TOP ARTICLES IN FAMILY MEDICINE 2019

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NEVADA ACADEMY OF FAMILY PHYSICIANS

Objectives

- At the end of this presentations, participants will:
  - Be familiar with some of the more important and interesting information from the prior year.
  - Understand the key clinical implications of these findings and recommendations.
  - Improve their ability to critique the medical literature.
  - Enjoy themselves. (we hope)

ARTICLES

All articles available on the Nevada Academy of Family Medicine website

www.nvafp.com

Original Investigation | Substance Use and Addiction

Acute Effects of Smoked and Vaporized Cannabis in Healthy Adults Who Infrequently Use Cannabis
A Crossover Trial

JAMA Network Open

Study

Objective: To evaluate the acute dose effects of smoked and vaporized cannabis using controlled administration methods.

Methods: Double blind crossover study with 17 healthy volunteers who smoked or vaped marijuana in 6 separate sessions. . None were regular marijuana uses and none used in the past 30 days. THC doses of 0, 10 and 25mg were smoked and vaped by each subject. **Results**: Mild effects were noted in both the smoked and vaped groups at the 10 mg dose. The 25 mg dose produced significant drug effects, increased incidence of adverse effects, and pronounced impairment of cognitive and psychomotor ability. Vaporized cannabis resulted in higher peak concentrations of THC qualitatively and stronger drug effects for most outcomes. Blood THC concentrations and heart rate peaked within 30 minutes after cannabis administration and returned to baseline within 3 to 4 hours. Several subjective drug effects and observed cognitive and psychomotor impairments persisted for up to 6 hours on average.

Discussion: This is a very well done study that demonstrated that 1) higher THC amounts leads to increased effects – with more negative effects in the 25mg dose, and 2) vaping leads to modestly quicker onset and more pronounced effects. Subjective effects lasted longer than elevated THC blood levels.

Bottom line: Vaping gives more bang for the buck than smoking and effects outlast blood levels.

Marijuana Use by Breastfeeding Mothers and Cannabinoid Concentrations in Breast Milk

PEDIATRICS
The Official Journal of the American Academy of Pediatrics
American Academy of Pediatrics

Kerri A. Bertrand, MPH,[a] Nathan J. Hanan, PharmD,[a,b] Gordon Honerkamp-Smith, MS,[a] Brookie M. Best, PharmD, MAS,[a,b] Christina D. Chambers, PhD, MPH[a,b,c]

Study

- **Objective**: To determine the concentration of THC in breastmilk after using marijuana.
- **Methods**: Between 2014 and 2017, 50 breastfeeding women who reported marijuana use provided 54 breast milk samples to a research repository, Mommy's Milk. Concentrations of Δ9-THC, 11-hydroxy-Δ-9-tetrahydrocannabinol, cannabidiol, and cannabinol were measured by using liquid chromatography mass spectrometry electrospray ionization.

Results:Δ9-THC was detectable in 34 (63%) of the 54 samples up to ~6 days after last reported use; the median concentration of Δ9-THC was 9.47 ng/mL **(range: 1.01–323.00)**.

The number of hours since last use was a significant predictor of log Δ9-THC concentrations. Adjusted for time since last use, the number of daily uses and time from sample collection to analysis were also significant predictors of log Δ9-THC concentrations

Discussion:

Marijuana is the most frequently used recreational drug by pregnant women and breastfeeding mothers. But little is known about how much of the active metabolites gets into breast milk. This study demonstrates that a significant concentration can be found in mothers milk and it sticks around.

THC levels in breast milk were 10 – 100 times lower than typically found in serum after a few puffs.

More research into the effects this will have on babies' brains is needed.

Bottom line: Big surprise – breast feeding moms should avoid marijuana. We don't know what is a "safe amount".

Marine n−3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer

VITAL Research Group January 3, 2019

The NEW ENGLAND JOURNAL of MEDICINE

Objective: clarifying the relation between supplemental n−3 fatty acids and risks of cardiovascular disease and cancer and obtaining more-definitive data on the benefit–risk balance of these supplements

Methods: randomized, placebo-controlled trial, with a two-by-two factorial design, of vitamin D3 (at a dose of 2000 IU per day) and marine n−3 fatty acids (at a dose of 1 g per day) in the primary prevention of cardiovascular disease and cancer among men 50 years of age or older and women 55 years of age or older in the United States. Primary end points were major cardiovascular events (a composite of myocardial infarction, stroke, or death from cardiovascular causes) and invasive cancer of any type. Secondary end points included individual components of the composite cardiovascular end point, the composite end point plus coronary revascularization (expanded composite of cardiovascular events), site-specific cancers, and death from cancer. Safety was also assessed

Results: 25,871 participants, median follow-up of 5.3 years, a major cardiovascular event occurred in 386 participants in the n−3 group and in 419 in the placebo group (hazard ratio, 0.92; 95% confidence interval [CI], 0.80 to 1.06; P = 0.24). Invasive cancer was diagnosed in 820 participants in the n−3 group and in 797 in the placebo group (hazard ratio, 1.03; 95% CI, 0.93 to 1.13; P = 0.56). key secondary end points, the hazard ratios were as follows: for the expanded composite end point of cardiovascular events, 0.93 (95% CI, 0.82 to 1.04); for total myocardial infarction, 0.72 (95% CI, 0.59 to 0.90); for total stroke, 1.04 (95% CI, 0.83 to 1.31); for death from cardiovascular causes, 0.96 (95% CI, 0.76 to 1.21); and for death from cancer (341 deaths from cancer), 0.97 (95% CI, 0.79 to 1.20). In the analysis of death from any cause (978 deaths overall), the hazard ratio was 1.02 (95% CI, 0.90 to 1.15). No excess risks of bleeding or other serious adverse events were observed.

Discussion: Supplementation with n−3 fatty acids did not result in a lower incidence of major cardiovascular events or cancer than placebo.

Bottom line: Sell your stock in omega-3 supplements.

Effects of n−3 Fatty Acid Supplements in Diabetes Mellitus

The ASCEND Study Collaborative Group*

The NEW ENGLAND JOURNAL of MEDICINE
OCTOBER 18, 2018

Objective: to assess the efficacy and safety of daily supplementation with n−3 fatty acids, as compared with placebo, in patients with diabetes without evidence of cardiovascular disease at trial entry

Methods: randomly assigned 15,480 patients with diabetes but without evidence of atherosclerotic cardiovascular disease to receive 1-g capsules containing either n−3 fatty acids (fatty acid group) or matching placebo (olive oil) daily. The primary outcome was a first serious vascular event (i.e., nonfatal myocardial infarction or stroke, transient ischemic attack, or vascular death, excluding confirmed intracranial hemorrhage). The secondary outcome was a first serious vascular event or any arterial revascularization.

Results: mean follow-up of 7.4 years (adherence rate, 76%), a serious vascular event occurred in 689 patients (8.9%) in the fatty acid group and in 712 (9.2%) in the placebo group (rate ratio, 0.97; 95% confidence interval [CI], 0.87 to 1.08; P = 0.55). The composite outcome of a serious vascular event or revascularization occurred in 882 patients (11.4%) and 887 patients (11.5%), respectively (rate ratio, 1.00; 95% CI, 0.91 to 1.09). Death from any cause occurred in 752 patients (9.7%) in the fatty acid group and in 788 (10.2%) in the placebo group (rate ratio, 0.95; 95% CI, 0.86 to 1.05). There were no significant between-group differences in the rates of nonfatal serious adverse events.

Discussion: no significant difference in the risk of serious vascular events between those who were assigned to receive n−3 fatty acid supplementation and those who were assigned to receive placebo.

Bottom line: Primary prevention in DM with omega-3…no help. There are other options with much better "bang for the buck"!

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

REDUCE-IT Investigators*

The NEW ENGLAND JOURNAL of MEDICINE
JANUARY 3, 2019

Objective: We hypothesized that the risk of cardiovascular events would be lower with icosapent ethyl therapy than with placebo among patients in whom elevated triglyceride levels served as a marker of residual risk despite statin therapy.

Methods: multicenter, randomized, double-blind, placebo-controlled trial involving patients with established cardiovascular disease or with diabetes and other risk factors, who had been receiving statin therapy and who had a fasting triglyceride level of 135 to 499 mg per deciliter (1.52 to 5.63 mmol per liter) and a low-density lipoprotein cholesterol level of 41 to 100 mg per deciliter (1.06 to 2.59 mmol per liter). The patients were randomly assigned to receive 2 g of icosapent ethyl twice daily (total daily dose, 4 g) or placebo. The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina. The key secondary end point was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

Results: 8179 patients were enrolled (70.7% for secondary prevention of cardiovascular events) and were followed for a median of 4.9 years. A primary end-point event occurred in 17.2% of the patients in the icosapent ethyl group, as compared with 22.0% of the patients in the placebo group (hazard ratio, 0.75; 95% confidence interval [CI], 0.68 to 0.83; P<0.001); the corresponding rates of the key secondary end point were 11.2% and 14.8% (hazard ratio, 0.74; 95% CI, 0.65 to 0.83; P<0.001). Afib and serious bleeding were more common in icosapent group.

Discussion: the risk of ischemic events, including cardiovascular death, was significantly lower among those who received 2 g of icosapent ethyl twice daily than among those who received placebo

Bottom line: Good study to shows that lowering TG in these types of patients can actually improve outcomes. Treating residual risk after LDL-C is at goal may be beneficial and this may be the way to do it.

Original Investigation | Cardiology

Association of Cardiorespiratory Fitness With Long-term Mortality Among Adults Undergoing Exercise Treadmill Testing

JAMA Network

Kyle Mandsager, MD; Serge Harb, MD; Paul Cremer, MD; Dermot Phelan, MD, PhD; Steven E. Nissen, MD; Wael Jaber, MD

Study
Objective: To assess the association of all-cause mortality and cardiorespiratory fitness in patients undergoing exercise treadmill testing.
Methods: Retrospective cohort study of 122,007 patients followed for a mean of 8.4 years (1.1 million person-years) who were referred for EST. CRF was stratified into performance groups: low (<25th percentile), below average (25th-49th percentile), above average (50th-74th percentile), high (75th-97.6th percentile), and elite (97.7th percentile). Main outcome was all cause mortality.
Results: Mean age was 53.4 years, 59.2% male, death occurred in 13 637 patients
Risk adjusted all-cause mortality was inversely proportional to cardiorespiratory fitness and was lowest in elite performers.

Discussion:

No drop-off at highest level of fitness.

Biggest jump is from low to below average.

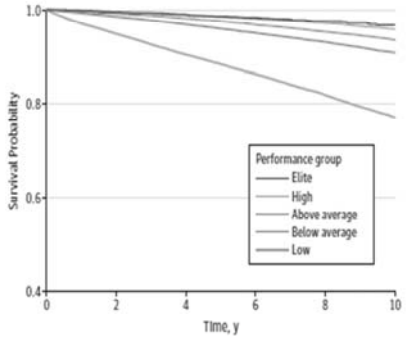
Retrospective – so shouldn't assume *causation*, but hard to come up with another explanation.

Bottom line:

Improving fitness for very unfit patients is at least as important as quitting smoking.

Imagine doing both!

Figure 1. Patient Survival by Performance Group



Variable	HR (95% CI)	P Value
Comorbidity		
Smoking	1.41 (1.36-1.46)	<.001
CAD	1.29 (1.24-1.35)	<.001
Diabetes	1.40 (1.34-1.46)	<.001
Hypertension	1.21 (1.16-1.25)	<.001
ESRD	2.78 (2.53-3.05)	<.001
Group comparison		
Low vs Elite	5.04 (4.10-6.20)	<.001
Low vs High	3.90 (3.67-4.14)	<.001
Low vs Above Average	2.75 (2.61-2.89)	<.001
Low vs Below Average	1.95 (1.86-2.04)	<.001
Below Average vs Elite	2.59 (2.10-3.19)	<.001
Below Average vs High	2.00 (1.88-2.14)	<.001
Below Average vs Above Average	1.41 (1.34-1.49)	<.001
Above Average vs Elite	1.84 (1.49-2.26)	<.001
Above Average vs High	1.42 (1.33-1.52)	<.001
High vs Elite	1.29 (1.05-1.60)	.02

Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: A Case for Fitness as a Clinical Vital Sign

A Scientific Statement From the American Heart Association

Circulation

Circulation. 2016;134:00–00.

- 37 page practice recommendation
- Cites 3 decades of evidence that "firmly established" relationship between CRF and mortality.
- Authors of the 2013 ASCVD risk calculator excluded CRF because evidence it would enhance risk classification was "inconclusive".
- The AHA/ACC now recognizes this as a mistake. (duh!)
- CRF is as strong a predictor of mortality as diabetes mellitus, smoking, hypertension and dyslipidemia
- < 5 METS associated with high mortality and >8 METS with a significant reduction in mortality (30-50%!)
- Every MET increase in fitness (especially at the low end), is associated with a 10 – 20% decrease in mortality!!!
- CRF can be improved (even just walking 3 times a week)

Discussion:

The challenge is putting this into practice. How do we evaluate fitness?

Recommended methods include: Maximal testing with CPS, Maximal exercise testing w/o CPX, Submaximal exercise testing, ….. Estimations.

Bottom line:

We need to start incorporating CRF (or, more likely, LACK of CRF) into risk calculators.

Estimations aren't ideal, but good enough

Low, medium and high levels of CRF correspond to HR of approximately 1.5, 1.0 and 0.75 for mortality

Relationship between Clinic and Ambulatory Blood-Pressure Measurements and Mortality

J.R. Banegas, L.M. Ruilope, A. de la Sierra, E. Vinyoles, M. Gorostidi, J.J. de la Cruz, G. Ruiz-Hurtado, J. Segura, F. Rodríguez-Artalejo, and B. Williams

The NEW ENGLAND JOURNAL of MEDICINE

Hypertensive "phenotypes"

- White-coat hypertension refers to elevated clinic and normal 24-hour blood pressure in untreated patients in the whole cohort.
- White-coat uncontrolled hypertension refers to elevated clinic and normal 24-hour blood pressure in treated patients in the whole cohort.
- Masked hypertension refers to normal clinic and elevated 24-hour blood pressure in untreated patients in the whole cohort.
- Masked uncontrolled hypertension refers to normal clinic and elevated 24-hour blood pressure in treated patients in the whole cohort.
- Sustained hypertension refers to elevated clinic and 24-hour blood pressure in untreated patients in the whole cohort.
- Sustained uncontrolled hypertension refers to elevated clinic and 24-hour blood pressure in treated patients in the whole cohort.

Relationship between Clinic and Ambulatory Blood-Pressure Measurements and Mortality

J.R. Banegas, L.M. Ruilope, A. de la Sierra, E. Vinyoles, M. Gorostidi, J.J. de la Cruz, G. Ruiz-Hurtado, J. Segura, F. Rodríguez-Artalejo, and B. Williams

The NEW ENGLAND JOURNAL of MEDICINE
APRIL 19, 2018

Objective: examined the associations of blood pressure measured in the clinic (clinic blood pressure) and 24-hour ambulatory blood pressure with all-cause and cardiovascular mortality in a large cohort of patients in primary care
Methods: registry-based, multicenter, national cohort that included 63,910 adults recruited from 2004 through 2014 in Spain. Clinic and 24-hour ambulatory blood-pressure data were examined in the following categories: sustained hypertension (elevated clinic and elevated 24-hour ambulatory blood pressure), "white-coat" hypertension (elevated clinic and normal 24-hour ambulatory blood pressure), masked hypertension (normal clinic and elevated 24-hour ambulatory blood pressure), and normotension (normal clinic and normal 24-hour ambulatory blood pressure).
Results: 24-hour systolic pressure was more strongly associated with all-cause mortality (hazard ratio, 1.58 per 1-SD increase in pressure; 95% confidence interval [CI], 1.56 to 1.60, after adjustment for clinic blood pressure) than the clinic systolic pressure (hazard ratio, 1.02; 95% CI, 1.00 to 1.04, after adjustment for 24-hour blood pressure). Masked hypertension was more strongly associated with all-cause mortality (hazard ratio, 2.83; 95% CI, 2.12 to 3.79) than sustained hypertension (hazard ratio, 1.80; 95% CI, 1.41 to 2.31) or white-coat hypertension (hazard ratio, 1.79; 95% CI, 1.38 to 2.32).
Discussion: Ambulatory blood-pressure measurements were a stronger predictor of all-cause and cardiovascular mortality than clinic blood-pressure measurements. White-coat hypertension was not benign, and masked hypertension was associated with a greater risk of death than sustained hypertension

Bottom line: Reinforces that clinic-based BP readings are not as accurate to help with outcomes assessment and tx planning…Too much white coat effect, too little proper technique, too rushed! At a minimum use home BP log and may be worth the expense to purchase and regularly use a 24-h ABPM to aid HTN tx decisions. In most cases it's billable and covered by insurance and Medicare (use ICD10 R03.0)

(HCPCS code **93788** is defined as "ABPM utilizing a system such as magnetic tape and/or computer disk, for 24 hours or longer; scanning analysis with report.")

JAMA Internal Medicine | Original Investigation

Benefits and Harms of Antihypertensive Treatment in Low-Risk Patients With Mild Hypertension

The Journal of the American Medical Association JAMA

Study
Objective: To examine whether antihypertensive treatment is associated with a low risk of mortality and cardiovascular disease (CVD) in low-risk patients with mild hypertension.
Methods: Longitudinal cohort study from Clinical Practice Research Datalink from 1/1/98 to 9/30/18. Patients 18 – 74 with mild untreated HTN (140-159/90-99) and no CVD or CVD risk factors. The rates of mortality, CVD, and adverse events among patients prescribed antihypertensive treatment at baseline, compared with those who were not prescribed such treatment, using Cox proportional hazards regression.
Results: A total of 19 143 treated patients (mean age, 54.7; 55.9% women; 55.5% white were matched to 19 143 similar untreated patients. During a median follow-up of 5.8 years no evidence of an association was found between antihypertensive treatment and mortality or between antihypertensive treatment and CVD. Treatment was associated with an increased risk of adverse events, including
hypotension (HR, 1.69; [NNH10yrs, 41),
syncope (HR, 1.28; NNH10, 35), electrolyte abnormalities (HR, 1.72; NNH10, 111), and acute kidney injury (HR, 1.37; NNH10, 91).

Discussion: This study did not find evidence to support aggressive therapy of mild hypertension, as recommended by some recent guidelines. It did, however find an increased risk.

Bottom line: Be cautious in recommending medical therapy for mild hypertension

The JNC 8 guidelines seem to have it right!

Number Needed to Treat*

- Putting NNTs into perspective As a general rule of thumb, an NNT of 5 or under for treating a symptomatic condition is usually considered to be acceptable and in some cases even NNTs below 10.

NNTs for Some Common Medical Treatments

Condition	Treatment	Outcome	NNT
H. Pylori	Triple therapy	Eradication	1.1
Peptic Ulcer	H. Pylori tx vs. H_2 tx for 6-8 weeks	Ulcer cure at 1 year	1.8
Migraine	1 dose sumatriptan vs. placebo	Headache relief at 2 hours	2.6
Bacterial conjunctivitis	Topical abx vs. placebo	For early clinical remission (3-5 days)	5
Herpes Zoster	Acyclovir vs. placebo	Prevent PHN at 6 months	Not effective

- What one considers a "good enough" NNT is going to be a judgment call based not only on the NNT itself but also on a carefully balanced consideration the following:

□ how robust the treatment outcome is (does it completely cure the patient or just make them a small percentage better?)

□ the cost (is it expensive?)

□ the risk of treatment (are side effects common? serious?)

□ is there a better treatment available?

*https://www.uws.edu/wp-content/uploads/2013/10/Number_Needed_to_Treat.pdf

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

THE LANCET

Gaziano, J Michael; Brotons, Carlos; Coppolecchia, Rosa; Cricelli, Claudio; Darius, Harald; et al.
The Lancet; London Vol. 392, Iss. 10152, (Sep 22, 2018): 1036-1046. DOI:10.1016/S0140-6736(18)31924-X

Objective: to assess the efficacy and safety of aspirin versus placebo in patients with a ***moderate estimated risk of a first cardiovascular event.***

Methods: randomised, double-blind, placebo-controlled, multicentre study done in seven countries. Eligible patients were aged 55 years (men) or 60 years (women) and older and had an average cardiovascular risk, deemed to be moderate on the basis of the number of specific risk factors. We excluded patients at high risk of gastrointestinal bleeding or other bleeding, or diabetes. Patients were randomly assigned (1:1) with a computer-generated randomisation code to receive enteric-coated aspirin tablets (100 mg) or placebo tablets, once daily

Results:In the intention-to-treat analysis, the primary endpoint occurred in 269 (4·29%) patients in the aspirin group versus 281 (4·48%) patients in the placebo group (hazard ratio [HR] 0·96; 95% CI 0·81–1·13; p=0·6038). Gastrointestinal bleeding events (mostly mild) occurred in 61 (0·97%) patients in the aspirin group versus 29 (0·46%) in the placebo group (HR 2·11; 95% CI 1·36–3·28; p=0·0007). The overall incidence rate of serious adverse events was similar in both treatment groups (n=1266 [20·19%] in the aspirin group vs n=1311 [20·89%] in the placebo group.

Discussion:The event rate was much lower than expected, which is probably reflective of contemporary risk management strategies, making the study more representative of a low-risk population. The role of aspirin in primary prevention among patients at moderate risk could therefore not be addressed. Nonetheless, the findings with respect to aspirin's effects are consistent with those observed in the previously published low-risk primary prevention studies.

Bottom line: a thoughtful discussion between a clinician and a patient, given the need to weigh cardiovascular and possible cancer prevention benefits against the bleeding risks, patient preferences, cost, and other factors.

Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly

The NEW ENGLAND JOURNAL of MEDICINE

ASPREE Investigator Group

OCTOBER 18, 2018

Objective: Aspirin is a well-established therapy for the secondary prevention of cardiovascular events. However, its role in the primary prevention of cardiovascular disease is unclear, especially in older persons, who have an increased risk.
Methods: 19,000, Australia and the United States, 70 years of age or older (or ≥65 years of age among blacks and Hispanics in the United States) with no cardiovascular disease, dementia, or disability. Assigned to receive 100 mg of enteric-coated aspirin or placebo. The

- primary end point was a composite of death, dementia, or persistent physical disability; results for this end point are reported in another article in the *Journal*.
- Secondary end points included major hemorrhage and cardiovascular disease (defined as fatal coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal stroke, or hospitalization for heart failure).

Results:
- Incidence of the primary endpoint (i.e., death, dementia, or persistent physical disability) was virtually identical (≈10%) in aspirin and placebo groups.
- All-cause mortality was slightly higher with aspirin than placebo (5.9% and 5.2%). The difference was entirely attributable to significantly more cancer deaths with aspirin (3.1% vs. 2.3%).
- There were no differences between groups in any composite or individual CV endpoint. No subgroup (including people with multiple risk factors) derived CV benefit from aspirin.
- Major hemorrhage occurred significantly more frequently with aspirin than with placebo (3.8% vs. 2.8%).

Discussion:The use of low-dose aspirin as a primary prevention strategy in older adults resulted in a significantly higher risk of major hemorrhage and did not result in a significantly lower risk of cardiovascular disease than placebo.

Bottom line: further strengthens the case against use of aspirin for primary CV prevention, especially in the healthy elderly

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

The NEW ENGLAND JOURNAL of MEDICINE

The ASCEND Study Collaborative Group*

OCTOBER 18, 2018

Objective: to assess the efficacy and safety of enteric-coated aspirin at a dose of 100 mg daily, as compared with placebo, in persons who had diabetes without manifest cardiovascular disease at trial entry.
Methods: randomly assigned adults who had diabetes but no evident cardiovascular disease to receive aspirin at a dose of 100 mg daily or matching placebo. The primary efficacy outcome was the first serious vascular event (i.e., myocardial infarction, stroke or transient ischemic attack, or death from any vascular cause, excluding any confirmed intracranial hemorrhage). The primary safety outcome was the first major bleeding event (i.e., intracranial hemorrhage, sight-threatening bleeding event in the eye, gastrointestinal bleeding, or other serious bleeding). 15,480 participants underwent randomization, mean follow-up of 7.4 years,
Results: serious vascular events occurred in a significantly lower percentage of participants in the aspirin group than in the placebo group (658 participants [8.5%] vs. 743 [9.6%]; rate ratio, 0.88; 95% confidence interval [CI], 0.79 to 0.97; P = 0.01). In contrast, major bleeding events occurred in 314 participants (4.1%) in the aspirin group, as compared with 245 (3.2%) in the placebo group (rate ratio, 1.29; 95% CI, 1.09 to 1.52; P = 0.003), with most of the excess being gastrointestinal bleeding and other extracranial bleeding.
Discussion: Aspirin use prevented serious vascular events in persons who had diabetes and no evident cardiovascular disease at trial entry, but it also caused major bleeding events. The absolute benefits were largely counterbalanced by the bleeding hazard.

Bottom line: For every 100 people treated with aspirin, there is about 1 vascular event averted and 1 major bleed caused. Hmm….are they "event-averse" or "harm-averse"?

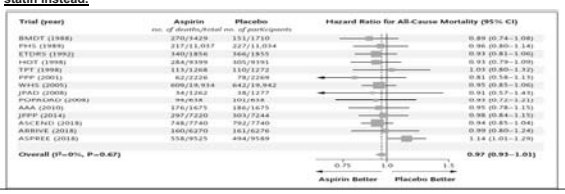
Also no indications of reduction of any type of GI cancers after 7.4y follow-up

Should Aspirin Be Used for Primary Prevention in the Post-Statin Era?

The NEW ENGLAND JOURNAL of MEDICINE

Paul M Ridker, M.D., M.P.H.

- the results of these contemporary aspirin trials, which showed minimal benefits and consistent bleeding risks, should be considered alongside the results of contemporary statin trials.
- In primary prevention trials, the use of statins was associated with a 25% decrease in the risk of major vascular events for every 38.6mg/dl (1 mmol/l) decrease in the LDL-C level (rate ratio with statin vs. placebo, 0.75; 95% CI, 0.69 to 0.82).
- This statistically certain benefit was associated with an enviable safety profile and was not associated with the bleeding complications seen with aspirin. The percentage of participants who were taking statins in the ASPREE, ARRIVE, and ASCEND trials was 34%, 43%, and 75%, respectively.
- For secondary prevention, in which risk is determined largely by the extent of atherosclerotic disease, the benefits of aspirin outweigh the risks of bleeding.
- In contrast, for primary prevention, in which risk is determined largely by age and the presence or absence of diabetes, the benefit–risk ratio for prophylactic aspirin in current practice is exceptionally small.
- **Thus, beyond diet maintenance, exercise, and smoking cessation, the best strategy for the use of aspirin in the primary prevention of cardiovascular disease may simply be to prescribe a statin instead.**



Linagliptin Effects on Heart Failure and Related Outcomes in Individuals With Type 2 Diabetes Mellitus at High Cardiovascular and Renal Risk in CARMELINA

Circulation

Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk

JAMA

The CARMELINA Randomized Clinical Trial

Objective: To assess the cardiovascular safety of linagliptin (Trajenta) in patients with CVD or high risk for CVD. Really to demonstrate that linagliptin does not cause heart failure in high risk patients (unlike another DPP-4, saxagliptin - Onglyza)
Methods: Secondary analysis of CARMELINA on heart failure hospitalizations, cardiovascular outcomes, and deaths, which had been prospectively gathered and then centrally adjudicated from the 6979 patients with type 2 diabetes from 27 countries.

Results: No significant difference in the incidence of heart failure hospitalization, death, MI, or CVA. between patients treated with linagliptin and those given placebo

Discussion: These are two well done, but sponsored (actually industry performed) retrospective studies of over 7,000 patients which did NOT find cardiovascular harm from linagliption.

Bottom line: Liniagliptin (Trajenta) is probably safe in diabetics with heart disease. But if they have heart disease they should probably be on a (SGLT2) inhibitor, such as empagliflozin or canagliflozin, based on the EMPA-REG and CANVAS trials. Or a GLP 1 like laragludite based on the LEADER Trial

Conflicts of Interest?

- Dr Rosenstock reported that he has served on scientific advisory boards and received honoraria or consulting fees from Eli Lilly, Sanofi, Novo Nordisk, Janssen, AstraZeneca, Boehringer Ingelheim and Intarcia; he has also received grants/research support from Merck, Pfizer, Sanofi, Novo Nordisk, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Genentech, Janssen, Lexicon, Boehringer Ingelheim, and Intarcia. Dr Perkovic reported that he has received research support from the Australian National Health and Medical Research Council (Project and Program Grant), served on steering committees for trials supported by AbbVie, Boehringer Ingelheim, Eli Lilly, Gilead, GlaxoSmithKline, Janssen, Novartis, Novo Nordisk, Pfizer, Retrophin, and Tricida and served on advisory boards, spoken at t scientific meetings, or both for AbbVie, Astellas Pharma, Astra Zeneca, Bayer, Baxter, Bristol-Myers Squibb, Boehringer Ingelheim, Durect Corporation, Eli Lilly, Gilead Sciences, GlaxoSmithKline, Janssen, Merck, Novartis, Novo Nordisk, Pfizer, Pharmalink, Relypsa, Roche, Sanofi, Servier, and Vitae. He has a policy of having honoraria paid to his employer. Dr Johansen reported that he is employed by Boehringer Ingelheim. Dr Cooper reported that he has received fees for advisory services to Boehringer Ingelheim. Dr Kahn reported that he has received personal fees from Boehringer Ingelheim, Elcelyx, Eli Lilly, Intarcia, Janssen, Merck, Neurimmune, and Novo Nordisk. Dr Marx reported that he has given lectures for Amgen, Boehringer Ingelheim, Sanofi-Aventis, Merck Sharp & Dohme, Bristol-Myers Squibb, AstraZeneca, Eli Lilly, Novo Nordisk, has received unrestricted research grants from Boehringer Ingelheim, and has served as an advisor for Amgen, Bayer, Boehringer Ingelheim, Sanofi-Aventis, Merck Sharp & Dohme, Bristol-Myers Squibb, AstraZeneca, and Novo Nordisk. In addition, he has served in trial leadership for Boehringer Ingelheim and Novo Nordisk. He reported that he declines all personal compensation from pharmaceutical or device companies. Dr Alexander reported that he has received personal fees from Abbvie, Bristol-Myers Squibb, CSL Behring, Jansen Pharmaceutics, ovo Nordisk, Pfizer, Portola, and Teikoku and institutional research support from Boehringer Ingelheim, Bristol-Myers Squibb, Cryolife, CSL Behring, Tenax Therapeutics, and VoluMetrix. Dr Pencina reported receipt of grants and personal fees from Boehringer Ingelheim and Merck and grants from Sanofi/Regeneron. Dr Toto reported that he is a consultant to Amgen, Boehringer Ingelheim, ZS Pharma, Relypsa, Novo Nordisk, Reata, and AstraZeneca and receives grant support from the National Institutes of Health. DrWanner reported that he has received fees for advisory services to Boehringer Ingelheim. Dr Zinman reported that he has received grant support from Boehringer Ingelheim, AstraZeneca, and Novo Nordisk and consulting fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, Novo Nordisk, and Sanofi-Aventis. DrWoerle reported that he is a former employee of Boehringer Ingelheim. Messrs Baanstra, Pfarr and Schnaidt and Drs Meinicke, George, and von Eynatten reported that they are employed by Boehringer Ingelheim. Dr McGuire reported that he has received personal fees from Boehringer- Ingelheim, Janssen Research and Development, Sanofi-Aventis, Merck Sharp & Dohme, Merck & Co, Eli Lilly , Novo Nordisk, GlaxoSmithKline, AstraZeneca, Lexicon, Eisai, Pfizer,Metavant, Applied Therapeutics, and Esperion. Funding/Support: This study was sponsored by Boehringer Ingelheim and Eli Lilly.

Association Between Use of Sodium-Glucose Cotransporter 2 Inhibitors, Glucagon-like Peptide 1 Agonists, and Dipeptidyl Peptidase 4 Inhibitors With All-Cause Mortality in Patients With Type 2 Diabetes

JAMA The Journal of the American Medical Association

2018;319(15):1580-1591.

A Systematic Review and Meta-analysis

Objective: To compare the efficacies of SGLT-2 inhibitors, GLP-1 agonists, and DPP-4 inhibitors on mortality and cardiovascular end points using network meta-analysis.

Methods: Randomized clinical trials enrolling participants with type 2 diabetes and a follow-up of at least 12 weeks were included, for which SGLT-2 inhibitors, GLP-1 agonists, and DPP-4 inhibitors were compared with either each other or placebo or no treatment. The primary outcome: all-cause mortality; secondary outcomes: cardiovascular (CV) mortality, heart failure (HF) events, myocardial infarction (MI), unstable angina, and stroke; safety end points: adverse events and hypoglycemia.

Results:236 trials randomizing 176 310 participants found SGLT-2 inhibitors (absolute risk difference [RD], −1.0%; hazard ratio [HR], 0.80 [95%credible interval {CrI}, 0.71 to 0.89]) and GLP-1 agonists (absolute RD, −0.6%; HR, 0.88 [95%CrI, 0.81 to 0.94]) were associated with significantly lower all-cause mortality than the control groups. SGLT-2 inhibitors (absolute RD, −0.8%; HR, 0.79 [95%CrI, 0.69 to 0.91]) and GLP-1 agonists (absolute RD, −0.5%; HR, 0.85 [95%CrI, 0.77 to 0.94]) were significantly associated with lower CV mortality than were the control groups. SGLT-2 inhibitors were significantly associated with lower rates of HF events (absolute RD, −1.1%; HR, 0.62 [95%CrI, 0.54 to 0.72]) and MI (absolute RD, −0.6%; HR, 0.86 [95%CrI, 0.77 to 0.97]) than were the control groups. GLP-1 agonists were associated with a higher risk of adverse events leading to trial withdrawal than were SGLT-2 inhibitors (absolute RD, 5.8%; HR, 1.80 [95%CrI, 1.44 to 2.25]) and DPP-4 inhibitors (absolute RD, 3.1%; HR, 1.93 [95%CrI, 1.59 to 2.35]).

Discussion: SGLT-2 inhibitors or GLP-1 agonists was associated with lower mortality than DPP-4 inhibitors or placebo or no treatment. Use of DPP-4 inhibitors was not associated with lower mortality than placebo or no treatment.

Bottom line: Good approach: TLC + maxed metformin + SGLT2 or GLP-1. ADA recommends, in most cases, using GLP-1 over insulin when an injectable in considered.

Effect of Increased Daily Water Intake in Premenopausal Women With Recurrent Urinary Tract Infections

JAMA Internal Medicine

A Randomized Clinical Trial

Study

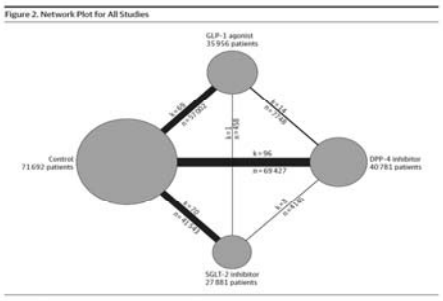
- **Objective**:To assess the efficacy of increased daily water intake on the frequency of recurrent cystitis in premenopausal women.
- **Methods**: Randomized open-label 12 month trial of 140 women with recurrent UTI's who reported drinking<1.5L assigned to regular fluid consumption or regular fluid plus 1.5L of water per day. Primary outcome was frequency of cystitis over 12months.
- **Results**: During the 12-month study period, the mean (SD) number of cystitis episodes was 1.7 (95% CI, 1.5-1.8) in the water group compared with 3.2 (95% CI, 3.0-3.4) in the control group, with a difference in means of 1.5 (95% CI, 1.2-1.8; $P < .001$). Overall, there were 327 cystitis episodes, 111 in the water group and 216 in the control group.

Discussion: This was an very well done study on an amazingly simple concept which really needed to be tested (as many recommendations to decrease UTI's have not panned out). My only concern is that of over doing it and causing dilutional hyponatremia.

Bottom line: In women with recurrent UTI's, ask them how much fluid they drink. If less than 1.5 liters, recommend increasing fluid intake.

Network Meta-analysis primer

- **Network meta-analysis comprises direct and indirect comparisons between multiple interventions, allowing comparisons to be made *when direct trial evidence is scarce*. Helps comparative effectiveness analysis when there are limited head-to-head comparison studies**
- **Respects randomization but does not represent randomized evidence. Presents observational data as the tx options have not all been directly compared in an RCT.**
- **Helps clinicians rank treatments in order of efficacy in achieving a specific outcome or goal**

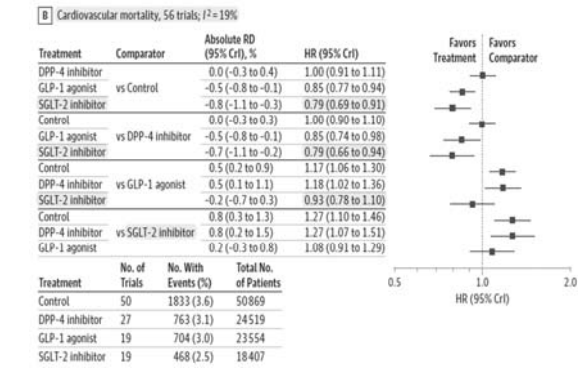


Graphical representation of network for all included trials. Connecting lines represent head-to-head comparisons between drugs, indicated by nodes. Multigroup trials contribute multiple comparisons, resulting in 258 comparisons from 736 trials. The thickness of lines between nodes is proportional to the number of trials comparing the treatments. The sizes of the nodes are proportional to the number of patients in each treatment. Patients may be included in multiple comparisons: for example, in a study of 3 groups consisting of control and 2 different drug classes, the control group is compared with each drug class. This is accounted for within the network model and does not constitute duplication of participants.

DPP-4 indicates dipeptidyl peptidase 4 GLP-1, glucagon-like peptide 1; k, the number of comparisons; n, the number of patients per comparison; and SGLT-2, sodium-glucose cotransporter 2.

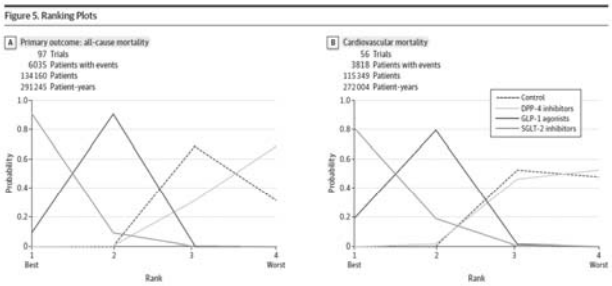
Forest Plot

visual representation of comparison of multiple treatments to a specific outcome



Ranking Plots

- Gives visual ranking of treatment (eg. Classes of DM medications in this study) with respect to a particular outcome.



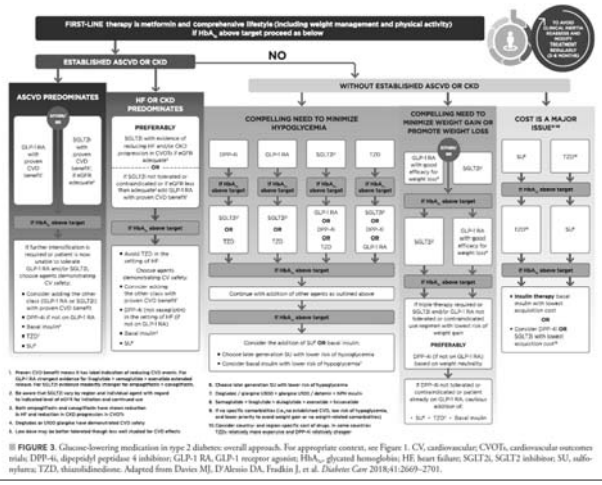


FIGURE 3. Glucose-lowering medication in type 2 diabetes: overall approach. For appropriate context, see Figure 1. CV, cardiovascular; CVOTs, cardiovascular outcomes trials; DPP-4i, dipeptidyl peptidase 4 inhibitor; GLP-1 RA, GLP-1 receptor agonist; HbA_{1c}, glycated hemoglobin; HF, heart failure; SGLT2i, SGLT2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione. Adapted from Davies MJ, D'Alessio DA, Fradkin J, et al. *Diabetes Care* 2018;41:2669–2701.

Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents

The NEW ENGLAND JOURNAL of MEDICINE
SEPTEMBER 6, 2018

Objective: investigate baloxavir (selective inhibitor of influenza cap-dependent endonuclease) effect on influenza

Methods: two randomized, double-blind, controlled trials involving otherwise healthy outpatients with acute uncomplicated influenza. After a dose-ranging (10 to 40 mg) placebo-controlled trial, we undertook a placebo- and oseltamivir-controlled trial of single, weight-based doses of baloxavir (40 or 80 mg) in patients 12 to 64 years of age during the 2016–2017 season. The dose of oseltamivir was 75 mg twice daily for 5 days. The primary efficacy end point was the time to alleviation of influenza symptoms in the intention-to-treat infected population.

Results: The median time to alleviation of symptoms was 53.7 hours (95% confidence interval [CI], 49.5 to 58.5) with baloxavir, as compared with 80.2 hours (95% CI, 72.6 to 87.1) with placebo (P<0.001). The time to alleviation of symptoms was similar with baloxavir and oseltamivir. Baloxavir was associated with greater reductions in viral load 1 day after initiation of the regimen than placebo or oseltamivir. Adverse events were reported in 20.7% of baloxavir recipients, 24.6% of placebo recipients, and 24.8% of oseltamivir recipients.

Discussion: Single-dose baloxavir was without evident safety concerns, was superior to placebo in alleviating influenza symptoms, and was superior to both oseltamivir and placebo in reducing the viral load 1 day after initiation of the trial regimen in patients with uncomplicated influenza. Evidence for the development of decreased susceptibility to baloxavir after treatment was also observed.

Bottom line: 1st option against flu for a long time. But appears to easily induce resistance. Not sure about this one, but one to keep on the radar for the future.

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

Objective: Clinical practice guidelines provide recommendations applicable to patients with or at risk of developing cardiovascular disease (CVD). Update 2015 guidelines

Top 10 Take-Home Messages to Reduce Risk of Atherosclerotic Cardiovascular Disease Through Cholesterol Management

1) In all individuals, emphasize a **heart-healthy lifestyle** across the life course.
2) In patients with **clinical ASCVD**, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or ***"maximally tolerated"*** statin therapy.
3) In **very high-risk ASCVD**, use a LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of non-statins to statin therapy (eg. Ezetimibe, PCSK9i).
4) In patients with ***severe primary hypercholesterolemia*** (LDL-C level ≥190 mg/dL [≥4.9 mmol/L]), without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk. Add ezetimibe if LDL>100. Consider PCSK9i if risk factors for subsequent ASCVD events.
5) In patients 40 to 75 years of age with **diabetes mellitus** and LDL-C ≥70 mg/dL (≥1.8 mmol/L), start **moderate-intensity statin** therapy without calculating 10-year ASCVD risk.

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

Top 10 Take-Home Messages to Reduce Risk of Atherosclerotic Cardiovascular Disease Through Cholesterol Management

6) In adults 40 to 75 years of age evaluated for **primary ASCVD prevention**, have a clinician–patient risk **discussion** before starting statin therapy.

7) In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL (≥1.8 mmol/L), at a **10-year ASCVD risk of ≥7.5%,** start a moderate-intensity statin if a **discussion** of treatment options favors statin therapy.

8) In adults 40 to 75 years of age without diabetes mellitus and 10-year risk of 7.5% to 19.9% (intermediate risk), **risk-enhancing factors** favor initiation of statin therapy (see No. 7).
- family history of premature ASCVD;
- persistently elevated LDL-C levels ≥160 mg/dL (≥4.1 mmol/L);
- metabolic syndrome;
- chronic kidney disease;
- history of preeclampsia or premature menopause (age <40 years);
- chronic inflammatory disorders (e.g., rheumatoid arthritis, psoriasis, or chronic HIV);
- high-risk ethnic groups (e.g., South Asian);
- persistent elevations of triglycerides ≥175 mg/dL (≥1.97 mmol/L);
- and, if measured in selected individuals,
- apolipoprotein B ≥130 mg/dL,
- high-sensitivity C-reactive protein ≥2.0 mg/L,
- ankle-brachial index <0.9
- lipoprotein (a) ≥50 mg/dL or 125 nmol/L, especially at higher values of lipoprotein (a)

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

Top 10 Take-Home Messages to Reduce Risk of Atherosclerotic Cardiovascular Disease Through Cholesterol Management

9) In adults 40 to 75 years of age without diabetes mellitus and with LDL-C levels ≥70 mg/dL- 189 mg/dL (≥1.8-4.9 mmol/L), at a 10-year ASCVD risk of ≥7.5% to 19.9%, if a decision about statin therapy is uncertain, consider measuring **CAC** (aka "coronary artery calcium" score).
- A CAC score of 1 to 99 favors statin therapy, especially in those ≥55 years of age.
- For any patient, if the CAC score is ≥100 Agatston units or ≥75th percentile, statin therapy is indicated unless otherwise deferred by the outcome of clinician–patient risk discussion.

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

Top 10 Take-Home Messages to Reduce Risk of Atherosclerotic Cardiovascular Disease Through Cholesterol Management

10) Assess adherence and **percentage response** to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed.

- Good adherence to various LDL-lowering diets will reduce LDL-C levels by 10% to >15%
- Addition of ezetimibe or bile acid sequestrants to statin therapy typically provides an additional 15% to 25% reduction in LDL-C.
- PCSK9 inhibitors reduce LDL-C by 50-60%
- Statins:

Table 3. High-, Moderate-, and Low-Intensity Statin Therapy*

	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

Finding the Balance Between Benefits and Harms When Using Statins for Primary Prevention of Cardiovascular Disease

A Modeling Study

Annals of Internal Medicine

ORIGINAL RESEARCH | 1 JANUARY 2019

Study

- **Objective**: To reanalyze the risk at which statin therapy offers a benefit.
- **Methods**: "Quantitative benefit-harm balance modeling study" of primary prevention trials, observational trials and a preference study.
- **Results**: Net benefit occurred at different risk levels varying with age, gender and the specific drug. Younger men (40 – 44) benefitted at a 10 year risk of 14%, whereas older men (70-75) benefitted only after the 10 year risk was 21%. For women the risk break point was slightly higher at all ages.

Discussion:

The statistics used in this study are very complex and they likely over-estimated the harms.

Approach developed by National Cancer Institute.

However, the take home point is probably valid – Older patients have higher risks from medications and may have lower benefit, especially if it takes years for the benefit to manifest.

Remember, this is for PRIMARY prevention!

Swiss study – doesn't reflect our demographic diversity.

Bottom line:

Once again, be more cautious when prescribing medications to older patients.

Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care

BMJ

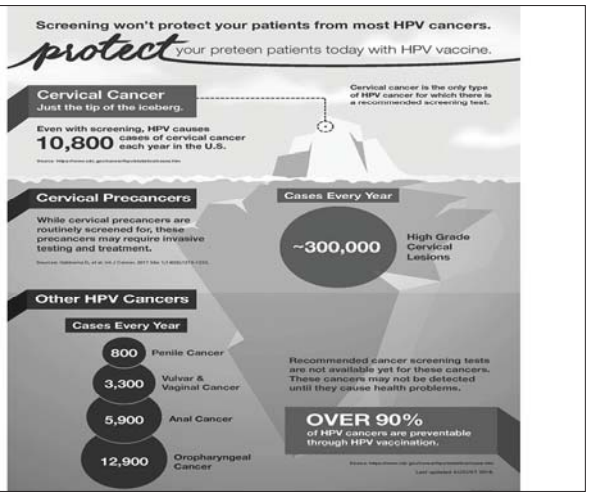
Objective: To investigate the associations between direct oral anticoagulants (DOACs) and risks of bleeding, ischaemic stroke, venous thromboembolism, and all cause mortality compared with warfarin.

Methods: Prospective open cohort study. 103 270 patients with atrial fibrillation and 92 791 without atrial fibrillation between 2011 and 2016. Major bleeding leading to hospital admission or death. Specific sites of bleeding and all cause mortality were also studied.

Results: **with atrial fibrillation,** compared with warfarin, apixaban was associated with a
- decreased risk of major bleeding (adjusted hazard ratio 0.66, 95% confidence interval 0.54 to 0.79) and intracranial bleeding (0.40, 0.25 to 0.64);
- dabigatran was associated with a decreased risk of intracranial bleeding (0.45, 0.26 to 0.77).
- An increased risk of all cause mortality was observed in patients taking rivaroxaban (1.19, 1.09 to 1.29) or on lower doses of apixaban (1.27, 1.12 to 1.45).
- **without atrial fibrillation**, compared with warfarin, apixaban was associated with a decreased risk of major bleeding (0.60, 0.46 to 0.79), any gastrointestinal bleeding (0.55, 0.37 to 0.83), and upper gastrointestinal bleeding (0.55, 0.36 to 0.83);
- rivaroxaban was associated with a decreased risk of intracranial bleeding (0.54, 0.35 to 0.82).
- Increased risk of all cause mortality was observed in patients taking rivaroxaban (1.51, 1.38 to 1.66) and those on lower doses of apixaban (1.34, 1.13 to 1.58).

Discussion: Overall, apixaban was found to be the safest drug, with reduced risks of major, intracranial, and gastrointestinal bleeding compared with warfarin. Rivaroxaban and low dose apixaban were, however, associated with increased risks of all cause mortality compared with warfarin.

Bottom line: reassurance about the safety of DOACs as an alternative to warfarin across all new incident users. Probably apixaban is safest and all are equally as effective as warfarin. Bye-bye warfarin!!!



Comparative effectiveness and safety of statins as a class and of specific statins for primary prevention of cardiovascular disease: A systematic review, meta-analysis and network meta-analysis of randomized trials with 94,283 participants

AHJ

In press, January 2019

Henock G Yebyo, Hélène E Aschmann, Marco Kaufmann, Milo A Puhan

- **Objective**: comprehensive systematic review, meta-analysis and network meta-analysis of RCTs to estimate the effectiveness and safety of statins as a class and of individual statins for primary prevention of CVD
- **Methods**: searched in PubMed for existing systematic reviews and individual open-label or double-blinded randomized controlled trials that compared a statin with a placebo or another, which were published in English until January 01, 2018. We performed a random-effect pairwise meta-analysis of all statins as a class and network meta-analysis for the specific statins on different benefit and harm outcomes
- **Results**:
- Benefits: statistically significant risk reductions on non-fatal MI (Risk Ratio [RR] 0.62, 95% CI 0.53–0.72), CVD mortality (RR 0.80, 0.71–0.91), all-cause mortality (RR 0.89, 0.85–0.93), non-fatal stroke (RR 0.83, 0.75–0.92), unstable angina (RR 0.75, 0.63–0.91), and composite major cardiovascular events (RR 0.74, 0.67–0.81).
- Harms: statistically significantly relative and absolute risks of myopathy (RR 1.08, 1.01–1.15; Risk difference [RD] 13, 2–24 per 10,000 person-years); renal dysfunction (RR 1.14, 1.02–1.29; RD 20, 3–42 per 10,000 person-years); and hepatic dysfunction (RR 1.16, 1.02–1.31; RD 8, 1–16 per 10,000 person-years).
- **Discussion**: statins as a class as well as specific statins were effective in preventing cardiovascular events and all-cause mortality in primary prevention populations, but on the other hand increased risk of unwanted side effects. Atorvastatin and rosuvastatin appeared to be the most effects and atorvastatin the safest statin across most of the outcomes.

Bottom line: I'd say pick atorva or rosuva as your "go-to" statins

Spironolactone Versus Clonidine as a Fourth-Drug Therapy for Resistant Hypertension

The ReHOT Randomized Study (Resistant Hypertension Optimal Treatment)

Hypertension 2018;71:681–690

- **Objective**: to compare spironolactone versus clonidine as the fourth drug in patients with resistant hypertension
- **Methods**: multicenter, randomized trial. Pts with resistant hypertension (no office and ambulatory blood pressure [BP] monitoring control, despite treatment with 3 drugs, including a diuretic, for 12 weeks) were randomized to an additional 12-week treatment with spironolactone (12.5–50 mg QD) or clonidine (0.1–0.3 mg BID). The primary end point was BP control during office (<140/90 mm Hg) and 24-h ambulatory (<130/80 mm Hg) BP monitoring. Secondary end points included BP control from each method and absolute BP reduction.
- **Results**: Compared with the spironolactone group (n=95), the clonidine group (n=92) presented similar rates of achieving the primary end point (20.5% versus 20.8%, respectively; relative risk, 1.01 [0.55–1.88]; *P*=1.00). Secondary end point analysis showed similar office BP (33.3% versus 29.3%) and ambulatory BP monitoring (44% versus 46.2%) control for spironolactone and clonidine, respectively. However, spironolactone promoted greater decrease in 24-h systolic and diastolic BP and diastolic daytime ambulatory BP than clonidine.

Discussion: clonidine was not superior to spironolactone in true resistant hypertensive patients, but the overall BP control was low (≈21%). Considering easier posology and greater decrease in secondary end points, spironolactone is preferable for the fourth-drug therapy.

Bottom line: Hard to treat with 21% achieving control. Though similar in outcomes, the ease of once daily dosing and greater decrease in overall BP – pick spironolactone. Monitor K+ at 3 weeks after initiation and after titrations. Consider eplerenone (daily to BID dosing) if gynecomastia occurs with spirono.

Effect of Screening With Primary Cervical HPV Testing vs Cytology Testing on High-grade Cervical Intraepithelial Neoplasia at 48 Months

The HPV FOCAL Randomized Clinical Trial

JAMA The Journal of the American Medical Association 2018;320(1):43-52

Objective: To evaluate histologically confirmed cumulative incident cervical intraepithelial neoplasia (CIN) grade 3 or worse (CIN3+) detected up to and including 48 months by primary HPV testing alone (intervention) or liquid-based cytology (control).

Methods: Randomized clinical trial conducted in an organized Cervical Cancer Screening Programin Canada. 19 009 women were randomized to the intervention (n = 9552) and control (n = 9457) groups. Women in the intervention group received HPV testing; those whose results were negative returned at 48 months. Women in the control group received liquid-based cytology (LBC) testing; those whose results were negative returned at 24 months for LBC. Women in the control group who were negative at 24 months returned at 48 months. At 48-month exit, both groups received HPV and LBC co-testing. The primary outcome was the cumulative incidence of CIN3+ 48 months following randomization. The cumulative incidence of CIN2+was a secondary outcome.

Results: 19 009 women, screening with primary HPV testing resulted in significantly lower likelihood of CIN3+ at 48 months compared with cytology (2.3/1000 vs 5.5/1000).

Discussion: Among women undergoing cervical cancer screening, the use of primary HPV testing compared with cytology testing resulted in a significantly lower likelihood of CIN3+ at 48 months. Further research is needed to understand long-term clinical outcomes as well as cost-effectiveness.

Bottom line: Eventually, HPV detection is likely to supersede cervical cytology for primary screening. Death knell for Pap smears beginning to sound???

How will universal HPV Vaccination affect this?

Radical Prostatectomy or Watchful Waiting in Prostate Cancer — 29-Year Follow-up

The NEW ENGLAND JOURNAL of MEDICINE

Study

- **Objective**: To show that radical prostatectomy (RP) benefits some men compared to watchful waiting
- **Methods**: Follow up of the SPCG-4 study of 695 men with localized prostate cancer who were randomized to watchful waiting or RP. Mean follow up of 23 years.
- **Results**: The mean PSA values were 13.5 in the RP and 12.3 in the WW groups. Overall death was 72% in the RP group and 84% in the WW group (NNT 9.2). Death from prostate cancer was 19.6% vs 31.3% (NNT 8.5), metastatic disease 26.6% vs 43/3% (NNT 6).
- In men with extracapsular extension the death rate was 29% compared to 6% in those without extension, Gleason score of 7 (4+3) or greater had a 10 fold increased risk of death.

Discussion:

In this group of men with predominantly clinically detected prostate cancer (almost 95%), radical prostatectomy offered survival and morbidity benefits to men less than 65 years of age.

Absolute benefit of RP doubled from 10 year to 23 years of follow up.

Much larger benefit than found in the 19yr follow up in the PIVOT trial.

NO mention of harms from surgery! (Incontinence averages 18% higher and ED 24% higher with PR)

Bottom line:

In men younger than 65 with clinically detected prostate cancer, there appears to be a benefit in prostatectomy compared to watchful waiting. How this translates to the average US man is hard to tell.

Digital Rectal Examination for Prostate Cancer Screening in Primary Care: A Systematic Review and Meta-Analysis

ANNALS OF FAMILY MEDICINE
2018;16:149-154

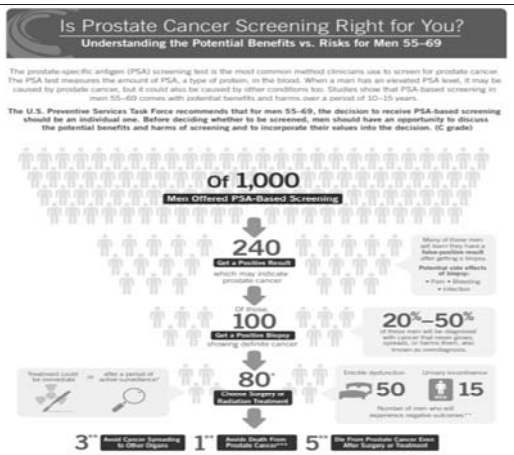
Objective: to evaluate the diagnostic accuracy of DRE in screening for prostate cancer in primary care settings

Methods: searched MEDLINE, Embase, DARE (Database of Abstracts of Reviews of Effects), Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and CINAHL (Cumulative Index to Nursing and Allied Health Literature) from their inception to June 2016. Six reviewers, in pairs, independently screened citations for eligibility and extracted data. Pooled estimates were calculated for sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of DRE in primary care settings using an inverse variance meta-analysis. We used QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2) and GRADE (Grades of Recommendation Assessment, Development, and Evaluation) guidelines to assess study risk of bias and quality.

Results: 8,217 studies, of which 7 studies with 9,241 patients were included after the screening process. All patients analyzed underwent both DRE and biopsy. Pooled sensitivity of DRE performed by primary care clinicians was 0.51 (95% CI, 0.36-0.67; I2 = 98.4%) and pooled specificity was 0.59 (95% CI, 0.41-0.76; I2 = 99.4%). **Pooled PPV was 0.41** (95% CI, 0.31-0.52; I2 = 97.2%), and **pooled NPV was 0.64** (95% CI, 0.58-0.70; I2 = 95.0%). The quality of evidence as assessed with GRADE was very low.

Discussion: Given the considerable lack of evidence supporting its efficacy, we recommend against routine performance of DRE to screen for prostate cancer in the primary care setting.

Bottom line: Save your patients and yourself time and discomfort, as it just does not appear to be worth it. Maybe our urology colleagues are better suited? Inter-examiner reliability between urologists in identifying a prostate finding as suspicious for cancer has been found to be only "fair" after adjusting for chance agreement (κ = 0.22, *P* =.009)



https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/prostate-cancer-screening1?ds=1&s=prostatewp-content/uploads/2018/05/USPSTF_ProstateCancer_Infographic_FINAL-5-4.pdf

Choosing Wisely:

Don't routinely screen for prostate cancer using a prostate-specific antigen (PSA) test or digital rectal exam.

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Search Recommendations

Rationale and Comments:	There is convincing evidence that PSA-based screening leads to substantial overdiagnosis of prostate tumors. Many tumors will not harm patients, while the risks of treatment are significant. Physicians should not offer or order PSA screening unless they are prepared to engage in shared decision making that enables an informed choice by patients.
Sponsoring Organizations:	• American Academy of Family Physicians

http://www.choosingwisely.org/patient-resources/psa-test-for-prostate-cancer/

Thank you!