOACs can be held for no more than 36-48 hours prior to the procedure.

+Holding a DOAC for longer periods of time may be required for patients with moderate-severe renal dysfunction, especially if using dabigatran.

Dharam J. Kumbhani et al. J Am Coll Cardiol 2021; 77:629-658.

DOAC Dose Adjustment

+When used in combination with antiplatelet medications, dosing of DOAC medications usually follows the Food and Drug Administration guidance for stroke prevention in AF or treatment of VTE.

+ However, rivaroxaban may be administered at 15 mg daily (reduce to 10 mg daily for creatinine clearance <50 ml/min) when combined with P2Y₁₂ inhibitors, based on the PIONEER-AF PCI study.

Management of Heart Failure

Ali Elfandi, MD, FACC



Ejection Fraction and Heart Failure

Reduced (HFrEF)

Impairment in LV contraction

Definite therapeutic recommendations

Preserved (HFpEF)

Impairment in LV filling/relaxation (but likely heterogeneous causes in the population)

Generalizations

The world of heart failure is divided ~evenly between HFrEF and HFpEF





Adapted: ESC Guidelines, 2016



LV Structural Remodeling



Concentric (Thickened) Sarcomeres added in parallel Diastolic HF (HFpEF) Impaired relaxation/filling



Eccentric (Dilated) Sarcomeres added in series Systolic HF (HFrEF) Impaired contraction*

*Can have concomitant diastolic dysfunction





Remodeling in HFrEF



LaPlace's Law: Increased Wall Stress in Remodeled LV





<u>Reverse</u> Remodeling in HFrEF





Preload and Stroke Volume (Ventricular Performance) Frank-Starling Mechanism

Stroke Volume

Length-tension relationship: Increased preload leads to increased contractile force.

LVEDP or PCWP







Neurohormonal Activation in Heart Failure



	Compensatory role	Maladaptive effect
Norepinephrine	 Increased HR Increased contractility 	 Cardiac hypertrophy Apoptosis Arrhythmia
Angiotensin 2	 Vasoconstriction Sodium reabsorption 	 Cardiac fibrosis/hypertrophy Fetal gene expression
Aldosterone	 Sodium reabsorption 	Myocardial fibrosis







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Staging Heart Failure *A Contemporary Paradigm*

- Stage A At high risk for HF but no structural heart disease
- Stage B Structural heart disease but w/o signs or symptoms of HF
- Stage C Structural heart disease with prior or current symptoms
- Stage D Refractory HF requiring specialized interventions

Hunt et al., Circulation 2001;104:2996

- HTN, DM, CAD, cardiotoxins
- LVH, LVSD, MI, asx valve dz
- Sx LVSD or asx on Tx
- Recurrent hosp, need for Tx/VAD



A 65 y.o. man presents for follow-up of HFrEF. He reports stable symptoms of exertional dyspnea with climbing steps but no difficulties with other activities. Had throat swelling on lisinopril.

His exam demonstrates BMI 28, BP 120/70, HR 80, no JVD, faint apical gallop, clear lungs, unremarkable abdomen, no edema, good pulses, warm. ICD in place.

EKG NSR 75, old anterior MI, narrow QRS. Labs Na 136, Cr 1. 7, K 4.0; LVEF 30%.



His medications include:

Valsartan 160 mg bid, carvedilol 25 mg bid, spironolactone 25 mg qd, furosemide 20 mg qd.

You recommend:

- A. Hydralazine/Isordil for valsartan
- B. Sacubitril/valsartan for valsartan
- C. Add amlodipine
- D. Ivabradine
- E. No changes



His medications include:

Valsartan 160 mg bid, carvedilol 25 mg bid, spironolactone 25 mg qd, furosemide 20 mg qd.

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- E. No changes





A 35 year-old man presents with shortness of breath for 6 weeks. He's been sleeping in a chair for the past month. He tells you that his brother died suddenly several years ago in his 30s. He drinks socially.

On exam, comfortable, BP 110/75, HR 115. JVD 16cm, lungs clear, precordial heave present. Gallop rhythm w/ diffuse precordial systolic murmur. Liver edge palpable. Ext warm w/ trace pedal edema.

EKG shows NSR 110 bpm and narrow QRS. Echo shows LVEF 30%, LVEDD 5.5, mild TR/MR, LAE.



In addition to diuretics, the next drug you recommend is:

AMERICAN

- A. Carvedilol
- B. Spironolactone
- C. Lisinopril
- D. Metoprolol succinate
- E. Atenolol

In addition to diuretics, the next drug you recommend is:

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- D. Metoprolol succinate
- E. Atenolol



Norepinephrine in Heart Failure



Cohn JN, NEJM 1984;311:819



Clinical Pharmacology of Beta-blockers

	β ₁ /β ₂ Receptor <u>Selectivity</u>	Vasodilator <u>Mechanism</u>	Lipid <u>Solubility</u>	
Bisoprolol	120	0	0	
Metoprolol	75	0	0	
Carvedilol	10-40	α_1 antagonist	++	
Bucindolol	1	Direct	++	
Labetalol	1	α_1 antagonist	++	



Beta-blockers in HFrEF *Clinical guidelines*

- Use agents and target doses used in clinical trials.
- Initiate when euvolemic, off of i.v. vasoactive agents and prior to hospital d/c.
- Titrate upward every 2 to 4 weeks as long as stable.
- Most trials held titration for HR <60 or SBP <90.
- Adjust other agents if dyspnea, BP, or wgt gain occur in order to titrate to target doses.
- In ADHF, can usually treat without changing BB dose.



Target Beta-Blocker Doses

- Carvedilol
 - MOCHA
 - US Carvedilol Trials
 - COPERNICUS
- Metoprolol succinate
 - MERIT-HF
- Bisoprolol
 - CIBIS I and II

25 mg BID 50 mg BID

200 mg daily

10 mg daily

Beta blockers in CHF A little is better than none



Antagonizing the Renin-Angiotensin System



ACE Inhibitors in Heart Failure

- Improve symptoms, clinical status, and exercise capacity
- Improves cardiac function
- Reduces hospitalizations
- Attenuates remodeling
- Prolongs survival
- Reduces vascular events (ie. HOPE)



Dose does matter...

The ATLAS Trial

		Low Dose	<u>High Dose</u>	ratio	D
	All cause mortality	717 (44.9%)	666 (42.5%)	0.92 (0.82-1.03)	0.128
	All cause mortality + Hospitalization	1338 (83.8%)	1250 (79.7%)	0.88 (0.82-0.96)	0.002
	All cause mortality + CHF hosp.	964 (60.4%)	864 (55.1%)	0.85 (0.78-0.93)	<.001
2	acker, Circ 1999;100:2312				CARDIOLOGY

Henevel
TABLE 3 Drugs Commonly Used for HFrEF (Stage C HF)

Drug	Initial Daily Dose(s)	Maximum Doses(s)	Mean Doses Achieved in Clinical Trials	References
ACE inhibitors				
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Enalapril	2.5 mg BID	10-20 mg BID	16.6 mg QD	(129)
Fosinopril	5-10 mg QD	40 mg QD	N/A	
Lisinopril	2.5-5 mg QD	20-40 mg QD	32.5-35.0 mg QD	(130)
Perindopril	2 mg QD	8-16 mg QD	N/A	÷
Quinapril	5 mg BID	20 mg BID	N/A	
Ramipril	1.25-2.5 mg QD	10 mg QD	N/A	-
Trandolapril	1 mg QD	4 mg QD	N/A	-
ARBs				
Candesartan	4-8 mg QD	32 mg QD	24 mg QD	(137)
Losartan	25-50 mg QD	50-150 mg QD	129 mg QD	(136)
Valsartan	20-40 mg BID	160 mg BID	254 mg QD	(134)
ARNI				
Sacubitril/valsartan	49/51 mg BID (sacubitril/valsartan) (therapy may be initiated at 24/26 mg BID)	97/103 mg BID (sacubitril/valsartan)	375 mg QD; target dose: 24/26 mg, 49/51 mg OR 97/103 mg BID	(138)
If channel inhibitor				
Ivabradine	5 mg BID	7.5 mg BID	6.4 mg BID (at 28 d) 6.5 mg BID (at 1 y)	(155-157)
Aldosterone antagonists				
Spironolactone	12.5-25 mg QD	25 mg QD or BID	26 mg QD	(142)
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Carvedilol	3.125 mg BID	50 mg BID	37 mg QD	(161)
Carvedilol CR	10 mg QD	80 mg QD	N/A	-
Metoprolol succinate extended release (metoprolol CR/XL)	12.5-25 mg QD	200 mg QD	159 mg QD	(139)
Isosorbide dinitrate and hydralazine				
Fixed-dose combination	20 mg isosorbide dinitrate/ 37.5 mg hydralazine TID	40 mg isosorbide dinitrate/ 75 mg hydralazine TID	90 mg isosorbide dinitrate/ ~175 mg hydralazine QD	(162)
Isosorbide dinitrate and hydralazine	20-30 mg isosorbide dinitrate/ 25-50 mg hydralazine TID or QD	40 mg isosorbide dinitrate TID with 100 mg hydralazine TID	N/A	(163)

Modified (Table 15) from the 2013 HF guideline (9).

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BID, twice daily; CR, controlled release; CR/XL, controlled release; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; N/A, not applicable; QD, once daily; and TID, 3 times daily.

ACE Inhibitors

Take home points

- Use target doses used in clinical trials.
- Intolerance due to cardiorenal limitations associated with poor prognosis.
- Adverse effects: cough, angioedema, dysgeusia, anemia.
- Increase in Cr up to 0.5 mg/dL expected.
- Most studies have excluded pts with Cr > 2.5 mg/dL.





When to Use ARBs in Heart Failure

- ACC/AHA recommendations
 - Alternative when ACEI not tolerated (Class I)
 - Added to an ACEI (Class IIb)
 - (after β blocker titration)
 - ACEI, ARB, and aldo ant. NOT recommended (Class III)
- Alternative to ACEI
 - ACEI should be tried first (altho Class I if already started)
 - Caution with angioedema
- Persistent hypertension or symptoms
 - Use optimal doses of ACEI and β blockers first



What about Hydralazine and Isordil? The A-HeFT Trial





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ESTABLISHED IN 1812

SEPTEMBER 11, 2014

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Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

•NYHA II – IV •BNP >150 pg/ml (>100 if 12m HFH) •NT-proBNP >600 pg/ml (>400 if 12m HFH) •LVEF <35% •ACEi or ARB

•BP >100 mmHg •eGFR >30 cc/min/1.73m²

•Run-in phase



PARADIGM-HF: Other Endpoints



McMurray, NEJM 2014; Desai et al. EHJ 2015

2017 ACC/AHA/HFSA HF Guidelines

COR	LOE	Recommendations
I.	B-R	ACEI <u>OR</u> ARB <u>OR</u> ARNI in conjunction with beta-blockers + MRA (where appropriate) is recommended for patients with chronic HFrEF to reduce morbidity and mortality.
1	B-R	In patients with chronic, symptomatic HFrEF NYHA class II or III who tolerate and ACE inhibitor or ARB, <u>replacement</u> by an ARNI is recommended to further reduce morbidity and mortality
	B-R	ARNI should NOT be administered concomitantly with ACEi or within 36 hours of last ACEi dose
Ш	C=EO	ARNI should NOT be administered to patients with a history of angioedema

Yancy, et al. Circulation 2016



You see your patient one week after hospital discharge and double up his metoprolol succinate from 50 mg daily to 100 mg daily.

He calls your nurse a week later with orthopnea, PND, and nocturia. You ask him to come in.

On exam, his heart rate is 80, blood pressure is 100/70, his venous pressures are 18 cm of water, his murmur is louder, and now accompanied by an S3. His lungs are clear and there is no peripheral edema.





The next most appropriate step is:

- A. Increase his furosemide.
- B. Decrease his beta-blocker.
- C. Add digoxin.
- D. Decrease his losartan.
- E. Increase his beta-blocker.





The next most appropriate step is:

A. Increase his furosemide.

- B. Decrease his beta-blocker.
- C. Add digoxin.
- D. Decrease his losartan.
- E. Increase his beta-blocker.





Diuretics in heart failure Things to keep in mind

- They activate the SNS and RAS axes so use the lowest doses possible to maintain euvolemia.
- Have not been shown to improve mortality (and may even increase it).
- Diuretic resistance most commonly caused by poor oral bioavailability, compensatory distal tubular Na reabsorption, and renal insufficiency.
- Thiazides and aldosterone antagonists should be given before loop diuretics.
- Don't forget concomitant sodium restriction.



Your patient has tolerated metoprolol succinate 200 mg qd and goes back to work. However, he continues to have trouble taking a shower and carrying groceries. There has been no weight gain. You see him in the office for routine evaluation. His blood pressure is 100/65 mmHg.

You decide to:

- A. Change to carvedilol.
- B. Add spironolactone.
- C. Add amiodarone.
- D. Add rosuvastatin.
- E. Decrease his beta-blocker.



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- E. Decrease his beta-blocker.



Aldosterone in Heart Failure

- Released from adrenal cortex and other tissues in response to angiotensin II, ACTH, and potassium
- Promotes Na retention, K and Mg wasting
- Induces myocardial and vascular fibrosis
- Activates sympathetic NS and inhibits parasympathetic NS
- Extra-adrenal aldosterone production (ie. heart)
- Increases by >20X in heart failure
- Aldosterone "escape" from ACE inhibition



Aldosterone Antagonists in NYHA II HF

EMPHASIS-HF

•2737 pts •All NYHA Class II •>85% ß-blockers •>90% ACEI/ARB •10% device therapy

•Exclusion: GFR <30, K > 5.0
•Eplerenone 50mg qd (40mg)
•Labs q 4 mos

All cause mortality reduced
More hyperkalemia
Less hypokalemia

Α 100-Hazard ratio, 0.63 (95% CI, 0.54-0.74) Hospitalization for Heart Failure or Death from Cardiovascular Causes (%) P<0.001 60 50-40-Placebo 30-20-Eplerenone 10-3 Years since Randomization No. at Risk Placebo 1373 848 512 199 1364 925 562 232 Eplerenone AMERICAN

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Aldosterone Antagonists

Clinical Considerations

- Should be considered in most patients with heart failure and EF < 40%.
- Potassium and renal function should be assessed regularly.
- Contraindicated in hyperkalemia (K > 5.0), advanced renal insufficiency (CrCl < 30 cc/min, Cr > 2.5 mg/dl).
- Be cautious in the elderly, those with diabetes, and concomitant use of CYP3A4 inhibitors (eplerenone).
- Consider eplerenone post-MI and in those with side effects to spironolactone.
- Preferable to potassium supplementation.



Table. Principles of HFrEF Medication Dose Titration

1. Know target doses of HFrEF medications used in clinical trials.

- Relatively low blood pressure alone is not a contraindication to use HFrEF medications; follow symptoms and end-organ dysfunction.
- β-Blockers should be titrated to target doses; ACEi/ARB/ARNi dosing should be adjusted to facilitate BB titration.
- 4. Titrate all meds to target dosing if BP allows, every 2-4 weeks..
- Regular monitoring of symptoms, blood pressure, heart rate, and laboratory testing of electrolytes and renal function should guide dose titration.
- Tolerating only low-dose HFrEF medications or worsening intolerance of such medications should prompt consideration of referral to a HF center capable of advanced therapies (eg, transplantation, mechanical circulatory support).

...GDMT titrated to a goal systolic BP less than 130 mmHg Class I, LOE C Allen LA, Fang JC. CircHF 2017



In HFrEF, which of the following decreases heart failure hospitalizations?

A. Aspirin.

- B. Warfarin.
- C. Digoxin.
- D. Simvastatin.
- E. Clopidogrel.





Digoxin General notes

- Digoxin can be considered for symptomatic HFrEF
 - No clinical trial data for NYHA IV
 - Class Ila (but not in 2017 update)
- The dose should be 0.125 0.25 mg daily
 - Beneficial neurohormonal effects occur at lower doses
 - Dig levels for confirmation of toxicity (not for titration)
 - Serum dig level should generally be <1.0 ng/ml
- Rate control of atrial fibrillation w/ doses >0.25 mg daily is not recommended

A 50 year old woman is seen one week after hospital discharge. Noted to be short of breath walking into office. CRT-D placed 3 months ago.

Meds: Lisinopril 2.5 mg qd, carvedilol 3.125 mg bid, spironolactone 12.5 mg qd, furosemide 160 mg bid.

On exam, 5' 5" and 170 pounds. HR 90, BP 90/50, RR 16. JVD difficult to appreciate. Lungs clear, loud gallop notable. Abdomen unremarkable. Minimal edema. Tepid to touch.

NT-proBNP at discharge was 2200; on admission 1400.





Next most appropriate action is:

A. Increase carvedilol.

- B. Change lisinopril to sacubitril/valsartan.
- C. Increase spironolactone.
- D. Add digoxin.
- E. Refer to HF center.



Next most appropriate action is:

A. Increase carvedilol.

B. Change lisinopril to sacubitril/valsartan.

- C. Increase spironolactone.
- D. Add digoxin.

E. Refer to HF center.



lvabradine

2017 HF guidelines – Class Ila

 Ivabradine can be beneficial to reduce HF hosp for pts w/ NYHA II-III stable chronic HFrEF who are receiving GEM, including a BB at maximum tolerated dose, and who are in SR with a HR of 70 bpm or greater at rest.



Heart failure is a clinical diagnosis

Major criteria

- Orthopnea / PND
- Venous distension
- Rales
- Cardiomegaly
- Acute pulm edema
- JVD > 16 cm
- HJR
- Circulation time > 25 s

Framingham criteria

Minor criteria

- Ankle edema
- Night cough
- Exertional dyspnea
- Hepatomegaly
- Pleural effusion
- Tachycardia (>120)
- Decreased VC
- Wgt loss w/ CHF tx

CHF = 2 major or 1 major + 1 minor



Natriuretic Peptides

Vasodilation **Natriuresis Adrenergic antagonist RAS** antagonist **↑**Renal failure **↑**Age **♦**Obesity **↑**Female

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Wall stress Endothelin Norepinephrine Vasopressin

Causes of Natriuretic Peptide Elevation

Cardiac •Right HF, e.g. PE •ACS •LVH Valvular heart disease Atrial fibrillation/CV Myocarditis Cardiac surgery

Noncardiac Advancing age •Anemia Renal failure •**OSA** Critical illness Bacterial sepsis Severe burns Toxic-metabolic



Assessing Natriuretic Peptides in HF Take home points

- Primarily useful when there is diagnostic uncertainty (Class I)
- Provides prognostic value (Class I)
- Unclear benefit to guiding HF therapy (Class II)
- May be low in obesity
- Not specific for LV failure
- NT-BNP roughly 3-5X BNP





Heart Failure Management

More Than Just Drugs

- Dietary counseling
- Patient education
- Physical activity
- Medication compliance
- Aggressive follow-up
- Sudden death assessment
- Managing expectations and prognosis

Close and frequent follow-up is essential for the successful treatment of heart failure



Management of HFrEF

- RAS antagonism remains the cornerstone of therapy for heart failure w/ reduced EF
- Beta blockers should be carefully titrated to goal doses in stable patients
- Aldosterone antagonists are indicated in symptomatic systolic heart failure



TABLE 3 Drugs Commonly Used for HFrEF (Stage C HF)

Drug	Initial Daily Dose(s)	Maximum Doses(s)	Mean Doses Achieved in Clinical Trials	References
ACE inhibitors				
Captopril	6.25 mg TID	50 mg TID	122.7 mg QD	(158)
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Modified (Table 15) from the 2013 HF guideline (9).

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BID, twice daily; CR, controlled release; CR/XL, controlled release; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; N/A, not applicable; QD, once daily; and TID, 3 times daily.

HF hospitalizations and mortality

Don't forget the big picture



Case presentation

- An 85 yo woman presents with exertional dyspnea, orthopnea, and lower extremity edema. BP 185/50, HR 60. JVD 16. 1+ edema.
- Echo shows LVEF 50%, WT 14 mm, EDD 5.0 cm, LA 4.5 cm, RVSP 60 mmHg, mild TR, 2+ MR, AVA 1.5 cm².
- EKG atrial fibrillation, narrow QRS.
- BNP 300, Cr 1.5, Hgb 10.





The most appropriate diagnosis is:

- A. Pulmonary arterial hypertension
- B. Heart failure w/ preserved EF
- C. Coronary artery disease
- D. Hypertrophic cardiomyopathy





HFPEF Mortality Is High and Comparable to HFREF





Owan T, Redfield, et al. NEJM 2006
Heart Failure w/ Preserved EF

A Heterogeneous disorder





Heart Failure w/ Preserved EF A Diagnosis of Exclusion

- CAD
- Valvular disease
- Arrhythmias
- Secondary causes of hypertension
- Pulmonary disease
- Anemia
- Obesity/deconditioning
- Pulmonary arterial hypertension
- Pericardial disease



Heart Failure w/ Preserved EF "Therapy"

Class I

- Control hypertension
- Judicious use of diuretics

Class II

- Revascularization
- Manage afib according to guidelines
- BBs, ACEIs, ARBs reasonable for hypertension
- ARBs might be considered to decrease hosp
- AldoAnt might be considered to decrease hosp

Yancy C, et al. 2017 ACC/AHA/HFSA HF guidelines

(LOE:B) (LOE:C)

(LOE:C) (LOE:C) (LOE:C) (LOE:B) (LOE:B)



A 65 year old woman with a history of depression presents to ED with chest pain which started while she was her husband's funeral. Her ECG had 2 mm ST elevation in anterior leads and troponin was mildly elevated. Angiography showed patent coronary arteries. Her LV gram is shown.







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Pelliccia, Circulation, 2017

Which of the following is true regarding her condition?

- A. Her LVEF will continue to deteriorate and she should be urgently evaluated for cardiac transplantation.
- B. Typically men develop this condition more commonly than women
- C. A catecholamine surge is thought to be a key factor leading to this condition.
- D. Apical involvement is required for the diagnosis of this condition.
- E. Emotional but not physical stress can lead to this condition.





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- D. Apical involvement is required for the diagnosis of this condition.
- E. Emotional but not physical stress can lead to this condition.



Takotsubo (Stress) Cardiomyopathy

- "Broken heart syndrome"
- Female, post-menopausal predominance
- Increased prevalence of a history of psychiatric or neurological comorbid conditions
- Triggered by emotional or physical stress
- Recently positive emotional events have been described as triggers (winning a jackpot)
- + Cardiac enzymes, ECG changes (ST elevation), can have concomitant CAD (15%) but LV dysfunction is disproportionate and not in territory of one coronary artery
- Apical ballooning is classic but other patterns described



Four Types of Takotsubo Cardiomyopathy (n=1750)

Apical (82%)



Midventricular (15%)

Templin, NEJM, 2015

Basal (2%) N=39 (2.2%) н N=26 (1.5%) Focal (1.5%) MERICAN COLLEGE of

Takotsubo (Stress) Cardiomyopathy

- "Broken heart syndrome"
- Post-menopausal, female predominance
- Higher prevalence of psychiatric or neurological comorbid conditions
- Emotional or physical stress
- + Cardiac enzymes, ECG changes (ST elevation), can have concomitant CAD (15%) but LV dysfunction not in territory of one coronary artery
- Apical ballooning classic but other patterns described
- Ventricular arrhythmias (pause-dependent Torsades) in subacute phase
- Rapid recovery of LVEF typical but natural history is not as benign as previously thought (5.6% rate of death/year)
- Catecholamine surge is thought to be key pathophysiological event



Templin, NEJM, 2015; Akashi, Nat. Rev Cardiol, 2015; Pelliccia, Circulation, 2017, Ghadri, EHJ, 2018

Pathophysiology: Role of Catecholamines



Akashi, Nat. Rev Cardiol, 2015; Pelliccia, Circulation, 2017

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Thank you



Aortic Valve Disorders

Ali Elfandi, MD FACC

Outline



Aortic Stenosis



Aortic regurgitation



Bicuspid aortic valve

Aortic Stenosis







Natural History of Aortic Stenosis



Ross J Jr. and Braunwald E: Circ 38(Suppl 5):61, 1968





2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease

Developed in collaboration with and endorsed by the American Association for Thoracic Surgery, American Society of Echocardiography, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons

Table 4. Stages of VHD



Stage	Definition	Description
А	At risk	Patients with risk factors for development of VHD
В	Progressive	Patients with progressive VHD (mild to moderate severity and asymptomatic)
С	Asymptomatic severe	Asymptomatic patients who have the criteria for severe VHD: C1: Asymptomatic patients with severe VHD in whom the LV or RV remains compensated space C2: asymptomatic patients with severe VHD with decompensation of LV or RV
D	Symptomatic severe	Patients who have developed symptoms as a result of VHD



Sec. 1. 1	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Stages/criteria	No cardiac damage	LV damage	LA or mitral damage	Pulmonary vasculature or tricuspid damage	RV damage
Echocardiogram		Increased LV mass index: >115 g/m ² in males, >95 g/m ² in females	Indexed LA volume >34 ml/m ²	Systolic pulmonary hypertension ≥60 mmHg	Moderate-severe RV dysfunction
		E/e ⁻ >14	Moderate–severe mitral regurgitation	Moderate-severe tricuspid regurgitation	
		LVEF <50%	AF		

The stages are defined according to the extent of cardiac damage as detected by transthoracic ECG. LA = left atrial; LV = left ventricular; LVEF = left ventricular ejection fraction; RV = right ventricular. Source: Généreux et al.³ Reproduced with permission from Oxford University Press.

Asymptomatic Severe AS Predictors of Reduced Event-free Survival

- Grand Marine Marine $10 \ge 5.0-5.5 \text{ m/s}$
- Severe Ca⁺⁺, []rate progression, severe LVH
- Abnl response to exercise, 00 PA pressure
- I strain, strain rate, twist; I
- LGE on cardiac MRI
- 0 BNP



Exercise Testing

Asymptomatic Severe AS



Question

An 88-year-old woman presents to clinic for progressive dyspnea on exertion and lower extremity edema. Her past history includes osteoarthritis and hypertension. She takes aspirin 81 mg daily, metoprolol succinate 25 mg daily, amlodipine 5 mg daily.

On exam, her blood pressure is 130/60 mm Hg, pulse is 70 bpm, and respirations are 16 breaths per minute. Her jugular venous pressure is 10 cm H_20 . There are bibasilar crackles. She has a late-peaking, harsh systolic murmur along the right upper sternal border with a single S_2 . There is 2+ bilateral lower extremity edema.

Her echocardiogram shows a severely calcified aortic valve with reduced leaflet excursion. Peak velocity across the valve is 3.3 m/sec with a mean gradient of 28 mm Hg. The calculated valve area was 0.8 cm² and dimensionless index is 0.22. The LV is mildly dilated with an LVEF of 25-30% and global hypokinesis. Which of the following is the most appropriate next step in the management of this patient?

- a) Exercise myocardial perfusion scan.
- b) Right and left heart catheterization.
- c) Cardiac magnetic resonance imaging.
- d) Transesophageal echocardiography.
- e) Dobutamine stress echocardiography

a) Exercise myocardial perfusion scan.

- b) Right and left heart catheterization.
- c) Cardiac magnetic resonance imaging.
- d) Transesophageal echocardiography.
- e) Dobutamine stress echocardiography

AS Severity Normal Flow (SVi>35)

	Peak velocity (m/s)	Mean Gradient (mmHg)	AVA (cm ²)	AVAi (cm²/m²)	
Normal		<10	3.0 - 4.0		
Mild	2.6 - 2.9	<20	>1.5	>0.85	
Moderate	3.0 - 4.0	20 - 39	1.0 - 1.5	0.6 - 0.85	
Severe					
Very Severe					

Continuity Equation:

 $AVA = \frac{LVOT \text{ area} \times LVOT \text{ TVI}}{A \text{ ortic valve TVI}}$ LVOT

LVOT area = πr^2



Timing of Intervention of AS



COR	LOE	Recommendations
		1. In adults with severe high-gradient AS (Stage D1) and symptoms of exertional
1	Α	dyspnea, HF, angina, syncope, or presyncope by history or on exercise testing, AVR
		is indicated.
1		2. In asymptomatic patients with severe AS and an LVEF <50% (Stage C2), AVR is
l	B-NK	indicated.
		3. In asymptomatic patients with severe AS (Stage C1) who are undergoing cardiac
1	B-NR	surgery for other indications, AVR is indicated.

Asymptomatic Aortic Stenosis Timing of Intervention

Recommendations	COR	LOE
AVR is recommended for asymptomatic patients with severe AS (stage C2) and LVEF <50%	I	В
AVR is indicated for patients with severe AS (stage C or D) when undergoing other cardiac surgery	Í	В



Asymptomatic Aortic Stenosis Timing of Intervention

Recommendations	COR	LOE
AVR is reasonable for asymptomatic patients	lla	В
AVR is reasonable in asymptomatic patients (stage C1) with severe AS and decreased exercise tolerance or an exercise fall in BP	lla	В
AVR may be considered for asymptomatic patients with severe AS (stage C1) and rapid disease progression and low surgical risk	llb	С



Figure 2. Timing of Intervention for AS



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Spectrum of Low Flow Low Gradient AS



Pibarot P, Dumesnil JG. JACC 20112; 60:145-53

Low Flow Low Gradient Severe AS



Pibarot P, Dumesnil JG. JACC 2012; 60:145-53

LF/LG AS with Reduced EF



Clavel M-A et al EHJ 2016; 37:2645-57





Baseline

Dobutamine



Vmax 3.5 m/s Mean ΔP 32 mm Hg

Vmax 4.9 m/s Mean ΔP 56 mm Hg

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Picano E et al. JACC 2009;54:2251-60

AHA/ACC 2014 Guideline

Aortic Stenosis (D2): Timing of Intervention

AVR is reasonable in patients with LF/LG severe AS with reduced EF (stage D2) with a dobutamine stress study that shows an aortic velocity IIa B $\geq 4 \text{ m/s}$ (or mean $\Delta P \geq 40 \text{ mm Hg}$) with an AVA $\leq 1.0 \text{ cm}^2$ at any dobutamine dose	Recommendation	COR	LOE
	AVR is reasonable in patients with LF/LG severe AS with reduced EF (stage D2) with a dobutamine stress study that shows an aortic velocity ≥ 4 m/s (or mean $\Delta P \geq 40$ mm Hg) with an AVA ≤ 1.0 cm ² at any dobutamine dose	lla	B

LF/LG AS with Normal EF





Adapted from Clavel M-A et al EHJ 2016; 37:2645-57

AHA/ACC 2014 Guideline Aortic Stenosis (D3): Timing of Intervention

Recommendation	COR	LOE
AVR is reasonable in patients with LF/LG severe AS (stage D3) who are normotensive and have I I I I I I I I I I I I I I I I I I I	lla	С


Choice of TAVR Versus Surgical AVR in the Patient With Severe Symptomatic AS (2019*)



TAVR Limitations (Older Patients, Older Studies)

- PPM requirement (~10%)
- Paravalvular leak (~1-2%)
- Stroke (~2%)
- Vascular complications
- Valve durability
- Leaflet thrombosis
- ?BAV



Question

 A 54-year-old man presents for routine evaluation for known chronic aortic valve regurgitation due to bicuspid aortic valve. He remains asymptomatic. His vital signs include a heart rate of 84 bpm and blood pressure of 140/50 mm Hg. His physical examination reveals a grade 2/6 systolic ejection murmur along the left sternal border and a grade 3/4 diastolic flow murmur. His echocardiogram reveals severe aortic regurgitation*. Which of the following echocardiographic parameters would be an indication for surgical aortic valve replacement at this time?

- a) A left ventricular end-diastolic dimension of 6.0 cm
- b) A vena contracta width of 0.7 cm.
- c) A left ventricular end-systolic dimension of 5.3cm
- d) A LVEF of 55%
- e) An aortic regurgitant fraction of 65%

- a) A left ventricular end-diastolic dimension of 6.0 cm
- b) A vena contracta width of 0.7 cm.
- c) A left ventricular end-systolic dimension of 5.3cm
- d) A LVEF of 55%
- e) An aortic regurgitant fraction of 65%

Aortic Regurgitation Medical Therapy

Recommendations	COR	LOE
Treatment of hypertension (Systolic BP >140 mm Hg) is recommended in patients with chronic AR (stages B and C), preferably with dihydropyridine calcium channel blockers or angiotensin-converting enzyme (ACE) inhibitors/angiotensin-receptor blockers (ARBs)	I	В
Medical therapy with ACE inhibitors/ARBs and beta blockers is reasonable in patients with severe AR who have symptoms and/or LV dysfunction (stages C2 and D) when surgery is not performed because of comorbidities	lla	В
	CC CA	RDIOLOGY

Aortic Regurgitation Intervention

Recommendations	COR	LOE
AVR is indicated for symptomatic patients with severe AR regardless of LV systolic function (stage D)	Ţ	В
AVR is indicated for patients with severe AR (stage C or D) who are undergoing other cardiac surgery	I	С



Aortic Regurgitation: Intervention (cont.)

Recommendations	COR	LOE
AVR is reasonable for asymptomatic patients with severe AR with normal LV systolic function (LVEF \geq 50%), but severe LV dilation (stage C2, LVESD >50 mm)	lla	В
AVR is reasonable in patients with moderate AR (stage B) who are undergoing other cardiac surgery	lla	С
AVR may be considered for asymptomatic patients with severe AR and normal LV systolic function (stage C1, LVEF ≥50%) but severe LV dilation (LVEDD >65 mm) if surgical risk is low*	llb	С





Figure 4. Timing of Intervention for Patients with AR.

Colors correspond to Table 2.

Diagnostic Testing: Routine Follow-up



Table 5. Frequency of Echocardiograms in Asymptomatic Patients with VHD and Normal LV Function

	Type of Valve Lesion			
Stage	Aortic Stenosis*	Aortic Regurgitation	Mitral Stenosis	Mitral Regurgitation
Progressive	• Every 3–5 y (mild	• Every 3–5 y (mild	Every 3–5 y	• Every 3–5 y (mild severity)
(Stage B)	severity; V _{max} 2.0–2.9	severity)	(MV area >1.5 cm ²)	
	m/s)			
	• Every 1–2 y moderate	• Every 1–2 y (moderate		• Every 1–2 y (moderate
	severity; V _{max} 3.0–3.9	severity)		severity)
	m/s)			

Patients with mixed valve disease may require serial evaluations at intervals earlier than recommended for single-valve lesions. These intervals apply to most patients with each valve lesion and do not take into consideration the etiology of the valve disease. *With normal stroke volume.

Diagnostic Testing: Routine Follow-up



 Table 5. Frequency of Echocardiograms in Asymptomatic Patients with VHD and Normal LV Function

	Type of Valve Lesion			
Stage	Aortic Stenosis*	Aortic Regurgitation	Mitral Stenosis	Mitral Regurgitation
Severe	• Every 6–12 mo	• Every 6–12 mo	• Every 1–2 y (MV area	Every 6–12 mo
asymptomati	$(V_{max} \ge 4 m/s)$		$1.0-1.5 \text{ cm}^2$)	
c (Stage C1)		• Dilating LV: More frequently	• Every year (MV area <1.0 cm ²)	Dilating LV: More frequently

Patients with mixed valve disease may require serial evaluations at intervals earlier than recommended for single-valve lesions. These intervals apply to most patients with each valve lesion and do not take into consideration the etiology of the valve disease.

*With normal stroke volume.

Monitoring with TTE

Patients with known or suspected VHD:

- Initial evaluation (class I)
- Change in symptoms or physical exam (class I)
- Periodic monitoring (class I)

	Aortic Stenosis	Aortic Regurgitation	Mitral Stenosis	Mitral Regurgitation
Stage B	Mild: 3-5 y	Mild: 3-5 y	MVA > 1.5 cm ² : 3-5 y	Mild: 3-5 y
	Mod: 1-2 y	Mod: 1-2 y		Mod: 1-2 y
Stage C	6-12 mo	6-12 mo	MVA 1.0-1.5 cm ² : 1-2 y	6-12 mo
		Dilating LV: [] freq	MVA < 1.0 cm ² : 1 y	Dilating LV: [] freq



Question

• A 55-year-old woman is referred to you for evaluation and treatment of aortic regurgitation (AR). She has a known history of bicuspid aortic valve (BAV). She exercises four to five times per week and reports no symptoms. Her medical history includes hyperlipidemia. Her current medications include atorvastatin 40 mg.

On physical examination her blood pressure is 126/54 mm Hg with a heart rate of 84 bpm. Her lungs are clear to auscultation. The apical impulse is normal and nondisplaced. A soft, grade 2/4 diastolic decrescendo murmur is present. A systolic ejection click is noted. There is no S_3 or S_4 , and no peripheral edema.

Transthoracic echocardiogram demonstrates an LV ejection fraction of 59% with an end-systolic dimension of 33 mm and an end-diastolic dimension of 50 mm. The aortic root diameter is 3.9 cm at the sinuses of Valsalva. There is a BAV with severe AR*.

Which of the following is the next best step the treatment of this patient?

- a) Metoprolol succinate 25 mg.
- b) No additional medications
- c) Metoprolol succinate 25 mg.
- d) Extended release nifedipine 30 mg.
- e) Enalapril 5 mg.

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- b) No additional medications
- c) Metoprolol succinate 25 mg.
- d) Extended release nifedipine 30 mg.
- e) Enalapril 5 mg.

Question 1

55 year old male with pmh DM, HTN, HLD presenting with recent onset dyspnea on exertion, lower extremity edema, intermittent chest pain

Exam notable for III/VI late peaking crescendo-decrescendo systolic murmur.

Transthoracic echocardiography is performed.





LVEF 60% LVOT diameter 1.8 cm Mean AoV Gradient 21 mmHg AoV VTI 76.8 cm LVOT VTI 23.4 cm Max velocity 3.1 m/s Calculated AVA 0.8 cm² Calculated AVA 0.4 cm2/m2 Stroke volume index 33 mL/m²



Question 1

55 year old male with pmh DM, HTN, HLD presenting with recent onset dyspnea on exertion, lower extremity edema, intermittent chest pain

Exam notable for III/VI late peaking crescendo-decrescendo systolic murmur.

Transthoracic echocardiography is performed.

What is the next recommended step?

- A. Exclude erroneous echo measurements.
- B. Perform low-dose dobutamine stress echocardiography.
- C. Obtain aortic valve calcium score by MDCT.
- D. Perform transesophageal echocardiogram.
- E. Perform invasive aortic valve study.



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	Peak velocity (m/s)	Mean Gradient (mmHg)	AVA (cm ²)	AVAi (cm²/m²)
Normal		<10	3.0 - 4.0	
Mild	2.6 - 2.9	<20	>1.5	>0.85
Moderate	3.0 - 4.0	20 - 39	1.0 - 1.5	0.6 - 0.85
Severe				
Very Severe				

Continuity Equation:

 $AVA = \frac{LVOT \text{ area} \times LVOT \text{ TVI}}{Aortic \text{ valve TVI}} \qquad LVOT \text{ area} = \pi r^2$

Pitfalls of echo

Underestimating AS severity

- 1. Malalignment of CW doppler beam with the direction of aortic flow resulting in underestimation of gradient, overestimation of AVA.
- 2. Overestimate LVOT velocity if PW region of interest is too close to AoV
- 3. Underestimate AoV vmax due to doppler malalignment

Overestimating AS severity

- 1. Underestimation of the LVOT diameter measurement.
- 2. Underestimate LVOT velocity if PW region of interest is too far from valve



Underestimation of LVOT area

- Greatest source of error in calculating AVA
- Given than LVOT diameter is squared (area = πr²), a small error will have a large impact on the calculation of SV & AVA and may lead to a false conclusion of LFLG severe AS
- Either due to:
 - Technical issues: off axis measurement, poor windows, calcification
 - Assumed circular shape LVOT in continuity equation when it is in fact elliptical

When TTE images are not adequate to measure LVOT diameter, 3D echo, TEE or CT is recommended if this information is needed for clinical decision making



LVOT Cross Sectional Area





 $Area_{LVOT} \times VTI_{LVOT} / VTI_{AV} = AVA$

 $\pi(1^2)$ x 26 / 90 = AVA 3.14 x 26 / 90 = 0.9 cm2

4.47 x 26 / 90 = 1.3 cm2





A 42 year old asymptomatic male is referred for evaluation of bicuspid aortic valve, found on echo ordered by PCP for murmur. He is an avid runner and denies recent change in exercise tolerance. He has no family history of bicuspid aortic valve, aortic aneurysms, sudden death. On physical exam, his BP is 108/69, HR of 59 BPM. Auscultation is notable for II/VI early peaking crescendo-decrescendo murmur and II/VI decrescendo diastolic murmur.

His transthoracic echocardiogram is reviewed:







Question 2

A 42 year old asymptomatic male is referred for evaluation of bicuspid aortic valve, found on echo ordered by PCP for murmur. He is an avid runner and denies recent change in exercise tolerance. He has no family history of bicuspid aortic valve, aortic aneurysms, sudden death. On physical exam, his BP is 108/69, HR of 59 BPM. Auscultation is notable for II/VI early peaking crescendo-decrescendo murmur and II/VI decrescendo diastolic murmur.

His transthoracic echocardiogram is reviewed:

Which of the following is indicated:

- A. Monitoring with echo in 1 year.
- B. Initiation of beta blocker therapy.
- C. Initiation of afterload-reducing therapy.
- D. Referral for surgery based on the severity of his valvular disease
- E. Referral to surgery based on the presence of bicuspid aortic valve and aortopathy





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Bicuspid Aortic Valve



- Prevalence of 1-2%
- M:F 2:1
- Echo features:
 - Many anatomic variations, most commonly fusion of left and right coronary cusps
 - Inequality in the size of the leaflets
 - Ovoid opening shape of the orifice
 - Eccentric closure line
 - Systolic doming
- Associated complications:
 - Aortic stenosis
 - Aortic regurgitation
 - Endocarditis
 - Aortopathy
 - Coarctation



BAV Phenotypes



JACC Cardiovasc Imaging. 2013 Feb;6(2):150-61.

Imaging in Bicuspid Aortic Valve

Imaging	Class
Initial TTE in patients with bicuspid AV	1
Aorta MRA or CTA if aortic root and ascending aorta not fully visualized on TTE	
Serial evaluation by TTE, MRA, CTA if aorta > 4.0 cm, annual imaging if aorta > 4.5 cm	
5	
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257-185	CARDIOLO

BAV Aortopathy



Verma S and Siu SC. NEJM 2014; 370:1920-9.





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AMERICAN COLLEGE of CARDIOLOGY Figure 6. Intervention for replacement of the aorta in patients with a BAV.

Colors correspond to Table 2.

*Family history of aortic dissection, aortic growth rate ≥0.5 cm per year, and/or presence of aortic coarctation.





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Diagnostic Testing: Routine Follow-Up of Patients with BAV



Interventions: Replacement of the Aorta in Patients with BAV



COR	LOE	Recommendations
1	B-NR	1. In asymptomatic or symptomatic patients with a BAV and a diameter of the aortic sinuses or ascending aorta >5.5 cm, operative intervention to replace the aortic sinuses and/or the ascending aorta is recommended.
2a	B-NR	2. In asymptomatic patients with a BAV, a diameter of the aortic sinuses or ascending aorta of 5.0 to 5.5 cm, and an additional risk factor for dissection (e.g., family history of aortic dissection, aortic growth rate >0.5 cm per year, aortic coarctation), operative intervention to replace the aortic sinuses and/or the ascending aorta is reasonable if the surgery is performed at a Comprehensive Valve Center.

Thank you

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