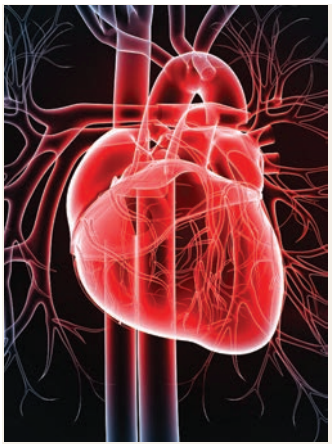

LOURDES CARDIOLOGY

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HEARTBEAT

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New Rules and Information You Can Use in the Office Tomorrow

In this *Heartbeat* I'm going to discuss the loosened restrictions on metformin use in patients with renal insufficiency, a different treatment strategy for vasovagal syncope and the use of a new potassium (K+) binding agent that is safer than kayexalate, which will allow titration of lifesaving medications that can cause life-threatening elevations in serum K+.

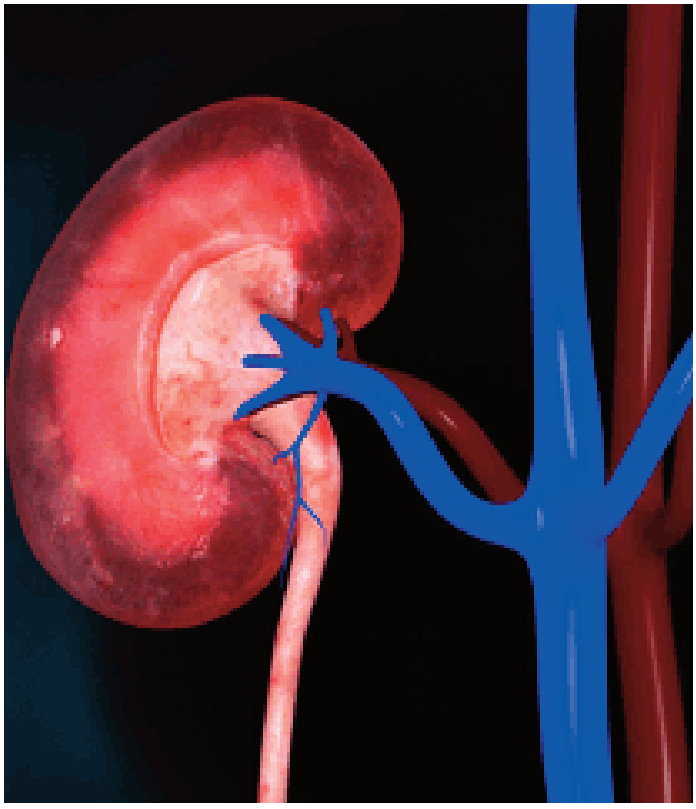
Happiness is the new rule for metformin.

New prescribing guidelines for metformin were released in June from the U.S. Food and Drug Administration (FDA) based on review of new data.[1, 2, 3, 4] The headlines are as follows: You can use metformin in anyone whose estimated glomerular filtration rate (eGFR) is > 30 mL/minute/1.73 m^2 and you do not have to stop metformin in someone undergoing a dye study unless their eGFR is < 60 mL/minute/1.73 m^2.

Metformin is the drug of first choice for type 2 diabetes—given its beneficial effects on hemoglobin A1c, weight and cardiovascular mortality—along with diet and exercise.[5] Recommendations were that it should not be used in anyone with abnormal renal function because of the danger of lactic acidosis. We used to use serum creatinine cut-points to determine when we should prescribe metformin in patients with any degree of renal insufficiency. Now the FDA has done away with that guideline and recommends using the more accurate eGFR instead of serum creatinine. This has really expanded the number of patients that we can safely keep on metformin.

New Rules:

- Test the eGFR in any patient before you start metformin and at least annually thereafter. If it's > 45 mL/minute/1.73 m^2, you are fine. That patient is fully eligible to be started on metformin. Patients with other risk factors for kidney disease, such as advanced age, should have their eGFRs checked more frequently.
- The FDA does not recommend starting metformin in patients with an eGFR between 30 and 45 mL/minute/1.73 m^2. But they still consider metformin safe if your patient is on metformin already and seems



to be deriving some benefit. So, patients down to an eGFR of 30 mL/minute/1.73 m^2 can remain on their metformin.

- Patients with an eGFR < 30 mL/minute/1.73 m^2 should not be on metformin.
- We do not have to stop metformin in every patient undergoing a radiographic dye study. If the eGFR is > 60 mL/minute/1.73 mm^2, don't worry about it. They can continue taking their metformin throughout. This change makes me happy and should save us all a lot of time and effort.
- If the eGFR is < 60 mL/minute/1.73 mm^2—meaning between 30 and 60—then, as we did before, you stop the metformin before the patient undergoes the dye study and recheck in 48 hours to make sure that the eGFR is still in a safe range and restart accordingly.

Does Fludrocortisone Work in Vasovagal Syncope?

The first long-term randomized, controlled, double-blind study that has been performed for any therapy for vasovagal syncope (neurocardiogenic) features a strong pathophysiologic basis for fludrocortisone (Florinef).[6] Saline infusions in tilt table testing studies have led to a reduction of syncope with further tilt testing. Fludrocortisone increases renal salt and water retention and results in increased plasma volume blocking the physiological cascade leading to vasovagal reflex syncope. It has been my mainstay of therapy for orthostatic hypotension and autonomic dysfunction. I always tell my patients to increase salt and water intake but this treatment is probably more consistently effective. Vasovagal syncope is thought to be due to inappropriate vasodilation, which results in reduced venous return. This makes a strong case for the therapeutic rationale of fludrocortisone.

Recurrent vasovagal syncope showed an overall trend toward reduced syncope, which was statistically significant in those who achieved the 0.2 mg daily dose of fludrocortisone. The dose range in the study was 0.05 mg to 0.2 mg daily, so some patients may have been under-dosed. The highest recommended dose for

orthostatic hypotension is 0.3 mg. Subgroup analysis showed that most patients that showed benefit had baseline systolic BPs < 110 mmHg.

We don't have a lot to offer these patients once cardiac causes have been excluded. Many drugs have been tested for the treatment of vasovagal syncope. For the most part, the results have been disappointing. The list includes beta-blockers, disopyramide, scopolamine, theophylline, ephedrine, etilefrine, midodrine, clonidine and serotonin reuptake inhibitors.

Based on this study, the accompanying editorial [7] and my own experience, I feel that *fludrocortisone is worth a try in patients, with frequent vasovagal syncope episodes, who are young and healthy with low systolic BP.*

Fludrocortisone should not be used in patients with HF or hypertension, as the most common side effects are fluid retention (edema) and elevated BP.

New Possible Life-Saving Treatment

There is overwhelming evidence that the renin-angiotensin-aldosterone blockers (RAABs) are life- savers in a number of illnesses affecting the heart (heart failure [HF] secondary to systolic dysfunction) and kidney (proteinuric diabetic chronic kidney disease [CKD]). These agents are also beneficial in CKD and hypertension with or without comorbidities (such as

HF). Unfortunately hyperkalemia is already common in these conditions and using RAABS (ACE-inhibitors, angiotensin receptor blockers and aldosterone antagonists)further increase serum K+.

Control of hyperkalemia in these patients with CKD and in those with HF has proved to be difficult. Dietary limitation, vigorous use of diuretic therapy, provision of bicarbonate, and limiting the use or lowering the dose of drugs that increase potassium levels may control potassium so that specific potassium-binding therapy is not needed. Kayexalate is a nasty drug either orally or by enema and can't be tolerated long-term.

Two studies with patients consistent with the groups I described give us an alternative to stopping or decreasing the dosage of RAABSs and mitigating their potential life-saving benefits. [8, 9]

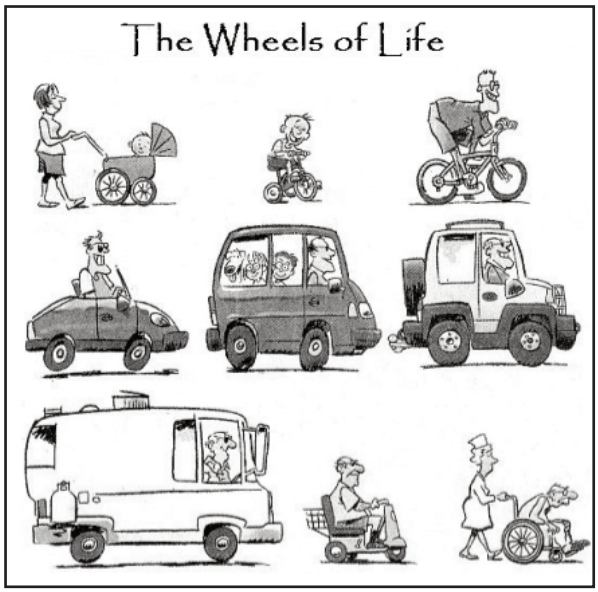
The studies conclude that in patients with CKD who were receiving RAABs and who had hyperkalemia, patiromer (PAT) was associated with a decrease in serum potassium levels and, as compared with placebo, a reduction in the recurrence of hyperkalemia. PAT is a powder mixed with water that binds K+ in the GI tract to decrease absorption and has significantly less diarrhea than kayexalate. Mild hyperkalemia (K+ = 5.1-5.4 mmol/L) was treated with PAT 4.2 g BID, and moderate-severe hyperkalemia (K+ = 5.5-6.4 mmol/L) with PAT 8.4 g BID.

The FDA approved PAT to treat hyperkalemia late last year. The drug is not recommended for emergency treatment of severe hyperkalemia. PAT also binds other orally administered drugs, which could decrease absorption. Therefore, administration of other drugs should be delayed by at least six hours after administration. PAT is made by Relypsa, as Veltassa. The drug is expected to cost nearly $600 for a 30-day supply.

I would *consider trying this in my cardiomyopathy (HF) patient so I can institute life-saving treatment with RAABs,* just as I would consider a pacemaker for this same patient who couldn't tolerate a beta-blocker because of bradycardia.

The Smoking Gun?

Kearns and colleagues report that an industry-funded study hid sugar's link to heart disease.[10] Two co-authors of a paper from 1967 were paid approximately $50,000 each.[11] A sugar trade association not only paid for, but also initiated and influenced research expressly to absolve sugar from being a major risk factor for coronary heart disease—the smoking gun. It is appalling that this data has influenced dietary practice for more than 30 years, contributing to the rise of diabetes. Unfortunately, this isn't ancient history, as the sugar industry conflicts of interest continue today as mentioned in last month's *Heartbeat*.



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