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# Keeping Your Patients with Heart Failure Out of the Hospital: Preventing Drug-Induced Exacerbations of Heart Failure

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# Disclosure

- The authors have no conflicts of interest to disclose

# Learning Objectives

1. Distinguish medications that exacerbate heart failure (HF) from those that cause de novo myocardial dysfunction.
2. Given a medication associated with exacerbation of HF, describe a proposed mechanism for worsening myocardial function.
3. List general approaches to preventing drug-induced exacerbation of HF.
4. Given a patient with HF on a medication associated with HF exacerbation, devise a medication therapy plan for preventing further decompensation.

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JW is transferred to your institution for further management of acute decompensated heart failure (ADHF) with cardiogenic shock.
Please take a moment to review the pertinent information from his case.

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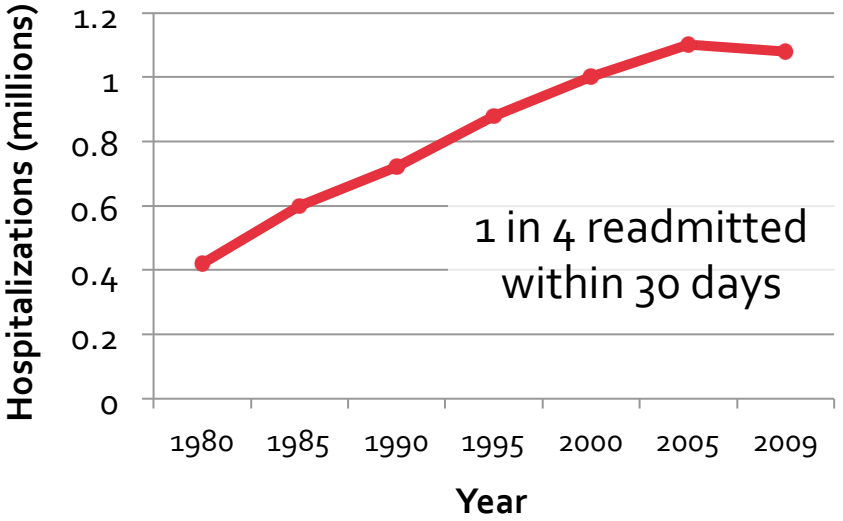
# What precipitated this patient's ADHF?

The lifetime risk of developing heart failure is

**1** In **5**

## Heart Failure Hospitalizations




JAMA. 2009 Jul 22;302(4):394-400. Circulation. 2013 Jan 1;127(1):143-52. Circ Cardiovasc Qual Outcomes. 2009 Sep;2(5):407-13

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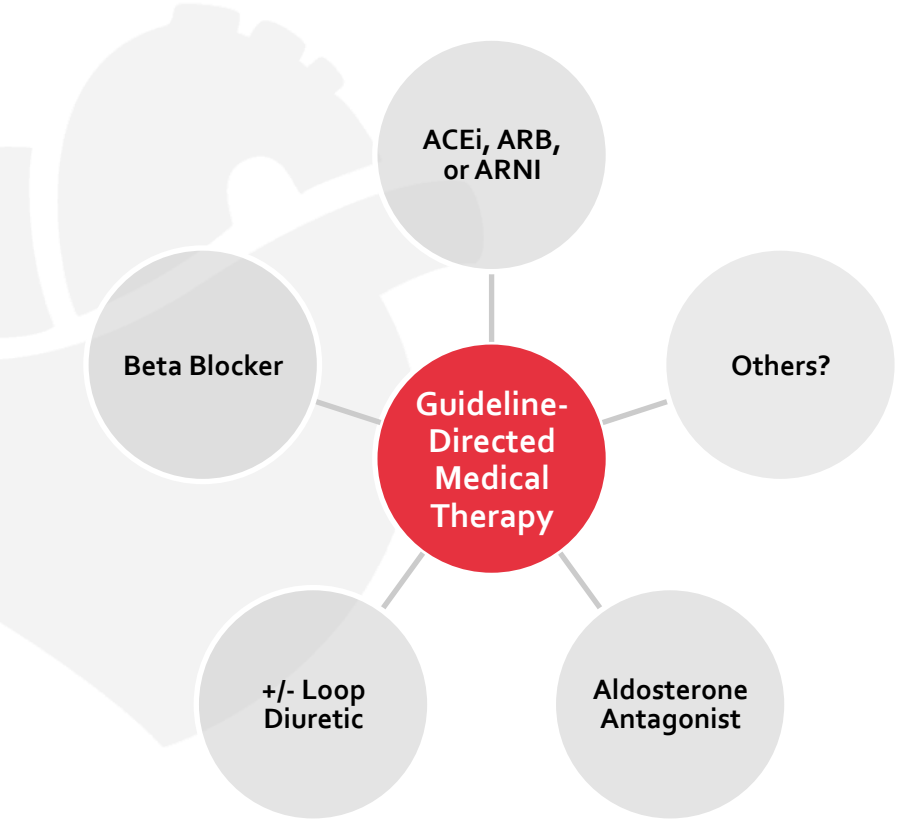


- Polypharmacy commonly defined as taking ≥ 5 medications
- Nearly half of patients with heart failure over the age of 65 have ≥ 5 co-existing conditions
- Does not account for non-prescription medications, herbal supplements, and vitamins (1 in 9 report using)

ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, ARNI = angiotensin II receptor blocker / neprilysin inhibitor. Circulation. 2016 Aug 9;134(6):e32-69. Curr Cardiol Rep. 2012 Jun;14(3):276-84. J Card Fail. 2009 Sep;15(7):600-6.

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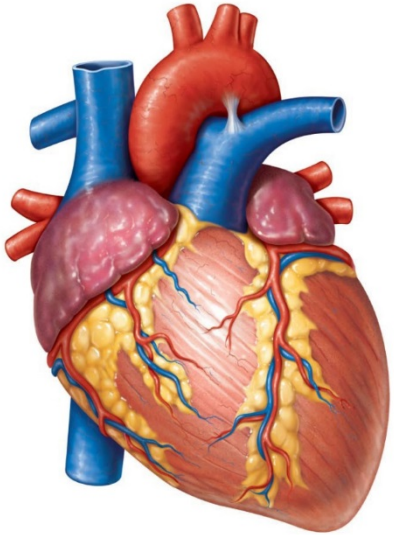
# Mechanisms of Drug-Induced Heart Failure

## 1 Myocardial Toxicity

Direct cellular injury (e.g., toxic free radicals), commonly seen with chemotherapeutic agents (not the focus of this presentation)



## 2 Exacerbation of Underlying Myocardial Dysfunction

- Decreased cardiac output
- Increased systemic vascular resistance
- Increased sodium and fluid retention
- Drug-drug interactions that impair benefit of heart failure therapies

# Beta Blockers

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# "Start Low, Go Slow"

| Agent | Starting Dose | Target Dose | Titration Schedule |
|---|---|---|---|
| **Bisoprolol** | 1.25 mg qday | 10 mg qday | Every 1 week until 3.75 mg, then every 4 weeks |
| **Carvedilol** | 3.125-6.25 mg bid | 25-50 mg bid | Every 2 weeks |
| **Metoprolol XL** | 12.5-25 mg qday | 200 mg qday | Every 2 weeks |

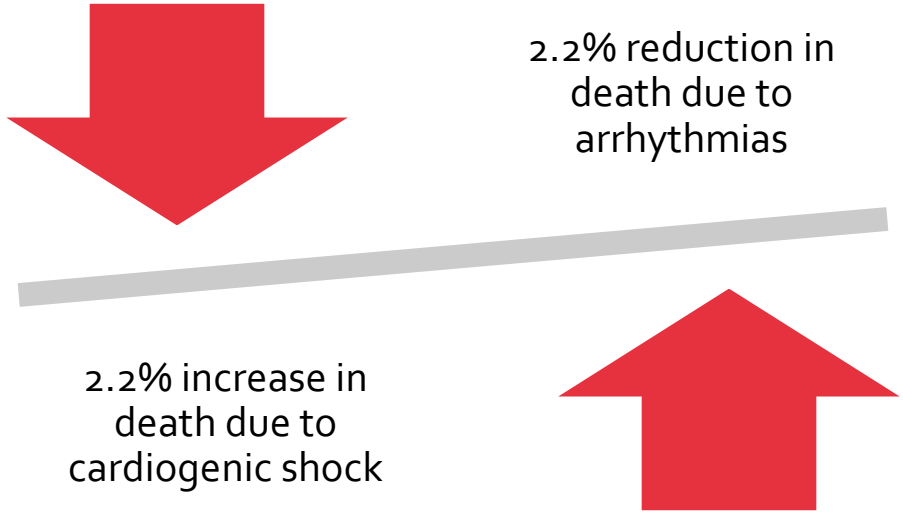
- Can be continued in ADHF (in absence of cardiogenic shock) unless thought to be the cause of ADHF
- Can be safely initiated at low doses at discharge from ADHF hospitalization

Lancet. 1999 Jan 2;353(9146):9-13. Lancet. 1999 Jun 12;353(9169):2001-7. N Engl J Med. 2001 May 31;344(22):1651-8. Eur Heart J. 2009 Sep;30(18):2186-92. J Am Coll Cardiol. 2004 May 5;43(9):1534-41.

# Other Indications for Beta Blockers

Risk of exacerbation often overlooked when treating other conditions (e.g., acute coronary syndrome, atrial fibrillation)

The COMMIT trial evaluated early beta blockade following acute myocardial infarction, where metoprolol was up-titrated to 200 mg in first 24-48 hours.




Lancet 2005; 366: 1622–32.

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# Calcium Channel Blockers

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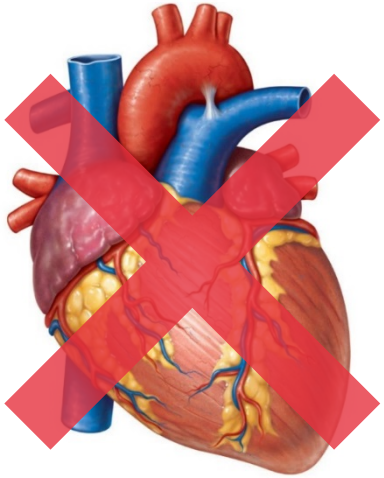
# Calcium Channel Blockers

## Non-Dihydropyridines (Diltiazem, Verapamil)

- Can exacerbate heart failure via negative inotrope and chronotropic effects
- Unlike beta blockers, no long-term remodeling benefits



## What about Dihydropyridines?

Circulation. 1991 Jan;83(1):52-60.

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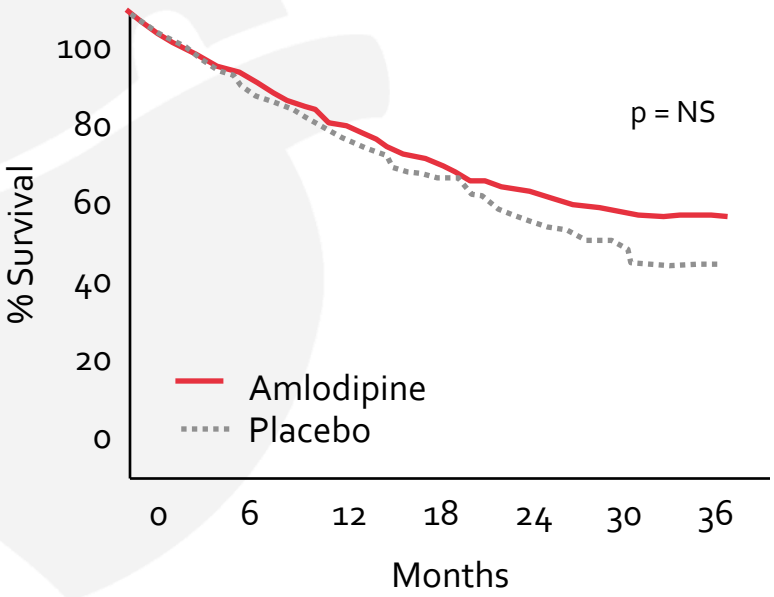
## PRAISE

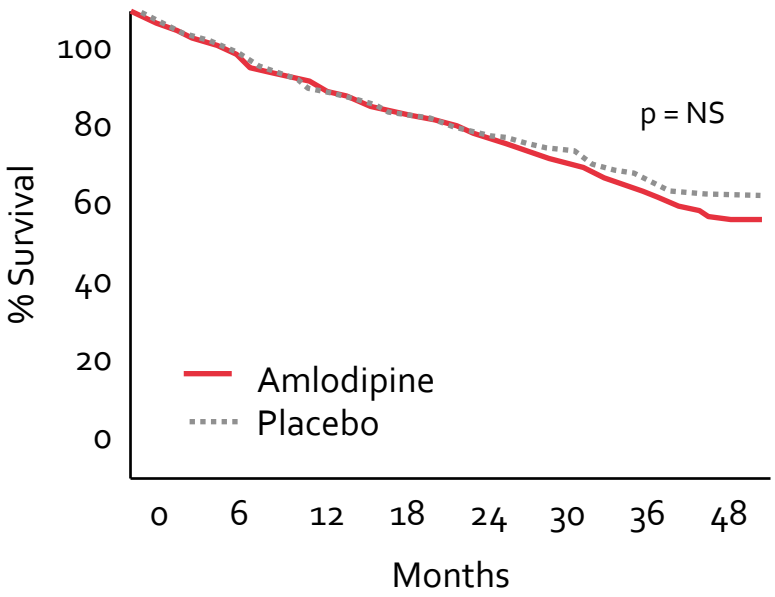
Any Chronic Heart Failure (EF < 30%)




**50% increased risk** of both pulmonary edema and peripheral edema ($p < 0.05$)

## PRAISE-2

Nonischemic Cardiomyopathy (EF < 30%)




Nearly **3x increased risk** of pulmonary edema, **60% increased risk** of peripheral edema ($p=0.001$)

EF = ejection fraction.

N Engl J Med. 1996 Oct 10;335(15):1107-14. JACC Heart Fail. 2013 Aug;1(4):308-14.

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# Antiarrhythmics

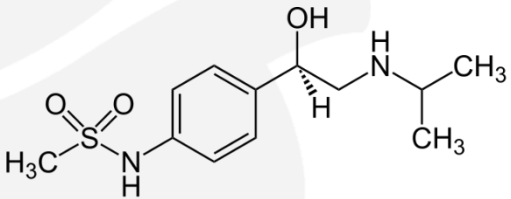
# Class I Antiarrhythmics

| Class | Agent | Risk in Heart Failure |
|---|---|---|

*Oral procainamide no longer available in the US.

N Engl J Med. 1991 Mar 21;324(12):781-8. Eur Heart J. 1985 Aug;6(8):664-71. Eur J Clin Pharmacol. 1975 Apr 4;8(3-4):167-73. Eur Heart J. 1992 Jan;13(1):22-7.

# Sotalol (A Tale of Two Isomers)

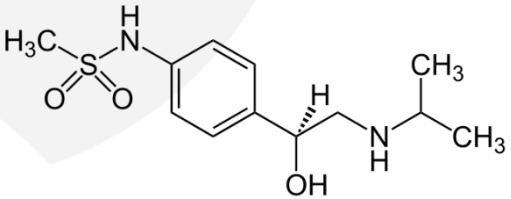



**D-Sotalol**

Class III Antiarrhythmic

Increased mortality in patients with LV dysfunction after myocardial infarction

\+ ?




**L-Sotalol**

Beta Blocker

Reduced re-infarction rate and was associated with numerically fewer deaths after MI

LV = left ventricular, MI = myocardial infarction.

Lancet. 1996 Jul 6;348(9019):7-12. Lancet. 1982 May 22;1(8282):1142-7

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# Dronedarone

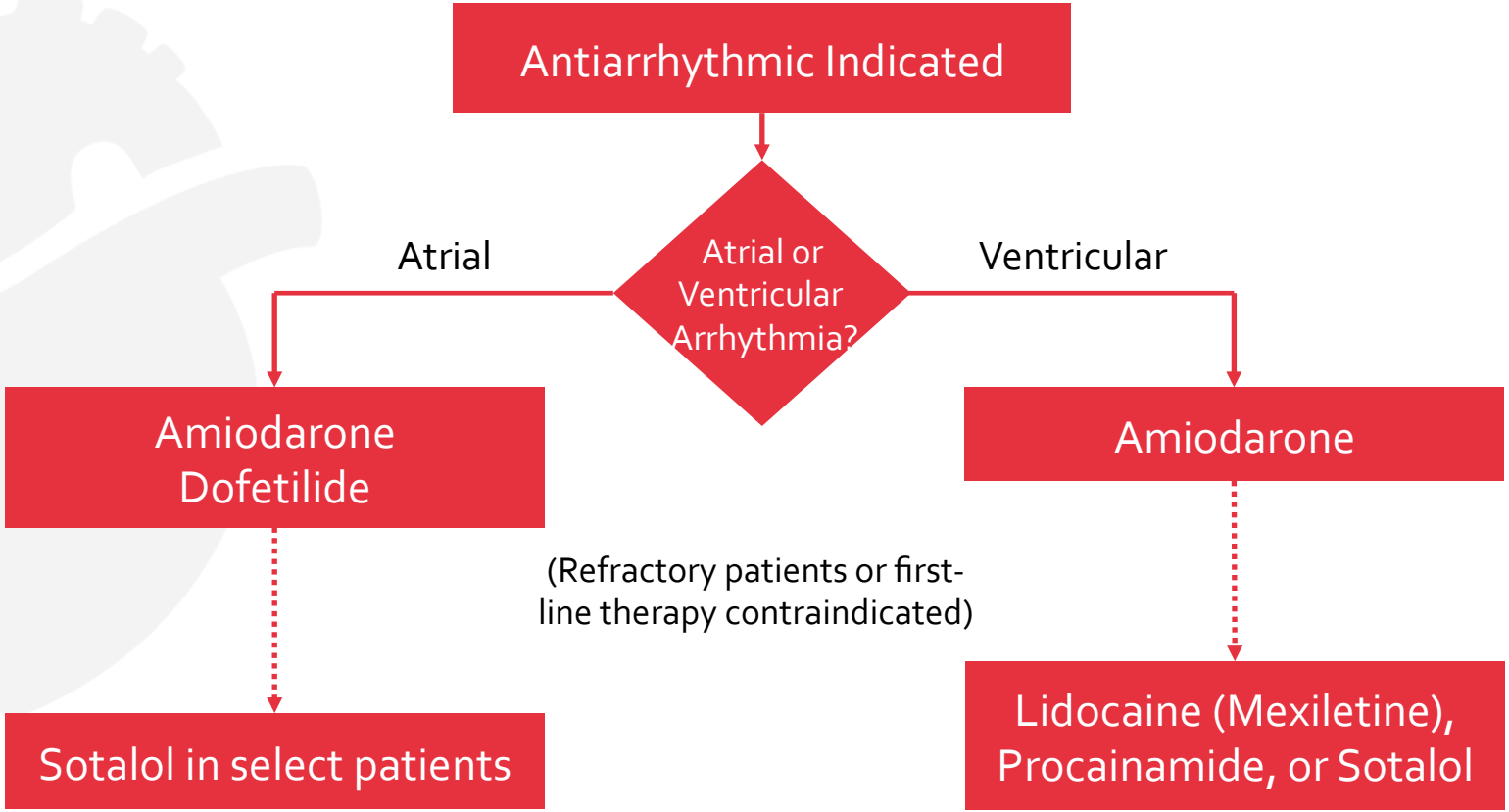
**ANDROMEDA**

- Advanced heart failure (coexisting arrhythmia not a requirement for inclusion)
- Terminated early due to increased mortality

**PALLAS**

- Permanent atrial fibrillation (2/3 with heart failure history, most with preserved EF)
- Terminated early due to increased mortality

N Engl J Med. 2008 Jun 19;358(25):2678-87. N Engl J Med. 2011 Dec 15;365(24):2268-76.




Adapted from: Circulation. 2014 Dec 2;130(23):2071-104.

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# How could this patient's atrial fibrillation have been managed differently?

# Intravenous Sedatives

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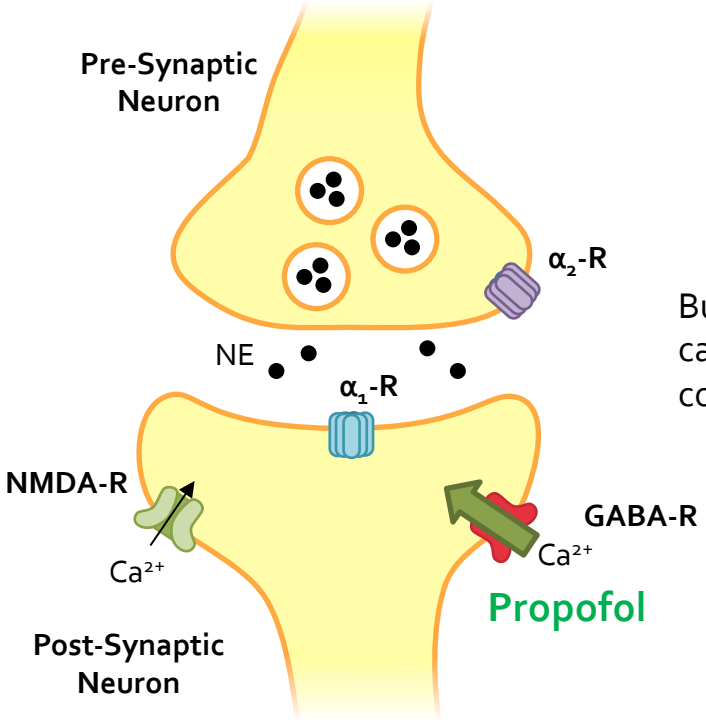
# Propofol




But does the effect of propofol on calcium exchange impair cardiac contractility?

GABA = gamma aminobutyric acid, NE = norepinepherine,
NMDA = N-methyl-D-aspartate, R = receptor

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$$CO = HR \times SV$$

**Propofol can decrease preload secondary to venodilation, especially in setting of hypovolemia**

- Preload (volume)
- Afterload (impedance)
- Contractility (strength)

CO cardiac output, HR heart rate, SV stroke volume

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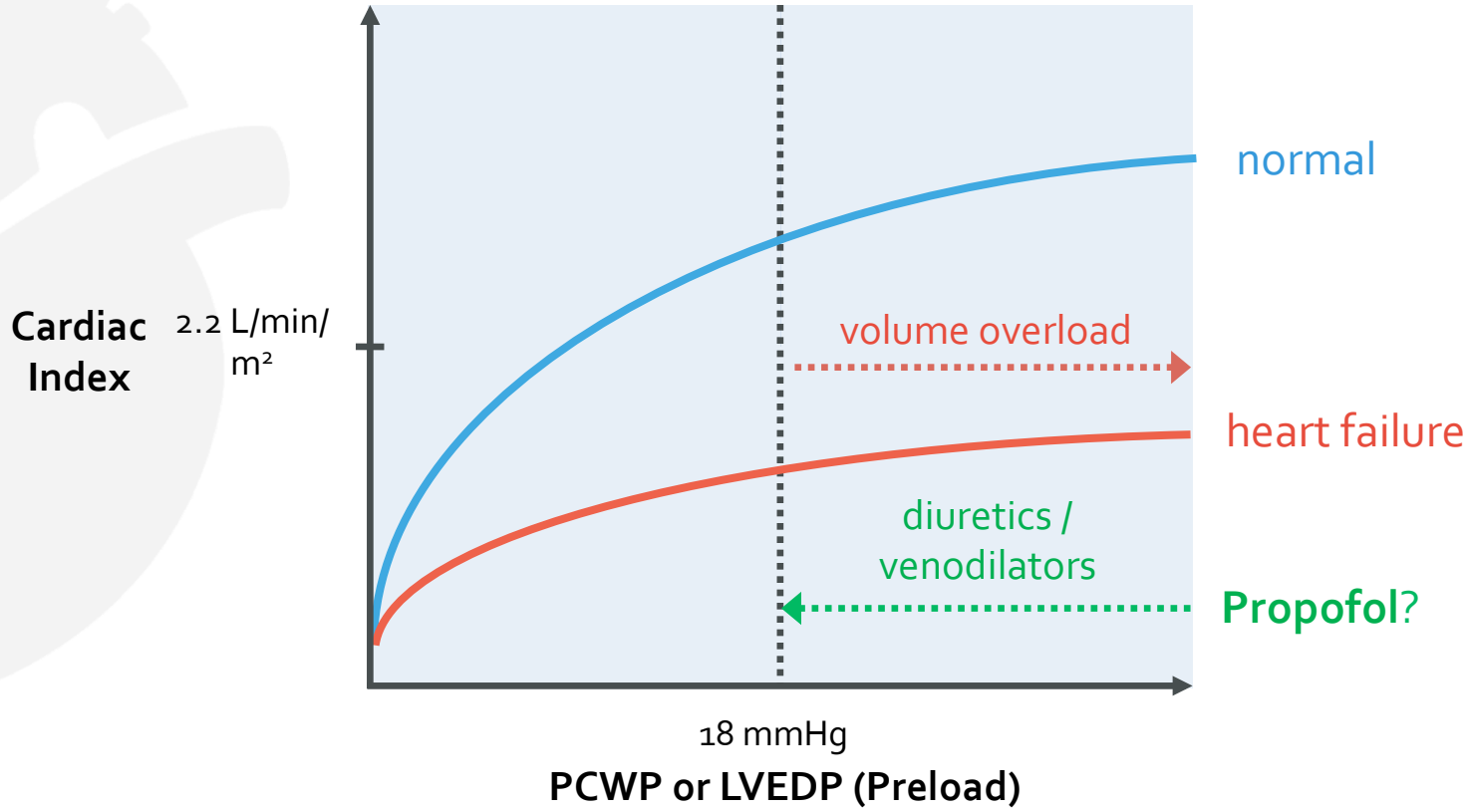


PCWP = pulmonary capillary wedge pressure, LVEDP = left ventricular end-diastolic pressure

Semin Cardiothorac Vasc Anesth. 2006 Mar;10(1):43-8. Circulation. 2016 Aug 9;134(6):e32-69.

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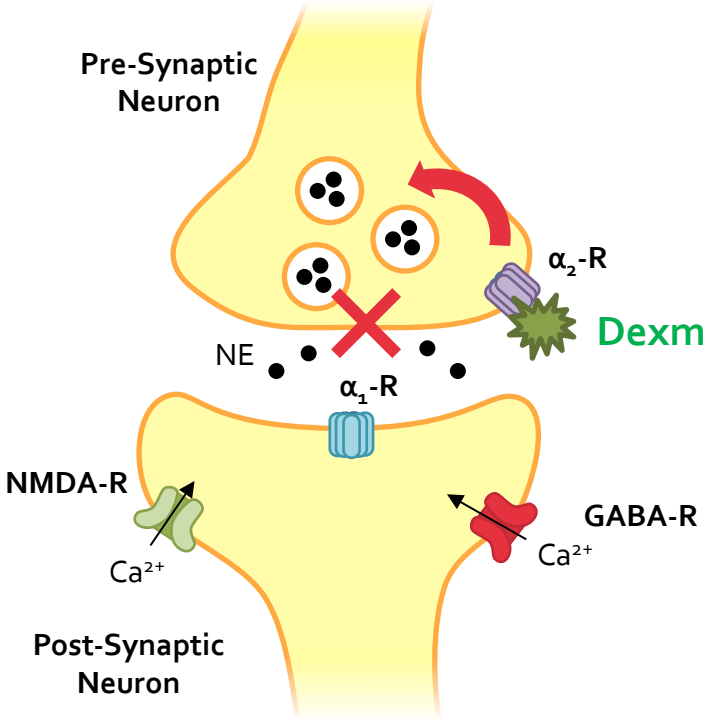
# Dexmedetomidine




But what about the effects of dexmedetomidine on other $\alpha_2$ receptors?

GABA = gamma aminobutyric acid, NE = norepinepherine,
NMDA = N-methyl-D-aspartate, R = receptor

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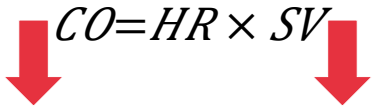



**Effects of dexmedetomidine at cardiac $\alpha_2$ receptors may result in decreased heart rate and thus cardiac output**

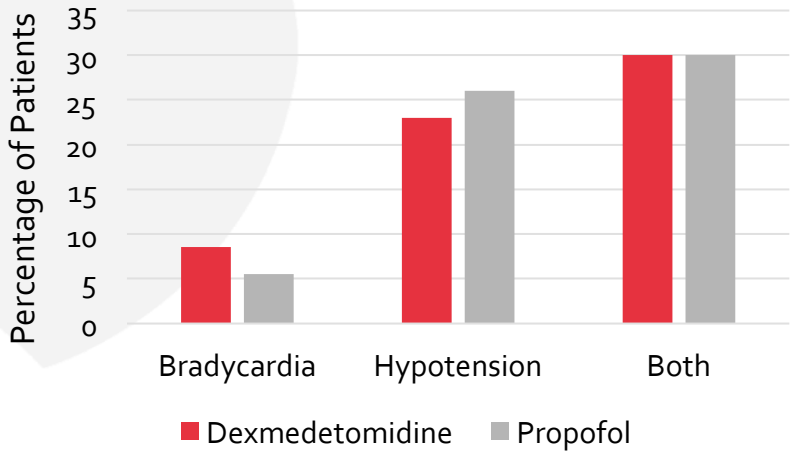
**Effects on peripheral $\alpha_2$ receptors results in variable effects on afterload**

CO cardiac output, HR heart rate, SV stroke volume

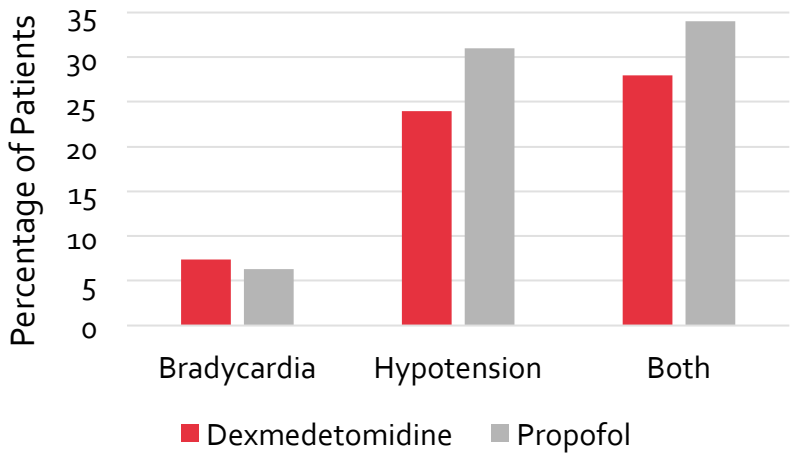
# Propofol vs. Dexmedetomidine

*No significant differences in hemodynamic effects among patients admitted to neurocritical care unit (n = 324)*

*Unmatched Cohort*




*Propensity-Matched Cohort*




Adapted from: Crit Care Med. 2014 Jul;42(7):1696-702

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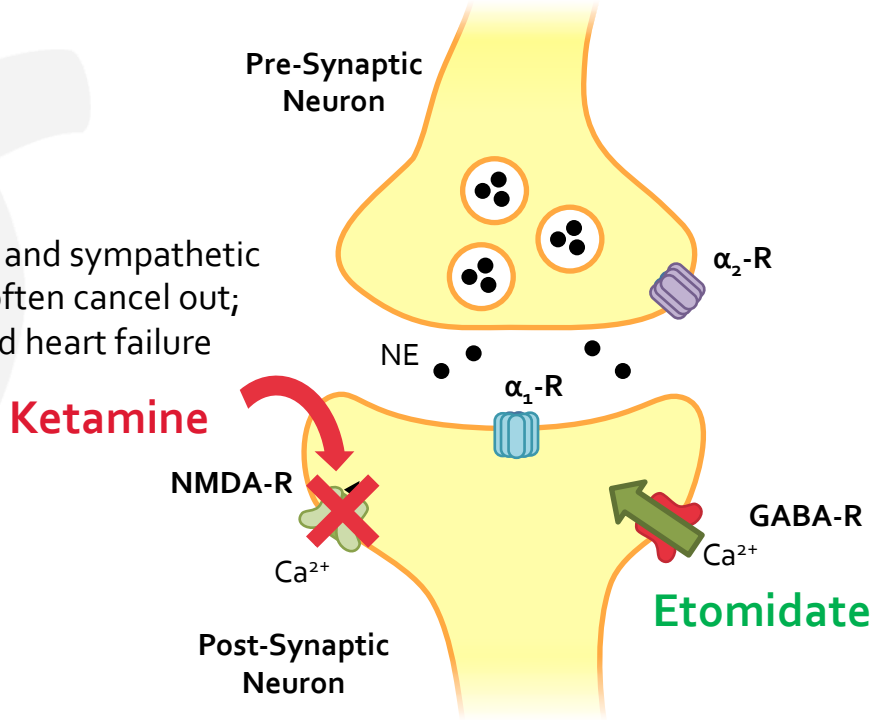
# Miscellaneous Agents

Negative inotropic and sympathetic activation effects often cancel out; caution in advanced heart failure




Minimal myocardial depression; preferred for inducing anesthesia in patients with structural heart disease

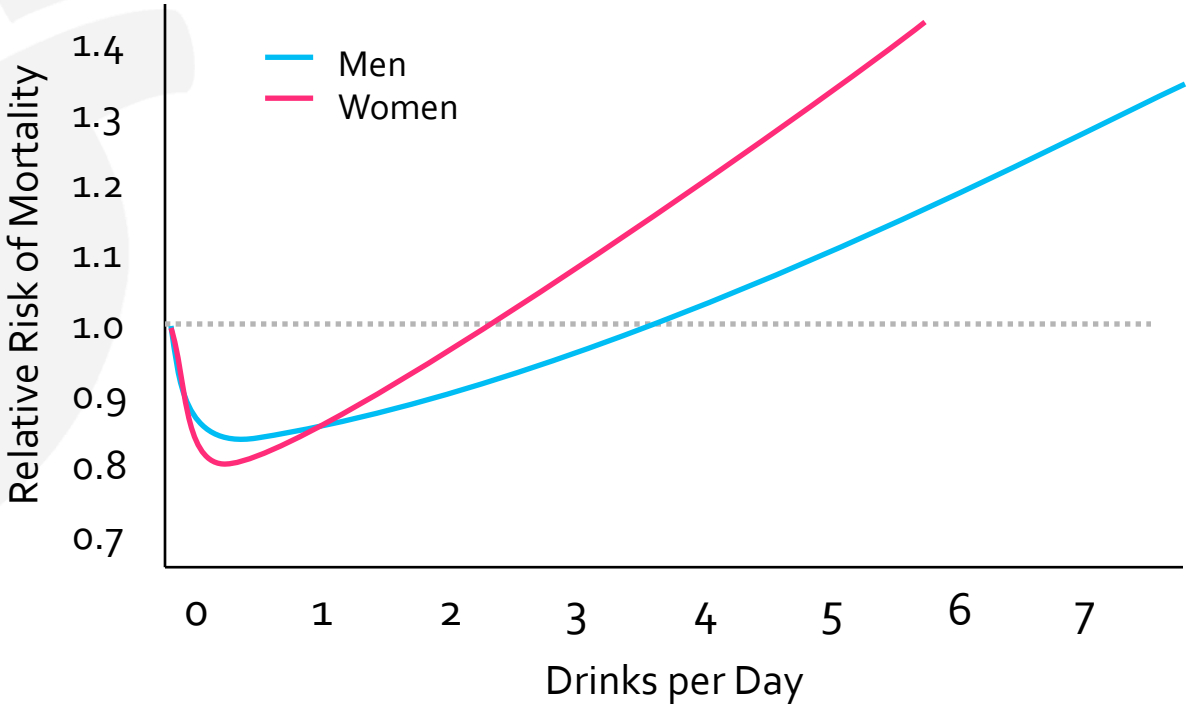
GABA = gamma aminobutyric acid, NE = norepinepherine, NMDA = N-methyl-D-aspartate, R = receptor

# How should this patient's sedation be managed?

(Assuming he is negative for alcohol withdrawal)

# Illicit Substances

# Alcohol




Adapted from: Arch Intern Med. 2006 Dec 11-25;166(22):2437-45.

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# Alcohol

## Chronic

- Common cause of dilated cardiomyopathy
- Risk increased at ≥ 7-8 drinks per day for 5-10 years
- Abstinence advocated but moderation may help

## Acute

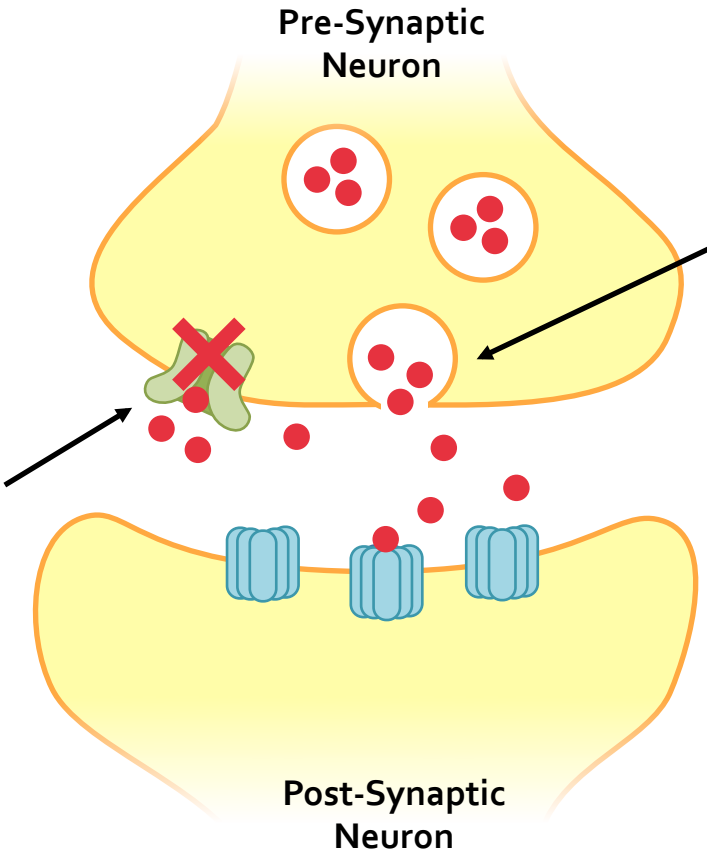
- ADHF may result from myocardial depression and/or volume overload
- Moderation should be recommended at a minimum

J Am Coll Cardiol. 2013 Oct 15;62(16):e147-239. Ann Intern Med. 2002 Feb 5;136(3): 192-200

# Stimulants

All stimulants increase sympathetic activity albeit by two different mechanisms:

Reduced neurotransmitter reuptake (e.g., cocaine)




Increased neurotransmitter release (e.g., amphetamines)


**Increases in heart rate and contractility may offset afterload; effect on cardiac output will vary**

**Acute ingestion increases afterload, which can reduce stroke volume and provoke flash pulmonary edema**

*Chronic stimulant use contributes to the same neurohormonal mechanism responsible for other types of heart failure with reduced ejection fraction.*

CO cardiac output, HR heart rate, SV stroke volume. Am J Med. 2007 Feb;120(2): 165-71. Child Adolesc Psychiatr Clin N Am. 2008 Apr;17(2):459-74, xi.

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# Stimulants

## Illicit Substances

- Just stop!

## Medically Indicated

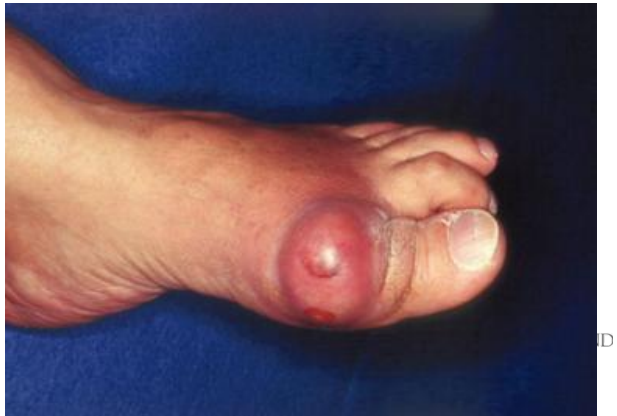
- Avoid when possible
- Cognitive-behavioral therapy
- Consider non-stimulants (e.g., atomoxetine, $\alpha_2$ agonist)

J Am Coll Cardiol. 2013 Oct 15;62(16):e147-239.

# What should be done about this patient's reported alcohol use?

# "My big left toe is killing me"

- At its worst, 9/10 pain
- Patient presents wearing flip-flops
- Pain similar to prior gout attack a few years ago
- Patient took three doses of ibuprofen 400 mg over the last 24 hours with some pain relief
- Additional data:
  - Creatinine clearance 50 ml/min



http://img.medscapestatic.com/pi/meds/ckb/48/39048tn.jpg

# Non-steroidal anti-inflammatory drugs (NSAIDs)

- Heerdink, ER et al. 1998
  - Cohort study to evaluate risk of HF among those 50 yrs or older and receiving a diuretic and NSAID
  - Combination of diuretic and NSAID use associated with an increased risk of HF hospitalization adjusted relative risk (RR) 1.8 (95% confidence interval (CI), 1.4-2.4)
- Rotterdam Study 2002
  - Follow-up evaluation of a patients enrolled in prospective cohort study, which evaluated the prevalence, incidence and determinants of select diseases in the elderly
  - Relative risk of first occurrence of HF in those with current NSAID use was 1.1 (95% CI 0.7-1.7)
  - The adjusted RR of HF relapse was 9.9 (95% CI, 1.7-57.0) for patients with HF and at least 1 NSAID prescription
- Huerta, C et al. 2006
  - Cohort with nested case-control of patients in a general practice
  - Relative risk of HF admission in current users of NSAIDs with prior HF was 8.6 (95% CI 5.3 to 13.8)
  - No effect of NSAID dose or duration on HF admission risk

Arch Intern Med 1998;158:1108-12. Arch Intern Med 2002;162:265-70. Heart 2006;92:1610–1615.

# NSAIDs/Cyclo-oxygenase 2 inhibitors

- Cohort study to evaluate the risk of death and hospitalization due to acute MI or HF associated with use of NSAIDs in those with HF
- Dose-dependent increase risk of death, hospitalization for HF and MI

| | Death<br>HR* (95% CI), p value | HF hospitalization<br>HR* (95% CI), p value |
|---|---|---|
| Celecoxib | 1.75 (1.63-1.88), p <0.001 | 1.24 (1.12-1.39), p <0.001 |
| Diclofenac | 2.08 (1.95- 2.21), p <0.001 | 1.35 (1.24-1.48), p <0.001 |
| Ibuprofen | 1.31 (1.25-1.37), p <0.001 | 1.16 (1.10-1.23), p <0.001 |
| Naproxen | 1.22 (1.07-1.39), p=0.004 | 1.18 (1.00-1.40), p =0.05 |
| Other NSAIDs | 1.28 (1.21-1.35), p <0.001 | 1.27 (1.18-1.36), p <0.001 |

* Adjusted hazard ratio (HR) for age, sex, year of first hospitalization for HF, comorbidity, severity and concomitant medical treatment

Arch Intern Med. 2009;169(2):141-149.

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# NSAIDs/Cyclo-oxygenase 2 inhibitors

- Proposed mechanism of adverse effect in those with decreased effective circulating blood volume
  - Inhibition of prostaglandin synthesis leads to:
    - Decreased renal blood flow
    - Sodium and water reabsorption

- Recommendation:
  - Avoid use

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Drugs 2003; 63: 525-534. J Am Coll Cardiol. 2013 ;62:e147-239.

# Corticosteroids

| | Duration of actions (hours) | Relative glucocorticoid activity | Relative mineralocorticoid activity |
|---|---|---|---|
| ***Glucocorticoids*** | | | |
| Hydrocortisone | 8-12 | 1 | 1 |
| Prednisone | 12-36 | 4 | 0.8 |
| Methylprednisolone | 12-36 | 5 | minimal |
| Dexamethasone | 36-72 | 30 | minimal |
| ***Mineralocorticoid*** | | | |
| Fludrocortisone | 12-36 | 10-15 | 125-150 |

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Allergy, Asthma Clin Immunol 2013, 9:30.

# Corticosteroids

- Current glucocorticoid use associated with elevated HF risk in retrospective, case-control study of patients ≥ 50 years old with at least one glucocorticoid prescription (adjusted odds ratio (OR) 2.66; 95% CI, 2.46-2.87)

| Prednisone daily equivalent dose | Adjusted OR for HF risk |
|---|---|
| < 7.5 mg | 1.95 (95% CI 1.72 to 2.21) |
| 7.5 – 20 mg | 2.27 (95% CI 2.00 to 2.59) |
| > 20 mg | 3.69 (95% CI 3.26 to 4.18) |

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Heart 2004, 90:859–65.

# Corticosteroids Effect on Sodium and Water Excretion

- Liu, C et al. 2015
  - Low-dose prednisone x 10 days (15 mg/d, n =8) increased urine output in patients with symptomatic HF vs. standard of care (n=10, $p < 0.05$)
  - Medium (30 mg/d, n = 10) and high-dose prednisone (60 mg/d, n = 10) increased 24 hour sodium excretion vs. control ($p<0.01$ and $p<0.05$, respectively)
  - Weight reduction, at day 10

| | |
|---|---|
| Placebo | 1.5 ± 1.1 kg |
| Low-dose prednisone | 3 ± 1.8 kg |
| Medium-dose prednisone | 3.9 ± 3.2 kg |
| High-dose prednisone | 4.1 ± 2.8 kg |

- Recommendations:
  - Use when clinically indicated and no alternative exists
  - Use lowest dose and shortest course of therapy possible
  - Monitor for worsening/progression of HF symptoms

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Heart 2004, 90:859–65. J Cardiovasc Pharmacol 2015;66:316–322.

# What medication(s) should be recommended to manage this patient's gout?

# Acute Gout Treatment Recommendations

| Colchicine | Corticosteroids | NSAIDs |
| --- | --- | --- |
| • Use if early presentation | • Unable to use colchicine<br>• Intra-articular: monoarticular gout<br>• Oral: Polyarticular gout | • Use should be avoided |

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Am Fam Physc 2014;90:831-36. Can J Cardiol 2016;32:296-310.

# Pharmacy Curb-side Consult

- You practice in a HF clinic and provide care for JW
- His primary care provider would like to know if it would be OK for him to receive one of the newer medications for type 2 DM
- HF status (at visit two weeks ago): New York Heart Association (NYHA) Class II symptoms and euvolemic
- Hemoglobin A1c is 8.6% (two years ago it was 8%)
- Current medications for DM: metformin 1000 mg BID
- Laboratory data: within normal limits except serum creatinine 2 mg/dl (stable)

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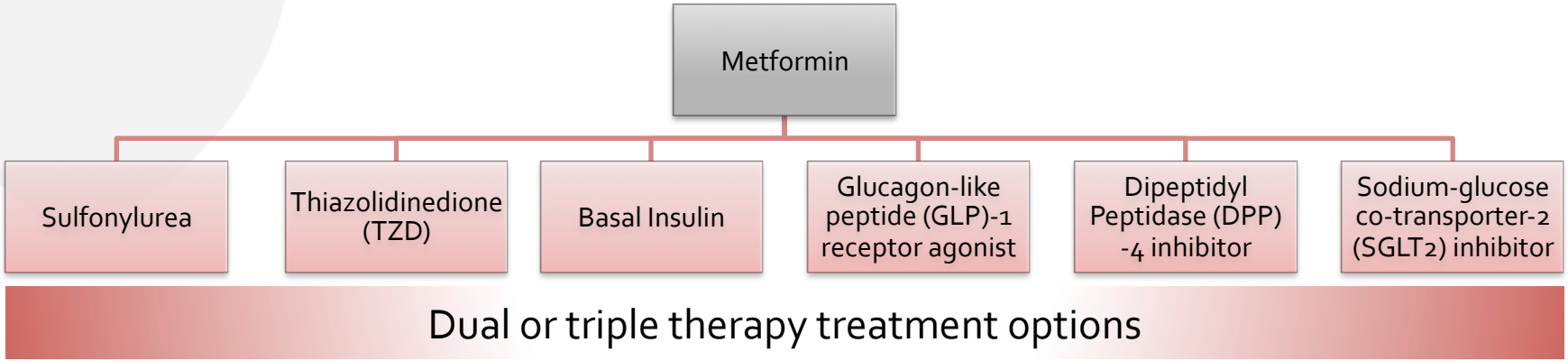
DM = diabetes mellitus

# Antihyperglycemic Therapy for Type 2 Diabetes*

| Monotherapy | Dual therapy | Triple therapy |
|---|---|---|
| • Initiation of therapy: A1c < 9%<br>• Metformin, unless contraindicated | • Initiation of therapy: A1c ≥ 9%<br>• A1c not achieved with 3 mo. of monotherapy | A1c not achieved with 3 mo. of dual therapy |




* If A1c ≥ 10%, blood glucose ≥ 300 mg/dl or overt symptoms– consider injectable therapy

Diabetes Care 2017;40(Suppl. 1):S64–S74.

| | |
|---|---|
| Metformin | • Recommended as first-line therapy<br>• Contraindications similar to general population |
| Sulfonylurea | • Safe for use<br>• Contraindications similar to general population |
| Insulin | • Safe for use<br>• Use may predict risk for developing HF |
| GLP-1 receptor agonist | • No increased risk of HF observed in clinical trials with lixisenatide, liraglutide or semaglutide |

Diabetes Care 2001;24: 1614-19. Eur Heart J 2016;37: 2129-2200. Diabetes Care 2017;40(Suppl. 1):S64–S74. Ann Intern Med. 2017;166:191-200. N Engl J Med 2016;375:311-22. JAMA 2016;316:500-08. N Engl J Med 2016;375:1834-44.

# Thiazolidinediones

- Mechanism of adverse effect
  - Not established
  - Dose-related fluid retention; risk increased when combined with insulin
- Boxed warning
  - Initiation of therapy in those with NYHA Class III/IV symptoms is contraindicated
  - Use not recommended for those with symptomatic HF
  - Reduce the dose or discontinue therapy if HF symptoms develop during therapy
  - Use can cause or exacerbate HF
- Recommendations for use
  - Consider alternative treatment options for those with a depressed left ventricular ejection fraction (LVEF)
  - Do not initiate in those with HF symptoms
  - Discontinue therapy if HF symptoms develop

Pioglitazone. Product labeling. Accord Healthcare Inc. 2016; Rosiglitazone. Product labeling. West-ward Pharmaceutical Corp. 2009; BMJ 2011;342:d1309; Am J Cardiovasc Drugs 2011;11: 115-128.

# DPP-4 Inhibitors

## Alogliptan

*EXAMINE Trial*

- Overall, no difference in the risk of HF hospitalization with alogliptin vs. placebo: HR, 1.19 (95% CI, 0.90–1.58), p=0.220
- Without HF history, alogliptin associated with increased HF hospitalization risk: HR, 1.76 (95% CI, 1.07–2.90), p=0.026
- Product labeling
  - Consider risk vs. benefit prior to initiation if patient at risk for developing HF
  - Consider discontinuation if HF develops

## Linagliptan

- Not associated with an increased risk of HF hospitalization
- Product labeling: no comment

Cardiovasc Diabetol 2012;11: 3. N Engl J Med 2013; 369:1327-35. Lancet 2015;385: 2067–76/ J Diabetes Its Complications 2016;30:1378–1384. Nesina (alogliptin) package insert. Takeda Pharmaceuticals America, Inc. 2016. Tradjenta (linagliptan) package insert. Boehringer Ingelheim Pharmaceuticals, Inc. 2015.

# DPP-4 Inhibitors

## Saxagliptan

- SAVOR-TIMI 53 Trial: risk of HF hospitalization increased with saxagliptan (3.5%) vs. placebo (2.8%) HR, 1.27 (95% CI, 1.07-1.51), p = 0.007
  - Risk increased: prior HF symptoms, an elevated baseline N-terminal pro-natriuretic peptide , or an estimated glomerular filtration rate (eGFR) $\leq$ 60 ml/min/$m^2$
- Product labeling
  - Consider risk vs. benefit in those at risk for developing HF
  - Monitor for signs and symptoms during therapy; patients to report symptoms immediately
  - Consider discontinuation if HF develops

## Sitagliptan

- TECOS trial: No difference in the risk of HF between those receiving sitagliptan or placebo
- Retrospective cohort studies:
  - Baseline HF: adjusted OR, 1.84 (95% CI, 1.16 to 2.92)
  - Those on dialysis: adjusted HR, 1.52 (95% CI, 1.21–1.90)
- Product labeling: no comment

N Engl J Med 2015; 373:232-42. JAMA Cardiol 2016:1:126-35. Diabet Med 2016;33:621–30. Sci Rep 2016;6:304-99. Onglyza (saxagliptan) package insert. Astra Zeneca Pharmaceuticals LP. 2016. Januvia (sitagliptan) package insert. Merck & Co., Inc., 2015.

# DPP-4 Inhibitors: Recommendations for Use

| Patient Presentation | Management Strategy |
|---|---|
| New or worsening HF symptoms after initiation of therapy | Evaluate potential causes. Consider replacing DPP-4 inhibitor therapy with an alternative. |
| Current or prior HF symptoms and/or renal impairment | Use an alternative agent. |
| Left ventricular dysfunction (i.e., left ventricular ejection fraction < 40%) without current/prior HF symptoms | Consider alternative agent.<br><br>If used, monitor for HF signs/symptoms. |
| Known cardiovascular disease or risk of heart failure | Consider risk vs. benefit.<br><br>If used, monitor for HF signs/symptoms. |

http://blogs.pharmacy.umaryland.edu/atrium/2016/09/16/are-dipeptidyl-peptidase-dpp-4-inhibitors-safe-in-patients-with-heart-failure/

# SGLT2 Inhibitors

- EMPA-REG Outcome Trial
  - Type 2 DM, ≥ 18 y/o, established CVD and eGFR ≥ 30 ml/min/$m^2$
  - Risk of CV death causes, nonfatal myocardial infarction, or nonfatal stroke: lower with empagliflozin (10.5%) vs. placebo (12.1%)
    HR 0.86( 95.02% CI, 0.74 to 0.99; P=0.04
  - Hospitalization for HF: empagliflozin (9.4%) vs. placebo (14.5), p=0.003
  - Why a benefit?
    - Diuretic and natriuretic properties
    - Reduction in SBP
- Late-breaking/on going clinical trials
  - CVD-REAL Study
  - Canagliflozin Cardiovascular Assessment Study (CANVAS)
  - Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58)

N Engl J Med 2015; 373:2117-2128. Am Heart J 2013;166:217-223.e11. https://clinicaltrials.gov/show/NCT01730534

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# Which antihyperglycemic medication(s) could be considered for this patient?

# Pregabalin

- Mechanism: not well established
- Peripheral edema
  - Alone: ~ 6-8%
  - Combination with TZD: 19%
- Several case reports/series
- Onset: 3 days – 2 months
- Resolution: with discontinuation and management of HF symptoms
- Product labeling
  - May cause edema; no association with complications including HF
  - Use caution in NYHA III/IV HF
  - Use caution with TZD

Neurontin (gabapentin) Package insert. Parke-Davis. 2009; Lyrica (pregabalin) Package insert. Pfizer. 2016. J Cardiac Fail 2007;13:227-29. Br K Clin Pharmacol 2008;66:327-28. AĞRI 2011;23:80-83.

# Additional Medications that Can Exacerbate HF

| | Onset of Symptoms | Possible Mechanism | Recommendations for Use |
|---|---|---|---|
| Itraconazole | Immediate to intermediate | Negative inotrope | Serious, life-threatening infections |
| Carbamezepine | Immediate (if overdose) to intermediate | Negative chronotrope and inotrope suppresses sinus node automaticity and AV conduction | Evaluate risk vs. benefit |
| Tricyclic antidepressants | Intermediate to delayed | Negative inotrope, proarrhythmic | Avoid use |

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Circulation. 2016;134:e32–e69.

# Additional Medications that Can Exacerbate HF

| | Onset of Symptoms | Possible Mechanism | Recommendations for Use |
|---|---|---|---|
| Citalopram | Intermediate | Dose-dependent QTc prolongation | Do not exceed 40 mg/day |
| TNF-alpha inhibitors | Intermediate | Cytokine mediated | Evaluate product labeling for each agent; use of infliximab should be avoided in those with NHYA Class III/ IV symptoms |

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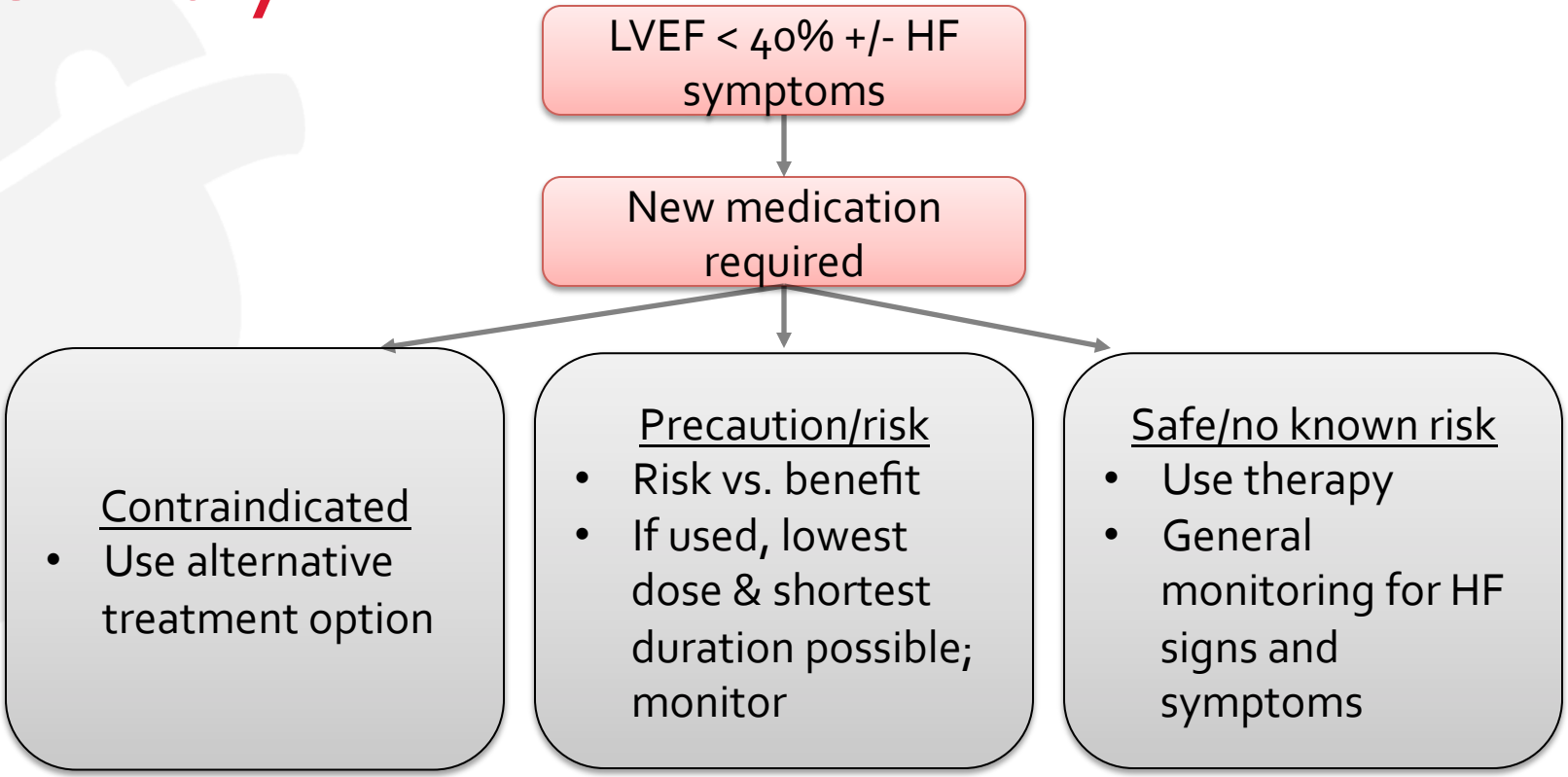
Circulation. 2016;134:e32–e69.

# Summary


LVEF < 40% +/- HF symptoms
New medication required
Contraindicated
• Use alternative treatment option
Precaution/risk
• Risk vs. benefit
• If used, lowest dose & shortest duration possible; monitor
Safe/no known risk
• Use therapy
• General monitoring for HF signs and symptoms

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# Keeping Your Patients with Heart Failure Out of the Hospital: Preventing Drug-Induced Exacerbations of Heart Failure

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- Rounds photograph: https://bostontrauma.files.wordpress.com/2014/01/surgical-critical-care-team-rounding-1.jpg
- Heart diagram: Marieb & Hoehn. Anatomy & Physiology, 9e. Pearson, 2013.