TOP 10 CARDIOVASCULAR DRUGS USED OFF LABEL!!!

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OBJECTIVES

At the conclusion of this lecture the successful learner will be able to:

1. Identify how an FDA approved and off label indication differ and the implications of that differential designation
2. Identify which 10 FDA approved cardiovascular drugs have the most promising off label uses for treating other cardiac or noncardiac disorders
3. Describe the mechanisms of action for the purported off label uses of these drugs
4. Identify which national guidelines or consensus statements recommend the off-label use of drugs

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DISCLOSURE

Dr White has received funding from AstraZeneca to support a research project on andexanet alfa in patients with Factor Xa induced major bleeding. This topic will not be discussed during the lecture and should not constitute a conflict of interest. Since this talk is about non-FDA approved indications, he will be speaking about off label uses of drugs throughout the presentation. Where there are superior FDA approved options, he identifies them within the presentation where applicable.

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FDA INDICATIONS

- Preclinical trials must be conducted and submitted with an IND application, including an overview of studies that will be conducted in Phases 1-3
  - Trials not preceded by an IND could be excluded from FDA review in the NDA
  - Process reduces the risk that trials w/o benefits or with ADEs are hidden from FDA review
- Clinicians have the ability to use FDA approved drugs off label, meaning they are used to treat diseases or disorders without an FDA indication
  - Some off label indications are well justified, others are not
  - Can be based on incidental findings or an expected pharmacologic action

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NUMBER TEN

5

HEPARIN/LMWH

FDA Indications: Prophylaxis and treatment of VTE and PE, AF with embolization, treatment of disseminated intravascular coagulation, prevention of clotting in arterial and cardiac surgery, prophylaxis and treatment of peripheral arterial embolism, use as an anticoagulant in blood transfusions, extracorporeal circulation, and dialysis procedures

Off Label Indication: Pregnancy preservation w/ Factor V Leiden mutation. Recommended for pregnant women with past VTE or homozygous for FVL gene deficiency.

https://www.jabfm.org/content/17/4/306#:~:text=Patients%20with%20a%20VTE%20during%20the%20current%20pregnancy,the%20risk%20of%20epidural%20hematoma%20from%20regional%20anesthesia.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/017037Orig1s187lbl.pdf

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HEPARIN/LMWH

- **Mechanism:** Protein C cannot fully bind and inhibit Factor V
  - Estrogen enhances the clotting risk resulting in placental thrombosis and detachment
- Pregnant women heterozygous for Factor V Leiden have a 5- to 10-fold increase in VTE, homozygous have a 50- to 100-fold increased risk
- Study 1: Heparin/LMWH reduces the risk of VTE during pregnancy
  - Prophylaxis with LMWH resulted in 93% live birth rate vs. 80% in the placebo group
- Study 2: Enoxaparin 40mg/day and 80mg/day live birth rate of 69% and 83% vs. 20% in untreated controls.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC116643/

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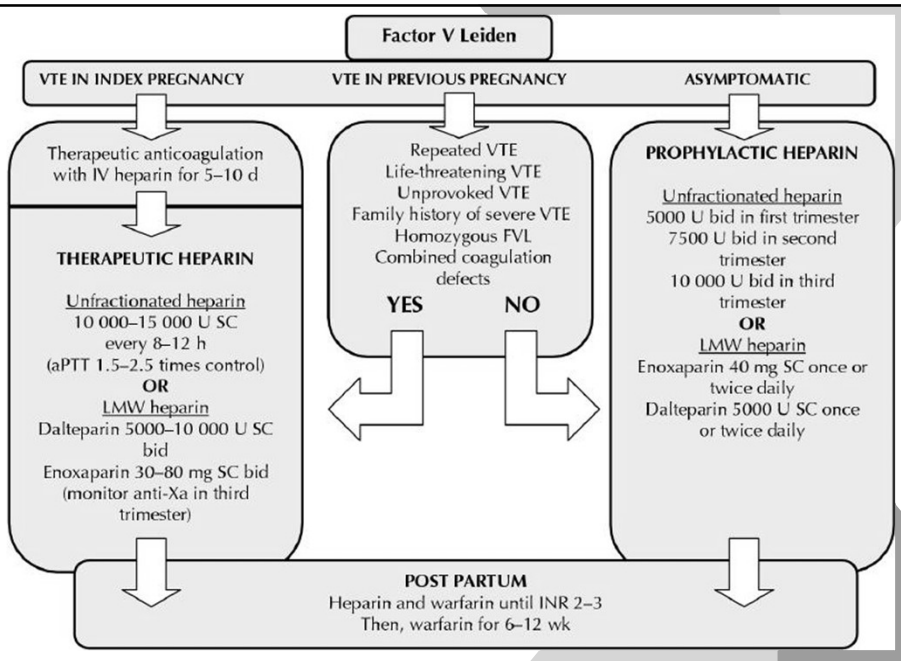

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC116643/

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NUMBER NINE

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THIAZIDES

FDA Indications: Edema in heart failure or nephrotic syndrome, hypertension

Off Label Use: Treat hypocalcemia, prevent calcium oxalate kidney stones, reduce polydipsia in nephrogenic diabetes insipidus

Mechanism for Hypocalcemia and Kidney Stones: Thiazides blocking the Na+/H+ pump in the distal convoluted tubule (reducing SVR and BP) BUT, also blocks a Ca++ pump there as well

- Reducing Ca++ excretion raises serum concentrations and reduces the Ca++ needed to form Ca++ stones in kidney

https://www.ncbi.nlm.nih.gov/books/NBK557838/
https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/040735s004,040770s003lbl.pdf

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THIAZIDES

- Nephrogenic diabetes insipidus: ADH binds to the V2 receptors in the collecting ducts, but not enough sodium is available to allow it to work
  - Thiazides enhance interstitial Na+ concentrations enhancing ADH effects
  - Study: Chlorthalidone titrated to effect reduced urine volume from 8L to 4L
- Prostaglandin E2 interferes with thiazides collecting duct Na+ enhancing properties so indomethacin is used concomitantly to boost effects
- Doesn't work in central diabetes insipidus: Not enough ADH made to collect free water in the collecting ducts.
  - FDA approved treatments: vasopressin, desmopressin

https://academic.oup.com/ndt/article/15/12/1903/1814415

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NUMBER EIGHT

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DISOPYRAMIDE

FDA Indication: Disopyramide is indicated for the treatment of life threatening sustained ventricular tachycardia

Off Label Indication: Adjunctive therapy for symptomatic obstructive hypertrophic cardiomyopathy if beta-blockers or non-DHP CCBs are insufficient

Mechanism: Disopyramide has a powerful negative inotropic effect, precluding its use in ventricular arrhythmias but the ADE is therapeutic in obstructive hypertrophic cardiomyopathy

- Mavacamten is a new cardiac myosin inhibitor that supplanted disopyramide as a first line adjunct option.

https://journals.sagepub.com/doi/10.1177/10600280221117812
https://www.drugs.com/pro/disopyramide.html

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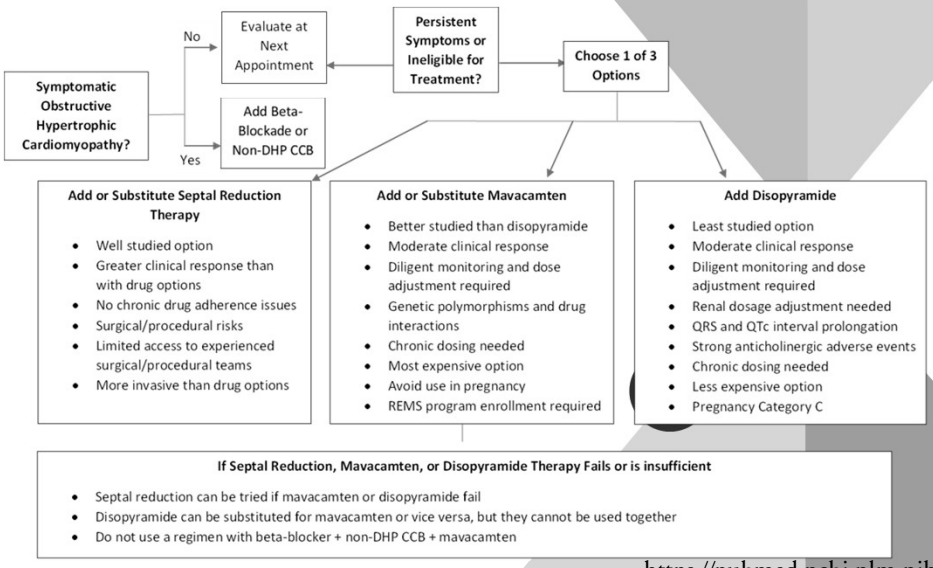
DISOPYRAMIDE



https://pubmed.ncbi.nlm.nih.gov/35950315/

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ASSESSMENT QUESTION 1

Which of the following drugs has been used to enhance the chances of delivering a baby in patients with Factor 5 Leiden and what is the mechanism of benefit?

a) Thiazide diuretics – reduced calcium in the placenta stopping crystalline blockage of the umbilical cord
b) LMWH – preventing placental thrombosis in patients who are hypercoagulable
c) Disopyramide – decreases inotropic effect in hypertrophic cardiomyopathy causing placental detachment

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c) Disopyramide – decreasing the inotropic effect in hypertrophic cardiomyopathy that leads to placental detachment

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NUMBER SEVEN

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FERRIC MALTODEXTRAN

FDA Indications: treatment of iron deficiency anemia in adults intolerant to oral iron or who have non-dialysis dependent chronic kidney disease.

Off Label Indication: 2017 AHA/ACC Heart Failure Guidelines 2017 - Class IIB recommendation in HF patients with iron deficiency

Mechanism: Inadequate oxygen carrying from anemia or low iron content in RBCs worsens tissue oxygenation in HFrEF

https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021135Orig1s037lbl.pdf

https://www.acc.org/latest-in-cardiology/articles/2021/03/03/17/59/affirming-what-we-know-about-iv-iron-in-patients-with-acute-heart-failure#:~:text=The%202017%20ACC%2FAHA%20focused%20update%20to%20the%20HF,in%20patients%20with%20both%20chronic%20and%20acute%20HF.

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FERRIC MALTODEXTRAN

AFFIRM-AHF: R, DB, PC trial of hospitalized adults with acute heart failure (LVEF <50%) and iron deficiency (ferritin <100 μg/L, or 100–299 μg/L with transferrin saturation <20%)

- Randomly assigned (1:1) to receive intravenous ferric carboxymaltose (n=558) or placebo (n=550) for up to 24 weeks
- CV hospitalizations and CV deaths less with carboxymaltose group than placebo (RR 0.80, 95% CI 0.64–1.00, p=0.050)
  - Fewer heart failure hospitalizations (RR 0·74; 95% CI 0·58–0·94, p=0·013)
  - No difference in CV death between groups (HR 0.96, 95% CI 0.70–1.32, p=0·81)

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32339-4/fulltext#:~:text=Randomised%20clinical%20trials%20have%20shown%20that%20intravenous%20ferric,failure%20hospitalisations%20or%20cardiovascular%20mortality%20in%20these%20patients.

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NUMBER SIX

20

AMIODARONE

FDA Indication: Recurrent ventricular fibrillation or recurrent hemodynamically unstable ventricular tachycardia.

Off Label Indications: AHA/ACC Guideline for the treatment of atrial fibrillation

- Amiodarone is an acceptable antiarrhythmic option when other therapies are unavailable or ineffective for preventing atrial fibrillation recurrence

Mechanism: Blockade of Ikr and Iks potassium channels, Ca+ channels, and antiadrenergic effects.

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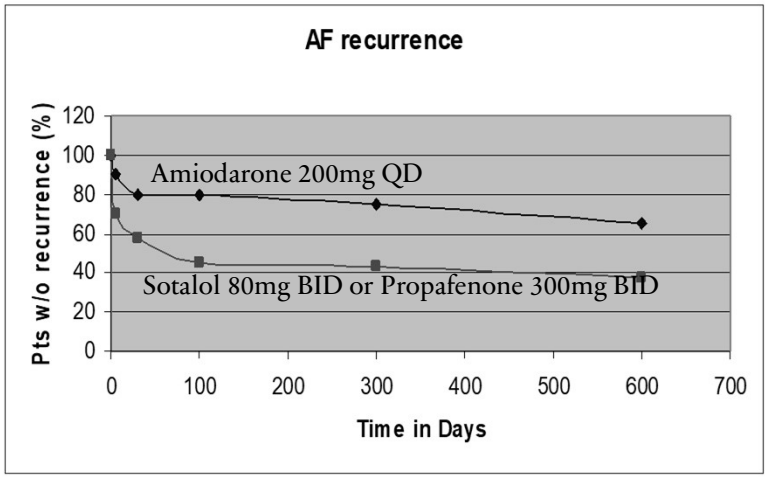
CANADIAN TRIAL OF ATRIAL FIBRILLATION INVESTIGATORS



CTAFI. N Engl J Med 2000;342:913-20.

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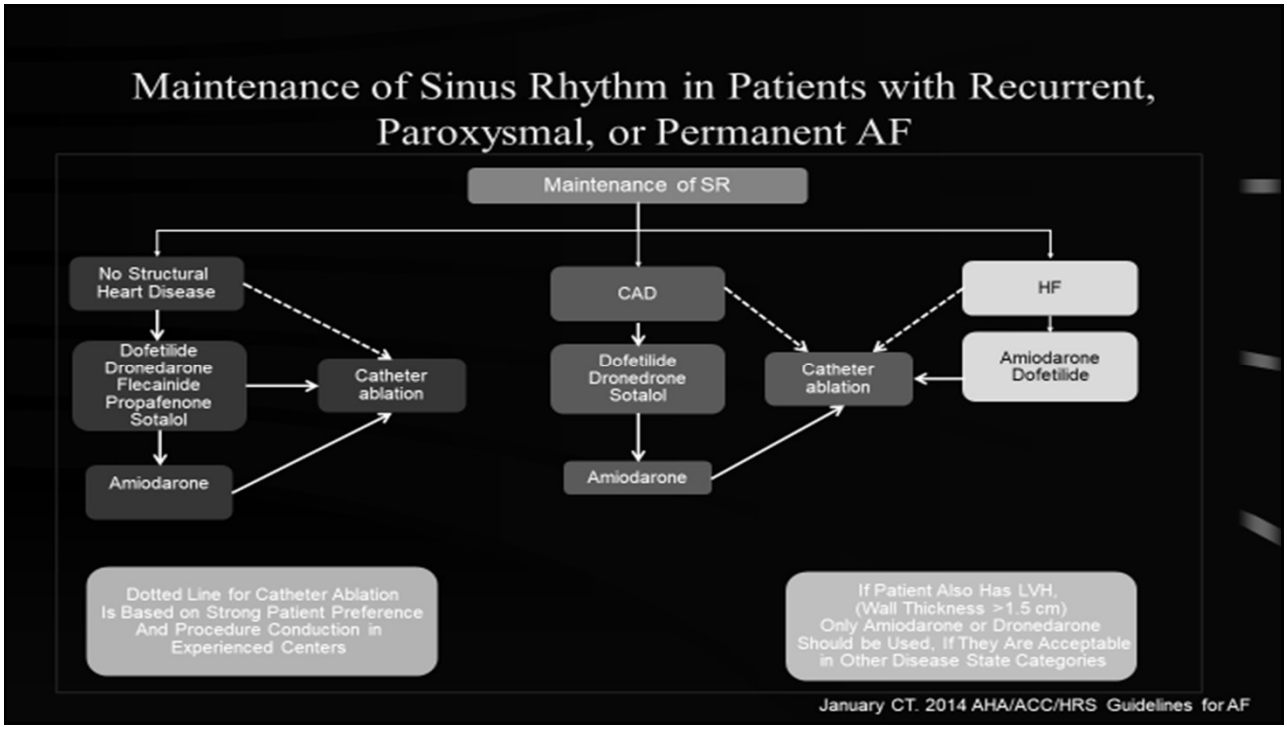

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NUMBER FIVE

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CALCIUM CHANNEL BLOCKERS

FDA Indications: Rate control in atrial tachycardia and fibrillation (NDH-CCB), conversion of PSVT (NDH-CCB), hypertension, pulmonary hypertension, hypertrophic cardiomyopathy, and angina

Off Label Uses: Raynaud's phenomenon, treatment of anal fissures

Mechanism: Blood vessel dilation enhancing blood flow to targeted areas in the body

https://my.clevelandclinic.org/health/treatments/22316-calcium-channel-blockers#:~:text=Off-label%20uses%20of%20calcium-channel%20blockers%20include%3A%201%20Raynaud%E2%80%99s,High-altitude%20pulmonary%20edema%2C%20a%20type%20of%20altitude%20sickness.

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CCBS

- Raynaud's is a disease of abnormal vasoconstriction to fingers and toes to cold weather
  - Common in pts with collagen vascular diseases (scleroderma, SLE, RA, Sjorgrens, vasculitis, etc)
  - Treatments of choice include oral CCBs (1st line), oral prazosin, and nitroglycerin ointment applied to digits (all off-label therapies)
- Annal fissures are tears in the anal mucosa from reduced anal blood flow, excessive muscle contractions, and/or constipation induced straining
  - Treatments of choice include nitroglycerin cream/ointment (1st), oral CCBs, and fiber (all off label)

https://my.clevelandclinic.org/health/diseases/9849-raynauds-phenomenon

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ASSESSMENT QUESTION 2

Which of the following drug is effective for treating anal fissures and what is the mechanism of action?

a) IV iron – iron deficiency anemia promotes anal fissure formation
b) Amiodarone – potassium channels in the anus are overactive leading to apoptosis of anal mucosal cells
c) CCBs – peripheral vasoconstriction to anal tissue worsens damage and reduces wound healing

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NUMBER FOUR

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PRAZOSIN

FDA Indications: Treatment of hypertension

Off Label Indications:

- Raynaud's phenomenon – Remember a few slides ago with CCBs…
- PTD Nightmares - The VA/DoD Clinical Practice Guideline for Management of PTSD
  - Level B recommendation for prazosin to treat sleep disorders and nightmares (fair evidence of benefit and benefits outweigh harm)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3839512/
https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/017442s041lbl.pdf
Kung S, et al.Treatment of nightmares with prazosin: a systematic review. Mayo Clin Proc. 2012 Sep; 87(9): 890—900.

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PRAZOSIN

Mechanism: Norepinephrine is a stress hormone that stimulate alpha-1 adrenoceptors in the brain, increasing the risk and severity of nightmares

Meta-analysis of six R, DB, PC studies (n=429)

- Prazosin significantly improved PTSD scores (SMD = -0.31; 95% confidence intervals [CI]: -0.62, -0.01), nightmares (SMD = -0.75; 95% CI: -1.24, -0.27), and sleep quality (SMD = -0.57; 95% CI: -1.02, -0.13)
- Prazosin is an adjunct to standard PTSD therapy: trauma informed psychotherapy (with or without psychedelics), SSRIs/SNRIs
  - Other off label options include clonidine ands atypical antipsychotics

https://pubmed.ncbi.nlm.nih.gov/32362287/

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NUMBER THREE

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CLONIDINE

FDA Indications: Hypertension

Off Label Uses: Substance use disorder (alcohol, opioids), treating facial tics with Tourette's or ADHD

Mechanisms:

- Clonidine is an alpha-2 adrenergic agonist, which reduces the release of catecholamines in peripheral nerve terminals
  - Withdrawal from opioids and alcohol causes sympathetic overdrive (sweating, diarrhea, vomiting, abdominal cramps, chills, anxiety, insomnia, and tremor)
  - Facial tics are rapid and recurring muscular twitching motions due to sympathetic outflow

https://www.ncbi.nlm.nih.gov/books/NBK310652/

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CLONIDINE

- Clonidine is "probably more effective than placebo" at reducing tics
- The Tourette's Syndrome Study Group conducted a multicenter RCT of 136 children with ADHD and chronic tic disorder
  - Pts received clonidine, methylphenidate, or placebo
  - Improvement in tics was reported in 66.7% of patients with clonidine alone ($p = 0.002$) and 44.4% with methylphenidate alone ($p = 0.21$)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7337131/

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CLONIDINE

American Society of Addiction Medicine: Recommends clonidine as a first line adjunct to support opioid withdrawal

- It has been extensively used off-label for this purpose orally or trans-dermally at doses of 0.1–0.3 mg every 6–8 hours with a maximum dose
- of 1.2 mg daily to assist in the management of opioid withdrawal symptoms.
- Clonidine can be combined with benzos for anxiety, loperamide for diarrhea, and acetaminophen/NSAIDs for pain

https://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-pocketguide.pdf?sfvrsn=35ee6fc2_0

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NUMBER TWO

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BETA-BLOCKERS

FDA Approved Indications: Hypertension, heart failure, post-myocardial infarction treatment

Non-FDA Indications:

- Mechanism: Stage fright/performance anxiety - public speaking, sport, performing arts (dancing, acting, and music) drives sympathetic nervous system symptoms: increased heart rate, hand tremor, hyperventilation, shaky voice, blushing, sweating
- Portal hypertension: non-selective BBs block β2, results in splanchnic vasoconstriction and decreases portal pressure. α1-adrenergic blockade decreases intrahepatic resistance, with a consequent greater reduction in portal pressure

Faigel HC. The effect of beta blockade on stress-induced cognitive dysfunction in adolescents. Clin Pediatr (Phila). 1991 Jul;30(7):441-5.

https://journals.lww.com/cld/Fulltext/2022/03000/Nonselective_Beta_Blockers_in_Portal_Hypertension_.9.aspx

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BETA-BLOCKERS

Clinical Trials of BBs in Performance Anxiety:

- Propranolol 40mg, 1.5 hours before music recitals, dramatically reduced S/S of performance anxiety without impacting performance vs. placebo (n=29).
- Propranolol 40mg, 1 hour before the SAT in people with severe exam anxiety with increase in verbal by 50 points and math by 80 points (n=32).
- Propranolol 40mg, 1 hours before 3rd year residents performed ophthalmologic microsurgery, There was a highly significant effect of propranolol in decreasing anxiety ($p = 0.0058$) and reducing surgical tremor ($p < 0.0001$)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9456064/

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BETA-BLOCKERS

- Beta-blockers banned in professional gun shooting, archery, billiards, golf, darts, and auto racing competitions
- Steady hand, less tremulous, less heart pounding in chest

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BETA-BLOCKERS

- Damage prevents normal passage of first pass blood through liver
  - Portal hypertension can lead to esophageal varices, GI bleeding, and ammonia creation that can lead to hepatic encephalopathy
- Nonselective beta-blockers 1st line treatment to reduce portal hypertension
  - Monotherapy can correct pressures in 30-50% of patients
  - Long-acting nitrate is adjunct therapy to boost portal BP reduction
- Is carvedilol better than propranolol in portal HTN?
  - Carvedilol 12.5-25mg vs. propranolol 40-80mg in 6 RCTs evaluating hepatic venous pressure gradient
- Study 1: -21 vs. -13 mmHg, Study 2: -28 vs. -23 mmHg, Study 3: -28 vs. -22 mmHg, Study 4: -19 vs. -12 mmHg, Study 5: -19 vs -10 mmHg, Study 6: -19 vs. -12 mmHg

https://onlinelibrary.wiley.com/doi/10.1111/liv.12360

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NUMBER ONE

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SPIRONOLACTONE

FDA Indication: HFrEF to increase survival, manage edema, and reduce the need for hospitalization for heart failure. Add-on therapy for the treatment of hypertension.

Off Label Indications w/ Indications:

- Acne vulgaris – block testosterone induced sebum production
- Hirsutism – blocks testosterone induced hair growth
- Androgenic alopecia – reduces DHT induced head hair loss
- Edema from hepatic cirrhosis and nephrotic syndrome – standard mechanism of diuresis

https://www.ncbi.nlm.nih.gov/books/NBK557838/

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SPIRONOLACTONE

Acne vulgaris: 395 adult women (age ≥21years; median age, 32) with severe acne unresponsive to other oral treatments.

- 66.1% experienced a complete response and 85.1% experienced a response >50%
- Median effective dosage was 100 mg daily (Dose 50-200 mg daily).
- Median time to initial response was 3 months with maximal response at 5 months

Hirsutism: 30% reduction in facial or body hair in studies

- Dosage 50-100 mg twice daily combined with either 35 mcg ethinyl estradiol and 0.5 mg of norethindrone or with 50 mg of ethinyl estradiol and 1 mg of ethynodiol diacetate.

https://www.aad.org/dw/dw-insights-and-inquiries/2020-archive/july/spironolactone
https://pubmed.ncbi.nlm.nih.gov/2357784/

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SPIRONOLACTONE

Androgenic alopecia

- Daily spironolactone (100-200mg) oral for 6-12 months showed hair growth in 44% of the women preventing further hair loss in another 44%
- Spironolactone was used as a monotherapy in 67 (23.4%, n=286) and in combination with minoxidil, laser therapy, or iron supplementation
  - Took 3-6 months for onset of action

https://www.jaad.org/article/S0190-9622(21)02208-8/fulltext

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ASSESSMENT QUESTION 3

Which of the following drugs is properly linked to the off-label indication it is commonly used for?

a) Beta-blockers – Raynaud's phenomenon
b) Prazosin – Nightmares in PTSD patients
c) Clonidine – Stage fright

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ASSESSMENT QUESTION 3

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ASSESSMENT QUESTION 4

Which of the following drugs is used off label for the treatment of abnormal face and body hair growth in patients and what is the mechanism of action?

a) Spironolactone – blocking the effects of testosterone
b) Beta-blockers – blocking epinephrine induced follicular stimulation
c) Clonidine – central outflow of norepinephrine causes abnormal hair growth

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ASSESSMENT QUESTION 4

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CONCLUSIONS

- Off label doesn't mean unsafe or ineffective but rather, not enough studies conducted according to FDA procedures to acquire FDA indication
- Cardiovascular drugs are used to treat other cardiac diseases but also kidney stones, SUD, diabetes insipidus, stage fright, and many others
- There are more diseases than available effective and safe treatments, patients may require innovative thinking to find a therapy that works for them
- If you see an incidental finding, it could be a lead to an off-label therapy
  - Spironaloctone was clinician discovered when used for heart failure and females with abnormal hair growth and acne expressed benefits

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