Clinical Pearls in Renal Medicine

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Disclosures

• None of my financial holdings will have any influence on the topics I have chosen to present at today's Family Medicine CME conference. I do not own any equity positions in the any of the pharmaceutical companies that manufacture the drugs I am going to discuss.
Clinical Case # 1

A 54 year-old male with type 2 diabetes and early CKD stage 3 felt to be secondary to diabetic nephropathy comes to your office for follow up. BP's at home on losartan 50 mg/day and chlorthalidone 12.5 mg/day are 150/95 mm Hg. BP is 154/94 mm Hg and there is no edema. Creatinine is 1.5 mg/dL, e GFR is 52 ml/min, and urine P/C ratio is 0.8.
Clinical Case # 1: Question

Which of the following is the most appropriate next step to treat his hypertension and proteinuria in diabetic nephropathy?

- Double losartan to 100 mg/day
- Double chlorthalidone to 25 mg/day
- Add lisinopril 10 mg/day
- Add amlodipine 5 mg/day
- Add carvedilol 12.5 mg bid
Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy

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Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy

• Purpose of the paper

• Designed to test the safety and efficacy of combination therapy ACE inhibitor and an ARB as compared with ARB mono therapy

• 1448 VA patients with type 2 DM and DN were randomized to losartan plus lisinopril vs losartan mono therapy for 48 months
Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy

• Primary end points
  • Decline in e GFR
  • ESRD
  • Death
Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy

- Secondary end points
- First occurrence of a decline in eGFR
- Tertiary end points
  - Cardiovascular events
  - Change the slope of the e GFR
  - Change in albuminuria in one year
Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy

• Adverse events and safety
• All cause mortality
• AKI
• Hyperkalemia
• $[K+] > 6.0$ meq/L
Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy

- Study terminated early in October of 2012
- Safety concerns over the following adverse events
  - AKI
  - Hyperkalemia
Figure 1A
Table 2
Table 3
Combined Angiotensin Inhibition for the Treatment of Diabetic Nephropathy: Take home points

• Recommendation: Avoid combination therapy with ACE inhibitors and ARB's in patients with diabetic nephropathy
  • No benefit in outcomes in any parameters measured
  • Higher incidence of complications

• Unanswered questions:
  • Do these findings apply to other renal diseases and other populations other than patients with diabetic nephropathy?
  • Do these findings apply to combining ACE inhibitors or ARB's with aldosterone receptor antagonists such as spironolactone?
Clinical Case # 2

- A 51 year old Caucasian female with type 2 diabetes for 7 years and stage 3 CKD comes to your office for follow up. She is taking glyburide 5 mg/day, lisinopril 20 mg/day and chlorthalidone 12.5 mg every other day. Her BMI is 34, BP is 130/85 mm Hg, and there is no edema. Creatinine is 1.3 mg/dL with an e GFR of 46 ml/min. Hgb A1C is 8.1%.
Clinical Case # 2: Question

- Which of the following would you do to treat her diabetes and lower her Hgb A1C?
  - Double glyburide to 10 mg/day
  - Discontinue glyburide and start glipizide at 20 mg/day
  - Begin insulin therapy
  - Begin metformin at 500 mg/day and increase to 2000 mg/day to achieve target A1C
Review

Metformin in Patients With Type 2 Diabetes and Kidney Disease
A Systematic Review

Silvio E. Inzucchi, MD; Kasia J. Lipska, MD, MHS; Helen Mayo, MLS; Clifford J. Bailey, PhD; Darren K. McGuire, MD, MHSc

Metformin in Patients with Type 2 Diabetes and Kidney Disease: A Systematic Review

• Purpose of the Paper

• To review whether or not there is truly an increased incidence of metformin associated lactic acidosis (MALA) in patients with impaired kidney function
Metformin in Patients with Type 2 Diabetes and Kidney Disease: A Systematic Review

- 65 papers selected between 1950-2014 that were of the following categories:
  - Pharmacokinetic/metabolic investigations: 10
  - Case series: 20
  - Cross-sectional, observational, and pharmacosurveillance: 31
  - Meta analyses: 3
  - Clinical trial: 1
Metformin in Patients with Type 2 Diabetes and Kidney Disease: A Systematic Review

- Current labeling guidelines from the FDA

Box. Current US Food and Drug Administration Prescribing Guidelines for Metformin as Related to Kidney Function

- Metformin is contraindicated in "renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥1.5 mg/dL [males], ≥1.4 mg/dL [females]) or abnormal creatinine clearance (CrCl)."
- Metformin "should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced."

Source: Metformin final printed labeling.²
Metformin in Patients with Type 2 Diabetes and Kidney Disease: A Systematic Review

- Although metformin clearance is decreased in CKD, drug levels remain within the therapeutic range when the e GFR is > 30 ml/min
- No consistent link between metformin and lactic acidosis has been found
- Incidence of lactic acidosis is rare
- Frequency of lactic acidosis in patients taking metformin is very low
Metformin in Patients with Type 2 Diabetes and Kidney Disease: A Systematic Review

• Conclusion from the data reviewed:
  
• As long as kidney function is stable and the patient is observed closely, metformin is unlikely to measurably increase the risk of lactic acidosis in those with mild to moderate CKD

• e GFR: 30-60 ml/min
Table 2

Expanded use of metformin in patients with CKD:
Take home points

- Drug levels and lactate levels in patients with stage 3 CKD generally remain within the therapeutic and normal range, respectively.

- The overall incidence of lactic acidosis in metformin users is indistinguishable for the background rate in the overall population with diabetes.

- Observational studies suggest a potential benefit from metformin on micro-vascular outcomes in patients with CKD.

- Caution: No benefit in macro-vascular complications when A1C is “Optimal” at 7.0%.

- Expansion of metformin use in patients with Stage 3 CKD seems appropriate given the potential benefit and over the implied risk.
Clinical Case # 3

- A 45 year old male with CKD stage 3 is seen in your office for a routine appointment. He is feeling well and has no complaints. Current medications include lisinopril, insulin, amlodipine, and spironolactone. PE reveals a BP of 131/80 mm Hg. There are no crackles and there is no edema. Labs reveal [K+] of 5.9 meq/L. Urine protein/creatinine ratio is 0.4 Creatinine is stable at 1.7 mg/dL.

- You counsel him on dietary K+ intake and prescribe chlorthalidone, 12.5 mg/day

- He returns 4 weeks later without any complaints and he states he has implemented the dietary and medication change(s) from the last visit

- [K+] in 5.6 meq/L
Clinical Case # 3:
Question

- Which of the following would you recommend next to treat his hyperkalemia?
  - Stop the lisinopril
  - Stop the spironolactone
  - Prescribe Sodium polystyrene sulfonate (Kayexalate)
  - Prescribe Patiromer 8.4 grams bid
  - Double the chlorthalidone to 25 mg/day
Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors
Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors

• Purpose of the paper

• To evaluate the safety and efficacy of patiromer in patients with chronic kidney disease who were receiving at least one RAAS inhibitor and who had hyperkalemia.
What is Patiromer?

- Patiromer
  - Non absorbed spherical bead that binds potassium in exchange for calcium
  - Works predominantly in the distal colon
  - FDA approved for the treatment of hyperkalemia in 2015
  - Very little of the drug is absorbed so little calcium is absorbed
Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors

- Study design

- Single blind treatment phase for 4 weeks
  - 4.2 or 8.4 grams of Patiromer initially
  - Up to 21.4 grams needed to achieve goal [K+]

- Placebo controlled randomized withdrawal phase for 8 weeks
  - Patiromer or placebo
Figure 1
Figure 3
Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors

• Safety and tolerability

• Monitoring of adverse events

  • Hypokalemia: 3.0%

  • GI side effects: Most common

    • Constipation: 11%

    • Diarrhea: 3%
New therapies for the treatment of hyperkalemia: Take home points

- New agent FDA approved in 2015: Patiromer
  - Allow patients to safely continue RAAS inhibitors that seem to benefit them the most
  - Poised to replace resin therapy as a safe long-term oral therapy for hyperkalemia

- Unanswered questions
  - Will this agent be useful in treating acute hyperkalemia?
  - Will the potassium lowering effect be maintained for greater than 28 days?

- Long Term Safety profile: Unknown
Learning Objectives

• At the conclusion of this activity, members of the audience will be able to

• Apply the principles of EBM to make decisions about the dual blockade of the RAAS in treating patients with hypertension or CKD with proteinuria

• Determine which patients with type 2 DM and CKD would benefit from the use of metformin without the risk of lactic acidosis

• Evaluate the safety and efficacy of a new oral medication approved for the treatment of hyperkalemia
Conclusion

• Combination angiotensin inhibition for the treatment of diabetic nephropathy has no proven benefit and increases the risk for AKI and hyperkalemia

• Expanded use of metformin in CKD stage 3 appears safe and awaiting FDA approval for expanded use in this patient population

• Newer therapies for long term treatment of hyperkalemia may allow for ongoing use of agents that block the RAAS that are often prescribed in CKD