4 (+) Articles that will sharpen your outpatient practice.

James “Jimmy” Hotz, MD FACP

November 22, 2019

Conflict of interest

*No current conflict of interest.

I am an academic traditionalist working for the Roudebush Veterans Affairs medical center doing outpatient and inpatient internal medicine. I also hold positions for the Indiana University School of Medicine as well as the Indiana University Internal Medicine Residency. My research interest is in resident wellness and I am internally funded by the department of medicine.

In the past I did write board review questions for the NEJM knowledge plus series but am not longer doing this.

Outline

1-Canagliflozin (and the SGLT2s)->renal and heart drugs? CREDENCE-Trial

->Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy-NEJM 2019 [5]

2-Statins-just the facts!

->Statin Safety and Associated Adverse Events: A Scientific Statement From the American Heart Association [7]

3-Iron-just a dab will do you!

->Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomized controlled trials [9]

4-Aspirin-not all it is cracked up to be in primary prevention. ARRIVE-trial

-> Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomized, double-blind, placebo-controlled trial [12]

Case #1

A 64 year old female with a history of type 2 diabetes complicated with mild albuminuria (hemoglobin a1c 7.2; managed on 500mg of metformin monotherapy), hypertension (well controlled at 115/75 mm/Hg on 5mg amlodipine and 40mg of benazepril), and chronic kidney disease stage 3a (creatinine of 1.2 and eGFR of 52) presents to your clinic for a routine follow up. She is feeling well overall but wants to know if anything more can be done to protect her kidneys. In addition to working on lifestyle and exercise you might propose adding which of the following medications to help protect her renal function?

A-Glargine

B-Glipizide

C-Canagliflozin

D-Alogliptan

Correct answer C-Canagliflozin

Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy-NEJM 2019 [5]

Study Design- Randomized, double-blind placebo-controlled trial. 4401 patients

Methods- Patients with type 2 diabetes and albuminuric CKD (gfr 30-90ml/min + albuminuia) received canagliflozin 100 mg/day or placebo. All were on renin-angiotensin system blockade.

Primary outcome of the study was a composite of ESRD (dialysis, renal transplantation, or GFR <15), doubling of the serum creatinine level, or death from renal or cardiovascular (CV) causes.

Results: trial stopped early due to significant results->

->primary outcome event rate of 43.2/1000 person-years in the canagliflozin group and 61.2/1000 person-years in the placebo group (HR, 0.70; 95% CI, 0.59 to 0.82; *P* <0.000001).

>The HR for ESRD was 0.68 (95% CI, 0.54 to 0.86; *P* =0.002).

->CV benefit of canagliflozin with a reduced HR of combined end points of CV death, myocardial infarction, or stroke of 0.80 (95% CI, 0.67 to 0.95; *P* =0.01)

SGLT2s- Sodium-glucose co-transporter 2 inhibitors “Diabetic drugs?”

Empagliflozin-heart-EMPA-REG [1]-lowered rate of primary composite cardiovascular outcome and of death

Empagliflozin-renal-EMPA-REG [2]-slowed progression of renal disease and renal events

Dapagliflozin-heart DAPA-HF [3]-reduced risk of heart failure or death from cardiac causes

Dapagliflozin-CAD-DECLARE–TIMI 58 [4]-Lower rate of cardiovascular death or hospitalization for heart failure. No difference in rate of MACE

Canagliflozin-Renal-CREDENCE [5] risk of kidney failure and cardiovascular events was lower in the canagliflozin group (interestingly did not show increase in limb loss)

Canagliflozin-CAD-Canvas [6] lower risk of cardiovascular events than those who received placebo but a greater risk of amputation, primarily at the level of the toe or metatarsal.

*EMPA-REG funded by Boehringer Ingelheim and Eli Lilly; DAPA-HF and DECLARE-funded by AstraZeneca; CREDENCE and Canvas trials funded by Janssen Research

Drawbacks and thoughts

Canagliflozin->Cost-per Good RX $485.40 for 30 days, 20% off the average retail price of $614.04 per 30 days; most insurance do not cover.

->Empagliflozin- 96% of Medicare Part D and Medicare Advantage plans cover this drug.

*Risk Eugycemic DKA->most case reports are in the fasting patient, potential risk of Fournier's gangrene->only about ~50 reported cases, most recent studies do not support SGLT2 causing Urinary tract infections [19].

*The SGLT2 Class appears to have a class effect for renal and cardiac protection among other benefits (weight loss and better blood pressure control).

Clinicians need to work with patients on shared decision making in using this newer class on diabetics medications. Cost is currently the key deterring factor.

*New JAMA article that would be good to review [20] shows that the number needed to harm for starting basal insulin is 1 in 37 for an adverse cardiovascular event- Retrospective cohort study among 132 737 studying effects of adding second line agents.

Case #2

A 58 year old male with a history of hypertension (well controlled on chlorthalidone 12.5mg), smoking (1 pack per day), and hyperlipidemia presents to your office for an annual check up. During the visit your when discussing his hyperlipidemia you calculate his cardiovascular risk to be 12.5% over the next 10 years using the ASCVD risk Estimator Plus [21]. In addition to discussing smoking cessation and lifestyle changes you discuss adding atorvastatin 20mg. He ask you about the risk of serious muscle injury (including rhabdomyolysis) that he read about on the internet. What is his relative risk of this type of muscle damage from statins?

A-10%

B-1%

C-0.1%

D-x<0.1%

Correct answer D-x<0.1%

12.5% Intermediate — **Current 10-Year ASCVD Risk****

Lifetime ASCVD Risk: **69%** Optimal ASCVD Risk: **4.8%**

Current Age * 58
Age must be between 20-79

Sex * ✔ Male | Female

Race * ✔ White | African American | Other

Systolic Blood Pressure (mm Hg) * 120
Value must be between 90-200

Diastolic Blood Pressure (mm Hg) 75
Value must be between 60-130

Total Cholesterol (mg/dL) * 170
Value must be between 130 - 320

HDL Cholesterol (mg/dL) * 42
Value must be between 20 - 100

LDL Cholesterol (mg/dL) 128
Value must be between 30-300

History of Diabetes? * Yes | ✔ No

Smoker? * ✔ Current | Former | Never

On Hypertension Treatment? * ✔ Yes | No

On a Statin? ✔ Yes | No

On Aspirin Therapy? Yes | No

12.5% Intermediate **Current 10-Year ASCVD Risk****

Lifetime ASCVD Risk: **69%** Optimal ASCVD Risk: **4.8%**

Project Risk Reduction by Therapy

Reset

View Advice Summary for this Patient

- **BP:** For Elevated BP, manage with nonpharmacological therapy.
- **LDL-C:** Moderate intensity statin is recommended if decided upon as part of a clinician-patient discussion.
- **Diabetes:** N/A
- **Smoking:** Advise patient to quit. Use combination of behavioral and pharmacotherapy. Avoid second hand smoke.

	High Intensity	Moderate Intensity	Low Intensity
LDL-C lowering†	≥50%	30%–49%	<30%
Statins	**Atorvastatin (40 mg‡) 80 mg** **Rosuvastatin 20 mg (*40 mg*	**Atorvastatin 10 mg** (20 mg) **Rosuvastatin** (5 mg) **10 mg** **Simvastatin 20–40 mg§**	Simvastatin 10 mg
	…	**Pravastatin 40 mg** (80 mg) **Lovastatin 40 mg** (80 mg) Fluvastatin XL 80 mg **Fluvastatin 40 mg BID** Pitavastatin 1–4 mg	**Pravastatin 10–20 mg** **Lovastatin 20 mg** Fluvastatin 20–40 mg

Statin Safety and Associated Adverse Events A Scientific Statement From the American Heart Association-Feb 2019 [7]

In clinical practice 10% stop statin due to usually muscle symptoms in USA->other countries the number is 2-4%->Denmark rate was 6% went to 11% after negative studies of statins in the news! [7]

Paper->Position statement from the American Heart Association->Brings together in a well thought out logical manner available Double blind randomized control data, Meta-analyses, and controlled observation studies->in doing so discuses the positives and negatives of each format.

Goes in depth in the evidence for the potential side effects of statins in patients with different disease states. It includes many unique populations.

Actual statin risk by the numbers

Myopathy-x<0.1 %

Rhabdomyolysis x~0.01%

Diabetes x~0.2% per yr of treatment; hem a1c increase in pts with diabetes is 0.1% mechanism is unknown

Serious hepatotoxicity x~0.001%

Myalgia difference in randomized control trials statins vs placebo->x<1%; patients needing to stop statin in randomized trials x<0.1%

Adverse Event Term	Definition
SAMS	Muscle symptoms reported during statin therapy but not necessarily caused by the statin
Myalgia	Muscle pain or aches
Myopathy	Unexplained muscle pain or weakness accompanied by CK concentration >10 times ULN
Rhabdomyolysis	Severe form of myopathy, with CK typically >40 times ULN, which can cause myoglobinuria and acute renal failure

No clear evidence that statins can lead to cancer, cataracts, cognitive dysfunction/Alzheimer's or Parkinson's disease, peripheral neuropathy, erectile dysfunction, or tendonitis

Be sure to look for drug interactions->gemfibrozil, diltiazem, cyclosporine, colchicine, protease inhibitors, etc!

"Drug-Drug Interactions, lovastatin and simvastatin are particularly vulnerable to drug interactions because of their extensive first-pass metabolism, mainly via CYP3A4" [7]

Hemorrhagic stroke-some trial indicate there could be some very small absolute risk increase in patients with previous stroke->however the protective effect from ischemic stroke and Myocardial infarction is greater….there is no risk for brain hemorrhage for statins in the primary prevention of strokes

No need to track AST/ALT-IDEAL trial pts with baseline ALT elevations, ALT went down when taking 80 of atorvastatin

Rosuvastatin can cause transient proteinuria and microscopic hematuria at 40mg->no evidence that they lead to long term worsening of proteinuria or renal function.

CKD-appear safe in all stages including ESRD->some need dose adjustment-Atorvastatin no adjustment needed

Drawbacks and thoughts

Cost-Atorvastatin is free at Meijer.

Drawbacks to statins-very few when looking at the actual data.

Clinic applications to consider->If a patient raises some concer->potentially hold statin->push vitamin d level to ~50-80 ng/ml (consider using d3 5k->more stable compound->each 1k d3 you add increases vitamin d level by 7 (be careful in patient with significant CKD). Once the level of vitamin d is 50-80 retry the statin

~90% of patient who were previously intolerant to ≥2 statins due to myalgia, myopathy, myositis, or myonecrosis->were able to tolerate statins with the elevated level of vitamin d. [22]

Case #3

A 37 year old female with a history of obesity, prediabetes, and heavy bleeding menstrual cycles presents to your outpatient clinic for her annual visit. As part of her lab work you ordered a complete blood cell count which is notable for low but normal hemoglobin (12 g/dl) value and low but normal mean corpuscular volume (82). However her iron studies noted a low ferritin (14 ng/ml) and an elevated total iron binding capacity (490 ng/ml).

How would you best replace her iron?

A-Ferrous sulfate 325mg 3 times a day

B-Ferrous sulfate 325mg 2 times a day

C-Ferrous sulfate 325 mg every day

D-Ferrous sulfate 325 mg every other day

E-No need to replace iron

Correct answer-D-Ferrous sulfate 325 mg every other day

Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomized controlled trials-Lancet 2017 [9]

Study design: 2 prospective, open label, randomized controlled trials

Methods: 40 Iron deficient females (ferritin x<25) and mostly non anemic age 18-40 were given radiolabeled ferrous sulfate. Group one given 60mg of iron once a day others were given the same amount every other day for 14 vs 28day respectively. Baseline hemoglobin ~13 g/dl and ferritin 13.8 in study one and 20 in study 2

Outcomes studied: Iron bioavailability and serum hepcidin concentrations. Secondary was hemoglobin concentration, serum ferritin, and fecal calprotectin.

"Cumulative fractional iron absorptions were 16·3% (9·3, 28·8) in the consecutive-day group versus 21·8% (13·7, 34·6) in the alternate-day group (p=0·0013), and cumulative total iron absorption was 131·0 mg (71·4, 240·5) versus 175·3 mg (110·3, 278·5; p=0·0010). During the first 14 days of supplementation in both groups, serum hepcidin was higher in the consecutive-day group than the alternate-day group (p=0·0031)" [9]

Second study crossover design 20 women->10 women placed in daily and 10 in bid (120mg at once vs 60bid iron)->in the end no difference noted in iron absorption but there was a noted elevation in hepcidin in bid dosing.

Alternate-day oral supplementation with 60 mg iron results in **34% higher iron absorption** than with consecutive-day supplementation. Iron absorption decreased from day 1 to day 2 and hepcidin increased. No affect on fecal calprotectin.

Iron side effects nausea/abdominal pain alternative day dosing 24%/12% vs consecutive 46%/21% .

Conclusion- "In iron-depleted women, providing iron supplements daily as divided doses increases serum hepcidin and reduces iron absorption. Providing iron supplements on alternate days and in single doses optimizes iron absorption and might be a preferable dosing regimen."[9] Though hemoglobin levels did not differ greatly during the short study the difference in iron absorption in study one was 44mg (greater in the every other day study) which would over time yield a significant difference in hemoglobin.

Funding: Swiss National Science Foundation

*Typical Ferrous sulfate has 65mg of elemental iron per tablet for comparison.

Drawbacks and thoughts

It is important to remember who is being studied here->mostly non anemic female patients with iron deficiency. I would hesitate to extrapolate this study to a populations outside of the study populations. (lowest hgb in the study was 11.7)

This was a small but well done trial->would like to see a trial done in a larger population. Also consider performing a similar trial in anemic patients.

Hepcidin is a the key modulator of iron regulatory hormone we need to keep in mind those factors that affect its level. [23] As levels of this hormone increase->iron absorption, recycling, and storage all decrease. Things that increase hepcidin-inflammation, malignancy, infection, too much iron. Also is diurnal in fluctuation and increases as the day goes on.

Things that decrease hepcidin->anemia and hypoxemia (certain genetic mutations as well.)

Work with your patients-in my own clinical practice I attempt to do every other day iron in my patients that fit this study->drawbacks every other day medication can be difficult to remember to take.

Similar findings were seen in a 2015 study [10]-54 non anemic women with low ferritin-suggest that q 48hr dosing of (lower dose 40-80mg of iron) iron appear ideal for iron absorption compared to bid and daily dosing.

If you are still interested consider reviewing a 2005 study [11] discusses benefits of low dose iron supplements in the elderly with anemia.

Case #4

A 62 Year old male with a history of hyperlipidemia, essential hypertension, previous smoking, and being overweight (Body mass index 28.3 kg/m2) presents to your office for his regularly scheduled office visit. At the visit you celebrate his 4 kilogram weight loss, well controlled lipids on atorvastatin 40mg (LDL 49), and well controlled blood pressure of 115/75 on chlorthalidone 12.5mg and amlodipine 5mg. He relates that he really wants to reduce his risk for future heart disease and wants to know your opinion on starting aspirin. What is the best next step in the management of this patient?

A-Start a 325mg aspirin.

B-Start 182 mg aspirin.

C-Start an 81 mg aspirin.

D-Continue his efforts at weight loss and healthy life styles.

Correct answer-D-Continue his efforts at weight loss and healthy life styles.

Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomized, double-blind, placebo-controlled trial-Lancet 2018 [12]

Design-randomized double-bind placebo controlled-7 countries, at moderate cardiovascular risk, excluded patients with diabetes or high risk of bleeding

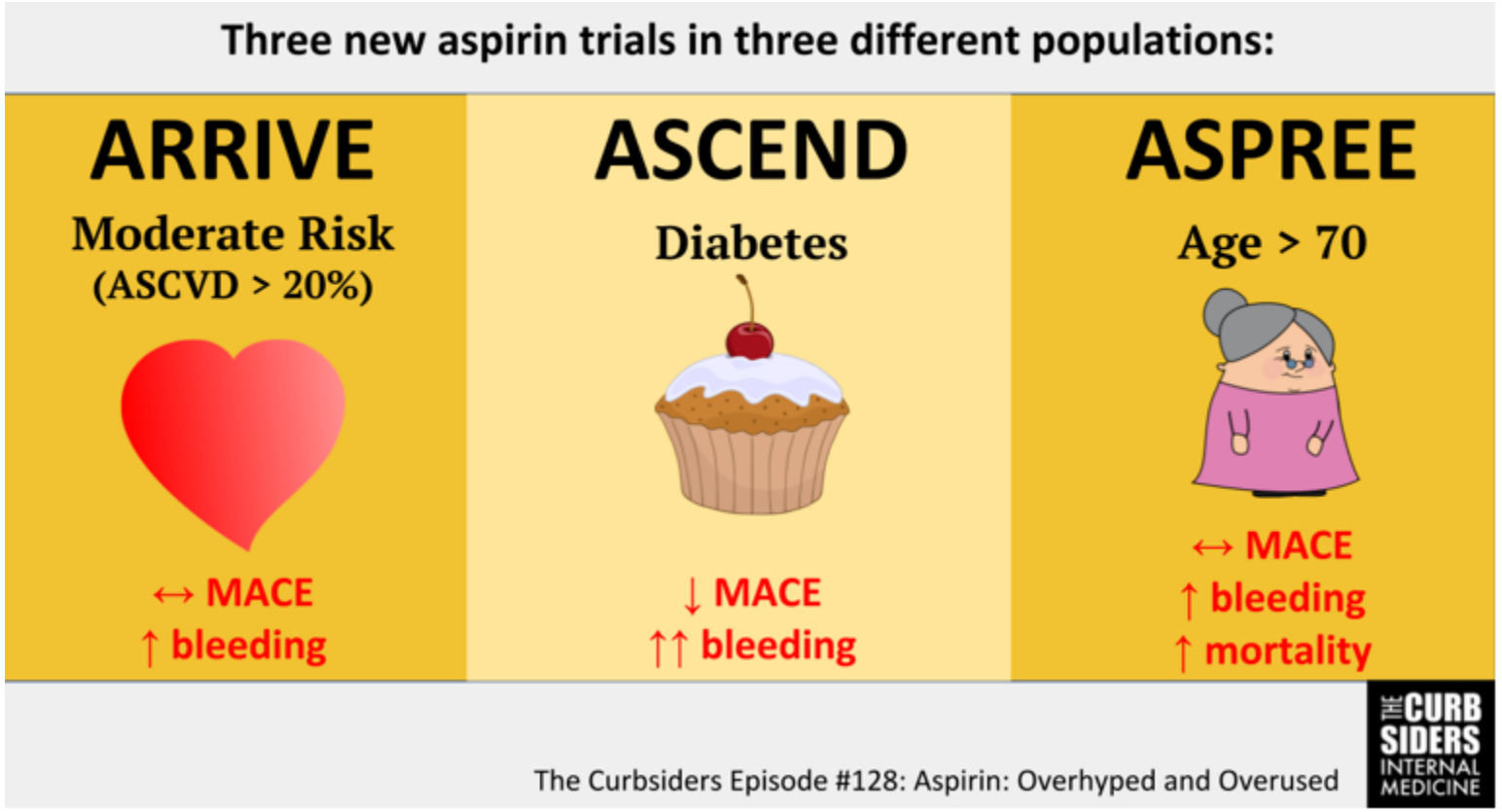
12546 patients, 501 sites, median follow up 60months, 100mg enteric coated aspirin, average age 63.9yo. Mostly male ~70%, Mostly white->only ~2.2% other, ~28% smokers, ~28BMI

“Primary efficacy endpoint was a composite outcome of time to first occurrence of cardiovascular death, myocardial infarction, unstable angina, stroke, or transient ischemic attack. Safety endpoints were hemorrhagic events and incidence of other adverse events” [12]

Results-aspirin showed no reduction in Major Adverse Cardiovascular Events (MACE) and there was a 2 fold higher risk of bleeding but both arms rate of bleeding was very low.

Rate of MACE was ~4.5% in study this is lower than historical studies

Sister trials summary-rec listen to the Curb Siders' episode [24]



ASCEND trial-RCT-15k patients, 7.5 years follow up; Adults with diabetes; results 12% reduction in Major Adverse Cardiovascular Event (MACE); 29% higher risk of bleeding.
Number Needed to Treat 673 patients per year to prevent one MACE
Number Needed to Harm 823 patients per year to cause one bleeding event
Absolute risk reduction 1.1%
ASPREE trial-RVT; 20k 70+ year olds; with 5 years of follow up. Aspirin did not decrease the rate of MACE. 38% higher risk of bleeding. Aspirin did not increase disease free survival. 14% higher mortality in the aspirin group (was actually related to cancer-similar rates of cancer not seen in other studies)
*additional reading see Annals 10/15/19

Drawbacks and thoughts

The event rate was much lower than expected thus the role of aspirin in a moderate risk population could not be properly addressed.

Please note these 3 studies are discussing primary prevention and not secondary prevention (history of TIA/MI/CVA/PVD)!

Aspirin is not the panacea it was once thought to be. We should continue push the base of primary prevention ->push proper lifestyle, smoking cessation, weight control, lipid control, and blood pressure control.

Consolidate quick points for your patients on Aspirin so they can uses this data with you to help make a decision. The final call needs to be individualized.

In my diabetic patients I talk to them about the number needed to harm and the number needed to treat and we use this for shared decision making.

Works cited

https://www.nejm.org/doi/full/10.1056/NEJMoa1504720 #1 empagliflozin-heart-EMPA-REG

https://www.nejm.org/doi/full/10.1056/NEJMoa1515920 #2 empagliflozin-renal-EMPA-REG

https://www.nejm.org/doi/full/10.1056/NEJMoa1911303 #3 Dapagliflozin-heart DAPA-HF

https://www.nejm.org/doi/full/10.1056/NEJMoa1812389 #4 Dapagliflozin-CAD-DECLARE–TIMI 58

https://www.nejm.org/doi/full/10.1056/NEJMoa1811744 #5 Canagliflozin-Renal-CREDENCE

https://www.nejm.org/doi/full/10.1056/NEJMoa1611925 #6 Canagliflozin-CAD-Canvas

https://www.ahajournals.org/doi/pdf/10.1161/ATV.0000000000000073 #7 Statin Safety

http://www.onlinejacc.org/content/73/24/e285?_ga=2.165003455.1406627324.1570035798-519974113.1554302423 #8 AHA/ACC/NLA lipid guidelines.

www.thelancet.com/haematology Vol 4 November 2017 # 9 Iron 2017

https://doi.org/10.1182/blood-2015-05-642223 #10 iron 2015

https://doi.org/10.1016/j.amjmed.2005.01.065 #11 iron 2005

https://www.thelancet.com/action/showPdf?pii=S0140-6736%2818%2931924-X #12 ARRIVE

https://www.nejm.org/doi/full/10.1056/NEJMoa1804988 #13 ASSEND

Works cited

https://www.nejm.org/doi/full/10.1056/NEJMoa1803955 #14 ASPREE

https://www.nejm.org/doi/full/10.1056/NEJMe1812000 #15 NEJM commentary on trial

https://doi.org/10.1016/S0140-6736(09)60318-4 #16 Lancet BMI Mortality

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4104704/pdf/nihms603921.pdf #17Waist circumference and Mortality

https://www.goodrx.com/canagliflozin #18

https://annals.org/aim/article-abstract/2739786/sodium-glucose-cotransporter-2-inhibitors-risk-severe-urinary-tract-infections #19

https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2719133 #20

http://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/ #21

http://www.najms.org/article.asp?issn=1947-2714;year=2015;volume=7;issue=3;spage=86;epage=93;aulast=Khayznikov #22

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1240030/ #23

https://thecurbsiders.com/podcast/128-aspirin-overhyped-overused #24

Special thanks to my Team: Amber, Jane, George, and Chris!