The Prudent Prescriber

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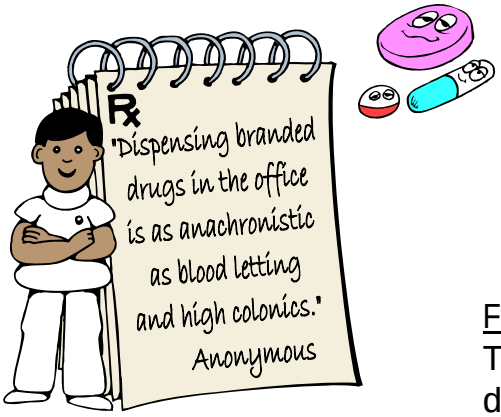


April 2017

Pharm Reps ≠ Rational Prescribing (PR) (RP)

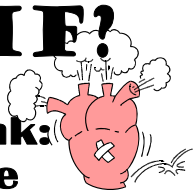
Diabetes Surrogates, a New Treatment Paradigm Another Insulin Glargine

Fake News?

The latest FDA guidance for industry for diabetes (2008) advises that drugs that lower HbA1C levels can be ”reasonably expected to reduce the long-term risk of microvascular complications.” They go on to conclude that, ”reliance on HbA1C remains an acceptable primary efficacy endpoint for approval of drugs seeking an indication to treat hyperglycemia secondary to diabetes mellitus.”

Since the 1990s, the prevailing concept has been that risk reduction could be achieved by focusing on reaching target values of HbA1C regardless of the strategies used. This is spurious science. Consider the pathways that we have wandered down before with management of heart disease. Lowering homocysteine levels with folic acid! Lowering cholesterol levels with statins! Decreasing homocysteine levels and cholesterol levels have both been shown NOT to be predictive surrogate markers for decreasing cardiovascular risk.

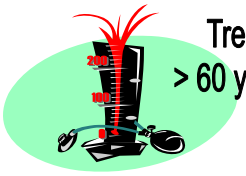
CHF?



Think:
Ace
Aldactone
B-blocker
Dig
Diuretic

Avoid these expensive “me-too” drugs:

Intermezzo
Vimovo
Livalo
Pristiq
Viibyrd
Edarbi
Daliresp



Treat patients > 60 years to 150/90

Antibiotics do NOT

help acute bronchitis

ß-blockers in post-MI save lives

Pill splitters save BIG

NOW AVAILABLE ON THE GENERIC MARQUEE

Frova→frovatriptan
Voltaren gel→diclofenac Na 1% gel
Crestor→rosuvastatin
Nuvigil→armodafinil
Jalyn→dutasteride/tamsulosin
Ortho Tri-Cyclen Lo→Tri-Lo-Marzia, Tri-Lo-Sprintec, & others

A Changing Paradigm

To their credit in 2008, the FDA began to require post-approval trials that could reasonably evaluate cardiovascular risk associated with new glucose lowering agents. (JAMA March 14, 2017)

How many times have I quoted the UKPDS trial (reported in 1998) to colleagues and patients? The evidence regarding the cardiovascular benefits of metformin in that trial was based on a small subgroup of patients (n= 342). We are now blessed with much more robust studies that include thousands of patients with diabetes who are exposed to the newer drugs.

Here are two examples:

- EMPA-REG OUTCOME Trial A sodium-glucose transporter 2 inhibitor, empagliflozin (Jardiance) (30 tabs, 25 mg $352 at Sam's Club, GoodRx 4/15/17) was studied in 7,020, type 2 diabetic patients randomized to 10mg or 25mg of empagliflozin or placebo, followed for an average of 3.1 years. (Zinman et al, NEJM 2015; 373(22); 2117-2128) The primary outcome was a combination of non-fatal stroke, non-fatal MI and cardiovascular mortality. The primary outcome was found in 10.5% of the empagliflozin group and in 12.1% of the placebo group (NNT=63). **There were significantly lower rates of death from cardiovascular causes (3.7% vs. 5.9%, NNT=46) and death from any cause (5.7% and 8.3%, NNT=38).** For the primary and key secondary outcomes, hazard ratios for the comparison between the 10mg dose of empagliflozin versus placebo and the 25mg dose versus placebo were virtually identical to those in the pooled analysis.

  The authors: "Many patients did not reach their glycemic targets, with an adjusted mean glycated hemoglobin level at week 206 of 7.81% in the pooled empagliflozin group and 8.16% in the placebo group. Our trial was designed to assess the specific effects of empagliflozin on clinical outcomes... We infer that the mechanisms behind the cardiovascular benefits of empagliflozin are multidimensional and possibly involve changes in arterial stiffness, cardiac function, and cardiac oxygen demand, as well as cardiorenal effects, reduction in albuminuria, reduction in uric acid..."

- LEADER Trial In a second study, a total of 9,340 diabetic patients underwent randomization to either liraglutide (Victoza) (3 pens of 18mg/3ml, $714 Sam's Club, best price GJ on GoodRx 4/15/17) or placebo. The median follow-up was 3.8 years. The primary outcome (time to first non-fatal MI, non-fatal stroke and cardiovascular death) occurred in significantly fewer patients in the liraglutide group (13.0%) than in the placebo group (14.9%) (NNT=58). **Fewer patients died from cardiovascular causes in the liraglutide group (4.7%) than in the placebo group (6.0%) (NNT=77) The rate of death from any cause was lower in the liraglutide group (8.2%) than in the placebo group (9.6%) (NNT=71).** (NEJM.2016; 375(4): 311–322). At the end of the study, the average HbA1C was only 0.25% higher in the placebo group compared to the liraglutide group.

My Take: I am not championing either of these drugs, (both avariciously priced and with empagliflozin in women, increased genital infections, 2.5% placebo vs 10% empagliflozin), but I support investing in similar studies that explore alternative mechanisms for cardiovascular benefits and harms. It is exciting that we now have some meaningful, patient oriented outcomes for these newer diabetes drugs. Ohhhh, that they were not so #*%@ expensive.

Nota Bene:

1) Higher doses of the two tested drugs did not improve outcomes.
2) The differences in the HbA1Cs between the two active drugs and their placebo groups were minimal. Something other than glycemic control is driving these positive outcomes.
3) These large studies are impressive in the face that both demonstrate decreased cardiovascular and all cause mortality!
4) Be careful in generalizing the results of this research to healthier patients, as the majority of the patients in both studies were diabetics at high risk for a cardiovascular event.
5) Finally, stay skeptical! Both studies were paid for by BIG PHARMA. The lists of author disclosures go on forever and ever.

Basaglar (Insulin glargine)

- FDA approved: December, 2016.
- 100 units/ml, long acting insulin that is approved as a" follow-on" to Lantus. (truncated review pathway)
- NOT a biosimilar approved product based on the route of approval, but evidence to demonstrate that Basaglar is sufficiently similar to Lantus to justify its safety and effectiveness.
- Clinical studies in both type 1(535 patients) and type 2 (759 patients) showed that Basaglar was non-inferior to Lantus at 24 weeks.
- Packaged as a box of five 3mL syringes (1,500 total units).
- The cost of Basaglar is $380.22 (AWP); about 17% less expensive than Lantus at $447.31 (AWP). GoodRx prices in Grand Junction pharmacies on 4/16/17 ranged: Basaglar, $332-$347 vs Lantus $389- $407.
- My Take: This is a disappointing, but not unexpected minimal reduction in price for the second glargine product. Hopefully some managed-care companies will make Basaglar available on the generic tier (it is not a generic) to make the patient's pharmacy transaction a little less painful. Everything that I know about this new product points to a clinical equivalent of Lantus. Write for "Basaglar", as a prescription for "insulin glargine" could be filled with either product.

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