A Decade of Goodness
Favorite Blasts

David Fiore, MD, FAAFP

UNR Med, Dept of Family Medicine

Jason Crawford, MD, MPH, FAAFP

Silver Sage Center for Family Medicine

Renown Institute for Heart and Vascular Health

NEVADA ACADEMY OF FAMILY PHYSICIANS

ARTICLES

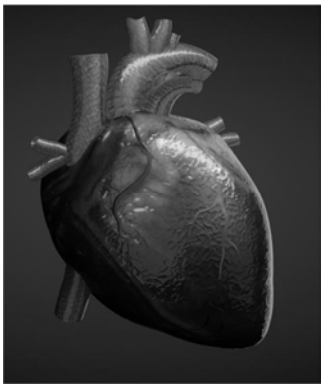
Most articles available on the Nevada Academy of Family Medicine website

www.nvafp.com

Objectives

- At the end of this presentation, 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)

Cardiovascular



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

AHA SCIENTIFIC STATEMENT

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. 2016;134:e653–e699. December 13, 2016

- The purpose of this statement is to review current knowledge related to the association between CRF and health outcomes, increase awareness of the added value of CRF to improve risk prediction, and suggest future directions in research..
- CRF is as strong a predictor of mortality as established risk factors such as cigarette smoking, hypertension, high cholesterol, and T2DM.
- CRF can be measured directly, expressed as maximal oxygen consumption (VO2max), or estimated from the peak work rate achieved on a treadmill or a cycle ergometer or from non-exercise algorithms.
- Small increases in CRF (eg, 1–2 METs) are associated with considerably (10% to 30%) lower adverse cardiovascular event rates.
- While avoiding the costs and and modest risk associated with exercise testing, non-exercise algorithms using readily available clinical variables may provide reasonably accurate estimates of CRF.

Nonfasting for Routine Lipid Testing From Evidence to Action

JAMA Internal Medicine

Helke A. Bischoff-Ferrari, MD, DrPH;

JAMA Intern Med. 2016;176(7):1005-1006.

Samia Mora, MD, MHS

Study

- **Objective**: To determine if a non-fasting lipid panel is accurate for predicting CVD and if so, how to implement it more widely.
- **Methods**: Review of relevant articles and guidelines. (Not well defined)

Results:

- Non-fasting Total and High Density Cholesterol vary very little with fasting levels. Therefore non-HDL cholesterol does not vary much either. LDL cholesterol does increase slightly (~8mg/dl) and Triglycerides increase modestly (~25mg/dl).
- Non-fasting lipids may be a better predictor of CVD than fasting levels.

Discussion

- Multiple guidelines allow for, or recommend, non-fasting lipid testing.
- The ACA/AHA guidelines recommend fasting lipids preferred (not required).

Bottom line: ***For some patients getting a fasting lab can be very inconvenient or uncomfortable. Don't feel bad if you order a non-fasting level. I think that's where we're headed.***

Three Minutes of All-Out Intermittent Exercise per Week Increases Skeletal Muscle Oxidative Capacity and Improves Cardiometabolic Health

PLOS ONE | Issue 11 | e111489 November 2014 | Volume 9 |

Jenna B. Gillen[1], Michael E. Percival[1], Lauren E. Skelly[1], Brian J. Martin[1], Rachel B. Tan[1], Mark A. Tarnopolsky[1,2], Martin J. Gibala[1]*

Study

- 14 obese, healthy subjects (BMI 30), age 29 (+-9) yrs
- 18 training sessions over 6 weeks on cycle ergometer.
- 2 min warm up, 3X20 sec "all out" sprints interspersed with 2 min of recovery, 3 min cool down.
- Peak Oxygen uptake (VO2 Max) increased 12%, Mean BP decreased 7%, Blood glucose decreased in men.
- Citrate synthase increased 40%

Concerns:

- Very small study
- Many people don't like maximal intensity exercise – even if briefly
- What's the clinical significance.

Bottom Line

- Suggesting very brief, very intense, exercise may remove barriers on some people.

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association. Learn and Live.

Triglycerides and Cardiovascular Disease : A Scientific Statement From the American Heart Association

Michael Miller, Neil J. Stone, Christie Ballantyne, Vera Bittner, Michael H. Criqui, Henry N. Ginsberg, Anne Carol Goldberg, William James Howard, Marc S. Jacobson, Penny M. Kris-Etherton, Terry A. Lennie, Moshe Levi, Theodore Mazzone and Subramanian Pennathur

QUESTIONs:

What are the effects of elevated triglycerides?

How should it be treated?

May 24, 2011

BACKGROUND:

The extent to which triglycerides directly promote CVD or represent a biomarker of risk has been debated for 3 decades.

TAKE HOME:

Lifestyle changes: diet, weight loss, exercise, alcohol reduction

Meds: Statin, Omega 3 fatty acids (2 options now: lovaza, vascepa) Niacin

Focus on LDL reduction first

Add on fibrate? I say no unless >500 in non-diabetics or >350 in diabetics.

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

1) In all individuals, emphasize a **heart-healthy lifestyle** across the life course.

1) In patients with **clinical ASCVD**, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or ***"maximally tolerated"*** statin therapy.

1) 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).

1) 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.

1) 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

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).

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).

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.

Safety and Benefit of Discontinuing Statin Therapy in the Setting of Advanced, Life-Limiting Illness A Randomized Clinical Trial

Original Investigation

JAMA The Journal of the American Medical Association

JAMA Internal Medicine Published online March 23, 2015

Jean S. Kutner, MD, MSPH; Patrick J. Blatchford, PhD; Donald H. Taylor Jr, PhD; Christine S. Ritchie, MD; Janet H. Bull, MD; Diane L. Fairclough, DrPH; Laura C. Hanson, MD; Thomas W. LeBlanc, MD; Greg P. Samsa, PhD; Steven Wolf, MS; Noreen M. Aziz, MD, PhD; David C. Currow, BMed; Betty Ferrell, PhD; Nina Wagner Johnston, MD; S. Yousuf Zafar, MD; James F. Cleary, MD; Sandesh Deo, MD; Patricia S. Goode, MD; Arif H. Kamal, MD; Cyndi Kassner, PhD; Elisabeth A. Kvale, MD; Janelle G. McCallum, RN, MSN; Adebayo B. Ogunseitan, MD; Steven Z. Pantilat, MD; Russell K. Portenoy, MD; Margo Prince-Paul, PhD; Jeff A. Sloan, PhD; Keith M. Sweetz, MD; Charles F. Von Gunten, MD, PhD; Amy P. Abernethy, MD, PhD

Objective: To evaluate the safety, clinical, and cost impact of discontinuing statin medications for patients in the palliative care setting.

Methods: multicenter, parallel-group, unblinded, pragmatic clinical trial. Eligibility included adults with an estimated life expectancy of between 1 month and 1 year, statin therapy for 3 months or more for primary or secondary prevention of cardiovascular disease, recent deterioration in functional status, and no recent active cardiovascular disease. Participants were randomized to either discontinue or continue statin therapy and were monitored monthly for up to 1 year. The study was conducted from June 3, 2011, to May 2, 2013

Results:381 patients were enrolled, Mean (SD) age was 74.1 years, 22.0% of the participants were cognitively impaired, and 48.8% had cancer. The proportion of participants in the discontinuation vs continuation groups who died within 60 days was not significantly different (23.8% vs 20.3%; 90%CI, −3.5%to 10.5%; P = .36) and did not meet the noninferiority end point. Total QOL was better for the group discontinuing statin therapy (mean McGill QOL score, 7.11 vs 6.85; P = .04). Few participants experienced cardiovascular events (13 in the discontinuation group vs 11 in the continuation group).
Discussion:

Bottom line

- All medications should be repeatedly reviewed in the elderly.

Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials

Lancet 2019; 393: 407–15

Cholesterol Treatment Trialists' Collaboration*

NEW!

- **Objective**: compare the effects of statin therapy at different ages
- **Methods**: meta-analysis, randomized trials of statin therapy were eligible if they aimed to recruit at least 1000 participants with a scheduled treatment duration of at least 2 years.

Results: 14 483 (8%) of 186 854 participants in the 28 trials were older than 75 years at randomization , and the median follow-up duration was 4·9 years.

21% (RR 0·79, 95% CI 0·77–0·81) proportional reduction in major vascular events per 39 mg/dl reduction in LDL cholesterol across all age groups

24% (RR 0·76, 95% CI 0·73–0·79) proportional reduction in major coronary events per 39 mg/dl reduction in LDL, irrespective of age

The proportional reduction in major vascular events was similar, irrespective of age, among patients with pre-existing vascular disease (p=0·2), but *appeared smaller among older than among younger individuals not known to have vascular disease (p =0·05).*

Discussion: Statin therapy produces significant reductions in major vascular events irrespective of age, but there is less direct evidence of benefit among patients older than 75 years who do not already have evidence of occlusive vascular disease.

Bottom line: #1 statins work, #2 if no preexisting disease, >75yo, then benefit/risk discussion appropriate. Additional RCTs for this age group underway to help answer

Journal of the American Geriatrics Society

NEW!

The Association Between Low-Density Lipoprotein Cholesterol and Incident Atherosclerotic Cardiovascular Disease in Older Adults: Results From the National Institutes of Health Pooled Cohorts

Michael G. Nanna, MD, Ann Marie Navar, MD, PhD, Daniel Wojdyla, MSc, and Eric D. Peterson, MD, MPH

- Examined individual-level cohort data from the National Institutes of Health Pooled Cohorts (Framingham Study, Framingham Offspring Study, Multi-Ethnic Study of Atherosclerosis, and Cardiovascular Health Study), which prospectively measured CVD risk factors and incident disease. Elaluated associations between LDL-C and incident ASCVD (stroke, myocardial infarction, and cardiovascular death)
- Prospective cohort study, adults 75+
- Among adults without other risk factors (free of smoking, diabetes, and hypertension) AND with risk factors, event rates were similar between those with and without hyperlipidemia.

A Clinical Trial of STAtin Therapy for Reducing Events in the Elderly (STAREE) (STAREE)

- The STAREE study will examine whether treatment with statin (atorvastatin 40mg) compared with placebo will prolong overall survival or disability free survival amongst healthy elderly people (≥70 years).

Study Design

Study Type	Interventional (Clinical Trial)
Estimated Enrollment	18000 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose:	Prevention
Official Title:	A Study of STAtins for Reducing Events in the Elderly (STAREE)
Study Start Date	July 2015
Estimated Primary Completion Date	December 2022
Estimated Study Completion Date	December 2023

Effect of Bempedoic Acid vs Placebo Added to Maximally Tolerated Statins on Low-Density Lipoprotein Cholesterol in Patients at High Risk for Cardiovascular Disease
The CLEAR Wisdom Randomized Clinical Trial

JAMA. 2019;322(18):1780-1788.
JAMA

Anne C. Goldberg, MD[1]; Lawrence A. Leiter, MD[2]; Erik S. G. Stroes, MD, PhD[3]; et al

- **STUDY:** **NEW!!!!**
  - **QUESTION:** Compare the safety and efficacy of bempedoic acid compared with placebo among patients already on intensive or maximum-tolerated statin therapy.
  - **METHOD:** Patients were randomized in a 2:1 fashion to either bempedoic acid 180 mg or placebo once daily for 52 weeks. All patients were on maximal tolerated statin and other lipid-lowering therapy.
  - inclusion criteria:
    - Pre-existing atherosclerotic cardiovascular disease (ASCVD) and/or heterozygous familial hypercholesterolemia (FH)
    - Baseline low-density lipoprotein cholesterol (LDL-C) ≥100 mg/dl (2.6 mmol/L) at screening and ≥70 mg/dl (1.8 mmol/L) following placebo run-in while receiving maximally tolerated statins
- **RESULTS:**
  - The primary outcome, change in LDL-C at week 12 from baseline for bempedoic acid compared with placebo, was -15.1% vs. 2.4%, p < 0.001.
  - Serious side effects: 20.3% vs. 18.7%, p = 0.63
  - Three-point major adverse cardiac events: 2.7% vs. 4.7%, p > 0.05
- **DISCUSSION**: bempedoic acid is safe and effective in reducing LDL-C compared with placebo among patients with ASCVD or heterogeneous FH on maximum-tolerated statin therapy. No difference was noted for clinical outcomes, although the trial was not powered for this.
- **BOTTOM LINE: promsing new agent to add to arsenal as an add-on option for ASCVD patients not at goal on max-tolerated statin tx**

Effect of 1 or 2 Doses of Inclisiran on Low-Density Lipoprotein Cholesterol Levels
One-Year Follow-up of the ORION-1 Randomized Clinical Trial

JAMA Cardiology
JAMA Cardiol. 2019;4(11):1067-1075.

Kausik K. Ray, FRCP[1]; Robert M. Stoekenbroek, MD[2]; David Kallend, FRCS[2]; et al

NEW!!!

- STUDY:
  - QUESTION: Can inclisiran reduce mean low-density lipoprotein cholesterol (LDL-C) exposure with an infrequent dosing regimen, thereby offering sustained LDL-C lowering with infrequent dosing?
    - Inclisiran — a non–FDA-approved, long-acting, synthetic, small interfering RNA (siRNA) molecule — disrupts hepatic production of proprotein convertase subtilisin–kexin type 9 (PCSK9), an enzyme that binds to LDL particles.
  - METHOD: Prespecified analysis of a randomized, double-blind, placebo-controlled multicenter phase 2 clinical trial. Participants were followed up monthly for LDL-C levels and proprotein convertase subtilisin-kexin type 9 (PCSK9) measurements as well as safety until their LDL-C levels had returned to within 20% of their change from baseline (maximum 360 days). The study included patients with elevated LDL-C despite maximally tolerated statin therapy.
- DISCUSSION: Treatment with inclisiran resulted in durable reductions in LDL-C over 1 year. Inclisiran may offer a novel approach to LDL-C reduction with the convenience of infrequent dosing.
- **BOTTOM LINE: Could revolutionize lipid therapy for some patients. On the horizon as a potenial new agent in addition to currently available PCSK9i (Repatha, Praluent). expensive? YOU BET!!**

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association. Learn and Live.

Duration of Treatment With Nonsteroidal Anti-Inflammatory Drugs and Impact on Risk of Death and Recurrent Myocardial Infarction in Patients With Prior Myocardial Infarction : A Nationwide Cohort Study

Anne-Marie Schjerning Olsen, Emil L. Fosbøl, Jesper Lindhardsen, Fredrik Folke, Mette Charlot, Christian Selmer, Morten Lamberts, Jonas Bjerring Olesen, Lars Køber, Peter R. Hansen, Christian Torp-Pedersen and Gunnar H. Gislason

Circulation 2011, 123:2226-2235: May 9, 2011

QUESTION:
Are NSAID's safe in patients with prior MI?

STUDY:
Denmark, Pts >30 with first MI (1997-2006)
NSAID use monitored by national registry
Hazard ration of ~1.5 for NSAID use and death/recurrent MI
Ibuprofen and naproxen had lowest risk

TAKE HOME:
No! Avoid NSAIDs if possible in patients with CAD.
Use Naproxen (or Ibuprofen if they really need an NSAID

Say goodbye to warfarin

The NEW ENGLAND JOURNAL of MEDICINE
SEPTEMBER 17, 2009

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Question: Does this oral thrombin inhibitor prevent strokes in pts with Afib as good as warfarin?

Answer: Yes, but with increase dyspepsia and slight increase rates of MI (2 cases/1000 patients treated annually).

CONCLUSIONS

In patients with atrial fibrillation, dabigatran given at a dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage. Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage. (ClinicalTrials.gov number, NCT00262600.)

The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE

Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism

Sam Schulman, M.D., Clive Kearon, M.D., Ajay K. Kakkar, M.D., Patrick Mismetti, M.D., Sebastian Schellong, M.D., Henry Eriksson, M.D., David Baanstra, M.Sc., Janet Schnee, M.D., and Samuel Z. Goldhaber, M.D., for the RE-COVER Study Group*

QUESTION: Is dabigatran as effective as warfarin in treating VTE?

ANSWER: Yes.

Conclusion:
For the treatment of acute venous thromboembolism, a fixed dose of dabigatran is as effective (*recurrent VTE 2.4% vs 2.1%)*as warfarin, has a safety profile that is similar to that of warfarin, and does not require laboratory monitoring.

Oral Rivaroxaban for Symptomatic Venous Thromboembolism

The EINSTEIN Investigators*

N ENGL J MED 363;26 NEJM.ORG DECEMBER 23, 2010

Question: The "Acute DVT study" – Is fixed dose regimen of this direct factor Xa inhibitor as safe and efficacious as standard therapy with enoxaparin and warfarin for acute DVTs?

Answer: Yes

Take home: Look for this to gain FDA approval soon and supplant warfarin for DVT tx. No monitoring, safe, efficacious, pending further investigation. Goodbye rat poison!

CONCLUSIONS

Rivaroxaban offers a simple, single-drug approach to the short-term and continued treatment of venous thrombosis that may improve the benefit-to-risk profile of anticoagulation. (Funded by Bayer Schering Pharma and Ortho-McNeil; ClinicalTrials.gov numbers, NCT00440193 and NCT00439725.)

Lancet. 2014 Mar 15;383(9921):955-62. doi: 10.1016/S0140-6736(13)62343-0. Epub 2013 Dec 4.

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials.

Ruff CT[1], Giugliano RP[2], Braunwald E[2], Hoffman EB[2], Deenadayalu N[2], Ezekowitz MD[3], Camm AJ[4], Weitz JI[5], Lewis BS[6], Parkhomenko A[7], Yamashita T[8], Antman EM[2].

Author information

Abstract

BACKGROUND: Four new oral anticoagulants compare favourably with warfarin for stroke prevention in patients with atrial fibrillation; however, the balance between efficacy and safety in subgroups needs better definition. We aimed to assess the relative benefit of new oral anticoagulants in key subgroups, and the effects on important secondary outcomes.

METHODS: We searched Medline from Jan 1, 2009, to Nov 19, 2013, limiting searches to phase 3, randomised trials of patients with atrial fibrillation who were randomised to receive new oral anticoagulants or warfarin, and trials in which both efficacy and safety outcomes were reported. We did a prespecified meta-analysis of all 71,683 participants included in the RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI 48 trials. The main outcomes were stroke and systemic embolic events, ischaemic stroke, haemorrhagic stroke, all-cause mortality, myocardial infarction, major bleeding, intracranial haemorrhage, and gastrointestinal bleeding. We calculated relative risks (RRs) and 95% CIs for each outcome. We did subgroup analyses to assess whether differences in patient and trial characteristics affected outcomes. We used a random-effects model to compare pooled outcomes and tested for heterogeneity.

FINDINGS: 42,411 participants received a new oral anticoagulant and 29,272 participants received warfarin. New oral anticoagulants significantly reduced stroke or systemic embolic events by 19% compared with warfarin (RR 0·81, 95% CI 0·73-0·91; p<0·0001), mainly driven by a reduction in haemorrhagic stroke (0·49, 0·38-0·64; p<0·0001). New oral anticoagulants also significantly reduced all-cause mortality (0·90, 0·85-0·95; p=0·0003) and intracranial haemorrhage (0·48, 0·39-0·59; p<0·0001), but increased gastrointestinal bleeding (1·25, 1·01-1·55; p=0·04). We noted no heterogeneity for stroke or systemic embolic events in important subgroups, but there was a greater relative reduction in major bleeding with new oral anticoagulants when the centre-based time in therapeutic range was less than 66% than when it was 66% or more (0·69, 0·59-0·81 vs 0·93, 0·76-1·13; p for interaction 0·022). Low-dose new oral anticoagulant regimens showed similar overall reductions in stroke or systemic embolic events to warfarin (1·03, 0·84-1·27; p=0·74), and a more favourable bleeding profile (0·65, 0·43-1·00; p=0·05), but significantly more ischaemic strokes (1·28, 1·02-1·60; p=0·045).

INTERPRETATION: This meta-analysis is the first to include data for all four new oral anticoagulants studied in the pivotal phase 3 clinical trials for stroke prevention or systemic embolic events in patients with atrial fibrillation. New oral anticoagulants had a favourable risk-benefit profile, with significant reductions in stroke, intracranial haemorrhage, and mortality, and with similar major bleeding as for warfarin, but increased gastrointestinal bleeding. The relative efficacy and safety of new oral anticoagulants was consistent across a wide range of patients. Our findings offer clinicians a more comprehensive picture of the new oral anticoagulants as a therapeutic option to reduce the risk of stroke in this patient population.

Anticoagulant therapy for acute venous thrombo-embolism in cancer patients: A systematic review and network meta-analysis

PLOS ONE

Anne Rossel, Helia Robert-Ebadi, Christophe Combescure, Olivier Grosgurin, Jérôme Stirnemann, Alfredo Addeo, Nicolas Garin, Thomas Agoritsas, Jean-Luc Reny, Christophe Marti

Published: March 21, 2019 • https://doi.org/10.1371/journal.pone.0213940

New!

NEW STUDY

OBJECTIVE: compare the efficacy and safety of direct oral anticoagulants (DOAC), vitamin K antagonists (VKA) and LMWH in patients with CAT

METHOD: We searched Pubmed, Embase and CENTRAL for randomised controlled trials comparing DOAC, VKA and LMWH in patients with CAT. Pairwise and network meta-analyses were computed for venous thromboembolism (VTE) recurrence and bleeding complications.

RESULTS:

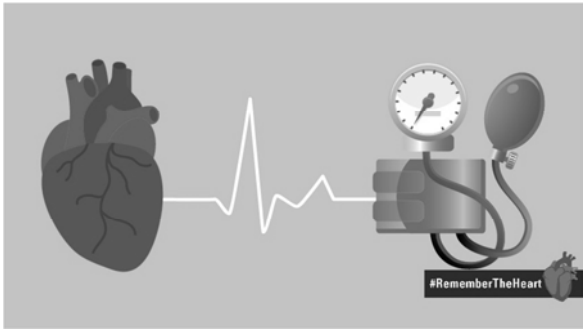
We identified 14 studies, including 4,661 patients.

- In pairwise comparison, DOAC were superior to LMWH to prevent VTE recurrence (HR 0.63; 95% CI 0.42–0.96) and LMWH was superior to VKA (HR 0.53; 95% CI 0.40–0.70).
- The rate of major bleeding was higher with DOAC compared to LMWH (HR 1.78; 95% CI 1.11–2.87).
- In the network meta-analysis, DOAC had a lower, but non-significant, rate of VTE recurrence compared to LMWH (HR 0.74; 95% CI 0.54–1.01).
- Both DOAC (HR 0.42; 95% CI 0.29–0.61) and LMWH (HR 0.57; 95% CI 0.44–0.75) were associated with lower rates of recurrence compared to VKA.
- No significant difference in major bleeding rate was observed in the network meta-analysis.

DISCUSSION: DOAC are effective to prevent VTE recurrence in patients with CAT but are associated with an increased risk of bleeding compared to LMWH. T

BOTTOM LINE: **DOACs are options, consider bleed risk and cancer type (avoid in GI cancers)**

Blood Pressure



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus

The ACCORD Study Group*

Published online March 14, 2010

Clinical Question

In patients with T2DM at high risk for CV events, does intensive BP control (SBP <120 mmHg) reduce rates of nonfatal MI, nonfatal stroke, or CV mortality when compared to standard BP control (SBP <140 mmHg)?

Bottom Line

In patients with T2DM at high risk for CV events, targeting SBP <120 mmHg did not reduce rates of nonfatal MI, nonfatal stroke, or CV mortality when compared to a target SBP <140 mmHg.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 26, 2015 VOL. 373 NO. 22

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

Clinical Question

In patients at high risk for CVD but who do not have a history of stroke or diabetes, does intensive BP control (target SBP <120 mm Hg) yield superior CV outcomes compared to standard treatment (target SBP 135-139 mm Hg)?

Bottom Line

In patients at high risk for CVD but who do not have a history of stroke or diabetes, intensive BP control (target SBP <120 mm Hg) improved CV outcomes and overall survival compared to standard therapy (target SBP 135-139 mm Hg), while modestly increasing the risk of some serious adverse events.

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 373;22 NEJM.ORG NOVEMBER 26, 2015

The SPRINT Research Group*

- **Objective**: To assess the benefit of treatment of systolic blood pressure to a target of less than 120 mm Hg with treatment to a target of less than 140 mm Hg.
- **Methods**: Randomly assigned (open label) 9361 adults with a systolic blood pressure of 130 mm Hg or higher and an increased cardiovascular risk, but without diabetes, to a systolic blood-pressure target of less than 120 mm Hg (intensive treatment) or a target of less than 140 mm Hg (standard treatment).

Results:

- SBP was 121.4 in the intensive treatment group and 136.2 in the standard Rx group. Stopped early at 3.26 years due to signif lower primary composite endpt and all-cause mortality
- Greater benefits seen in patients >75yo.
- Rates of serious adverse events of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure, but not of injurious falls, were higher in the intensive-treatment group than in the standard-treatment group.
- NNT to prevent a primary outcome in 3.25 years 61, all cause death 90, cardiovascular death 172.
- Intensive Rx group had more progression to CKD (GFR <60): 1.21% vs 0.35% per year (HR 3.49)

Discussion:

- Open label stopped early
- Contrast with the ACCORD Trial
- Large reduction in heart failure but not MI or CVA
- Excluded DM,
- Chlorthalidone not HCTZ

Bottom line: Treat healthy patients with high risk for CAD w/o DM more aggressively.

Title: 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

Authors: James PA, Oparil S, Carter BL, et al.

Citation: *JAMA* 2013;Dec 18:[Epub ahead of print]

1) In the general population **aged ≥60 years**, initiate pharmacologic treatment to lower blood pressure (BP) at systolic blood pressure (SBP) ≥150 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg and treat to a goal SBP <150 mm Hg and goal DBP <90 mm Hg. (**Strong Recommendation – Grade A**)

2) In the general population **aged ≥60 years**, if pharmacologic treatment for high BP results in lower achieved SBP (e.g., <140 mm Hg) and treatment is well tolerated and without adverse effects on health or quality of life, treatment does not need to be adjusted. (**Expert Opinion – Grade E**)

Hypertension

JACC

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

- "The new guidelines – the first comprehensive set since 2003 – lower the definition of high blood pressure …nearly half of the U.S. adult population (46 percent) having high blood pressure…triple among men under age 45…. However, only a small increase is expected in the number of adults requiring antihypertensive medication."
- "The new ACC/AHA guidelines were developed with nine other health professional organizations and were written by a panel of 21 scientists and health experts who reviewed more than 900 published studies."
- (From the ACC)

INFLUENCE OF CIRCADIAN TIME OF HYPERTENSION TREATMENT ON CARDIOVASCULAR RISK: RESULTS OF THE MAPEC STUDY

Journal
Chronobiology International
The Journal of Biological and Medical Rhythm Research
Volume 27, 2010 - Issue 8

Ramón C. Hermida, Diana E. Ayala, Artemio Mojón & José R. Fernández

- STUDY:
  - OBJECTIVE: The prospective MAPEC study was specifically designed to test the hypothesis that bedtime chronotherapy with ≥1 hypertension medications exerts better BP control and CVD risk reduction than conventional therapy, i.e., all medications ingested in the morning.
  - METHOD: 2156 hypertensive subjects, 1044 men/1112 women, 55.6 ± 13.6 (mean ± SD) yrs of age, median followup of 5.6yrs. Randomized to ingest all their prescribed hypertension medications upon awakening or ≥1 of them at bedtime.
- RESULTS:
  - median follow-up of 5.6 yrs, subjects ingesting ≥1 BP-lowering medications at bedtime exhibited a significantly lower relative risk of total CVD events than those ingesting all medications upon awakening (0.39 [0.29–0.51]; number of events 187 versus 68; $p < .001$)
  - The difference between the treatment-time groups in the relative risk of major events (including CVD death, myocardial infarction, ischemic stroke, and hemorrhagic stroke) was also highly statistically significant (0.33 [0.19–0.55]; number of events: 55 versus 18; $p < .001$).
- DISCUSSION: Bedtime chronotherapy with ≥1 BP-lowering medications, compared to conventional upon-waking treatment with all medications, more effectively improved BP control, better decreased the prevalence of non-dipping, and, most importantly, significantly reduced CVD morbidity and mortality.
- **BOTTOM LINE: Consider bedtime BP med dosing to improve control and outcomes – seems easy!**

ESC European Society of Cardiology
European Heart Journal (2019) 0, 1–12
doi:10.1093/eurheartj/ehz754
CLINICAL RESEARCH
Hypertension

NEW!

Bedtime hypertension treatment improves cardiovascular risk reduction: the Hygia Chronotherapy Trial

- 19 084 hypertensive patients were assigned (1:1) to ingest the entire daily dose of >_1 hypertension medications at bedtime (n = 9552) or all of them upon awakening (n = 9532).
- During the 6.3-year median patient follow-up, 1752 participants experienced the primary CVD outcome (CVD death, myocardial infarction, coronary revascularization, heart failure, or stroke). Patients of the bedtime, compared with the upon-waking, treatment-time regimen showed significantly lower hazard of the primary CVD outcome [0.55 (95% CI 0.50–0.61)]
- Bottom Line:
  - Take BP meds (and statins) before bed if possible.

JAMA Internal Medicine | Original Investigation

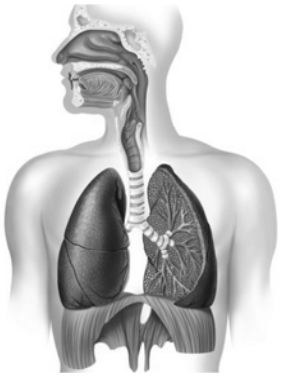
NEW!

Clinical Outcomes After Intensifying Antihypertensive Medication Regimens Among Older Adults at Hospital Discharge

Timothy S. Anderson, MD, MAS, MA; Bocheng Jing, MS; Andrew Auerbach, MD; Charlie M. Wray, DO, MS; Sei Lee, MD; W. John Boscardin, PhD; Kathy Fung, MS; Sarah Ngo, MLIS; Molly Silvestrini, BA; Michael A. Steinman, MD

- Retrospective review of VA patients 65 and older discharged 2011 – 2013.
- Reviewed intensification of BP medications upon discharge.
- 4056 hospitalized older adults with hypertension (mean [SD] age, 77 [8] years; 3961 me [97.7%]), equally split between those who did vs did not receive antihypertensive intensifications at hospital discharge.
- Within 30 days, patients receiving intensifications had a higher risk of readmission (haza ratio [HR], 1.23; 95%CI, 1.07-1.42; number needed to harm [NNH], 27; 95%CI, 16-76) a serious adverse events (HR, 1.41; 95%CI, 1.06-1.88; NNH, 63; 95%CI, 34-370).
- At 1 year, no differences were found in cardiovascular events (HR, 1.18; 95%CI, 0.99-1 or change in systolic BP among those who did vs did not receive intensifications (mean 134.7 vs 134.4; difference-in-differences estimate, 0.6mmHg; 95%CI, −2.4 to 3.7mmHg
- **BOTTOM LINE**
  - **Hospitalists are great at hospital medicine**

Respiratory



Annals of Internal Medicine
Vol. 163 No. 7 • 6 October 2015

Corticosteroid Therapy for Patients Hospitalized With Community-Acquired Pneumonia

A Systematic Review and Meta-analysis

Reed A.C. Siemieniuk, MD; Maureen O. Meade, MD; Pablo Alonso-Coello, MD, PhD; Matthias Briel, MD, MSc; Nathan Evaniew, MD; Manya Prasad, MBBS; Paul E. Alexander, MSc, PhD; Yutong Fei, MD, PhD; Per O. Vandvik, MD, PhD; Mark Loeb, MD, MSc; and Gordon H. Guyatt, MD, MSc

Study

- **Objective**: To examine the effect of adjunctive corticosteroid therapy on mortality, morbidity, and duration of hospitalization in patients with CAP.
- **Methods**: Prior (2010) Cochrane review, plus searched for articles from 2010 – 2015 on "pneumonia" and "corticosteroids". Excluded studies on ventilator assisted pneumonia and PCP. Identified 3281 citations, included 13 RCT's with 9 not included in the previous Cochrane review. Five of 13 studies had "low risk of bias" accounting for 70.4% of patients. Moderate heterogeneity.
- **Results:** Reduction in mortality (RR 0.67, ARR 2.6, NNT 38), Mechanical Ventilation (RR 0.45), ICU admissions (RR 0.69) and hospital days (by one day).

Discussion:

- Very promising, but small number of events limits external validity.
- Many patients were excluded from the studies.

Bottom line

- The more severe the pneumonia, the more likely to see benefit. Watch for complications!

JAMA The Journal of the American Medical Association
February 17, 2015 Volume 313, Number 7

Effect of Corticosteroids on Treatment Failure Among Hospitalized Patients With Severe Community-Acquired Pneumonia and High Inflammatory Response

A Randomized Clinical Trial

Study

- Objective: "To assess the effect of corticosteroids in patients with severe community-acquired pneumonia and high associated inflammatory response"
- Methods: Multicenter, randomized, double-blind placebo controlled study in 35 centers in Spain, June 2014 – Feb 2012. Adults with severe CAP (ATS criteria or risk class V for the pneumonia severity index) and a CRP >150. Appropriate exclusion (included uncontrolled DM). Randomized 1:1 to 0.5mg/kg methylprednisolone q12hr for 5 days or placebo, started within 36 hours of admission. Primary measure was treatment failure (early (<72hrs) , late (72-120hrs)).
- **Results**: Treatment failure was lower in the treatment group (13% vs3 1%), mortality not signif different (10% vs 15%, p=.37). Hyperglycemia was not signif different (18% vs 12%). NNT to prevent one treatment failure was 5.5.

Discussion:

- Primarily a reduction in progression of X-ray. While this has been correlated with worse outcomes, it's not a POEM.
- Use of CRP may not be needed (24% of screened patients didn't meet cut off).
- Almost half of screened patients with CAP were excluded. (uncontrolled DM, Flu, other)

Bottom line

- One more study suggesting that steroids are helpful in adult patients with severe CAP
- Consistent with "Surviving Sepsis Campaign" (2012) for ICU patients with pneumonia.

Antibiotic Treatment Strategies for Community-Acquired Pneumonia in Adults

Douwe F. Postma, M.D., Cornelis H. van Werkhoven, M.D., Leontine J.R. van Elden, M.D., Ph.D., Steven F.T. Thijsen, M.D., Ph.D., Andy I.M. Hoepelman, M.D., Ph.D., Jan A.J.W. Kluytmans, M.D., Ph.D., Wim G. Boersma, M.D., Ph.D., Clara J. Compaijen, M.D., Eva van der Wall, M.D., Jan M. Prins, M.D., Ph.D., Jan J. Oosterheert, M.D., Ph.D., and Marc J.M. Bonten, M.D., Ph.D., for the CAP-START Study Group*

The NEW ENGLAND JOURNAL of MEDICINE
N ENGL J MED 372;14 NEJM.ORG APRIL 2, 2015

Objective: We compared strategies of empirical treatment (allowing deviations for medical reasons) with beta-lactam monotherapy, beta-lactam–macrolide combination therapy, or fluoroquinolone monotherapy…in inpatient, non-ICU patients with CAP.

Methods: cluster-randomized, crossover trial with strategies rotated in 4-month periods, we tested the noninferiority of the beta-lactam strategy to the beta-lactam–macrolide and fluoroquinolone strategies with respect to 90-day mortality, in an intention-to-treat analysis, using a noninferiority margin of 3 percentage points and a two-sided 90% confidence interval.

Results: The crude 90-day mortality was 9.0% (59 patients), 11.1% (82 patients), and 8.8% (78 patients), respectively, during these strategy periods. In the intention-to-treat analysis, the risk of death was higher by 1.9 percentage points (90% confidence interval [CI], −0.6 to 4.4) with the beta lactam–macrolide strategy than with the beta-lactam strategy and lower by 0.6 percentage points (90% CI, −2.8 to 1.9) with the fluoroquinolone strategy than with the beta-lactam strategy. These results indicated noninferiority of the beta-lactam strategy.

Discussion: Among patients with clinically suspected CAP admitted to non-ICU wards, a strategy of preferred empirical treatment with beta-lactam monotherapy was noninferior to strategies with a beta-lactam–macrolide combination or fluoroquinolone monotherapy with regard to 90-day mortality.

Bottom line: In an age of increasing attention to judicious use of abx, perhaps beta-lactam is enough. Mounting evidence to show this.

NEW!

Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial

Jon Hardy*, Christina Baggott*, James Fingleton, Helen K Reddel, Robert J Hancox, Mattin Harwood, Andrew Corin, Jenny Sparks, Daniela Hall, Dorfah Sabbagh, Saras Mane, Alexandra Volikova, John Martindale, Matthew Williams, Philippa Shirtcliffe, Mark Holliday, Mark Weatherall, Richard Beasley, on behalf of the PRACTICAL study team†

- 52 week open label study in NZ, adults 18 – 75 with asthma using SABA's. Randomly assigned budesonide+formoterol prn versus scheduled budesonide + prn formoterol.
- Severe exacerbations per patient per year were lower with as-needed budesonide–formoterol than with maintenance budesonide plus terbutaline as needed (absolute rate per patient per year 0·119 *vs* 0·172; relative rate 0·69, 95% CI 0·48–1·00; p=0·049).
- Nasopharyngitis was the most common adverse event in both groups, occurring in 154 (35%) of 440 patients receiving as-needed budesonide–formoterol and 144 (32%) of 448 receiving maintenance budesonide plus terbutaline as needed.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

NEW!

Controlled Trial of Budesonide–Formoterol as Needed for Mild Asthma

- 52 week open label three group trial: albuterol as needed for asthma symptoms) (albuterol group); budesonide twice daily plus as-needed albuterol (budesonide maintenance group); or budesonide–formoterol as needed) (budesonide–formoterol group).
- The annualized exacerbation rate in the budesonide–formoterol group was lower than that in the albuterol group (absolute rate, 0.195 vs. 0.400; relative rate, 0.49; 95% confidence interval [CI], 0.33 to 0.72; P<0.001) and did not differ significantly from the rate in the budesonide maintenance.
- The number of severe exacerbations was lower in the budesonide–formoterol group than in both the albuterol group (9 vs. 23) and the budesonide maintenance group (9 vs. 21).

Pediatrics

Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy

The NEW ENGLAND JOURNAL of MEDICINE

George Du Toit, M.B., B.Ch., Graham Roberts, D.M., Peter H. Sayre, M.D., Ph.D., Henry T. Bahnson, M.P.P.
Suzana Radulovic, M.D., Alexandra F. Santos, M.D., Helen A. Brough, M.B., B.S., Deborah Phippard, Ph.D
Monica Basting, M.A., Mary Feeney, M.Sc., R.D., Victor Turcanu, M.D., Ph.D., Michelle L. Sever, M.S.P.H., Ph.D.,
Margarita Gomez Lorenzo, M.D., Marshall Plaut, M.D., and Gideon Lack, M.B., B.Ch., for the LEAP Study Team*

N ENGL J MED 372;9 NEJM.ORG FEBRUARY 26, 2015

Objective: evaluated strategies of peanut consumption and avoidance to determine which strategy is most effective in preventing the development of peanut allergy in infants at high risk for the allergy.
Methods: Randomly assigned 640 infants with severe eczema, egg allergy, or both to consume or avoid peanuts until 60 months of age. Participants 4 - 11 months of age at randomization were assigned cohorts based on skin testing to peanut extract. The primary outcome, which was assessed independently in each cohort, was the proportion of participants with peanut allergy at 60 months of age.
Results:

- Among the 530 infants in the intention-to-treat population who initially had negative results on the skin-prick test, the prevalence of peanut allergy at 60 months of age was 13.7% in the avoidance group and 1.9% in the consumption group (P<0.001).
- Among the 98 participants in the intention-to-treat population who initially had positive test results, the prevalence of peanut allergy was 35.3% in the avoidance group and 10.6% in the consumption group (P = 0.004).
- There was no significant between-group difference in the incidence of serious adverse events

Discussion:

- We've been moving in this direction for while.

Bottom line

- **Let them eat cake! (or at least peanut butter)**

JAMA | Original Investigation

Timing of Allergenic Food Introduction to the Infant Diet and Risk of Allergic or Autoimmune Disease
A Systematic Review and Meta-analysis

JAMA The Journal of the American Medical Association
JAMA. 2016;316(11):1181-1192.

Despo Ierodiakonou, MD, PhD;

Study

- **Objective**: To systematically review and meta-analyze evidence that timing of allergenic food introduction during infancy influences risk of allergic or autoimmune disease.
- **Methods**:

Meta-analysis of studies between 1946 and 2006 on the timing of introduction of "allergenic" food in the first year of life. Both intervention and observational studies. Outcome was reported allergic or autoimmune disease or allergic sensitization.
Results:

- Of 16 289 original titles screened, data were extracted from 204 titles reporting 146 studies. There was moderate-certainty evidence from 5 trials (1915 participants) that early egg introduction at 4 to 6 months was associated with reduced egg allergy
- There was moderate-certainty evidence from 2 trials (1550 participants) that early peanut introduction at 4 to 11 months was associated with reduced peanut allergy
- There was high-certainty evidence that timing of gluten introduction was not associated with celiac disease risk.

Discussion:
Significant limitations of this study include the fact that very few studies were found that adequately addressed the question. Also significant variability of the food preparations and the results (most found no benefit if early introduction). However no evidence was found that delaying introduction of peanut and egg based food was beneficial.

Bottom line: ***There doesn't seem to be any benefit in delaying introduction of peanuts and eggs past 4 months, and may be some benefit in early introduction.***

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Pacifier Restriction and Exclusive Breastfeeding

Laura R. Kair, Daniel Kenron, Konnette Etheredge, Arthur C. Jaffe and Carrie A. Phillipi

Pediatrics 2013;131;e1101; originally published online March 18, 2013;

- Common wisdom and academy recommendations hold that pacifier use interferes with establishing breastfeeding.
- A Cochrane Review of only 2 studies did not find an association.
- Another systematic review of 4 studies found mixed results.
- Study of 2249 infants before and after a pacifier restriction policy, comparing breast feeding rates.
- Before implementation 79% of babies were exclusively breastfed, 68% after.
- Breast plus formula increased from 18% to 28%.
- Exclusive bottle fed increased from 1.8% to 3.4%

- Caveats:
  - Before and after design
  - Increase in private insurance (39% to 45%)
  - Single institution

  - BOTTOM LINE: Let them pacify.

JAMA | Original Investigation

Association Between Early Participation in Physical Activity Following Acute Concussion and Persistent Postconcussive Symptoms in Children and Adolescents

JAMA The Journal of the American Medical Association
JAMA December 20, 2016 Volume 316, Number 23

Study
Objective: To investigate the association between participation in physical activity within 7 days postinjury and incidence of persistent postconcussive symptoms (PPCS)
Methods:

- Prospective, multicenter cohort study patients aged 5.00-17.99 years with acute concussion from 9 Canada network emergency departments (EDs

Results:

- 2413 participants. On unadjusted analysis, early physical activity participants had lower risk of PPCS than those with no physical activity (24.6%vs 43.5%; Absolute risk difference [ARD], 18.9%[95%CI,14.7%-23.0%]).

Discussion:
Cohort study – children were NOT assigned to activity levels (possible confounding)
No guidelines have been published since this study. CDC guidelines still recommend not progressing if any symptoms.
ASSM has not weighed in.
Many sports docs are slowly progressing activity if MILD symptoms.
Bottom line:
Probably better to resume mild activity early and to progress slowly.
Limit screen time!

Infectious Disease

Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*

The NEW ENGLAND JOURNAL of MEDICINE

Objective: We designed a multicontinental randomized study, Strategic Timing of Antiretroviral Therapy (START), to determine the risks and benefits of the immediate initiation of antiretroviral therapy in asymptomatic HIV-positive patients who have a CD4+ count of more than 500 cells per cubic millimeter, as compared with deferring initiation until the CD4+ count is 350 cells per cubic millimeter.

The START trial was designed and conducted by the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT).

Methods: 4685 patients were followed for a mean of 3.0 years, randomly assigned HIV-positive adults who had a CD4+ count of more than 500 cells per cubic millimeter to start antiretroviral therapy immediately (immediate-initiation group) or to defer it until the CD4+ count decreased to 350 cells per cubic millimeter or until the development of the acquired immunodeficiency syndrome (AIDS) or another condition that dictated the use of antiretroviral therapy (deferred-initiation group). The primary composite end point was any serious AIDS-related event, serious non–AIDS-related event, or death from any cause.

Results: The primary end point occurred in 42 patients in the immediate-initiation group (1.8%; 0.60 events per 100 person-years), as compared with 96 patients in the deferred-initiation group (4.1%; 1.38 events per 100 person-years), for a hazard ratio of 0.43 (95% confidence interval [CI], 0.30 to 0.62; P<0.001).

Discussion: On May 15, 2015, on the basis of an interim analysis, the data and safety monitoring board determined that the study question had been answered and recommended that patients in the deferred-initiation group be offered antiretroviral therapy.
Bottom line: Universal guidelines = start Anti-retroviral Tx (ART) at time of diagnosis.

Shortened Antimicrobial Treatment for Acute Otitis Media in Young Children

Alejandro Hoberman, M.D.

N Engl J Med 2016; 375:2446-2456

The NEW ENGLAND JOURNAL of MEDICINE

Study:

- **Objective**: Evaluate if limiting the duration of antimicrobial treatment in acute otitis media in young children constitutes a potential strategy to reduce the risk of antimicrobial resistance among children with acute otitis media.
- **Methods**: We assigned 520 children, 6 to 23 months of age, with acute otitis media to receive amoxicillin–clavulanate either for a standard duration of 10 days or for a reduced duration of 5 days followed by placebo for 5 days. We measured rates of clinical response (in a systematic fashion, on the basis of signs and symptomatic response), recurrence, and nasopharyngeal colonization, and we analyzed episode outcomes using a noninferiority approach. Symptom scores ranged from 0 to 14, with higher numbers indicating more severe symptoms

Results: Children who were treated with amoxicillin–clavulanate for 5 days were more likely than those who were treated for 10 days to have clinical failure (77 of 229 children [34%] vs. 39 of 238 [16%]; difference, 17 percentage points [based on unrounded data]; 95% confidence interval, 9 to 25).

Discussion: Among children 6 to 23 months of age with acute otitis media, reduced-duration antimicrobial treatment resulted in less favorable outcomes than standard-duration treatment; in addition, neither the rate of adverse events nor the rate of emergence of antimicrobial resistance was lower with the shorter regimen.

Bottom line: ***For now, 10 days appears to be the most effective duration for tx of young children for acute OM. (Didn't look at 7 days)***

Fluoroquinolone Antibacterial Drugs: Drug Safety Communication - FDA Advises Restricting Use for Certain Uncomplicated Infections

FDA U.S. FOOD & DRUG ADMINISTRATION

- **ISSUE**: FDA is advising that the serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections who have other treatment options. For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options.
- An FDA safety review has shown that fluoroquinolones when used systemically (i.e. tablets, capsules, and injectable) are associated with disabling and potentially permanent serious side effects that can occur together. These side effects can involve the tendons, muscles, joints, nerves, and central nervous system.
- **Health care professionals** should stop systemic fluoroquinolone treatment immediately if a patient reports serious side effects, and switch to a non-fluoroquinolone antibacterial drug to complete the patient's treatment course.

Bottom Line: ***We should not prescribe systemic fluoroquinolones to patients who have other treatment options for acute bacterial sinusitis (ABS), acute bacterial exacerbation of chronic bronchitis (ABECB), and uncomplicated urinary tract infections (UTI) because the risks outweigh the benefits*** in these patients. Stop fluoroquinolone treatment immediately if a patient reports serious side effects, and switch to a non-fluoroquinolone antibacterial drug to complete the patient's treatment course.

Diabetes

Effects of Intensive Glucose Lowering in Type 2 Diabetes

The Action to Control Cardiovascular Risk in Diabetes Study Group*

The NEW ENGLAND JOURNAL of MEDICINE

June 12, 2008

N Engl J Med 2008; 358:2545-2559

- **STUDY:**
  - **OBJECTIVE:** In patients with T2DM, does intensive glycemic control targeting a HbA1c <6% versus standard glycemic control targeting a HbA1c 7-7.9% reduce the risk of CV events?
  - **METHOD:**
    - Randomized 10,251 patients with long-standing T2DM to either intensive (HbA1c <6%) or standard glycemic control (HbA1c 7-7.9%).
    - a double 2x2 factorial design study. Half of the patients were randomized to fenofibrate add-on to a statin medication in ACCORD Lipid and half were randomized to a BP target in ACCORD BP.
  - **RESULTS:**
    - median follow-up of 3.7 years, the trial was stopped early because intensive glycemic control was associated with increased all-cause (1.41% vs. 1.14%; P=0.04; NNH 370) and CV mortality (0.79% vs. 0.56%; P=0.02).
- **DISCUSSION:** Intensive glycemic control in older patients with longstanding T2DM did not:
  - Prevent adverse CV events
  - Prevent major microvascular complications
  - Extend life
- And…did not enhance health-related quality life (*Diabetes Care*. 2011, Apr 34:807)
- **BOTTOM LINE: Overly aggressive glycemic management leads to worse outcomes**

Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes

The NEW ENGLAND JOURNAL of MEDICINE

June 12, 2008

N Engl J Med 2008; 358:2560-2572 The ADVANCE Collaborative Group*

- RCT, sulfonylurea-based intensive glycemic therapy targeting a HbA1c ≤6.5%, 10% reduction in combined micro- and macrovascular events compared with standard therapy. mostly reduced nephropathy, but no reduction in the risk of macrovascular events.
- In addition, intensive glycemic control was associated with an increased risk of severe hypoglycemia and an increased rate of hospitalization.
- **BOTTOM LINE: Intensive glycemic control targeting HbA1c ≤6.5% improves microvascular outcomes but has no impact on macrovascular outcomes in patients with T2DM.**

Follow-up of Blood-Pressure Lowering and Glucose Control in Type 2 Diabetes

Sophia Zoungas, M.D., Ph.D., John Chalmers, M.D., Ph.D., Bruce Neal, M.D., Ph.D., Laurent Billot, M.Sc., Qiang Li, M.Biostat., Yoichiro Hirakawa, M.D., Ph.D., Hisatomi Arima, M.D., Ph.D., Helen Monaghan, B.Sc., Rohina Joshi, M.D., Ph.D., Stephen Colagiuri, M.D., Ph.D., Mark E. Cooper, M.D., Ph.D., Paul Glasziou, M.D., Ph.D., et al., for the ADVANCE-ON Collaborative Group*

- post-trial follow-up for a median of 5.9 years (blood-pressure–lowering comparison) or 5.4 years (glucose-control comparison)
- There was no evidence that intensive glucose control during the trial led to long-term benefits with respect to mortality or macrovascular events.
- **BOTTOM LINE: No long-term benefit demonstrated**

Bariatric Surgery versus Intensive Medical Therapy for Diabetes — 5-Year Outcomes

Philip R. Schauer, M.D., Deepak L. Bhatt, M.D., M.P.H., John P. Kirwan, Ph.D., Kathy Wolski, M.P.H., Ali Aminian, M.D., Stacy A. Brethauer, M.D., Sankar D. Navaneethan, M.D., M.P.H., Rishi P. Singh, M.D., Claire E. Pothier, M.P.H., Steven E. Nissen, M.D., and Sangeeta R. Kashyap, M.D., for the STAMPEDE Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

N ENGL J MED 376;7 NEJM.ORG FEBRUARY 16, 2017

Study

- **Background/Objective:** Long-term results from randomized, controlled trials that compare medical therapy with surgical therapy in patients with type 2 diabetes are limited
- **Methods**: Three-group, randomized, controlled, nonblinded, single-center study involving 150 obese patients who had type 2 diabetes,
- **Results**
- All measures improved more in the surgical groups than in the medical groups, with gastric bypass superior to sleeve gastrectomy (HbA1c 7.0 vs 8.5, wt loss 5.3kg vs 23.2)
- **Discussion**:
- Nonblinded study at one center, only 150 patents.
- Although the results are impressive, they were almost all DOE's (HbA1c, Lipids). No difference in retinopathy. QALY was somewhat better in the surgical groups.

Bottom line: Surgery beats medical therapy for many patients with diabetes and obesity.

Cancer

Breast Cancer Mortality After a Diagnosis of Ductal Carcinoma In Situ

Steven A. Narod, MD, FRCPC; Javaid Iqbal, MD; Vasily Giannakeas, MPH; Victoria Sopik, MSc; Ping Sun, PhD

JAMA The Journal of the American Medical Association

JAMA Oncol. doi:10.1001/jamaoncol.2015.2510 Published online August 20, 2015.

Study

- **Objective**: To estimate the 10 and 20 year mortality from DCIS and to establish if the mortality rate is influenced by age, ethnicity and initial treatment.
- **Methods**: Observational study of women with the Dx of DCIS from 1988 to 2011 (10,196 women) using SEER data. Risk of dying was compared with that of women in general population.

Results:

- Mean age of Dx was 53.8 years and mean duration of follow-up was 7.5 years.
- 20 year breast cancer mortality was 3.3%, and was higher for younger women at time of Dx (HR 2.58) and for black women (HR 2.42).
- At 10 years radiation therapy in addition to lumpectomy reduced ipsalateral invasive recurrence (2.5% vs 4.9%) but not breast cancer specific death (0.8% vs 0.9%).
- The risk of ipsilateral invasive recurrence at 20 years was 5.9% and the risk of contralateral invasive recurrence was 6.2%.

Discussion:

- Observational study
- Lower mortality from DCIS than previous studies (overdiagnosis more likely than better RX since no mortality difference based on Rx type)

Bottom line

- Evolving approach to DCIS, much like prostate cancer. Aggressive Rx doesn't appear to alter mortality
- Need to better distinguish high risk lesions
- Modify risk factors: obesity, HRT, alcohol,

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 4, 2011 VOL. 365 NO. 5

Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team*

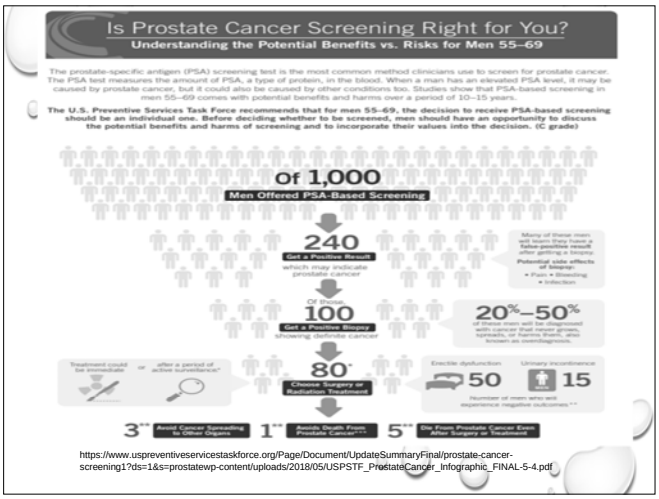
QUESTION:
Does annual low dose CT scanning in current or former smokers reduce lung-CA mortality?

Study: RCT, 53,454 current or former smokers aged 55-74 years randomly assigned to undergo three annual screenings with either low-dose CT (26,722 participants) or single-view posteroanterior chest radiography (26,732). Data were collected on cases of lung cancer and deaths from lung cancer that occurred through December 31, 2009.

TAKE HOME, Does annual low dose CT scanning in current or former smokers reduce lung-CA mortality?

YES…1.33% vs 1.66% lung-cancer specific mortality rate. Number needed to screen to prevent 1 lung cancer death about 320.

But…High false positive rate can lead to high costs and morbidity related to screening and its sequelae. Perhaps a cost-effectiveness analysis first?



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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Screening and Prostate-Cancer Mortality in a Randomized European Study

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D., Teuvo L.J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Marcos Lujan, M.D., Hans Lilja, M.D., Marco Zappa, Ph.D., Louis J. Denis, M.D., Franz Recker, M.D., Antonio Berenguer, M.D., Liisa Määttänen, Ph.D., Chris H. Bangma, M.D., Gunnar Aus, M.D., Arnauld Villers, M.D., Xavier Rebillard, M.D., Theodorus van der Kwast, M.D., Bert G. Blijenberg, Ph.D., Sue M. Moss, Ph.D., Harry J. de Koning, M.D., and Anssi Auvinen, M.D., for the ERSPC Investigators*

N Engl J Med 2009;360:1320-8.

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)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mortality Results from a Randomized Prostate-Cancer Screening Trial

Gerald L. Andriole, M.D., E. David Crawford, M.D., Robert L. Grubb III, M.D., Saundra S. Buys, M.D., David Chia, Ph.D., Timothy R. Church, Ph.D., Mona N. Fouad, M.D., Edward P. Gelmann, M.D., Paul A. Kvale, M.D., Douglas J. Reding, M.D., Joel L. Weissfeld, M.D., Lance A. Yokochi, M.D., Barbara O'Brien, M.P.H., Jonathan D. Clapp, B.S., Joshua M. Rathmell, M.S., Thomas L. Riley, B.S., Richard B. Hayes, Ph.D., Barnett S. Kramer, M.D., Grant Izmirlian, Ph.D., Anthony B. Miller, M.B., Paul F. Pinsky, Ph.D., Philip C. Prorok, Ph.D., John K. Gohagan, Ph.D., and Christine D. Berg, M.D., for the PLCO Project Team*

N Engl J Med 2009;360:1310-9.

Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomized controlled trials.
Ronco G, et al. The international HPV screening working group. *Lancet,* 2013 Nov

PURPOSE: To find out whether HPV testing offered any advantages over cytology in detecting invasive cancer,

METHOD:: Four large trials have compared the two methods of screening. These were conducted in England (the ARTISTIC trial), Sweden (Swedescreen), the Netherlands (POBASCAM), and Italy (NTCC). Reseachers combined the individual patient data from the 176 000 women involved in the trials and followed them for an average of 6.5 years.

FINDINGS: They identified 107 invasive cervical carcinomas and found that overall the detection of cancer was significantly higher in the women who had undergone HPV testing than in those who had smear tests (rate ratio of cancer detection with HPV versus cytology 0.6 (95% confidence interval 0.4 to 0.89).[1]

INTERPRETATION: HPV-based screening provides 60-70% greater protection against invasive cervical carcinomas compared with cytology. Data of large-scale randomized trials support initiation of HPV-based screening from age 30 years and extension of screening intervals to at least 5 years.

Primary cervical screening with high risk human papillomavirus testing: observational study

thebmj

Matejka Rebolj,[1,2] Janet Rimmer,[3] Karin Denton,[4,5] John Tidy,[6] Christopher Mathews,[1,2] Kay Ellis,[7] John Smith,[7] Chris Evans,[8] Thomas Giles,[8] Viki Frew,[9] Xenia Tyler,[9] Alexandra Sargent,[10] Janet Parker,[11] Miles Holbrook,[11] Katherine Hunt,[5] Penny Tidbury,[5] Tanya Levine,[12] David Smith,[12] Julietta Patnick,[13] Ruth Stubbs,[3] Sue Moss,[1] Henry Kitchener[14]

NEW!

What: Observational study of 578,547 women 2013-2014 screened for with cytology or HPV testing.
Results: HPV testing led to 80% more colposcopies but detected more CIN 3 or worse (40% increase) and more cervical cancer (30% increase).

ACOG:
Women aged 21–29 years should have a Pap test alone every 3 years. HPV testing is not recommended.
Women aged 30–65 years should have a Pap test and an HPV test (***co-testing***) every 5 years (preferred). It also is acceptable to have a Pap test alone every 3 years.

Take Home: May be time to change guidelines???

Ann Intern Med. 2014 Jul 1;161(1):46-53. doi: 10.7326/M13-2881.

Screening pelvic examinations in asymptomatic, average-risk adult women: an evidence report for a clinical practice guideline from the American College of Physicians.

Bloomfield HE, Olson A, Greer N, Cantor A, MacDonald R, Rutks I, Wilt TJ.

Abstract

BACKGROUND: Pelvic examination is often included in well-woman visits even when cervical cancer screening is not required.

PURPOSE: To evaluate the diagnostic accuracy, benefits, and harms of pelvic examination in asymptomatic, nonpregnant, average-risk adult women. Cervical cancer screening was not included.

DATA SOURCES: MEDLINE and Cochrane databases through January 2014 and reference lists from identified studies.

STUDY SELECTION: 52 English-language studies, 32 of which included primary data.

DATA EXTRACTION: Data were extracted on study and sample characteristics, interventions, and outcomes. Quality of the diagnostic accuracy studies was evaluated using a published instrument, and quality of the survey studies was evaluated with metrics assessing population representativeness, instrument development, and response rates.

DATA SYNTHESIS: The positive predictive value of pelvic examination for detecting ovarian cancer was less than 4% in the 2 studies that reported this metric. No studies that investigated the morbidity or mortality benefits of screening pelvic examination for any condition were identified. The percentage of women reporting pelvic examination–related pain or discomfort ranged from 11% to 60% (median, 35%; 8 studies [n = 4576]). Corresponding figures for fear, embarrassment, or anxiety ranged from 10% to 80% (median, 34%; 7 studies [n = 10 702]).

LIMITATION: Only English-language publications were included; the evidence on diagnostic accuracy, morbidity, and mortality was scant; and the studies reporting harms were generally low quality.

CONCLUSION: No data supporting the use of pelvic examination in asymptomatic, average-risk women were found. Low-quality data suggest that pelvic examinations may cause pain, discomfort, fear, anxiety, or embarrassment in about 30% of women.

PRIMARY FUNDING SOURCE: Department of Veterans Affairs.

Ann Intern Med. 2014 Jul 1;161(1):67-72. doi: 10.7326/M14-0701.

Screening pelvic examination in adult women: a clinical practice guideline from the American College of Physicians.

Qaseem A, Humphrey LL, Harris R, Starkey M, Denberg TD; Clinical Guidelines Committee of the American College of Physicians.

Collaborators (13)

Abstract

DESCRIPTION: The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on the utility of screening pelvic examination for the detection of pathology in asymptomatic, nonpregnant, adult women.

METHODS: This guideline is based on a systematic review of the published literature in the English language from 1946 through January 2014 identified using MEDLINE and hand-searching. Evaluated outcomes include morbidity; mortality; and harms, including overdiagnosis, overtreatment, diagnostic procedure-related harms, fear, anxiety, embarrassment, pain, and discomfort. The target audience for this guideline includes all clinicians, and the target patient population includes asymptomatic, nonpregnant, adult women. This guideline grades the evidence and recommendations using the ACP's clinical practice guidelines grading system.

RECOMMENDATION: ACP recommends against performing screening pelvic examination in asymptomatic, nonpregnant, adult women (strong recommendation, moderate-quality evidence).

Screening for Gynecologic Conditions With Pelvic Examination: A Systematic Review for the U.S. Preventive Services Task Force

U.S. Preventive Services TASK FORCE

- **Objective:** To systematically review literature on health benefits, accuracy, and harms of the screening pelvic examination for gynecologic conditions for the US Preventive Services Task Force (USPSTF).
- **Data Sources:** MEDLINE, PubMed, and Cochrane Central Register of Controlled Trials for relevant English-language studies published through January 13, 2016, with surveillance through August 3, 2016.
- **Study Selection:** Two reviewers independently screened abstracts and studies. The search yielded 8678 unique citations; 316 full-text articles were reviewed, and 9 studies including 27,630 patients met inclusion criteria.
- **Main Outcomes and Measures:** Morbidity; mortality; diagnostic accuracy for any gynecologic cancer or condition except cervical cancer, gonorrhea, and chlamydia, which are covered by other USPSTF screening recommendations; harms (false-positive rates, false-negative rates, surgery rates).
- **Results:** No trials examined the effectiveness of the pelvic examination in reducing all-cause mortality, reducing cancer- and disease-specific morbidity and mortality, or improving quality of life.
- **BOTTOM LINE: No direct evidence was identified for overall benefits and harms of the pelvic examination as a 1-time or periodic screening test. Limited evidence was identified regarding the diagnostic accuracy and harms of routine screening pelvic examinations in asymptomatic primary care populations. How has this changed your practice?**

Original Investigation | Less Is More

ONLINE FIRST

January 6, 2020

Prevalence of Potentially Unnecessary Bimanual Pelvic Examinations and Papanicolaou Tests Among Adolescent Girls and Young Women Aged 15-20 Years in the United States

New!

Jin Qin, ScD[1]; Mona Saraiya, MD, MPH[1]; Gladys Martinez, PhD[2]; et al

Key Points

Question What is the prevalence of potentially unnecessary bimanual pelvic examinations and Papanicolaou tests among US women aged 15 to 20 years?

Findings In this population-based, cross-sectional study using data from 2011 to 2017, an estimated 2.6 million women aged 15 to 20 years in the United States (22.9%) received a bimanual pelvic examination in the past year, and 54.4% of these examinations were potentially unnecessary. An estimated 2.2 million young women (19.2%) received a Papanicolaou test in the past year, and 71.9% of these tests were potentially unnecessary.

Meaning The findings suggest that many young women receive potentially unnecessary bimanual pelvic examinations and Papanicolaou tests.

CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016

JAMA

Deborah Dowell, MD, MPH; Tamara M. Haegerich, PhD; Roger Chou, MD

JAMA. 2016;315(15):1624-1645. doi:10.1001/jama.2016.1464
Published online March 15, 2016.

1. Nonpharmacological (e.g. exercise, cognitive behavioral therapy) and non-opioid pharmacological therapies are preferred for managing chronic pain.
2. Opioids should be prescribed only after setting clear treatment goals focused on both improving function and decreasing pain.
3. Risks of opioid use for chronic pain should be discussed explicitly.
4. Immediate-release opioids are strongly, if not exclusively, preferred over extended-release or long-acting opioids; methadone is not the preferred choice for a long-acting opioid and should only be used by clinicians with special expertise.
5. Clinicians should initiate opioids at the lowest effective dose. When dosage must be escalated, doses should be limited to 50 MMEs (morphine mg equivalents; 50 MMEs=50 mg of hydrocodone or 33 mg of oxycodone) daily in most circumstances, and 90 MMEs daily without special justification.
6. Opioid prescriptions for acute pain should be limited to 3 days in most circumstances.
7. Benefits and harms of opioid therapy should be reviewed within 1 to 4 weeks of starting therapy or increasing dose and regularly thereafter.

CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016

Deborah Dowell, MD, MPH; Tamara M. Haegerich, PhD; Roger Chou, MD

8. Opioid use should be avoided in patients with sleep-disordered breathing or with renal or hepatic insufficiency, in those who are pregnant, and in elders (age, ≥65). **Clinicians should consider making naloxone available for patients at high risk for overdose.**

9. Data from state prescription monitoring programs should be reviewed at the initiation of opioid therapy and periodically thereafter.

10. Clinicians should consider using urine drug testing at initiation of opioid therapy and periodically thereafter.

11. Concomitant benzodiazepine use increases risk for overdose and should be avoided.

12. Clinicians should monitor patients for opioid-use disorder (addiction or excessive use) and arrange for evidence-based treatment as needed.

Bottom Line:

"The important question is not whether opioids are contraindicated by regulation, but whether opioids are likely to return the patient to a state of functional behavior or have a role in helping them maintain their independence and daily activities."

In 2015: 23,000 deaths, surpasses MVAs as leading cause of accidental deaths in USA.

"Opioid use in chronic non-cancer pain leads to substantial excess mortality from both overdose and other causes. Implementing and adhering to CDC guideline is a good way to start addressing these issues."

Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes

BMJ 2017 ; 359 doi: https://doi.org/10.1136/bmj.j5024 (Published 22 November 2017)
Cite this as: *BMJ* 2017;359:j5024

thebmj

- **Objectives** To evaluate the existing evidence for associations between coffee consumption and multiple health outcomes.
- **Results** The umbrella review identified 201 meta-analyses of observational research with 67 unique health outcomes and 17 meta-analyses of interventional research with nine unique outcomes.
- Daily consumption of 3 cups of coffee — regular or decaffeinated — was associated with a 17% lower risk for all-cause mortality, relative to no coffee consumption.
- Caffeinated coffee was linked to lower risks for cardiovascular disease, coronary heart disease, and stroke, with benefits highest at 3–5 cups daily.
- Both regular and decaf coffee appeared to lower risk for type 2 diabetes.
- In terms of harms, high coffee consumption in pregnancy was tied to pregnancy loss, low birth weight, and preterm birth. High consumption was also associated with higher fracture risk in women, but not men.
- **Bottom line: Coffee consumption seems generally safe within usual levels of intake,**
- **Editorial comment: "The evidence is so robust and consistent ... that we can be reassured that drinking coffee is generally safe."**

Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century

PNAS

Anne Case[1] and Angus Deaton[1]

Woodrow Wilson School of Public and International Affairs and Department of Economics, Princeton University, Princeton, NJ 08544

Background: Between 1970 and 2013, a combination of behavioral change, prevention, and treatment brought down mortality rates for those aged 45–54 by 44%.

Results: This paper documents a marked increase in the all-cause mortality of middle-aged white non-Hispanic men and women in the United States between 1999 and 2013.

This increase for whites was largely accounted for by increasing death rates from **drug and alcohol poisonings, suicide, and chronic liver diseases and cirrhosis.**

If the white mortality rate for ages 45−54 had held at their 1998 value, 96,000 deaths would have been avoided from 1999–2013, 7,000 in 2013 alone. If it had continued to decline at its previous (1979–1998) rate, half a million deaths would have been avoided in the period 1999–2013, comparable to lives lost in the US AIDS epidemic through mid-2015.

Although all three educational groups saw increases in mortality from suicide and poisonings, and an overall increase in external cause mortality, **increases were largest for those with the least education**. The mortality rate from poisonings rose more than fourfold for this group, from 13.7 to 58.0, and mortality from chronic liver diseases and cirrhosis rose by 50%.

A serious concern is that those currently in midlife will age into Medicare in worse health than the currently elderly.

Changes in midlife death rates across racial and ethnic groups in the United States: systematic analysis of vital statistics

Steven H Woolf,[1] Derek A Chapman,[1] Jeanine M Buchanich,[2] Kendra J Bobby,[2] Emily B Zimmerman,[1] Sarah M Blackburn[1]

thebmj
2018;362:k3096

New!

- Trend analysis of US vital statistics among racial and ethnic groups.1999 – 2016
- Mortality in midlife in the US has increased across racial-ethnic populations for a variety of conditions

The Depths of Despair Among US Adults Entering Midlife

Lauren Gaydosh PhD, Robert A. Hummer PhD, Taylor W. Hargrove PhD, Carolyn T. Halpern PhD, Jon M. Hussey PhD, Eric A. Whitsel MD, Nancy Dole ... (show all authors)

AJPH

- National Longitudinal Study of Adolescent to Adult Health, of US adolescents who participated in 1 or more of 5 waves (1994–2017)
- We found evidence of rising despair among this cohort over the past decade. This increase was not restricted to low-educated Whites or to rural areas

Thank you!