

Guideline-Directed Medical Therapy (GDMT): Four Pillars of Cardiorenal Protection

Andrew Bland, MD, FACP, FAAP

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Guideline-Directed Medical Therapy: Four Pillars of Cardiorenal Protection

Learning Objectives

By the end of this session, you should be able to: 1. Identify the four pillars of modern GDMT and their mechanisms 2. Understand why ACE inhibitors outperform ARBs for mortality reduction 3. Recognize the unique benefits of ARNIs (angiotensin receptor-neprilysin inhibitors) 4. Explain why SGLT2 inhibitors have transformed cardiorenal medicine 5. Apply GDMT principles to HFrEF, HFpEF, and CKD patients 6. Counsel patients on sick day management with comprehensive GDMT

The Four Pillars: Overview

Modern cardiorenal protection rests on four complementary drug classes acting through distinct mechanisms:

Pillar	Drug Class	Mechanism	Benefit
1. RAAS Inhibition	ACE-I, ARB, ARNI	Block angiotensin II cascade	☐ 20-40% mortality
2. SGLT2 Inhibitors	SGLT2-i	Reduce glucose reabsorption, hemodynamic benefits	☐ 25-30% HF hosp, 37% CKD prog
3. MRA (Aldosterone)	Spirolactone, finerenone	Block aldosterone at tissue level	☐ 30-37% mortality
4. Beta-Blockers	Carvedilol, metoprolol succinate, bisoprolol	Heart rate control, reduce oxygen demand	☐ 31% mortality in HFrEF

Expected Outcomes with Optimal Therapy

Outcome	Monotherapy	Dual Therapy	Triple	Quadruple
HF hosp reduction	20-25%	35-45%	50-60%	60-70%
CKD progression reduction	20-30%	40-50%	55-65%	65-75%
CV mortality reduction	10-15%	20-30%	30-40%	40-50%
Number Needed to Treat	~100	~50	~30	~4 to prevent one death

Pillar 1: RAAS Inhibition—The Hierarchy of Effectiveness

RAAS inhibitors form the foundation of therapy, but **not all are equal**. Evidence reveals a clear hierarchy.

ACE Inhibitors vs. ARBs: A Critical Distinction

ACE Inhibitors WIN for mortality reduction: - All-cause mortality reduction: **11%** (HR 0.90) - Number needed to treat: **70 patients** to prevent one death - Absolute risk reduction: ~1.4% - Mechanism: Bradykinin potentiation (unique benefit—increases NO and prostaglandins)

ARBs fail to reduce mortality: - All-cause mortality reduction: **NOT significant** (HR 0.99) - Number needed to treat: **446 patients** (vs 70 for ACE-I) - Bradykinin-sparing mechanism means loss of additional cardioprotective effects

Clinical Pearl: In HFrEF with CKD, ACE inhibitors are superior to ARBs for survival. ARBs are acceptable alternatives only for ACE-I intolerance (cough, angioedema).

Special Consideration: RAAS Inhibitors in CKD

The Paradox: While ACE-I dominate for HF mortality, ARBs show similar renal benefits: - Both reduce doubling of serum creatinine by ~30-40% - Both reduce albuminuria reduction similarly - ARBs may have slight advantage for ESRD prevention in diabetes

Resolution: The modern approach: start with ACE-I for mortality benefit, understand that transition to ARNI is often the next step (requires washout period in CKD due to prolonged ACE-I half-life in reduced kidney function).

Angiotensin Receptor-Neprilysin Inhibitors (ARNIs)

The New Gold Standard

Sacubitril/valsartan combines: - Valsartan (ARB component) - Sacubitril (neprilysin inhibitor)

PARADIGM-HF Trial (HFREF): PubMed | Outcome | ARNI | ACE-I | Benefit | |----|---|---|---| | CV death/HF hosp | 21.8% | 26.5% | **20% reduction | | All-cause mortality | 17.0% | 19.8% | **16% reduction** | | NNT | 21 | - | 1 death prevented per 21 treated |**

How it Works: - Valsartan blocks angiotensin II (like ARB) - Sacubitril inhibits neprilysin (which normally breaks down natriuretic peptides) - Result: Enhanced natriuretic peptide signaling PLUS angiotensin blockade = synergistic benefit

Important Caveat: In CKD, ACE inhibitors have prolonged half-lives (lisinopril: 12h normal kidney function □ 30h in severe CKD). ARNI transition requires 36+ hours washout in normal kidney function, but up to 5-7 days in severe CKD to prevent angioedema.

Clinical Pearl: For CKD patients likely to transition to ARNI, consider starting with ARB rather than ACE-I to avoid prolonged washout delays.

Pillar 2: SGLT2 Inhibitors—The Game Changer

SGLT2 inhibitors have revolutionized cardiorenal medicine because they benefit ALL patients (diabetic and non-diabetic) across the entire HF and CKD spectrum.

Mechanism: Elegantly Simple, Powerfully Effective

Normal kidney: SGLT2 reabsorbs nearly 100% of filtered glucose in proximal tubule

SGLT2 inhibitor effect: 1. **Natriuresis & diuresis** without RAAS activation (unlike loop diuretics which trigger neurohormonal compensation) 2. **Reduced renal hypoxia** by decreasing metabolic workload on proximal tubule 3. **Hemodynamic adjustment** through afferent arteriole vasoconstriction (reduces intraglomerular pressure—this is BENEFICIAL long-term) 4. **Metabolic reprogramming** creating fasting-like state

Clinical Evidence Across the Spectrum

Trial	Population	HF Outcome	Kidney Outcome	Key Finding
DAPA-HF	HFREF, 42% with CKD	26% □ CV death/HF hosp	29% □ kidney composite	Benefits in ALL eGFR ranges
EMPEROR-Reduced	HFREF, 48% with CKD	25% □ CV death/HF hosp	50% □ kidney composite	Greater benefit if CKD present
EMPEROR-Preserved	HFpEF, 50% with CKD	21% □ CV death/HF hosp	95% □ kidney composite	First positive HFpEF trial
DAPA-CKD	CKD ± diabetes, 38% with HF	29% □ HF hosp/CV death	39% □ kidney progression	Reduced NEW heart failure
EMPA-KIDNEY	CKD broad spectrum	39% □ HF hosp	28% □ kidney progression	Benefits in normoalbuminuric CKD

Expected Changes on SGLT2 Inhibitors

Expected (reassure patients): - Initial eGFR dip of 3-5 mL/min in first weeks (hemodynamic, reversible) - Blood pressure reduction 3-5 mmHg - Genital fungal infections (educate on hygiene, treat early) - Polyuria/increased urination

Red Flag (discontinue): - Diabetic ketoacidosis (rare, mainly T1DM) - Signs of euglycemic DKA (nausea, vomiting, malaise even with normal glucose) - Fournier's gangrene (rare but FDA-warned)

Which Agent to Choose?

Dapagliflozin: 10 mg daily, no dose adjustment for renal function, continue down to eGFR 20

Empagliflozin: 10 mg daily, no dose adjustment, continue down to eGFR 20

Both have equivalent evidence; choice based on cost/availability

Pillar 3: Mineralocorticoid Receptor Antagonists (MRAs)

Aldosterone blockade addresses the “final common pathway” of RAAS activation.

Steroidal MRAs: Established but Limited

Spirolactone (RALES Trial): - 30% mortality reduction in severe HFrEF - NNT = 10 (impressive!) - BUT: Gynecomastia in 10% of men, menstrual irregularities in women - High hyperkalemia risk (5-10% absolute increase)

Eplerenone (EMPHASIS-HF): - 37% reduction in CV death/HF hosp in mild HFrEF - More selective, fewer endocrine side effects - Still carries hyperkalemia risk

Non-Steroidal MRA: Finerenone (The Future)

Advantages: - Balanced heart-kidney tissue distribution - No androgen or progesterone receptor affinity (no gynecomastia/menstrual issues) - **Lower hyperkalemia risk** vs steroidal MRAs - Effective in HFpEF (unlike limited data for spironolactone)

FINEARTS-HF (HFpEF): - 29% reduction in CV death + worsening HF events - Effect consistent across LVEF >40%, including true HFpEF (EF >60%) - Hyperkalemia much lower than steroidal MRAs

Clinical Pearl: Finerenone is indicated for type 2 diabetes + CKD + albuminuria (UACR ≥30 mg/g), with eGFR ≥25 and K⁺ ≤5.0.

Pillar 4: Beta-Blockers

Three beta-blockers have proven mortality benefit in HFrEF:

Agent	Type	Benefit
Carvedilol	Non-selective + alpha-blocking	65% mortality reduction*
Metoprolol succinate	Beta-1 selective	34% mortality reduction*
Bisoprolol	Beta-1 selective	34% mortality reduction*

*Relative risk reductions from meta-analysis

Important Distinction by Ejection Fraction: - **HFrEF (EF <40%):** Clear mortality benefit (~31% reduction) - **HFmrEF (EF 40-49%):** Similar benefit to HFrEF (4.7% absolute CV mortality reduction) - **HFpEF (EF ≥50%):** NO mortality benefit; potential for HARM if EF >60%

Implementation Strategy: Getting Patients to Optimal Therapy

Speed Matters

Evidence supports **rapid sequential initiation** rather than months-long titration:

Recommended Timeline: 1. **Immediate:** Start SGLT2 inhibitor (can start day 1, any eGFR ≥20) 2. **Immediate:** Optimize ACE-I/ARB to target dose 3. **Weeks 2-4:** Switch to ARNI if HFrEF and tolerated 4. **Weeks 4-12:** Add MRA if not contraindicated 5. **Concurrent:** Initiate and titrate beta-blocker

Expected Outcomes

With all four pillars: Can reduce all-cause mortality by 40-50%

Analysis from GWTG-HF registry: Quadruple therapy reduces mortality by 24.8% vs. no GDMT = **NNT of 4 to prevent one death**

The Critical Vulnerability: Sick Day Management

Patients on comprehensive GDMT have a serious vulnerability: **Their adaptive mechanisms are pharmacologically blocked.**

Why This Matters

During acute illness (gastroenteritis, sepsis, respiratory infection): - Body needs RAAS activation to maintain blood pressure (it's BLOCKED) - Kidneys need to retain potassium during stress (it's BLOCKED) - Natural diuresis would help with volume (it's SUPPRESSED)

Result: Risk of **severe AKI, life-threatening hyperkalemia, hemodynamic collapse**

Sick Day Protocol

Hold these medications: - SGLT2 inhibitors - ACE-I/ARB/ARNIs - Diuretics (loop and thiazide)

May continue: - Beta-blockers - MRAs (depending on kidney function/potassium)

Resume when: - Adequate oral intake restored - Vomiting/diarrhea resolved - Normal kidney function returned

Hyperkalemia Prevention: - Strict dietary potassium restriction during illness - Early potassium binder use if history of hyperkalemia - Check electrolytes early in illness course

Clinical Pearls

1. **ACE-I > ARB for mortality.** When tolerating, ACE-I superior to ARB despite similar renal benefits.
 2. **ARNI is the goal in HFrEF.** Transition patients from ACE-I to ARNI when clinically stable. Plan longer washout (5-7 days) in CKD.
 3. **SGLT2-i work in EVERYONE.** Diabetic or not, HFrEF or HFpEF, eGFR 20 or 90—these agents benefit cardiorenal outcomes.
 4. **Expected eGFR decline is not nephrotoxicity.** Initial 3-5 mL/min drop represents beneficial hemodynamic adjustment. Continue therapy.
 5. **MRA choice matters.** Finerenone preferred in CKD over spironolactone due to lower hyperkalemia and no endocrine effects.
 6. **Sick days require medication holidays.** Educate all patients on GDMT about holding medications during acute illness.
 7. **Four pillars provide synergy.** Combined therapy benefits exceed sum of individual agents through complementary mechanisms.
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Practice Questions

Question 1: A 58-year-old with HFrEF (EF 32%) and eGFR 48 is on lisinopril 10 mg daily and furosemide 40 mg daily. Creatinine is stable. Which steps should you take next?

Answer: (1) Uptitrate lisinopril toward target dose (usually 40 mg); (2) Add dapagliflozin 10 mg daily immediately; (3) Check K⁺ after 2 weeks—if ≤ 4.8 , plan transition to ARNI. (4) Add beta-blocker if not already on one; (5) Consider MRA if K⁺ remains ≤ 5.0 after ARNI transition.

Question 2: A 72-year-old on full GDMT (lisinopril, SGLT2-i, MRA, beta-blocker) presents with 3-day history of vomiting and diarrhea from gastroenteritis. K⁺ is 5.2 mEq/L. What's your advice?

Answer: Hold SGLT2 inhibitor, lisinopril, and MRA temporarily. May continue beta-blocker. Encourage salt and fluid intake (opposite of usual CKD advice). Check electrolytes and kidney

function. Resume medications once oral intake restored and vomiting resolved. This is why sick day planning matters!

Question 3: Compare mortality reduction between a patient on ACE-I monotherapy vs. one declining all GDMT. What's the NNT?

Answer: ACE-I: NNT ~70. This means 70 patients treated with ACE-I prevents ONE death. This is why we should persevere in getting all components of GDMT—combined four-pillar therapy achieves NNT of 4 (18x more effective).

Key Takeaways

- Four pillars** provide synergistic cardiorenal protection with ~50% mortality reduction
 - ACE-I > ARB** for mortality, but ARNI > ACE-I (goal: ARNI in HFrEF)
 - SGLT2 inhibitors** revolutionized management—benefit ALL patients across HF/CKD spectrum
 - MRA benefit proven** with modern agents (finerenone preferred in CKD)
 - Rapid sequential initiation** is superior to slow titration
 - Sick day protocols** are essential—patients must hold GDMT during acute illness
 - NNT of 4** for quadruple therapy makes implementation a moral imperative
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See Also

Related Student Handouts

- Cardiorenal Syndrome Overview
- SGLT2 Inhibitors in Detail
- Adding GLP-1 Receptor Agonists
- HFpEF: Special Considerations
- Diabetic Kidney Disease
- RAAS Inhibitors and Renal Protection

Clinical Content (01-Clinical-Medicine/Nephrology & Cardiology)

- Cardio-Renal Ecosystem Hub
- Heart Failure Clinical Reference
- CKD Hub - Full Clinical Reference

Atomic Notes (ZK)

- Cardiorenal Syndrome as Bidirectional Dysfunction
- RAAS System and Blood Pressure Regulation

Butler-COM Resources

- Butler COM - Nephrology Deep Dive
 - Butler COM - Heart Failure GDMT Deep Dive
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Related Topics

- Cardiorenal Syndrome Overview
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- Adding GLP-1 Receptor Agonists
- HFpEF: Special Considerations