Cardiovascular Pharmacology Boot Camp

NTI Preconference
Orlando 2019
Session PC 114

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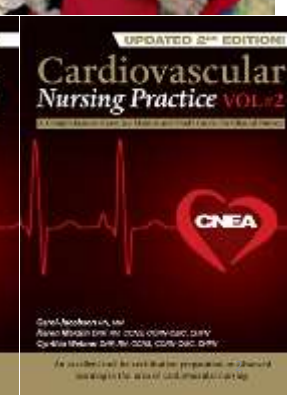
2019 1

1



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Opening Thought

We have a hunger of the mind which asks for knowledge of all around us, and the more we gain, the more is our desire; the more we see, the more we are capable of seeing.

Maria Mitchell

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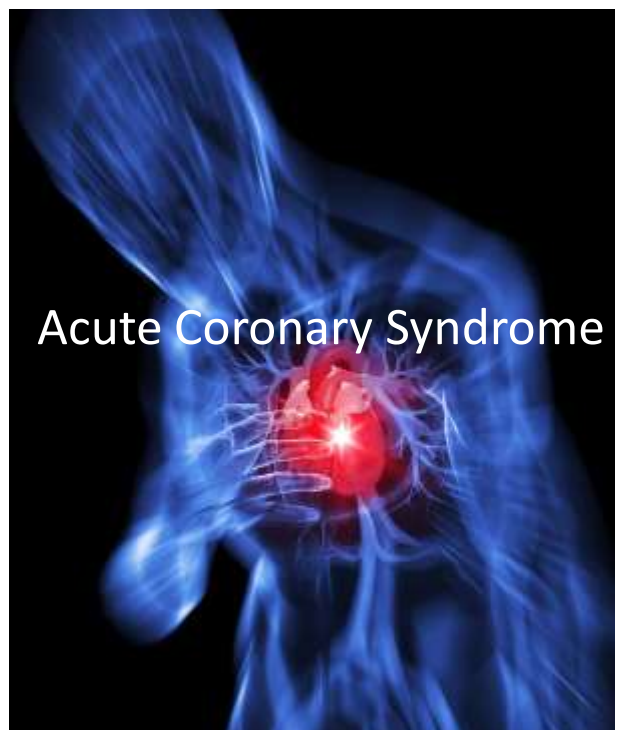

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Acute Coronary Syndrome (ACS)

A spectrum of conditions compatible with acute myocardial ischemia and /or infarction that are usually due to an abrupt reduction in coronary blood flow.

- No ST Elevation
  - Non STEMI
  - Unstable Angina
- ST Elevation
  - STEMI

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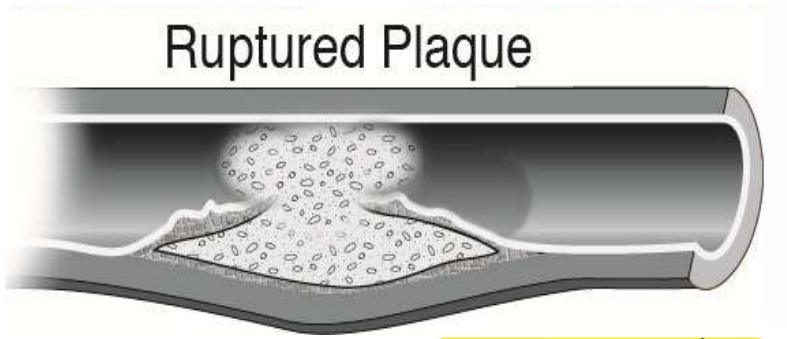
5

Acute Coronary Syndrome refers to any rupture of plaque or thrombotic event that leads to symptomatic ischemia or infarction.



STEMI

NonSTEMI / Unstable Angina

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6

Drugs Used to Alter Clotting in ACS

- **Fibrinolytics**
  - **STEMI**
  - tPA
    - Alteplase
    - Retaplase
    - Tenecteplase
  - Streptokinase (no longer used)
- **Anticoagulants**
  - **STEMI / NonSTEMI / UA**
  - Unfractionated Heparin
  - Low Molecular Weight Heparin
  - Direct Thrombin Inhibitors
  - Factor Xa Inhibitors
- **Antiplatelets**
  - **STEMI / NonSTEMI / UA**
  - *GP IIb/ IIIa Inhibitors*
    - Eptifibitide (Integrelin)
    - Tirofiban (Aggrastat)
    - Abciximab (Repro)
  - *ADP Receptor Blockers*
    - Clopidogrel
    - Prasugrel
    - Ticagrelor
  - *Thromboxane A_2 Inhibitor*
    - ASA

2019 7

7

Clot Formation: Clotting Cascade

Intrinsic Pathway

- Trauma inside vessels
- Initiated by vascular injury and direct exposure to collagen
  - Site of activated platelet
  - Site of endothelial damage
  - Subendothelial layer where collogen is exposed
- Initiation of clotting is 2-6 minutes

Extrinsic Pathway

- Activated by damaged external surfaces
- Initiated by endothelial release (secondary to tissue injury) of thromboplastin tissue factor
- Initiation of clotting is 15 to 20 seconds

A clot can be produced by activation of either the intrinsic or extrinsic pathway.

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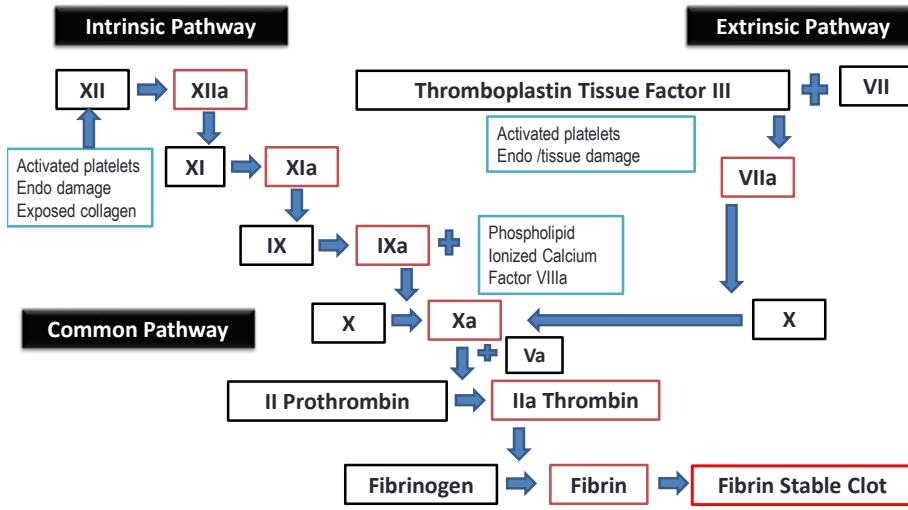
8

The Clotting Cascade



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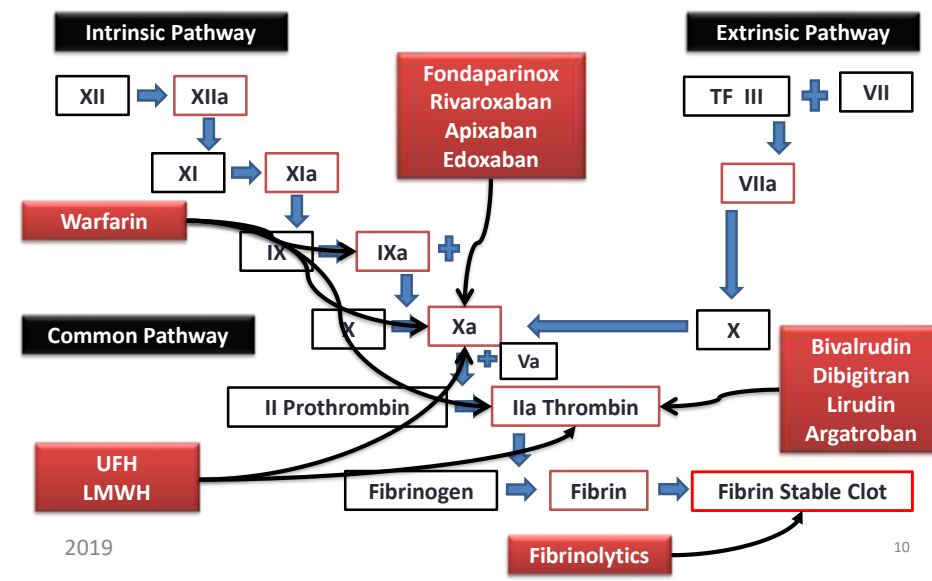
9

The Clotting Cascade



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10

Anticoagulants

- Unfractionated Heparin
- Low Molecular Weight Heparin
- Direct Thrombin Inhibitors
- Factor Xa Inhibitors
- Warfarin
- Dabigatran
- Rivaroxaban
- Apixaban
- Edoxaban

2019 11

11

Unfractionated Heparin

- Works in the intrinsic and common pathway
- Antithrombin activator that inhibits factors Xa and IIa (thrombin)
  - Antithrombin III lyses factor Xa and thrombin and inhibits clotting
  - When heparin binds with antithrombin III the inhibition is increased 1000 times
- Concern that unfractionated heparin results in platelet activation - although thrombin is a strong platelet activator and heparin is an antithrombin drug
- Anticoagulation is almost instant
- ½ life relatively short
- Antidote: Protamine 1 mg per 100 units

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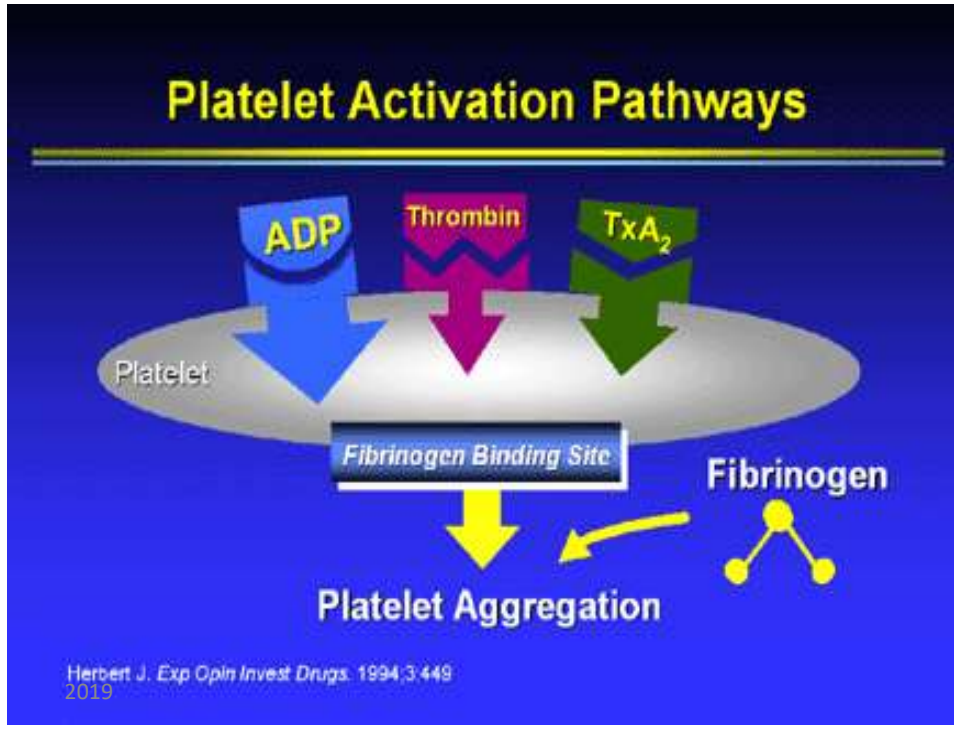
12



13

Unfractionated Heparin Dosing

ACS

- Initial load of 60 u/kg IV
  - Maximum 4000U
- Initial infusion is 12u/kg/hr
  - Maximum is 1000 u/hr
- Continue 48 hours or until PCI is performed

VTE

- Prophylaxis
  - 5000 u SC q8-12 hours
- Acute DVT or PE
  - Initial load of 80 u/kg IV
    - Alternative 5000U
  - Initial infusion is 18u/kg/hr
    - Alternative is 1000 u/hr

Use of unfractionated heparin in atrial fibrillation is off label

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14

More About Heparin

- aPTT (activated partial thromboplastin time) is used to monitor effectiveness and safety
  - Goal is aPTT 1.5 -2Xs the control
  - Weight based heparin dosing reaches goal 90%
- OR – Anti factor Xa levels
  - 0.3-0.7 IU/ml
- Baseline aPTT, PT/INR, platelets and CBC
- Increased bleeding can occur with renal failure
  - Heparin has dual clearance mechanism
    - Saturable via reticuloendothelial system

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15

Heparin Induced Thrombocytopenia

Mild Thrombocytopenia HIT 1	Severe Thrombocytopenia HIT 2
• Non-immune HIT • Mild thrombocytopenia • Occurs in 10-20% of patients • Platelet count usually remains above 100,000	• Immune induced HIT • Occurs in 1- 3% of patients • Platelet aggregation resulting in venous or arterial thrombosis (HITT – **Thrombocytopenia with Thrombosis**) • Onset 5 to 14 days after exposure to heparin **(sooner if previous exposure)** • Platelet count usually < 100,000 • Usually a drop of > 20,000

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16

More on Immune Mediated HIT

- Heparin can cause increase blood concentration of platelet factor 4 (PF4)
- PF4 can combine with heparin and create a complex
- Heparin/PF4 complex stimulates production of antiheparin/PF4 complex antibodies (IgG)
  - **Antibodies continue to produce even after cause has been removed**
- Antibodies cause platelet activation leading to a hypercoagulable state -> thromboembolic complications
- Assess platelets every 2-3 days from day 4-14

17

4Ts Score

	Points		
	2	1	0
Thrombocytopenia	>50% fall and platelet nadir ≥20 × 10^9/l	30–50% fall or platelet nadir 10–19 × 10^9/l	<30% fall or platelet nadir <10 × 10^9/l
Timing of thrombocytopenia onset	clear onset between days 5 and 10	no clear onset because of missing platelet count	no recent heparin, but platelets ≤4 × 10^9/l
Thrombosis	new thrombosis	progressive or recurrent thrombosis	none
Thrombocytopenia cause	no cause other than heparin	possible other cause	definite other cause

0-3: Low Probability
4-5: Intermediate Probability
6-8: High Probability

18

Testing for HIT

- Immunoassay vs Functional Assay
  - Functional assays have greater specificity than immunoassays
  - Functional assays: time consuming and not widely available
- ELISA: **Initial test** - Immunoassay
  - 99% sensitive, poor specificity
  - **High negative predictive value**
- SRA: Serotonin release assay – Functional Assay
  - Based on HIT antibodies causing platelets aggregate and release serotonin
- **Heparin-induced platelet aggregation assay (HIPA) – Functional Assay**
  - **Gold standard for diagnosis (highly specific and very sensitivity)**
- HIT antibodies are usually IgG class
  - Take 5 days to form
  - IgG antibodies associated with platelet activation and increased thrombin generation
  - Antibodies not necessarily associated with thrombotic risk
  - Can disappear 3 months after exposure

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19

Treatment of HIT

1. Discontinue and avoid all heparin.
   - Platelet count <100,00 or > 50% drop from baseline
2. Give a non-heparin alternative anticoagulant
   - Direct thrombin inhibitors (argatroban, bivalirudin)
3. **Postpone warfarin pending substantial platelet count recovery (give vitamin K if warfarin has already been started).** Warfarin is associated with protein C deficiency and increased risk for microthrombosis
4. **Avoid platelet transfusions – leads to platelet activation.**
5. Test for HIT antibodies
6. Investigate for lower-limb deep-vein thrombosis.

2019 20

20

Low Molecular Weight Heparin

- **Enoxaparin, dalteparin, tinzaparin, and nadroparin**
- **Smaller in size**

- Primarily antithrombin by inhibiting factor Xa
  - Causes less inactivation of thrombin
  - Less bleeding than unfractionated heparin (UFH)

- More predictable anticoagulant response
- No need to monitor APTT
  - Anti Xa levels can be drawn 4 hours after SQ dose

- Lower incidence of heparin induced thrombocytopenia
- Less platelet activation concern than with UFH

2019 21

21

Low Molecular Weight Heparin

- Can be self administered with Sub–Q administration (for VTE indications)

- ½ life 4-6 hours
- Protamine reverses 60% of drug effect

- Renal failure results in increased risk of bleeding because LMWH is renally cleared
  - Special dosing for chronic renal insufficiency with enoxaparin

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22

Enoxaparin Dosing

Prevention of DVT
- 40 mg SC daily in most situations
- 30 mg SC daily for renal adjustment (CR Clearance < 30 ml/min)

Embolism with Atrial Fib
- 1 mg/kg SC q12 hours

NSTE-ACS
(or as adjunct in STEMI)
- 1 mg/kg SC q12 hours
- 1mg/kg SC daily if CR Clearance < 30 ml/min
- IV loading dose of 30 mg – in select patients
- Continued for duration of stay or until PCI

Venous Thrombosis/DVT
- 1mg/kg SC q12 or 1.5 mg/kg daily depending of specific circumstances

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23

Direct Thrombin Inhibitor

- **Ability to inactivate fibrin bound thrombin**
- Less binding to plasma proteins, therefore more reliable anticoagulation effect
- Indications
  - HIT /HITT
  - Approved in NSTE-ACS (Use only in patients with early invasive strategy) / PCI
    - **Non inferior to heparin with a GPIIb/IIIa with less bleeding**
    - Monitor in the cath lab with ACT

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- Lipirudin / desirudin (hirudin)
- Argatroban
- Bivalirudin*
  - 0.10 mg/kg loading
  - 0.25 mg/kg per hour
  - Until diagnostic angiography or PCI is performed

25

25

Synthetic Factor Xa Inhibitor Fondaparinux (Arixtra)

- Neutralizes Factor Xa and interrupts the clotting cascade
- Does not inhibit thrombin
- No reported HIT / HITT
- Indications
  - Venous thromboembolism and PE
  - DVT prophylaxis
  - ACS
- Contraindicated in severe renal dysfunction
- No laboratory monitoring is needed – PT/aPTT not sensitive

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26

Synthetic Factor Xa Inhibitor

- DVT Prophylaxis: 2.5mg SC once daily in adults ≥ 50 kg
- ACS
  - 2.5 mg SC daily for duration of hospital stay up to 8 days or until time of revascularization
  - If STEMI an initial dose 2.5mg should be given IV before starting daily SC
  - **Cannot be used as sole anticoagulant during PCI – add DTI or UH**
- Acute DVT or PE – weight based for between 5mg and 10mg SC daily
  - Can use as a bridge for 5-7 days if warfarin is long term anticoagulation choice
  - Start warfarin on day 1 or 2 but continue Fondaparinux for at least 24 hours after therapeutic INR is achieved

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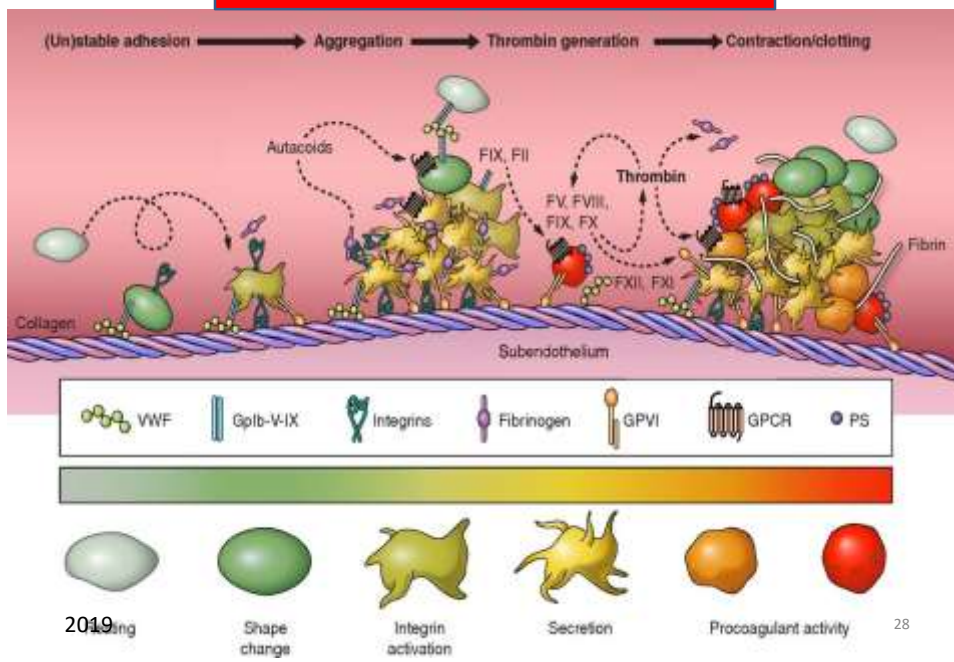
27

Platelets and Clotting



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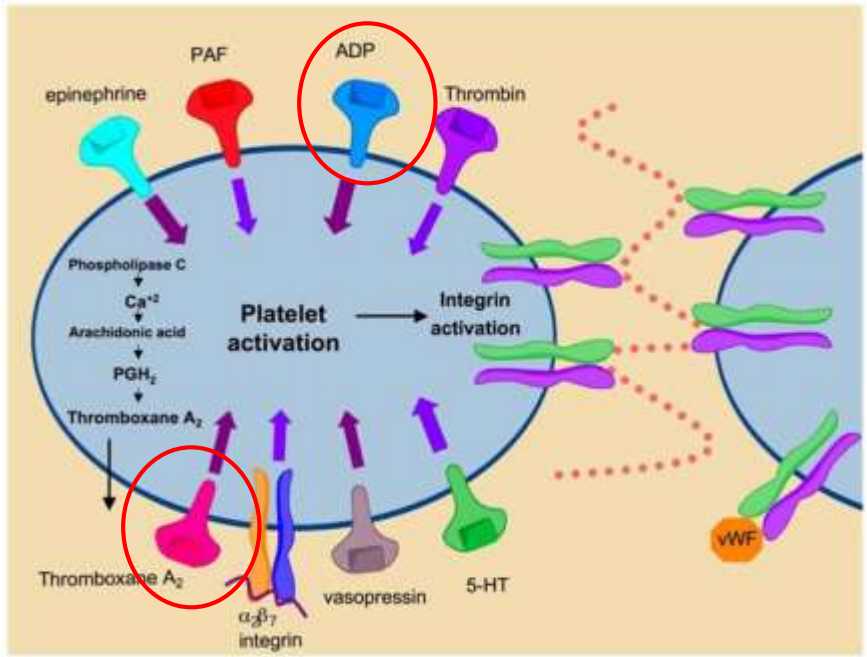

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New Dual Antiplatelet Therapy Guidelines Update

STEMI	PCI
NSTE	CABG
Stable Ischemic CAD	Non Cardiac Surgery

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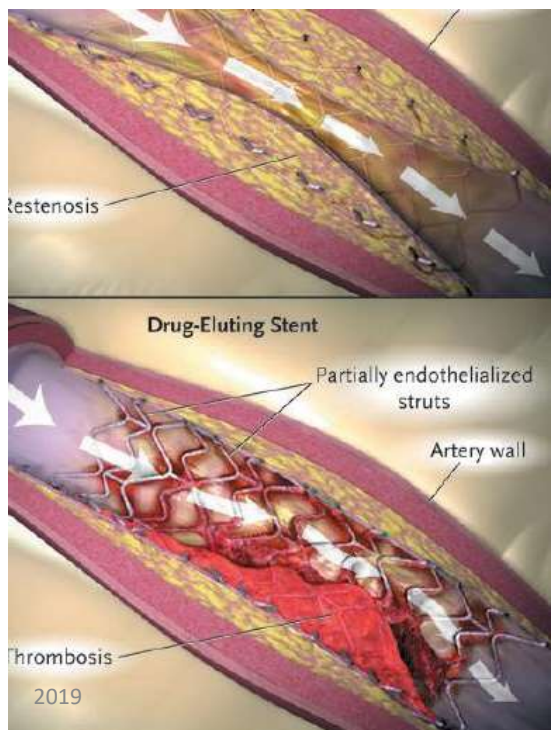
30



Stent <u>Restenosis</u> Compared to Stent <u>Thrombosis</u>

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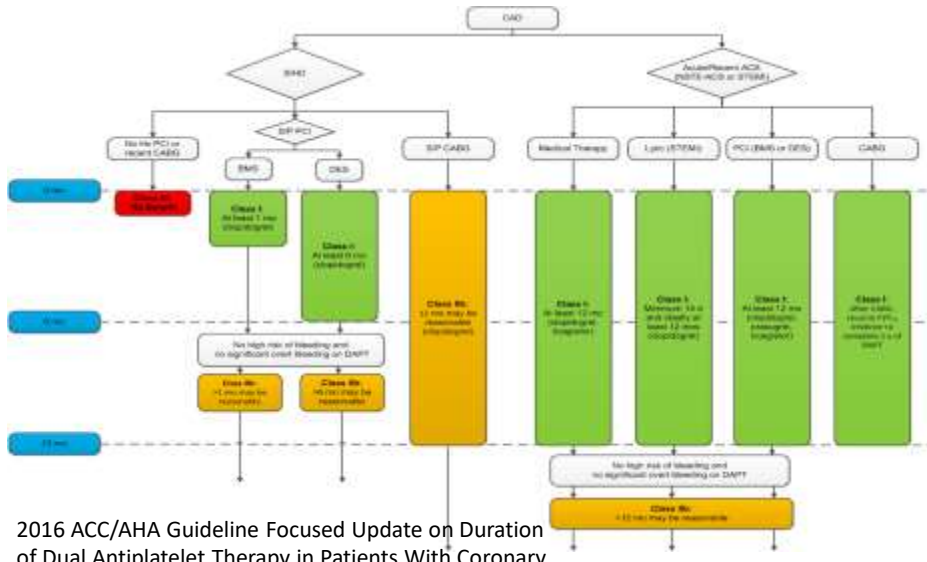
Figure 1. Master Treatment Algorithm for Duration of $P2Y_{12}$ Inhibitor Therapy in Patients With CAD Treated With DAPT



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

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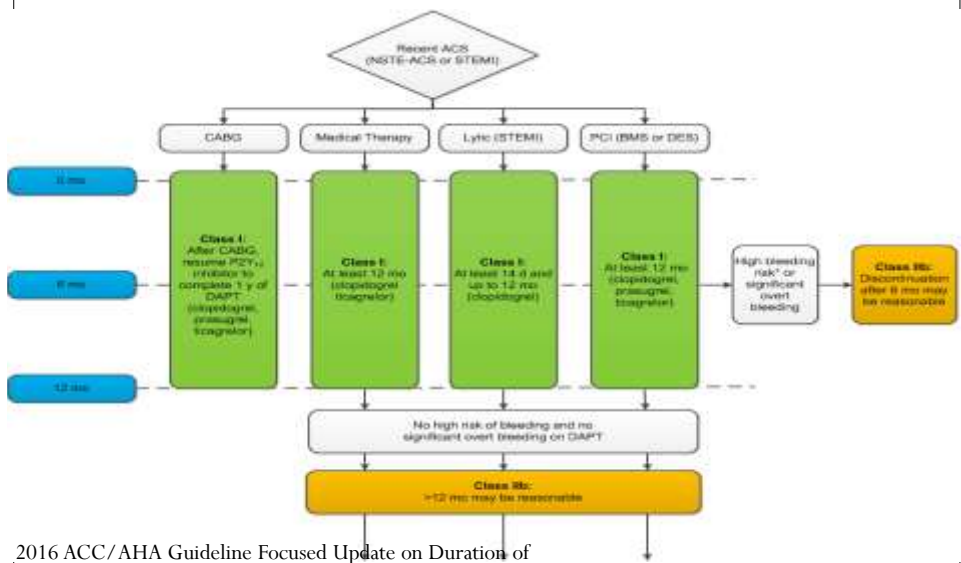
Figure 5. Treatment Algorithm for Duration of $P2Y_{12}$ Inhibitor Therapy in Patient With Recent ACS (NSTE-ACS or STEMI)



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

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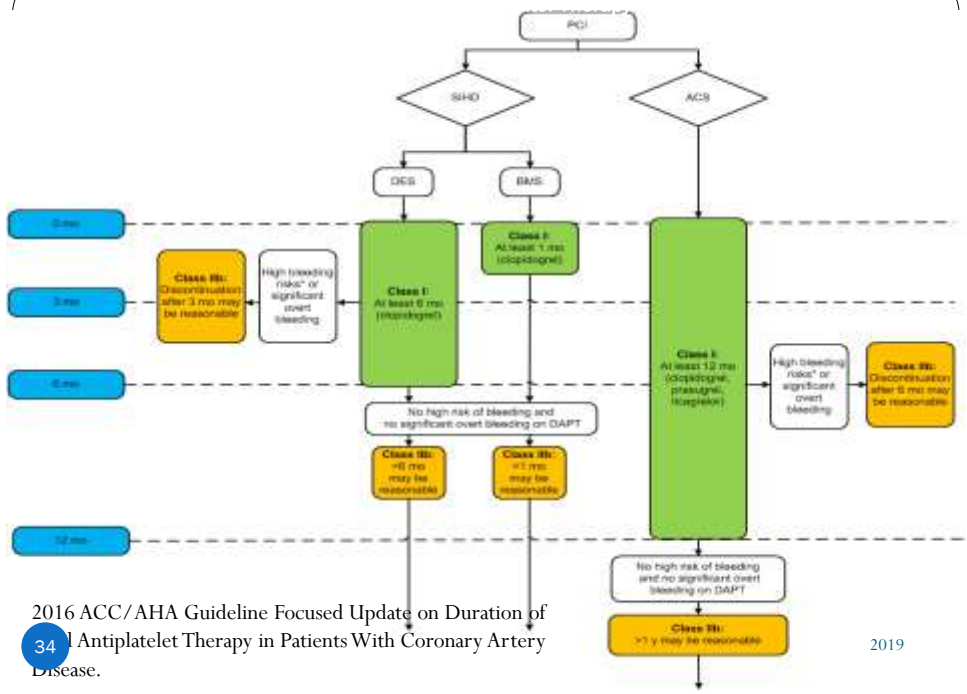

2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease.

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34

New Study – Released 2017

- The DAPT-STEMI trial showed that among patients who remain event-free at 6 months following PCI with a ZES for STEMI, cessation of DAPT at the 6-month mark vs. continuing for an additional 6 months (12 months total from stent implantation) is noninferior for clinical outcomes at 2 years.

Kedhi E, Fabris E, van der Ent M, Kennedy MW, Buszman P, von Birgelen C, Cook S, Wedel H, Zijlstra F. A prospective, randomized, open-label trial of 6-month versus 12-month dual antiplatelet therapy after drug-eluting stent implantation in ST-elevation myocardial infarction: Rationale and design of the "DAPT-STEMI trial". American Heart Journal. 2017 Jun 30;188:11-7.

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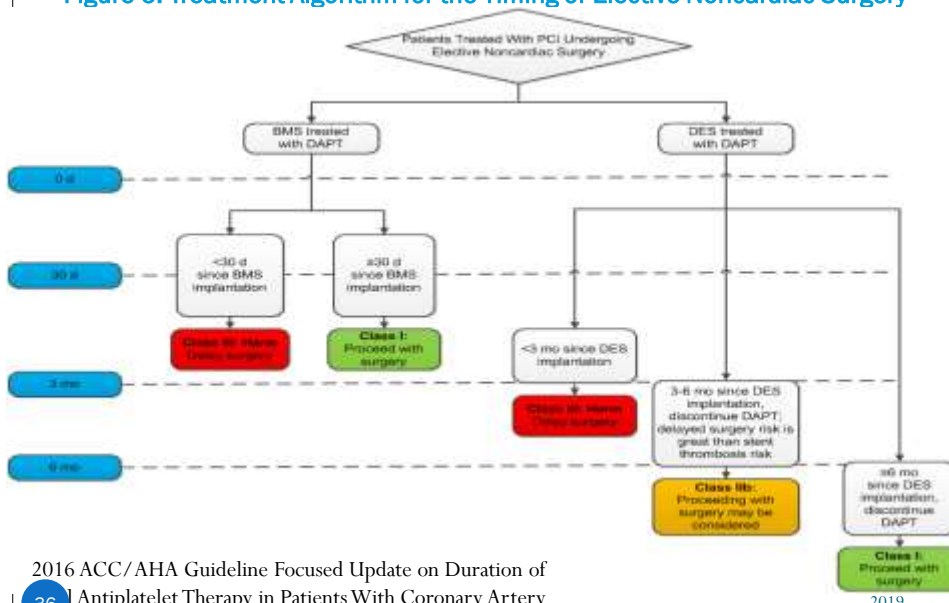
Figure 6. Treatment Algorithm for the Timing of Elective Noncardiac Surgery



2016 ACC/AHA Guideline Focused Update on Duration of [illegible] Antiplatelet Therapy in Patients With Coronary Artery Disease.

36 2019

36

Factors Used to Calculate a "DAPT Score"

Variable	Points
Age ≥75 years	-2
Age 65 to <75 years	-1
Age <65 years	0
Current cigarette smoker	1
Diabetes mellitus	1
MI at presentation	1
Prior PCI or prior MI	1
Stent diameter <3 mm	1
Paclitaxel-eluting stent	1
CHF or LVEF <30%	2
Saphenous vein graft PCI	2

A score of ≥2 is associated with a favorable benefit/risk ratio for prolonged DAPT while a score of <2 is associated with an unfavorable benefit/risk ratio.

Levine GN, Bittl JA, Brindis RG, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease. *J Am Coll Cardiol* 2016; doi=10.1016/j.jacc.2016.03.513.

37

37

Aspirin

- Diminishes platelet reactivity
- Produces rapid clinical antithrombotic effect caused by immediate and near-total inhibition of thromboxane A2 production (released with vascular injury).
  - Thromboxane A2 is also potent vasocontrictor
- Inhibits COX1 and COX2
  - **Other NSAIDS reversibly bind to COX1 preventing inhibition by ASA and may cause prothromotic events**
- Inhibits the endothelium's production of prostaglandin I_2 which decreases platelet aggregation and induces vasodilation.
  - Prostaglandin I_2 is also involved in inflammation.
- Reduces mortality
- Increase myocardial oxygen supply
- **Use in ACS**
  - Administered as soon as possible after presentation
  - Initial dose: 162 mg to 325 mg chewed (non-enteric coated)
  - Long Term: 81 mg daily
  - If ASA intolerant load with clopidogrel and then daily dose

2019 38

38

$P2Y_{12}$ Receptor Inhibitors / ADP Receptor Blockers

- Clopidogrel (Plavix)
  - 600 mg initial dose
  - 75 mg daily
- Prasugrel (Effient)
  - 60 mg initial dose
  - 10mg daily
  - Contraindicated: ≥ 75, < 60 kg, previous TIA, CVA
- Ticagrelor (Brilinta)
  - 180mg initial dose
  - 90mg **twice** daily
  - Not to be given with ASA doses > 100mg

- Adenosine Diphosphate (ADP) - Stored in platelets and released upon platelet activation
- ADP interacts with $P2Y_{12}$ chemoreceptors to enhance adhesiveness and aggregation of platelets through the activation of the GP IIb/IIIa pathway

2019 39

39

$P2Y_{12}$ Receptor Inhibitors / ADP Receptor Blockers

- Thienopyridines
  - Clopidogrel
  - Prasugrel
- Non thienopyridine
  - Ticagrelor

40

Thienopyridines

- Thienopyridines are a class of ADP / $P2Y_{12}$ receptor blockers
  - Clopidogrel (Plavix)
  - Prasugrel (Effient)
  - **Irreversibly** inhibits $P2Y_{12}$ receptor

41

Clopidogrel Indications

- Alternative to ASA therapy in those who cannot take ASA
- Option in NSTE-ACS for the second antiplatelet agent
  - Ticagrelor and prasugrel have upgraded indications
- Recommended agent in elective PCI with bare metal stent

2019 42

42

Clopidogrel

Issue of Non Responders

- ACCF/AHA Clopidogrel Clinical Alert
- FDA Boxed Warning March 2010
- Role of genotype testing or routine platelet function testing
  - Class II b recommendation pending results of randomized controlled clinical trials.
- **Prodrug**
  - 2 step process
  - Involves several *CYP450* isoenzymes
    - *CYP2C19* isoenzyme responsible for almost half of the first step formation
    - 3 major genetic polymorphisms are associated with loss of function
    - Observational studies have shown an association between an increased risk of adverse cardiovascular events and the presence of one nonfunctioning allele

2019 43

43

Clopidogrel and PPIs
11/8/2010: Expert Consensus Document

- PPIs: CYP2C19 inhibiting
- Using proton pump inhibitors (PPIs) and antiplatelet drugs (thienopyridines) together is an appropriate way of treating patients with cardiovascular (CV) disease who are at high risk of upper gastrointestinal (GI) bleeds, despite recent concerns about an adverse interaction between these two types of drugs, according to an *Expert Consensus Document released jointly today by the American College of Cardiology (ACC), the American College of Gastroenterology (ACG), and the American Heart Association (AHA).*

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44

Clopidogrel and PPIs
2012: World Journal of Gastroenterology

- Because PPI induced risk reduction clearly overweighs the possible adverse cardiovascular risk in patients with high risk of gastrointestinal bleeding, combination of clopidogrel with the less CYP2C19 inhibiting pantoprazole should be recommended.
- Several pharmacodynamic studies found a significant decrease of the clopidogrel platelet antiaggregation effect for omeprazole, but not for pantoprazole.
- More recent RCT and retrospective co-hort studies have not resulted in same concerns with PPIs as observational studies suggested.

2019 45

45

Prasugrel

- **TRITON TIMI 38 Trail**
  - 13,608 patients with moderate to high risk ACS – all referred for PCI; 3,534 STEMI
  - Randomized to clopidogrel 300mg load and 75mg daily or prasurgrel 60mg load and 10mg daily
  - Median follow up 14 ½ months
- Prasugrel (compared to Clopidogrel) associated with
  - Significant 2.2% reduction in absolute risk and a 19% reduction in relative risk in the composite endpoint of death due to CV disease, nonfatal MI, or nonfatal stroke during the follow up period
  - Significant increase in TIMI major hemorrhage (1.8% vs 2.4%)
- Prasugrel approved 2009

Wiviott et al., 2007. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007; 357:2001-2015

46

Prasugrel

- **TRILOGY**
  - Prasugrel versus clopidogrel in patients with NSTEMI or unstable angina who were not treated with PCI
  - 7,243 patients
  - **No statistically significant difference in primary outcome (**composite of: death from cardiovascular causes, myocardial infarction, or stroke) among patients under the age of 75 years
  - A weak trend toward a reduced risk in the prasugrel group after 12 months (P = 0.07)
  - **Rates of severe and intracranial bleeding were similar in the two groups in all age groups. This is different than TRITON TIMI 38. Dose was adjusted in Trilogy for weight < 60 kg and age ≥ 75 years.**
  - Conclusion: More research needed
  - **Higher recommendation for prasugrel in NSTE over clopidogrel in early invasive option only**

47

Take Away Prasugrel Points

- Less concern with PPI administration
- Less concern regarding non responders
  - Prodrug but not as dependent on *CYP2C19* isoenzyme

- Only used in patients with planned PCI
  - No benefit to administration before the time of angiography
- Increased bleeding risk
  - ≥ 75 years old
  - ≤60 KG
- Cannot be used:
  - Previous CVA / TIA

2019 48

48

Ticagrelor (Non-Thienopyridine)

- **Reversibly** binds to $P2Y_{12}$ receptor
- Not a PRO drug: does not requiring metabolic activation
- FDA approved July 2011
- Prevention of thrombotic events in patients with acute coronary syndromes.
- Loading dose 180 mg then **90 mg twice daily**
- Contraindicated in history of intracranial bleeding, active pathological bleeding, severe hepatic impairment
- **Higher recommendation for ticagrelor in NSTE over clopidogrel in either ischemia guided or early invasive option**

2019 49

49

Clopidogrel versus Ticagrelor

Take Aways

- PLATO trial
  - **Better anti-ischemic effect compared to clopidogrel**
  - **No significant increase in major bleeding**
  - **Faster onset and shorter duration than clopidogrel (known as reversible mode of action)**
  - **BID dosing is a potential concern for compliance**
  - **North American effect – thought to be due to higher dose ASA**
    - **Must not be given with maintenance ASA doses > 100mg**
  - **Although shorter ½ life – recommendation to be held 5 days before surgery.**
  - **Dyspnea 14%** (reduces clearance of adenosine; inhibition of P2Y12 on sensory neurons - ? Increase sensation of dyspnea

Wallentin, L. et al., 2009. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med, 361:1045-1057
Thromb Haemost. 2012 Dec;108(6):1031-6. doi: 10.1160/TH12-08-0547. Epub 2012 Oct 16.

50

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Clopidogrel (Thienopyrodine)	Prasugrel (Thienopyrodine)	Ticagrelor (Non -Thienopyrodine)
600 mg initial dose 75 mg daily	60 mg initial dose 10mg daily	180mg initial dose 90mg twice daily
• Alternative to ASA therapy in those who cannot take ASA • Option in NSTE-ACS as the second antiplatelet agent; Recommended agent in elective PCI	• Approved 2009 • Triton TIMI 38 (compared to clopidogrel) - All patients to cath lab - Significant reduction in risk but also significant increase in major bleeding	•Approved 2011 •PLATO trial - Better anti-ischemic effect compared to clopidogrel - No significant increase in major bleeding
• Issue of Non Responders • Prodrug: 2 step process • CYP2C19 isoenzyme responsible for almost half of the first step formation • Variant alleles of above gene associated with loss of function- up to 25 to 30% • Routine genetic testing or platelet fx testing NOT rec • Potential concern with PPIs: ntoprazole has less CYP2C19 inhibition	• When tested in patients being managed medically (Trilogy) – no significant difference in outcomes compared to clopidogrel - Used only in patients having PCI • Cannot use: (bleeding risk) ≥ 75 years old ≤60 KG Previous CVA / TIA • Prodrug but not as dependent on CYP2C19 isoenzyme	• Not a pro drug • Higher recommendation for ticagrelor in NSTE over clopidogrel in either ischemia guided or early invasive option • BID dosing concern for adherence • Cannot take with more than 100 mg of ASA • Hold 5 days for major surgery despite shorter ½ life • Dyspnea

51 2019

51

Long Term Management of ACS

Medications to improve prognosis

- Aspirin
- Clopidogrel / Prasugrel / Ticagrelor
- Statin

2019 52

52

Long Term Management of ACS

Medications to improve prognosis

- Beta-blockers
- ACE inhibitors
  - Definite in select patients / reasonable in all
  - ARBs if ACE-I intolerant
- Aldosterone antagonists
  - EF ≤ 40 with HF or diabetes

Impact long term ventricular remodeling

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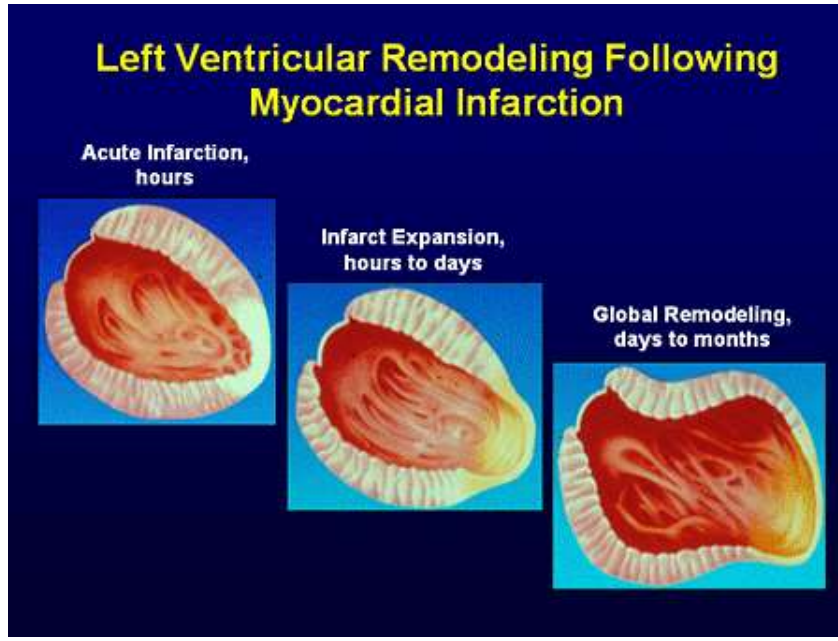
53



2019 54

54

ACS Clinical Case

- You are seeing a patient recently admitted S/P anteroseptal myocardial infarction with successful stenting to the left anterior descending artery. The patient's troponin peaked at 12.7 ng/mL. Most recent troponin 4.7 ng/mL. Blood pressure has been stable at 126/72 mmHg. HR is 74 BPM. LVEF during cardiac cath was 45%. The patient has been ordered metoprolol tartrate 12.5 mg two times daily and lisinopril 2.5 mg daily. The patient is also on aspirin, prasugrel, and atorvastatin. You observe the patient is having more frequent PVCs including occasional couplets and triplets.

- **What should we do?**

55

Beta Blockers in ACS

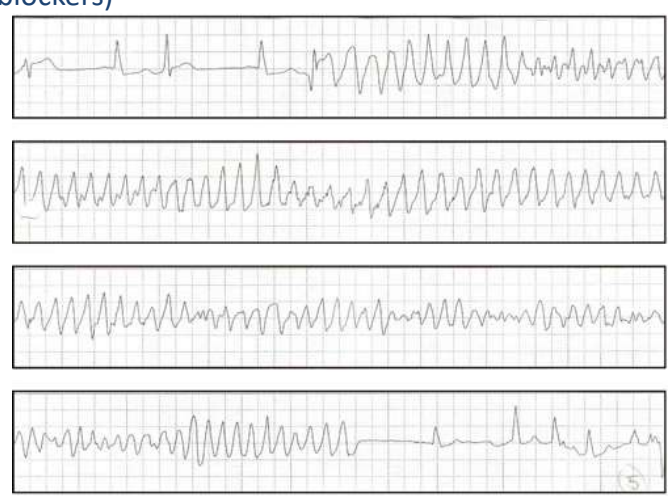
- Immediate as well as long term mortality benefit
- Immediate beta-blocker therapy
  - Reduces the magnitude of infarction and incidence of associated complications
    - Decreases myocardial oxygen demand
  - Reduces rate of reinfarction
  - Reduces frequency of life-threatening ventricular tachyarrhythmias.
- Long term benefit post ACS
  - Decreases myocardial oxygen demand
    - HR Benefit
  - Enhances overall well being
  - Slows disease progression
  - Inhibits ventricular remodeling and apoptosis
  - Inhibits adverse effects of SNS
  - Reduces mortality and repeat hospitalizations

2019 56

56

Polymorphic VT with NORMAL QTc:

- Seen frequently in ischemic conditions (role of beta blockers)



2019 57

57

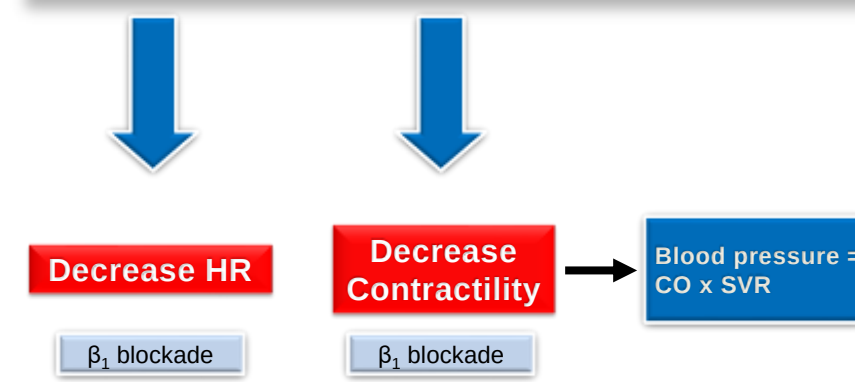
Beta Blockers at Presentation

- **DO NOT** administer in acute presentation **IF:**
  - STEMI precipitated by cocaine
    - Risk of exacerbating coronary spasm
  - Heart blocks (unless pacemaker is in place)
    - 1st degree AV block with PR ≥ 0.24 sec
    - 2nd or 3rd degree AV block
  - Heart rate < 60 BPM
  - SBP < 100 mm Hg
  - Moderate LV failure is present (signs of HF or shock)
  - Active asthma or reactive airway disease

2019 58

58

A Closer Look at Beta Blockers Decreases Myocardial Oxygen Demand



2019 59

59

Beta Blockers

Nonselective	Cardio Selective
Blocks both Beta $_1$ and Beta $_2$	**Blocks Beta 1**
• Propranolol (Inderal)	• Acebutolol (Sectral)
• Timilol (Blocadren)	• Metoprolol tartrate (Lopressor)
• Nandolol (Corgard)	• Metoprolol succinate (Toprol XL)
• Sotolol (Betapace)	• Atenolol (Tenormin)
• Labetolol (Normodyne, Trandate) (also alpha blockade)	• Esmolol (Breviblock)
• Carvedilol (Coreg) (also alpha blockade)	• Bisoprolol (Z Beta)
	• Nebivolol (Bystol) (also nitric oxide vasodilatory properties)

2019 60

60

Medication Pearls in Myocardial Infarction

- Start beta blocker prior ACE-inhibitor
  - Beta blockers most important medication to reduce mortality early
  - However, cannot be given in patients at high risk for shock
- Do not start beta blocker and ACE-I at the same time
- Hold ACE inhibitors for BP < 100 mm Hg systolic or < 30 mm Hg below baseline.
  - Ideally ACE-I should be initiated within 24 hours

2019 61

61

Beta Blockers Recommended by Disease State

Post MI	Heart Failure
• Atenolol • Carvedilol ☆ • Metoprolol ☆ • Propanolol • Timololol • Bisoprolol	• Bisoprolol • Carvedilol ☆☆ • Metoprolol Succinate (XL) ☆

Use GDMT for stable heart failure in all patients with ACS and LVEF ≤ 40%.

2019 2

62

Dose Equivalents

Carvedilol	Metoprolol Tartrate	Metoprolol Succinate
3.125 mg BID	12.5 mg BID	25 mg daily
6.25 mg BID	25 mg BID	50 mg daily
12.5 mg BID	50 mg BID	100 mg daily
25 mg BID	100 mg BID	200 mg daily

2019 63

63

Guideline Directed Medical Therapy for ACS / CAD

Mortality Reducing Agents

- ✓ Dual Antiplatelet Therapy
  - ✓ 12 months all ACS patients
- ✓ Beta Blocker
  - ✓ All ACS patients
- ✓ ACE Inhibitor
  - Anterior MI or LVEF ≤ 40%
  - Reasonable in all patients
- ✓ Eplerenone
  - LVEF ≤ 40% and either HF or diabetes
- ✓ Statin
  - Regardless of baseline LDL-C

2019

Additional Medications to Control Angina in Medical Management

- Calcium channel blockers
- Long acting nitrate
- Ranolazine (Ranexa)
- SL Nitroglycerin

64

64

Additional medications to control ischemia for medical management / angina

Calcium channel blockers

- Nondihydropyridines if used as substitute for beta blocker
  - Cardizem
  - Verapamil
- Dihydropyridines if suspected spasm
  - "INE" CCB

2019

- Long acting nitrate
  - Isosorbide Dinitrate
  - Isosorbide Mononitrate
- Ranolazine (Ranexa)

65

65

Ranolazine (Ranexa)

- Indicated for treatment of chronic angina
- Mechanism of action in treating angina is unknown
  - Possible relaxation of myocardium
- Does not impact heart rate or blood pressure
- Dose: 500-1000mg BID
- May prolong QTc interval
- May worsen renal failure – DC if marked increase in serum creatinine
- Contraindicated in hepatic cirrhosis – 3 fold increase in QT prolongation

2019 66

66

SL NTG Instruction

- No more than 1 dose of SL NTG
  - If chest discomfort is unimproved or is worsening 5 min after 1 NTG call 9-1-1 immediately before taking additional NTG.
  - May take additional NTG while waiting EMS.
  - Chew ASA while waiting EMS.

- In chronic stable angina if symptoms are significantly improved by 1 dose of NTG may repeat NTG every 5 min for a maximum of 3 doses and call 9-1-1 if symptoms have not resolved completely.

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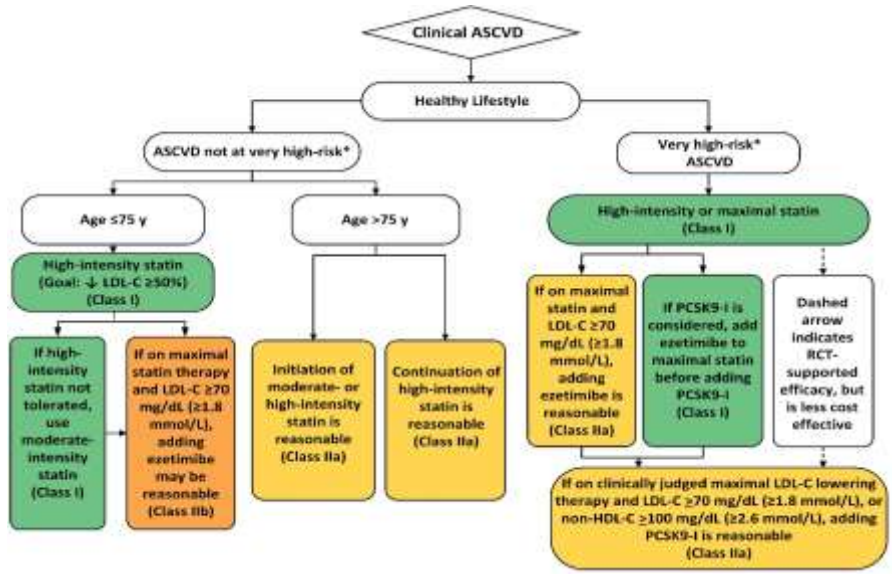
67

Secondary Prevention



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68

Table 4. Very High-Risk* of Future ASCVD Events

Major ASCVD Events
Recent ACS (within the past 12 mo)
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation)

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Table 4 continued

High-Risk Conditions
Age ≥65 y
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes mellitus
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m^2)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

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Table 5. Diabetes-Specific Risk Enhancers That Are Independent of Other Risk Factors in Diabetes Mellitus

Risk Enhancers
• Long duration (≥10 years for type 2 diabetes mellitus (S.4.3-20) or ≥20 years for type 1 diabetes mellitus) • Albuminuria ≥30 mcg of albumin/mg creatinine • eGFR <60 mL/min/1.73 m^2 • Retinopathy • Neuropathy • ABI <0.9

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71

HMG CoA Reductase Inhibitors (Statins) (3-hydroxy-3-methylglutary coenzyme A)

AGENTS	MECHANISM OF ACTION
• Atorvastatin (Lipitor) • Pravastatin (Pravachol) • Fluvastatin (Lescol) • Simvastatin (Zocor) • Lovastatin (Mevacor) • Rosuvastin (Crestor) • Pitavastatin (Livalo)	• Inhibition of HMG-CoA reductase • HMG –CoA reductase catalyzes an early step in cholesterol biosynthesis ✓ Decrease mortality ✓ Reduce risk of major coronary events by 30% ✓ Stimulate plaque regression

Pleiotropic Effects: Improvement of endothelial dysfunction, increased nitric oxide bioavailability, antioxidant properties, inhibition of inflammatory responses, and stabilization of atherosclerotic plaques

2019 72

72

Statin Dosing

High Intensity	Moderate Intensity
Group 1: All patients ≤75 years with ASCVD	All patients > 75 years with ASCVD - consider
Group 2: Patients (age ≥ 21) with LDL-C≥ 190 mg/dL	
Group 3: Diabetic patients (age 40-75) with a 10 year ASCVD ≥7.5%	Diabetic patients with a 10 year ASCVD <7.5% (Group 3)
Group 4: Persons 40-75 years with a ≥7.5% 10-year ASCVD risk should receive moderate- to high-intensity statin therapy.	
All patients > 75 years?	Patients with indication for high intensity but who are not able to take high intensity

2019 73

73

Statin Dosing

- High intensity: daily dose that lowers LDL-C by ≥ 50%
- Moderate intensity: daily dose that lowers LDL-C by 30% to 50%

Atorvastatin (80 mg daily) in the PROVE-IT TIMI 22 demonstrated reduced mortality and ischemic events in patients with acute coronary syndrome.

2019 74

74

Statin Therapy: Greatest LDL-C Lowering Effect:

- Atorvastatin
  - 80 mg: 55-60% reduction
  - 40 mg: 50% reduction
  - 20 mg: 43% reduction
  - 10 mg: 35-39% reduction
- Rosuvastatin
  - 40 mg: 55-63% reduction
  - 20 mg: 47-55% reduction
  - 10 mg: 46-52% reduction
  - 5 mg: 45% reduction

2019 75

75

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%	Daily dose lowers LDL–C on average, by <30%
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20–40 mg‡ Pravastatin 40 -80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg bid Pitavastatin 2–4 mg	Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg

2019 76

76

Statin Therapy

- Short or unknown half life: administration in evening for maximum efficacy
  - Simvastatin, lovastatin, and immediate release fluvastatin
- Hydrophilic (fluvastatin, pravastatin, and rosuvastatin*)
  - Minimally metabolized by the cytochrome P450 (CYP450) enzyme system
  - Lowest rates of myopathy *
- The lipid soluble statins are associated with insulin resistance and an increased Hemoglobin A1C.
  - Use cautiously with medications with strong CYP3A4 inhibition
  - Benefit of cardiovascular risk reduction is felt to outweigh the downside of elevated glucose levels.

2019 77

77

Characteristics of Specific Statins			
	Administration Time of Day	Water or Lipid Soluble	Degree Metabolized by CYP34A
Atorvastatin	Any time	Lipid soluble	Major degree
Fluvastatin (Immediate Release)	Evening	Relatively water soluble	Minor degree
Fluvastatin (Extended Release)	Any time	Relatively water soluble	Minor degree
Lovastatin	Evening	Lipid soluble	Major degree
Pravastatin	Any time	Water soluble	Minor degree
Rosuvastatin	Any time	Water soluble	Minor degree
Simvastatin	Evening	Lipid soluble	Major degree
Pitavastatin	Anytime	Lipid soluble	Minor degree
Source: Lexicomp, 2016; GNP, 2013.			

78

Statin Intolerance (Now SAMS)

- True statin intolerance is uncommon
- Most common: myalgias and weakness in large proximal muscle groups
- Rule out hypothyroidism, vitamin D deficiency, recent exercise and drug-drug interactions
- Increased risk in women, individuals of Asian descent, and the elderly

- Approach
- Stop current statin
- If symptoms resolve then rechallenge with same statin (lower dose)
- If recurrence – stop.
- When symptoms resolve start new statin
  - Consider hydrophilic
  - Lower dose
  - Longer acting statin 3 days a week.

ACC Statin Intolerance App

2019 79

79

Statin Therapy: Myopathy

CPK Levels

- Total CPK levels prior to initiation if at increased risk for adverse events and repeated for suspected myopathy.

Lipophilic statins are associated with increased myopathy risk due to increased ability to enter muscle cells and alter membrane structure.

Risk Factors

- Advanced age (> 80 years)
- Frailty
- Small body size
- Renal insufficiency
- Under treated hypothyroidism
- Co-administration of other drugs such as colchicine and fenofibrates

2019 80

80

Statin Therapy and Liver Enzymes

- Liver enzymes should be assessed at baseline and as clinically indicated.
- **Routine monitoring of liver enzymes is not necessary.**
- Statin therapy can result in an elevation of liver enzymes not associated with liver toxicity.
  - Association with higher dose statins.
- Contraindicated in active liver disease or in persistently and unexplained elevated liver enzymes.
  - AST and ALT > 3x the upper limit of normal.
- **Considered safe in patients with mild to moderately elevated liver enzymes attributable to chronic conditions such as nonalcoholic fatty liver and hepatitis C.**

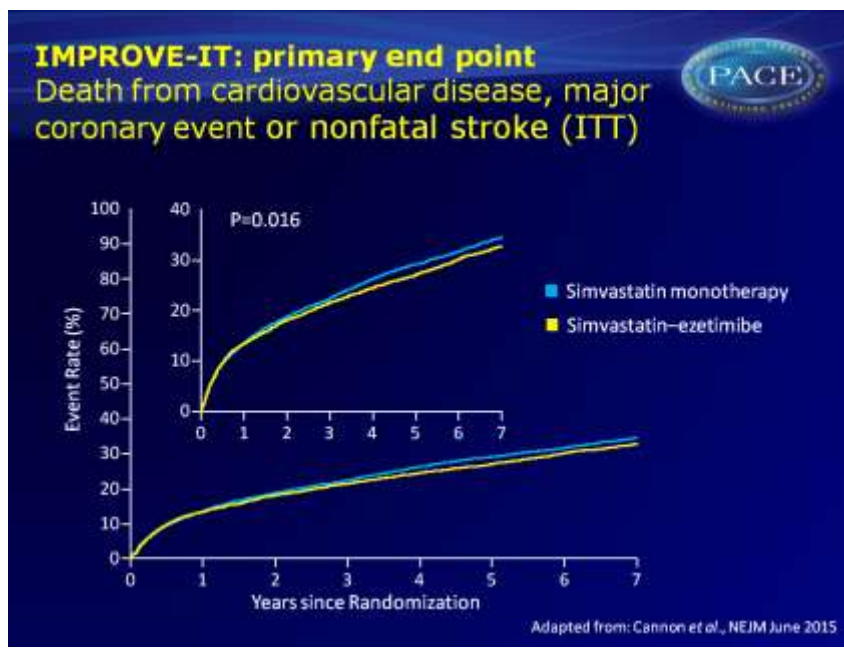
2019 81

81

Ezetimibe (Zetia)

- Intestinal absorption inhibitor
  - Reduced cholesterol absorption in the small intestine
  - Decreased delivery of cholesterol to the liver
  - Reduction in hepatic cholesterol stores
  - Increased clearance of cholesterol from the blood
- Benefit:
  - Monotherapy—18% reduction in LDL-C
  - Combination therapy with statin —25% reduction in LDL-C
- IMPROVE IT study

82



83

PCSK9 Inhibitor

- Proprotein Convertase Subtilisin Kexin Type 9
  - Enzyme encoded by the *PCSK9 gene* on chromosome 1.
  - The 9th member of the Proprotein Convertase family of proteins that activate other proteins
  - **Binds to the receptor for LDL particles - prevents removal of LDL from circulation**
- PCSK9 Inhibitor
  - **Binds to PCSK9 and increases number of LDL receptors available to clear circulating LDL cholesterol from the blood.**

2019 84

84

PCSK9 Inhibitors

Repatha (Evolocmab)	Praluent (Alirocumab)
• Approved by FDA Aug 2015 • Amgen • Every 2 week injection • Approved for patients who have heterozygous or homozygous familial hypercholesterolemia, HeFh or HoFh, which is an inherited condition that causes high LDL cholesterol levels. • **Also approved for patients who have had a heart attack or stroke.**	• Approved FDA Jul 2015 • Sanofi and Regeneron • Every 2 week injection • Approved for patients who have heterozygous or homozygous familial hypercholesterolemia, HeFh or HoFh, which is an inherited condition that causes high LDL cholesterol levels. • **Also approved for patients who have had a heart attack or stroke**

Treatment in conjunction with highest tolerated statin dose and diet modification.

2019 85

85

PCSK9 Inhibitors

Repatha (Evolocmab)

- LDL Reduction:
  - 64% and 58% (140 mg every 2 weeks and 420 mg SQ every 4 week) with max statin
- The effect of Repatha® on cardiovascular morbidity and mortality has not been determined.
- Adverse Effects
  - nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions

Praluent (Alirocumab)

- LDL Reduction:
  - 45% and 58% (75mg and 150mg dose) with max statin
  - The effect of PRALUENT on heart problems such as heart attacks, stroke, or death is not known.
- Adverse Effects
  - Nasopharyngitis, injection site reactions, influenza

Both Agents: ↑ in self-reported cognitive adverse effects in RCTs

86

FOURIER Trial

- Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk - May 2017
- Randomized, double-blind, placebo-controlled, multinational clinical trial in which patients at 1242 sites in 49 countries
- Age 40-85
- Clinically evident atherosclerotic cardiovascular disease
- Fasting LDL cholesterol level of ≥70 mg /dl while taking an optimized regimen of lipid-lowering therapy
- Randomly assigned to SQ injections of **evolocumab**
  - 140 mg every 2 weeks or 420 mg every month
- Primary end point
  - Major cardiovascular events defined as: Composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization.
- Secondary end point
  - Composite of cardiovascular death, myocardial infarction, or stroke

87

FOURIER Trial

- 27,564 patients
- Duration of follow up 26 months
- Primary end point
  - Occurred in 1344 patients (9.8%) in the evolocumab group and in 1563 patients (11.3%) in the placebo group (hazard ratio, 0.85; 95% CI, 0.79 to 0.92; P<0.001)
- Secondary end point
  - Occurred in 816 patients (5.9%) in the evolocumab group and in 1013 patients (7.4%) in the placebo group (hazard ratio, 0.80; 95% CI, 0.73 to 0.88; P<0.001)

The primary endpoint of FOURIER is the composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization.

There were reductions of 21 to 27% in the risk of myocardial infarction, stroke, and coronary revascularization **but no observed effect on the rates** of hospitalization for unstable angina, **cardiovascular death** or hospitalization for worsening heart failure, or death from any cause

2019 88

88

PCSK9 Inhibitors

- ?Cost prohibitive
- $14,500 per year per person
- One projection – PCSK9 inhibitors will add $592 billion in drug cost to US while decreasing the cost of CV burden by $28 billion
- 74 patients would need to be treated with PCSK9 inhibitor over a period of 2 years to prevent a cardiovascular death, or myocardial infarction, or stroke in one person. At the cost $2,146,000.
- Atorvastatin 80 mg $125.00 (wholesale) annually
  - NNT 100 x 3 years = $37,500

2019 89

89

Fibric Acids

- Indicated for hyperlipidemia with **Hypertriglyceridemia**
- Agents
  - Fenofibrate (Tricor)
  - Gemfibrozil (Lopid)
- Mechanism of Action
  - Unclear
  - Decreases VLDL-C synthesis
  - Reduces triglycerides by stimulating lipoprotein lipase activity
  - Decreases hepatic TG production

2019 90

90

Fibric Acids

- SE: dyspepsia, rash, alopecia, fatigue, HA, impotence, anemia; myositis flu like syndrome, cholelithiasis, abnornal liver function studies
- Contraindicated in severe renal (renally excreted) and hepatic disease, pre-existing gall bladder disease

---

- ACCORD Study
  - No reduction in cardiovascular mortality or non-fatal myocardial infarction or stroke when a fenofibrate was added to simvastatin in patients with type 2 diabetes mellitus(Ginsberg et al., 2010).
- The FIELD study
  - Effects of long-term fenofibrate therapy on cardiovascular events in people with type 2 diabetes did not show a statistically significant reduction in major coronary events in persons treated with fenofibrate therapy compared to placebo (Keech et al., 2005).

2019 91

91

Statin plus Fibrate Combination Therapy

- May be associated with a greater risk of myopathy and rhabdomyolysis
- The myopathy risk is enhanced under these situations:
  - High doses of statins
  - Renal insufficiency (Cr > 2.0)
  - Concomitant medications:
    Itraconazole, Ketoconazole
    Cyclosporin A
    Erythromycin
  - Age > 70 years

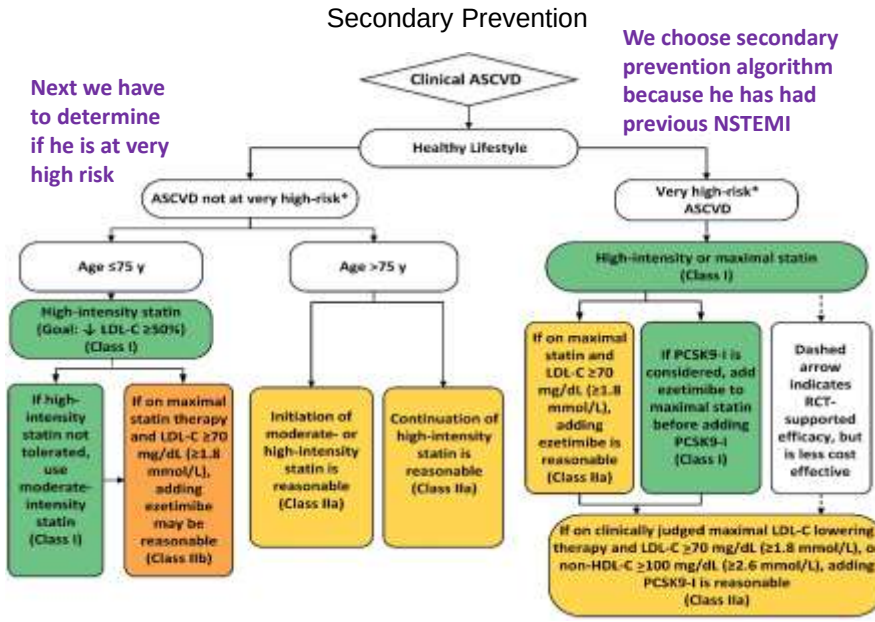
92

Lipid Management Clinical Decision Making Example

- 78 year old male admitted with exacerbation of heart failure with reduced ejection fraction.
  - History of NSTEMI 5 years ago and is S/P DES to the circumflex.
  - He has additional history of CKD III, DM Type 2, HTN, and Dyslipidemia
  - Home meds are: ASA, clopidogrel 75 mg , furosemide 40 mg BID , carvedilol 6.25 mg BID, lisinopril 5 mg daily, and atorvastatin 20 mg
  - Last LDL-C 87mg/dL

- ***Let's use the algorithm and then engage with patient in clinical decision making.***

93



Next we have to determine if he is at very high risk

We choose secondary prevention algorithm because he has had previous NSTEMI

If he is not at very high risk – age is more important

Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions

94

Table 4. Very High-Risk* of Future ASCVD Events

Major ASCVD Events
Recent ACS (within the past 12 mo) **NO**
History of MI (other than recent ACS event listed above) **YES**
History of ischemic stroke **NO**
Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation) **NO**

He has had one major ASCVD event so we have to evaluate high risk conditions.

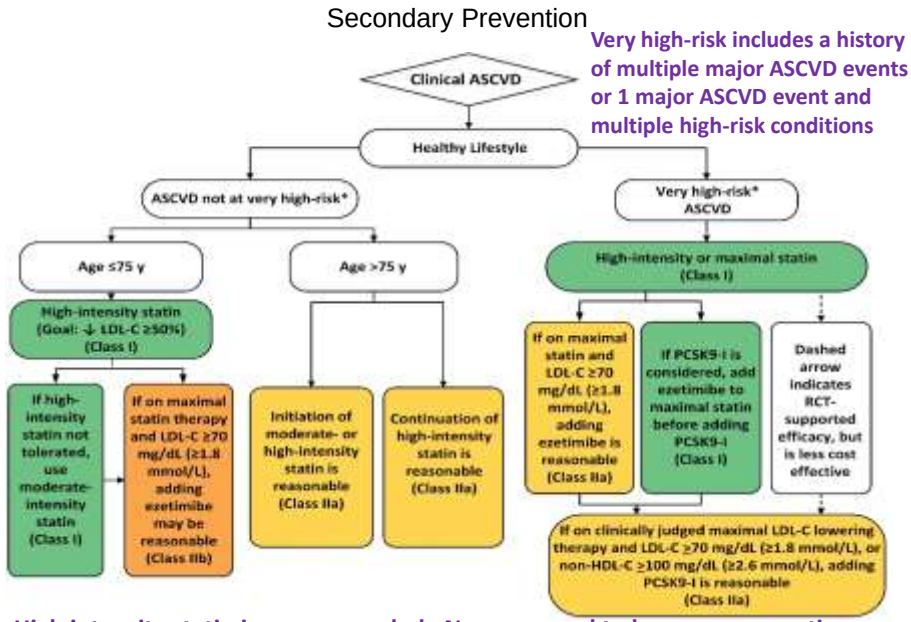
95

Table 4 continued

High-Risk Conditions
Age ≥65 y Yes
Heterozygous familial hypercholesterolemia No
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s) No
Diabetes mellitus Yes
Hypertension Yes
CKD (eGFR 15-59 mL/min/1.73 m^2) Yes
Current smoking No
Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe No
History of congestive HF Yes

Patient has 5 high risk conditions plus one major ASCVD event.

96



High intensity statin is recommended. Now we need to have a conversation with patient to determine if 20 mg of atorvastatin is maximally tolerated. 20 mg is not high intensity.

97

Tobacco Cessation Treatment

December 2018

ACC Expert Consensus Decision Pathway

Barua, R. S., Rigotti, N. A., Benowitz, N. L., Cummings, K. M., Jazayeri, M. A., Morris, P. B., ... & Wiggins, B. S. (2018). 2018 ACC Expert Consensus Decision Pathway on Tobacco Cessation Treatment: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *Journal of the American College of Cardiology*, *72*(25), 3332-3365.

98

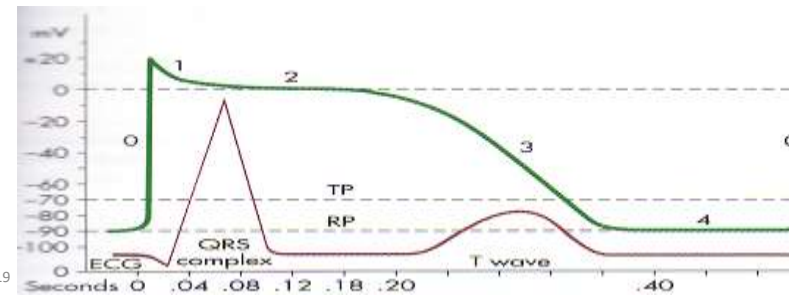
PHARMACOLOGY IN ATRIAL FIBRILLATION

99

The Electronics

Action Potential of Cardiac Cells

- Phase 0: Rapid depolarization – Sodium Influx (beginning of QRS complex)
- Phase 1: Brief, rapid initiation of repolarization



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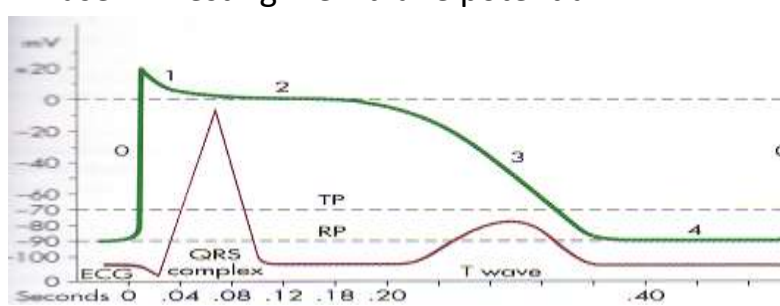
100

The Electronics

- Phase 2: Slowing of the repolarization – Calcium Influx – correlates with ST segment
- Phase 3: Sudden acceleration in the rate of repolarization - Potassium Efflux – Correlates with T wave
  - rapid delayed rectifier potassium current; IKr
- Phase 4: Resting membrane potential



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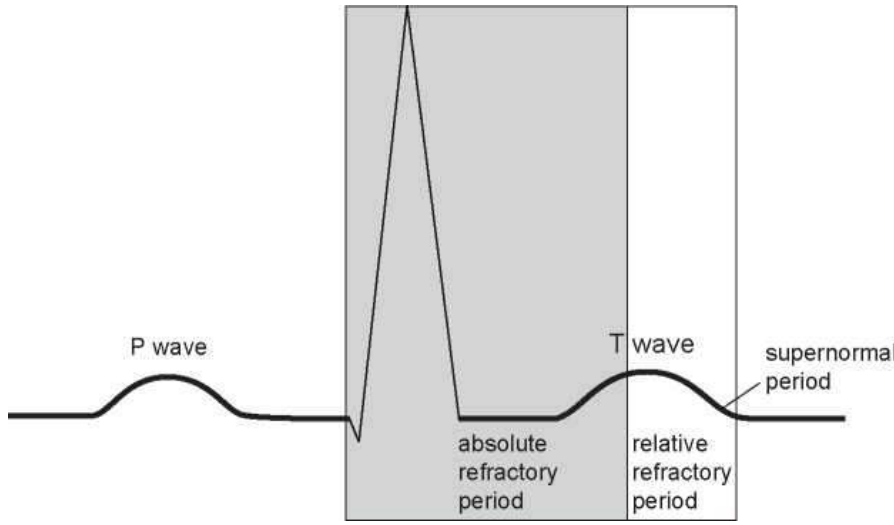
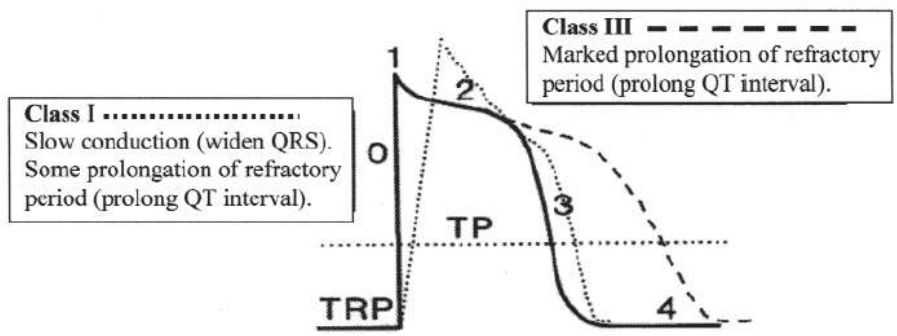
101


P wave
T wave
supernormal period
absolute refractory period
relative refractory period

102


Class I
Slow conduction (widen QRS).
Some prolongation of refractory period (prolong QT interval).
Class III
Marked prolongation of refractory period (prolong QT interval).
0
1
2
3
4
TP
TRP

103

Antiarrhythmic Medications Effecting the Action Potential

- **Class I** – Fast sodium channel blockers
  - IA:Quinidine, Procainamide, Disopyramide
  - IB: Lidocaine, Mexiletine
  - IC: Flecainide, Propafenone
- **Class III** – Potassium channel blockers
  - Amiodarone, Dronedarone, Ibutilide, Dofetilide, Sotalol
- **Class IV** – Calcium channel blockers
  - Verapamil, Diltiazem

Class II ???

2019 104

104

Class 1 Agents: Sodium Channel Blockers

Ventricular Arrhythmias

- Limited role in ventricular arrhythmias and prevention of sudden cardiac death
  - Lack of evidence for survival benefit
  - Increased mortality in chronic use in patients with ischemic disease
- Exceptions
  - Quinidine **(Brugada)**
  - Lidocaine (refractory VT / witnessed cardiac arrest)
  - Mexiletine **(congenital long QT)**
  - Flecainide **(catecholaminergic polymorphic VT)**
  - Also in patients with ICD with VT refractory to ablation and other medications

Atrial Fibrillation

- Conversion to and maintenance of SR in structurally normal hearts
  - Flecainide
  - Propafenone

2019 105

105

Class 2: Beta Blockers

Ventricular Arrhythmias

- Reduce SCD in HFrEF
- Reduce mortality in polymorphic VT after MI
- Can enhance efficacy of other antiarrhythmic therapy
- Propanolol and nadolol are first line for:
  - Long QT
  - Catecholaminergic polymorphic VT

Atrial Arrhythmias

- Rate control

106

Class 3 Agents: Potassium Channel Blockers

Ventricular Arrhythmias

- Amiodarone
  - Survival benefit controversial
  - High efficacy
  - IV to reduce recurrent arrhythmias during resuscitation
- Sotalol
  - Suppresses ventricular arrhythmias
  - Does not improve survival

Atrial Fibrillation

- Rhythm Control
  - Ibutilide
  - Dofetilide
  - Amiodarone
  - Dronedarone
  - Sotalol
- Rate Control: Amiodarone

107

Class 4 Agents: Calcium Channel Blockers

Ventricular Arrhythmias

- Nondihydropyridines: No role in most ventricular arrhythmias
- IV verapamil can cause hemodynamic collapse if given for VT in patients with previous MI
- In structurally normal hearts diltiazem or verapamil can be given for outflow tract VT
- Oral and IV verapamil for idiopathic interfascicular reentrant LVT

Atrial Fibrillation

- Nondihydropyridines
  - Rate control
  - Not to be used in HFrEF

108

Antiarrhythmics in Atrial Fibrillation

109

AFFIRM Trial (2002)

- Compared rate control and rhythm control in patients with AF to determine which approach was associated with better survival outcome
- Results
  - **Mortality rate nearly equal in the two groups**
  - More ischemic strokes in rhythm control group (anticoagulation often DC'd with NSR)
  - More adverse drug effects in rhythm control group
  - More hospitalizations in rhythm control group

110

AFFIRM

- Conclusions:
  - Rhythm control offers no survival advantage over rate control
    - Trend toward increased mortality with rhythm control
  - Potential advantages to rate control: fewer adverse drug effects
  - Anticoagulation should be continued in all AF patients at risk for stroke regardless of rate or rhythm control strategies

111

RACE (2002)

- Compared rate control and rhythm control in patients with recurrent persistent AF
  - End point was composite of CV death, admission for HF, thromboembolic event, severe bleeding, severe side effects from drugs
- Results:
  - Primary end point occurred in 17.2% of rate control group and 22.6% of rhythm control group (trend in favor of rate control)
  - Thromboembolism more frequent in rhythm control group
  - More adverse drug effects in rhythm control group

2019 112

112

RACE

- Conclusions:
  - Rate control is <u>not inferior</u> to rhythm control for prevention of death and morbidity from CV causes in patients with persistent AF
  - Cardiovascular risk (including risk of stroke) is not reduced with rhythm control even when sinus rhythm is maintained
  - Anticoagulation therapy should continue in all AF patients at risk for stroke regardless of rate or rhythm control therapy

2019 113

113

Rate Vs Rhythm Control Recommendations

- Data from 7 trials do not support a routine strategy of rhythm control in patients with atrial fibrillation with or without HF
- Rate control recommended in most patients with AF
- Rhythm control can be considered based on specific patient considerations
  - Continuing symptoms on rate control
  - Exercise intolerance with rate control drugs
  - Patient preference

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114

Registry data showing support for rhythm control in select patients to decrease disease progression.
(Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation)

HOWEVER!

2019 115

115

- ✓ **Persistent symptoms including HF exacerbations**
- ✓ **To prevent progression of paroxysmal atrial fibrillation to permanent in young patients**

MOST COMMON REASONS FOR RHYTHM CONTROL

116

Antiarrhythmics in Atrial Fibrillation			
Class	Specific Medications	Purpose of Medication	Major Cardiac Side Effects
Class I A	Disopyramide	**Rhythm Control**	Torsade de pointes, HF
	Procainamide	**Rhythm Control**	Torsade de pointes
	Quinidine	**Rhythm Control**	Torsade de pointes
Class I B	Not used in atrial fibrillation		
Class I C	Flecainide	**Rhythm Control**	Ventricular tachycardia , HF, Atrial Flutter
	Propofenone	**Rhythm Control**	Ventricular tachycardia , HF, Atrial Flutter
Class II	Beta Blockers	**Rate Control**	
Class III	Amiodarone	**Rhythm / Rate Control**	Torsade de pointes (rare) **** Organ toxicity***
	Dronedarone	**Rhythm Control**	
	Dofetilide	**Rhythm Control**	Torsade de pointes
	Ibutilide	**Rhythm Control**	Torsade de pointes
	Sotalol (Also contains beta blocker)	**Rhythm Control (also controls rate)**	Torsade de pointes Torsade de pointes, HF, Beta blocker side effects
Class IV	Calcium Channel Blockers	**Rate Control**	

117

Antiarrhythmic Drugs (AAD) in Atrial Fib Metanalysis

- AAD significantly reduce occurrence of atrial fib
  - NNT 2 to 9
- Adverse effects frequently result in discontinuation
- All but amiodarone and propafenone were proarrhythmic
- Quinidine and disopyramide associated with increased mortality
- Dronedarone not included
- Stroke, HF, and other outcomes not addressed
- Most trials enrolled healthy patients and had short follow up

Lafuente-Lafuente C, Mouly S, Longas-Tejero MA, et al. Antiarrhythmic drugs for maintaining sinus rhythm after cardioversion of atrial fibrillation: a systematic review of randomized controlled trials. Arch Intern Med. 2006;166:719-28.

118

Medications Used to Convert to Sinus Rhythm in Patients with Atrial Fibrillation

Ibutilide (50% of patients within 30 minutes)
Dofetilide
Flecainide (pill in the pocket*)
Propafenone (pill in the pocket*)
* Initial conversion trial while monitored

Amiodarone

Success rates higher in atrial flutter.

119

Anticoagulation and Cardioversion

- General: 3 weeks prior and 4 weeks post
  - For Afib unknown duration or > 48 hours
  - Regardless of CHADS2VASc
- If urgent need
  - Anticoagulate ASAP
  - Continue for 4 weeks
- Alternative is start anticoagulation prior to TEE guided with anticoagulation 4 weeks post
- If CHADS2VASc (0 men / 1 women) and duration < 48 hours anticoagulation is optional

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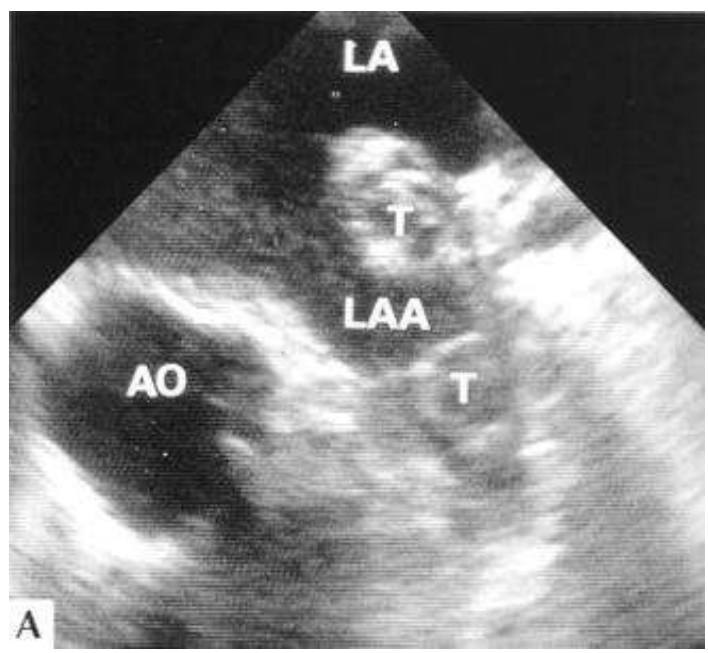
120



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121

Medications Most Commonly Used to Maintain Sinus Rhythm in Patients with Atrial Fibrillation

Drug efficacy is only modest. Asymptomatic recurrence is common. DO NOT stop anticoagulation or rate control.

Amiodarone
Dofetilide
Dronedarone
Flecainide
Propafenone
Sotalol

Usually not used in first occurrence atrial fib that resolves. Always focus on reversing cause.

It may be reasonable to continue maintenance drugs in patients with occasional breakthrough atrial fib – if drug has reduced symptoms and overall atrial fib burden. These medications should be stopped when atrial fibrillation becomes permanent.

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122

Drug Selection

- Drug selection is guided by safety more than efficacy
  - Structural heart disease / significant hypertrophy
  - Risk of Torsades
  - Renal and hepatic function / age
  - Toxicity profile
    - All antiarrhythmics can precipitate or worsen bradycardia due to sinus node dysfunction or AV node conduction abnormalities
      - History of syncope, bradycardia, PR prolongation, or BBB should raise concerns
      - Pacemaker may be needed
    - Amiodarone is never a first line agent if other options exist

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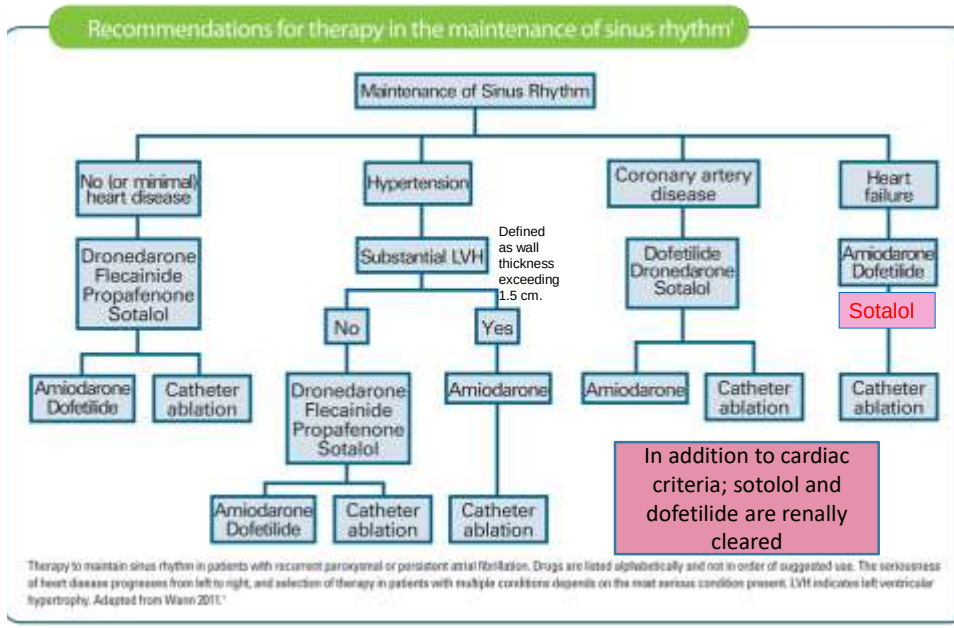
123



124

Case Example

- 66 year old male patient presents back to hospital with shortness or breath and lightheadedness that he recognized was associated with recurrent atrial fibrillation. He was discharged 6 weeks earlier after he came to the ED with similar symptoms and was found to be in new onset atrial fibrillation. He underwent a successful TEE guided cardioversion and was discharged home on two new medications: metoprolol tartrate 25 mg BID and apixaban 5 mg BID for a CHA_2DS_2VASc score of 2 for HTN and age. His hypertension has been long standing and resistant and he takes 3 additional medications prescribed by a hypertension specialist. Because he is very symptomatic in atrial fibrillation a rhythm control strategy is planned.

125

Case Example

- **Will he need an antiarrhythmic medication?**
- **What are the options?**
- **Are any additional diagnostic tests warranted?**

126

Beers Criteria / List

- Antiarrhythmic drugs (Class Ia, Ic, III)
  Amiodarone Dofetilide Dronedarone
  Flecainide Ibutilide Procainamide Propafenone
  Quinidine Sotalol

Consider safety of these medications in all patients.

127

Effects of Class 1 Antiarrhythmics

- All Class 1 antiarrhythmics by definition block the fast sodium channel
  - Different drugs do this to a different degree
  - IC > IA > IB

- Blocking of the fast sodium channel interferes with rapid depolarization and decreases conduction velocity
  - This will increases the duration of the cardiac action potential
  - *Note: This effect is seen in the action potential of the purkinge fibers but not in the action potential of the nodal tissue*

2019 128

128

Benefits of Reducing Rate and Degree of Depolarization

- Decrease in conduction velocity in non-nodal tissue is called negative dromotropy.

- This is suppresses reentrant tachycardias because reentrant tachycardias are caused by abnormal conduction.

2019 129

129

Effects of Class 1 Antiarrhythmics

- In addition to blocking the fast sodium channel (Phase 0) – some class I agents also block the potassium channel (Phase 3) (I_{kr})
- Potassium channel blockade directly affects the duration of the cardiac action potential and the effective refractory period.
- Benefits and disadvantages of effecting refractory period
  - Beneficial in reentrant tachycardias
  - Can increase risk for Torsades
- Different drugs do this to a different degree
  - IA (increase refractory period) > IC (no effect) > IB (decrease refractory period)

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130

Effects of Class 1 Antiarrhythmics

Depression of Automaticity

- Can suppress abnormal automaticity
- Not related to sodium channel effect
- Mechanism not fully understood

Anticholinergic Effect

- Strong inhibitors of vagal activity
- Offsets some of benefit (i.e. an increase ventricular rate during the treatment of atrial arrhythmias)
- Can increase SA rate and conduction through the AV node

2019 131

131

Class I C Antiarrhythmics

Action Potential	**Potent** inhibition of fast sodium channel; decrease in maximal rate of phase 0 depolarization
Actions	Slow His-Purkinge conduction and cause QRS widening QT intervals are also usually prolonged **No effect on refractory period** May increase PR interval in SR Increases defibrillation threshold Also have negative inotropic effect
Cautions	Proarrhythmic effects
Uses	Life threatening ventricular arrhythmias Conversion to SR (Flecainide)
Drugs	**Flecainide (Tambocor)** **Propofenone (Rhythmol)**

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132

Special Considerations in Class 1C Drugs

- Beta blockers or non-dihydropyridine should be given ≥ 30 minutes prior to prevent RVR due to 1:1 conduction during atrial flutter
  - These medications can cause slowing of the atrial rate in atrial flutter, resulting in 1:1 AV conduction and an increased ventricular rate
- Increase in QRS is associated with proarrhythmic risk
  - Great caution with conduction system disease without a pacemaker in place

2019 133

133

Class I C Antiarrhythmics

Flecainide (Tambocor) CAST Trial: propensity for fatal proarrhythmic effects	✓ Not a first line agent for ventricular arrhythmias ✓ **Used in atrial fibrillation for conversion and maintenance of SR (pill in the pocket)** ✓ **Will slow conduction over accessory pathways in WPW tachycardias** ✓ **Metabolized by CYP2D6 (genetically absent in 7 to 10% of patients)**, renal excretion **Avoid:** Sinus or AV node dysfunction, infranodal conduction disease, structural heart disease, ischemic heart disease, atrial flutter Brugada syndrome, renal or liver disease **SE**: Hypotension, sinus node dysfunction, AV block, ventricular proarrhythmias (monomorphic VT in scar), drug induced Brugada, atrial flutter with 1:1 conduction; exacerbation HFrEF, non cardiac effects uncommon (dizziness, tremor, vision disturbances, dyspnea, nausea)

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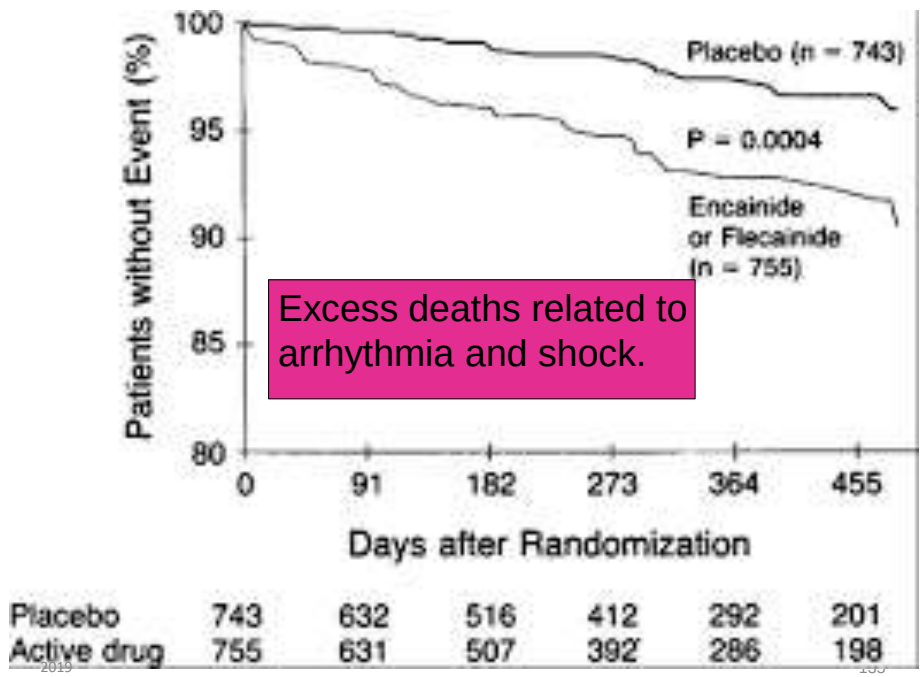
134



135

Class I C Antiarrhythmics

Propafenone (Rhythmol)	Used in atrial fibrillation for rhythm control and life threatening ventricular arrhythmias; PVC Also has small beta blocking actions and calcium channel blocking effects that can worsen HF **Metabolized by CYP2D6 (genetically absent in 7 to 10% of patients – poor metabolizers); Inhibits P-glycoprotein: ↑digoxin concentration; Inhibits CYP2C9: ↑warfarin concentration (↑INR 25%)** **Avoid:** Sinus or AV node dysfunction, infranodal conduction disease, structural heart disease, atrial flutter Brugada syndrome, asthma / bronchospastic lung disease, liver disease **SE**: Hypotension, ventricular proarrhythmias, drug induced Brugada syndrome atrial flutter with 1:1 conduction, metallic taste; non cardiac effects uncommon nausea, diarrhea, xerostomia, tremor, blurred vision
2019	136

136

Case Example

- You are caring for a 43 year old female admitted with a community acquired complicated intraabdominal infection. She is being hydrated and treated with IV ciprofloxacin 400 mg q 12 hours. She has required ondansetron (Zofran) 4 to 8 mg IV for nausea at regular intervals. Her only past medical history is depression and she is on citalopram (Celexa) 40 mg. She was recently referred to cardiology for palpitations and has an appointment scheduled in one week as an outpatient. She has had a 48 hour holter monitor and an echocardiogram done and the results are to be reviewed at the outpatient visit.

2019 137

137

Case Example

You are monitoring her in lead V1. The high heart rate alarm goes off and review of rhythm strip reveals atrial fibrillation with a ventricular rate in the 130s. When you assess her she states she feels palpitations as she has been experiencing at home intermittently. You notify the physician who consults cardiology. After 35 minutes she spontaneously converts to SR.

138

Case Example

Cardiology calls you in response to the consult. Cardiology states that they have reviewed the Holter and echocardiogram. She had 5 runs of paroxysmal atrial fibrillation on her Holter. The echocardiogram was normal. The cardiologist tells you that her atrial fibrillation is not due to her current infectious state since she had it prior to admission. He states that he wants to start her on a rhythm control drug to prevent the progression from paroxysmal to persistent or permanent atrial fibrillation. He states he is going to put orders in for flecainide and he will be in to see her in the morning.

What are your concerns?

139

Class III Antiarrhythmics

Action Potential	Inhibits potassium ion fluxes during phase II and III of the action potential
Actions	Directly on myocardium to delay repolarization (prolongs QT); prolongs effective refractory period in all cardiac tissue; By definition act only on repolarization phase and should not impact conduction
Cautions	Proarrhythmic Effects (amiodarone less)
Uses	Drug dependent
Drugs	**Amiodarone (Pacerone, Cordorone)** **Dronedarone (Multaq)** **Ibutilide (Corvert)** **Dofetilide (Tikosyn) – most pure class III** **Sotalol (Betapace)**

2019 140

140

Class III Antiarrhythmics

Amiodarone (ARREST Trial) **Survival to hospital admission improved 29%**	✓ Approved for life threatening refractory ventricular arrhythmias; considered before lidocaine in pulseless VT or V fib; considered ahead of lidocaine for stable VT with impaired cardiac function ✓ PVC burden ✓ **Use in atrial fibrillation is off label** ~~✓ Slows conduction in accessory pathways~~ ✓ Originally marketed as anti-anginal (potent vasodilator) ✓ Relaxes smooth and cardiac muscle, reduces afterload and preload (well tolerated in heart failure and cardiomyoapthy) ✓ **Proarrhythmias less frequent** ✓ Is also a weak sodium channel blocker, also has effects similar to class II and IV (blocks 7 different ion channels) (also has anticholinergic properties

2019 141

141

Amiodarone Dosing

- **Life-threatening ventricular arrhythmias**
  - Rapid loading infusion 150 mg administered at a rate of 15 mg/minute (over 10 minutes); initial infusion rate should not exceed 30 mg/minute
  - The slow loading phase is 360 mg at a rate of 1 mg/minute (over 6 hours)
  - First maintenance phase of the infusion is 540 mg at a rate of 0.5 mg/minute (over 18 hours).
  - After the first 24 hours, maintenance infusion rate of 0.5 mg/minute should be continued; the rate of the maintenance infusion may be increased to achieve effective arrhythmia suppression.
  - In the event of breakthrough episodes supplemental infusions of 150 mg administered at a rate of 15 mg/minute (over 10 minutes) may be given.
- **For cardiac arrest secondary to pulseless ventricular tachycardia or ventricular fibrillation**
  - Initial adult loading dose is 300 mg (diluted in 20–30 mL of a compatible IV solution) given as a single dose, rapid IV

2019 142

142

Amiodarone Dosing for Atrial Fibrillation

- 600 to 800 mg daily in divided doses until 10 g is reached
- 200 mg daily as maintenance
- 100 mg daily may be used for lean body mass or older age

✓ Antiarrhythmic effect and QT prolongation can be delayed for days to weeks
  Oral amiodarone converts about 25% of patients with persistent atrial fib several weeks after loading
  Loading accelerates time to antiarrhythmic effect
✓ Giving with food increases absorption
✓ When using for rhythm control you also get a rate control agent

2019 143

143

More on Amiodarone Dosing

- IV cardioversion of atrial fibrillation
- 150 mg over 10 min, then 1 mg/min for 6 h, then 0.5 mg/min for 18 h or change to oral dosing
- **Peripheral IV concentration not to exceed 2mg/ml**

2019 144

144

Pharmacological Considerations for Amiodarone

- Multiple drug interactions: Inhibits most CYPs, Inhibits P-glycoprotein
  - Increases effect / level of digoxin, warfarin, dabigatran, statins
- **When starting: decrease digoxin, warfarin, and rate control medications**
- **Levels of amiodarone may be decreased by grapefruit juice – inhibits the production of the major metabolite of amiodarone**
- Large volume of distribution in adipose tissue
- **Mean ½ elimination for oral chronic therapy 40 to 55 days, active metabolite 61 days; single IV dose 9 to 36 days, active metabolite 9 to 30 days**

2019 145

145

When to Avoid Amiodarone

- Sinus or AV node dysfunction
- Infranodal conduction disease
- **Lung disease / liver disease**
- Prolonged QT interval

- **Younger patients requiring long term antiarrhythmic therapy**

146

Amiodarone and Iodine

- Amiodarone is Iodinated benzofuran derivative
- Inorganic iodine is released
- Could cause complications related to thyroid function, **but this is a metabolic effect and is not related to an immunologic response to iodine in radiocontrast or food**
- (Brouse, Sara D., and Stanley M. Phillips. "Amiodarone Use in Patients with Documented Allergy to Iodine-Containing Compounds."Pharmacotherapy: *The Journal of Human Pharmacology and Drug Therapy* 25.3 (2005): 429-434.).

- **"Hypersensitivity reaction to amiodarone in a patient with a previous reaction to an iodinated radiocontrast agent." *Annals of Pharmacotherapy* 41.7-8 (2007): 1310-1314.).**
- Their argument is based upon the "Naranjo probability scale" or algorithim and the package insert.
- **The label of amiodarone has the following statement "Cordarone is contraindicated in patients with a known hypersensitivity to the drug or to any of its components, including iodine."**

147

Amiodarone Adverse Effects

- Phlebitis (IV)
- Hypotension, dizziness, **bradycardia**, AV block, QT prolongation, torsades de pointes (rare)
- Increases defibrillation threshold; **slows VT below ICD detection rate**
- GI upset (with oral administration give with food)
- Constipation

2019 148

148

Potential Extra Cardiac Effects

By weight amiodarone is 37% iodine

Pulmonary toxicity without initial symptoms; pulmonary fibrosis Potentially lethal interstitial pneumonitis		**Photosensitivity / blue grey skin pigmentation**
Hepatotoxicity: hepatitis, cirrhosis	Corneal micro deposits Optic neuropathy / neuritis	Thyroid dysfunction
Ataxia, peripheral neuropathy, tremor		

Toxic side effects increase with length of use and increased dose

Amiodarone partially inhibits the peripheral conversion of T4 to T3. Serum T4 and reverse T3 may be increased and T3 may be decreased. Clinical hypo or hyper thyroidism can occur.

2019 149

149

Amiodarone Monitoring

- ECG for HR, AV block and QT interval
  - Monitor potassium and magnesium
- Baseline PFTs and CXR
  - Annual CXR
  - Monitor for signs of pulmonary toxicity (i.e. non productive cough, dyspnea)
- Semi annual LFTs
- Baseline thyroid function
  - Monitor for signs / symptoms of thyroid dysfunction
  - Q 3 to 6 months
- Monitor for CNS effects (ataxia, tremor, dizziness, peripheral neuropathy, and delirium)
- Regular ophthalmic exams
- Monitor pacing and defibrillation thresholds if device in place
- **Therapeutic level is 0.5 to 2.5 mg/L**
  - **Desethyl metabolite is active and present in equal concentration to the parent drug.**

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150

New 2014 Atrial Fibrillation Guidelines

CHANGE IN RECOMMENDATION REGARDING AMIODARONE FOR PATIENTS WITH PRE-EXCITATION

2019 151

151

- **Lethal Outcome After Intravenous Administration of Amiodarone in Patient with Atrial Fibrillation and Ventricular Preexcitation**

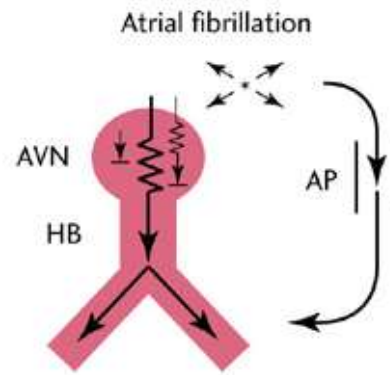
- MUJOVIĆ NEBOJŠA M.D.[1],
- SIMIĆ DRAGAN M.D.[1],
- ANTONIJEVIĆ NEBOJŠA M.D.[1] and
- ALEMPIJEVIĆ TAMARA M.D.[2]

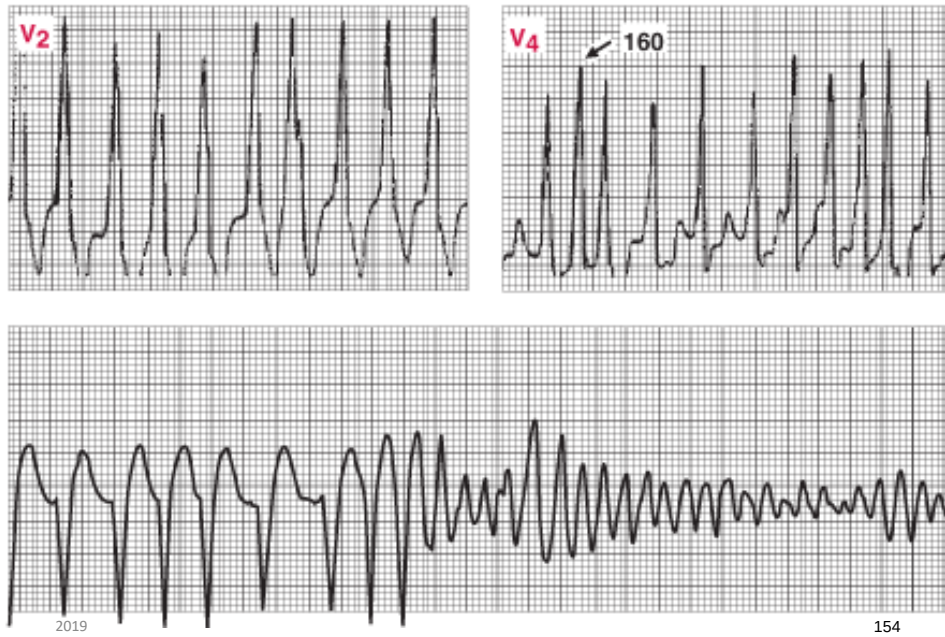
- **Journal of Cardiovascular Electrophysiology**
- Volume 22, Issue 9, pages 1077–1078, September 2011

- Article first published online: 18 FEB 2011
- DOI: 10.1111/j.1540-8167.2011.02013.x

WPW and Atrial Fibrillation

- Mechanism of Action
  - Development of Atrial Fibrillation in WPW
    - 10-32% of patients
  - Refractory period of accessory pathway





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154

Amiodarone Efficacy / Safety

Direct Comparison

- More effective in maintenance of SR
  - Dronedarone
  - Propafenone
  - Sotalol

Amiodarone associated with an increase in noncardiac mortality in HF patients with NYHA class III in Sudden Cardiac Death in Heart Failure Trial

Mixed Treatment Comparison

- Compared to
  - Dronedarone
  - Flecainide
  - Propafenone
  - Sotalol
- Amiodarone
  - Largest reduction of atrial fib occurrence
  - **Highest rate of serious adverse events and treatment withdrawals due to serious adverse events**

2019 155

155

Newest Antiarrhythmic

- Dronedarone (Multaq)
  - Rejected by FDA 2006
  - Approved by FDA 2009
  - Decreases hospitalizations in atrial fibrillation
  - Proposed safer alternative to amiodarone in terms of extra cardiac side effects

Dronedarone

- Similar to amiodarone without iodine component and less fat soluble
- Class III antiarrhythmic (K^+ channel blocker) with effects from all four classes
- **Less effective than amiodarone at maintaining sinus rhythm but also less toxic**
- Elimination half-life 13-19 hours
- Has both rate and rhythm control effects but is primarily indicated for rhythm control

Dronedarone (Clinical Trial ATHENA)

- MULTAQ reduced the combined endpoint of cardiovascular hospitalization or death from any cause by 24.2% when compared to placebo.
- **Difference attributed entirely to reduction in hospitalization due to AF. No mortality benefit.**
- Approved for maintenance of sinus rhythm in patients with history of paroxysmal or persistent AF or flutter with EF > 35% who are in sinus rhythm or will be cardioverted.
- Dose: 400 mg PO bid with meals (no grapefruit juice)

158

ACCF/AHA/HRS Atrial Fibrillation Guidelines

Class II A Recommendation:

Dronedarone is reasonable to decrease the need for hospitalization for cardiovascular events in patients with paroxysmal AF or after conversion of persistent AF. Dronedarone can be initiated during outpatient therapy (*Level of Evidence: B)*

Reduces risk of recurrent atrial fibrillation after cardioversion by 25%.

159

ACCF/AHA/HRS Atrial Fibrillation Guidelines

Class III Recommendation (HARM)

- Dronedarone **should not** be administered to patients with class III or IV heart failure or patients who have had an episode of decompensated heart failure in the past 4 weeks, especially if they have depressed left ventricular function (left ventricular ejection fraction 35%) (LOE:B)
- **> two fold increase in mortality in HF patients**
- Antiarrhythmic drugs for rhythm control **should not** be continued when AF becomes permanent (LOE: C) including dronedarone (LOE:B)

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160

ANDROMEDA (Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating M… rease)

Dronedarone increased mortality after a median follow-up of only 2 months; 8.1% in the dronedar… grou… placebo …oup died. (HR: 2.13; 95% CI: 1.07 to 4.25; p=0.03)

Terminated Early for Safety

…idence to Support the …ecommendation

2019 161

161

More on Dronedarone

PALLAS Trial - 2011

- **Randomized Age ≥ 65 in permanent atrial fibrillation (at least 6 month) and risk for major vascular events to dronedarone or placebo**
- Enrolled 3236 patients
- **Stopped early** (3.7 months for placebo and 3.9 for dronedarone) due to adverse outcomes in dronedarone arm
  - Dronedarone mortality nearly 2 times greater
- Dronedarone increased rates of heart failure, stroke, and death from cardiovascular causes in patients with permanent atrial fibrillation who were at risk for major vascular events.

2019 162

162

Dronedarone Contraindications

- Permanent / longstanding persistent Afib/Fl
- Recently decompensated HF requiring hospitalization or Class III - IV HF
- 2nd or 3rd degree AV block or sick sinus syndrome
- Bradycardia <50 bpm
- Concomitant use of a strong CYP3A inhibitor (i.e. grapefruit, verapamil, diltiazem)
- QTc Bazett interval ≥500 ms
- Concomitant use of drugs or herbal products that prolong the QT interval and may induce Torsade de Pointes
- Liver or lung toxicity related to the previous use of amiodarone
- Severe hepatic impairment
- Pregnancy and nursing mothers

2019 163

163

Dronedarone Pharmacological Considerations

Metabolism

- Metabolized by CYP3A: Caution with inhibitors (examples: verapamil, diltiazem, macrolide antibiotics) and inducers
- Inhibits CYP3A, CYP2D6, Pglycoprotein: ↑concentrations of some statins, sirolimus, tacrolimus, beta blockers, digoxin

Specific Drug to Drug Considerations

- Digoxin
  - Can potentiate effect of dronedarone
  - Stop or decrease dose
  - Increase monitoring of digoxin levels
- Calcium Channel Blockers
  - Increase Dronedarone exposure
  - May interfere with AV conduction
  - Can be used but low doses initially
- Beta-blockers
  - May provoke bradycardia
- Statins
  - **Avoid simvastatin dose > 10mg**
- Warfarin
  - Does not alter INR

164

Dronedarone Monitoring

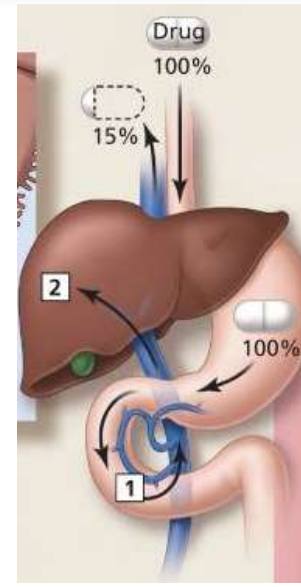
Monitor

- Rhythm
  - ECG at least every 3 months
  - **QTc ≥ 500 ms**
  - **Bradycardia**
  - AV Blocks
  - Development of AF
- **Creatinine**
  - **Like amiodarone, dronedarone inhibits renal tubular secretion of creatinine, which can increase plasma creatinine levels with no decrease in GFR**
- Potassium and Magnesium
- Evidence of heart failure
- Evidence of pulmonary toxicity
- Signs of liver impairment
  - Liver enzymes and bilirubin "periodically"

165

CYP3A4 Metabolite

- Cytochrome P450, Family 3, Subfamily A, Polypeptide 4
- Drug metabolism involves oxidation by enzymes belonging to the cytochrome P450 superfamily
- CYP3A4 involved in the bioINACTIVATION of about 50% of all drugs
- Located in epithelial cells lining small intestines and colon, and in the parenchymal cells of the liver
- Orally administered drugs metabolized twice before entering systemic circulation - > % of drug that is then bioavailable



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166

Grapefruit and CYP3A4

- Chemical in grapefruit – Furanocoumarins
- Furanocoumarins metabolized by CYP3A4
- Furanocoumarins irreversibly inactivate CYP3A4
- Results in INCREASED drug bioavailability after 2nd pass
- Drug with lower oral bioavailability have more significant consequences

Dronedarone 4% bioavailable on empty stomach and 15% bioavailable after high fat meal

Take with meals

Reported serious adverse effects with grapefruit (including juice) when taken with dronedarone

- Torsade de pointes
- Rhabdomyolysis
- Myelotoxicity
- Respiratory depression
- Gastrointestinal bleeding
- Nephrotoxicity

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167

Harmony Clinical Trial

- Small trial of 134 patients
- Reduced dose dronedarone (150 mg or 225 mg) combined with ranolazine (750 mg) BID to reduce atrial fib burden
- Found to be effective and well tolerated / safe

2019 168

168

Ranolazine (Ranexa)

- Indicated for treatment of chronic angina
- Mechanism of action in treating angina is unknown
  - Possible relaxation of myocardium
- Does not impact heart rate or blood pressure
- **Blocks late sodium channel and less potently Phase 3 potassium channel**
  - **May decrease VT**
- Dose: 500-1000mg BID
- May prolong QTc interval
- May worsen renal failure – DC if marked increase in serum creatinine
- Contraindicated in hepatic cirrhosis

2019 169

169

Class III Antiarrhythmics

Ibutilide (Corvert)	✓ **Indicated for rapid conversion of atrial fib or flutter to sinus rhythm; IV use only over 10 minutes**; also facilitated cardioversion ✓ Rather than blocking outward potassium currents – promotes influx of sodium through slow inward sodium channel ✓ Converting agent: anticoagulation prophylaxis if indicated and post cardioversion

2019 170

170

Class III Antiarrhythmics

Dofetilide (Tikosyn) • Renal, age, body size dose adjustment • **Prescribing limited by REMS program** • **Initiation and dose increase have to occur in hospital**	✓ More "pure" class III agent ✓ Conversion to and maintenance of SR in A fib and flutter ✓ 1 year efficacy in trials 58 to 79% ✓ Reserved for very symptomatic patients, **monitored 3 days in hospital,** not used QTc > 440msec (500msec) ✓ Widens the QT; no negative inotropic effects, neutral effect on mortality from arrhythmias post MI and in in HF **Avoid**: QT prolongation (avoid any other QT prolonging medication), renal disease, hypokalemia (diuretic therapy), **Metabolized:** by CYP3A: verapamil, HCTZ, cimetidine, ketoconazole, trimethoprim, prochlorperazine, and megestrol are contraindicated; discontinue amiodarone at least 3 mo before initiation **SE**: Torsades, HA

2019 171

171

CLINICAL PEARL

IV Ibutilide effective 50% of time within < 30 minutes

- More effective in atrial flutter
- Can be used as pretreatment for electrical cardioversion

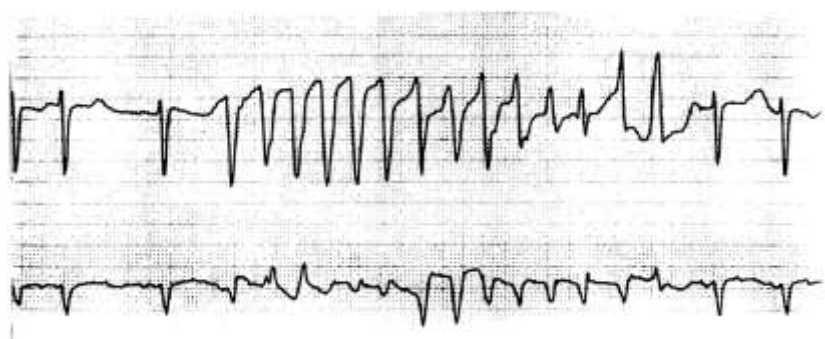
ALWAYS check potassium level prior to use of ibutilide– potassium level should be in high normal range.

Hypomagnesaemia should also be corrected. May administer magnesium for prophylaxis.

Avoid in patients with LVEF < 30% or with any baseline QT prolongation.

172

Simultaneous 2-lead ECG (leads II and V1) showing initiation and termination of torsade de pointes in patient in AF after ibutilide infusion.



VanderLugt J T et al. Circulation. 1999;100:369-375

- ✓ Occurs in 3 to 4% of patients
- ✓ Cardiac monitoring for 4 hours post administration
- ✓ Emergency equipment available

173

Class III Antiarrhythmics

Sotalol

*** Do not substitute Sorine for sotalol AF**

- **Renal dose adjustment**
- **Does not undergo any significant metabolism**

Few non cardiac SE

2019

- ✓ Used in atrial arrhythmias and life threatening ventricular arrhythmias; appears to decrease defibrillation threshold
- ✓ Indicated for stable monomorphic VT or Polymorphic VT with normal QT in ACLS protocol
- ✓ Non selective beta blocking agent with class III properties
- ✓ **Significant class III effects are only seen at doses > 160 mg**
- ✓ Proarrhythmic potential (prolonged QT): start in hospital in patients with no ICD or who are in Afib [black box warning – 3 days hospitalization]
- ✓ Effective in preventing reoccurring arrhythmias (30 to 50% at one year) * not a converting agent
- ✓ **Do not use**: Bradycardia < 50 bpm, SSS, & 2d or 3rd degree AVB (unless pacemaker) Cr Cl < 40 ml/min; prolonged QT (baseline > 450 msec), hypokalemia (diuretic therapy), uncontrolled HF, bronchospastic disease

174

174

More on Sotalol

- Sotalol D in SWORD trial demonstrated increased mortality in patients with HF
  - Pure potassium channel blocker with no clinically significant beta blocker effect
- May lead to HF decompensation so avoid in LVEF < 20%

2019

175

175

Pharmacological Considerations in Rate Control

Beta Blockers

- **Most commonly used: 70%**
- IV - New onset AF RVR
  - Esmolol, propranolol, and metoprolol
- Oral – Persistent / Permanent AF
  - Atenolol, metoprolol, nadolol, propranolol, and sotalol
  - Metoprolol better at rate control in HFrEF
- **Reports of better rate control long term**
- Use non selective agents with caution in co-existing COPD
- **Effective in preventing post operative atrial fibrillation**

2019 177

Calcium Channel Blockers

- **Nondihydropyridine CCB: 54%**
- Diltiazem / verapamil
- Used in both acute and chronic rate control
- SHOULD NOT be used in patients with LV systolic dysfunction and decompensated HF owing to their negative inotropic effect
- May be used in preserved LVEF
- SHOULD NOT be used in patients with pre-excitation
  - May shorten AP refractoriness

177

A Closer Look at Calcium Channel Blockers

	Verapamil	Dihydropyridines	Diltiazem
Heart Rate	▼▼	▲	▼
Direct AV Nodal Effects	▼▼	------	▼
Contractility	▼▼	▼	▼
Arterial Vasodilatation	▲▲	▲▲▲	▲

2019 178

178

More on Calcium Channel Blockers

- Both verapamil and diltiazem reduce resting and exercise heart rate and can improve exercise tolerance
- Should not be used in decompensated HF or HFrEF but may be used in HFpEF
  - Edema is also SE
- Should not be used in pre-excitation due to potential to shorten refractory period of accessory pathway

2019 179

179

IV Dosing in Rate Control

- Beta Blockers: Outlined in previous charts
- Diltiazem
  - 25 mg/kg IV bolus over 2 min, then 5-15 mg/h
  - t ½ life for injection 2 to 5 hours
- Digoxin
  - 0.25 mg IV with repeat dosing to a maximum of 1.5 mg over 24 h
- Amiodarone
  - 300 mg IV over 1 h, then 10–50 mg/h over 24 h

Oral agents are recommended unless immediate rate control is necessary or enteral route is contraindicated

2019 180

180

Amiodarone & Rate Control

- Only agent for rate and rhythm control
- Oral and IV amiodarone do not have identical electrophysiological properties
- A rate control option in critical care
  - Oral if other options contraindicated or ineffective
  - Less effective and longer to get control (7 versus 3 hours) compared to diltiazem
    - May get hemodynamic compromise with rapid loading
- **If used for rate control: wash out necessary before another rhythm control drug could be used : t ½ life 40 to 55 days**
- **What if it converts?**

2019 181

181

Pharmacological Considerations in Rate Control

- Dronedarone is not a rate control medication in permanent atrial fib
- No calcium channel blockers, digoxin, or amiodarone if pre-excitation is suspected in acute setting
- In hemodynamically unstable afib with RVR: **Cardioversion**
  - **Hypotension**
  - **Ischemia**
  - **Decompensated HF**

2019 182

182

Digoxin

Impact on Conduction

- ↑ vagal activity
- ↓ conduction velocity through the AV node
  - HOWEVER: Sympathetic stimulation easily overrides the inhibitory effects of digoxin on AV node conduction
- No better than placebo in converting atrial fib to Sinus Rhythm
- The conduction velocity ↑in the atria, but ↓ in the AV node.
- Automaticity is also increased, in the atria, AV node, Purkinje fibers and ventricles.

Rate Control in AF

- Not effective during exercise
- Beta blockers are preferred for rate control in HFrEF
  - » Addition of digoxin to BB can be beneficial for rate control in HF
- Calcium channel blockers have replaced digoxin as agent for rate control in atrial arrhythmias in non HFrEF patients
- Digoxin remains good option in acute setting when blood pressure is marginal
  - **Give IV slowly over 5 minutes**
  - *** Longer onset of action**
    - » **> 1 hour**
    - » **6 hr to peak**

2019 183

183

Digoxin

Contraindications / Cautions

- Women
- Elderly
- Renal dysfunction
- Acute MI / Ischemia
- Ventricular arrhythmias, Heart Block, Sick Sinus Syndrome
- WPW
- Hypertrophic or restrictive cardiomyopathy
- Amyloid heart disease
- Electrolyte abnormalities
  - Hypokalemia ↑ risk of toxicity
  - Hypocalcemia ↓ sensitivity to digoxin
  - Don't give IV calcium if digoxin toxic

2019 184

184

Digoxin

- Has a narrow therapeutic range
- Toxicity may occur at therapeutic levels or lower
  - Especially hypokalemia, hypomagnesemia, hypothyroidism
- Lower doses routinely used - 0.125 mg daily or less frequently
  - Especially if > 70 years of age, impaired renal function, or low lean body mass
- Multiple other medication interaction and will cause increased digoxin levels – digoxin dose needs decreased
  - Propafenone, amiodarone, dronedarone, verapamil, quinidine, clarithromycin, erythromycin, and itraconazole
- Dialysis is not effective with digoxin toxicity because of high tissue binding of digoxin

Assess Dig Level 3-5 days after initiation

2019 185

185

More About Digoxin Toxicity

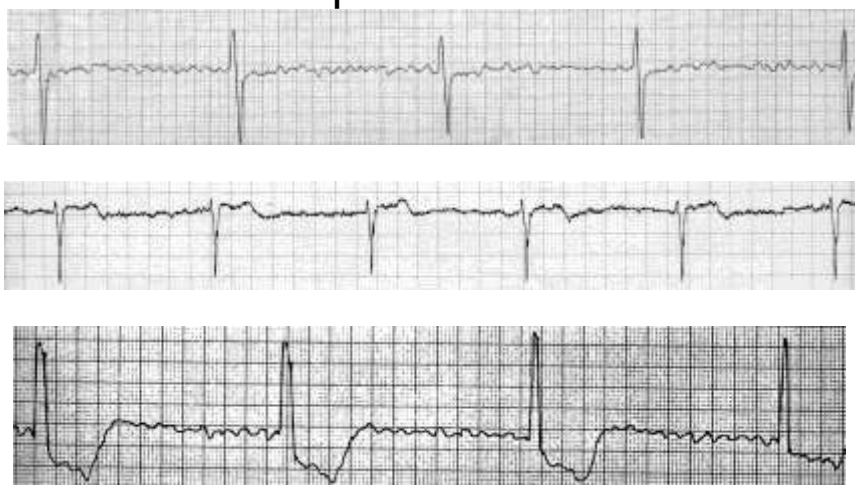
- EKG Changes with Toxicity
  - Increased automaticity with impaired conduction is common
    - Re-entrant tachycardias
    - Paroxysmal atrial tachycardia with AV Block
    - Heart block
- GI Symptoms with Toxicity
  - N & V (most frequent 1st sign)
  - Anorexia
- Neurologic Symptoms with Toxicity
  - Headache
  - Confusion
  - Visual disturbances: halos, change in color perception

Digoxin use associated with increased mortality in AFFIRM (? arrhythmia related); in DIG trial mortality was increased for level > 0.9 ng/mL, in an AFFIRM sub group analysis no increase mortality in those with digoxin as baseline therapy.

2019 186

186

Atrial Fibrillation with Complete Heart Block



2019 187

187

Additional Rate Control Information

RACE II

- Strict versus lenient rate control
- Strict
  - Resting HR < 80
  - Exercise < 110
- Lenient
  - Resting HR < 110
- No benefit of strict rate control

- Note: Study population did not include a high percentage of patients with heart failure.

2019 188

188

Atrial Fibrillation 2011 Focused Update

ACCF/AHA/ al Fib Guidelines

Class III Rec n:

Treatment to achieve ol of heart rate (<80 bpm at rest or <110 bp -minute walk) is not beneficial compared t esting heart rate <110 bpm in patients wit have stable ventricular functi tion fraction >0.40) and no or accep toms the arrhythmia, though uncontro ycardia time be associated with a reversible dec e in ventricu performance *(Level of Evidence: B)*

2014 189

189

2014 Guideline Update

A randomized trial suggested that a lenient (<110 bpm) rate control strategy was as effective as a strict strategy (<80 bpm) in patients with persistent/permanent AF. However, the writing committee still advocates for the latter (Class IIa), as the results of this single trial were not thought to be definitive.

Resting HR < 80 bpm reasonable in patients who are symptomatic.
Assess HR during exercise.

Resting HR < 110 bpm may be considered in asymptomatic patients with preserved EF.

2014 190

190

Case Example

- 84 year old male patient with history of severe spinal stenosis presents to ED with light headedness and is found to be in atrial fibrillation with HR in 110 at rest. He was recently discharged after a NSTEMI for which he received an intracoronary stent. His most recent echo revealed a LVEF of 30%. He is on carvedilol 6.25 mg BID, lisinopril 10 mg daily, ASA 81 mg, clopidogrel 75 mg daily, and atorvastatin 40 mg daily.
- **You are seeing in consult.**
- **Rate or rhythm control?**
- **Options for agents?**
- **Will you anticoagulated? See the poll question.**

191

Live Content Slide

When playing as a slideshow, this slide will display live content

Poll: Would you anticoagulate this 84 year old patient with a history of recent nonSTEMI with DES to the LAD, reduced LVEF, and severe spinal stenosis who presents to ED with symptomatic new onset atrial fibrillation with a HR of 110.

192

Welcome Back!
Let's have a great afternoon.

193

2019 Guideline Update

ANTICOAGULATION IN ATRIAL FIBRILLATION

194

Class I

For patients with AF and an elevated CHA_2DS_2-VASc score of 2 or greater in men or 3 or greater in women, oral anticoagulants are recommended.

- **Warfarin (LOE: A)**
- **Dabigatran (LOE: B)**
- **Rivaroxaban (LOE: B)**
- **Apixaban (LOE: B) or**
- **Edoxaban (LOE: B-R)**

195

Class I A

- **NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin in NOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve).**
- **Among patients treated with warfarin, the international normalized ratio (INR) should be determined at least weekly during initiation of anticoagulant therapy and at least monthly when anticoagulation (INR in range) is stable.**

196

Class I

Selection of anticoagulant therapy should be based on the risk of thromboembolism, irrespective of whether the AF pattern is paroxysmal, persistent, or permanent.

For patients with atrial flutter, anticoagulant therapy is recommended according to the same risk profile used for AF.

Reevaluation of the need for and choice of anticoagulant therapy at periodic intervals is recommended to reassess stroke and bleeding risks.

2019 197

197

Class I

For patients with AF who have mechanical heart valves, warfarin is recommended.

Renal function and hepatic function should be evaluated before initiation of a NOAC and should be reevaluated at least annually.

For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) who are unable to maintain a therapeutic INR level with warfarin, use of a NOAC is recommended.

2019 198

198

Class II a

For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and a CHA_2DS_2-VASc score of 0 in men or 1 in women, it is reasonable to omit anticoagulant therapy.

2019 199

199

Considerations with Renal Dysunction	**For patients with AF who have a CHA_2DS_2-VASc score of 2 or greater in men or 3 or greater in women and who have end-stage chronic kidney disease (CKD; creatinine clearance [CrCl] <15 mL/min) or are on dialysis, it might be reasonable to prescribe warfarin (INR 2.0 to 3.0) or apixaban for oral anticoagulation.**	**For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve) and moderate-to-severe CKD (serum creatinine ≥1.5 mg/dL [apixaban], CrCl 15 to 30 mL/min [dabigatran], CrCl ≤50 mL/min [rivaroxaban], or CrCl 15 to 50 mL/min [edoxaban]) with an elevated CHA_2DS_2-VASc score, treatment with reduced doses of direct thrombin or factor Xa inhibitors may be considered (e.g., dabigatran, rivaroxaban, apixaban, or edoxaban).**

200

200

Class III

- **In patients with AF and end-stage CKD or on dialysis, the direct thrombin inhibitor dabigatran or the factor Xa inhibitors rivaroxaban or edoxaban are not recommended because of the lack of evidence from clinical trials that benefit exceeds risk.**
- **The direct thrombin inhibitor dabigatran should not be used in patients with AF and a mechanical heart valve.**

2019 201

201

Bridging

- **Bridging therapy with unfractionated heparin or low-molecular-weight heparin is recommended for patients with AF and a <u>mechanical heart valve</u> undergoing procedures that require interruption of warfarin. Decisions on bridging therapy should balance the risks of stroke and bleeding.**
- For patients with AF <u>without</u> mechanical heart valves who require interruption of warfarin for procedures, decisions about bridging therapy (unfractionated heparin or low-molecular-weight heparin) should balance the risks of stroke and bleeding and the duration of time a patient will not be anticoagulated.

2019 202

202

Triple Therapy

- Clopidogrel preferred over prasugrel in triple therapy
- For patients on triple therapy a transition to double therapy at 4 to 6 weeks is reasonable
- Double therapy with clopidogrel and dabigatran 150 mg BID is reasonable over triple therapy
- Double therapy with clopidogrel or ticagrelor and warfarin is reasonable over triple therapy
- Double therapy with clopidogrel and 15 mg rivaroxaban daily is reasonable over triple therapy

203

Preventing Thromboembolism

- Warfarin established as gold standard for nonvalvular AF
  - Eliminates excess rates of ischemic stroke, reduces stroke severity and reduces post stroke mortality
  - Target INR of 2.0-3.0 for Atrial Fibrillation
  - Superior to ASA and ASA plus clopidogrel

Dosing post mechanical valve

- 2.0-3.0 or 2.5 to 3.5 based on individual valve
- New On- X Aortic Valve INR goal 1.5 -2.0

Dosing for Thromboembolism

- 2.0-3.0

204

Warfarin

- Vitamin K antagonist
- Synthesis of vitamin K-dependent coagulation factors II, VII, IX, and X and anticoagulant proteins C and S is inhibited.
- Onset of action 24-72 hours
- Peak effect: 5-7 days
- MANY, MANY, MANY drugs, foods and beverages alter the impact of coumadin.
- Binge drinking increases PT/INR
- Chronic daily alcohol use decreases PT/INR.
- Vitamin K rich foods may decrease PT/INR
- Maintain a CONSISTENT diet.

205

New Oral Anticoagulants (NOACS)

Generic	Trade Name	Class	Dosing for Atrial Fibrillation
Dabigatran	Pradaxa	Direct thrombin inhibitor	▪150 mg PO BID ▪75 mg PO BID with Cr. Cl. 15 to 30 mL/minute
Rivaroxaban	Xarelto	Factor Xa inhibitor	Dose 20 mg PO daily
Abixaban	Eliquis	Factor Xa inhibitor	▪ Dose: 5 mg BID ▪ Dose: 2.5 mg BID (≥2 of the following) Creatinine > 1.5 mg/dL Age ≥ 80 years Weight ≤ 60 kg
Edoxaban	Savaysa	Factor Xa inhibitor	60 mg daily for Cr. Cl. > 50 to ≤ 95 30 mg daily for Cr. Cl. 15 to 50 **Contraindicated** if Cr. Cl >95 mL/Min

206

NOACS

Generic	Peak Plasma Level	Elimination Half-life	Clearance
Dabigatran	1.5 hrs	12-18 hours	Mostly by kidneys
Rivaroxaban	3 hrs	5-9 hours (> 75 years old up 11-13 hours)	Hepatic and renal excretion
Apixaban	Rapid absorption	8-15 hours	25% cleared by the kidneys
Edoxaban	1-2 hrs	10-14 hours	~50% cleared by kidneys Concern with normal renal function

2019 207

207

Drug	A Fib Study	Highlights: Note – all studies tested for primary endpoint of stroke (ischemic and hemorrhagic) and systemic embolism
Dabigatran	RE-LY trial (Connolly et al, 2009)	●150 mg BID superior to warfarin (p< 0.001) (stroke / systemic embolism) ●Ischemic stroke and hemorrhagic stroke both lower Rate of major bleeding same (potential concern for GI bleeding) ● Did not test approved 75 mg dose ● 32 to 33 % of patients with CHADS2 score ≥ 3
Rivaroxaban	ROCKET AF (Patel et al., 2011)	● Non-inferiority of rivaroxaban (P<0.001) (stroke / systemic embolism) ● No significant difference in the risk of major bleeding, intracranial and fatal bleeding occurred less frequently in the rivaroxaban group ● 86 to 87% of patients had CHADS2 score ≥ 3
Apixaban	ARISTOTLE (Granger et al., 2011.)	● Primary objective: Found to be non inferior to warfarin (p = <0.001) ● Secondary objective: Found to be superior to warfarn (p= 0.01) ● Major bleeding: Statistically less with apixaban (p<0.001) ● Interesting: No statistical difference in ischemic stroke.
Edoxaban	ENGAGE AF-TIMI 48	● Non-inferior to warfarin (P = < 0.001) for high dose and (P = 0.005) for low dose ● Significantly lower rates of bleeding & CV death compared to warfarin at both doses (Not less GI bleeding)

2019 208

208

Hold Times for Newer Oral Agents

	Surgery with high risk for bleeding (i.e. CABG)		Surgery Low Bleeding Risk	
Dabigatran	▪ 3 to 5 days. ▪ For urgent cases until clotting times are normal or until four half-lives has passed ▪ Hold times for surgery are dependent on renal function ▪ DO NOT USE INR. Can be falsely elevated		Minimum hold time for low risk surgery and normal renal function is ≥ 24 hours	
Rivaroxaban / Apixaban	Renal impairment Cr. Cl.: ≥ 50 = 3 days Cr. Cl. < 50 = 4 days	Liver impairment Mild: 2 days Mod: At least 4 days Severe: At least 7 days	Renal impairment Cr. Cl.: ≥ 50 = 1 days Cr. Cl. < 50 = 3 days	Liver impairment Mild: 1 day Mod: At least 2 days Severe: At least 5 days
Edoxaban	Not specifically addressed in product information.		Minimum hold time of at least 24 hours	

209

Assessment of Bleeding

	Assessment of Bleeding Risk
Dabigatran	▪ Bleeding risk can be assessed by an ecarin clotting time if available ▪ If not available, a PTT can be assessed to determine clearance of the drug because dabigatran has been shown to prolong aPTT (aPTT not used for quantitative assessment) ▪ > 2.5 x upper normal limit 12 to 24 hours after drug may be indicative of high risk for bleeding ▪ Thrombin time is most sensitive test. Diluted thrombin time (DTT) is a quantitative test (calibrated Hemoclot®)
Rivaroxaban Apixaban Edoxaban	• PT may provide qualitative assessment of presence of factor Xa; not sensitive for quantitative anticoagulation effect • Point of care INR should not be used to gauge anticoagulation effects • Chromogenic assay can provide quantitative assessment – not widely available, not fully studied, not recommended at this time

210

Antidotes

Dabigatran	Factor Xa Inhibitors
• Praxbind® (idarucizumab) • FDA Approved 10/19/2015 • Specific Reversal Agent for Pradaxa® (dabigatran etexilate) • IV administration • 2.5 Grams IV over 5-10 minutes • Follow with 2nd dose no longer than 15 minutes	• Andexanet alfa (AndexXa®) • Universal reversal agent for factor Xa inhibitors • FDA DID NOT approve August 2016 • Resubmitted August 2017 • Approved May 3, 2018 • Limited release in 2018 • Expand release in 2019

2019 211

211

Antidotes

Dabigatran	Factor Xa Inhibitors
• **Idarucizumab is recommended for the reversal of dabigatran in the event of life-threatening bleeding or an urgent procedure.**	• **Andexanet alfa can be useful for the reversal of rivaroxaban and apixaban in the event of life-threatening or uncontrolled bleeding.**

2019 212

212

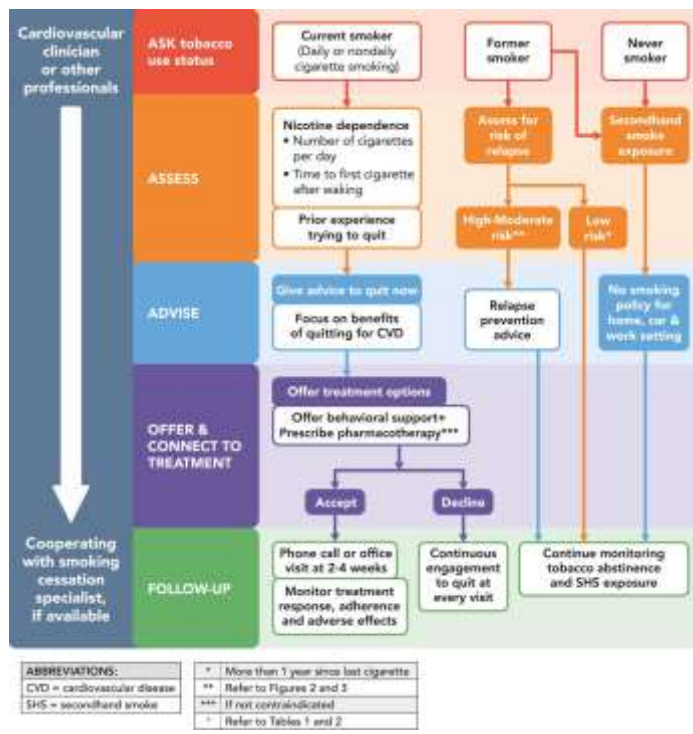
Tobacco Cessation Treatment

December 2018

ACC Expert Consensus Decision Pathway

Barua, R. S., Rigotti, N. A., Benowitz, N. L., Cummings, K. M., Jazayeri, M. A., Morris, P. B., ... & Wiggins, B. S. (2018). 2018 ACC Expert Consensus Decision Pathway on Tobacco Cessation Treatment: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *Journal of the American College of Cardiology*, *72*(25), 3332-3365.

213



214

Offer Treatment

Pharmacotherapy	Behavioral Support
• Offer to all • May be able to start in patients not yet ready to quit – ↑ chance of moving to readiness • Write prescription even if OTC medication	• More effective than pharmacotherapy alone • Tobacco cessation program • Telephone Quitline – 1-800-QUIT-NOW • Smokefree.gov – National Cancer Institute – Online Programs – apps • Becomeanes.org – Support from experts an online community

215

Pharmacotherapy

- Nicotine Replacement Therapy (NRT)
  - Provides nicotine to reduce withdrawal symptoms
- Bupropion
  - Principal mode of action is on withdrawal symptoms following smoking cessation
  - Mimics nicotinic effects on dopamine and noradrenaline
- Varenicline
  - Partial agonist at the a4b2 nicotinic cholinergic receptor that mediates brain dopamine release
  - Activates the nicotine receptor, producing about 50% of the maximal effects as nicotine effects
  - Reduces the intensity of nicotine withdrawal symptoms
  - Binds to the nicotine receptor, preventing receptor binding by nicotine from cigarette smoke and reducing the rewarding effects of smoking.

216

Nicotine Replacement Therapy

Patches

✓ OTC availability

Continuous Dose Patch: Provides steady dose throughout day.	
Dosages No Renal or Hepatic Adjustments	21 mg : ≥ 10 cigarettes per day 14 mg: < 10 cigarettes per day 7 mg 21 mg x 6 weeks ➡ 14 mg x 2 weeks ➡ 7mg x 2 weeks. 14 mg x 6 weeks ➡ 7mg x 2 weeks Adjust dose up (experiencing withdrawal) or down (side effects) initially
Therapy	Apply one daily. Wear for 16-24 hours. If nicotine craving on arising wear 24 hours. If sleep disturbances occur remove patch at bedtime.
Combination Therapy	May be used in combination with bupropion 2 forms of NRT (continuous + bolus) encouraged
Use in CV Patients	A meta-analysis of NRT studies found: increase in CV symptoms (tachycardia and arrhythmia) which is expected from the sympathomimetic effects of nicotine, but no increase in major CV events (death, myocardial infarction, stroke).
Contraindications	Not indicated for those who smoke < 10 cigarettes per day, pregnant women, adolescents, or users of smokeless tobacco.
Special Considerations 2019	Apply to area of skin on upper body or outer arm. Rotate sites. Nonhairy, clean, dry skin. The patch cannot be cut. Should be folded - sticky sides together and placed in original pouch before disposal. Remove prior to MRI.

Sources: Barua et al. 2018, Lexicom 2019, Lande, 2012; Fiore et al., 2008.

217

Nicotine Replacement Therapy

Intermittent Dose: Provides bolus dosing for situation cravings.	
Dosages No Renal or Hepatic Adjustments	**Lozenges 4 mg or 2 mg ; Gum 4 mg or 2 mg** ✓ OTC availability - 4 mg if first cigarette is within 30 minutes of awakening - 2 mg if > 30 minutes after awakening. - Gum: Max 24 per day. Lozenges: Max 20/day **Nicotine Inhaler 10 mg cartridge** ~ 80 puffs / cartridge Ø OTC availability -Puff until cravings disappear – max 16 cartridges /day - Discontinue if unable to stop after 4 weeks of therapy **Nicotine Nasal Spray 10 mg/ml.** 0.5 mg/spray ~ 200 sprays / bottle - 1-2 doses/hour (Dose= 1 spray each nostril) – delivers 1mg of nicotine - Do not exceed 10 sprays per hour. Maximum dose 40mg/day (80 sprays) - Use beyond 6 months not recommended
Combination Therapy	May be used in combination with bupropion 2 forms of NRT (continuous + bolus) encouraged
Contraindications	Not indicated for those who smoke < 10 cigarettes per day, pregnant women, adolescents, or users of smokeless tobacco.
Special Considerations 2019	Lozenges: No food or drink 15 minutes prior to use – decreased effectiveness. Nasal Spray: Has most side effects of all NRT including local irritation Nicotine Inhaler: Mimics hand t mouth ritual of smoking

Sources: Barua et al. 2018, Lexicom 2019, Lande, 2012; Fiore et al., 2008.

218

Nicotine Replacement Therapy in Patients with CVD

Nicotine potentially contributes to worsening of CVD through its sympathomimetic properties

- Constriction of diseased coronary arteries
- Promoting coronary spasm
- Proatherogenic lipid profiles
- Insulin resistance
- Proarrhythmic effects.
- Endothelial dysfunction
- Myocardial fibrosis

However:

1. Nicotine levels from NRT generally much lower than those from cigarette smoking
2. NRT does not expose users to combustion products in cigarette smoke that are involved in CVD pathogenesis.

219

Bupropion

Ø OTC availability	
Dosages	Start 1-2 weeks prior to smoking cessation. Sustained release form is used. Start 150mg once a day x 3 days and then increase to BID.
Duration of therapy	Pick cessation date during second week of therapy. Usually 7 to 12 weeks; discontinue if cessation has not occurred by 7-12. Can carry to 6 months to 1 year- especially if history of relapse.
Use in combination therapy	May be used with NRT
Use in cardiovascular patients	Efficacious in smokers with stable CVD. No demonstrated efficacy in smokers hospitalized with ACS. Start post hospital stay.
Contraindications	Seizure disorders, bulimia or anorexia nervosa, use of MAO inhibitors, active process of discontinuing alcohol or sedative use. Antidepressants can increase risk of suicidal thoughts – careful consideration! NO increase in the risk of suicidal thoughts and behavior with antidepressant use in subjects aged 65 and older.
Special Considerations	Use with caution in renal impairment and hepatic impairment (higher doses)

Sources: Barua et al. 2018, Lexicom 2019, Lande, 2012; Fiore et al., 2008.

220

Varenicline (Chantix)

Ø OTC availability

Dosages	Day 1 to 3: 0.5 mg daily Day 4 to 7: 0.5 mg BID Day 8+: 1mg BID CrCl < 30 mL/minute: Max dose 0.5 mg BID No Hepatic Adjustments
Duration of therapy	Quit date can be flexible 1-4 weeks after stat date. Prescribed for a minimum of 12 weeks. For patients who have successfully stopped smoking after 12 weeks, an additional 12 weeks is considered to improve the chance of continued cessation.
Combination therapy	Can be used with NRT.
Use in cardiovascular patients	More effective than placebo in smokers with stable CVD. Use with caution in ACS. Most recent trials demonstrate no increased CV risk with varenicline. **EVITA Trail:** 12 weeks of varenicline initiated in hospitalized patients with ACS produced significantly greater smoking cessation rates compared with placebo—a finding that persisted for 52 weeks . 2016: FDA removed black box warning regarding increased neuropsychiatric effects of varenicline. (EAGLES Trial: > 8,000 smokers. There was no evidence of more frequent neuropsychiatric side effects with varenicline than with NRT or placebo.
Contraindications	Alcohol may enhance toxic effects of alcohol and nicotine.
Special Considerations	The most common side effect is nausea. Starting at a low dose and titrating up, taking after eating, and taking with a full glass of water can decrease nausea.

2019

221

Varenicline

- Proven to be more effective in promoting smoking cessation than single NRT or bupropion in several clinical trials

2019 222

222

Hospitalized Smokers

- Admission to the smoke-free environment of a hospital requires temporary tobacco abstinence and provides an opportunity to receive assistance and initiate a quit attempt
- Initiation of smoking cessation counseling in the hospital with follow up for at least 1 month increases long-term quit rates by 37%

2019 223

223

Joint Commission 3-item Tobacco Quality Measure Set for U.S. Hospitals

1. TOB-1: Assess tobacco use status of all admitted patients.
2. TOB-2: Offer tobacco cessation treatment in the hospital to all current smokers.
3. TOB-3: Offer tobacco cessation treatment at hospital discharge.

2019 224

224

Expert Consensus Decision Pathway Key Points

1. Tobacco use, especially cigarette smoking, is a major risk factor for CVD–associated morbidity and mortality
2. Cigarette smoking is a chronic relapsing substance use disorder caused by addiction to nicotine.
3. Current evidence strongly supports combining pharmacotherapy with behavioral/psychosocial interventions as the most effective way to help smokers sustain abstinence.
4. Provider and system barriers in implementing and sustaining smoking cessation treatment need to be recognized and addressed to improve the smoking cessation care in the clinical setting

2019 225

225

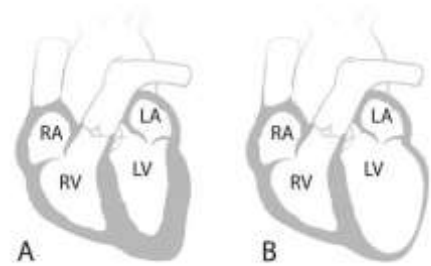
PHARMACOLOGY IN HEART FAILURE

2019 226

226

HFrEF - Systolic Dysfunction

- 40 to 50% of HF Population
- **Hallmark:** Decreased LV Ejection Fraction ≤ 40%
  - Impaired wall motion and ejection; dilated chamber
- Coronary artery disease is cause in 2/3 of patients
- Remainder: Other causes of LV dysfunction/cardiomyopathy



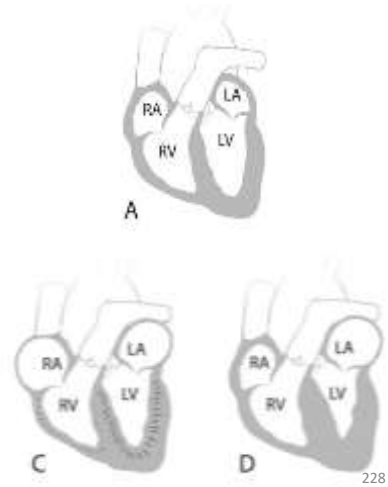
Note: Cardiomyopathy can exist without the clinical syndrome of HF.

2019 227

227

HFpEF - Diastolic Dysfunction

- 50% of the population
- Filling impairment
  - Normal chamber size
  - Normal or increased LVEF
- Caused by
  - **Hypertension**
  - **Ischemic heart disease**
  - **Obesity**
  - Valve disease
  - Restrictive myopathy (C)
  - Ventricular hypertrophy (D)
  - Idiopathic



Often seen in elderly women with HTN

2019 228

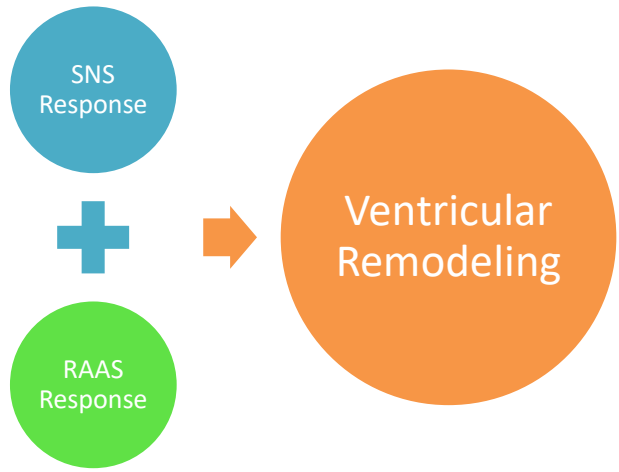
228

Comparison of ACCF/AHA Stages of HF and NYHA Functional Classifications			
ACCF/AHA Stages of HF		NYHA Functional Classification	
A	At high risk for HF but without structural heart disease or symptoms of heart failure	None	
B	Structural heart disease but without signs or symptoms of HF	I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF.
C	Structural heart disease with prior or current symptoms of HF	II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF.
		III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF.
D	Refractory HF requiring specialized interventions	IV	Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.

2019 229

229

The Real Culprit: Neurohormonal Response



2019 230

230

Activation of SNS

- First Responder
  - Decreased cardiac output (CO) → ↓ BP → activates baroreceptors and vasomotor regulatory centers in medulla
- Increase circulating catecholamines
  - Stimulates alpha1 and beta receptors
    - Increased HR
    - Peripheral vasoconstriction
    - Increased contractility

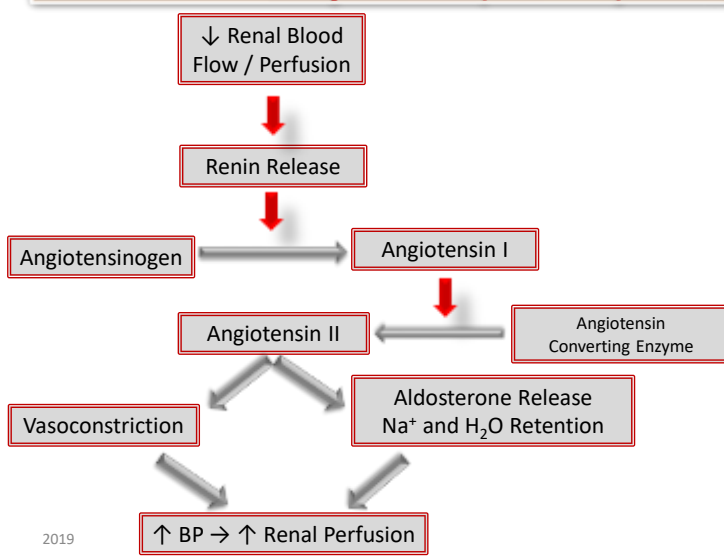
Positive effect: ↑ CO and BP

Negative effect: ↑ O_2 demand → ischemia, arrhythmias, sudden death

2019 231

231

Renin-Angiotensin Aldosterone System (RAAS)



2019 232

232

Beta Blockers

- **Point 1: Why do we use them when they decrease contractility?**
  - Inhibits adverse effects of SNS activation
    - Decrease myocardial oxygen consumption
      - Decreases HR
      - Decreases contractility (however, benefit outweighs)
  - Inhibits ventricular remodeling and apoptosis
  - Slows disease progression
  - Can improve LVEF
  - Decreases mortality/hospitalization
  - Reduce symptoms, improve clinical status, and enhance the patient's overall sense of well-being

2019 233

233

Evidence Based Beta Blocker

- **Cannot assume class effect**
- **Bisoprolol – β1**
  - CIBIS III randomized trial – 2005 (enalapril)
- **Metoprolol succinate - β1**
  - MERIT-HF randomized trial – 1999 (placebo)
- **Carvedilol - β1, β2, α1 (Noncardioselective)**
  - CAPRICORN randomized trial – 2001 (placebo)
  - COMET randomized trial – 2003 (metoprolol tartrate)

2019 234

234

Beta Blocker

- Hypotension
  - Consider administration opposite of ACE-I or decrease in diuretic dose
- Erectile Dysfunction
  - May be less prevalent with carvedilol

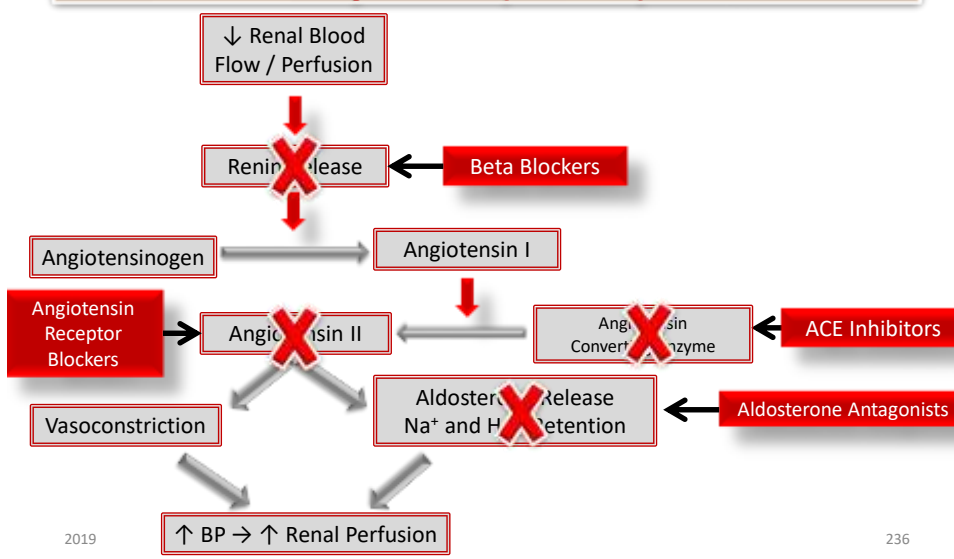
NURSING PRACTICE CONSIDERATION: Educate patients regarding initial expectation of fatigue.

PEARL: Fatigue may be multifactorial – address over diuresis, sleep apnea and screen for depression

2019 235

235

Renin-Angiotensin Aldosterone System (RAAS)



2019 236

236

ACE Inhibitors and Angiotensin II Receptor Blockers

- Angiotensin-converting enzyme inhibitors ("pril" medications)
  - Benazepril, captopril, enalapril, fosinopril, lisinopril, perindopril, quinapril, ramipril,, trandolapril
- Angiotensin II Receptor Blockers ("sartan" medications)
  - Candesartan, eprosartan, irbesartan, losartan, telmisartan, valsartan,

ACE I and ARB are considered to have a class effect.

2019 237

237

A Closer Look at ACE Inhibitors / ARBs

ACE Inhibitors impact preload and afterload

Reduce Preload	Reduce Afterload
• Prevents venous vasoconstriction • Inhibiting release of aldosterone	• Reduces workload of LV • Decreases systemic vascular resistance without reflex stimulation of heart rate and contractility

238

238

A Closer Look at ACE-Is / ARBs

- Overall cardioprotective, vasculoprotective effect, and renal protective
  - Prevents ventricular remodeling
  - Reduce mortality in patients with systolic heart failure
  - Reduction of left ventricular mass in LV hypertrophy
  - Slows progression of both renal disease in diabetes and hypertensive nephrosclerosis

239

239

Cough in ACE-I

- Increases bradykinin release and can produce cough
  - Release of bradykinin causes constriction of non-vascular smooth muscle in bronchus
  - Cough is side effect in 10-20% of patients
- Need to assure cough is not sign of worsening heart failure
- Patient should be changed to an angiotensin receptor blocker (ARB) if unable to tolerate cough

If ACE Inhibitors are contraindicated due to renal function, blood pressure or potassium so are ARBs.

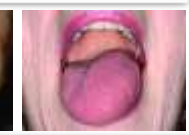
2019 240

240

ACE Inhibitor and Angioedema

- Secondary to excessive accumulation of bradykinin
- Occurs in 0.7% of treated patients
- Likely genetic – non histamine angioedema
- Usually soon after administration but could occur after years of use
- African Americans have a 4-5x greater risk
- Women have a 2x higher risk than men
- Class effect reaction:
  - Absolute contraindication to further ACE I use

Bradykinin Facts:
- 9-Amino Acid Peptic Chain
- Causes vasodilation
- Causes naturesis
- Broken down by angiotensin converting enzyme
- Therefore:
  ACE I ↑ release of bradykinin

Treatment:
- Stop ACE I
- Antihistamines / corticosteroids usually not effective
- Epinephrine only if there is airway compromise
- FFP 2-4 units – suppresses bradykinin inhibits edema progression
- Ecallantide- suppresses bradykinin generation
- Icatibant - bradykinin B2 receptor antagonist

Difference from "normal" allergic reactions
- No allergic trigger
- Starts with focal swelling
- Slower progression
- Absence of uticaria or itching

241

Angiotensin Receptor Blockers Angioedema

- No absolute contraindication to ARB in patient with angioedema from ACE I
  - ACC/AHA/HFSA Guideline Update - ARB to be used in place of ACE I when there has been cough or angioedema with ACE I (Yancy et al. *Circulation*. 2016;134)
- Risk of angioedema with ARB is low
  - Rate of angioedema in ARB population the same as placebo group[1]
  - Rate of angioedema highest in ACE I group when comparing patients on ARB, betablocker and ACE I
    - Equal rate of angioedema between beta blocker and ARB groups[2]
- In patients with history of angioedema with ACE I
  - 4-10% of patients who developed angioedema with ACE I have developed angioedema with ARB[3,4]
  - Sample sizes are small

1. Makani H et al. Am J Cardiol 2012
2. Toh S et al. Arch Intern Med 2012
3. Haymore et al. Ann Allergy Asthma Immunol 2009
4. Beavers, C. J. et al . *Annals of Pharmacotherapy*, 2012

242

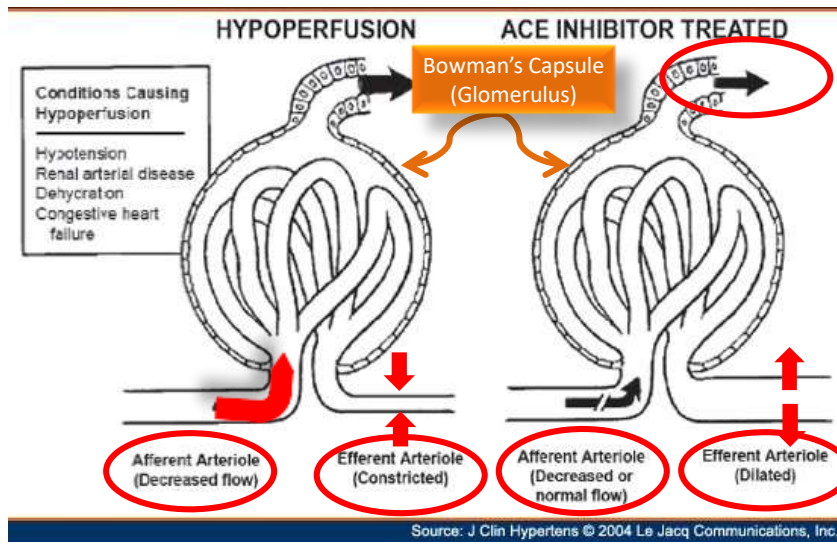
ACE Inhibitors / ARBs and Renal Function: Sorting Out the Confusion

- Renal protective in CHRONIC kidney disease (CKD)
  - – ↓ intraarterial hypertension protecting kidneys from hyperfiltration which can cause glomerular injury
- However, can cause ACUTE kidney injury (AKI) in patient's at risk (i.e. low stroke volume) due to preventing the compensatory mechanism of efferent vasoconstriction
  - – When there is decreased blood flow into the glomerulus via the afferent arterioles, the efferent arterioles constrict to raise glomerular filtration pressure on the back end
  - – ACE-I prevent efferent vasoconstriction

243

243

ACE Inhibitors / ARBs and GFR

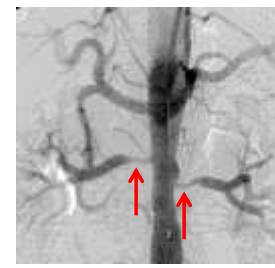


244

ACE Inhibitors/ARBs and Renal Function: Implications for Bilateral Renal Artery Stenosis

ACE inhibitors /ARBs will cause acute renal failure in the presence of bilateral renal artery stenosis (BRAS)

- In BRAS: Fixed flow into the glomerulus via the afferent arterioles
  - an improvement in stroke volume will not improve flow into the glomerulus
- Dilation of efferent arterioles with no ability to improve blood flow through the afferent arterioles → decreased glomerular filtration
- Use of an ACE inhibitor/ARB prevents the normal compensatory response of efferent vasoconstriction



A ↓ in GFR >30% - consider renal artery stenosis as a possibility
(National Kidney Foundation)

245

ACE Inhibitors /ARBs and Renal Function

- Creatinine can be allowed to be 35% above baseline without stopping the drug.
  - As forward flow to the glomerulus improves there is less need for efferent vasoconstriction to compensate and glomerular filtration will stabilize

Note difference between AKI and CKD

- **AKI: Hold regardless of creatinine**
- **CKD: May give until creatinine of ≥ 3.0**

ESRD: ACE Inhibition ok . SBP most often limiting factor. Need reasonable SBP for dialysis.

2019 246

246

ACE Inhibitor / ARB Monitoring and Contraindications

- Assess renal function and potassium within 1 to 2 weeks of initiation if outpatient
- High risk features for AKI
  - Hypotension
  - Azotemia
  - Diabetes
  - Hyponatremia
- High risk features for hyperkalemia
  - Potassium supplementation in combination with aldosterone antagonist.
- Monitor BP

Contraindications

- Bilateral renal artery stenosis
- Creatinine > 3 mg /dL in CKD
- AKI (until resolved)
- Potassium > 5.0 mEq/L
- Systolic BP < 80 mmHg

May consider holding short term in patients at high risk for AKI.

2019 247

247

Angiotensin Receptor Blockers End in "SARTAN"

- Directly blocks angiotensin II after its formation
- ACE Inhibitors remain the first choice for inhibition of RAAS
- ARB's are a reasonable alternative to ACE Inhibitor if intolerant to ACE Inhibitor due to cough
- Reasonable alternative to ACE I as 1st line therapy for patients with mild / moderate HF & reduced LVEF, especially if already take ARB for other reason (HTN)
- **Combination of ACE I and ARB – not routinely recommended** (ACCF/AHA HF 2013 Guidelines Class III)
- **Combination of ACE I, ARB and Aldosterone Antagonist may cause harm.** (ACCF/AHA HF 2013 Guidelines Class III)

2019 248

248

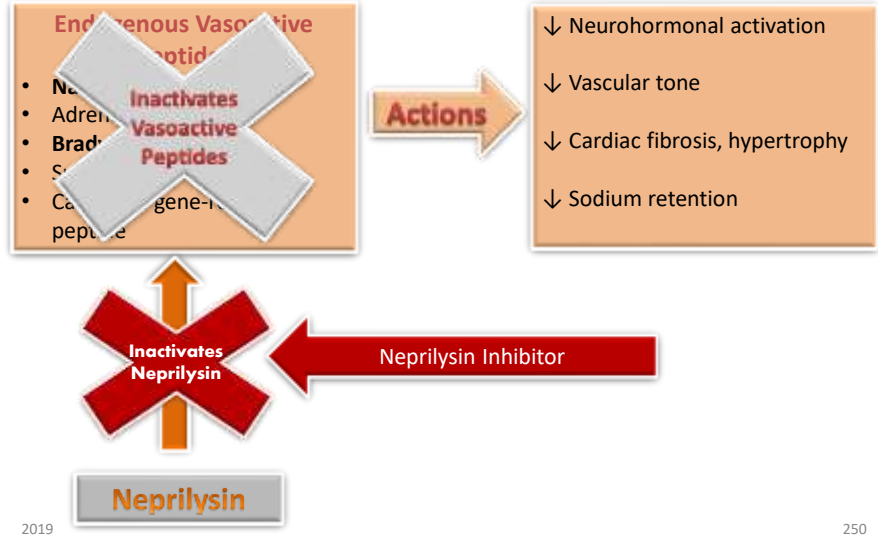
ENTRESTO

- **New class of medication: ARNI**
  - ***A*ngiotensin *R*eceptor Blocker with *N*eprilysin *I*nhibitor**
- **Combo drug: sacubitril (Neprilysin Inhibitor) with valsartan (ARB)**
- **PARADIGM-HF Trial**
- Multinational, randomized, double-blind trial
- Comparing ENTRESTO with enalapril
- 8,442 adult patients with symptomatic chronic heart failure (NYHA class II–IV) and systolic dysfunction (left ventricular ejection fraction ≤40%).
- Results:
  - 20% reduction in the rate of death or hospitalization for heart failure
  - 16% reduction in the rate of all-cause death compared to enalapril at 3.5 years of follow-up.

2019 249

249

Neprilysin Inhibition



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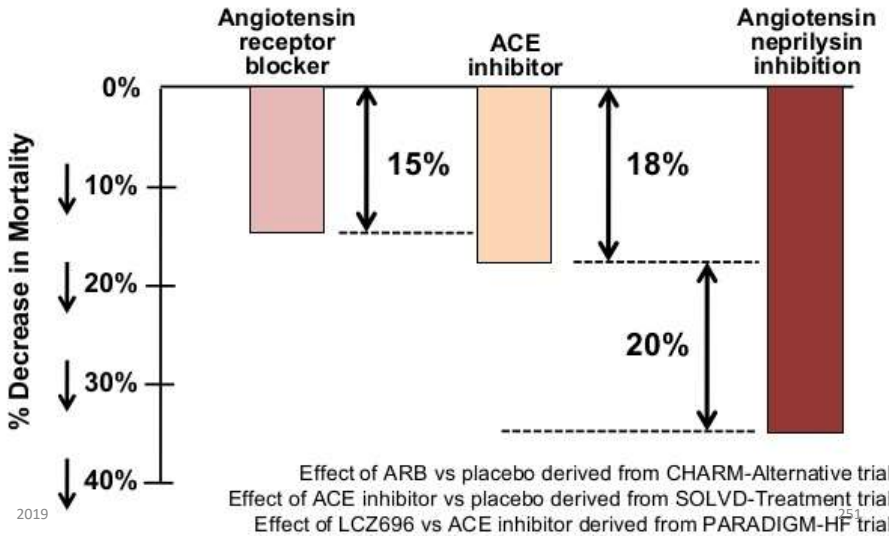
250

Angiotensin Neprilysin Inhibition With LCZ696 Doubles Effect on Cardiovascular Death of Current Inhibitors of the Renin-Angiotensin System



251

Entresto Dosing

Valsartan in Entresto is more bioavailable in Entresto than valsartan alone.

Dosing equivalents:

Valsartan In Entresto = Valsartan alone

26 mg in Entresto = 40 mg alone
51 mg in Entresto = 80 mg alone
103 mg in Entresto = 160 mg alone

Tiered Dosing:

Sacubitril /Valsartan (Paradigm HF listed doses)
24 mg / 26 mg (50 mg)
49 mg / 51 mg (100 mg)
97 mg / 103 mg (200 mg)

2019 252

252

Entresto

- Do not administer with ACE I
  - Increased risk of angioedema
  - Stop ACE I for 36 hours before starting Entresto
  - Do not administer in patients with history of angioedema
- Monitor kidney function, blood pressure and potassium levels
- BNP levels will not be accurate with Entresto but pro-BNP levels may be used

253

Side Effect Profile

Entresto	Enalapril
• Hypotension 18% • Hyperkalemia 12% • Cough 9% • Dizziness 6% • Renal failure/AKI 5%	• Hypotension 12% • Hyperkalemia 14% • Cough 13% • Dizziness 5% • Renal failure/AKI 5%

Practice Pearls!

254

ACC/AHA/HFSA Guideline Update

Recommendations for RAS Inhibition with ACE I or ARB or ARNI (Stage C HFrEF)

COR	LOE	Recommendations
I	ACE I: A	Inhibition of the RAS with ACE I OR ARB OR ARNI in conjunction with evidence-based betablocker, and aldosterone antagonist in selected patients, is recommended for patients with chronic HFrEF to ↓ mortality and morbidity.
	ARB: A	
	ARNI: B-R	

COR= Class of Recommendation (strength); green is recommended (Strong)
LOE = Level of Evidence (Quality); A = high quality evidence; B = moderated quality evidence; R = randomized

Yancy C, et al. *Circulation*. 2016
Yancy C, et al. *Circulation. 2017*

2019 255

255

ACC/AHA/HFSA Guideline Update

Recommendations for RAS Inhibition with ACE I or ARB or ARNI (Stage C HFrEF)

COR	LOE	Recommendations
I	ACE I: A	Use of ACE I is beneficial for patients with prior or current symptoms of chronic HF*r*EF to ↓ morbidity and mortality
	ARB: A	The use of ARB to ↓ morbidity and mortality is recommended in patients with prior or current symptoms of chronic HF*r*EF who are *intolerant to ACE inhibitors because of cough or angioedema*
	ARNI: B-R	In patients with chronic symptomatic HF*r*EF NYHA class II or III who tolerate an ACE I or ARB, replacement by ARNI is recommended to **further ↓ morbidity and mortality**

COR= Class of Recommendation (strength); green is recommended (Strong)
LOE = Level of Evidence (Quality); A = high quality evidence; B = moderated quality evidence; R = randomized

Yancy C, et al. *Circulation*. 2016
Yancy C, et al. *Circulation. 2017*

2019 256

256

Aldosterone Antagonists
Mineralocorticoid Receptor Antagonist (MRA)

Diuretic effect is not primary reason for administration.

ACC/AHA Class IA Recommendation
- LVEF ≤ 35% with NYHA Class II-IV Heart Failure

257

Aldosterone Antagonists

RALES Trial Published 1999 – 1663 pts	EMPHASIS-HF Published 2011 – 2737 pts
• NYHA Class III-IV	• NYHA Class II
• LVEF ≤ 35%	• LVEF ≤ 35%
• Standard Rx. vs Standard Rx. with spironolactone	• Standard Rx. vs Standard Rx. with eplerenone
• 30% ↓ in mortality	• 24% ↓ in all cause mortality
• 35% ↓ in hospitalization	• 42% ↓ in HF hospitalization

258

Aldosterone Antagonist

Spironolactone (Aldactone)	Eplerenone (Inspra)
• Non selective MRA – Blocks aldosterone and androgen; stimulates progesterone • Initial Dose: 12.5-25mg daily • Target Dose: 50mg daily or 25mg BID	• Selective MRA • Initial Dose: 25 mg daily • Target Dose: 50mg daily
Major Side Effect: gynecomastia (10%), sexual dysfunction and menstrual problems due to non selectivity	**ELIMINATES most gynecomastia and sexual side effects associated with Aldactone**

2019 259

259

Clinical Considerations

- Potassium sparing medications
- Any potassium supplements should be stopped after initiating - consider potassium based salt substitutes
- Counsel patients about avoiding foods high in potassium

Prior to initiation:
- **Creatinine should be Men ≤ 2.5 mg/dl Women ≤ 2.0 mg/dl**
- **Potassium should be < 5.0 mEq/L**

2019

Lab Monitoring

- Potassium and renal function
  - Assess 2-3 days after initiation
  - Again at 7 days
  - At 1 month mark.
  - If stable - every 3 months.
  - Recheck when adding or increasing ACE I / ARB / ARNI
- Monitor for hyponatremia.

260

260

Hydralazine & Isosorbide Dinitrate

- The combination of hydralazine and isosorbide dinitrate (ISDN) is recommended to REDUCE MORBIDITY AND MORTALITY for :
  - Self-described African Americans with NYHA class III–IV HFrEF receiving optimal therapy with ACE inhibitors and beta blockers, unless contraindicated (Class I, LOE: A)
  - Anyone with current or prior symptomatic HFrEF who cannot be given an ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insufficiency, unless contraindicated (Class IIa, LOE: B)

Self-identified African Americans are thought to have a less active renin-angiotensin system and a lower bioavailability of nitric oxide than those self-identified as white.

261

261

Hydralazine & Isosorbide Dinitrate

- African American Heart Failure Trail (2004) - A-HeFT
- 1050 self-described African American patients
- NYHA Class III or IV
- LVEF ≤ 35% or ≤ 45% with a dilated left ventricle
- Currently on standard therapy with BB and ACE I for at least 3 months prior to enrollment
- Randomized to standard therapy + placebo (1 tablet TID) or standard therapy + 37.5mg of hydralazine and 20mg of ISDN (combined in one tablet TID)
- Dose increased to 2 tablets TID if no side effects with 1 tablet TID
- Trial ended early due to significantly higher rate of mortality in placebo group
  - 43% reduction in rate of death from any cause
  - 33% reduction in the rate of first hospitalization for heart failure in treatment group
  - Significant improvement in quality of life score in treatment group

262

262

Hydralazine & Isosorbide Dinitrate

- Initiation:
  - Hydralazine 37.5 mg / ISDN 20mg 3 times daily
- Target dose:
  - Total **DAILY** dose of Hydralazine 225 mg (75mg TID) and ISDN 120 mg (40mg TID)
- Bidil – combo drug:
  - Hydralazine 37.5mg / ISDN 20mg
  - 1 up to 2 tablets TID
- Adherence difficult
- Adverse Reaction
  - Headache
  - Dizziness
  - GI complaints

Consider slower titration to enhance tolerance

263

263

Digoxin

Stage C Recommendations

- Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF (Class IIa, LOE: B)

- **Improved symptoms, exercise tolerance and quality of life**
- NYHA Class II-III HF treated with digoxin 2-5 years had modestly reduced combined risk of death and hospitalization
- **NO EFFECT ON MORTALITY**

2019

264

264

Digoxin

- Lower doses routinely used - 0.125 mg daily
  - Especially if > 70 years of age, impaired renal function, or low lean body mass
- No need for loading dose in HF
- Discontinuation of digoxin associated with worsening heart failure symptoms
  - Prevention of worsening heart failure by continuing digoxin at lower serum concentration (reduction in hospitalization and mortality)

Suggested Digoxin Level Goal in HF: 0.5-0.9ng/ml

2019 265

265

Digoxin benefit in women only when LVEF < 35%

- Digoxin level should be between 0.5 and 1.1 ng/ml
- Serum digoxin level ≥ 1.2 ng/ml associated with increased risk of death
  - Ahmed A, Aban IB, Weaver MT, Aronow WS, Fleg JL. Serum digoxin concentration and outcomes in women with heart failure: A bi-directional effect and a possible effect modification by ejection fraction. European journal of heart failure. 2006 Jun;8(4):409-19.

Digoxin therapy in men with heart failure LVEF≤ 45%

- Goal serum digoxin level of 0.5 to 0.8 ng/mL.
- Higher serum digoxin concentrations were associated with increased mortality in men
  - Rathore, S.S., Curtis, J.P., Wang, Y., Bristow, M.R. and Krumholz, H.M., 2003. Association of serum digoxin concentration and outcomes in patients with heart failure. *Jama*, *289*(7), pp.871-878.

Digoxin therapy is associated with an increased risk of death from any cause among women, but not men, with heart failure and depressed left ventricular systolic function.

2019

266

Impact of HR on Heart Failure

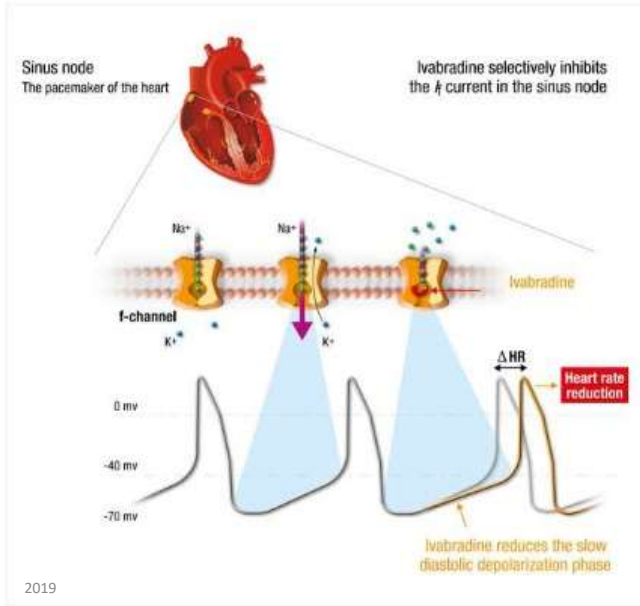
- In patients with coronary artery disease and left-ventricular dysfunction, a heart rate of 70 beats per minute (bpm) or higher was associated with a 34% increased risk of cardiovascular death and a 53% increase in admission to hospital for heart failure compared with heart rate lower than 70 bpm
- Heart rate is also directly related to risk of death, cardiovascular death, or admission to hospital in patients with heart failure
- Heart-rate reduction is associated with improved outcomes

1. Fox K et al. on behalf of the BEAUTIFUL investigators. Heart rate as a prognostic risk factor in patients with coronary artery disease and leftventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. Lancet 2008; 372: 817–21
2. Pocock SJ, et al. Predictors of mortality and morbidity in patients with chronic heart failure. Eur Heart J 2006; 27: 65–75.
3. Flannery G et al. Analysis of randomized controlled trials on the effect of magnitude of heart rate reduction on clinical outcomes in patients with systolic chronic heart failure re

Ivabradine (Corlanor)

- Sinus node inhibition
- Inhibition of the Hyperpolarization –activated cyclic nucleotide-gated channels (I_f channel or f-channel or “Funny” channel)
- I_f current is an inward Na^+/K^+ current that activates pacemaker cells of the SA Node
- Ivabradine binds the “Funny” channel in a current dependent fashion
- Slows diastolic depolarization → slows the firing of the SA Node → slows heart rate

Mechanism of Ivabradine



269

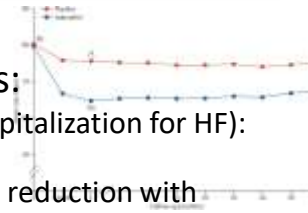
Ivabradine (Corlanor)

- **SHIFT Trial (2010)**
- Double-blinded, placebo-controlled, parallel-group study
- Symptomatic HF, LVEF $\leq$ 35%, in NSR with HR $\geq$ 70 bmp, admitted for HF in previous year, on stable HF treatment
- 6558 patients randomized to ivabradine 7.5mg BID or matching placebo
- Primary endpoint: composite of CV death or hospital admission for worsening HF

2019 270

270

Ivabradine (Corlanor)



- Median follow up 22.9 months
- Statistically significant outcomes:
  - Composite endpoint (CV death or Hospitalization for HF): 18% reduction with Ivabradine
  - Hospitalization for worsening HF: 26% reduction with Ivabradine
  - Deaths due to HF: 26% reduction in Ivabradine group (CV deaths and all cause deaths not statistically significant)
  - The higher the baseline heart rate the better the outcome
  - Quality of Life scores better with ivabradine
- Side Effects: Phosphenes (visual disturbances) reported in 3% of ivabradine group (1% in placebo – p<0.0001); more atrial fib in ivabradine group

2019 271

271

ACC/AHA/HFSA Guideline Update

Recommendations for Ivabradine (Stage C HFrEF)

COR	LOE	Recommendations
IIa	B-R	Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III), stable chronic HFrEF (LVEF ≤ 35%) who are receiving GDEM, including beta blocker at maximum tolerated dose, and who are in NSR with a heart rate of ≥ 70 bmp at rest.

COR= Class of Recommendation (strength); yellow, is reasonable/useful (Moderate)
LOE = Level of Evidence (Quality); B = moderated quality; 1 or more randomized trials;
GDEM: Guideline-directed evaluation and management

Yancy C. el al. *Circulation*. 2016
Yancy C. el al. *Circulation*. 2017

Most benefit:
Patients with contraindication to beta blocker
Patients with BB dose < 50% target
Resting HR (SR only) ≥ 77

Titrate q 2 weeks

2019 272

272

n-PUFAs
Omega-3 polyunsaturated fatty acids

- Considered adjunctive therapy in patients with symptomatic HFrEF or HFpEF
  - already receiving optimized recommended therapy with an ACEI (or ARB), a beta-blocker and MRA.
- Present in certain foods such as flaxseed and fish, as well as dietary supplements such as fish oil.
- Only certain preparations have shown an effect on the cumulative endpoint of CV death and hospitalization
- Should contain:
  - EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) as ethyl esters of at least 85%of total containing 850–882 mg EPA and DHA

2019 273

273

Medications to Avoid

No Benefit	Harm
• Nutritional supplement as treatment for HF – Coenzyme Q10 – Carnitine – Taurine – Antioxidants • Hormone therapies outside correcting deficiencies – Growth hormone – Thyroid hormone	• Antiarrhythmics • Calcium channel blockers – Myocardial depressant – Except amlodipine – neither harm nor benefit in HF –OK for HTN / ischemia control • NSAIDs – Cause sodium and water retention • Thiazolidinediones – Associated with increase incidence of HF

2019 274

274

Drugs Commonly Used for HFrEF (Stage C HF)

Drug	Initial Daily Dose(s)	Maximum Dose(s)	Mean Doses Achieved in Clinical Trials
			ACE Inhibitors
Captopril	6.25 mg 3 times	50 mg 3 times	122.7 mg/d (421)
Enalapril	2.5 mg twice	10 to 20 mg twice	16.6 mg/d(412)
Fosinopril	5 to 10 mg once	40 mg once	----------
Lisinopril	2.5 to 5 mg once	20 to 40 mg once	32.5 to 35.0 mg/d (444)
Perindopril	2 mg once	8 to 16 mg once	----------
Quinapril	5 mg twice	20 mg twice	----------
Ramipril	1.25 to 2.5 mg once	10 mg once	----------
Trandolapril	1 mg once	4 mg once	----------
			ARBs
Candesartan	4 to 8 mg once	32 mg once	24 mg/d (419)
Losartan	25 to 50 mg once	50 to 150 mg once	129 mg/d (420)
Valsartan	20 to 40 mg twice	160 mg twice	254 mg/d (109)
Aldosterone Antagonists			
Spironolactone	12.5 to 25 mg once	25 mg once or twice	26 mg/d (424)
Eplerenone	25 mg once	50 mg once	42.6 mg/d (445)

Helping Cardiovascular Professionals Learn, Advance, Heal

275

Drugs Commonly Used for HFrEF (Stage C HF) (cont.)

Drug	Initial Daily Dose(s)	Maximum Dose(s)	Mean Doses Achieved in Clinical Trials
Beta Blockers			
Bisoprolol	1.25 mg once	10 mg once	8.6 mg/d (118)
Carvedilol	3.125 mg twice	50 mg twice	37 mg/d (446)
Carvedilol CR	10 mg once	80 mg once	----------
Metoprolol succinate extended release (metoprolol CR/XL)	12.5 to 25 mg once	200 mg once	159 mg/d (447)
Hydralazine & Isosorbide Dinitrate			
Fixed dose combination (423)	37.5 mg hydralazine/ 20 mg isosorbide dinitrate 3 times daily	75 mg hydralazine/ 40 mg isosorbide dinitrate 3 times daily	~175 mg hydralazine/90 mg isosorbide dinitrate daily
Hydralazine and isosorbide dinitrate (448)	Hydralazine: 25 to 50 mg, 3 or 4 times daily and isorsorbide dinitrate: 20 to 30 mg 3 or 4 times daily	Hydralazine: 300 mg daily in divided doses and isosorbide dinitrate 120 mg daily in divided doses	----------

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276

Medical Therapy for Stage C HF*r*EF: Magnitude of Benefit Demonstrated in RCTs

GDMT	RR Reduction in Mortality	NNT for Mortality Reduction (Standardized to 36 mo)	RR Reduction in HF Hospitalizations
ACE inhibitor or ARB	17%	26	31%
Entresto	31%	21 (over 27 months)	
Beta blocker	34%	9	41%
Aldosterone antagonist	30%	6	35%
Hydralazine/nitrate	43%	7	33%

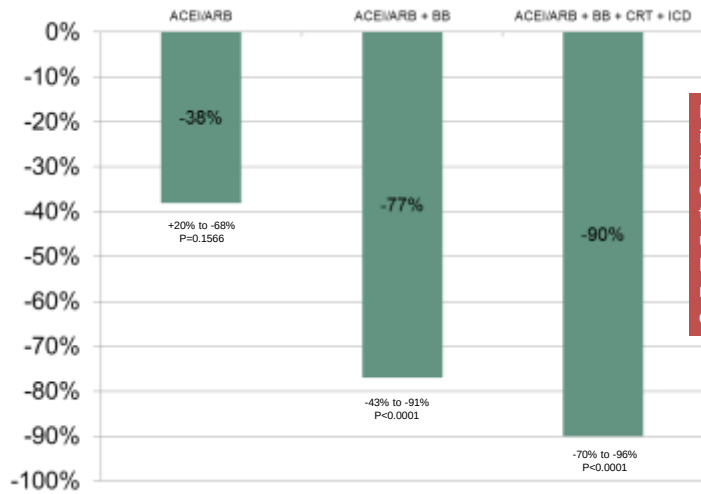
GDMT (except for diuretics)

- ✓ Improves symptoms
- ✓ Reduces burden of hospitalizations
- ✓ Provides survival benefit

277

Incremental Benefit with HF Therapies

(Cumulative % Reduction in Odds of Death at 24 Months Associated with Sequential Treatments)



If improvement in LVEF continue therapies unless reduced EF was due to reversible cause.

Fonarow GC,Yancy CW. *J Am Heart Assoc* 2012;1:16-26.

278

REMEMBER: Maximum tolerated dose is the goal for evidence based medications!!!

279

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EXPERT CONSENSUS DECISION PATHWAY

2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction

A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways

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280

Consensus Pathway Includes

- How to Initiate, Add, or Switch to New Evidence-Based Guideline-Directed Therapy for HFrEF
- How to Achieve Optimal Therapy Given Multiple Drugs for HF Including Augmented Clinical Assessment That May Trigger Additional Changes in
- When to Refer to an HF Specialist
- How to Address Challenges of Care Coordination
- How to Improve Adherence
- What Is Needed in Specific Patient Cohorts: African Americans, the Frail, and Older Adults
- How to Manage Your Patients' Cost of Care for HF
- How to Manage the Increasing Complexity of HF
- How to Manage Common Comorbidities
- How to Integrate Palliative Care and Transition to Hospice Care

2019 281

281

Initiation Pearls

- It is safe to initiate either a beta blocker or an ACE-I first in HF
- ACE-I is better tolerated when a patient is wet because RAAS activation is less during volume overload
- Aldosterone antagonist if indicated can be added before reaching target of other medications
  - Recommended doses are below what typically affects blood pressure
- Hydralazine and isosorbide dinitrate can be started after max tolerated ACE-I and BB

2019 282

282

Titration Pearls

Titrate generally every 2 weeks based on tolerance

- Start low and titrate to tolerance
- Patients need frequent monitoring
- More slowly in frail older adults
- May go more quickly in clinically stable patients

Beta blockers have priority in getting to target dose

- Patients may have transient worsening of symptoms / and elevation of BNP

Optimal therapy within 3 to 6 months of diagnosis

When titrating ACE-I, ARB, or ARNI have to consider renal function and potassium

- Assess 1 to 2 weeks after titration
- Reduce dose for hyperkalemia; GFR < 30 L/min/1.72 m2

ARNIs should be titrated every 2 to 4 weeks because of risk of hypotension

- BP assessment more important
- May need to decrease loop
- MUST assess for hyperkalemia
- Gradual uptitration over 6 weeks recommended to achieve maximal attainment of target dose

Loop diuretics

- Assess renal function 2 to 3 weeks after dose increase

2019 283

283

HFpEF

- No evidence based medical therapy
- ARBs may reduce hospitalizations but not mortality

Until Now

Focus on co-morbidities:

- HTN
  - Blood pressure control is imperative to prevent flash pulmonary edema
- Sleep apnea
- Atrial fibrillation
  - Rhythm control may be required to assure adequate preload
- Anemia
- CAD
- Diabetes
- Obesity

2019 284

284

TOPCAT Trial

- Treatment of Preserved Cardiac Function HF with Aldosterone Antagonist – published 2014
- Randomized 3,445 patients to spironolactone or placebo
  - 1678 from Russia/Republic of Georgia
  - 1767 from the Americas (US, Canada, Brazil, Argentina)
- Primary composite outcome: Time to CV death, aborted cardiac arrest, or hospitalization for management of HF
- No statistically significant benefit to spironolactone

Pitt B, et al. TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med. 2014;370:1383–1392

285

TOPCAT Post Hoc Analysis

- 4 fold difference identified in the composite event rate between groups enrolled in Russia/Georgia compared with those enrolled in the Americas
- All clinical event rates were markedly lower in Russia/Georgia
  - There was no detectable impact of spironolactone on any outcomes
- In the Americas
  - Rates of the primary outcome, cardiovascular death, and hospitalization for heart failure were significantly reduced by spironolactone.

Pfeffer, M. A.,et al. (2015). Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. *Circulation*, *131*(1), 34-42.

286

ACC/AHA/HFSA Guideline Update

Recommendations Aldosterone Antagonist in HFpEF

COR	LOE	Recommendations
IIb	B-R	In appropriately selected patients with HFpEF (with EF ≥45%, elevated BNP levels or HF admission within 1 year, estimated glomerular filtration rate >30 mL/min, creatinine <2.5 mg/dL, potassium <5.0 mEq/L), aldosterone receptor antagonists might be considered to decrease hospitalizations (83, 166, 167).

COR= Class of Recommendation (strength); yellow, is reasonable/useful (Moderate)
LOE = Level of Evidence (Quality); B = moderated quality; 1 or more randomized trials;
GDEM: Guideline-directed evaluation and management

Yancy C, Jessup M, et al. *Circulation*. 2017).

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287

Diuretics

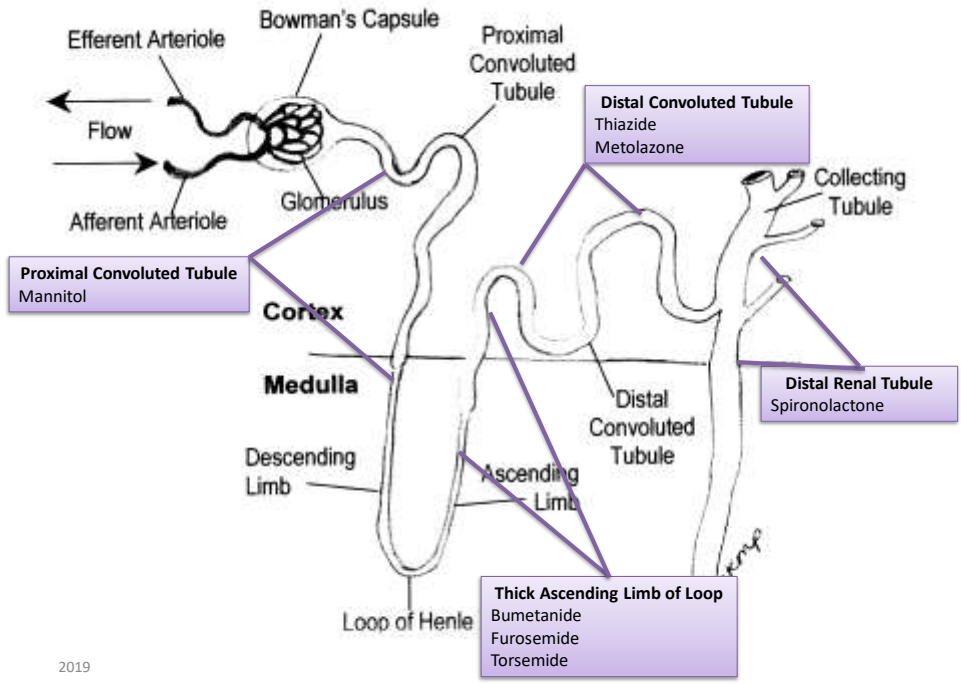
- Decrease congestive **symptoms** and exercise tolerance
  - **No mortality benefit**
- First line: Loop diuretics
  - Thiazide diuretic my be added
- Lab Monitoring
  - Electrolytes
  - Serum CO_2 for contraction alkalosis
  - Renal function

2019

- Monitor response to therapy
  - Adequate diuresis
    - BNP or NT-pro BNP goal
    - JVP assessment
    - Orthopnea
  - Over diuresis (volume contraction)
    - Hypotension
    - Dizziness
    - Orthostatic BP
      - Supine / standing

288

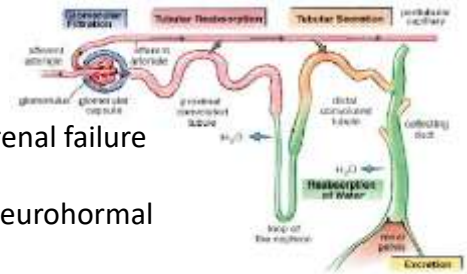
288



289

Renal Anatomy: Nephron and Loop Diuretics

- Inhibits reabsorption of sodium and chloride in ascending loop of Henle
- Loss of H_2O, K+, Na+, Cl-, magnesium, Ca++, H+
- More loss of H2O and less K+ and Na+ than thiazides
- Promotes venous vasodilatation
- Rapid onset and short duration
- Can be effective in presence of renal failure
- High ceiling diuretic
- Can decrease GFR and worsen neurohormal activation



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290

Loop Diuretics

- Bumetanide (Bumex)
- Furosemide (Lasix)
- Torsemide (Demadex)

- Equivalents
  - Furosemide 40 mg
  - Torsemide 20 mg
  - Bumetanide 1 mg

291

Differences in Loop Diuretics

Bumetanide	Furosemide	Torsemide
Lack of randomized control data with comparison to furosemide	BID Dosing when GFR is low	2 randomized trials comparing Torsemide and Furosemide
Better pharmacokinetic profile (oral bioavailability) than furosemide but torsemide has evidence of more efficacy and more safety	**Once daily dosing of loops can lead to rebound increase of sodium reabsorption**	Torsemide associated with reduction in HF and CV readmission in systolic HF with a trend towards reduction of all cause mortality.
Oral Bioavailability 80% Max dose 10mg / day Onset 30-60min Peak 1-2 hours Duration 4 hours May repeat every 4-5 hours	Oral Bioavailability 50% Max dose 600mg/day Onset 60min Peak 1-2 hours Duration 6-8 hours	Oral Bioavailability 80-100% Max dose 200mg/day Onset 60min Peak 1-2 hours Duration 6-8 hours May repeat every 6-8 hours

292

Principles for Loop Diuretic Therapy

- **Goal: eliminate clinical evidence of volume overload**
  - **Threshold medication**
- Outpatient weight loss goal of 0.5 to 1.0 kg per day
- Patients can be educated for adjustable diuretic dosing
  - Weight gain
  - **Change in oral intake or during periods of illness**

In Hospital: Convert home PO dose to IV at ≥ home dose

Early diuresis in ED associated with better outcomes

2019 293

293

IV Loop Diuretics

- DOSE Trial
  - NEJM: Felker et al., 2011
  - No significant difference in symptoms or renal function between continuous drip versus intermittent dosing
  - Non significant trend toward improvement in symptoms with high dose (IV at 2.5 x PO dose) versus low dose; (IV at same as PO dose) no change in renal function

Short ½ life: Sodium reabsorption will occur in the tubules once drug concentration declines. Thus – benefit of short or continuous infusion.

2019 294

294

Diuretic Resistance

- Reasons
  - High sodium levels
  - NSAIDs
  - Severe renal impairment
  - Renal hypoperfusion
- Strategies
  - Change the loop diuretic
  - IV instead of PO
  - Addition of thiazide
  - Higher dose spironolactone
  - Add low dose dopamine for hospitalized patients

295

Thiazide Diuretics

- Inhibit reabsorption of Na+ and Cl-
  - In the distal convoluted tubule
  - More sodium loss than loop diuretics
- Delayed onset but longer duration of action than loop diuretics
  - Give 30 minutes before a loop diuretic
- LOW CEILING DIURETICS
- Less potent diuretic but more potent antihypertensive effect compared to loops
- Diminished effectiveness in presence of renal failure

296

Thiazide Diuretics

Bendrofluazide (Naturetin)
Benthiazide (Aquatag, Exna)
Chlorothiazide (Diuril)
Chlorthalidone (Hygroton)
Cyclothiazide (Anhydron)
Hydrochlorothiazide (HCTZ) (HydroDiuril, Esidrix)
Hydroflumethazide (Saluron, Diucardin)
Indapamide (Lozol)
Metolazone (Zaroxolyn)
Polythiazide (Renese)
Trichlormethiazide (Metahydrin, Naqua)

2019

SIDE EFFECTS:
Blood Chemistry changes::
Hyponatremia (↓ Na^+)
Hypokalemia (↓ K^+)
Hypomagnesemia (↓ Mg^+)
Hyperglycemia (↑ blood sugar)
Hyperuricemia (↑ uric acid)
Hypercalcemia (↑ Ca^{++})
Decreased glomerular filtration in kidneys (↑ BUN, creatinine)
↑ cholesterol
↑ triglycerides
↓ HDL cholesterol
OTHER SIDE EFFECTS:
Impaired glucose tolerance
Gout
Impotence
Ventricular arrhythmias (↓ K^+)
Nausea, dizziness, headache

297

297

Differences in Loop Diuretics

Bumetanide	Furosemide	Torsemide
Lack of randomized control data with comparison to furosemide Better pharmacokinetic profile (oral bioavailability) than furosemide but torsemide has evidence of more efficacy and more safety	BID Dosing when GFR is low	2 randomized trials comparing Torsemide and Furosemide Torsemide associated with reduction in HF and CV readmission in systolic HF with a trend towards reduction of all cause mortality.
Oral Bioavailability 80% **Max dose 10mg / day** Onset 30-60min Peak 1-2 hours Duration 4 hours May repeat every 4-5 hours	Oral Bioavailability 50% **Max dose 600mg/day** Onset 60min Peak 1-2 hours Duration 6-8 hours May repeat every 6-8 hours	Oral Bioavailability 80-100% **Max dose 200mg/day** Onset 60min Peak 1-2 hours Duration 6-8 hours May repeat every 6-8 hours

2019 298

298

Diuretics and Renal Function

- Role of venous congestion in worsening renal function

Versus

- Role of volume depletion / hypotension and worsening renal function

299

Diuretics and Renal Function

- Moderate to severe renal dysfunction with fluid overload
  - Continue to treat with diuretics
- In severe fluid overload renal dysfunction my improve with continued treatment
- May need to hold ACE I secondary to AKI
- **Venous congestion plays a role in worsening renal function (not just hypoperfusion)**

300

Case Study

- 67 year old male with previous anterior wall STEMI with LVEF of 35% presents to Heart Failure Clinic after referral by primary cardiologist. ICD in place.
- Several month history of steady weight gain with worsening NYHA Classification and worsening functional status.
- Minimal direction from previous calls to primary cardiologist.

301

Case Study

- Presents in a wheelchair
- NYHA Functional Class ambulatory 4
- Dyspnea with minimal exertion but not at rest
- JVD 8cm above sternal angle
- Lungs clear
- Grade III systolic murmur at apex
- + Hepatojugular reflex
- 2+ lower extremity edema to knees
- Reports early satiety
- CKD Stage III with most recent creatinine 1.6
- Estimates weight is up 30 pounds

302

Case Study

- BP 110/82 mmHg
- HR 97
- RR 24
- Current Medications
  - Lisinopril 10 mg daily
  - Metoprolol tartrate 25 mg BID
  - Furosemide 60 mg BID
  - ASA 81 mg daily
  - Clopidogrel 75 mg daily
  - Atorvastatin 40 mg daily

Options?

2019 303

303

Impacting Cardiac Output to Improve Myocardial Performance

2019 304

304

The Heart as a Pump

Goal: Forward propulsion of blood to perfuse the body.

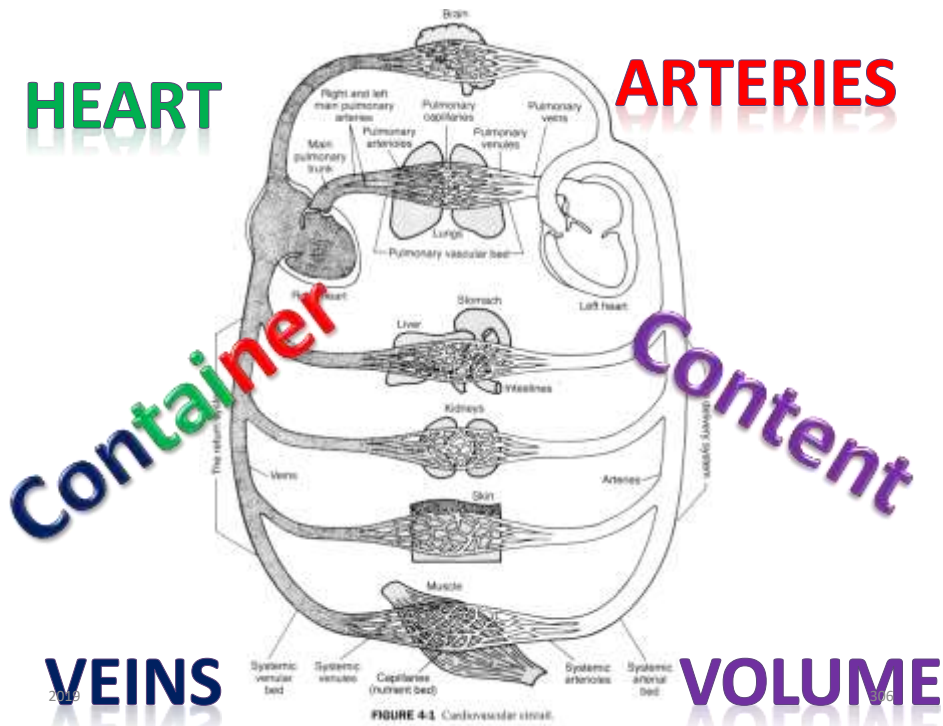
Flow is determined by:

√**Pressure**

√ **Resistance**

√ **Volume**

305



306

Basic Components of Cardiac Output

Cardiac Output

Volume of blood ejected by the ventricle **each minute**

Heart Rate X Stroke Volume

Volume of blood ejected by the ventricle **each beat**

Preload Afterload Contractility

Same four components also determine myocardial oxygen demand

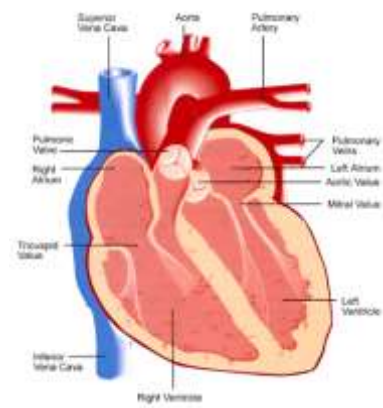
307

Determinants of Myocardial Performance

Stroke Volume
- Preload
- Afterload
- Contractility

Heart Rate

Synergy of Contraction
Synchrony of Contraction



308

Preload

- End-diastolic stretch on myocardial muscles fibers
- Right Ventricular: RA /CVP
  - JVD
- Left Ventricular: PAOP / PCWP

Afterload

- Pressure ventricle needs to overcome to eject blood volume
- Right Ventricle: Pulmonary Vascular Resistance (PVR)
- Left Ventricle: Systemic Vascular Resistance (SVR)
  - Diastolic BP / Pulse Pressure

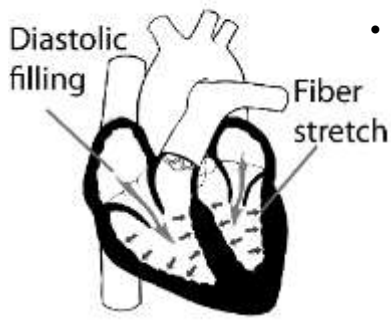
Contractility

- Ability of myocardium to contract independent of preload and afterload
- LVEF Assessment: Normal 55-60%

2019 309

309

Preload



Preload

The ventricle is PRELOADED with blood at the end of diastole:

Creates stretch on myocardial muscles fibers

- **Determined by:** Volume of blood filling the ventricle at end of diastole

Greater the volume the greater the stretch (muscle fiber length)

↓

Greater the stretch the greater the contraction

↓

Greater the contraction the greater cardiac output

TO A POINT

2019 310

310

Non-Invasive Preload Assessment

Right Ventricle

- JVD
- Hepatojugular reflux

Less Specific
- Peripheral edema
- Weight

2019

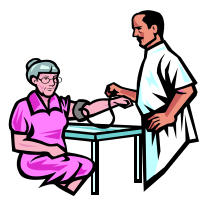
Left Ventricle

- Lungs Sounds
  - Clear lungs do not rule out volume overload
  - Role of lymph system
- CXR
  - Vascular congestion
  - Interstitial edema
  - Pulmonary edema
- Orthopnea / Bendopnea / PND
- S_3
- Hypoxemia
  - Diffusion abnormality

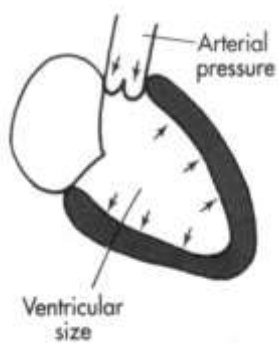
Less Specific
- Decrease in Blood Pressure and Urine Output
  - Fall in stroke volume

311

311



Afterload



Afterload

After the ventricle is loaded:

Pressure ventricle needs to overcome to eject blood volume

Systemic vascular resistance (SVR) is major component of left ventricular afterload
- Other components
  - Valve compliance
  - Arterial wall compliance
  - Viscosity of blood

Pulmonary vascular resistance (PVR) is major component of right ventricular afterload

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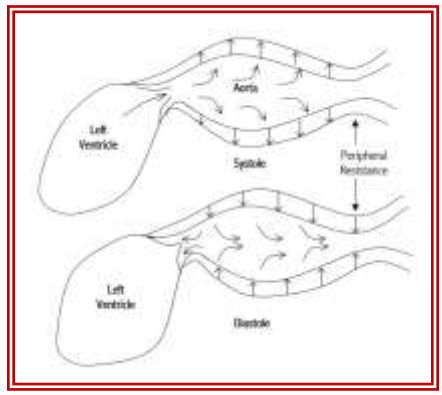
312

312

Afterload Assessment



- Left ventricle:
  - **Pulse pressure and DBP**
    - **Normal pulse pressure 35 to 40 mmHg**
- Right ventricle:
  - **Hypoxemia**
  - **Positive pressure ventilation / PEEP**

313

Key Principles in Understanding Hemodynamic Assessment

- Vascular tone is affected by:
  - Large vessel compliance
  - Peripheral vascular resistance (smaller vessels)
- Vessel resistance changes more quickly than large vessel compliance
  - Compensatory mechanism in shock

Increased Resistance (arterial vasoconstriction) = ↑Diastolic BP and narrowing of pulse pressure

314

Etiology of Decreased Cardiac Output

2019 315

315

Etiology of Hypotension

2019 316

316

BP = CO x SVR

- Low BP could be due to:
  - Low CO
    - HR too slow or too fast
    - Preload too low or too high
    - Contractility low
  - Low SVR
    - Vasodilation due to sepsis, anaphylaxis, altered neurological function, drugs

2019 317

317

Use of Pulse Pressure

- PP < 35 with tachycardia
  - **C.O. Problem**
  - Early sign of hypovolemia
  - Will also be seen with cardiogenic shock
  - Vasoconstriction is compensatory

- PP > 35 with tachycardia
  - **SVR Problem**
  - Early sign of sepsis
  - Vasodilation is primary pathology

2019 318

318

Contractility

Ability of myocardium to contract <u>independent</u> of preload or afterload

INOTROPIC STATE

- Related to degree of myocardial fiber stretch (preload) and wall tension (afterload).
- No accurate way to measure contractility
- Contractility influences myocardial oxygen consumption

2019 **Noninvasive Assessment: Ejection Fraction** 319

319

Important Points about Contractility

- Low cardiac output does not necessarily mean diminished contractility (i.e. hypovolemia)
- Correct preload and afterload problems first in a patient with a low ejection fraction
- Increasing contractility with medications will also increase myocardial oxygen demand

2019 320

320

Heart Rate

- Mathematically heart rate increases cardiac output
- Physiological limit where increased heart rate will decrease cardiac output due to decreased filling time (decreased preload)

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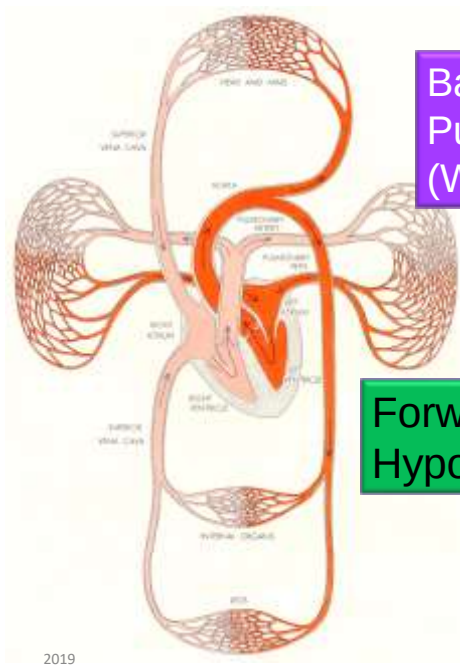
321



Backwards Failure: Pulmonary Congestion (Wet)

Forwards Failure: Hypoperfusion of Tissues

2019 322

322

Volume Overload vs. Hypoperfusion

Intravascular Volume Overload	Hypoperfusion
• Elevated jugular venous pressure • Hepatojugular reflex • Orthopnea • Dyspnea • Crackles • Weight gain • Peripheral edema • S3	• Narrow pulse pressure • Resting tachycardia • Cool Skin • Altered mentation • Decreased urine output • Increased BUN/Creatinine • Cheyne Stokes Respirations

2019 323

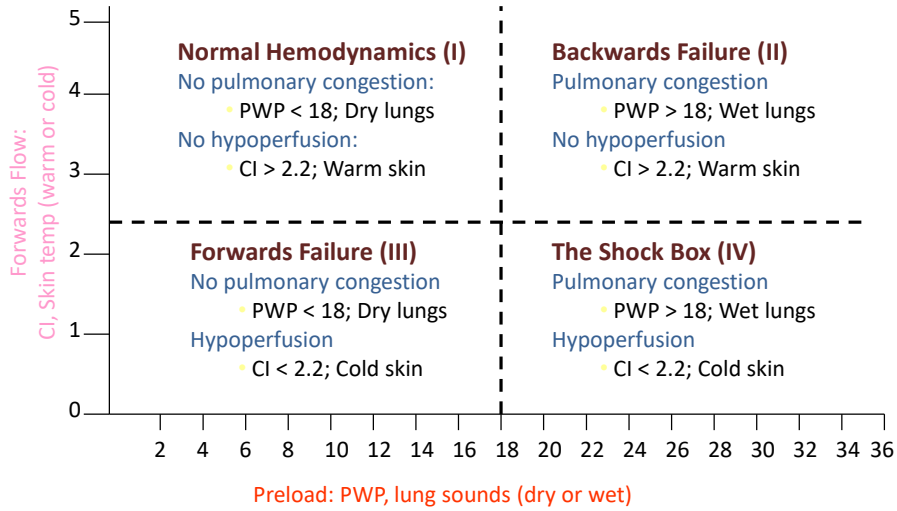
323

Warm and Dry Normal Perfusion No Congestion	**Warm and Wet** Normal Perfusion Congestion
Cold and Dry Low Perfusion No Congestion	**Cold and Wet** Low Perfusion Congestion

2019 324

324

Hemodynamic and Clinical Subsets



2019 325

325

Treatment for Acute Decompensation

WARM and WET
Congestion with Adequate Perfusion

- Differentiate volume overload from pressure overload
- Vasodilator / diuretic

COLD and DRY
Hypoperfusion with No Congestion

- If hypovolemic fluid challenge
- Consider inotrope if adequate volume status (only in systolic dysfunction)

COLD and WET
Hypoperfusion with Congestion

BP > 90 – vasodilator, inotrope if refractory

BP < 90 inotrope, vasopressor only if refractory

2019 326

326

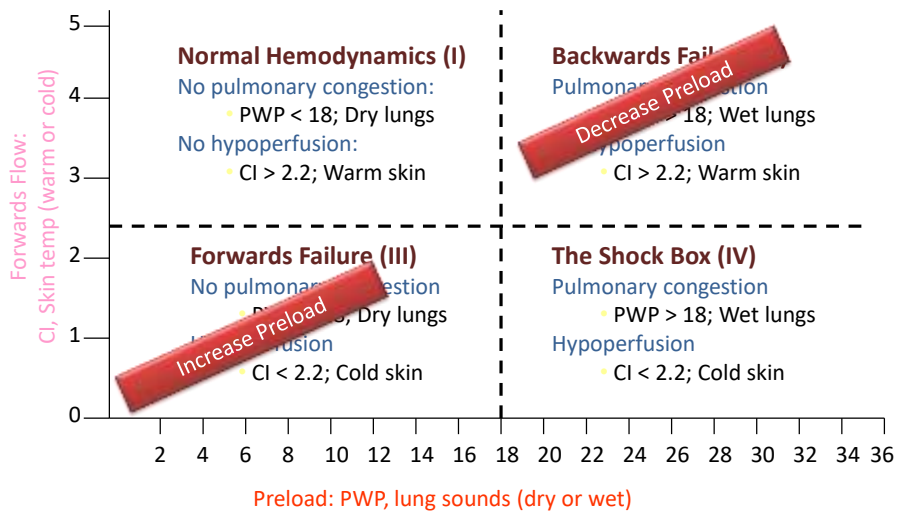
Treatment for Acute Decompensation

- **Reduce Preload**
  - Diuretics
  - Venous Vasodilators
    - Low dose NTG
    - Morphine
    - Neseritide
- **Increase Contractility**
  - Positive Inotropes
    - Dobutamine
    - Milronone
    - Dopamine
- **Reduce Afterload**
  - Arterial vasodilators
    - High dose Nitroglycerin
    - Nitroprusside
  - Inotrope if refractory

2019 327

327

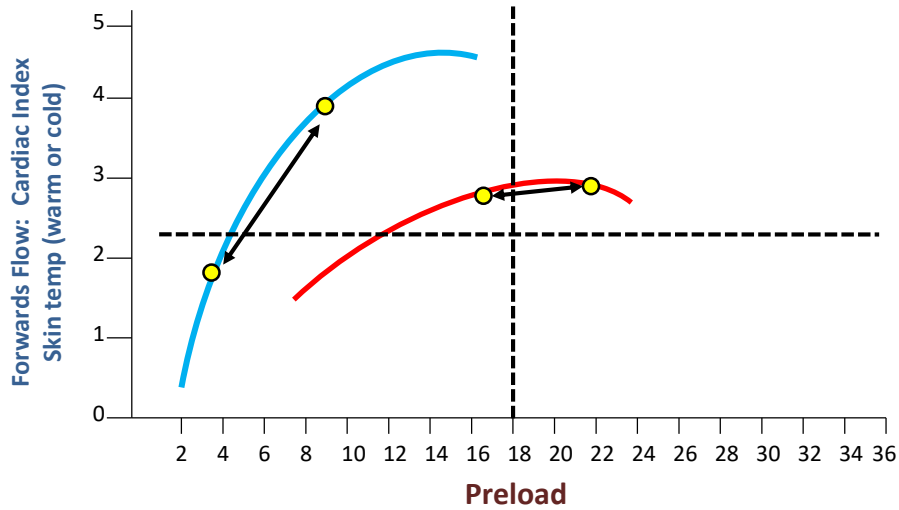
Hemodynamic and Clinical Subsets



2019 328

328

Preload changes: move patient along the current curve



2019 329

329

Pharmacological Options for INCREASING Preload

Volume expanders	▪ Isotonic crystalloids such as 0.9% saline or lactated ringers ▪ Colloids such as albumin ▪ Blood and/or blood products
Decrease dose or stop diuretics or drugs that cause venous vasodilatation.	▪ Decrease or stop medications such as: loop diuretics, intravenous nitroglycerin, neseritide, and morphine sulfate ***(Venous vasodilatation pools blood away from the heart and decreases preload – direct impact on right sided preload)***

Exercise also increases venous return to the heart.

2019 330

330

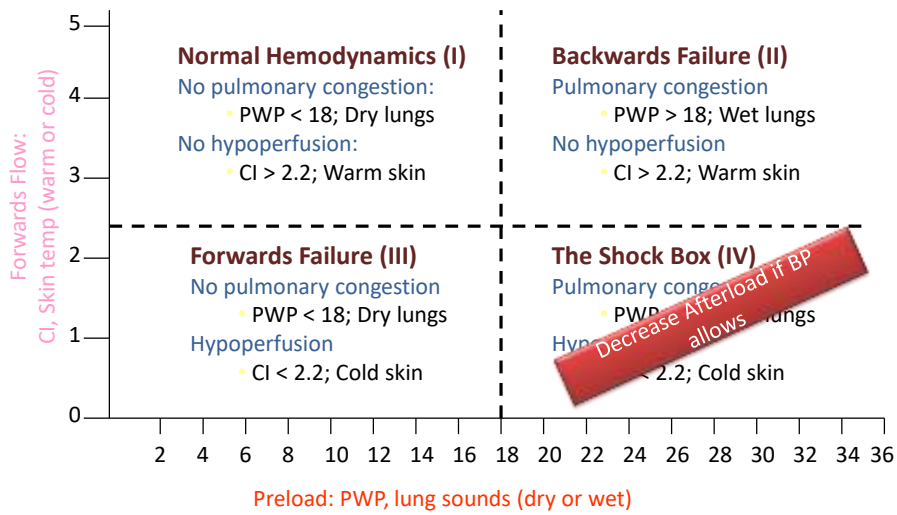
Pharmacological Options for DECREASING Preload

STOP OR DECREASE FLUID	
Diuretics	▪ A loop diuretic such as furosemide eliminates circulating volume
Venous Vasodilators	▪ Intravenous nitroglycerin, neseritide, or morphine sulfate ***(Venous vasodilatation pools blood away from the heart and decreases preload)***
ACE Inhibitors or Angiotensin II Receptor Blockers	**▪ Interrupt renin- angiotensin- aldosterone system. (RAAS). Aldosterone secretion is decreased and there is less sodium and water retention.**
Aldosterone antagonists	**▪ Spironolactone or epleranone ▪ Directly block aldosterone and there is decreased sodium and water retention.**

2019

331

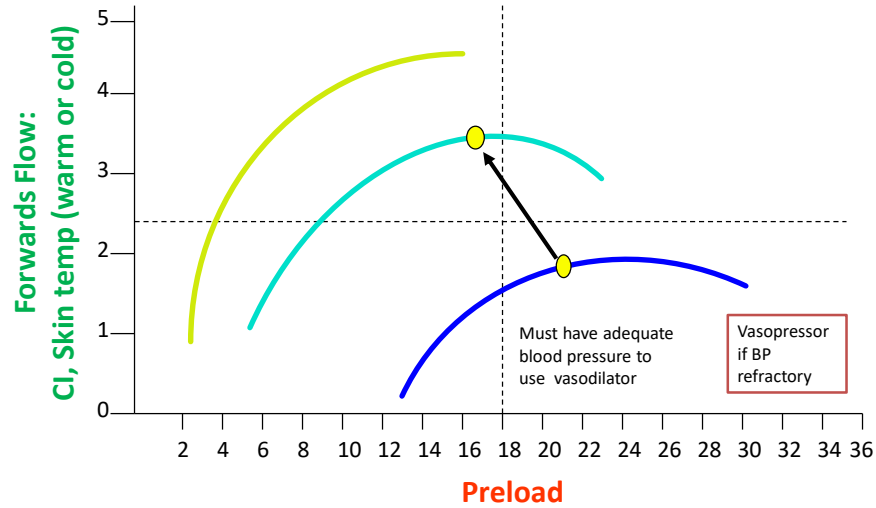
Hemodynamic and Clinical Subsets



2019 332

332

Reducing Afterload:: moves patient up and to the left
(improves forwards flow and reduces preload)



2019 333

333

Pharmacological Options for **DECREASING Afterload**	
All therapies involve <u>arterial</u> vasodilatation	
Smooth muscle relaxants	▪ Nipride ▪ Hydralazine
Calcium channel blockers	▪ Dihydropyridines (ending in "ine") calcium channel blockers such as amlodipine
Alpha$_1$ receptor blockers	▪ Labetolol (combination alpha and beta blocker) ▪ Prazoxin, Terazosin
Central anti-adrenergics Peripheral anti-adrenergics	Clonidine, Methyldopa Resperine, Guanthidine
ACE Inhibitors **Angiotensin II Receptor Blockers (ARBs)**	▪ Interrupt the RAAS and limit production of angiotensin II a potent arterial vasoconstrictor ▪ Medications ending in "pril" ▪ Directly block the effects angiotensin II ▪ Medications ending in "sartan"
Phosodiesterase Inhibitors (PDE Inhibitors)	▪ Milrinone ▪ Is used as an intravenous inotrope but also has arterial vasodilator properties

2019 334

334

Pharmacological Options for INCREASING Afterload

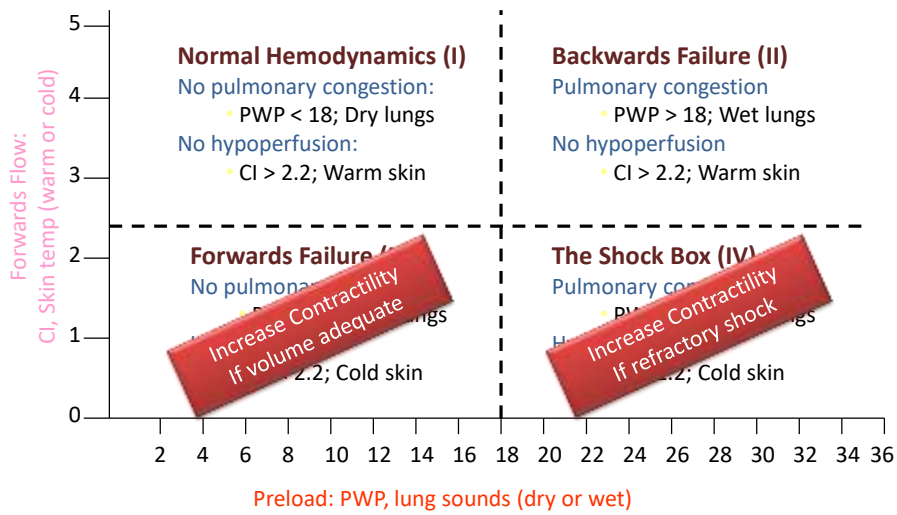
VASOPRESSOR: Term given to medications used to increase afterload.

Sympathomimetics stimulating the alpha receptors of the sympathetic nervous system	▪ Dopamine ▪ Norepinephrine ▪ Phenylephrine ▪ Epinephrine
Arginine Vasopressin	▪ Vasoconstrictive and antidiuretic effect ▪ Restores catecholamine sensitivity

2019 335

335

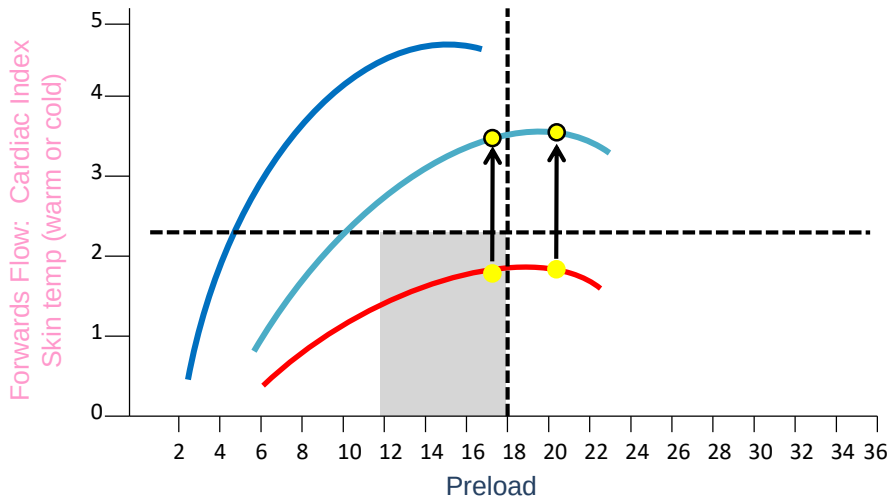
Hemodynamic and Clinical Subsets



2019 336

336

Contractility changes: move patient to a higher curve



2019 337

337

Pharmacological Options for **INCREASING Contractility**

INOTROPE: Term used for medications used to increase contractility

Sympathomimetics stimulating the β1 receptors of the sympathetic nervous system	▪ Dobutamine: most commonly used because it is predominant beta one stimulator ▪ Other sympathomimetics may have inotropic properties even if not used primarily for an inotropic purpose
Phosodiesterase Inhibitors (PDE Inhibitors)	▪ Milrinone ▪ Used as an intravenous inotrope but also has venous and arterial vasodilator properties
Cardiac Glycoside	▪ Digoxin ▪ Weak inotrope and is never used intravenously to support left ventricular dysfunction.

2019 338

338

Pharmacological Options for **DECREASING Contractility**

Beta Blockers blocking the β_1 receptors of the sympathetic nervous system	▪ Metoprolol ▪ Carvedilol ▪ "lol" medications
Calcium Channel Blockers	▪ Diltiazem ▪ Verapamil

2019 339

339

Pharmacological Options for **INCREASING Heart Rate**

Parasympatholytic	▪ Atropine
Sympathomimetics	▪ Epinephrine ▪ Dopamine

Note: The non-pharmacological intervention of pacing the heart with either an external, temporary or permanent pacemaker is often the preferred method of increasing the heart rate due to a set and controlled rate.

2019 340

340

Pharmacological Options for DECREASING Heart Rate

1. Beta Blockers blocking the β_1 receptors of the sympathetic nervous system	▪ "lol" medications ▪ Class II antiarrhythmics
2. Calcium Channel Blockers	▪ Diltiazem / Verapamil ▪ Class IV antiarrhythmic
3. Cardiac Glycoside	▪ Digoxin
4. Unclassified antiarrhythmic	▪ Adenosine: Slows conduction through the AV node
5. Other antiarrhythmics	▪ Class I and Class III antiarrhythmics ▪ Used to establish and / or maintain a normal rhythm and therefore control heart rate

2019 341

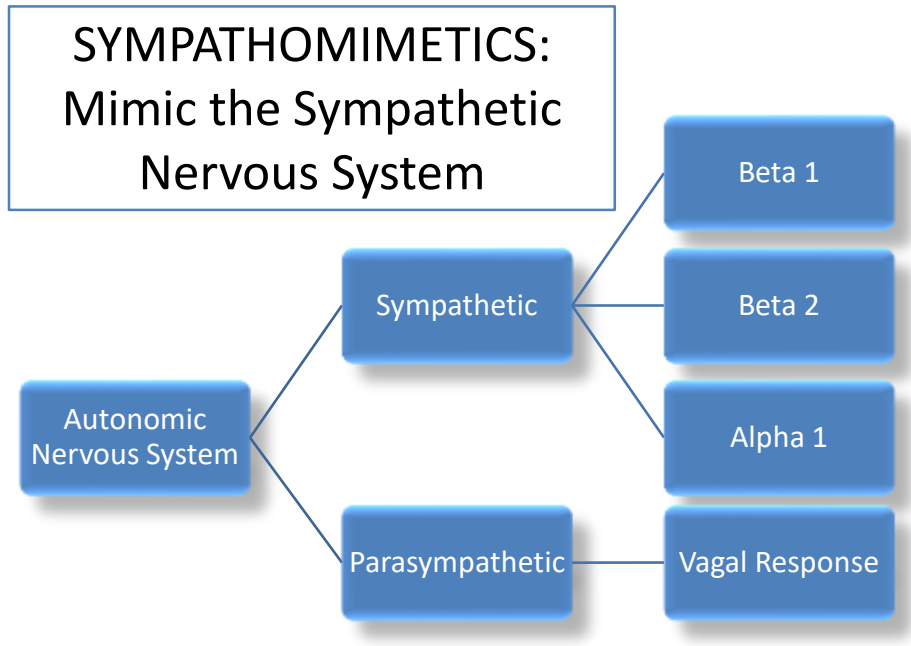
341

Let's Clear Up Some Terminology

- **VASOPRESSORS**
  - Term given to any medication in any class that is used to increase left ventricular afterload (systemic vascular resistance)
- **INOTROPES**
  - Term given to any medication in any class that is used to increase myocardial contractility
    - Increase mortality
    - Used in shock / decompensation when other treatments fail
    - Used as bridge to transplant or palliation

2019 342

342



343

Sympathetic Nervous System

$Alpha_1$ Receptors

Vasoconstriction of vessels

$Beta_1$ Receptors (1 Heart)

Increased heart rate
Chronotropic Response
Increased conductivity
Dromotropic Response
Increased contractility
Inotropic Response
Increased automaticity

$Beta_2$ Receptors (2 Lungs)

(Vessels, Lungs)
Bronchodilation
Peripheral Vasodilatation

2019 344

344

Epinephrine

Endogenous catecholamine

What receptors are stimulated:	β_1 and β_2 Alpha receptors
What are the resultant actions:	Increase contractility (+inotrope) β_1 Increased heart rate (+chronotrope) β_1 Bronchodilation β_2 Selective vasoconstriction (alpha)
When and why do we use:	ACLS first line drug for cardiac standstill- 1 mg every 3 to 5 min Hypotension or profound bradycardia 0.1 to 0.5 mcg/kg/min (7 to 35 mcg/min if 70 kg) Anaphylaxis 0.3 mg SQ/IM - may repeat dose Bronchodilator 0.3 to 0.5 mg SQ q 20 min (inhalation and nebulization also)
What are special nursing considerations:	Onset instant; Peak 20 minutes, SQ onset 5 to 10 min, inhalation 1 min Increases lactate release Extravasation: Leave cannula and needle in place, aspirate not flush line, dry warm compress proximal, elevate site 1 inch 2% topical NTG q 8 hours; Dilute 1 mg terbutaline in 10 ml NS; Inject locally across symptomatic sites

2019 345

345

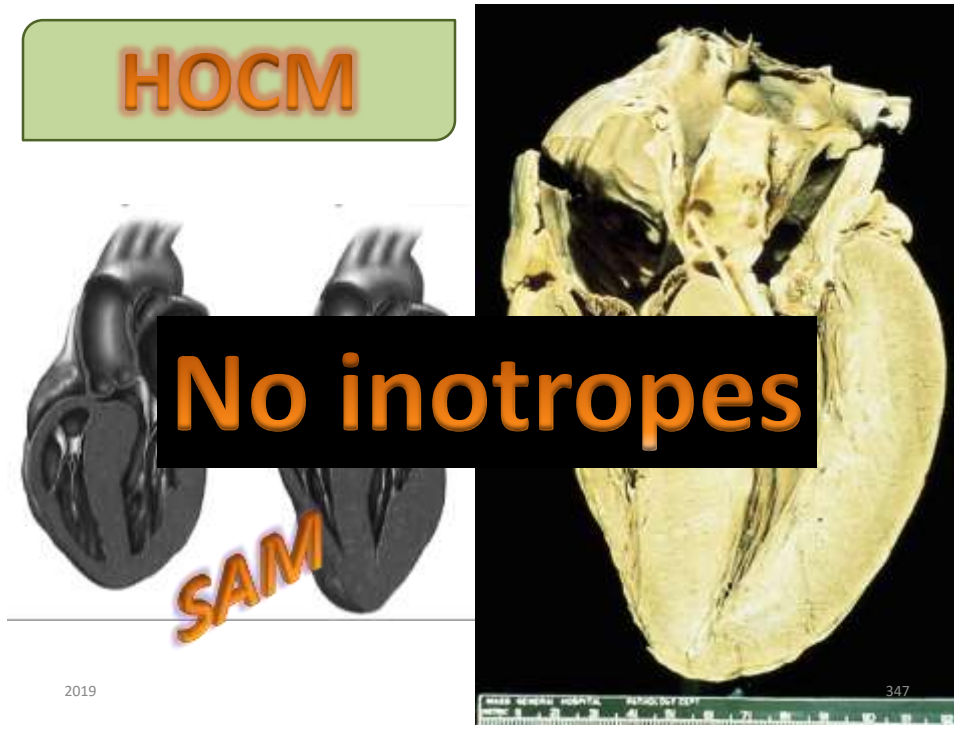
Dobutamine

Synthetic Compound

What receptors are stimulated:	Primarily β_1 Some alpha$_1$ receptor stimulation Some β_2 stimulation Modest β_2 (β_2 > alpha$_1$)
What are the resultant actions:	Increase contractility (+ inotrope) (β_1) Increase AV node conduction Modest vasodilation
When and why do we use:	**Used as an inotrope** (resultant preload reduction) with modest afterload reduction (ACC/AHA Guidelines for Heart Failure)
What are special nursing considerations: **VT, atrial tachyarrhythmias**	Onset 1 to 2 minutes; Peak 10 minutes Half-life 2 minutes Note: Blood pressure response is variable; β_2 causes vasodilatation; β_1 increases cardiac output and may increase BP Extravasation: Dilute 1 mg terbutaline in 10 ml NS; Inject locally across symptomatic sites

2019 346

346



347

Dobutamine for patients with severe heart failure: A systematic review and meta-analysis of randomised controlled trials (2012)

- Fourteen studies
- 673 participants
- 13 studies reported mortality.
- Minimal heterogeneity (I^2 = 4.5%).
- Estimate of the odds ratio for mortality for patients with severe heart failure treated with dobutamine compared with standard care or placebo
  - 1.47 (95% confidence interval 0.98–2.21, p = 0.06)
  - Trend towards worse outcomes but did not reach the conventional level of statistical significance

2019 348

348

Dopamine

Mimics endogenous dopamine; metabolic precursor of norepinephrine and epinephrine

What receptors are stimulated:	**Dopaminergic** at low doses (0.5-2.0 mcg/kg/min) β_1 also at moderate doses (2.0-10.0 mcg/kg/min) Pure alpha stimulation at high doses (> 10mcg/kg/min)
What are the resultant actions:	Increase GFR at low doses Increase contractility at moderate doses (greater effects on contractility than heart rate) Vasoconstriction (alpha) at high doses
When and why do we use:	Refractory hypotension / shock • Not indicated for routine treatment or prevention of acute renal failure • **II b recommendation to enhance diuresis in HF**
What are special nursing considerations:	Onset 1-2 minutes; Peak 10 minutes Maximal effects @20/mcg/kg/min Large IV line or central line Extravasation: Leave cannula and needle in place, aspirate not flush line, dry warm compress proximal, elevate site 1 inch 2% topical NTG q 8 hours; Dilute 1 mg terbutaline in 10 ml NS; Inject locally across symptomatic sites

2019 349

349

Norepinephrine

Endogenous precursor of epinephrine

What receptors are stimulated:	Primarily alpha stimulation Some β_1 (In lower doses β_1 can be more dominant)
What are the resultant actions:	Potent vasoconstrictor (increased afterload) Some increased contractility (+inotrope)
When and why do we use:	Refractory hypotension / shock (used as a vasopressor but will have inotropic properties)
What are special nursing considerations:	Onset: rapid; very short half-life Duration 1-2 minutes (BP checks q2 minutes while titrating) Large IV line or central line Extravasation: Leave cannula and needle in place, aspirate not flush line, dry warm compress proximal, elevate site 1 inch 2% topical NTG q 8 hours; Dilute 1 mg terbutaline in 10 ml NS; Inject locally across symptomatic sites

2019 350

350

Phenylephrine

Synthetic compound

What receptors are stimulated:	Direct effect: Dominant alpha stimulation No substantial β_1 effect at therapeutic doses Indirect effect: Releases norepinephrine
What are the resultant actions:	Vasoconstriction (increased afterload)
When and why do we use:	As a vasopressor for Unresponsive hypotension
What are special nursing considerations:	Pressor effect occurs almost immediately Persists for 10 to 15 minutes Can cause severe bradycardia Can significantly reduced cardiac output secondary increased afterload Extravasation: Leave cannula and needle in place, aspirate not flush line, dry warm compress proximal, elevate site 1 inch 2% topical NTG q 8 hours; Dilute 1 mg terbutaline in 10 ml NS; Inject locally across symptomatic sites

2019 351

351

Pearls for Practice

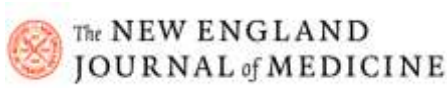
- Titrate up based on onset of action & peak action
- Wean based on duration of action / half life
- Consider systolic, diastolic, pulse pressure and mean

2019 352

352

Comparison of Dopamine to Norepinephrine in Shock

- Backer et al.
- Multi Center Randomized Controlled Trial
- New England Journal of Medicine
- March 4th 2010



- **There were no significant differences between the groups in the rate of death at 28 days or in the rates of death in the ICU, in the hospital, at 6 months, or at 12 months**
- More patients with arrhythmia in the dopamine group
- ***Rate of death was higher in predefined subgroup analysis for patients with cardiogenic shock treated with dopamine.***

2019 353

353

Non Sympathomimetic Vasopressor: Arginine Vasopressin

- Vasoconstrictive effects
  - Allowing for regional vasodilation
- Antidiuretic effects
- Restoration of catecholamine sensitivity
- Low dose exogenous
  - 0.04 units / min
- Use in refractory shock

2019 354

354

Other Considerations in Refractory Shock

Treat with Methylene Blue

- Off label use
- 1.5 to 2.0 mg/kg over 20 to 60 minutes x 1
- Effects are seen 1 to 2 hours after administration
- Direct inhibitory effect on endothelial nitric oxide synthase by oxygenation of enzyme bound ferrous iron
- Also reduces vasorelaxation by blocking formation of cGMP through binding iron in the heme complex

Consider Adrenal Insufficiency Causing Refractory Hypotension

Treat with Hydrocortisone

- Off label use
- 100 mg initial IV bolus followed by additional dosing over 24 hours – then taper

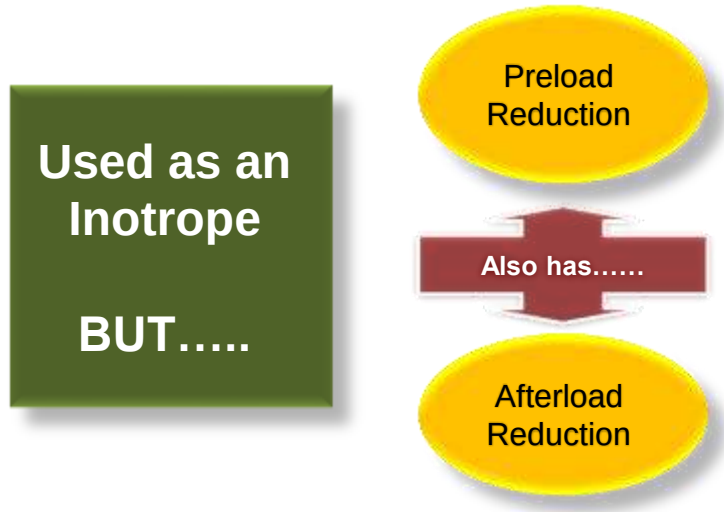
355

Phosphodiesterase Inhibitors

- New generation: Milrinone (Primacor)
- Creates + inotropic effect by increasing availability of calcium
  - Inhibits the degradation of cyclic AMP which is indirectly responsible for increasing the influx of calcium through the calcium channel
- Smooth muscle relaxant (venous and arterial vasodilator)
- Indications:
  - Refractory heart failure (in combination with dobutamine)
  - Left ventricular failure in MI
  - Patients waiting transplant
- Side Effects:
  - **Ventricular arrhythmias**
  - **Role of low dose betablockers in combination**
- Nursing Considerations:
  - Onset IV: Immediate
  - Peak: 10 minutes

356

Phosphodiesterase Inhibitors: Non Sympathomimetic Inotropes



2019 357

357

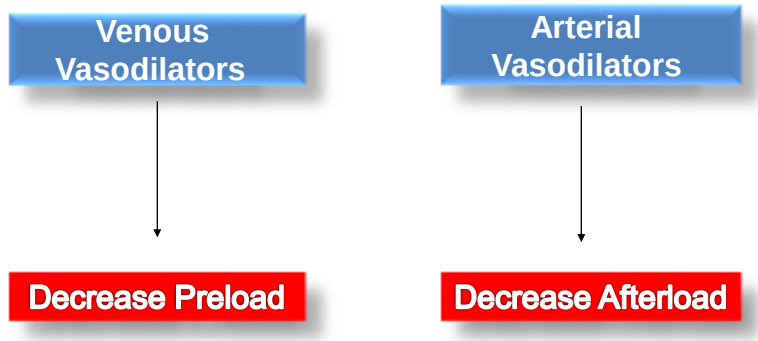
OPTIME Trial (2002)

- Milrinone approved by FDA based on hemodynamic data
- Future trials need to include symptom relief and post discharge outcome data
- OPTIME
  - Prospective trial, randomized, placebo controlled
  - 951 patients
  - Patients had indication for but not all required inotrope for end organ perfusion.
  - Results: No difference in LOS, No difference in subjective improvement
  - Treatment failures more common in milrinone group due to hypotension, more atrial fibrillation in milrinone
  - Not powered for mortality differences
  - **Conclusion: Hemodynamic improvement does not translate into clinical improvement**
  - **Routine milrinone not recommended**

2019 358

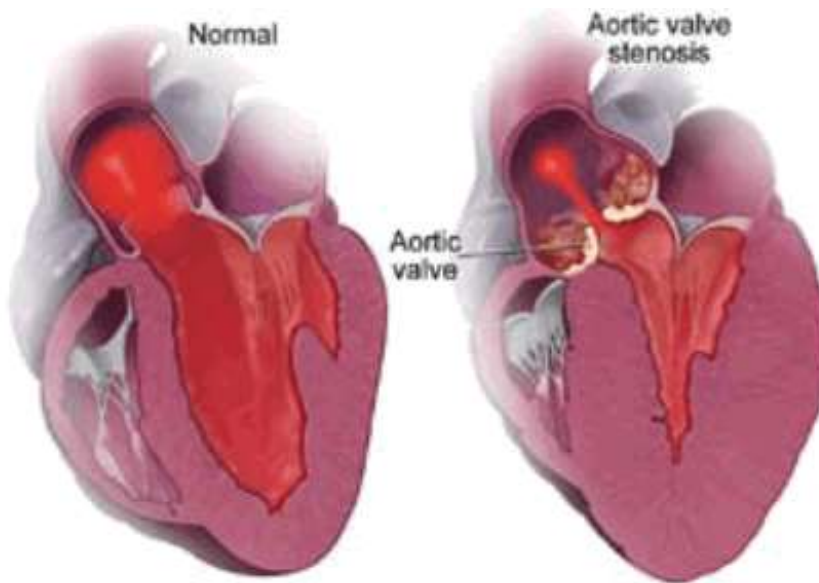
358

A Closer Look at Venous Versus Arterial Vasodilators



Use with caution with significant LV hypertrophy and any significant aortic or mitral stenosis.

359



Use all vasodilators with caution in HFpEF:
More volume sensitive.

360

Nitroglycerin

- Mixed venous and arterial vasodilator
  - Dosage < 1mcg/kg/min = venous vasodilator
  - Dosage > 1mcg/kg/min = arterial and venous vasodilator
- Primarily used as venodilator to quickly reduce preload
  - Ideal in HF accompanied by ischemia, hypertension, or mitral valve regurgitation
  - Sublingual tablets provide high enough dosage to dilate arteries and veins

Heart failure with HTN, ischemia, significant MR: good candidates

361

Nitroglycerin

- **Side Effects:**
  - **H/A,**
  - **Hypotension,**
  - **Flushing**
  - **Tachyphylaxis**
    - **20% resistance even at high doses**
- **Caution in patients with tachycardia or bradycardia – can cause paradoxical bradycardia**

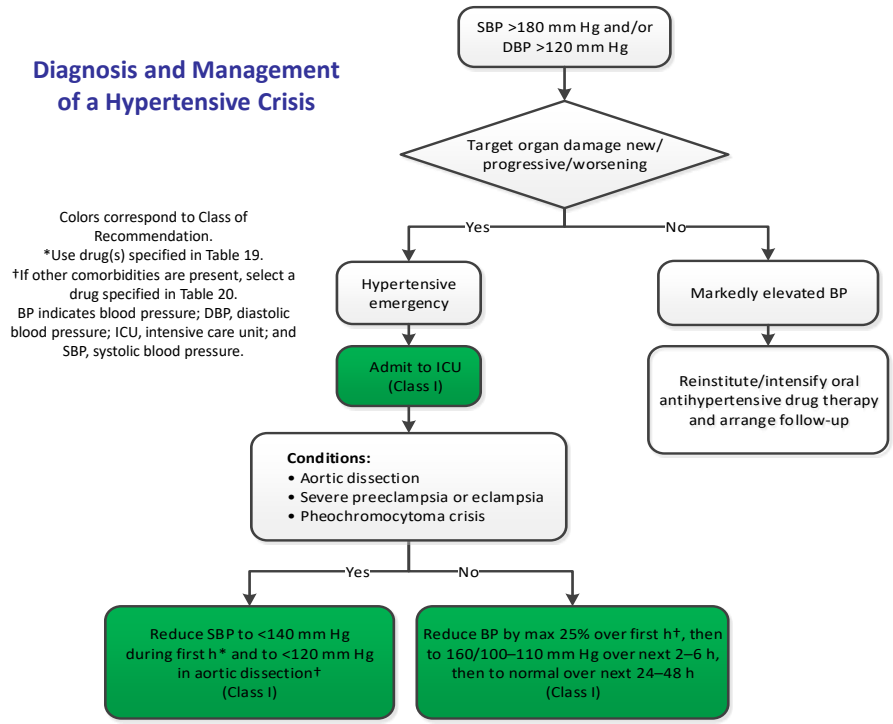
Nursing Considerations:

- Contraindicated with Sildenefil like drugs
- Caution (all venous vasodilators) with:
  - Hypertrophic cardiomyopathy, aortic stenosis, mitral stenosis right ventricular MI
- Treat H/A with pain meds and decrease dose
- Onset IV: 1-2 minutes
- Duration: 3-5 minutes

2019 362

362

Diagnosis and Management of a Hypertensive Crisis



Colors correspond to Class of Recommendation.
*Use drug(s) specified in Table 19.
†If other comorbidities are present, select a drug specified in Table 20.
BP indicates blood pressure; DBP, diastolic blood pressure; ICU, intensive care unit; and SBP, systolic blood pressure.

363

Live Content Slide

When playing as a slideshow, this slide will display live content

Poll: Which of the following drugs utilized in hypertensive emergency are contraindicated in patients with soy or egg allergies?

364

Dihydropyridine Calcium Channel Blockers

Nicardipine

HTN Emergency

- Initial dose 5 mg/hr
- Titrate q 5 min by 2.5 mg/her
- Max dose 15 mg/her

- Contraindicated in advanced aortic stenosis
- No dose adjustment needed in elderly

Clevidipine

HTN Emergency

- Initial 1-2 mg/hr
- Double every 90 sec till BP at target; then increase by less double every 5-10 min
- Max dose 32mg/hr

- Cannot use in soy/egg allergies
- Contraindicated: defective lipid metabolism; acute pancreatitis
- Lower end of dosing in elderly

2019 365

365

Combination Beta and Alpha Blockers

Labetalol

- Alpha 1 blocker
- Non selective beta blocker

- Initial 0.3 to 1.0 mg/kg (max dose 20 mg) slow IV injection every 10 minutes or 0.4 to 1.0 mg/kg/hr continuous infusion u to up to 3mg/kg/hr.
- Total cumulative dose 300 mg
- May repeat every 4 to 6 hours.

- Especially useful in hyper adrenergic syndromes
- Frequently used in aortic dissection
- Caution as per caution with other beta blockers

2019 366

366

Non Selective Alpha Blocker

Phentolamine

- IV bolus dose 5 mg
- Repeat every 10 minutes as needed to achieve target

- Indicated in emergencies induced by catecholamine excess
  - Pheochromocytoma
  - Interactions with monamine oxidase inhibitors
  - Cocaine toxicity
  - Amphetamine overdose
  - Clonidine withdrawal

2019 367

367

Nitroprusside

- Mixed venous and arterial dilator
- Also dilates pulmonary vasculature
- Nitric oxide dependent
- Decreases BP, SVR, PVR, PAOP, RAP

Uses:

- Hypertensive crisis
- CHF
- Acute Mitral Regurgitation
- Other indications for afterload reduction

Initial dose 0.3 - 0.5mcg/kg/min
Titrate in increments of 0.5mcg/kg/min
Max dose 10mcg/kg/min
Onset: 1-2 minutes
Duration: 1-10 minutes

2019 368

368

Nitroprusside

Side Effects

- Hypotension
- Cyanide toxicity:
  - tinnitus, blurred vision, delirium, seizures, muscle twitching, absent reflexes, dilated pupils
  - Increased risk with renal insufficiency
  - Thiosulfate can be administered for duration > 30 minutes or doses ≥ 4-10mcg/kg/min
  - Can cause irreversible neurological changes and cardiac arrest

Nursing Considerations

- Monitor BP carefully- arterial line recommended to prevent "overshoot"
- Dose adjustment needed for elderly
- Tachyphylaxis common with extended use
- Light sensitive

2019 369

369

Myocardial Performance Case Study

2019 370

370

Case Study

- 78 year old female is admitted to the hospital with shortness of breath.
- She has become increasingly short of breath with routine activity over the past 2 days. Today she is short of breath at rest.
- Her weight has increased 6 pounds in the past 3 days.
- She has not taken her medications for 4 days because her prescriptions ran out and she was waiting on her son to get back in town to get them filled.

2019 371

371

Home Meds and History

- Furosemide 20 mg daily
- Lisinopril 20 mg daily
- Metoprolol tartrate 25 mg BID
- Spironalctone 25 mg daily
- Warfarin 5 mg daily
- Synthroid
- OTC NSAIDs

- History of ischemic cardiomyopathy
- CABG @ age 70
- History of atrial fibrillation (? Remote)
- History TIA
- Last known ejection fraction 26%
- Osteoarthritis
- Hypothyroidism

2019 372

372

Physical Assessment / Diagnostics

- BP: 94/74 mmHg
- HR: 110's to 130's
- Rhythm: Atrial fib with RBBB and PVCs
- RR 28-32
- Pale and cool to touch
- Somewhat lethargic
- Heart Sounds with audible S3, systolic murmur 3/6 loudest at apex
- Lungs with crackles ½ up bilaterally
- JVD
- Right Upper quadrant tenderness
- 2+ peripheral edema to mid calf
- Urine output is 10cc in first hour
- SaO2 88% on 4L nasal cannula
- Mild right sided weakness
- K+ 4.9
- H & H 9.2 / 30.1
- BUN 42 / Creatinine 2.0

2019 373

373

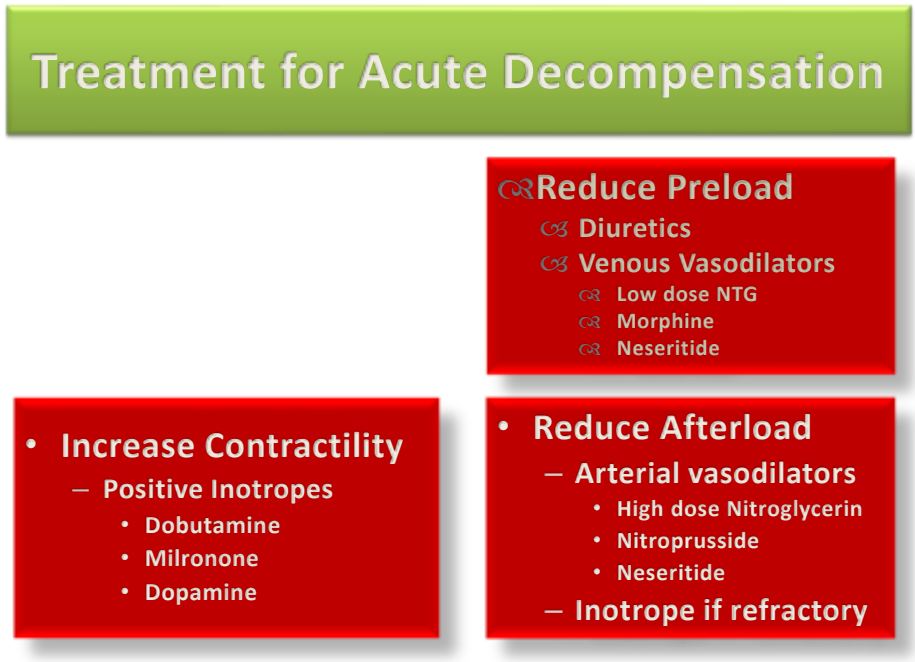
Case Study Evaluation

Warm and Dry: No Congestion Normal Perfusion	**Warm and Wet:** Congestion Normal Perfusion
Cold and Dry: No Congestion Low Perfusion	**Cold and Wet:** Congestion Low Perfusion

BP: 94/74
HR: 110's to 130's
RR 28-32
Pale and cool to touch
Somewhat lethargic
S3
Systolic murmur, 3/6 loudest at apex
Lungs: Crackles ½ up
+ JVD
RUQ quadrant tenderness
2+ edema
Urine output is 10cc/hr
SaO2 88% on 4L Mild Right sided weakness
K+ 4.9
H & H 9.2 / 30.1
BUN 42 / Creatinine 2.0

2019 374

374



375

2019 376

376

General Considerations American Geriatric Society – Beers Criteria for Elderly

www.americangeriatrics.org

Medical Therapy Issues in the Elderly

- Altered responses and vulnerability to drugs with:
  - Hypotensive action
  - Cerebral effects
- Caution with renally cleared drugs
- Be aware of BMI
- Poly pharmacy and comorbid conditions

START LOW and GO SLOW!!

Case Example

- 77 year old female patient previously diuretic naïve admitted with ascites from progressive liver disease secondary to primary sclerosing cholangitis.
- Discharged home on spironolactone 100 mg daily and furosemide 40 mg daily.
- Labs ordered 1 week.

379

Medication Reconciliation

- **Situation**: An accurate medication by history list, and subsequent admission and discharge medication reconciliations are priority interventions for hospitalized patients in order to provide safe and high quality care. Medications comprise a substantial component of the treatment plan for most hospitalized patients, and medication therapy is continued after discharge for the management of most chronic conditions.
- **Background:** In the **"**Results of the Medications At Transitions and Clinical Handoffs (MATCH) Study: An Analysis of Medication Reconciliation Errors and Risk Factors at Hospital Admission" **Over one-third of study patients (35.9%) experienced order errors; 85% of patients had errors originate in medication histories, and almost half were omissions. Cardiovascular agents were commonly in error (29.1%). If undetected, 52.4% of order errors were rated as potentially requiring increased monitoring or intervention to preclude harm; 11.7% were rated as potentially harmful.**
- **Assessment**: Accuracy in medication reconciliation has been identified as an opportunity to improve patient safety and to reduce avoidable admissions and readmissions.

380

Recommendations:

- The nurse's role in accurate medication reconciliation is to obtain a complete and accurate "medications by history". This list of medications is used for medication reconciliation both on admission and discharge.
- If the patient is able to participate, the patient (or family member responsible for medications) should be the primary source. Questions to consider:
- Any prescriptions ordered but not filled
- Any medications you have been told to stop taking or that you are not taking
- Any dose changes that have been made since a prescription was filled
- Any medication changes made at your recent provider appointments

2019 381

381

- **Review each individual medication, dose, and frequency - <u>DO NOT</u> ask the patient a general question covering all medications such as "Have there been any medication changes since the last time you were in the hospital?"**
- Pill bottle labels may not reflect the dose the patient is actually taking – medication doses may be increased or decreased in the outpatient setting.
- Getting a medication list from a pharmacy should only be used when the patient / family / caregiver are not able to give information. Rationale: the patient may use more than one pharmacy, the list reflects only what is prescribed - not what is actually being taken, and pharmacies do not receive orders for discontinued medications (this means that a pharmacy may have a medication listed that has been discontinued for safety reasons).

2019 382

382

- The medications by history from the last hospital discharge should not be used unless it is certain that the patient has had no changes to the medications or doses since discharge and unless it has been verified that the patient has actually been taking all the medications ordered at the last discharge.
- When patients are received from another hospital - home medications (not just hospital medications) need to be included in the medications by history list.
- Always ask the patient about any over the counter medications, vitamins, herbals, and PRN medications. Include the usual frequency of PRN medications if the patient takes on a consistent basis at home.
- If a discrepancy in a medication by history is found at any point after an admission or discharge medication reconciliation has been completed, the nurse must notify the provider so the reconciliation can be revised or corrected if indicated.

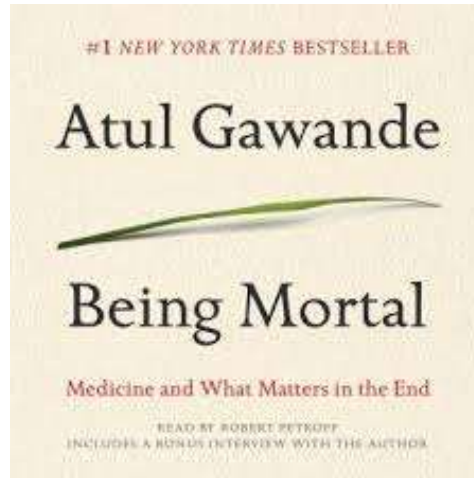
2019 383

383

- When discharging a patients and listing the time for the last dose of each medication please bring to the patient's attention that the times you have listed do not represent a medication schedule for them to follow at home. There are reports that some patients are using the times of the last dose as their schedule and are therefore taking BID or TID medications only once per day. Please emphasize any medications that are to be taken more than once per day.
- When sending the patients home on new medications please clarify with the patient if the medication is for short term only or if the medication is to be continued indefinitely for ongoing medical management. If the medication is intended for ongoing medical management please verify refills have been ordered or instruct patient regarding who to call to obtain a refill.

2019 384

384



Full of eye-opening research and riveting storytelling, *Being Mortal* asserts that medicine can comfort and enhance our experience even to the end, providing not only a good life but also a good end.

385

Our job is to support quality of life, which means two things: as much freedom from the ravages of disease as possible and the retention of enough function for active engagement in the world.

Juergen Bludau
From Being Mortal

386

2019

Vision Statement

Practice with joy.
Positively impact every patient and family on their journey and provide safe passage by meeting them where they are, connecting with them in a meaningful way, and delivering care with wisdom and intention.
- Karen and Cindy

387

387

THANK YOU!!!

Enjoy NTI!

BE THE BEST THAT YOU CAN BE EVERY DAY.
YOUR PATIENTS ARE COUNTING ON IT!

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2019 388

388