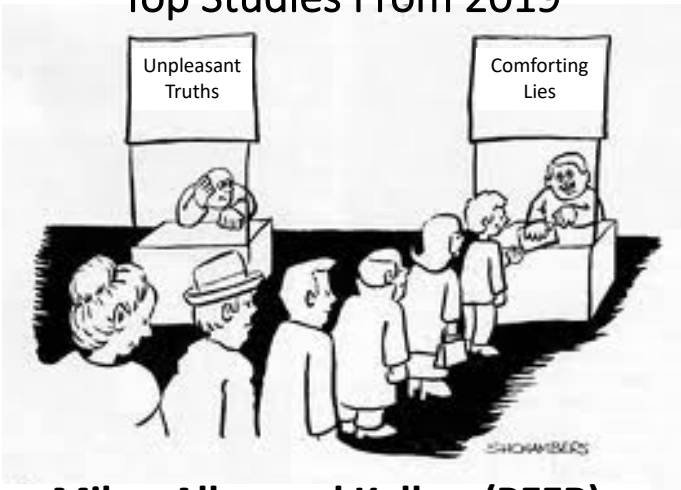
What's New, What's True, What's Poo: Top Studies From 2019



Mikes Allan and Kolber (PEER)
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MA

Faculty/Presenter Disclosures

- **Faculty: Mike Allan**
- **Salary: College of Family Physicians of Canada, University of Alberta, Locum**
- **Relationships with financial sponsors:**
  - **Grants/Research Support:** Alberta College of Family Physicians; Toward Optimized Practice, CIHR, PRIHS, etc
  - **Speakers Bureau/Honoraria:** ACFP, varying universities & College of family physicians, conferences
  - **Consulting Fees:** N/A
  - **Patents**: N/A
  - **Other:** A couple of Randomized Controlled Trials

NOTHING from Industry

MK

Presenters Disclosure

- **Faculty/Presenter: Mike K**
- **Relationships with commercial interests:**
  - **Grants/Research Support:** NA
  - **Speakers Bureau/Honoraria:** expenses (+/- honorarium) for BCCFPs, SRPC, BS Med, ACFP
  - **Consulting Fees:** Expert Drug Committee
  - **Employed:** University of Alberta, ACFP
  - **Non-profit grant sources:** ACFP, CIHR, PRIHS
  - **Kolber**: Electronic Medical Procedure Reporting System

PEER PATIENTS EXPERIENCE EVIDENCE RESEARCH

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Eggs: Bad for you, Good for you, and Keto Stable

- Observational/cohort 29,615 participants x 17.5 years. 45% male.
  - Looking egg consumption and cholesterol intake on CVD and mortality
- Results: Lots of statistical tests (>100)
  - Average person has 1 to 2.5 eggs/week. Each additional 3.5 eggs/wk =
    - Increase CVD HR 1.06 (AR 1.1%)
    - Mortality HR 1.08 (AR 1.9%)
    - Nothing if adjust for cholesterol intake.
  - Cholesterol consumption seems to impact outcomes but maybe not if account for meat consumption. And, does not agree with other research.

Bottom-Line: Eggs do not seem risky. Even if real, you need a lot (go from 2.5 to 6 eggs/wk every week for 17 yrs), gives 1-2% increased risk.

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JAMA. 2019;321(11):1081-1095.

Wait, weight,… what can we do about diabetes.

- RCT of 298 primary care patients: DM <6yrs, BMI 27-45, not on insulin.
  - Diet replacement (Counterweight-Plus) ~840 kcal/day for 3 months (+ 2 optional) then re-introduce food vs "control" Stopped all DM and BP meds (add if need)
  - In 2 yr follow-up if wt gain ≥2 kg, offered 2-4 week rescue
  - Baseline patient = 54 yo 59% male, BMI 35, A1c 7.6%
- Results: Control vs Intervention:
  - 1 yr: lost ≥15kg=0 vs 24% (NNT 5), DM remission 4% vs 46% (NNT 3),
    - Remission by wt lost <5kg (7%), 5-10kg (34%), 10-15 (57%), & >15kg (86%)
  - 2yr: lost ≥15kg=2% vs 11% (NNT 11), DM remission 3% vs 36% (NNT 4),
  - QoL (/100): ↓ 3 (control) vs ↑7 .
  - **Bottom-Line**: **Surprise, weight loss can truly treat DM.**

Lancet Diabetes Endocrinol. 2019;7(5):344-55. Lancet 2018; 391: 541–51

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Diabetes: Studies of Real Outcomes

Drug	Population (risk)	Time (yrs)	Surrogate	CVD	Death	Other
Dulaglutide	9901 (Lower)	5.4	A1c 0.6%, BP 1.7/0.5	12% vs 13.4%	NS (~1% less)	Microalbumin, + 3% quit A/E

Dulaglutide: Small effect x5 years but mostly Primary Prevention
Oral Semaglutide: Larger effect in x1.5 years but mostly Secondary Prevention

Lancet 2019 http://dx.doi.org/10.1016/ S0140-6736(19)31149-3
NEJM 2019 DOI: 10.1056/NEJMoa1901118 NEJM 2019;380:347-57. NEJM 2019;380:2295-306. NEJM 2019 DOI: 10.1056/NEJMoa1911303

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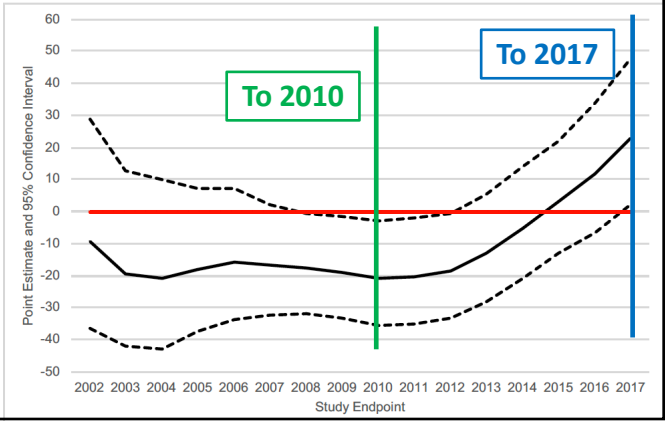
Is Cannabis the Solution to Opioid Overdose

- Ecological Study (whole state-wide data pooled)
- Bachhuber et al. (1999–2010): states introducing medical cannabis laws saw 25% reduction in opioid overdose death.
- Expanding to 2017,
  - Now reverse
- Looking at different laws (like recreational, low THC medical cannabis, etc).
  - Nothing certain or positive



Proc Natl Acad Sci U S A. 2019;116(26):12624-6.

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How long does a hip replacement last?

- Meta-analyses: 150 case series (44 usable) & Finland/Australia registries
  - Case Series = 13,212 hip replacements & registry = 215,676
  - Age ~58-74, 55-59% female, 62%-89% due to OA.
- Outcomes:

	≥15 years	≥20 years	≥25 years
Published Case Series	86%	79%	78%
Country Registries	89%	70%	58%

- **Bottom Line:** Almost 90% of hip replacements last ≥15 years and 58-78% last ≥25 years.

Lancet 2019; 393: 647–54.

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Do PPIs Really Cause all those AEs?

- Multi-country, RCT of 27,000 CAD patients: ASA, Riva, Riva + ASA[3]
  - Patients not on PPI (64%)→ randomized PPI or placebo.
    - Mean age 67 years, 80% ♂, Outcomes at 3 years

Outcome	PPI (% or #)	Placebo(% or #)	Difference
Pneumonia	3.6%	3.6%	No difference
Enteric infections	1.4%	1.0%	1 in 300 over 3 years
C Difficile	9	4	No difference
Bone Fractures	2.3%	2.4%	No difference
CKD	2.1%	1.9%	No difference

PPI AEs seen in Cohort Studies are confounded by "sick user" effect

[1]Gastro 2019;157:682, [2]Gastro 2019;157:403. [3]COMPASS NEJM 2017. DOI: 10.1056, COGENT NEJM 2010 10.1056

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The facts, while interesting, are irrelevant.

- Vitamin D: : ~26,000 USA patients, 49% male, mean 67, 2000 IU/day
  - All-cause mortality: HR=0.99 (0.87–1.12). No effect on cancer or CVD.
  - Preventing Diabetes: ~2,400 prediabetics, mean age 60, 4000 IU x 2.5 yrs
    - Did not prevent diabetes HR=0.88 (95% CI, 0.75–1.04)
- Omega-3: ~26,000 USA patients, 49% male, mean 67, 1000mg/day
  - All-cause Mortality: HR=1.02 (0.90–1.15). No effect on cancer or CVD
  - Icosapent: may be beneficial (Reduce IT trial)
- Family Doctors: Add 10 Primary Care doc/100,000: live 52 days longer
  - 10 more specialists : live 19 days longer.
  - Recommendation: "Physician payment reform is a key to making all of this happen." (Sondra Zabar -Editorial)

NEJM 2019;380:33. NEJM. 2019;381:520. NEJM 2019;380:23
JAMA Intern Med. doi:10.1001/jamainternmed.2018.7624. NEJM 2019;380(1):11-22

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THE MINISTER OF SILLY RESEARCH

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Diabetes: Studies of Real Outcomes

Drug	Population (risk)	Time (yrs)	Surrogate	CVD	Death	Other
Dapigliflozin	17160 (high)	4.2	A1c 0.4%, BP 2.7/0.7	NS (~0.5%) HF 2.5% v 3.3%	NS (~0.5%)	DKA 0.3% v 0.1% Gen Inf 0.9 v 0.1%

4744 HF pts [2/3 Class II, 1/3 Class III], mostly max therapy, 42% diabetic. At 1.5 yrs,
- HF hospitalization or CVD death: 16% v 21%. (NNT ~21)
- Death from any Cause: 12% v 14% (NNT 44)

Dapigliflozin: likely a better CHF drug than a DM drug.

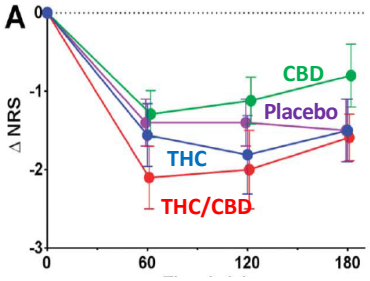
Canigliflozin: A drug that is helpful in diabetics with renal impairment.

NEJM 2019 DOI: 10.1056/NEJMoa1901118 NEJM 2019;380:347-57. NEJM 2019;380:2295-306. NEJM 2019 DOI: 10.1056/NEJMoa1911303

MA

Newest THC/CBD RCT

- 20 fibromyalgia – single doses 2 wks apart, x 4 products (cross-over)
  1. 22% THC and <1%CBD: Received 100 mg with 22.4-mg THC + ≤1-mg CBD.
  2. 6.3% THC and 8% CBD: Received 200 mg with 13.4-mg THC + 17.8-mg CBD.
  3. 9% CBD and <1% THC. Received 200 mg with <1-mg THC + 18.4-mg CBD
  4. Placebo
- Results:
  - Who got a ≥30% response,…
  - 90% THC/CBD, 65% THC, 55% placebo, 40% CBD
  - Drug High correlated with pain response
  - THC had more "psychedelic" effects,
  - Paranoid/anxiety and some AE (e.g. nausea) less with CBD



Bottom-Line: The effects are often not much over placebo, associated with being high & may depend on THC. CBD does have some less negative effects.

Pain. 2019 Apr;160(4):860-869.

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Injectable Corticosteroids in OA: AEs 2019

- Single centre 1 year case series: 459 US guided CS injections (307 Hip, 152 Knee) for OA → 241 had FU: xrays or MR[1]
- 36 SAEs in 36 patients: 30 in hip, 6 in knee
  - Rapidly progressing OA (n=26), 1 osteonecrosis (hip), 3 subchondral #s
- Cochrane 2015:[2] 27 RCTs (1767 pts): 5 RCTs (331 pts) reported SAEs
  - Serious AE ~3/1000 (meniscal lesion, cyst aspiration)
- JAMA 2017:[3] RCT 140 patients: CS vs placebo q 3/12 x 2 years
  - AEs – injection site pain (4 vs 2) No Osteonecrosis, #s, 0.11mm ↓ cartilage
- Infection: 1/14,000 - 50,000[4]
- **Bottom Line: large prospective cohort studies needed**

Radiology 2019; 00:1–8, *Cochrane* 2015, CD005328.
JAMA 2017;317(19):1967, TFP 2015

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What's Topical in Actinic Keratosis Treatment?

- 624 Dutch (mean age 73, 89% male). Multiple (mean 15) AK on face/vertex.
  - Only 8% level III (thicker keratosis) lesions.
  - 4 treatments: 5% Fluorouracil (5FU) cream, 5% imiquimod cream, methyl aminolevulinate photodynamic therapy (MAL-PDT), 0.015% ingenol mebutate

	Fluorouracil	Imiquimod	MAL-PDT	Ingenol
≥75% AKs Resolved	75%	54%	38%	29%
NNT for 5FU	-	5	4	3
Adverse Events	Erythema, erosions, vesicles, scaling		Pain/burning (NNH~2-3)	Same as 1st two

- **Bottom-Line**: Fluorouracil is the best field treatment for AK.
  - TFP: smaller RCTs, 5% FU had best numbers

N Engl J Med 2019;380:935-46.

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How effective is PEG for pediatric and adult chronic constipation?

At least 10 SRs of PEG vs other laxatives or placebo (5-25 RCT, 594-2310 participants, 2-52 wks).

- For adults: vs placebo - PEG relieves constipation NNT 2-3, ↑ stool frequency 2-3 more/wk;
  - vs lactulose - ↑ stool freq 1-2/wk
- For children: vs placebo - PEG ↑ stool freq 1.5-3/wk;
  - vs lactulose: ↑ stool freq 0.7-1.5/wk, ↑ likelihood of disimpact'n (NNT 5)
  - vs MOM: ↑ stool freq 0.7/wk
- PEG also resolved constipation, reduce abd pain, reduced need for added interventions

Peds treatment up to 6 months: (post disimpaction with 17g/kg/d PEG):

- "successful treatment" 67% vs 33% (NNT= 3)

- Context: ~$1.00 per day (at 17g); PEG 1st line in current guidelines

Bottom line: In adults and pediatric pts with chronic constipation, PEG is as or more effective than other agents. Compared with placebo, it relieves constipation in one in every 2-3 patients and adds 1-3 BM/wk. Pediatric maintenance study up to 6 months.

TFP #45, March 2015. Updated October 2019.
JPGN 2018;67: 732

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What's New is Old Again: Elderly patients & Statins

- 2015 - Tools for Practice: "No evidence to start statins in primary prevention patients >75."
- 2015 – Simplified Lipid Guideline: "Primary prevention patients > 75 yrs: We discourage routinely testing lipid levels, estimating CVD risk, and prescribing statins (moderate-level evidence)." (*few rare exceptions*)

- Meta-analysis of 186,854 pts (8% age ≥75) from 28 RCTs, followed ~5yrs
  - Divided up by 5 year age increments & with or without past CVD.

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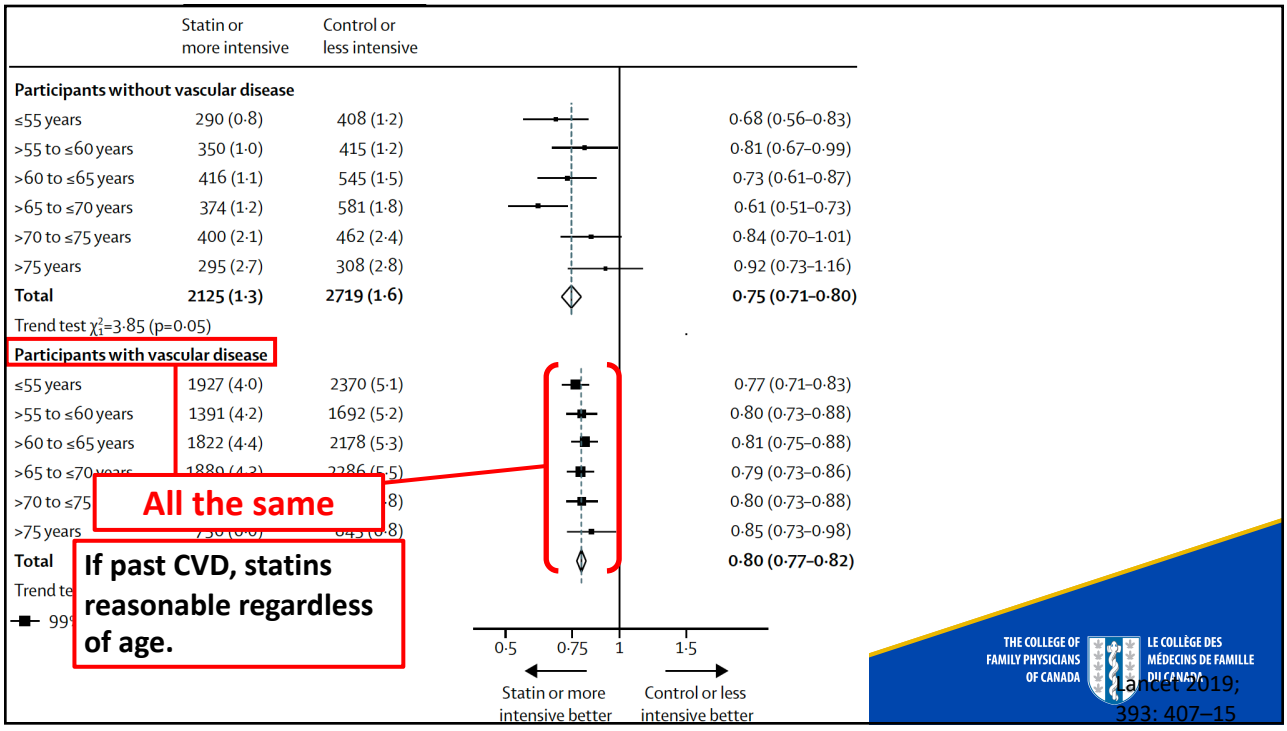
TFP #129, Jan 5, 2015. Can Fam Physician
2015; 61: 857-867. Lancet 2019; 393: 407–15



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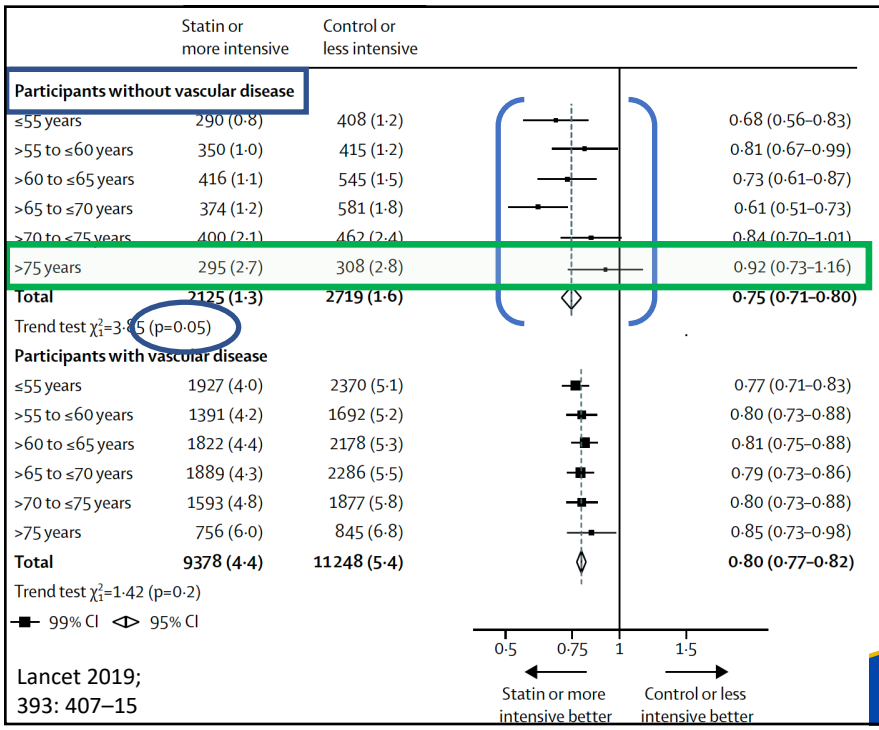
Lancet 2019; 393: 407–15



Lancet 2019; 393: 407–15

If no past CVD, statins generally reasonable. But, once elderly (>75) they may not work.

If past CVD, statins reasonable regardless of age.

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Vitamin D Dose: Bigger is always better

- RCT (303 Calgarians): 400IU or 4000IU or 10,000 IU/day oral x 3 years
  - 54% male, mean age 62, mean Vit D level 79 nmol/L, mean BMD T-score ~0

RESULTS	400 IU/day	4,000 IU/day	10,000 IU/day
New Vitamin D Level (nmol/L)	77	132	144 (200 at 18 mon)
Loss of Bone Mass Radius	-1.2 %	-2.4%	-3.5%
Loss of Bone Mass Tibia	-0.4%	-1.0%	-1.7%

  - Others similar
  - QoL, falls, fractures, stability testing, etc – No diff (study small + pt low risk)
- *4 RCTs (dose 60K/month - 500K/yr) - worse falls in 3 / worse fractures in 2.

Bottom-Line: Another study showing harms (albeit surrogate) of high dose vitamin D. Until we prove clear benefit, we should not give high doses.

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JAMA. 2019;322(8):736-745

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5 Steps to get the most out of your Vitamins

1) Take the vitamins to a friends' house ~2 km from your house. If you want to take your vitamin, walk to their house, pop the pill, walk home.
2) If you believe in higher dose vitamins, choose a home 5 kms from your house, run there at a comfortable pace, take two pills, and run home.
   - Note: You can just take one and get the same effect
   - Note 2: You can also take none
3) Put vitamins on your dinner plate with fresh and well seasoned/flavored vegetables, fruit, grains and protein. If compelled to try a vitamin, pick it up, lick it. How does it compare?
4) When you ingest more than the small amount of vitamins required for health, you pee out the excess. To avoid possible strain on your kidneys, place your vitamins directly into the toilet and flush.
5) Finally, if you really want your vitamins to work, package them up and send them to countries where vitamin deficiency are a serious health concern. The effect generosity may be the only supplement you need.

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