

New Blockbuster Drugs

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Objectives

- Recognize several newer blockbuster drugs important to internal medicine practice
 - Finerenone
 - Tafamidis, Acoramidis, and Vutrisiran
- Discuss an important new indication for dupilumab
- Review data outlining the efficacy and safety of these drugs

Disclosure of Conflicts of Interest

- I have no actual or potential conflicts of interest to disclose
- I am not being compensated in any way to discuss the chosen medications reviewed in this talk

Finerenone



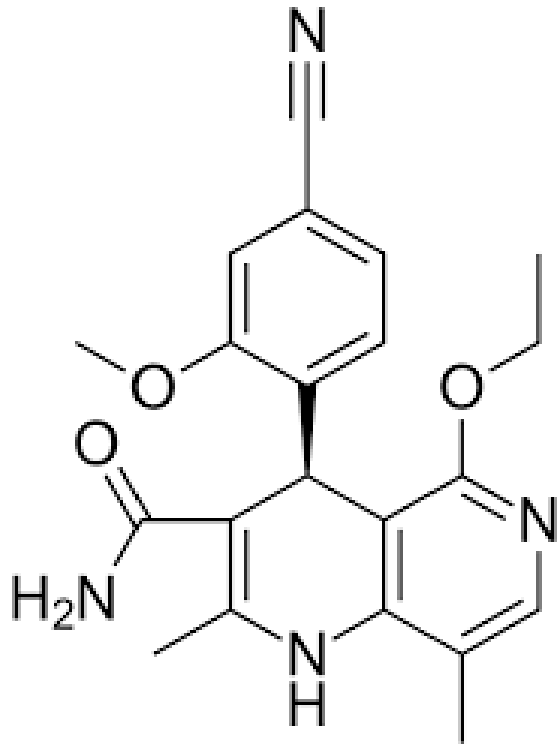
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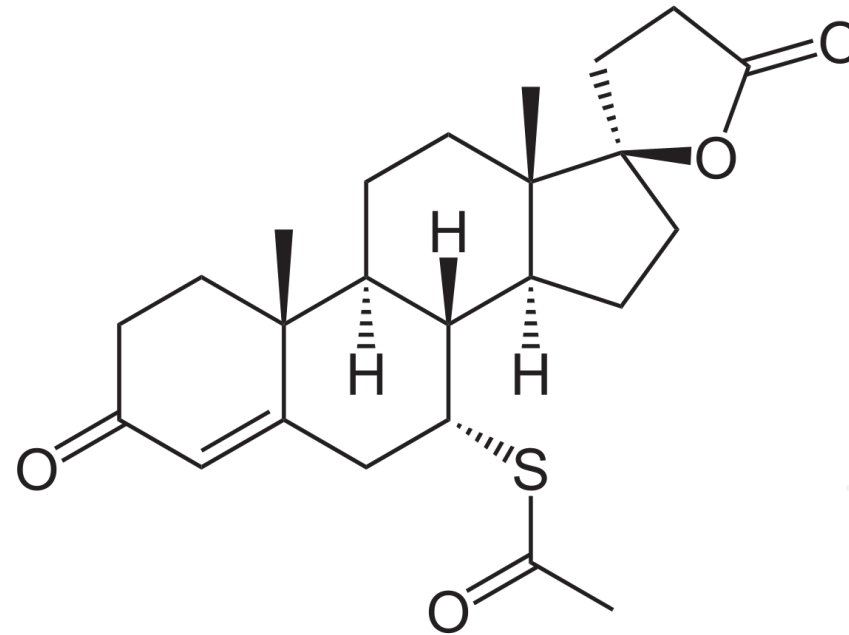
Mechanism

- Selective mineralocorticoid receptor antagonist (MRA) in kidneys, heart, and blood vessels
- Results in less sodium reabsorption and a reduction in inflammation which in turn reduces future fibrosis in the targeted tissues

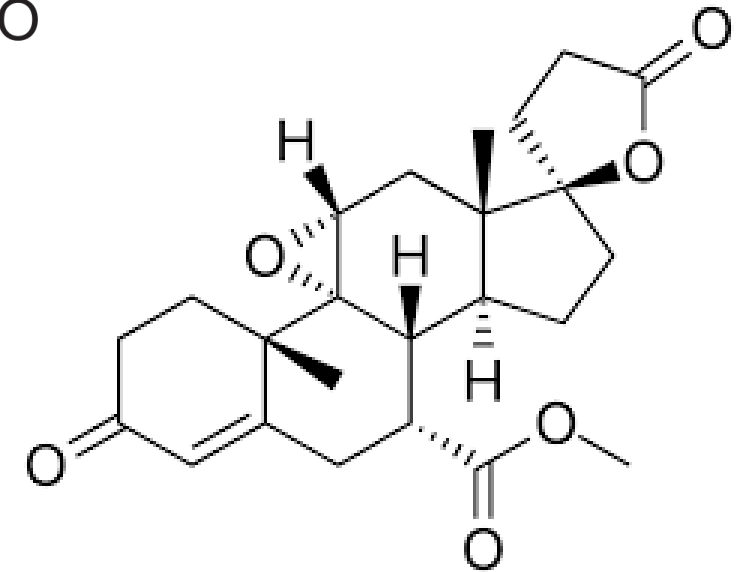
Non-Steroidal Structure



Finerenone



Spironolactone

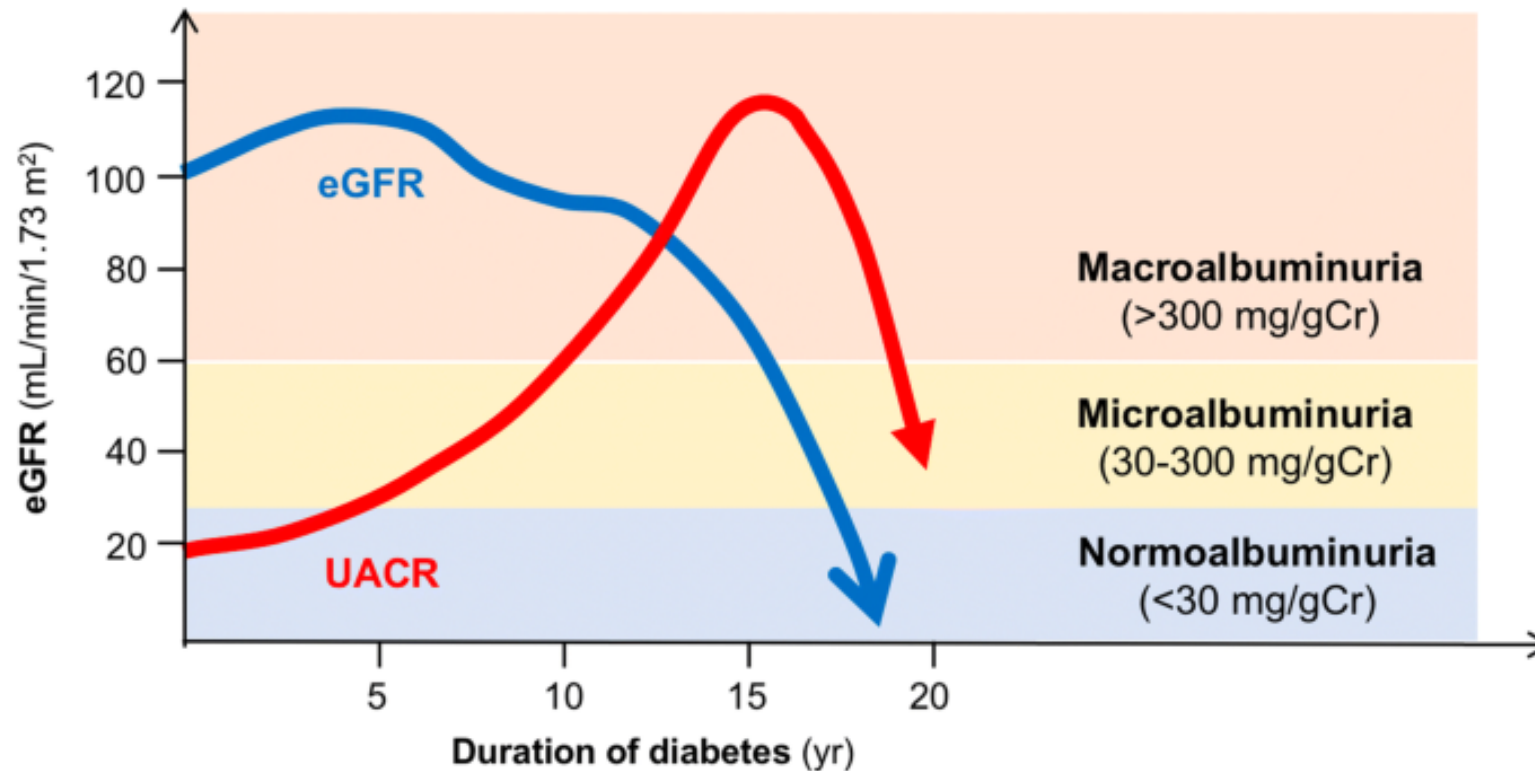


Eplerenone

FDA Approved Indications

- Chronic kidney disease (CKD) associated with type 2 diabetes (DM2)
 - eGFR ≥ 60 – 20 mg, decreased to 10 mg if not tolerated
 - eGFR 25-60 – 10 mg, increased to 20 mg as tolerated
 - eGFR < 25 – not recommended
- Heart failure with preserved ejection fraction (HFpEF)
 - eGFR ≥ 60 – 20 mg, increased to 40 mg as tolerated
 - eGFR 25-60 – 10 mg, increased to 20 mg as tolerated
 - eGFR < 25 – not recommended

Finerenone for Diabetic Kidney Disease



Finerenone for Diabetic Kidney Disease

- Pre-specified pooled analysis of two randomized trials for diabetic kidney disease with **elevated urine albumin to creatinine ratio (UACR)**
 - Both trials patients maximized on ACEI/ARB
 - Both excluded comorbid heart failure with reduced ejection fraction (HFrEF)
 - FIDELIO-DKD
 - **UACR 30 to <300 mg/g, eGFR 25 to <60 mL/min/1.73m², and diabetic retinopathy OR UACR 300 to 5000 mg/g and eGFR 25 to <75mL/min/1.73m²**
 - FIGARO-DKD
 - **UACR 30 to <300 mg/g and eGFR 25–90 mL/min/1.73m² OR UACR 300 to 5000 mg/g and eGFR ≥60 mL/min/1.73m²**

Finerenone for Diabetic Kidney Disease

- Outcomes (followed for ~2.5-3.5 years)
 - Composite of cardiovascular (CV) outcomes
 - Cardiovascular death
 - Non-fatal myocardial infarction
 - Non-fatal stroke
 - Hospitalization for heart failure
 - Composite of renal outcomes
 - First onset of kidney failure
 - Sustained $\geq 57\%$ decrease in eGFR from baseline over ≥ 4 weeks
 - Renal death

Finerenone for Diabetic Kidney Disease

Outcome	Finerenone vs. Placebo (n = 6519 vs. 6507)	95% Confidence Interval	P-Value
CV Composite	12.7% vs. 14.4%	0.86 (0.78-0.95)	<0.01
Renal Composite	5.5% vs. 7.1%	0.77 (0.67-0.88)	<0.01
Hospitalization for HF	3.9% vs. 5.0%	0.78 (0.66-0.92)	<0.01
Kidney Failure	3.9% vs. 4.6%	0.84 (0.71-0.99)	0.04
Sustained \geq 57% eGFR decline	3.9% vs. 5.5%	0.70 (0.60-0.83)	<0.01

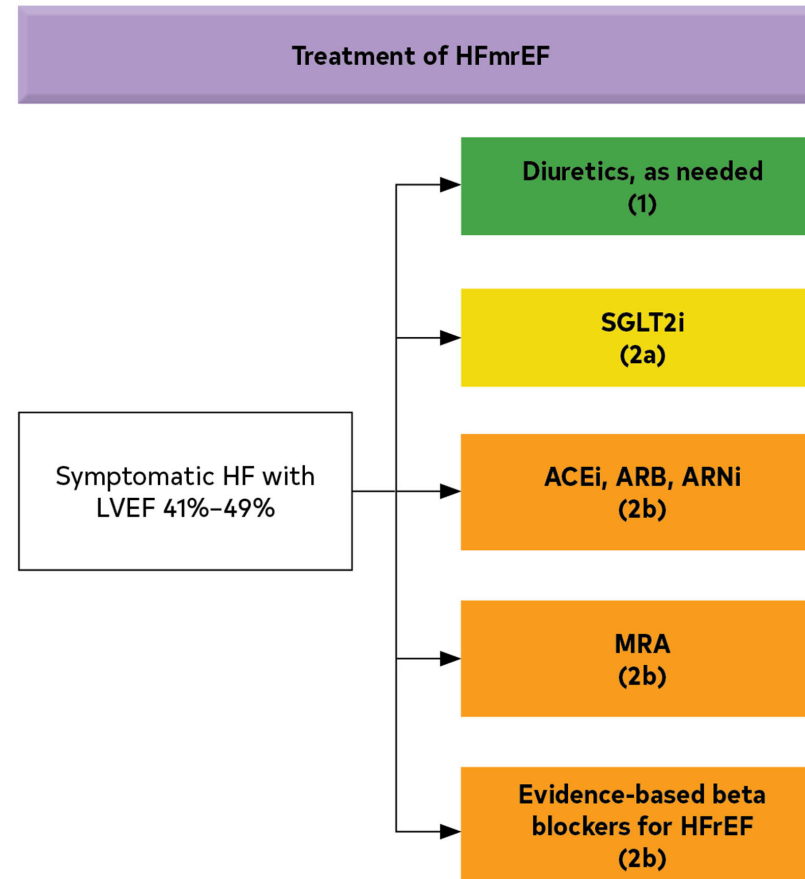
Impact Additive?

- UACR assessed in patients on maximized ACEI/ARB at 6 months
 - UACR reduced 32% with finerenone alone
 - UACR reduced 29% with SGLT2 alone
 - UACR reduced 52% with finerenone/SGLT2 combo
- Progression of CKD not assessed
- Hyperkalemia slightly LESS frequent in combination group

2024 KDIGO Guideline Recommendations

- Recommendation 3.8.1: We suggest a **nonsteroidal mineralocorticoid receptor antagonist** with proven kidney or cardiovascular benefit for adults with **DM2**, an **eGFR >25 ml/min/1.73 m²**, **normal serum potassium** concentration, and **albuminuria (>30 mg/g)** despite **maximum tolerated dose of ACEI/ARB**

Finerenone for Diabetic Kidney Disease



History of MRA for HFpEF

- TOPCAT randomized trial of spironolactone for HFpEF vs. placebo
 - Included patient with EF $\geq 45\%$
 - Composite outcome of total worsening heart failure events and death from cardiovascular causes **not** significantly better
 - Statistically significant reduction in hospitalization for HF
 - Major design flaws

Finerenone for HFpEF

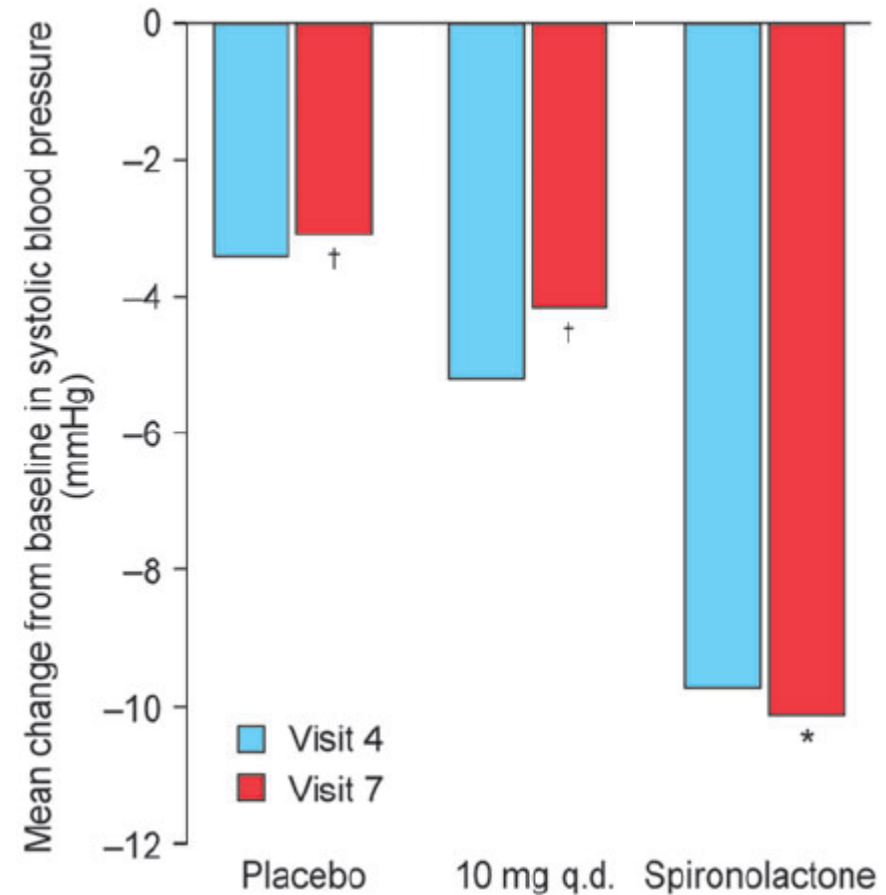
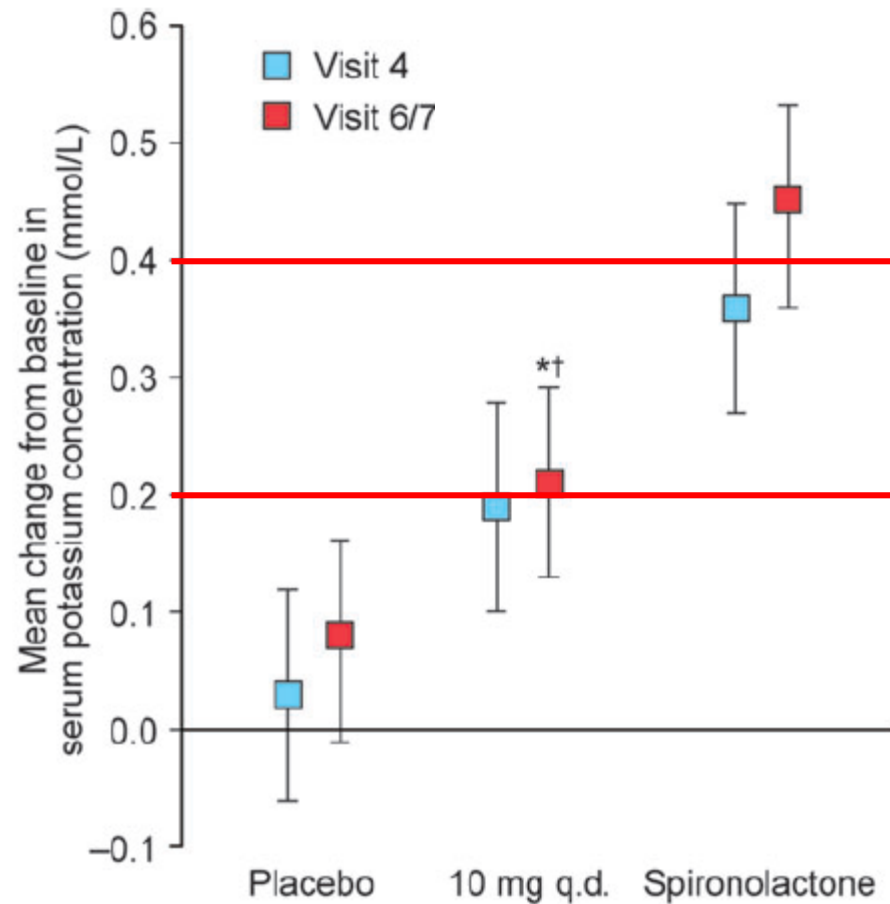
- Randomized trial in patients with EF \geq 40% vs. placebo
- Outcomes assessed over 32 months
- Composite of total worsening heart failure events and death from cardiovascular causes

Outcome	Finerenone vs. Placebo 95% Confidence Interval	P-Value
CV Composite	0.84 (0.74-0.95)	<0.01
Hospitalization for HF	0.82 (0.71-0.94)	<0.01
CV Death	0.93 (0.78-1.11)	NS

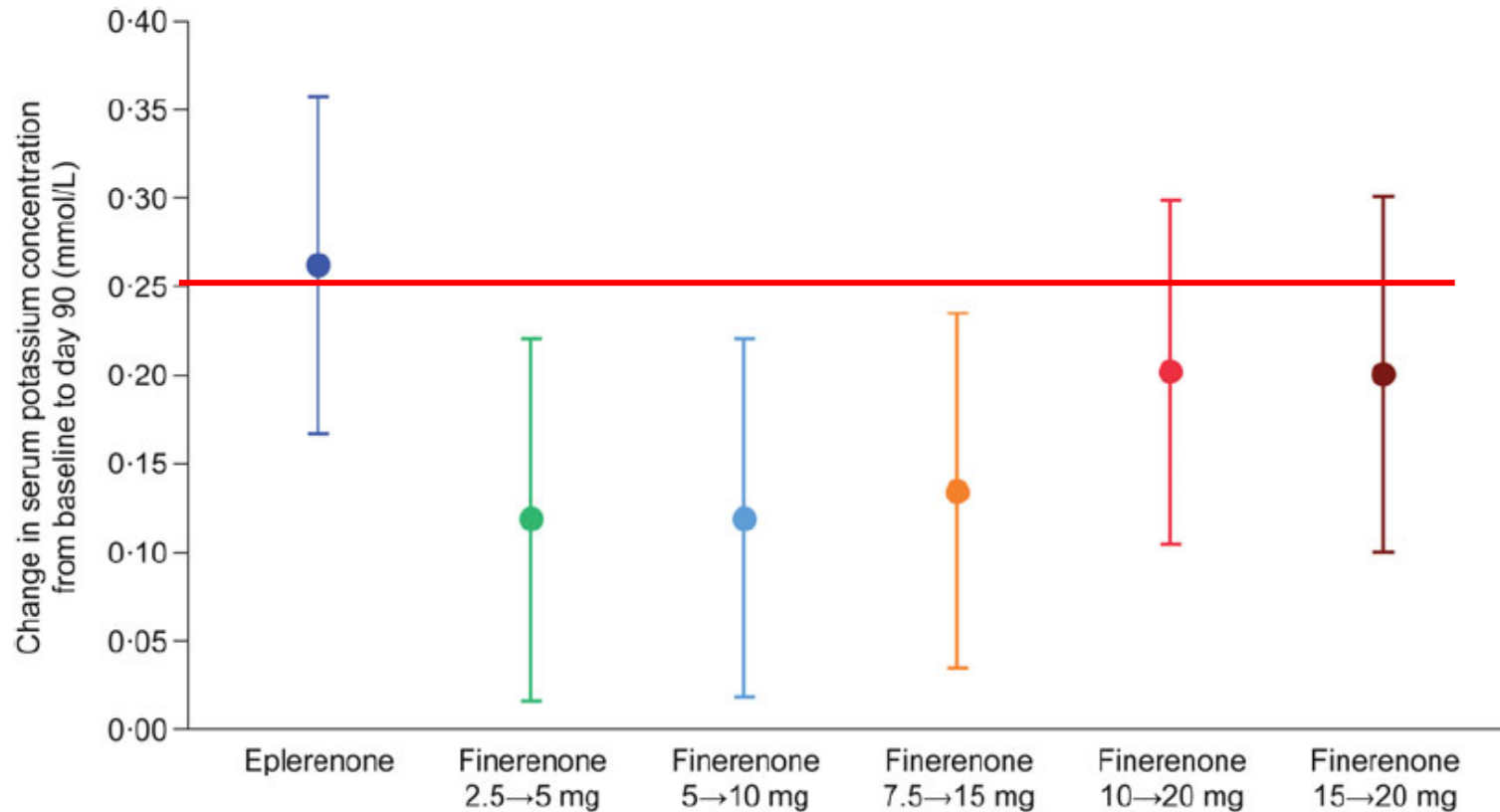
Class Comparison

Characteristic	Finerenone	Spirolactone	Eplerenone
Half Life	2-3 hr	>20 hr	4-6 hr
Active Metabolites	No	Yes, multiple	No
Selectivity/Binding Affinity	High/High	Low/High	Medium/Low
Tissue Distribution (heart to kidney)	1 to 1	1 to 3	1 to >6
Effect on SBP	+	+++	+
Effect on potassium	+	++	+
Price	~\$27/tab	~\$1/tab	~\$4/tab

Finerenone vs. Spironolactone



Finerenone vs. Eplerenone



Ongoing Questions

- Could eplerenone be an effective and safe alternative?
 - Not robustly studied – see FINALITY-HF trial below
- What about non-diabetic kidney disease with elevated UACR?
 - FIND-CKD trial ongoing
- What about HFrEF?
 - FINALITY-HF trial ongoing (patients intolerant to steroidal MRA's)

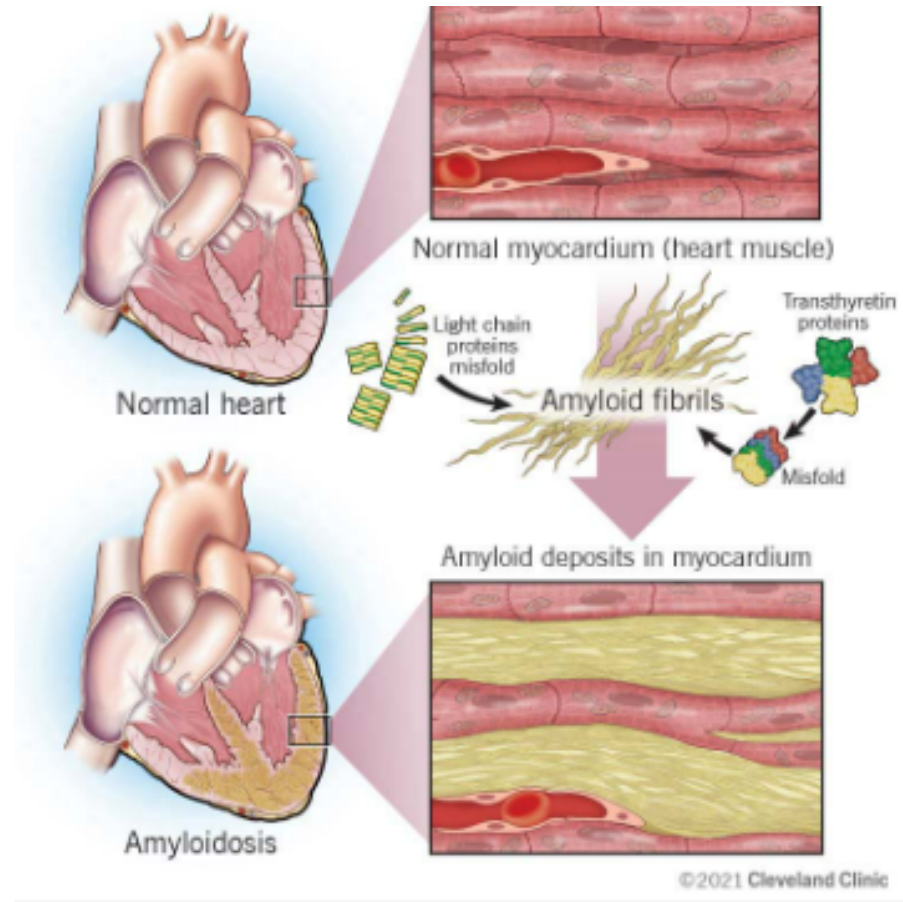
Transthyretin Amyloidosis with Cardiomyopathy Drugs



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Transthyretin Amyloidosis Cardiomyopathy



Mechanism

- Tafamidis/Acoramidis
 - Selective transthyretin (TTR) stabilizer, **slowing dissociation of the tetramer** into monomers which is the rate-limiting step in the amyloidogenic process
- Vutrisiran
 - Ribonucleic acid interfering conjugate that causes degradation of TTR messenger RNA (mRNA), resulting in a **reduction in TTR production in the liver**

FDA Approved Indications

- Tafamidis
 - Amyloid cardiomyopathy
 - 61 mg PO daily (or meglumine salt four 20 mg capsules once daily)
- Acoramidis
 - Amyloid cardiomyopathy
 - Two 356 mg tablets PO BID
- Vutrisiran
 - Polyneuropathy or cardiomyopathy associated with TTR mediated amyloidosis
 - 25 mg **SQ** every 3 months

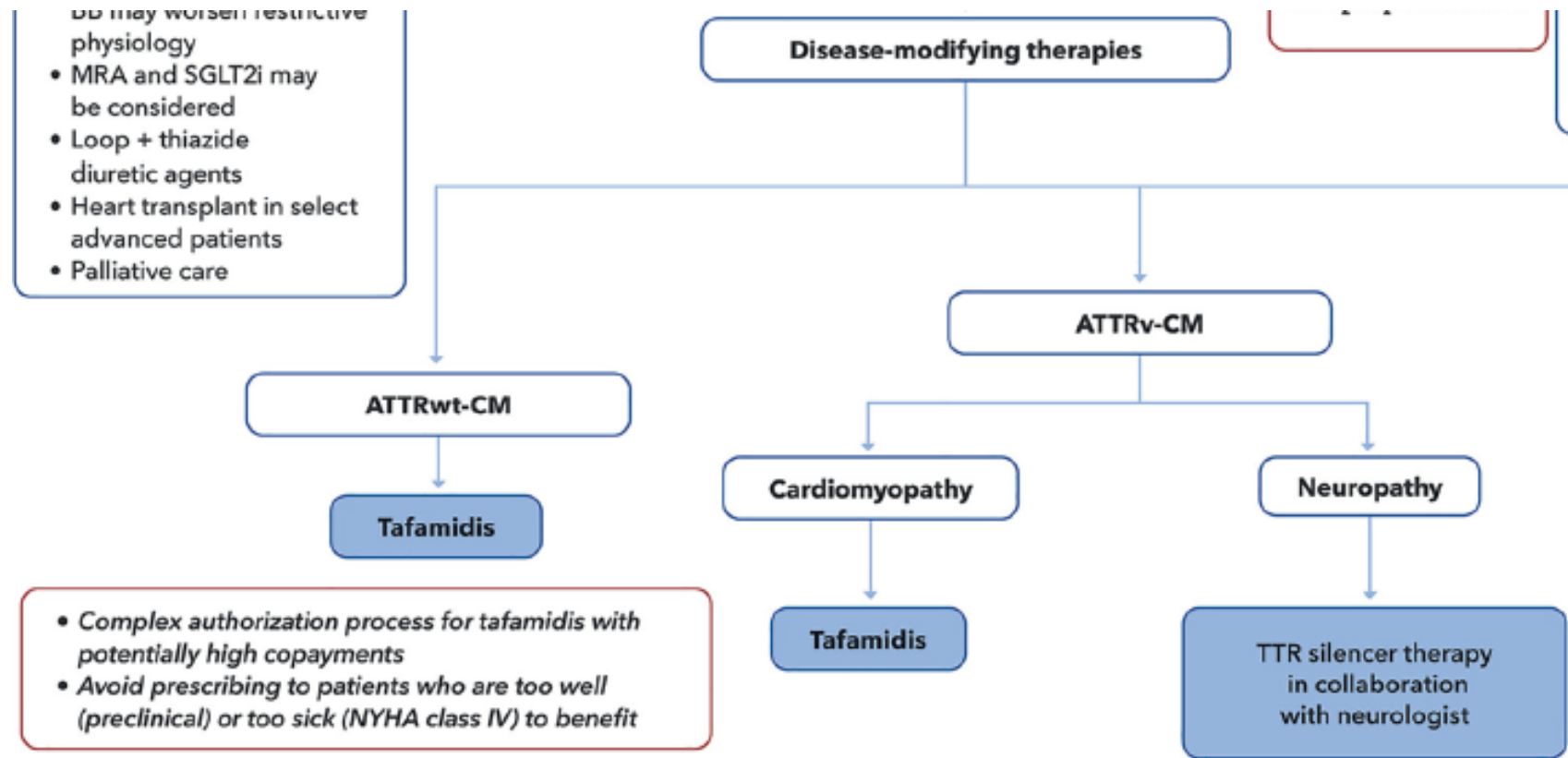
Randomized Controlled Trial Comparison

Characteristic	Tafamidis	Acoramidis	Vutrisiran
n	441	632	655
Key Exclusions	Age >90 yo NYHA Class IV CHF Asymptomatic or no cardiac involvement	Age >90 yo Tafamidis during first 12 mo Asymptomatic or no cardiac involvement	Age >85 yo NYHA Class IV CHF NYHA Class III CHF with NT-proBNP >3000 and eGFR <45 Asymptomatic or no cardiac involvement
Follow Up Time	30 months	30 months	36 months
Primary Outcomes	All cause mortality CV related hospitalization	All cause mortality CV related hospitalization Distance walked in 6 min Change in NT-proBNP	All cause mortality CV related hospitalization

Randomized Controlled Trial Comparison

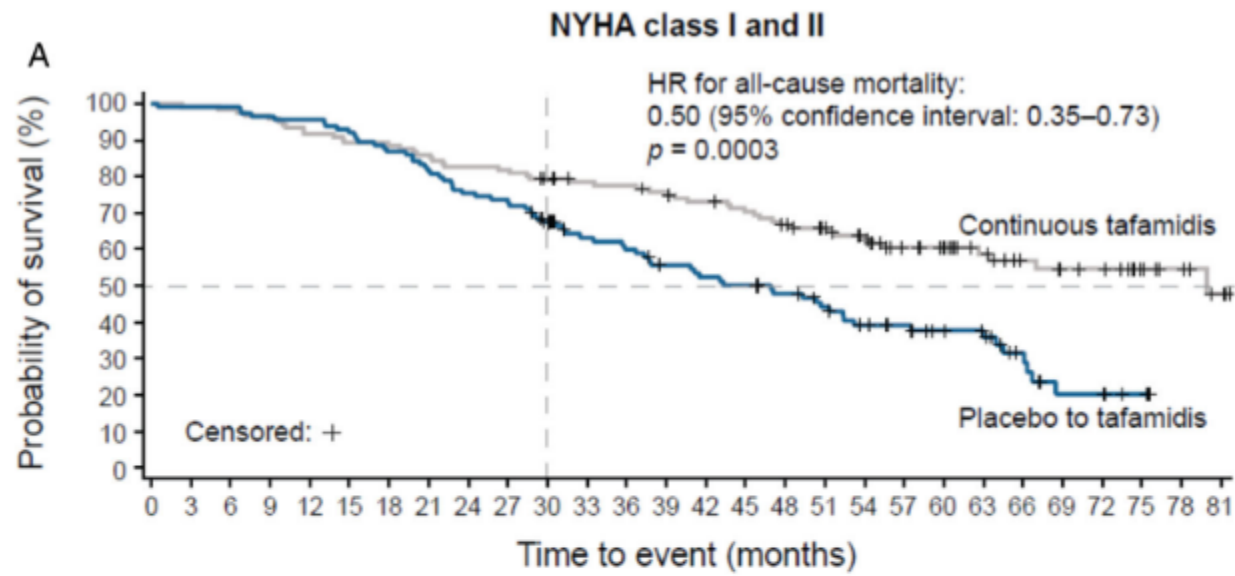
Characteristic	Tafamidis	Acoramidis	Vutrisiran
Results	<u>All cause mortality</u> 29.5% vs. 42.9% HR 0.7 95% CI [0.51 to 0.96] NNT = 8	<u>All cause mortality</u> 19.3% vs. 25.7% HR 0.77 95% CI [0.54 to 1.10] NNT = n/a	<u>All cause mortality</u> 16% vs. 21% HR 0.69 95% CI [0.49 to 0.98] NNT = 20
	<u>CV related hospitalizations</u> 52% vs. 61% RR 0.68 95% CI [0.56 to 0.81] NNT = 12	<u>CV related hospitalizations</u> 26.7% vs. 42.6% HR 0.60 95% CI [0.45 to 0.80] NNT = 7	<u>CV related hospitalizations</u> 34% vs. 41% RR 0.73 95% CI [0.61 to 0.88] NNT = 15

2023 ACC Expert Consensus

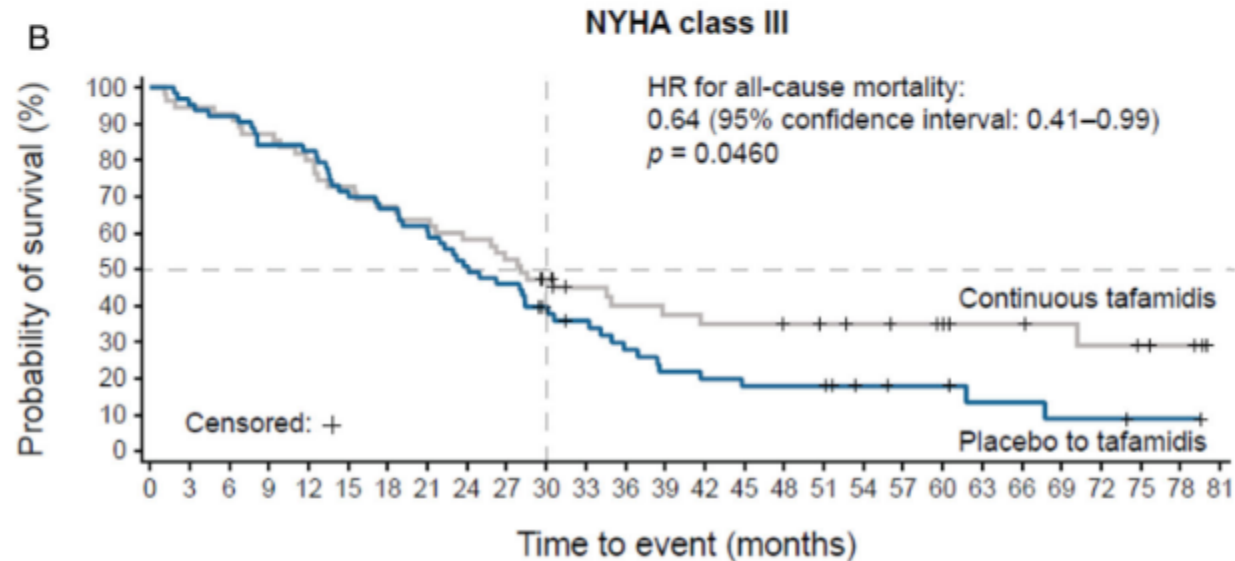


Ongoing Questions

- How late is too late to treat?
 - NYHA Class IV excluded
 - NYHA Class III subgroup results in tafamidis randomized trial
 - Statistically favored placebo for reduction in CV hospitalization (survivorship bias?)
 - Some exploratory extended data suggesting still benefit to be seen (conflicting)



n	121	120	119	116	111	108	107	104	100	99	93	89	88	84	81	77	72	67	61	49	43	34	26	23	22	14	10	6
n	114	113	113	110	109	105	99	93	86	84	71	59	56	50	47	45	42	36	30	27	22	19	12	6	6	3	0	0



Ongoing Questions

- How early is too early to treat?
 - Unknown, not studied
- What about combination therapy?
 - Reduced production (i.e. vutrisiran) AND slowed dissociation (i.e. tafamidis)
 - No statistically significant improvement in combination group but numerically reduced and likely under powered
 - Mortality (n = 259): HR 0.66 95% CI [0.37-1.20], P = 0.22
 - CV related hospitalizations (n = 259): HR 0.75 95% CI [0.38-1.47], P = 0.42

Dupilumab in COPD



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Mechanism

- Monoclonal antibody inhibitor of interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling which reduces cytokine-induced inflammatory responses, including the release of IgE.
- All components of mechanism not fully understood

FDA Approved Indications

- Atopic dermatitis
- Bullous pemphigoid
- Eosinophilic phenotype asthma
- Eosinophilic esophagitis
- Rhinosinusitis with nasal polyps
- **NEW: Refractory chronic obstructive pulmonary disease**
 - **300 mg SQ once QOW**

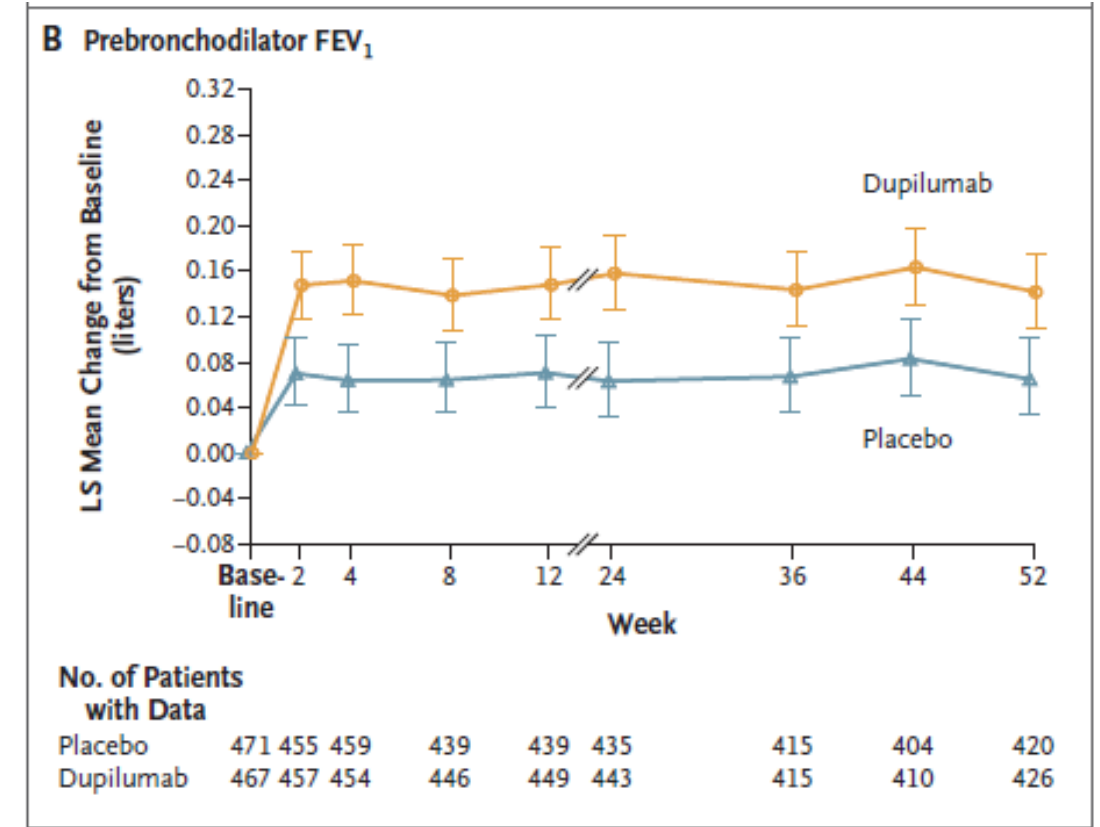
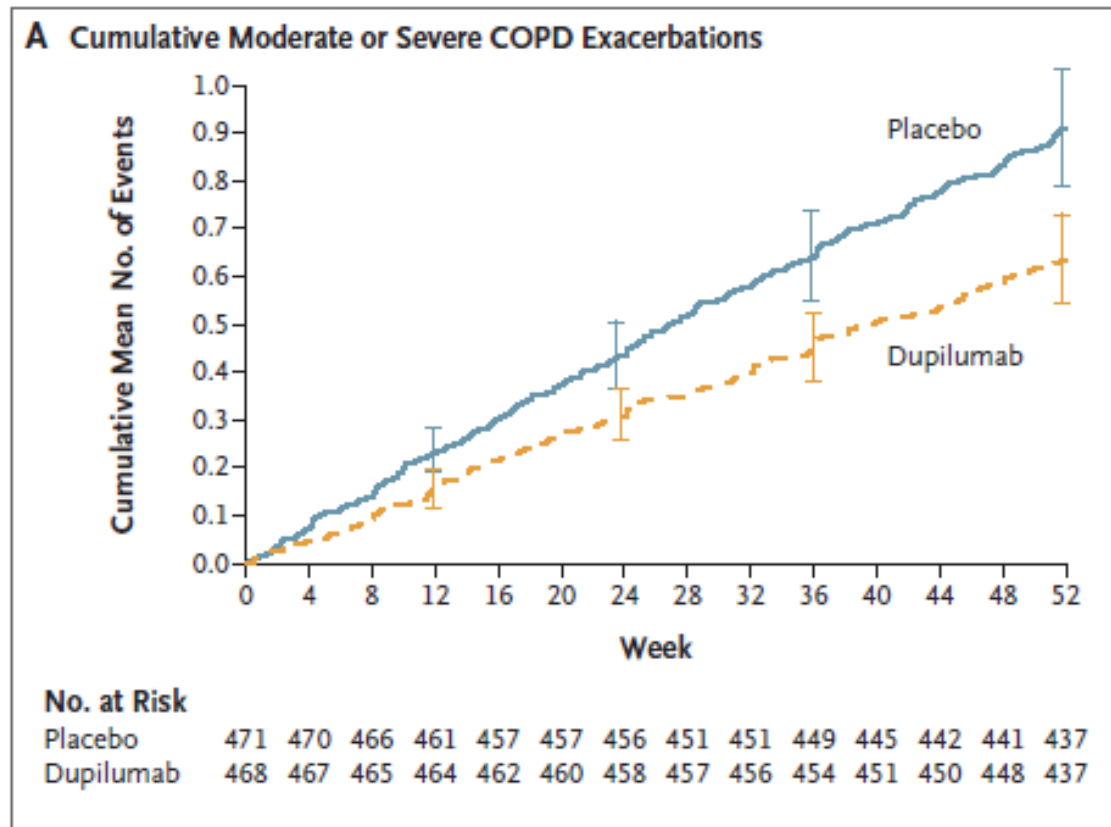
Dupilumab for COPD

- BOREAS Trial
 - Multinational RCT
 - Current or former smokers on LABA/LAMA/ICS
 - Blood eosinophil count >300 with signs of chronic bronchitis in last 3 months
 - Two moderate or one severe exacerbation in last year (while on triple inhalers)
 - Excluded patients with asthma and other confounding lung disease

Dupilumab for COPD

- BOREAS Trial
 - Primary Endpoint: Annualized rate of moderate to severe exacerbations
 - Dupilumab 0.78 [0.64 to 0.93] vs. 1.10 [0.93 to 1.30] – over 52 week follow up
 - RR 95% CI 0.70 [0.58 to 0.86] with P Value <0.001
 - Findings similar across all subgroups
 - Improvements in lung function parameters (FEV1) and patient reported outcomes seen within 2-4 weeks of starting treatment
 - No concerning differences in adverse events

Dupilumab for COPD



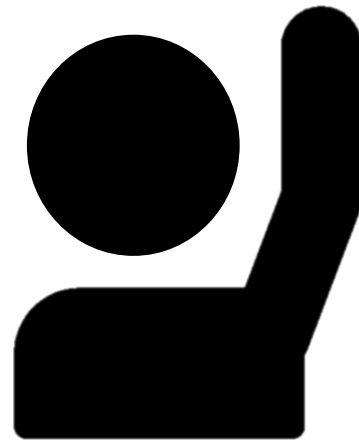
GOLD Guidelines

- If patients treated with LABA+LAMA+ICS still have exacerbations the following options may be considered:
 - Among those with **eosinophils ≥ 300 cells/uL** and symptoms of chronic bronchitis, consider adding dupilumab

Summary

- Finerenone has an important role in slowing the progression of CKD in patients with proteinuria
- Tafamidis, acoramidis, and vutrisiran are all options for management of TTR amyloidosis with cardiomyopathy
 - Cost considerations
- Dupilumab is a promising option to reduce exacerbations in COPD refractory to triple inhaled therapy in patients with eosinophil count ≥ 300 cells/uL

Questions?





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