Drug-Induced Cardiovascular Disorders

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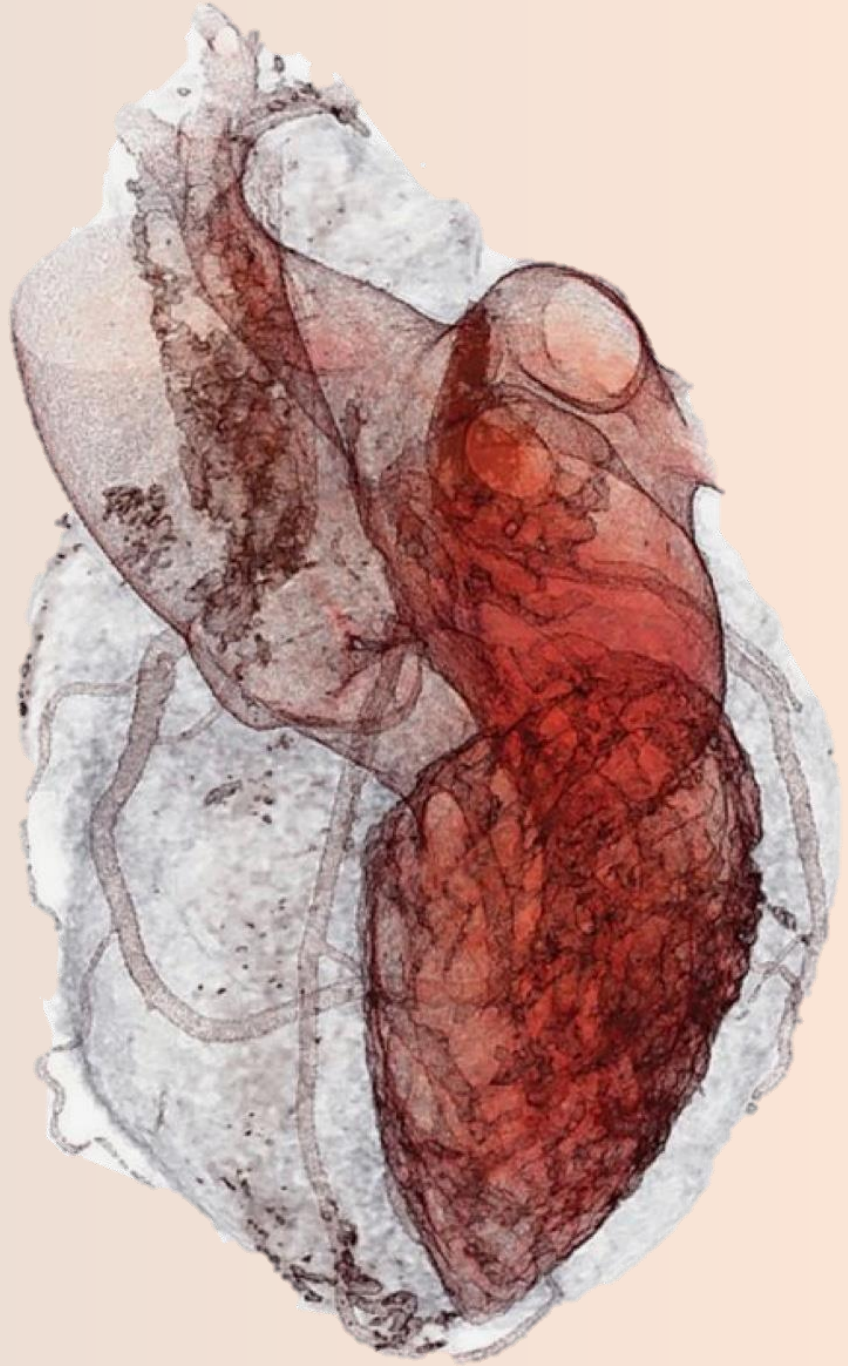
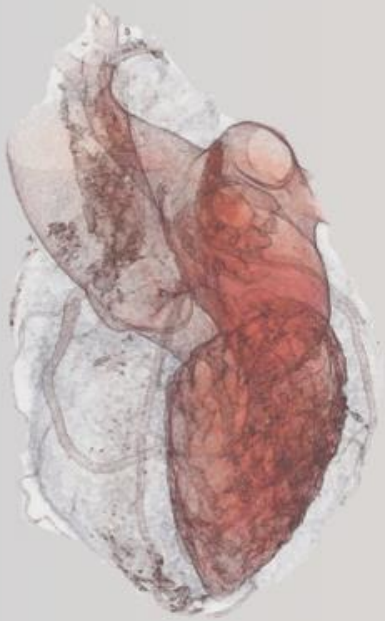
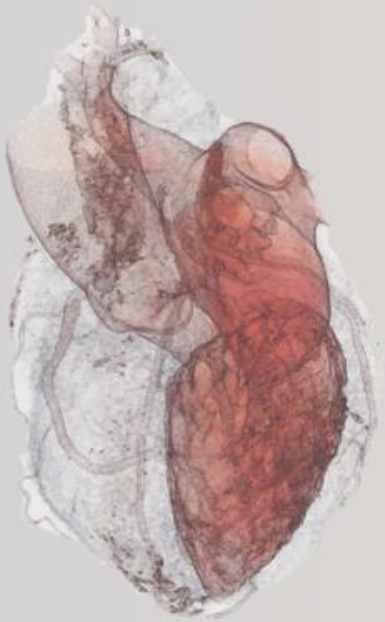




Case 1

- A middle-aged man comes to your pharmacy and asks for a pain-killer for his mother
- Her mother is a 78-year-old lady with a history of DM, and CABG (14 years ago) under treatment with:

- Aspirin 81 mg/d
- Atorvastatin 40 mg/d
- Metformin/Empagliflozin 1000/5 mg BD
- Losartan 25 mg/d

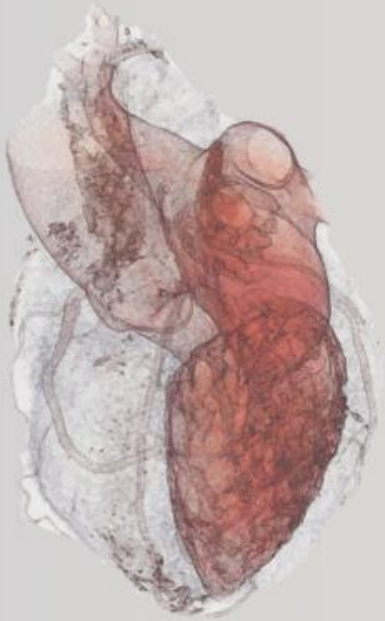


Case 1

- She is now complaining about knee pain which started from yesterday after walking 2 stairs up

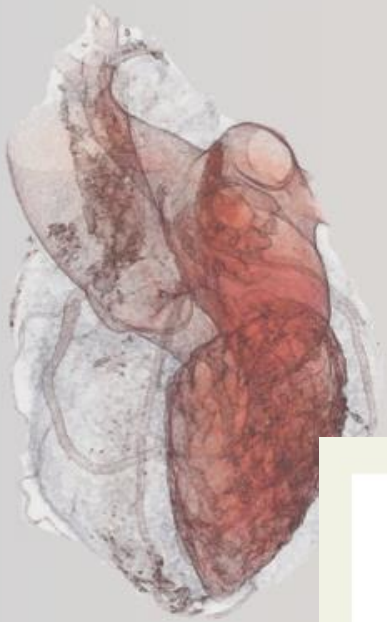
- Which of the following NSAIDs is not appropriate for her?

1. Diclofenac
2. Celecoxib
3. Meloxicam
4. Both A and B



Adverse CV and Bleeding Outcomes with NSAID Use

- During the past 2 decades, cardiovascular safety has been a major concern with regard to the use of NSAIDs
- Most individual agents have been reported to increase the risk for adverse cardiovascular events
- Recent guidelines have discouraged the use of NSAIDs in patients with established cardiovascular disease
- Bleeding events also increases with NSAID use in patients receiving antithrombotic medications



NSAID Comparison in Terms of COX Selectivity

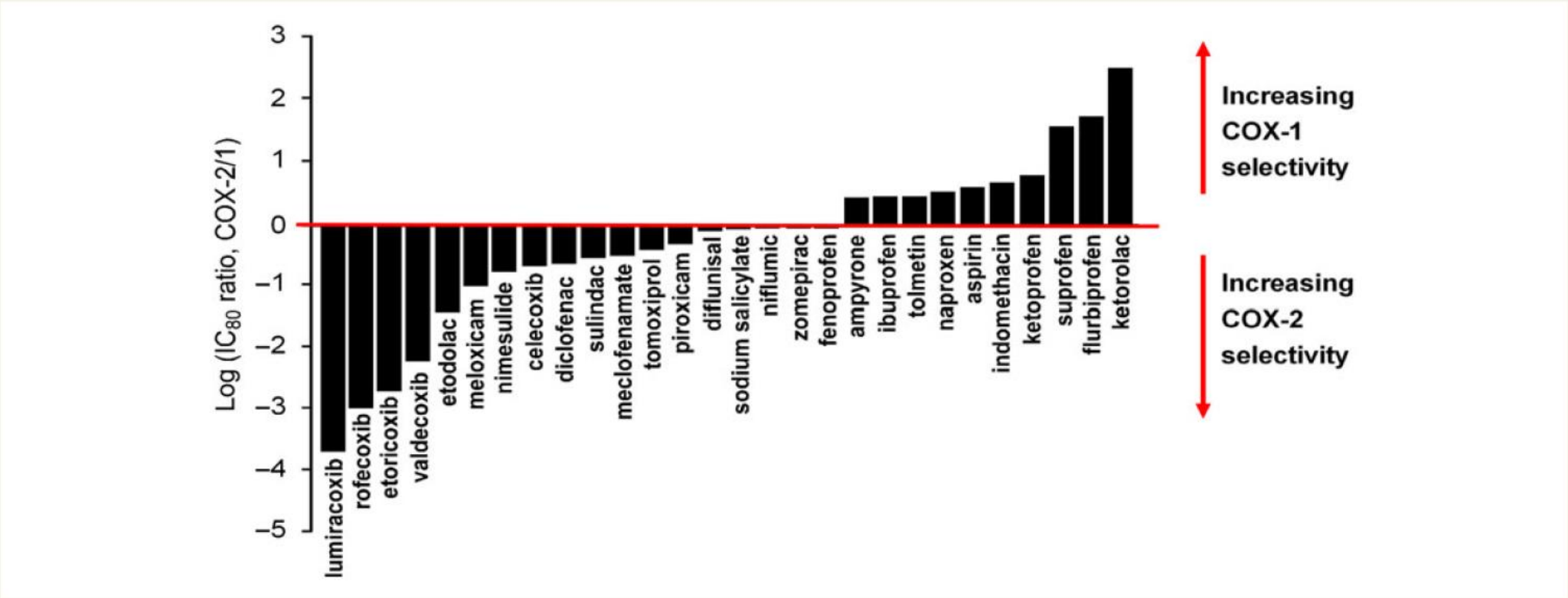
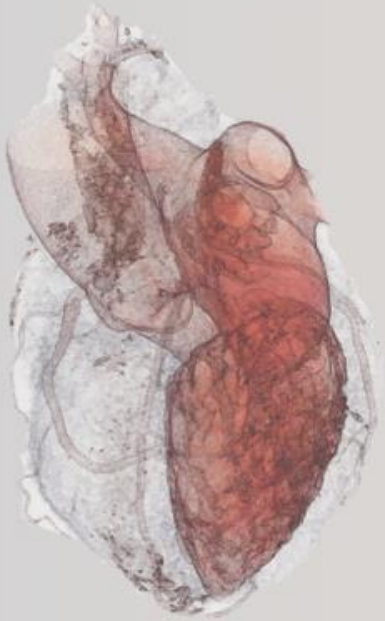


Figure 2 Relative COX selectivity of non-steroidal anti-inflammatory drugs displayed by the concentration of the drugs (IC_{80}) required to inhibit COX-1 and COX-2 activity by 80%.



Traditional Recommendations

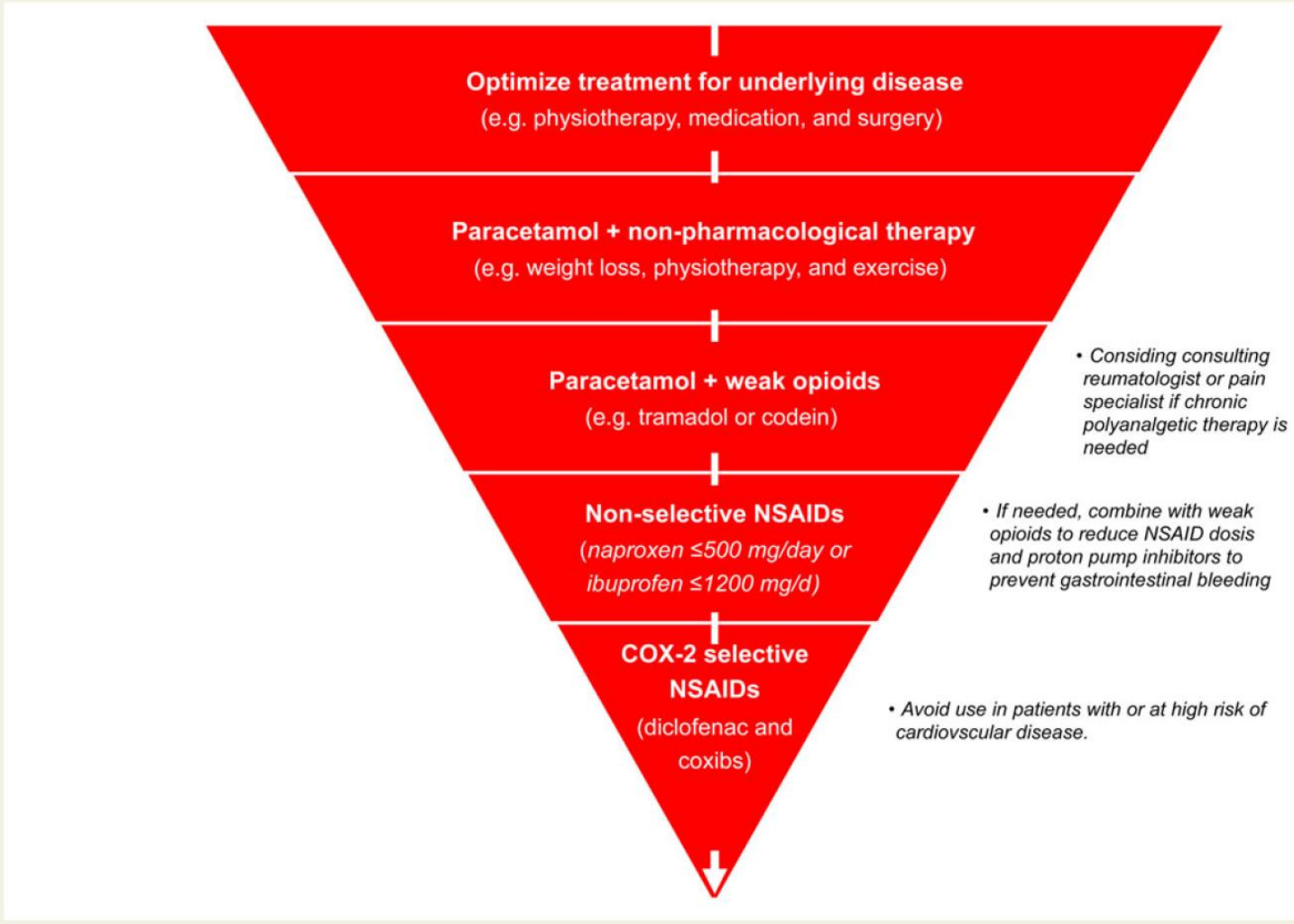
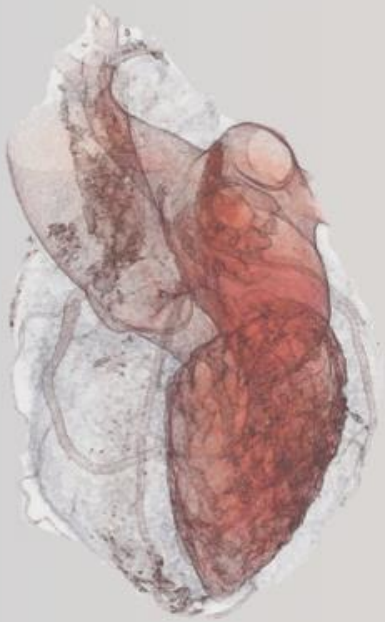


Figure 3 Stepwise approach to pharmacological treatment of musculoskeletal pain in patients with or at high risk of cardiovascular disease.



More Recent Evidence

The NEW ENGLAND JOURNAL of MEDICINE

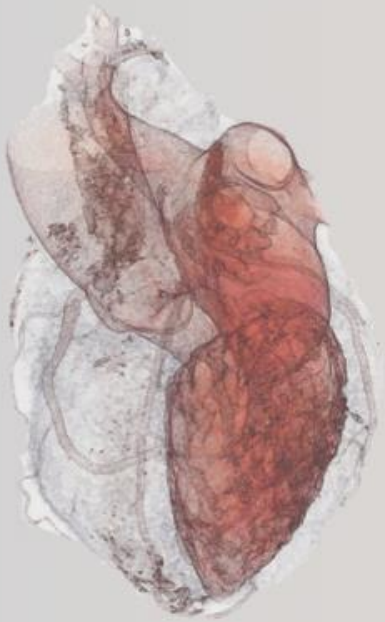
ESTABLISHED IN 1812 DECEMBER 29, 2016 VOL. 375 NO. 26

Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis

Steven E. Nissen, M.D., Neville D. Yeomans, M.D., Daniel H. Solomon, M.D., M.P.H., Thomas F. Lüscher, M.D., Peter Libby, M.D., M. Elaine Husni, M.D., David Y. Graham, M.D., Jeffrey S. Borer, M.D., Lisa M. Wisniewski, R.N., Katherine E. Wolski, M.P.H., Qiuqing Wang, M.S., Venu Menon, M.D., Frank Ruschitzka, M.D., Michael Gaffney, Ph.D., Bruce Beckerman, M.D., Manuela F. Berger, M.D., Weihang Bao, Ph.D., and A. Michael Lincoff, M.D., for the PRECISION Trial Investigators*

CONCLUSIONS

At moderate doses, celecoxib was found to be noninferior to ibuprofen or naproxen with regard to cardiovascular safety. (Funded by Pfizer; ClinicalTrials.gov number, NCT00346216.)



Even More Recent Evidence!

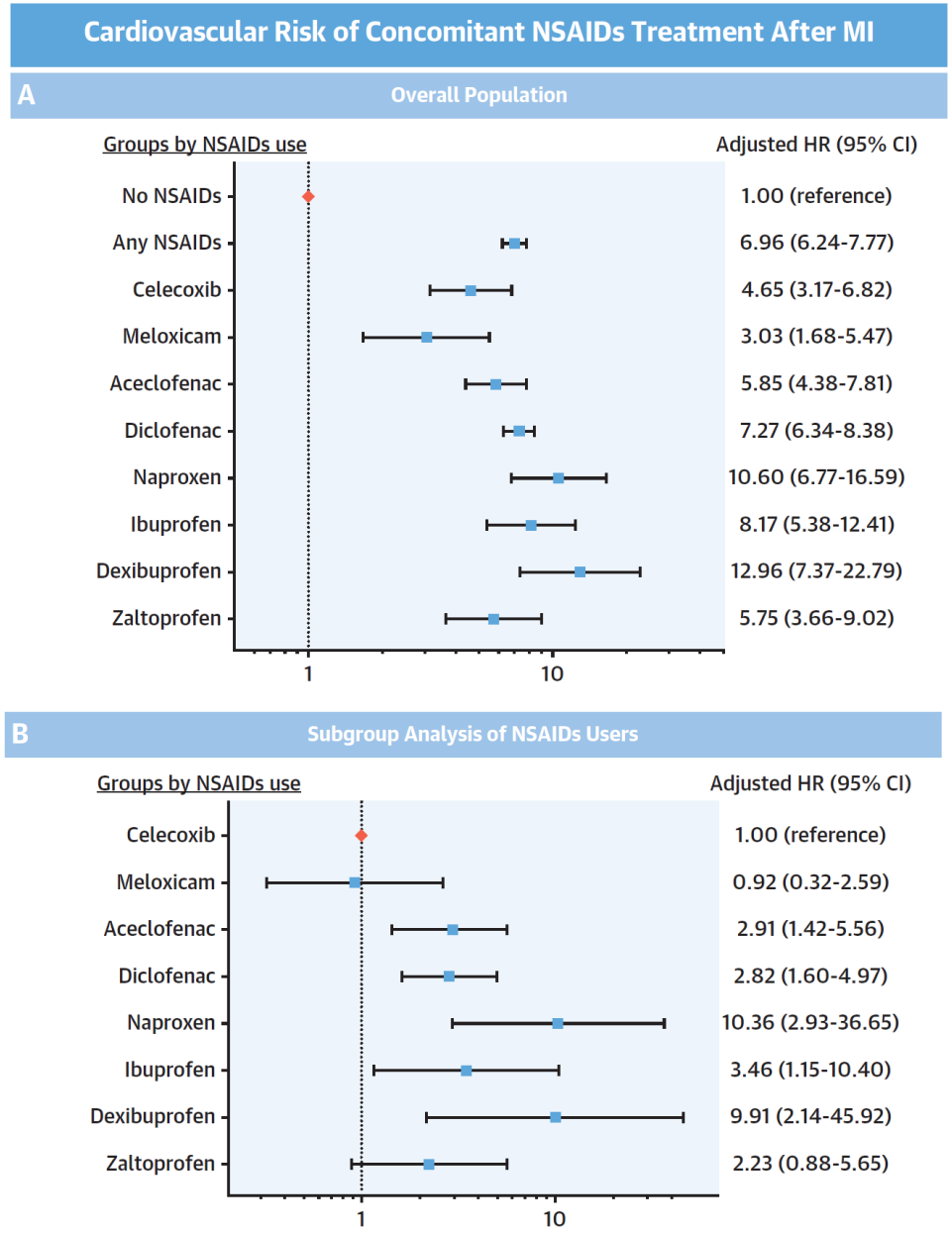
Cardiovascular and Bleeding Risks Associated With Nonsteroidal Anti-Inflammatory Drugs After Myocardial Infarction

Dong Oh Kang, MD,[a,*] Hyonggin An, PhD,[b,*] Geun U Park, MS,[c] Yunjin Yum, MS,[b] Eun Jin Park, MD,[a] Yoonjee Park, MD,[a] Won Young Jang, MD,[d] Woohyeun Kim, MD,[a] Jah Yeon Choi, MD,[a] Seung-Young Roh, MD,[a] Jin Oh Na, MD, PhD,[a] Jin Won Kim, MD, PhD,[a] Eung Ju Kim, MD, PhD,[a] Seung-Woon Rha, MD, PhD,[a] Chang Gyu Park, MD, PhD,[a] Hong Seog Seo, MD, PhD,[a] Cheol Ung Choi, MD, PhD[a]

METHODS This was a nationwide cohort study to enroll a study population from the Health Insurance Review and Assessment Service database in Korea between 2009 and 2013. Patients were divided into groups on the basis of the prescribed antithrombotic medications. The primary and secondary outcomes were thromboembolic cardiovascular and clinically relevant bleeding events. The risk for adverse clinical events was assessed by ongoing NSAID treatment and subtypes of NSAIDs.

RESULTS In total, 108,232 patients (mean age 64.2 ± 12.8 years, 72.1% men, mean follow-up duration 2.3 ± 1.8 years) with first diagnosed MI were enrolled. Concomitant NSAID treatment significantly increased the risk for cardiovascular events (hazard ratio [HR]: 6.96; 95% confidence interval [CI]: 6.24 to 6.77; $p < 0.001$) and bleeding events (HR: 4.08; 95% CI: 3.51 to 4.73; $p < 0.001$) compared with no NSAID treatment. Among NSAID subtypes, the risk for cardiovascular and bleeding events was lowest with the use of celecoxib (HR: 4.65; 95% CI: 3.17 to 6.82; $p < 0.001$, and 3.44; 95% CI: 2.20 to 5.39; $p < 0.001$, respectively) and meloxicam (HR: 3.03; 95% CI: 1.68 to 5.47; $p < 0.001$, and 2.80; 95% CI: 1.40 to 5.60; $p < 0.001$, respectively).

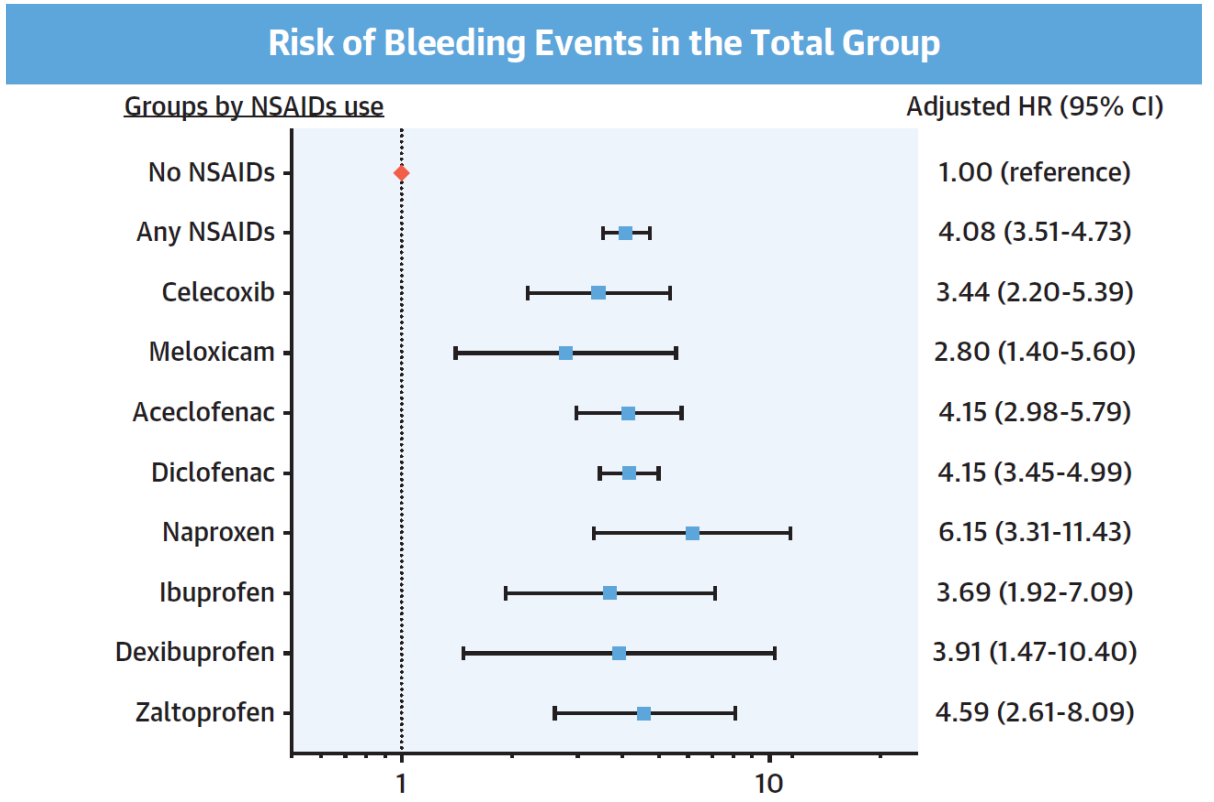
CENTRAL ILLUSTRATION Adjusted Risk for Cardiovascular Events According to Subtypes of Nonsteroidal Anti-Inflammatory Drugs in a Contemporary Cohort of Patients With Myocardial Infarction



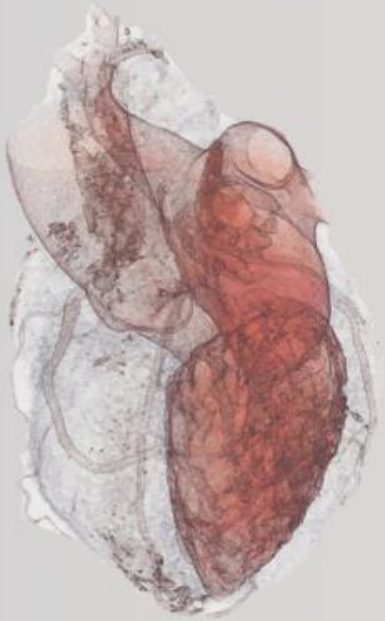
Kang, D.O. et al. J Am Coll Cardiol. 2020;76(5):518-29.

Results are adjusted for age, sex, baseline medical comorbidities, and concomitant medications prescribed within 30 days after the index myocardial infarction episode. No nonsteroidal anti-inflammatory drugs and the celecoxib group were defined as the reference groups for the **A** and **B**, respectively

FIGURE 1 Adjusted Risk of Bleeding Events According to Subtypes of NSAIDs in the Overall Population



Adjusted risk for bleeding events. Results are adjusted for age, sex, baseline medical comorbidities, and concomitant medications prescribed within the first 30 days after myocardial infarction. CI = confidence interval; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drug.

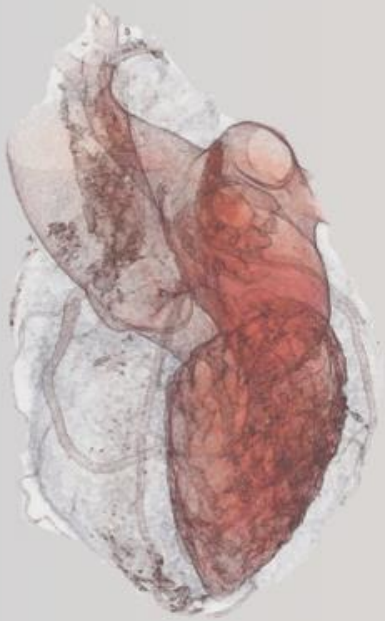


TAKE HOME MESSAGES!

1. Try to avoid the use of NSAIDs in patients with CV disease

2. If you have to use, use the lowest dose and the shortest period

3. Celecoxib is not considered the worst NSAID in patients with CV disease any more

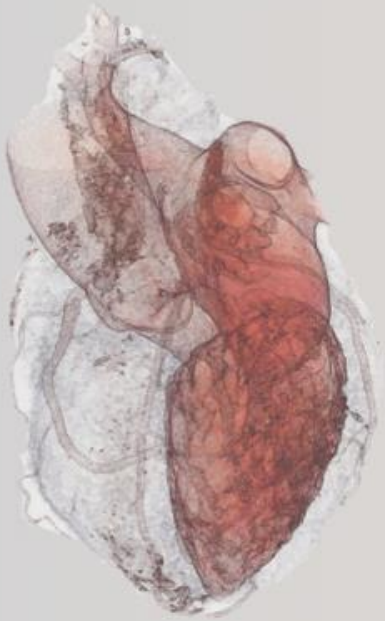


Case 2

- A 47-year old lady comes to your pharmacy and asks about her BP fluctuation in the last week
- She has a history of hypertension and is taking:

Valsartan/Amlodipine 160/10 mg/d

Indapamide 1.5 mg/d

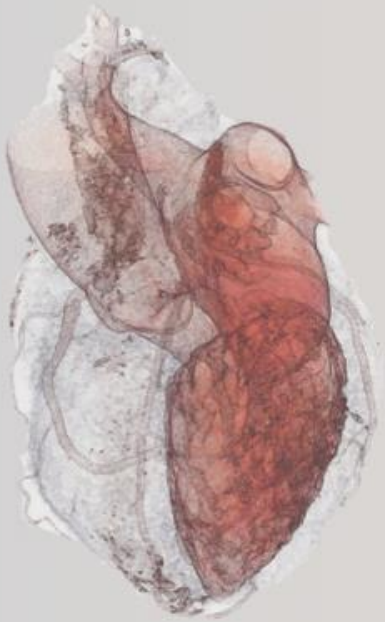


Case 2

- You ask about the recent changes in her regimen or medications and you understand that she has started taking licorice for her dyspepsia in the last weeks

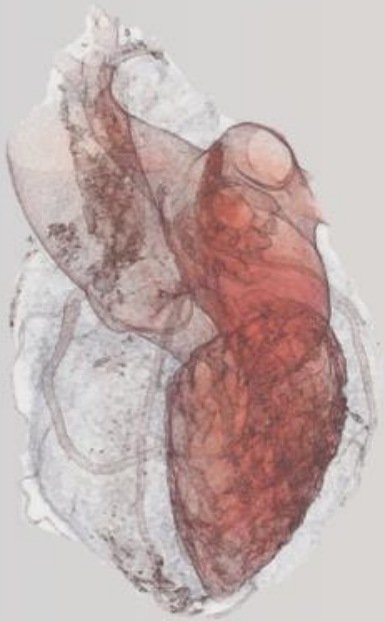
- Is there a relationship between licorice use and hypertension?

- What’s your recommendation?



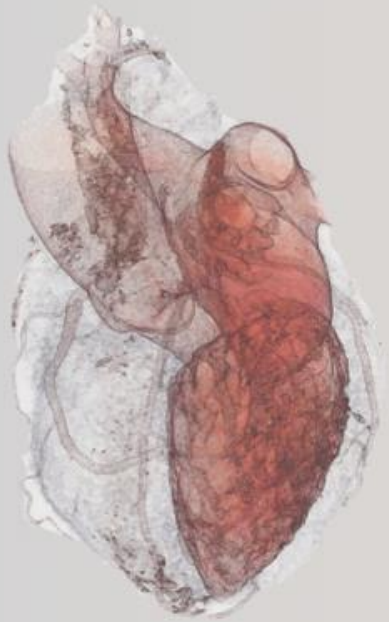
Drug-Induced Hypertension

Ingredient	Clinical Use	Notes
BP elevation mainly by volume retention		
Glucocorticoid	Replacement therapy, rheumatic disease collagen disease, dermatologic disease, allergic state, ophthalmic disease, inflammatory bowel disease, respiratory disease, hematologic and neoplastic disease, nephropathies	Hypertension occurs more often in elderly patients and in patients with a positive family history of primary HTN. Blood pressure rise is dose dependent, and at low doses, cortisol has less effect on BP.
Mineralocorticoid		
Licorice	A flavoring and sweetening agent	Dose-dependent, sustained increase in BP characterized by hypokalemia, metabolic alkalosis, and suppressed plasma renin activity and aldosterone levels.
Carbenoxolone	Ulcer medication	
9-alpha fluoroprednisolone	Skin ointments, antihemorrhoid cream	
9-alpha fluorocortisol	Ophthalmic drops, and nasal sprays	
Ketoconazole	Antimycotic	
Sex hormones		
Estrogen + progesterone	Contraception, replacement therapy	Mild, sustained BP elevation, more common in premenopausal women. History of high BP during pregnancy, a family history of HTN, cigarette smoking, obesity, black, diabetes, and renal disease increase the risk of developing HTN. Severe hypertension has been reported. Mild dose-dependent sustained increase in systolic BP.
Androgens	Prostate cancer	
Danazol (semisynthetic androgen)	Anabolic effect Endometriosis, hereditary angioedema	
NSAIDs	Analgesic, anti inflammatory	Mild, dose-dependent increase in BP. Elderly patients, those with pre-existing hypertension, salt-sensitive patients, patients with renal failure and patients with renovascular hypertension are at a higher risk to develop severe HTN. Calcium antagonists are the preferred choice of treatment.



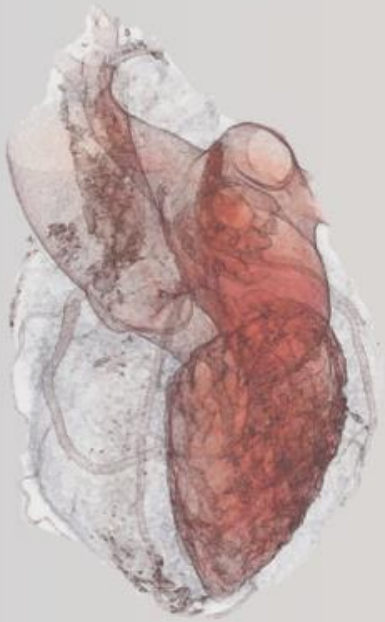
Drug-Induced Hypertension

BP elevation mainly by activation of the sympathetic nervous system		
Phenylephrine hydrochloride	Upper respiratory decongestant, ophthalmic drops	Dose-dependent, sustained increase in BP.
Dipivalyl adrenaline hydrochloride	Ophthalmic drops	Severe HTN has been reported.
Epinephrine (with beta-blocker)	Local anesthetic, anaphylactic reaction, bronchodilatation, decongestant, antihemorrhoidal treatment	
Phenylpropanolamine	Anorexic, upper respiratory decongestant	
Pseudoephedrine hydrochloride	Upper respiratory decongestant	
Tetrahydrozoline hydrochloride	Ophthalmic vasoconstrictor drops	
Naphazoline hydrochloride	Ophthalmic vasoconstrictor and nasal decongestant drops	
Oxymetazoline hydrochloride	Upper respiratory decongestant drops	
Caffeine	Analgesia, vascular headache, beverages	The reaction to caffeine is more pronounced in males, in those with a positive family history of HTN, and in African-American subjects. Caffeine may cause persistent BP effects in persons who are regular consumers, even when daily intake is at moderately high levels.
Herbal products	Complementary and alternative medicine	Mainly relate to dietary supplements that contain Ephedra alkaloids.



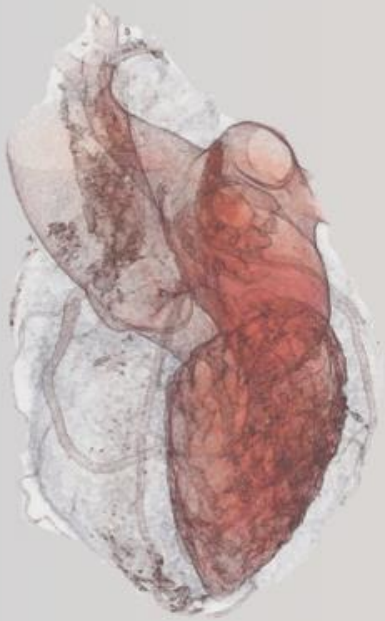
Drug-Induced Hypertension

Cocaine	Local anesthetics	Cocaine use is associated with acute but not chronic HTN. Transient severe increase in BP, especially when used with beta-blockers.
Ketamine hydrochloride	Anesthetic agent	Transient severe increase in BP has been reported.
Fentanyl citrate	Narcotic analgesic and anesthetic agent	
Smokeless tobacco	Alternative to smoking	
Methylphenidate	Attention deficit hyperactivity disorder	
Dexmethylphenidate		
Amphetamine		
Yohimbine hydrochloride	Impotence	Acute, dose-dependent increase in BP.
Sibutramine	Weight loss	Mild increase in BP.
Clozapine	Antipsychotic agent	
Glucagon	Prevent bowel spasm	Only in patients with pheochromocytoma.
Venlafaxine	Antidepressive and anti-anxiety agents	At dose above 300 mg/day.
Monoamine oxidase inhibitors	Antidepressive agents	Mainly with sympathomimetic amines and with certain food containing tyramine. Tranylcypromine is the most hazardous because of its stimulant action, whereas moclobemide and brofaromine are the least likely to induce hypertensive reaction.
Selegiline	Used mainly for Parkinson disease	
Tricyclic antidepressants	Antidepressive agent	More common in patients with panic disorders.
Buspirone	Anxiolytic agent	Mild dose-dependent increase in BP.
Fluoxetine	Antidepressive agents	In combination with selegiline.
Thioridazine hydrochloride	Psychotic and depressive disorders	Massive overdose may cause severe HT.
Physostigmine	Reverse anticholinergic syndrome, myasthenia gravis, glaucoma, Alzheimer disease	
Ritodrine hydrochloride	Inhibition of preterm labor	Hypertensive crisis has been reported.
Disulfiram	Management of alcoholism	Slight increase in BP. Severe HT may occur in alcoholic-induced liver disease.



Drug-Induced Hypertension

BP elevation mainly by activation of the rennin angiotensin system		
Lead	Industry	Also activates the sympathetic nervous system.
Cholesteryl ester transfer protein (CETP) inhibitor	Increases HDL cholesterol levels	
Torcetrapid		Not registered.
Dalcetrapib		Does not increase BP.
BP elevation mainly by direct vasoconstriction		
Cyclosporine A	Immunosuppressive agent, prophylaxis of organ rejection, autoimmune disease, dermatologic disorders	Dose-dependent mild to moderate increase in BP. Presence of HTN before transplantation, elevated creatinine levels and maintenance therapy with corticosteroids, increase the risk of HTN. Severe HTN has been reported.
Tacrolimus	Prophylaxis of organ rejection	Produces less hypertension than cyclosporine A.
Rapamycin	Prophylaxis of organ rejection	Produces little BP increase.
BP elevation mainly by combined mechanisms		
Recombinant human erythropoietin	Anemia of renal failure and of some malignancies	Dose-related mild increase in BP. The risk to develop or worsen HTN is increased in the presence of pre-existing HTN, the presence of native kidneys, a genetic predisposition to HTN, when the initial hematocrit is low and when it increases rapidly. Hypertensive crisis with encephalopathy has been reported.

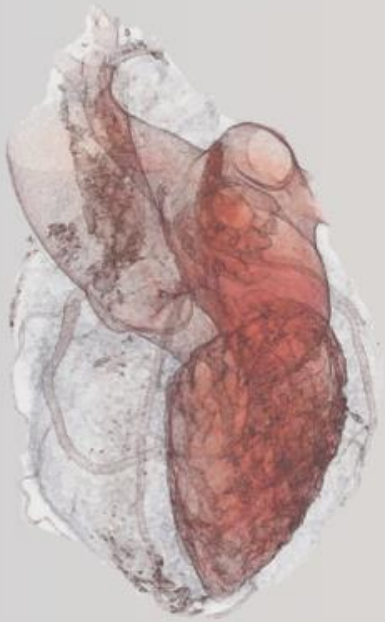


TAKE HOME MESSAGES!

1. Many drugs/substances may cause or exacerbate hypertension by different mechanisms

2. Try to avoid these substances as long as possible

3. In case there is no other options, monitor BP regularly to adjust the medications



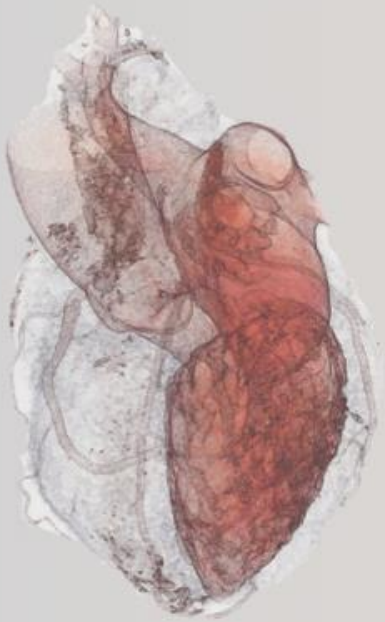
Case 3

- A 38-year old lady comes to your pharmacy and asks for a medication for GERD relief
- After taking history, you understand that she's been taking:

Citalopram 20 mg/d

Haloperidol 0.5 mg/qhs

- Prescribed by psychologist for her mood disorder in the last year



Case 3

- Which of the following medications you would not recommend at all?

1. Famotidine
2. Omeprazole
3. Domperidone
4. AlMg-S

Drug-Induced Long QT Syndrome

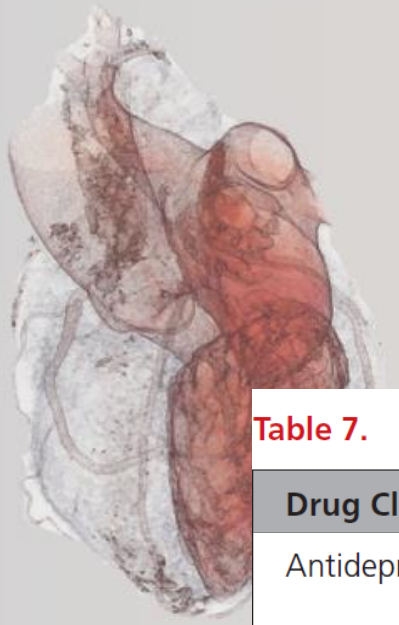
Table 7. QT Interval–Prolonging Drugs Known to Cause TdP

Drug Class	Drug	Incidence, %	Mechanism
Antiarrhythmic	Amiodarone	0.7–1.5*	I_{Kr} inhibition
	Disopyramide	…	I_{Kr} inhibition
	Dofetilide	1–10†	I_{Kr} inhibition, $I_{Na\text{-}L}$ augmentation
	Dronedarone	<0.1	I_{Kr} inhibition
	Flecainide	…	I_{Kr} inhibition
	Hydroquinidine	…	I_{Kr} inhibition
	Ibutilide	1.2–11.5	I_{Kr} inhibition, $I_{Na\text{-}L}$ augmentation
	Procainamide	0.3–6	I_{Kr} inhibition‡
	Quinidine	2–12	I_{Kr}, I_{K1}, and I_{to} inhibition
	Sotalol	0.2–23.6	I_{Kr} inhibition,§ $I_{Na\text{-}L}$ augmentation§

Drug-Induced Long QT Syndrome

Table 7. QT Interval–Prolonging Drugs Known to Cause TdP

Drug Class	Drug	Incidence, %	Mechanism
Antibiotic	Azithromycin	0.97‖	I_{Kr} inhibition, $I_{Na\text{-}L}$ augmentation
	Ciprofloxacin	…	I_{Kr} inhibition
	Clarithromycin	…	I_{Kr} inhibition
	Erythromycin	0.4	I_{Kr} inhibition, $I_{Na\text{-}L}$ augmentation
	Levofloxacin	0.2	I_{Kr} inhibition
	Moxifloxacin	…	I_{Kr} inhibition
	Roxithromycin	…	I_{Kr} inhibition
Antifungal	Fluconazole	…	I_{Kr} inhibition and inhibition of I_{Kr} trafficking
	Pentamidine	Up to 21	Inhibition of I_{Kr} trafficking
Antimalarial	Chloroquine	…	I_{Kr} inhibition
	Hydroxychloroquine	…	I_{Kr} inhibition
	Halofantrine	…	I_{Kr} inhibition



Drug-Induced Long QT Syndrome

Table 7. QT Interval–Prolonging Drugs Known to Cause TdP

Drug Class	Drug	Incidence, %	Mechanism
Antidepressant (SSRI)	Citalopram	…	I_{Kr} inhibition and inhibition of I_{Kr} trafficking
	Escitalopram	…	I_{Kr} inhibition and inhibition of I_{Kr} trafficking
Antipsychotic	Chlorpromazine	…	I_{Kr} inhibition
	Haloperidol	3.6	I_{Kr} inhibition
	Levomepromazine	…	…
	Levosulpride	…	…
	Pimozide	…	I_{Kr} inhibition
	Sulpiride	…	…
	Sultopride	…	…
	Thioridazine	…	I_{Kr} inhibition, $I_{Na\text{-}L}$ augmentation
Cholinesterase inhibitor	Donepezil	…	I_{Kr} inhibition
Opioid agonist	Methadone	…	I_{Kr} inhibition

Drug-Induced Long QT Syndrome

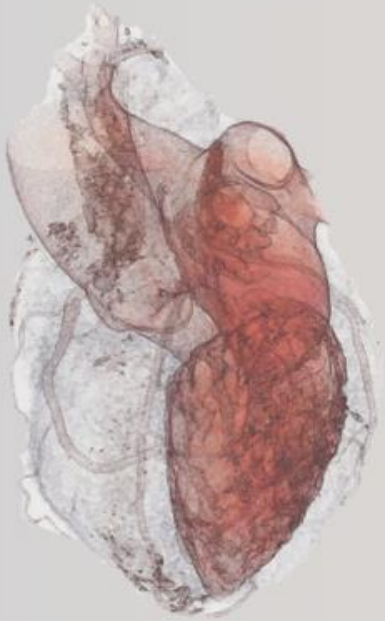
Table 7. QT Interval–Prolonging Drugs Known to Cause TdP

Drug Class	Drug	Incidence, %	Mechanism
Antiemetic	Domperidone	…	I_{Kr} inhibition
	Droperidol	<0.1	I_{Kr} inhibition
	Ondansetron	…	I_{Kr} inhibition

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 September 2014
EMA/465179/2014

Restrictions on the use of domperidone-containing medicines



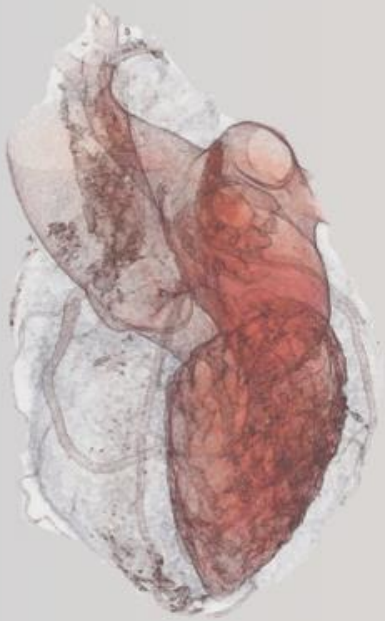
TAKE HOME MESSAGES!

1. Many drugs/substances may prolong QT and cause TdP

2. The potential for drug-induced TdP may be reduced by correcting modifiable risk factors

3. Serum potassium and magnesium should be maintained at >4.0 mEq/L and 2.0 mg/dL

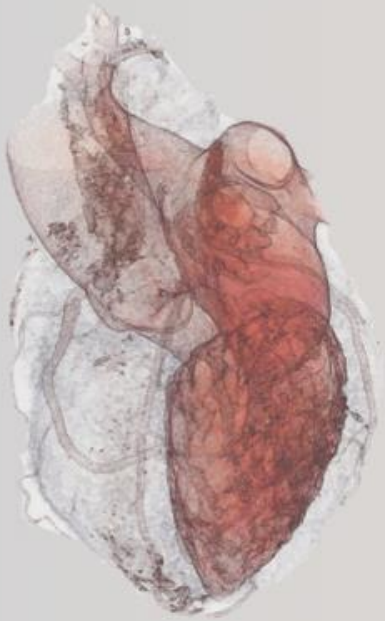
4. Concomitant administration of QT-prolonging medications should be avoided



Case 4

- A young gentleman comes to your pharmacy and wants to buy furosemide tablets

- When you ask about the reason, he says he needs this pill for his mother which has a worsening edema in her lower extremities



Case 4

- As the conversation continues you understand that his mother is diagnosed with HF and is taking:

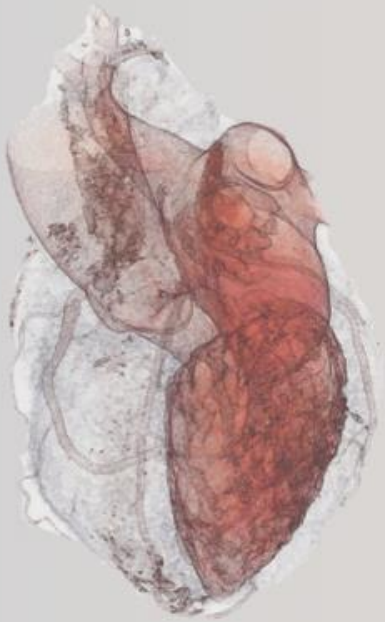
Sacubitril/Valsartan 100 mg BD

Empagliflozin 10 mg/d

Bisoprolol 5 mg/d

Spironolactone 25 mg/d

And other cardiovascular and anti-diabetic medications



Case 4

- He says that a GP has started pioglitazone 15 mg/d for his mother because of poor-controlled diabetes (elevated FBS despite taking metformin and empagliflozin)
- Does a drug-related problem happen here?
- What’s your recommendation?

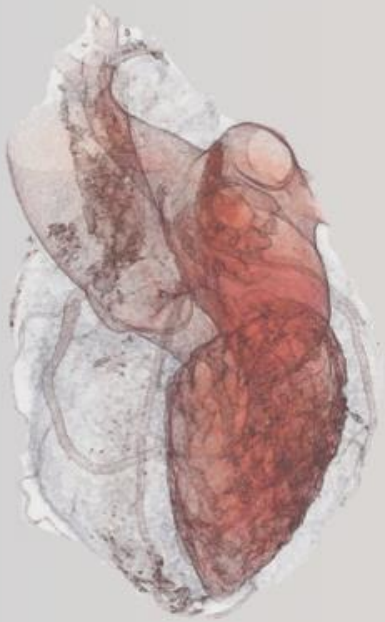


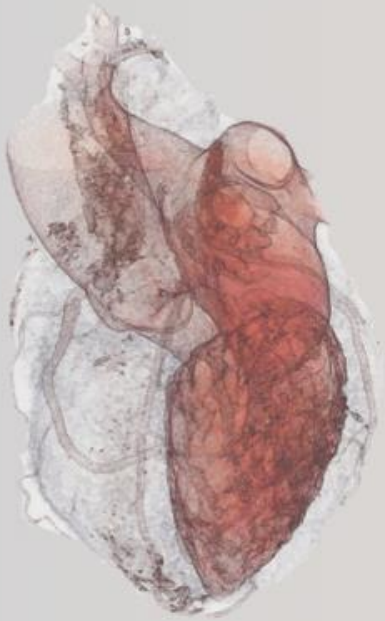
TABLE 35-3 Drugs That May Precipitate or Exacerbate Heart Failure

Negative inotropic effect
Antiarrhythmics (disopyramide, dronedarone, flecainide, propafenone, sotalol)
Beta-blockers (eg, propranolol, metoprolol, carvedilol)
Calcium channel blockers (eg, verapamil, diltiazem)
Itraconazole

Cardiotoxic
Doxorubicin, daunorubicin, epirubicin, idarubicin
Daunomycin
Cyclophosphamide
Pertuzamab
Trastuzumab
Bevacizumab
Mitoxantrone
Ifosfamide
Mitomycin
Lapitinib
Sunitinib
Sorafenib
Imatinib
Carbamazepine
Ethanol
Amphetamines (eg, cocaine, methamphetamine)

Sodium and water retention
NSAIDs
Cyclooxygenase-2 (COX-2) inhibitors
Rosiglitazone and pioglitazone
Glucocorticoids
Androgens and estrogens
Salicylates (high dose)
Sodium-containing drugs (eg, carbenicillin disodium, ticarcillin disodium)

Uncertain mechanism
TNF-α inhibitors (eg, adalimumab, infliximab, etanercept)
Dipeptidyl peptidase-4 (DPP-4) inhibitors (eg, saxagliptin)

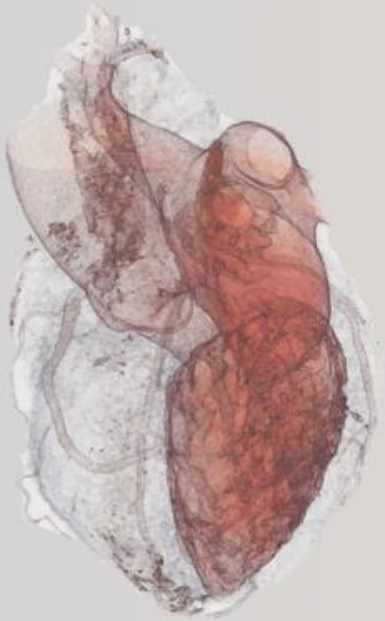


TAKE HOME MESSAGES!

1. Drugs with negative inotropic effects or those which may cause sodium and water retention can exacerbate HF symptoms

2. These substances should be avoided in patients with HF

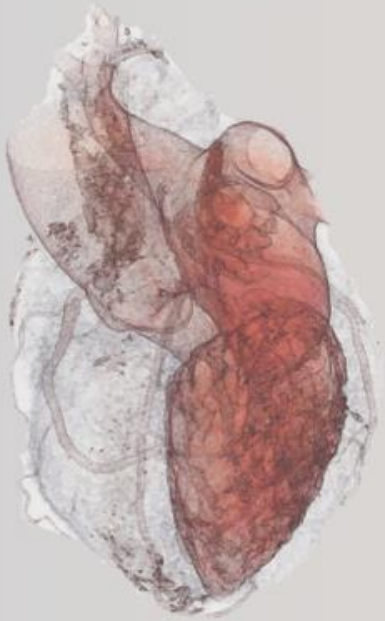
3. There are several substitutes for these medications



Case 5

- A 45-year old lady with breast cancer comes to your pharmacy to fill her prescription:

- Vial Adriamycin (Doxorubicin)
- Vial Cyclophosphamide
- Amp Dexamethasone
- Serum NS
- Amp Ondansetron
- Tab Aprepitant



Case 5

- She tells you it's her 6th session of chemotherapy and she feels shortness of breath and fatigue in the last week
- Is there a drug-related problem here?
- What's your recommendation before receiving her next session chemotherapy?

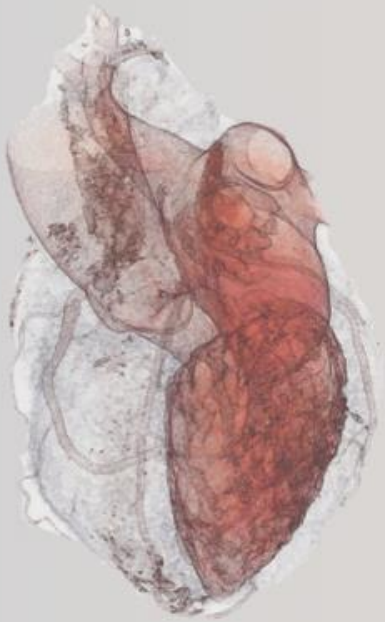


TABLE 35-3 Drugs That May Precipitate or Exacerbate Heart Failure

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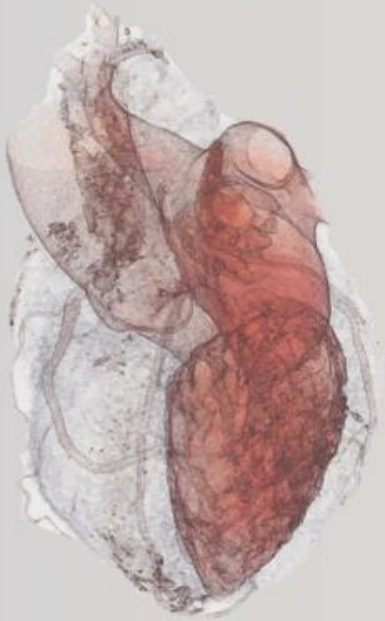
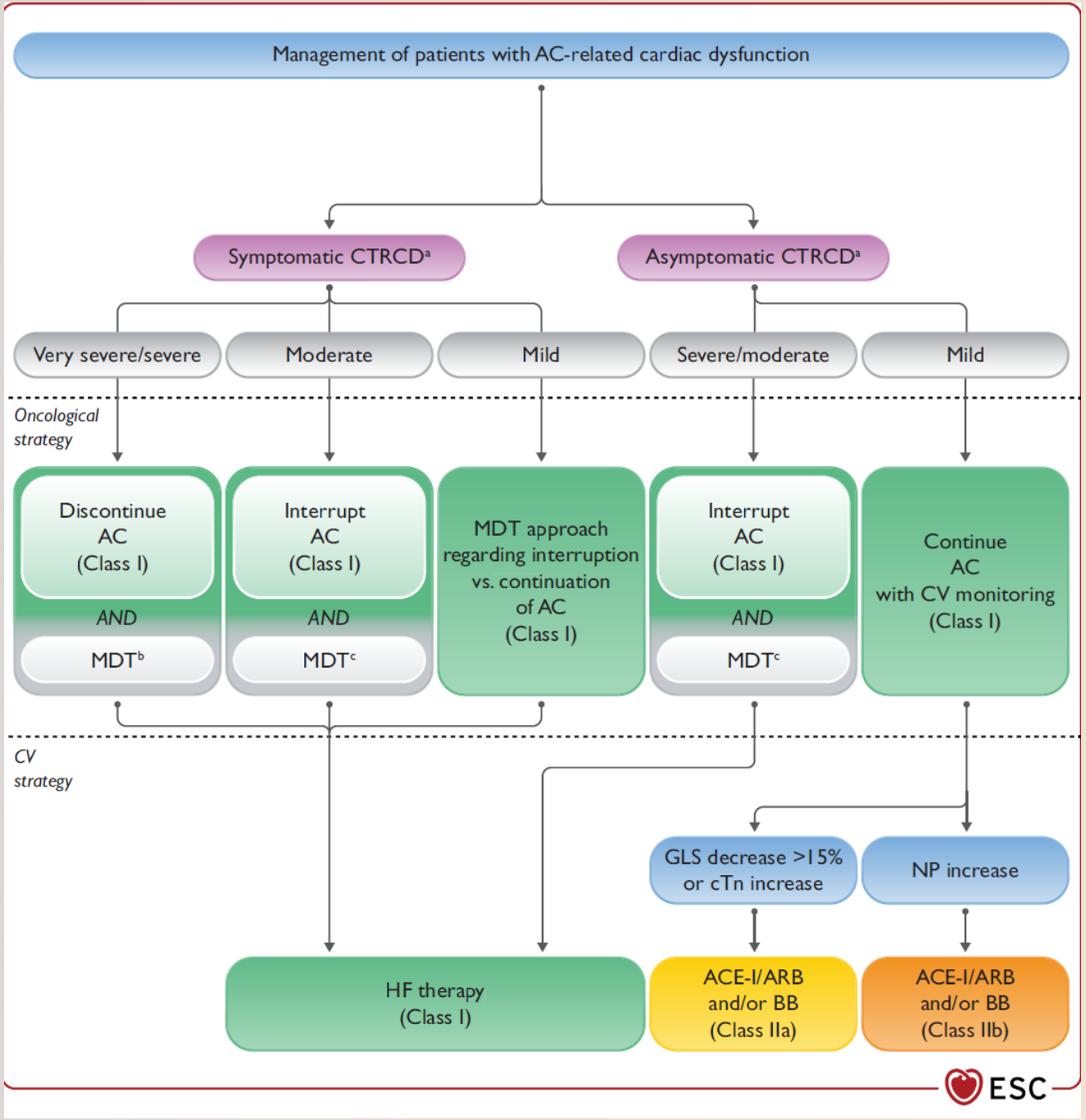
Beta-blockers (eg, propranolol, metoprolol, carvedilol)
Calcium channel blockers (eg, verapamil, diltiazem)
Itraconazole

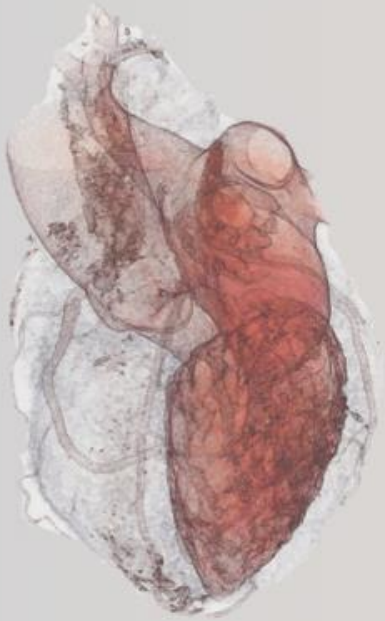
Cardiotoxic
Doxorubicin, daunorubicin, epirubicin, idarubicin
Daunomycin
Cyclophosphamide
Pertuzamab
Trastuzumab
Bevacizumab
Mitoxantrone
Ifosfamide
Mitomycin
Lapitinib
Sunitinib
Sorafenib
Imatinib
Carbamazepine
Ethanol
Amphetamines (eg, cocaine, methamphetamine)

Sodium and water retention
NSAIDs
Cyclooxygenase-2 (COX-2) inhibitors
Rosiglitazone and pioglitazone
Glucocorticoids
Androgens and estrogens
Salicylates (high dose)
Sodium-containing drugs (eg, carbenicillin disodium, ticarcillin disodium)

Uncertain mechanism
TNF-α inhibitors (eg, adalimumab, infliximab, etanercept)
Dipeptidyl peptidase-4 (DPP-4) inhibitors (eg, saxagliptin)




Management of patients with AC-related cardiac dysfunction
Symptomatic CTRCD[a]
Asymptomatic CTRCD[a]
Very severe/severe
Moderate
Mild
Severe/moderate
Mild
Oncological strategy
Discontinue AC (Class I)
AND
MDT[b]
Interrupt AC (Class I)
AND
MDT[c]
MDT approach regarding interruption vs. continuation of AC (Class I)
Interrupt AC (Class I)
AND
MDT[c]
Continue AC with CV monitoring (Class I)
CV strategy
GLS decrease >15% or cTn increase
NP increase
HF therapy (Class I)
ACE-I/ARB and/or BB (Class IIa)
ACE-I/ARB and/or BB (Class IIb)
ESC

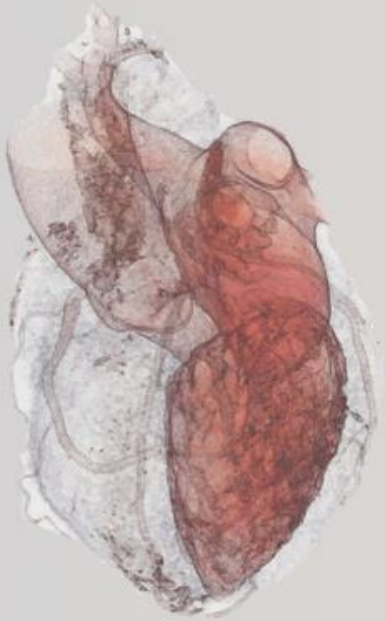


TAKE HOME MESSAGES!

1. Several anti-cancer medications (specially anthracyclines and anti-HER2) may cause cardiotoxicity

2. Patients should be monitored before and during chemotherapy based on their risk factors

3. In terms of developing cardiotoxicity, the patients should be referred for further evaluation and treatments



Case 6

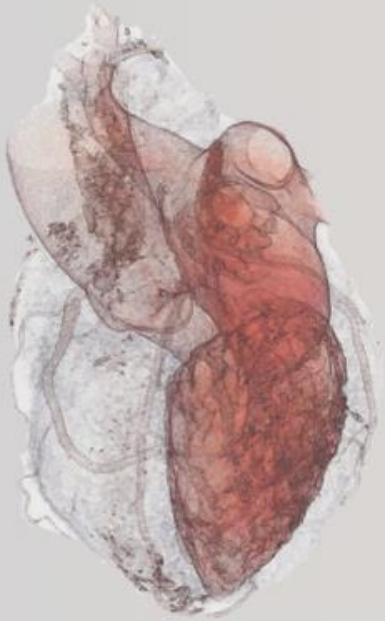
- A young man comes to your pharmacy and asks for propranolol to relieve his palpitation

- He has a history of atrial fibrillation and is taking:

Apixaban 5 mg BD

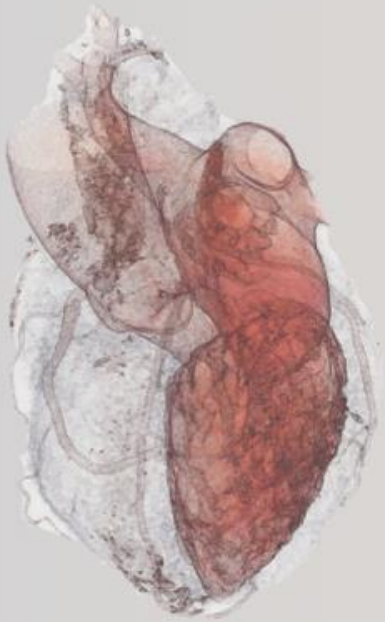
Bisoprolol 5 mg/d

- He is in a waiting list for AF catheter ablation



Case 6

- He says that he had a project to do in the last days and slept less than usual while taking lots of coffee and energy drinks to stay awake
- Why does his palpitation worsen?
- What’s your recommendation?



Drug-Induced Atrial Fibrillation

AHA SCIENTIFIC STATEMENT

Drug-Induced Arrhythmias

A Scientific Statement From the American Heart Association

Table 2. Drugs That May Cause/Exacerbate AF or AFL

Drug Class	Drug	Incidence, % or Odds/ Hazard/Incidence Ratio or Relative Risk	Mechanism
Stimulant	Caffeine	...	Phosphodiesterase inhibitor
	1,3 Dimethylamylamine*	...	Indirect sympathomimetic agent

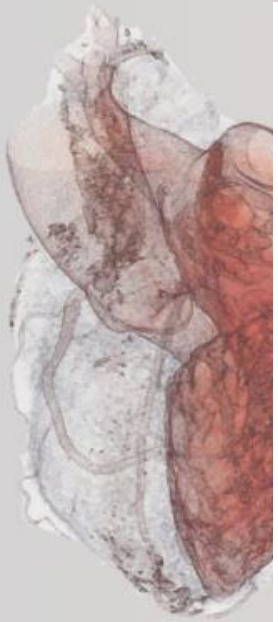


Table 1. Caffeine Content of Commonly Consumed Foods, Beverages, and Over-the-Counter Drugs in the United States.*

Source	Serving Size†	Milligrams of Caffeine
Coffee, brewed, coffee shop	12 fluid oz	235
Americano, coffee shop	12 fluid oz	150
Coffee, brewed	8 fluid oz	92
Coffee, instant	8 fluid oz	63
Espresso	1 fluid oz	63
Decaffeinated coffee	8 fluid oz	2
Black tea, brewed	8 fluid oz	47
Green tea, brewed	8 fluid oz	28
Chamomile or peppermint tea	8 fluid oz	0
Cola soft drink	12 fluid oz	32
Energy drink	8.5 fluid oz	80‡
Energy shot	2 fluid oz	200‡
Dark chocolate	1 oz	24
Milk chocolate	1 oz	6
Over-the-counter drug for alertness	1 tablet	200
Headache medication with caffeine	1 tablet	65

Coffee Consumption and Risk of Atrial Fibrillation in the Physicians' Health Study

Vijaykumar Bodar, MD; Jiaying Chen, MA; J. Michael Gaziano, MD, MPH; Christine Albert, MD, MPH; Luc Djoussé, MD, MPH, ScD

Background—Although coffee consumption is often reported as a trigger for atrial fibrillation (AF) among patients with paroxysmal AF, prospective studies on the relation of coffee consumption with AF risk have been inconsistent. Hence, we sought to assess the association between coffee consumption and risk of AF in men.

Methods and Results—We prospectively studied men who participated in the Physicians' Health Study (N=18 960). Coffee consumption was assessed through self-reported food frequency questionnaires. The incidence of AF was assessed through annual questionnaires and validated through review of medical records in a subsample. Cox proportional hazard models were used to calculate hazard ratios and 95% CIs of AF. The average age was 66.1 years. A total of 2098 new cases of AF occurred during a mean follow-up of 9 years. Hazard ratios (95% CI) of AF were 1.0 (reference), 0.85 (0.71-1.02), 1.07 (0.88-1.30), 0.93 (0.74-1.17), 0.85 (0.74-0.98), 0.86 (0.76-0.97), and 0.96 (0.80-1.14) for coffee consumption of rarely/never, ≤1 cup/week, 2 to 4 cups/week, 5 to 6 cups/week, 1 cup/day, 2 to 3 cups/day, and 4+ cups/day, respectively; adjusting for age, smoking, alcohol intake, and exercise (*P* for nonlinear trend=0.01). In a secondary analysis the multivariable adjusted hazard ratio (95% CI) of AF per standard deviation (149-mg) change in caffeine intake was 0.97 (0.92-1.02).

Conclusions—Our data suggest a lower risk of AF among men who reported coffee consumption of 1 to 3 cups/day. **(*J Am Heart Assoc*. 2019;8:e011346. DOI: 10.1161/JAHA.118.011346.)**

Key Words: atrial fibrillation • caffeine • cardiovascular disease • coffee • epidemiology and Nutrition

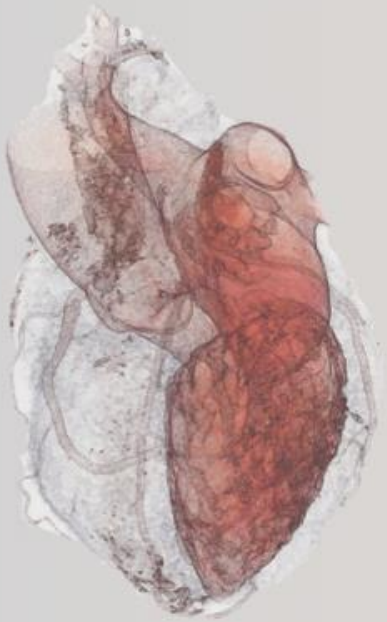
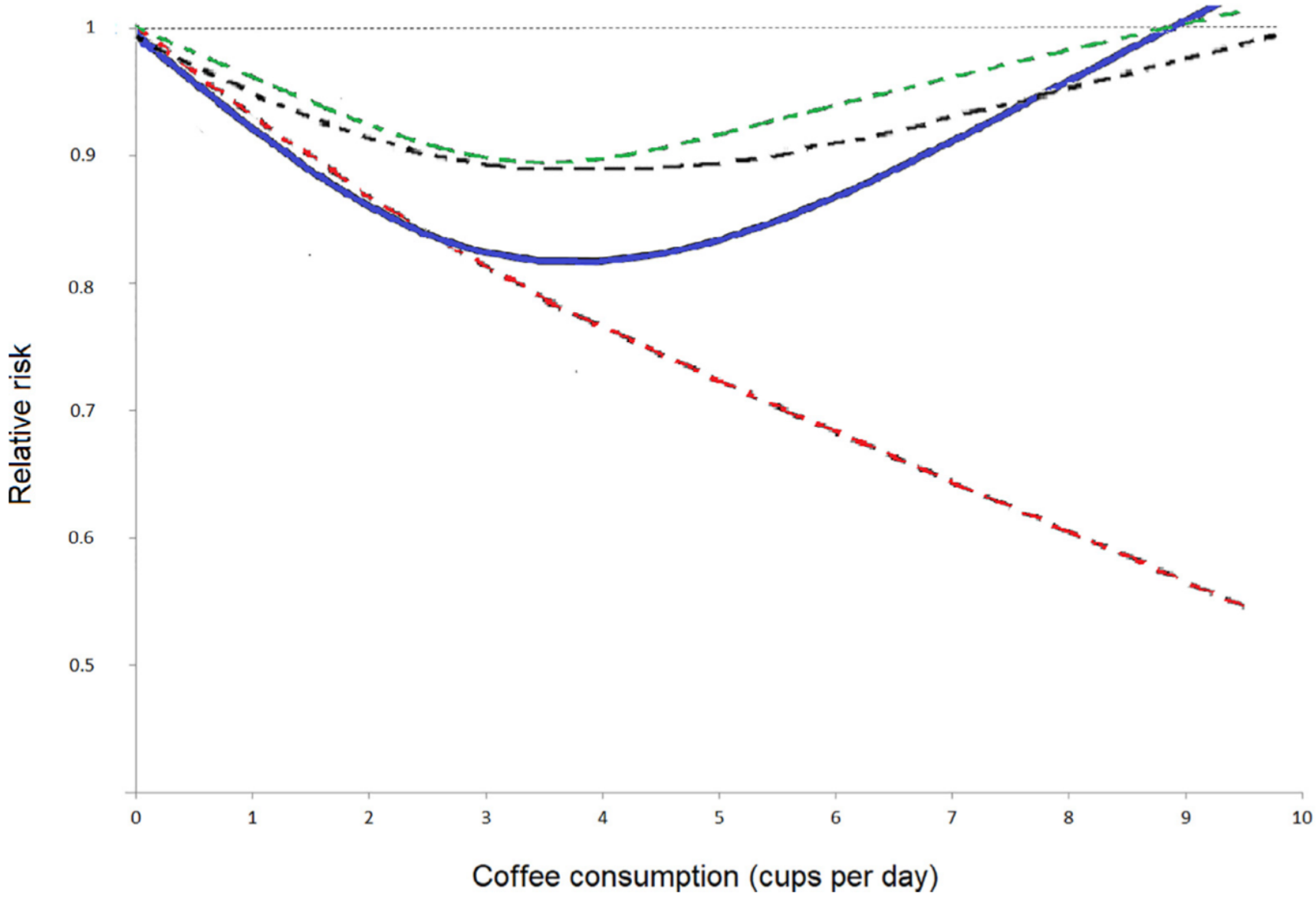


TABLE 2 Major Studies Examining Impact of Caffeinated Beverages on Atrial Arrhythmia

First Author (Ref. #), Year	Cases/Participants	% Males	Age, yrs	Follow-Up, yrs	Study Design	Key Findings
Mostofsky et al. (20), 2016	3,415/57,053	48	56.7 ± 4.4	13.5	Population-based cohort study	• Higher coffee intake was associated with lower rate of incident AF (linear trend: p = 0.02). • Compared to nondrinkers, OR: 0.86 (95% CI: 0.71 to 1.04) for 2-3 cups per day, and OR: 0.79 (95% CI: 0.64 to 0.98) for 6-7 cups per day
Dixit et al. (18), 2016	1,388	47	71.9 ± 5.0	NA	Observational study (24-h Holter)	• No correlation between atrial ectopics/h and intake of coffee (p = 0.28) or tea (p = 0.57). • No correlation between SVT runs and intake of coffee (p = 0.22) or tea (p = 0.90).
Liu et al. (39), 2016	401/801	56	63.0 ± 1.2	–	Case control	• Green tea was protective against incident AF (multivariate OR: 0.349; 95% CI: 0.25 to 0.48) in a dose-dependent manner (p for trend = 0.001).
Larsson et al. (56), 2015	7,041/76,475	55	61.5	12	Population-based cohort study	• No association between coffee consumption and risk of incident AF at all levels of consumption (multivariate RR: 0.98 for 2-3 cups/day; RR: 1.01 for ≥5 cups/day; p = 0.64 for trend).
Klatsky et al. (23), 2011	1,512/13,0054	44	–	17.6	Retrospective population cohort	• Higher coffee intake was associated with lower rates of hospitalization for AF (HR: 0.81; 95% CI: 0.69 to 0.96 for ≥4 cups/day) and SVT (HR: 0.63; 95% CI: 0.41 to 0.98 for ≥4 cups/day)
Shen et al. (57), 2011	296/4,526	44	62 ± 10	4.0	Prospective cohort	• No correlation between caffeine intake and risk of incident AF (for quartiles of intake for Q1 HR: 0.84; 95% CI: 0.62 to 1.15 vs. Q4 HR: 0.98; 95% CI: 0.7 to 1.39; p for trend = 0.84).
Conen et al. (58), 2010	945/33,638	0	53	14.4	Prospective cohort	• U-shaped relationship with lowest risk of incident AF in third quintile of intake with median 285 mg/day (HR: 0.78; 95% CI: 0.64 to 0.95; p for quadratic trend = 0.03). • None of the individual caffeine components (tea, coffee, cola, chocolate) was associated with incident AF.
Mukamal, et al. (59), 2009	163/1,369	70	59.8	6.9-9.9	Prospective cohort	• In patients with previous myocardial infarction, coffee drinkers in the 4 higher categories of intake had ~30% lower risk of developing AF (HR for ≥1 cups/day: 0.65; 95% CI: 0.40 to 1.05).
Frost et al. (60), 2006	555/47,949	47	56	5.7	Prospective cohort	• Compared with the lowest quintile, there was no association between caffeine intake and incident AF (lowest risk was third quintile, ~584 mg/day; HR: 0.85 (95% CI: 0.65 to 1.12).
Mattioli et al. (24), 2005	116/232	74	54 ± 7	–	Case control	• High coffee intake, >3 cups/day, was associated with a lower rate of spontaneous cardioversion from AF (OR: 0.3; 95% CI: 0.11 to 0.49; p = 0.008).
Wilhelmsenet al. (61), 2001	754/7,495	100	47 ± 55	25.2	Population-based cohort study	• Consumption of ≥5 cups/day was not associated with a higher risk of incident AF (OR: 1.09; 95% CI: 0.87 to 1.38), although moderate consumption reached borderline significance (OR: 1.24; 95% CI: 1.00 to 1.54).

AF = atrial fibrillation; CI = confidence interval; HR = hazard ratio; NA = not applicable; OR = odds ratio; RR = relative risk; SVT = supraventricular tachycardia.



Heart Failure

6,522 cases / 140,222 participants

Cardiovascular Disease

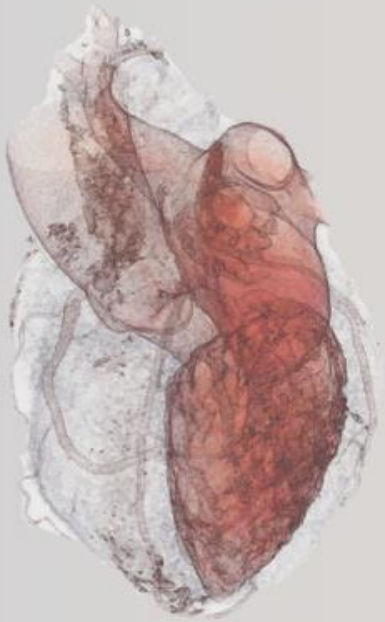
Median follow-up 10 years
36,352 cases / 1,279,804 participants

Stroke

Median follow-up 10.4 years
10,003 cases / 479,689 participants

Diabetes

Median follow-up 11 years
45,335 cases / 1,109,272 participants



RESEARCH SUMMARY

Acute Effects of Coffee Consumption on Health among Ambulatory Adults

Marcus GM et al. DOI: 10.1056/NEJMoa2204737

CLINICAL PROBLEM

Coffee is among the most commonly consumed beverages in the world, yet its acute effects on health are uncertain. In particular, despite the common admonition that coffee should be avoided owing to potential proarrhythmic effects, evidence for an association between the two is conflicting.

CLINICAL TRIAL

Design: A prospective, single-center, randomized, case-crossover trial assessed the acute effects of caffeinated coffee consumption on cardiac ectopy in adults.

Intervention: 100 participants were instructed, by means of daily text messages, to consume caffeinated coffee or to avoid caffeine during randomly assigned 2-day periods over the course of 14 days. Participants wore a continuously recording electrocardiogram patch to collect heart-rhythm data. They recorded each instance of coffee consumption by pressing a button on the patch, which time-stamped the drink. Smartphone-based virtual monitoring (geofencing) was used to track visits to coffee shops. The primary outcome was the mean number of premature atrial contractions per 24-hour period. Secondary outcomes included the daily number of premature ventricular contractions, minutes of sleep, and step counts.

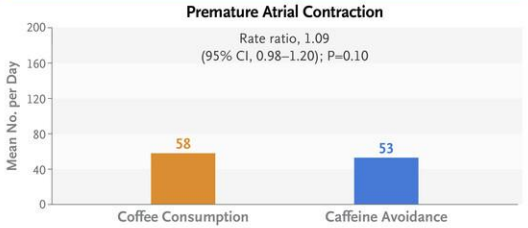
RESULTS

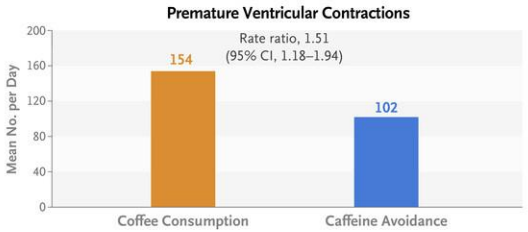
The mean number of premature atrial contractions did not differ significantly between days on which participants were randomly assigned to consume caffeinated coffee and days they were assigned to avoid caffeine. Consumption of coffee was associated with more premature ventricular contractions per day and fewer minutes of sleep per night — but more steps taken per day — than caffeine avoidance.

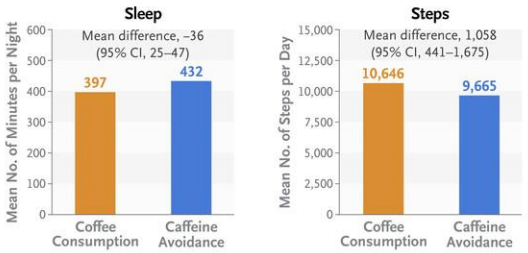
LIMITATIONS AND REMAINING QUESTIONS

- The trial was relatively small.
- The trial was not blinded, and factors other than caffeinated coffee may have influenced the results.
- The population was relatively young and healthy; the findings may not be generalizable to other persons, including those with cardiovascular disease or coexisting conditions.

Links: Full Article | NEJM Quick Take

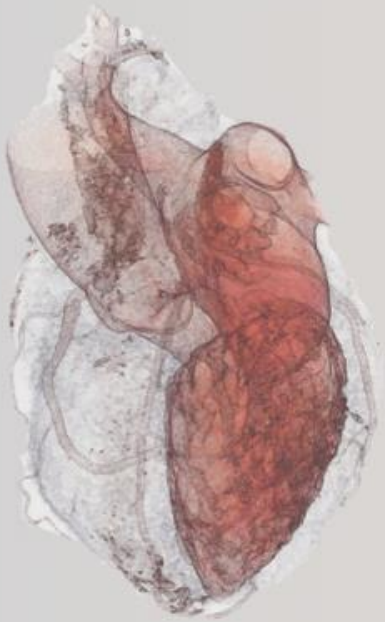






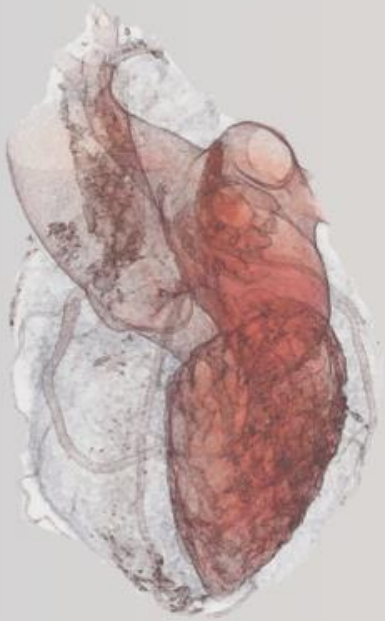
CONCLUSIONS

In this randomized trial, consumption of caffeinated coffee was not associated with more premature atrial contractions per day than avoidance of caffeine.



TAKE HOME MESSAGES!

1. Many clinicians continue to counsel patients with atrial or VAs to avoid all caffeinated beverages, particularly coffee
2. There is no evidence to support this approach.
3. Although there is no clearly defined threshold for caffeine harm, a regular intake of up to 300 mg/day appears to be safe and may even be protective against CVD
4. If, in individual cases where a clear temporal association between arrhythmia episodes and caffeine intake is apparent, then avoidance is sensible.



Take Care of Your Heart