Learning Objectives

Discuss recent research important for family physicians to update their diagnostic and treatment approaches to allergies, cardiovascular disease, hypertension, diet, pediatrics, diabetes, imaging and vitamin therapy. Objectives for each presentation are listed at the beginning of each talk. The presentations are based on a literature review of recently published research studies and meta-analyses. Evidence sources include PubMed, InfoPoems and Cochrane systematic reviews. These updates are not intended to be comprehensive reviews but updates of the current knowledge base.

Faculty

**Gary Ferenchick, MD, MS.** is Professor of Medicine at Michigan State University College of Human Medicine, where he practices general internal medicine and is deeply involved in MSU-CHM major curriculum renovation. He earned his master’s degree in human nutrition and medical degree from Michigan State University and completed his residency training in internal medicine at Michigan State University College of Human Medicine, where he has been a faculty member for over 25 years. Dr. Ferenchick is a Past-President of the Clerkship Directors in Internal Medicine. His research interest is the interface between medical education and information technology.

**John Hickner, MD, MS.** is Professor and Head of Family Medicine at the University of Illinois at Chicago and Editor-in-Chief of the *Journal of Family Practice*. After receiving his medical degree from Indiana University School of Medicine, Dr. Hickner completed his residency in family medicine at the Medical University of South Carolina and received a master’s degree in Biostatistics and Research Design from the University of Michigan School of Public Health. His main research focus is patient safety, especially testing safety and medication safety in primary care practice.

Speaker and Faculty Disclosures

*John Hickner* disclosed no relevant financial relationship or interest with a proprietary entity producing health care goods or services.

*Gary Ferenchick* disclosed no relevant financial relationship or interest with a proprietary entity producing health care goods or services.

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Objectives
1. Learn the importance of patient oriented evidence for interpreting medical studies
2. Learn an efficient way to search PubMed for clinically relevant information

Usefulness of medical information = (relevance x validity) / work

Relevance is a continuum:
Rat studies Surrogates Disease-specific All-cause mortality/QOL

Validity is a continuum:
Case study Case-control Cohort RCT Systematic review

Patient oriented evidence: anything that helps patients live a longer or better life.

Disease oriented evidence: everything else; surrogate or physiologic markers

POEM (Patient Oriented Evidence that Matters): a study that addresses a common or important condition, demonstrates improved patient oriented outcomes, and matters because it would change what we do.

Evidence-based sources to explore:
- Essential Evidence: www.essentialevidence.com
- Clinical Evidence: www.clinicalevidence.com
- Cochrane Library: www.cochrane.org
- DynaMed: www.dynamicmedical.com
- TRIP Database: www.tripdatabase.com
- Bandolier: www.medicine.ox.ac.uk/bandolier/

Search hints
- Use Clinical Queries at the PubMed site
- Select “Narrow” filter
- Use quotes to narrow search to only those words appearing next to each other, i.e. “acute bronchitis” eliminates “acute exacerbation of chronic bronchitis”
- Combination of drug and disease is useful: “acute bronchitis” azithromycin; “infectious mononucleosis” corticosteroid; influenza osletamivir
- Optionally, “See all” and then add additional limits (English, abstract, human)
- Use “Not” terms to exclude groups of articles
- Then, select “Related articles” once you have a good hit.
Allergic Conditions

John Hickner, MD, MS

Objectives

1. Describe the natural history of childhood milk, egg, and peanut allergies

2. Discuss the evidence for the effectiveness of several interventions for food allergies, especially peanuts.

3. Review miscellaneous recent studies regarding allergic conditions commonly seen by family physicians and other primary care clinicians

Allergic conditions are one of the most common issues confronting primary care clinicians. This chapter is not intended as a comprehensive review of allergies, but it provides a summary of the most recent published studies regarding childhood food allergies and several other important allergy updates. It is important to understand the natural history of allergic conditions before one can judge the effectiveness of treatments.

What is the natural history of milk, egg, and peanut allergies in children?

1. The natural history of milk allergy in an observational cohort

OBJECTIVE: There are few studies on the natural history of milk allergy. Most are single-site and not longitudinal, and these have not identified a means for early prediction of outcomes.

METHODS: Children aged 3 to 15 months were enrolled in an observational study with either: (1) a convincing history of egg allergy, milk allergy, or both with a positive skin prick test (SPT) response to the trigger food and/or (2) moderate-to-severe atopic dermatitis (AD) and a positive SPT response to milk or egg. Children enrolled with a clinical history of milk allergy were followed longitudinally, and resolution was established by means of successful ingestion.

RESULTS: The cohort consists of 293 children, of whom 244 were given a diagnosis of milk allergy at baseline. Milk allergy has resolved in 154 (52.6%) subjects at a median age of 63 months and a median age at last follow-up of 66 months. Baseline characteristics that were most predictive of resolution included milk-specific IgE level, milk SPT wheal size, and AD severity (all P < .001). Baseline milk-specific IgG4 level and milk IgE/IgG4 ratio were not predictive of resolution and neither was expression of cytokine-inducible SH2-containing protein, forkhead box protein 3, GATA3, IL-10, IL-4, IFN-γ, or T-bet by using real-time PCR in CD25-selected, casein-stimulated mononuclear cells. A calculator to estimate resolution probabilities using baseline milk IgE level, SPT response, and AD severity was devised for use in the clinical setting.

CONCLUSIONS: In this cohort of infants with milk allergy, approximately one half had resolved over 66 months of follow-up. Baseline milk-specific IgE level, SPT wheal size, and AD severity were all important predictors of the likelihood of resolution.


2. The natural history of egg allergy in an observational cohort

BACKGROUND: There are few studies on the natural history of egg allergy, and most are single-site and non-longitudinal and have not identified early predictors of outcomes.

OBJECTIVE: We sought to describe the natural course of egg allergy and to identify early prognostic markers.

METHODS: Children aged 3 to 15 months were enrolled in a multicenter observational study with either (1) a convincing history of an immediate allergic reaction to egg, milk, or both with a positive skin prick test (SPT) response to the trigger food and/or (2) moderate-to-severe atopic dermatitis and a positive SPT response to egg or milk. Children enrolled with a clinical history of egg allergy were followed longitudinally, and resolution was established based on successful ingestion.

RESULTS: The cohort with egg allergy consists of 213 children followed to a median age of 74 months. Egg allergy resolved in 105 (49.3%) children at a median age of 72 months. Factors that were most predictive of resolution included the following: initial reaction characteristics (isolated urticaria/angioedema vs other presentations), baseline egg-specific IgE level, egg SPT wheal size, atopic dermatitis severity, IgG4 level, and IL-4 response (all P < .05). Numerous additional baseline clinical and demographic factors and laboratory assessments were not associated with resolution. Multivariate analysis identified baseline egg-specific IgE levels and initial reaction characteristics as strongly associated with resolution; a calculator to estimate resolution probabilities using these variables was established.

CONCLUSIONS: In this cohort of infants with egg allergy, approximately one half had resolved over 74 months of follow-up. Baseline egg-specific IgE levels and initial reaction characteristics were important predictors of the likelihood of resolution.

3. The natural history and clinical predictors of egg allergy in the first 2 years of life: a prospective, population-based cohort study

BACKGROUND: There is a paucity of data examining the natural history of and risk factors for egg allergy persistence, the most common IgE-mediated food allergy in infants.

OBJECTIVE: We aimed to assess the natural history of egg allergy and identify clinical predictors for persistent egg allergy in a population-based cohort.

METHODS: The HealthNuts study is a prospective, population-based cohort study of 5276 infants who underwent skin prick tests to 4 allergens, including egg. Infants with a detectable wheal were offered hospital-based oral food challenges (OFCs) to egg, irrespective of skin prick test wheal sizes. Infants with challenge-confirmed raw egg allergy were offered baked egg OFCs at age 1 year and follow-up at age 2 years, with repeat OFCs to raw egg.

RESULTS: One hundred forty infants with challenge-confirmed egg allergy at age 1 year participated in the follow-up. Egg allergy resolved in 66 (47%) infants (95% CI, 37% to 56%) by 2 years of age; however, resolution was lower in children with baked egg allergy at age 1 year compared with baked egg tolerance (13% and 56%, respectively; adjusted odds ratio, 5.27; 95% CI, 1.36-20.50; P = .02). In the subgroup of infants who were tolerant to baked egg at age 1 year, frequent ingestion of baked egg (≥5 times per month) compared with infrequent ingestion (0-4 times per month) increased the likelihood of tolerance (adjusted odds ratio, 3.52; 95% CI, 1.38-8.98; P = .009). Mutation in the filaggrin gene was not associated with the resolution of either egg allergy or egg sensitization at age 2 years.

CONCLUSION: Phenotyping of egg allergy (baked egg tolerant vs allergic) should be considered in the management of this allergy because it has prognostic implications and eases dietary restrictions. Randomized controlled trials for egg oral immunotherapy should consider stratifying at baseline by the baked egg subphenotype to account for the differential rate of tolerance development.


4. Peanut allergy resolves in approximately 1 in 5 children in the first 4 years of life

Clinical question: What is the natural history of peanut allergy in the first 4 years of life?

Study design: Cohort (prospective)

Setting: Population-based

Synopsis: In conjunction with the Australian HealthNuts study, these investigators analyzed data obtained from 5276 twelve-month-old infants who underwent skin prick test screening to 4 common food allergens, including peanut. Infants with a detectable skin prick test response (equal to or greater than 1 mm) were referred for a formal OFC. Individuals masked to skin prick test results performed the OFCs and classified the results as positive or negative, based on standard diagnostic criteria. All children with a positive OFC result at age 1 year were assessed again, if possible, at 4 years of age. Follow-up included both a parental questionnaire and a repeat OFC. Of the original cohort of 12-month-old children with a positive OFC (n = 156), 139 (89%) had parents who completed the evaluation questionnaire and 103 (66%) of the children underwent repeat OFC testing at 4 years. Of these, 22 children had a negative OFC result. In the group of 36 children not undergoing formal OFC testing, 6 parents reported a history of peanut tolerance in their child, defined as an absence of adverse symptoms with regular ingestion of peanuts in the child’s diet. Thus, a total of 28 children from the original cohort (18%) had either a parental history of tolerating regular ingestion of peanuts or a negative OFC result. A history of tree nut and house dust mite sensitization, coexisting food allergies, eczema, and asthma were not predictive of persistent peanut allergy.

Bottom line: In this study, 18% of children with a positive oral food challenge (OFC) result to peanuts at 1 year of age showed no evidence of persistent peanut allergy at 4 years of age.


What interventions are effective for peanut and egg allergy and general food allergies?

5. Randomized trial of peanut consumption in infants at risk for peanut allergy

BACKGROUND: The prevalence of peanut allergy among children in Western countries has doubled in the past 10 years, and peanut allergy is becoming apparent in Africa and Asia. We 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: We randomly assigned 640 infants with severe eczema, egg allergy, or both to consume or avoid peanuts until 60 months of age. Participants, who were at least 4 months but younger than 11 months of age at randomization, were assigned to separate study cohorts on the basis of preexisting sensitivity to peanut extract, which was determined with the use of a skin-prick test—one consisting of participants with no measurable wheal after testing and the other consisting of those with a wheal measuring 1 to 4 mm in diameter. 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. Increases in levels of peanut-specific IgG4 antibody occurred predominantly in the
consumption group; a greater percentage of participants in the avoidance group had elevated titers of peanut-specific IgE antibody. A larger wheal on the skin-prick test and a lower ratio of peanut-specific IgG4:IgE were associated with peanut allergy.

CONCLUSIONS: The early introduction of peanuts significantly decreased the frequency of the development of peanut allergy among children at high risk for this allergy and modulated immune responses to peanuts. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, Brough HA, Phippard D, Basting M, Feeney M, Turcanu V, Sever ML, Gomez Lorenzo M, Plaut M, Lack G; LEAP Study Team. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med. 2015 Feb 26;372(9):803-13. (Funded by the National Institute of Allergy and Infectious Diseases and others; ClinicalTrials.gov number, NCT00329784.)

6. Effect of Avoidance on Peanut Allergy after Early Peanut Consumption

BACKGROUND: In a randomized trial, the early introduction of peanuts in infants at high risk for allergy was shown to prevent peanut allergy. In this follow-up study, we investigated whether the rate of peanut allergy remained low after 12 months of peanut avoidance among participants who had consumed peanuts during the primary trial (peanut-consumption group), as compared with those who had avoided peanuts (peanut-avoidance group).

METHODS: At the end of the primary trial, we instructed all the participants to avoid peanuts for 12 months. The primary outcome was the percentage of participants with peanut allergy at the end of the 12-month period, when the participants were 72 months of age.

RESULTS: We enrolled 556 of 628 eligible participants (88.5%) from the primary trial; 550 participants (98.9%) had complete primary-outcome data. The rate of adherence to avoidance in the follow-up study was high (90.4% in the peanut-avoidance group and 69.3% in the peanut-consumption group). Peanut allergy at 72 months was significantly more prevalent among participants in the peanut-avoidance group than among those in the peanut-consumption group (18.6% [52 of 280 participants] vs. 4.8% [13 of 270], \( P < 0.001 \)).

Three new cases of allergy developed in each group, but after 12 months of avoidance there was no significant increase in the prevalence of allergy among participants in the consumption group (18.6% vs. 4.8% [13 of 270] at 72 months, \( P = 0.25 \)). Fewer participants in the peanut-consumption group than in the peanut-avoidance group had high levels of Ara h2 (a component of peanut-protein-specific IgE) in addition to participants in the peanut-consumption group who continued to have a higher level of peanut-specific IgG4 and a higher peanut-specific IgG4:IgE ratio.

CONCLUSIONS: Among children at high risk for allergy in whom peanuts had been introduced in the first year of life and continued until 5 years of age, a 12-month period of peanut avoidance was not associated with an increase in the prevalence of peanut allergy. Long-term effects are not known.


7. Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants

BACKGROUND: The age at which allergenic foods should be introduced into the diet of breast-fed infants is uncertain. We evaluated whether the early introduction of allergenic foods in the diet of breast-fed infants would protect against the development of food allergy.

METHODS: We recruited, from the general population, 1303 exclusively breast-fed infants who were 3 months of age and randomly assigned them to the early introduction of six allergenic foods (peanut, cooked egg, cow's milk, sesame, whitefish, and wheat; early-introduction group) or to the current practice recommended in the United Kingdom of exclusive breast-feeding to approximately 6 months of age (standard-introduction group). The primary outcome was food allergy to one or more of the six foods between 1 year and 3 years of age.

RESULTS: In the intention-to-treat analysis, food allergy to one or more of the six intervention foods developed in 7.1% of the participants in the standard-introduction group (42 of 595 participants) and in 5.6% of those in the early-introduction group (32 of 567) (\( P = 0.32 \)). In the per-protocol analysis, the prevalence of any food allergy was significantly lower in the early-introduction group than in the standard-introduction group (2.4% vs. 7.3%, \( P = 0.01 \)), as was the prevalence of peanut allergy (0% vs. 2.5%, \( P = 0.003 \)) and egg allergy (1.4% vs. 5.5%, \( P = 0.009 \)); there were no significant effects with respect to milk, sesame, fish, or wheat. The consumption of 2 g per week of peanut or egg-white protein was associated with a significantly lower prevalence of these respective allergies than was less consumption. The early introduction of all six foods was not easily achieved but was safe.

CONCLUSIONS: The trial did not show the efficacy of early introduction of allergenic foods in an intention-to-treat analysis. Further analysis raised the question of whether the prevention of food allergy by means of early introduction of multiple allergenic foods was dose-dependent.


8. Sublingual immunotherapy for peanut allergy: Long-term follow-up of a randomized multicenter trial

BACKGROUND: We previously reported the initial results of the first multicenter, randomized, double-blind, placebo-controlled clinical trial of peanut sublingual immunotherapy (SLIT), observing a favorable safety profile associated with modest clinical and immunologic effects in the first year.

OBJECTIVE: We sought to provide long-term (3-year) clinical and immunologic outcomes for our peanut SLIT trial. Key end points were (1) percentage of responders at 2 years (ie, could consume 5 g of peanut powder or a 10-fold increase from baseline), (2)
percentage reaching desensitization at 3 years, (3) percentage attaining sustained unresponsiveness after 3 years, (4) immunologic end points, and (5) assessment of safety parameters.

METHODS: Response to treatment was evaluated in 40 subjects aged 12 to 40 years by performing a 10-g peanut powder oral food challenge after 2 and 3 years of daily peanut SLIT therapy. At 3 years, SLIT was discontinued for 8 weeks, followed by another 10-g oral food challenge and an open feeding of peanut butter to assess sustained unresponsiveness.

RESULTS: Approximately 98% of the 18,165 doses were tolerated without adverse reactions beyond the oropharynx, with no severe symptoms or use of epinephrine. A high rate (>50%) discontinued therapy. By study's end, 4 (10.8%) of 37 SLIT-treated participants were fully desensitized to 10 g of peanut powder, and all 4 achieved sustained unresponsiveness. Responders at 2 years showed a significant decrease in peanut-specific basophil activation and skin prick test titration compared with nonresponders.

CONCLUSIONS: Peanut SLIT induced a modest level of desensitization, decreased immunologic activity over 3 years in responders, and had an excellent long-term safety profile. However, most patients discontinued therapy by the end of year 3, and only 10.8% of subjects achieved sustained unresponsiveness.


9. Long-term treatment with egg oral immunotherapy enhances sustained unresponsiveness that persists after cessation of therapy

BACKGROUND: We previously reported the results of a randomized placebo-controlled study of egg oral immunotherapy (eOIT) in which 27.5% of subjects achieved sustained unresponsiveness (SU) after 2 years. Here we report the results of treatment through 4 years and long-term follow-up.

OBJECTIVE: We sought to evaluate the efficacy and safety of eOIT in participants treated up to 4 years.

METHODS: Children with egg allergy (5-18 years old) received eOIT (n = 40) for up to 4 years or placebo (n = 15) for 1 year or less. The key outcome was the percentage of subjects achieving SU by year 4. Safety and immunologic assessments were performed, and long-term follow-up questionnaires (LFQs) were administered after study conclusion (LFQ-1) and 1 year later (LFQ-2).

RESULTS: Of 40 eOIT-treated subjects, 20 (50.0%) of 40 demonstrated SU by year 4. For those subjects still dosing during years 3 and 4, mild symptoms were present in 12 (54.5%) of 22 subjects. At the time of the LFQ, more subjects receiving eOIT (LFQ-1, 23/34 [68%]; LFQ-2, 21/33 [64%]) were consuming unbaked and baked egg versus placebo (LFQ-1, 2/11 [18%], P = .006; LFQ-2, 3/12 [25%], P = .04). Of subjects achieving SU, 18 (90%) of 20 completed the LFQ, with 18 (100%) of 18 reporting consumption of all forms of egg. When compared with subjects not achieving SU, subjects achieving SU had higher IgG4 values (P = .001) and lower egg skin prick test scores (P = .0002) over time and a lower median baseline ratio of egg-specific IgE to total IgE (1.1% vs 2.7%, P = .04).

CONCLUSIONS: SU after eOIT is enhanced with longer duration of therapy and increases the likelihood of tolerating unbaked egg in the diet.


Are probiotics effective for preventing allergies?

10. Probiotics for the prevention of allergy: A systematic review and meta-analysis of randomized controlled trials

BACKGROUND: Allergic diseases are considered a health burden because of their high and constantly increasing prevalence, high direct and indirect costs, and undesirable effects on quality of life. Probiotics have been suggested as an intervention to prevent allergic diseases.

OBJECTIVE: We sought to synthesize the evidence supporting use of probiotics for the prevention of allergies and inform World Allergy Organization guidelines on probiotic use.

METHODS: We performed a systematic review of randomized trials assessing the effects of any probiotic administered to pregnant women, breast-feeding mothers, and/or infants.

RESULTS: Of 2403 articles published until December 2014 identified in Cochrane Central Register of Controlled Trials, MEDLINE, and Embase, 29 studies fulfilled a priori specified inclusion criteria for the analyses. Probiotics reduced the risk of eczema when used by women during the last trimester of pregnancy (relative risk [RR], 0.71; 95% CI, 0.60-0.84), when used by breast-feeding mothers (RR, 0.57; 95% CI, 0.47-0.69), or when given to infants (RR, 0.80; 95% CI, 0.68-0.94). Evidence did not support an effect on other allergies, nutrition status, or incidence of adverse effects. The certainty in the evidence according to the Grading of Recommendation Assessment Development and Evaluation approach is low or very low because of the risk of bias, inconsistency and imprecision of results, and indirectness of available research.

CONCLUSION: Probiotics used by pregnant women or breast-feeding mothers and/or given to infants reduced the risk of eczema in infants; however, the certainty in the evidence is low. No effect was observed for the prevention of other allergic conditions.

11. Probiotics for Prevention of Atopy and Food Hypersensitivity in Early Childhood: A PRISMA-Compliant Systematic Review and Meta-Analysis of Randomized Controlled Trials

Most studies investigated probiotics on food hypersensitivity, not on oral food challenge confirmed food allergy in children. The authors systematically reviewed the literature to investigate whether probiotic supplementation prenatally and/or postnatally could reduce the risk of atopy and food hypersensitivity in young children. PubMed, Embase, the Cochrane Central Register of Controlled Trials, and 4 main Chinese literature databases (Wan Fang, VIP, China National Knowledge Infrastructure, and SinoMed) were searched for randomized controlled trials regarding the effect of probiotics on the prevention of allergy in children. The last search was conducted on July 11, 2015. Seventeen trials involving 2947 infants were included. The first follow-up studies were analyzed. Pooled analysis indicated that probiotics administered prenatally and postnatally could reduce the risk of atopy (relative risk [RR] 0.78; 95% confidence interval [CI] 0.66-0.92; I²=0%), especially when administered prenatally to pregnant mother and postnatally to child (RR 0.71; 95% CI 0.57-0.89; I²=0%), and the risk of food hypersensitivity (RR 0.77; 95% CI 0.61-0.98; I²=0%). When probiotics were administered either only prenatally or only postnatally, no effects of probiotics on atopy and food hypersensitivity were observed. Probiotics administered prenatally and postnatally appears to be a feasible way to prevent atopy and food hypersensitivity in young children. The long-term effects of probiotics, however, remain to be defined in the follow-up of existing trials. Still, studies on probiotics and confirmed food allergy, rather than surrogate measure of food hypersensitivity, are warranted.  


Other recent randomized trials/meta-analyses of allergy treatment and prevention

12. RCT: Efficacy of a House Dust Mite Sublingual Allergen Immunotherapy for Adults With Allergic Asthma

BACKGROUND: The house dust mite (HDM) sublingual allergen immunotherapy (SLIT) tablet is a potential novel treatment option for HDM allergy-related asthma.

OBJECTIVES: To evaluate the efficacy and adverse events of the HDM SLIT tablet vs placebo for asthma exacerbations during an inhaled corticosteroid (ICS) reduction period.

DESIGN, SETTINGS, AND PARTICIPANTS: Double-blind, randomized, placebo-controlled trial conducted between August 2011 and April 2013 in 109 European trial sites. The trial included 834 adults with HDM allergy-related asthma not well controlled by ICS or combination products, and with HDM allergy-related rhinitis. Key exclusion criteria were FEV1 less than 70% of predicted value or hospitalization due to asthma within 3 months before randomization. Efficacy was assessed during the last 6 months of the trial when ICS was reduced by 50% for 3 months and then completely withdrawn for 3 months.

INTERVENTIONS: 1:1:1 randomization to once-daily treatment with placebo (n = 282) or HDM SLIT tablet (dosage groups: 6 SQ-HDM [n = 279] or 12 SQ-HDM [n = 282]) in addition to ICS and the short-acting β2-agonist salbutamol.

MAIN OUTCOMES AND MEASURES: Primary outcome was time to first moderate or severe asthma exacerbation during the ICS reduction period. Secondary outcomes were deterioration in asthma symptoms, change in allergen-specific immunoglobulin G4 (IgG4), change in asthma control or asthma quality-of-life questionnaires, and adverse events.

RESULTS: Among 834 randomized patients (mean age, 33 years [range, 17-83]; women, 48%), 693 completed the study. The 6 SQ-HDM and 12 SQ-HDM doses both significantly reduced the risk of a moderate or severe asthma exacerbation compared with placebo (hazard ratio [HR]: 0.72 [95% CI, 0.52-0.99] for the 6 SQ-HDM group, P = .045, and 0.69 [95% CI, 0.50-0.96] for the 12 SQ-HDM group, P = .03). The absolute risk differences based on the observed data (full analysis set) in the active groups vs the placebo group were 0.09 (95% CI, 0.01-0.15) for the 6 SQ-HDM group and 0.10 (95% CI, 0.02-0.16) for the 12 SQ-HDM group. There was no significant difference between the 2 active groups. Compared with placebo, there was a reduced risk of an exacerbation with deterioration in asthma symptoms (HR, 0.72 [95% CI, 0.49-1.02] for the 6 SQ-HDM group, P = .11, and 0.64 [95% CI, 0.42-0.96] for the 12 SQ-HDM group, P = .03) and a significant increase in allergen-specific IgG4. However, there was no significant difference for change in asthma control questionnaire or asthma quality-of-life questionnaire for either dose. There were no reports of severe systemic allergic reactions. The most frequent adverse events were mild to moderate oral pruritus (13% for the 6 SQ-HDM group, 20% for the 12 SQ-HDM group, and 3% for the placebo group), mouth edema, and throat irritation.

CONCLUSIONS AND RELEVANCE: Among adults with HDM allergy-related asthma not well controlled by ICS, the addition of HDM SLIT to maintenance medications improved time to first moderate or severe asthma exacerbation during ICS reduction, with an estimated absolute reduction at 6 months of 9 to 10 percentage points; the reduction was primarily due to an effect on moderate exacerbations. Treatment-related adverse events were common at both active doses. Further studies are needed to assess long-term efficacy and safety.  

13. Oral therapy for grass pollen allergy only marginally effective

Clinical question: Is the sublingual administration of grass pollen extract more effective than placebo in diminishing symptoms in patients with grass pollen allergy?

Study design: Meta-analysis (randomized controlled trials)

Setting: Various (meta-analysis)

Synopsis: These researchers searched, without language restriction, 4 databases, including the Cochrane Library, and identified 13 published randomized trials comparing the effect on symptoms of sublingual administration of grass pollen extract with placebo in 4659 patients with documented allergy to grass pollen. The studies evaluated the effectiveness of both available products, timothy grass pollen extract (Grastek [Grazax in Europe]) and 5-grass extract (Oralair). Two reviewers independently extracted the data, which were checked by 2 other reviewers. All studies were of good quality (using Jadad criteria). They didn't locate any unpublished data, but didn't find any evidence of publication bias. As compared with placebo, there was a small difference in clinical symptoms (standardized mean difference [SMD] -0.28; 95% CI -0.37 to -0.19; P < .001) and in the medication score (SMD -0.24; -0.31 to -0.17; P < .001). As compared with baseline scores, though, there was no difference between placebo and active treatment. The studies performed in Europe showed a greater benefit in symptom scores than the studies in North America, though not by much. Side effects were reported by 60% of the patients, including several episodes of anaphylaxis that required epinephrine.

Bottom line: Neither available sublingual grass pollen extract produced a profound effect on symptoms. Itchy eyes and runny noses were still common, as was the use of medication to control symptoms. Side effects were reported by 60% of the patients using the grass pollen extract.


14. Topical steroids for nasal polyps

Background. Chronic rhinosinusitis with nasal polyps (CRSwNP) represents inflammatory changes throughout the nose and sinuses from a group of disorders which all lead to swelling and overgrowth of the nasal mucosa. Topical corticosteroids have been the most widely used treatment, with each clinician using different regimes, at different doses, in different settings and with or without sinus surgery. CRSwNP requires ongoing medical management to prevent recurrence.

Objectives. To assess the effects of topical corticosteroids on CRSwNP and to analyse various subgroups, including patients who had sinus surgery immediately prior to the delivery of the corticosteroids, surgery any time prior to the topical corticosteroids or patients who had never had previous surgery. Also, to assess the most effective dose and delivery methods for topical corticosteroids.

Search methods. We searched the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; ICTRP and additional sources for published and unpublished trials. The date of the search was 10 April 2012.

Selection criteria. Randomised controlled trials studying topical corticosteroids for patients with CRSwNP. Data collection and analysis. At least two authors reviewed the search results and selected trials meeting the eligibility criteria, obtaining full texts and contacting authors. We documented our justification for the exclusion of studies. At least two authors extracted data using a pre-determined, standardised data form.

Main results. Forty studies (3624 patients) met the inclusion criteria. The trials were at low (21 trials), medium (13 trials) and high (six trials) risk of bias. The primary outcomes were sino-nasal symptoms, polyp size and polyp recurrence after surgery. When compared to placebo, topical corticosteroids improved overall symptom scores (standardised mean difference (SMD) -0.46; 95% confidence interval (CI) -0.65 to -0.27, P < 0.00001; seven trials, n = 445) and had a higher proportion of patients whose symptoms improved (responders) (risk ratio (RR) 1.71; 95% CI 1.29 to 2.26, P = 0.0002; four trials, n = 234). Topical corticosteroids also decreased the polyp score (SMD -0.73; 95% CI -1.00 to -0.46, P < 0.00001; three trials, n = 237) and had a greater proportion of patients with a reduction in polyp size (responders) (RR 2.09; 95% CI 1.65 to 2.64, P < 0.00001; eight trials, n = 785) when compared to placebo. Topical corticosteroids also prevented polyp recurrence after surgery (RR 0.59; 95% CI 0.45 to 0.79, P = 0.0004; six trials, n = 437). Subgroup analyses by sinus surgery status revealed a greater benefit in reduction of polyp score when topical steroid was administered any time after sinus surgery (SMD -1.19; 95% CI -1.54 to -0.83) compared to patients who had never had surgery (SMD -0.13; 95% CI -0.53 to 0.28, P = 0.00001). There was no difference between groups in terms of adverse events.

Authors' conclusions. Topical corticosteroids are a beneficial treatment for CRSwNP and the adverse effects are minor, with benefits outweighing the risks. They improve symptoms, reduce polyp size and prevent polyp recurrence after surgery. Patients having sinus surgery may have a greater response to topical corticosteroids but further research is required.


15. Hand washing children's dishes associated with fewer allergies

Clinical question: Can the way dishes are washed affect the development of allergies in children?

Study design: Cross-sectional

Setting: Population-based

Synopsis: The goal of this wide-ranging study was to see whether exposure to microbes early in life affected the development of allergies. The Swedish investigators sent questionnaires to parents of 1029 children, aged 7 to 8 years, in a single city, asking about the child's history of allergy, including any diagnosis of eczema, asthma, or allergic rhinoconjunctivitis, as well as asking about eating habits. To test for dietary microbes, the researchers asked parents about how they washed their dishes (using a dishwasher or by
hand); their use of farm-purchased milk, eggs, or unpasteurized milk; whether their diet included fermented foods (e.g., sauerkraut) or home-cooked foods; and the duration of their breastfeeding. Most of the children attended daycare and one third had a pet, but only 6% lived in a household in which a parent reported they smoked inside. After analyzing all these factors to look for associations, hand dishwashing, which occurred in only 12% of households, was associated with the greatest reduced risk of allergic disease development (odds ratio 0.57, 95% CI 0.37-0.85). The risk was further reduced in a dose-response pattern if the children were also served fermented food and if the family bought food directly from farms. The associations remained after adjusting for socioeconomic factors.

**Bottom line:** This study might cause one to quip, “Cleanliness is next to atopicness.” These results add further credence to the idea that the gastrointestinal system plays a big role in the development of our immune system (the “hygiene hypothesis”). Washing children's bottles and eating utensils by hand instead of using an automatic dishwasher was associated with a lower risk of developing an allergic disorder. The authors stop short of recommending low hygienic standards, but they suggest that fastidiousness might not allow the immune system to learn how to self-modulate.


**Bottom Lines**

1. Half of children with milk allergy will not be allergic to milk by age 5.
2. Half of children with egg allergy will not be allergic to egg by 2 to 5 years of age.
3. One in five children with peanut allergy will not be allergic to peanuts by age 4.
4. Early exposure to peanuts in allergy prone children greatly reduced the prevalence of peanut allergy.
5. Early exposure to peanut and egg protein (3 mo.) in breast fed infants cuts the rate of food allergy significantly.
6. Probiotics given to pregnant mothers and their infants reduces the prevalence of eczema.
7. Oral immunotherapies for asthma (house dust mite) and allergic rhinitis (grass) reduce symptoms only slightly.
8. Nasal steroids are effective for nasal polyps.
9. Exposure to dirt aint all bad!
Objectives | Understand and apply

1. The 2016 and 2017 ACC/AHA CHF guidelines concerning recommendations on the use of new classes of medications including the ARNI valsartan/sacubitril and the use of biomarkers in HF
2. That NSAIDs can lead to heart failure
3. In patients with Heart Failure with reduced ejection fraction (HRrEF), CAD and EF of < 35%, Cabg is superior to medical therapy in terms of survival
4. Evidence on Vitamin D for CHF
5. Evidence for TAVI (transcatheter aortic-valve implantation)
6. Updates in the management of atrial fibrillation

A peptide, neprilysin, is a new target in the treatment of CHF. According to the background information in the article accompanying abstract #1, Neprilysin is a neutral endopeptidase that “degrades several endogenous vasoactive peptides, including natriuretic peptides, bradykinin, and adrenomedullin. Inhibition of neprilysin increases the levels of these substances, countering the neurohormonal overactivation that contributes to vasoconstriction, sodium retention, and maladaptive remodeling.”

In 2016 the ACC/AHA updated their CHF Guidelines to include recommendations concerning the use of 2 new classes of medications for patients with Heart Failure with reduced ejection fraction (HRrEF). Note that the actual update was 5 pages long, and conflict of interest declarations for this update also went on for 5 pages (just saying!).

Updated ACC/AHA guidelines for patients with Stage 3 CHF with reduced ejection fraction (HFrEF)

First a word about the differences between the Stages of HF and the NYHA Classification

<table>
<thead>
<tr>
<th>Stages of HF</th>
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<tbody>
<tr>
<td>Stage A: Patients at risk for heart failure who have <strong>not yet developed structural heart changes</strong> (i.e. those with diabetes, those with coronary disease without prior infarct)</td>
</tr>
<tr>
<td>Stage B: Patients with <strong>structural heart disease</strong> (i.e. reduced ejection fraction, left ventricular hypertrophy, chamber enlargement) who have <strong>not yet developed symptoms of heart failure</strong></td>
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<tr>
<td>Stage C: Patients who have developed <strong>clinical heart failure</strong></td>
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<tr>
<td>Stage D: Patients with <strong>refractory heart failure</strong> requiring advanced intervention (i.e. biventricular pacemakers, left ventricular assist device, transplantation)</td>
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<td>Class</td>
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Second a word about the ACC/AHA guideline ratings

Class of Recommendation (COR) and Level of evidence (LOE) | ACC/AHA Guidelines

Class (Strength) of Recommendation (COR) Table
- **Class I (Benefit >>> Risk):** **Should be done | Is useful | (Strong)**
- **Class IIa (Benefit >> Risk):** Reasonable to do | Can be useful | (Moderate)
- **Class IIb (Benefit > Risk):** May be considered | Unknown usefulness (Weak)
- **Class III (No benefit or harm):** Not helpful or harmful

Level (Quality) of Evidence (LOE)
- **Level A:**
  - High quality evidence from ≥ 1 RCT
  - Meta-analysis of high-quality RCTs
  - > 1 RCT corroborated by high-quality registry studies
- **Level B-R (Randomized):**
  - Moderate quality evidence from ≥ 1 RCT
  - Meta-analyses of moderate quality RCTs
- **Level B-NR (Non-randomized):**
  - Moderate quality evidence from ≥ 1 high-quality nonrandomized/observational or registry studies
  - Meta-analyses of such studies
- **Level C-LD**
  - Randomized or nonrandomized/observational or registry studies with limitations of design or execution
  - Meta-analyses of such studies
  - Physiological or mechanistic studies in humans
- **Level C-EO**
  - Consensus opinion based upon clinical experience

The COR and LOE are determined independent of each other. Any COR can be paired with any LOE (notably LOE C does not imply the COR is weak)
New 2016 Recommendations | (paraphrased) for Stage C HF with Reduced Ejection Fraction

1. The clinical strategy of inhibition of the renin-angiotensin system with the following is recommended for patients with chronic HFrEF to reduce morbidity and mortality:
   - ACE inhibitors (COR 1 | Level of Evidence: A), OR
   - ARBs (COR 1 | Level of Evidence: A), OR
   - ARNI (COR 1 | Level of Evidence: B-R), in conjunction with evidence based
   - Beta blockers AND
   - Aldosterone antagonists in selected patients

2. “In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.” (COR 1: LOE B-R)
   - This ARNI has recently been approved for patients with symptomatic HFrEF and is intended to be substituted for ACE inhibitors or ARBs.
   - HF effects and potential off-target effects may be complex with inhibition of the neprilysin enzyme, which has multiple biological targets
   - To facilitate initiation and titration, the approved ARNI is available in 3 doses that include a dose that was not tested in the HF trial; the target dose used in the trial was 97/103 mg twice daily

3. “ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor”
   - Oral neprilysin inhibitors, used in combination with ACE inhibitors, can lead to angioedema and concomitant use is contraindicated and should be avoided
   - An ARNI should not be administered within 36 hours of switching from or to an ACE inhibitor.
   - ARNI should not be administered to patients with a history of angioedema

4. Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF ≤35%) who are receiving GDEM, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest (COR 2a | LOE B-R) (not covered in this chapter)

Benefit:
- All 3 classes are associated with ↓ morbidity and mortality in patients with CHF with reduced ejection fraction (HF/rEF)

Risk
- All 3 classes use with caution in patients with hypotension, renal insufficiency
- ACE and ARBS use with caution in patients with hyperkalemia
- ACE and ARNI also associated with angioedema
  - < 1% of patients on ACE get angioedema; more common in blacks and women
- ACE’s also inhibit kinase and increase bradykinin (can therefore ↑ cough in ~ 20% of patients)

FROM ACC/AHA Guideline
- “Data suggest that there are no differences among available ACE inhibitors in their effects on symptoms or survival.”
- “ACE inhibitors should be started at low doses and titrated upward to doses shown to reduce the risk of cardiovascular events in clinical trials” (See Appendix)
- “Abrupt withdrawal of ACE inhibition can lead to clinical deterioration and should be avoided.”

#1: POEM: Valsarartan/sacubitril reduces mortality more than enalapril 10 mg twice daily in patients with heart failure (PARADIGM-HF)

Clinical Question: Does inhibition of both angiotensin and neprilysin offer benefits beyond those of angiotensin inhibition alone?
Bottom Line: The combination of an angiotensin receptor blocker (sacubitril) and neprilsyn inhibitor (valsartan) reduces cardiovascular mortality more than an angiotensin-converting enzyme (ACE) inhibitor (enalapril) alone, with an acceptable safety and tolerability profile. The choice of dosage is concerning, however, as the study compared a fairly high dose of valsartan with a moderate dose of enalapril. (LOE = 1b)

Study Design: Randomized controlled trial (double-blinded) Funding: Industry
Allocation: Concealed Setting: Outpatient (any)

Synopsis: Neprilsyn is an endopeptidase that breaks down vasoactive peptides such as natriuretic peptide, bradykinin, and adrenomedullin. Sacubitril inhibits this compound's activity, which has the effect of blocking the vasoconstruction, sodium retention, and cardiac remodeling that accompany more advanced stages of heart failure. A previous trial compared sacubitril with an ACE inhibitor, but angioedema was a problem. In the current trial, patients were randomized to receive the combination of sacubitril and the angiotensin receptor blocker valsartan or to receive enalapril, an older ACE inhibitor. All patients were adults with New York Heart Association (NYHA) class II, III, or IV heart failure; an ejection fraction no greater than 40% (later changed to 35%); and an elevated type B-natriuretic peptide level. The authors excluded those with hypotension, a glomerular filtration rate of less than 30 mL/min/1.73 m2, a serum potassium level greater than 5.2 mmol/L, or history of angioedema or other side effects of ACE inhibitors or angiotensin receptor blockers. The authors ultimately enrolled 10,513 patients. They then had to run a gauntlet of 2 separate run-in phases: 1102 patients left the study because they did not tolerate enalapril, 977 left because they did not tolerate the valsartan/sacubitril combination, and another 43 left primarily because of protocol violations. This meant a total of 8399 patients were randomized to receive valsartan/valsartot 200 mg or enalapril 10 mg, each given twice daily. The dosage of valsartan is near the top of the recommended dosing range, while the dosage of enalapril is closer to the middle of the recommended range (10 to 40 mg per day) for that drug. Groups were balanced at the start of the study, with an average age of 63 years, 22% women, and the majority with NYHA class III (70%) or class III (24%) heart failure. Patients were followed up for a median of 27 months, at which time an independent data monitoring committee halted the trial. The primary outcome was a cardiovascular death or hospitalization for worsening heart failure. Obviously, this is an inappropriate composite, since they are very different outcomes. Looking at each outcome individually, however, there were fewer cardiovascular deaths in the intervention group (13.3% vs 16.5%; P < .001; number needed to treat [NNT] = 31) and fewer hospitalizations in the intervention group (12.8% vs 15.6%; P < .001; NNT = 36). All-cause mortality was also significantly lower in the intervention group (17% vs 19.8%; NNT = 36), as was a validated symptom score. There were no significant differences in rates of renal function decline or new onset atrial fibrillation. Subgroup analyses showed similar benefits by age, sex, race, and comorbidities. Significant hypotension was more common in the valsartan/sacubitril group (14.0% vs 9.2%; P < .001; number needed to treat [NNT] = 21), while cough and elevated serum creatinine levels were more common in the enalapril group. The valsartan/sacubitril group had lower mean blood pressures, supporting concerns of a "straw man" comparison with the selected dose of enalapril.


#2: PubMed: Only 21% of HF patients meet the PARADIGM-HF inclusion criteria

Aims: The PARADIGM-HF trial showed that sacubitril-valtsartan, an ARB-neprilsyn inhibitor, is more effective than enalapril for some patients with heart failure (HF). It is uncertain what proportion of patients with HF would be eligible for sacubitril-valtsartan in clinical practice.

Methods and Results: Between 2001 and 2014, 6131 patients consecutively referred to a community HF clinic with suspected HF were assessed. The criteria required to enter the randomized phase of PARADIGM-HF, including symptoms, NT-proBNP, and current treatment with or without target doses of ACE inhibitors or ARBs, were applied to identify the proportion of patients eligible for sacubitril-valtsartan. Recognizing the diversity of clinical opinion and guideline recommendations concerning this issue, entry criteria were applied singly and in combination. Of 1396 patients with reduced left ventricular ejection fraction (≤40%, HFrEF) and contemporary measurement of NT-proBNP, 379 were on target doses of an ACE inhibitor or ARB at their initial visit and, of these, 172 (45%) fulfilled the key entry criteria for the PARADIGM-HF trial. Lack of symptoms (32%) and NT-proBNP <600 ng/L (49%) were common reasons for failure to fulfill criteria. A further 122 patients became eligible during follow-up (n = 294, 21%). However, if background medication and doses were ignored, then 701 (50%) were eligible initially and a further 137 became eligible during follow-up.

Conclusions: Of patients with HF/HFrEF referred to a clinic such as ours, only 21% fulfilled the PARADIGM-HF randomization criteria, on which the ESC Guidelines are based; this proportion rises to 60% if background medication is ignored.


New 2017 CHF Recommendations | (paraphrased)

In 2017 the ACC/AHA published a focused update to their 2013 guidelines for the management of HF. The update focused on 1) the use ARNI in patients with HFrEF (covered above); 2) the use of biomarkers; 3) Management of Stage C HF with preserved EF (HFpEF).

Below are the new or modified recommendations that have a moderate or strong class of recommendation (COR I or IIa) COR or a Class III (no benefit or harm) recommendation (see appendix). Recommendations with a IIb COR are not included.
Biomarkers

According to this update, Natriuretic peptide biomarkers are used to track presence and severity of HF. BNP (B-type natriuretic peptide) and the NT-proBNP (N-terminal pro-B-type natriuretic peptide) both track similarly and both can be used. However do not use absolute values and cut points interchangeably. BNP is a substrate for nephrilysin (but not NT-proBNP); therefore ARNI (e.g. sacubitril or Entresto) will increase BNP levels. Recommendations

Prevention:
- NEW: In patients at risk of developing HF, natriuretic peptide biomarker-based screening followed by team based care …. can be useful to prevent LV dysfunction or HF (IIa B-R)

Diagnosis
- MODIFIED: In patients presenting with dyspnea, measurement of natriuretic peptide biomarkers is useful to support or exclude a diagnosis of HF (1 | A)

Prognosis
- MODIFIED: Measurement of baseline levels of natriuretic peptide biomarkers and/or cardiac troponin on admission to the hospital is useful to establish a prognosis in acutely decompensated HF
- NEW: During a HF hospitalization, a predischarge natriuretic peptide biomarker level can be useful to establish post-discharge prognosis (IIA | B-NR)

#3: PubMed: NT-proBNP guided treatment adds nothing to usual care

**Importance:** The natriuretic peptides are biochemical markers of heart failure (HF) severity and predictors of adverse outcomes. Smaller studies have evaluated adjusting HF therapy based on natriuretic peptide levels ("guided therapy") with inconsistent results.

**Objective:** To determine whether an amino-terminal pro-B-type natriuretic peptide (NT-proBNP)-guided treatment strategy improves clinical outcomes vs usual care in high-risk patients with HF and reduced ejection fraction (HFrEF).

**Design, Settings, and Participants:** The Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) study was a randomized multicenter clinical trial conducted between January 16, 2013, and September 20, 2016, at 45 clinical sites in the United States and Canada. This study planned to randomize 1100 patients with HFrEF (ejection fraction ≤40%), elevated natriuretic peptide levels within the prior 30 days, and a history of a prior HF event (HF hospitalization or equivalent) to either an NT-proBNP-guided strategy or usual care.

**Interventions:** Patients were randomized to either an NT-proBNP-guided strategy or usual care. Patients randomized to the guided strategy (n = 446) had HF therapy titrated with the goal of achieving a target NT-proBNP of less than 1000 pg/mL. Patients randomized to usual care (n = 448) had HF care in accordance with published guidelines, with emphasis on titration of proven neurohormonal therapies for HF. Serial measurement of NT-proBNP testing was discouraged in the usual care group.

**Main Outcomes and Measures:** The primary end point was the composite of time-to-first HF hospitalization or cardiovascular mortality. Prespecified secondary end points included all-cause mortality, total hospitalizations for HF, days alive and not hospitalized for cardiovascular reasons, the individual components on the primary end point, and adverse events.

**Results:** The data and safety monitoring board recommended stopping the study for futility when 894 (median age, 63 years; 286 [32%] women) of the planned 1100 patients had been enrolled with follow-up for a median of 15 months. The primary end point occurred in 164 patients (37%) in the biomarker-guided group and 164 patients (37%) in the usual care group (adjusted hazard ratio [HR], 0.98; 95% CI, 0.79-1.22; P = .88). Cardiovascular mortality was 12% (n = 53) in the biomarker-guided group and 13% (n = 57) in the usual care group (HR, 0.94; 95% CI, 0.65-1.37; P = .75). None of the secondary end points nor the decreases in the NT-proBNP levels achieved differed significantly between groups.

**Conclusions and Relevance:** In high-risk patients with HFrEF, a strategy of NT-proBNP-guided therapy was not more effective than a usual care strategy in improving outcomes.


Treating HTN to reduce the incidence of HF

New Recommendations
1. In patients at increased risk, or with Stage A HF, the optimal BP in those with HTN should be <130/80 mm. (COR I | B-R)
2. In patients with HF with reduced ejection fraction (HFrEF) and HTN prescribe GDMT to attain a systolic BP of < 130 (COR I | C-EO)
3. In patients with HF with preserved ejection fraction (HFpEF) after management of volume overload, prescribe GDMT to attain a systolic BP of < 130 (COR I | C-LD)

Sleep disordered Breathing

1. In patients with NYHA class II-IV HF and suspicion of sleep disordered breathing or excessive daytime sleepiness, a formal sleep assessment is reasonable (COR IIa | C-LD)

#4: PubMed: CABG | better outcomes after 10 years in patients with CAD and LVEF < 35%

**BACKGROUND:** The survival benefit of a strategy of coronary-artery bypass grafting (CABG) added to guideline-directed medical therapy, as compared with medical therapy alone, in patients with coronary artery disease, heart failure, and severe left ventricular systolic dysfunction remains unclear.

**METHODS:** From July 2002 to May 2007, a total of 1212 patients with an ejection fraction of 35% or less and coronary artery disease amenable to CABG were randomly assigned to undergo CABG plus medical therapy (CABG group, 610 patients) or medical therapy alone (medical-therapy group, 602 patients). The primary outcome was death from any cause. Major secondary outcomes included death from cardiovascular causes and death from any cause or hospitalization for cardiovascular causes. The median duration of follow-up, including the current extended-follow-up study, was 9.8 years.

**RESULTS:** A primary outcome event occurred in 359 patients (58.9%) in the CABG group and in 398 patients (66.1%) in the medical-therapy group (hazard ratio with CABG vs. medical therapy, 0.84; 95% confidence interval [CI], 0.73 to 0.97; P=0.02 by log-rank test). A total of 247 patients (40.5%) in the CABG group and 297 patients (49.3%) in the medical-therapy group died from cardiovascular causes (hazard ratio, 0.79; 95% CI, 0.66 to 0.93; P=0.006 by log-rank test). Death from any cause or hospitalization for cardiovascular causes occurred in 467 patients (76.6%) in the CABG group and in 524 patients (87.0%) in the medical-therapy group (hazard ratio, 0.72; 95% CI, 0.64 to 0.82; P<0.001 by log-rank test).

**CONCLUSIONS:** In a cohort of patients with ischemic cardiomyopathy, the rates of death from any cause, death from cardiovascular causes, and death from any cause or hospitalization for cardiovascular causes were significantly lower over 10 years among patients who underwent CABG in addition to receiving medical therapy than among those who received medical therapy alone. (Funded by the National Institutes of Health; STICH [and STICHES] ClinicalTrials.gov number, NCT00023595.)


#5: PubMed: ICD | No mortality benefit in CHF patients with non-ischemic cardiomyopathy

**Background** The benefit of an implantable cardioverter-defibrillator (ICD) in patients with symptomatic systolic heart failure caused by coronary artery disease has been well documented. However, the evidence for a benefit of prophylactic ICDs in patients with systolic heart failure that is not due to coronary artery disease has been based primarily on subgroup analyses. The management of heart failure has improved since the landmark ICD trials, and many patients now receive cardiac resynchronization therapy (CRT).

**Methods** In an randomized, controlled trial, 556 patients with symptomatic systolic heart failure (left ventricular ejection fraction, ≤35%) not caused by coronary artery disease were assigned to receive an ICD, and 560 patients were assigned to receive usual clinical care (control group). In both groups, 58% of the patients received CRT. The primary outcome of the trial was death from any cause. The secondary outcomes were sudden cardiac death and cardiovascular death.

**Results** After a median follow-up period of 67.6 months, the primary outcome had occurred in 120 patients (21.6%) in the ICD group and in 131 patients (23.4%) in the control group (hazard ratio, 0.87; 95% confidence interval [CI], 0.68 to 1.12; P=0.28). Sudden cardiac death occurred in 24 patients (4.3%) in the ICD group and in 46 patients (8.2%) in the control group (hazard ratio, 0.50; 95% CI, 0.31 to 0.82; P=0.005). Device infection occurred in 27 patients (4.9%) in the ICD group and in 20 patients (3.6%) in the control group (P=0.29).

**Conclusions:** In this trial, prophylactic ICD implantation in patients with symptomatic systolic heart failure not caused by coronary artery disease was not associated with a significantly lower long-term rate of death from any cause than was usual clinical care. (Funded by Medtronic and others; DANISH ClinicalTrials.gov number, NCT00542945.)


#6: Center for Medical Education: Vit D has no effect in CHF on exercise capacity but is safe

**BACKGROUND:** Low vitamin D is a common finding in heart failure and is associated with a poor prognosis.

**METHODS** These British authors report results of the randomized, double-blind VINDICATE study (Vitamin D Treating Patients with Chronic Heart Failure). Patients with optimally treated chronic heart failure with a left ventricular ejection fraction of 45% or lower and vitamin D deficiency (25[OH]D below 50nmol/L) were randomized to either vitamin D3 supplementation as cholecalciferol 4000 IU/day
October 1, 2015. The setting was 6 academic medical centers in California. Participants were hospitalized individuals 50 years or older.

### RESULTS

Secondary outcomes were all-cause readmission within 30 days, all-cause mortality at 30 and 180 days, and quality of life at 30 and 180 days. The dates of our study analysis were March 30, 2014, to September 30, 2013, to the intervention arm (715 patients) or to the usual care arm (722 patients) of the Better Effectiveness After Transition–Heart Failure (BEAT-HF) study and observed them for 180 days. The primary outcome was readmission for any cause within 180 days after discharge. The mean patient age was approximately 65, and 70% of the patients were male. The primary outcomes were left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) class, 6-minute walk distance, N-terminal pro-B-type natriuretic peptide (BNP), tumor necrosis factor-alpha (TNF-alpha), C-reactive protein (CRP), interleukin-10 (IL-10), parathyroid hormone (PTH), and renin.

### METHODS

Participants were randomized 1437 patients hospitalized for HF between October 12, 2011, and September 30, 2013, to the intervention arm (715 patients) or to the usual care arm (722 patients) of the Better Effectiveness After Transition–Heart Failure (BEAT-HF) study and observed them for 180 days. The mean patient age was approximately 65, and 70% of the patients were male. The primary outcomes were left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) class, 6-minute walk distance, N-terminal pro-B-type natriuretic peptide (BNP), tumor necrosis factor-alpha (TNF-alpha), C-reactive protein (CRP), interleukin-10 (IL-10), parathyroid hormone (PTH), and renin.

### CONCLUSIONS AND RELEVANCE:

Among patients hospitalized for HF, combined health coaching telephone calls and telemonitoring did not reduce 180-day readmissions. Secondary outcomes were all-cause readmission within 30 days, all-cause mortality at 30 and 180 days, and quality of life at 30 and 180 days. Results: Among 1437 participants, the median age was 73 years. Overall, 46.2% (664 of 1437) were female, and 22.0% (316 of 1437) were African American. The intervention and usual care groups did not differ significantly in readmissions for any cause 180 days after discharge, which occurred in 50.8% (363 of 715) and 49.2% (355 of 722) of patients, respectively (adjusted hazard ratio, 1.03; 95% CI, 0.88-1.20; P = .74). In secondary analyses, there were no significant differences in 30-day readmission or 180-day mortality, but there was a significant difference in 180-day quality of life between the intervention and usual care groups. No adverse events were reported.

### BACKGROUND:

Vitamin D deficiency has been associated with elevated risk for, and a poor prognosis of, cardiovascular diseases due to inflammation and endothelial dysfunction.

### METHODS:

These Chinese authors performed a systematic review and meta-analysis of seven randomized controlled trials of cardiovascular outcomes following vitamin D supplementation versus control treatment in 573 adults with chronic heart failure. The mean patient age was approximately 65, and 70% of the patients were male. The primary outcomes were left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) class, 6-minute walk distance, N-terminal pro-B-type natriuretic peptide (BNP), tumor necrosis factor-alpha (TNF-alpha), C-reactive protein (CRP), interleukin-10 (IL-10), parathyroid hormone (PTH), and renin.

### RESULTS:

Vitamin D supplementation significantly reduced serum levels of inflammatory mediators TNF-alpha (weighted mean difference [WMD] -2.42 pg/mL) and CRP (WMD -0.72 mg/L), as well as serum PTH (WMD -13.44 pg/mL) (all comparisons, p<0.05). When compared with conventional treatment, supplementation had no significant effect on IL-10, renin, LVEF, BNP or walking distance. The included trials are limited by deficiencies in methodology, small sample sizes, and heterogeneity.

### CONCLUSIONS:

These findings suggest that vitamin D supplementation decrease levels of serum PTH, TNF-alpha, and CRP in patients with chronic heart failure, but has no significant effect on LVEF, NYHA class, exercise tolerance, BNP or walking distance. The included trials are limited by deficiencies in methodology, small sample sizes, and heterogeneity.

### IMPORTANT

It remains unclear whether telemonitoring approaches provide benefits for patients with heart failure (HF) after hospitalization.

### OBJECTIVE:

To evaluate the effectiveness of a care transition intervention using remote patient monitoring in reducing 180-day all-cause readmissions among a broad population of older adults hospitalized with HF.

### DESIGN, SETTING, AND PARTICIPANTS:

We randomized 1437 hospitalized patients for HF between October 12, 2011, and September 30, 2013, to the intervention arm (715 patients) or to the usual care arm (722 patients) of the Better Effectiveness After Transition–Heart Failure (BEAT-HF) study and observed them for 180 days. The dates of our study analysis were March 30, 2014, to October 1, 2015. The setting was 6 academic medical centers in California. Participants were hospitalized individuals 50 years or older who received active treatment for decompensated HF.

### INTERVENTIONS:

The intervention combined health coaching telephone calls and telemonitoring. Telemonitoring used electronic equipment that collected daily information about blood pressure, heart rate, symptoms, and weight. Centralized registered nurses conducted telemonitoring reviews, protocolized actions, and telephone calls.

### MAIN OUTCOMES AND MEASURES:

The primary outcome was readmission for any cause within 180 days after discharge. Secondary outcomes were all-cause readmission within 30 days, all-cause mortality at 30 and 180 days, and quality of life at 30 and 180 days.

### RESULTS:

Among 1437 participants, the median age was 73 years. Overall, 46.2% (664 of 1437) were female, and 22.0% (316 of 1437) were African American. The intervention and usual care groups did not differ significantly in readmissions for any cause 180 days after discharge, which occurred in 50.8% (363 of 715) and 49.2% (355 of 722) of patients, respectively (adjusted hazard ratio, 1.03; 95% CI, 0.88-1.20; P = .74). In secondary analyses, there were no significant differences in 30-day readmission or 180-day mortality, but there was a significant difference in 180-day quality of life between the intervention and usual care groups. No adverse events were reported.

### CONCLUSIONS AND RELEVANCE:

Among patients hospitalized for HF, combined health coaching telephone calls and telemonitoring did not reduce 180-day readmissions.

### TRIAL REGISTRATION:

clinicaltrials.gov Identifier: NCT01360203.

### REFERENCE:

OBJECTIVES: To investigate the cardiovascular safety of non-steroidal anti-inflammatory drugs (NSAIDs) and estimate the risk of hospital admission for heart failure with use of individual NSAIDs.

DESIGN: Nested case-control study.

SETTING: Five population based healthcare databases from four European countries (the Netherlands, Italy, Germany, and the United Kingdom).

PARTICIPANTS: Adult individuals (age ≥18 years) who started NSAID treatment in 2000-10. Overall, 92 163 hospital admissions for heart failure were identified and matched with 8 246 403 controls (matched via risk set sampling according to age, sex, year of cohort entry).

MAIN OUTCOME MEASURE: Association between risk of hospital admission for heart failure and use of 27 individual NSAIDs, including 23 traditional NSAIDs and four selective COX 2 inhibitors. Associations were assessed by multivariable conditional logistic regression models. The dose-response relation between NSAID use and heart failure risk was also assessed.

RESULTS: Current use of any NSAID (use in preceding 14 days) was found to be associated with a 19% increase of risk of hospital admission for heart failure (adjusted odds ratio 1.19; 95% confidence interval 1.17 to 1.22), compared with past use of any NSAIDs (use >183 days in the past). Risk of admission for heart failure increased for seven traditional NSAIDs (diclofenac, ibuprofen, indomethacin, ketorolac, naproxen, nimesulide, and piroxicam) and two COX 2 inhibitors (etoricoxib and rofecoxib). Odds ratios ranged from 1.16 (95% confidence interval 1.07 to 1.27) for naproxen to 1.83 (1.66 to 2.02) for ketorolac. Risk of heart failure doubled for diclofenac, etoricoxib, indomethacin, piroxicam, and rofecoxib used at very high doses (≥2 defined daily dose equivalents), although some confidence intervals were wide. Even medium doses (0.9-1.2 defined daily dose equivalents) of indomethacin and etoricoxib were associated with increased risk. There was no evidence that celecoxib increased the risk of admission for heart failure at commonly used doses.

CONCLUSIONS: The risk of hospital admission for heart failure associated with current use of NSAIDs appears to vary between individual NSAIDs, and this effect is dose dependent. This risk is associated with the use of a large number of individual NSAIDs reported by this study, which could help to inform both clinicians and health regulators.


#10: PubMed: PCI no different from placebo procedure in patients with single vessel stenosis (> 70%) and SIHD

BACKGROUND: Symptomatic relief is the primary goal of percutaneous coronary intervention (PCI) in stable angina and is commonly observed clinically. However, there is no evidence from blinded, placebo-controlled randomised trials to show its efficacy.

METHODS: ORBITA is a blinded, multicentre randomised trial of PCI versus a placebo procedure for angina relief that was done at five study sites in the UK. We enrolled patients with severe (≥70%) single-vessel stenoses. After enrolment, patients received 6 weeks of medication optimisation. Patients then had pre-randomisation assessments with cardiopulmonary exercise testing, symptom questionnaires, and dobutamine stress echocardiography. Patients were randomised 1:1 to undergo PCI or a placebo procedure by use of an automated online randomisation tool. After 6 weeks of follow-up, the assessments done before randomisation were repeated at the final assessment. The primary endpoint was difference in exercise time increment between groups. All analyses were based on the intention-to-treat principle and the study population contained all participants who underwent randomisation. This study is registered with ClinicalTrials.gov, number NCT02062593.

FINDINGS: ORBITA enrolled 230 patients with ischaemic symptoms. After the medication optimisation phase and between Jan 6, 2014, and Aug 11, 2017, 200 patients underwent randomisation, with 105 patients assigned PCI and 95 assigned the placebo procedure. Lesions had mean area stenosis of 84·4% (SD 10·2), fractional flow reserve of 0·69 (0·16), and instantaneous wave-free ratio of 0·76 (0·22). There was no significant difference in the primary endpoint of exercise time increment between groups (PCI minus placebo 16·6 s, 95% CI -8·9 to 42·0, p=0·200). There were no deaths. Serious adverse events included four pressure-wire related complications in the placebo group, which required PCI, and five major bleeding events, including two in the PCI group and three in the placebo group.

INTERPRETATION: In patients with medically treated angina and severe coronary stenosis, PCI did not increase exercise time by more than the effect of a placebo procedure. The efficacy of invasive procedures can be assessed with a placebo control, as is standard for pharmacotherapy.


#11: PubMed: More exercise associated with lower mortality in patients with SIHD

BACKGROUND: Recommendations for physical activity in patients with stable coronary heart disease (CHD) are based on modest evidence.

OBJECTIVES: The authors analyzed the association between self-reported exercise and mortality in patients with stable CHD.

METHODS: A total of 15,486 patients from 39 countries with stable CHD who participated in the STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) study completed questions at baseline on hours spent each week taking mild, moderate, and vigorous exercise. Associations between the volume of habitual exercise in metabolic equivalents of task hours/week and adverse outcomes during a median follow-up of 3.7 years were evaluated.

RESULTS: A graded decrease in mortality occurred with increased habitual exercise that was steeper at lower compared with higher exercise levels. Doubling exercise volume was associated with lower all-cause mortality (unadjusted hazard ratio [HR]: 0.82; 95% confidence interval [CI]: 0.79 to 0.85; adjusting for covariates, HR: 0.90; 95% CI: 0.87 to 0.93). These associations were similar for cardiovascular mortality (unadjusted HR: 0.83; 95% CI: 0.80 to 0.87; adjusted HR: 0.92; 95% CI: 0.88 to 0.96), but myocardial infarction
and stroke were not associated with exercise volume after adjusting for covariates. The association between decrease in mortality and greater physical activity was stronger in the subgroup of patients at higher risk estimated by the ABC-CHD (Age, Biomarkers, Clinical-Coronary Heart Disease) risk score ($p$ for interaction $= 0.0007$).

**CONCLUSIONS:** In patients with stable CHD, more physical activity was associated with lower mortality. The largest benefits occurred between sedentary patient groups and between those with the highest mortality risk.

**REFERENCE:** Stewart RAH et al, for the STABILITY Investigators. Physical Activity and Mortality in Patients With Stable Coronary Heart Disease. J Am Coll Cardiol. 2017 Oct 3;70(14):1689-1700.

### ATRIAL FIBRILLATION

Most recommendations (51%) published in the ACC AHA atrial fibrillation guidelines are supported by C level “evidence” (e.g. expert opinion).

**#12: PubMed:** ACC AHA A Fib Guidelines 8.8% of recommendations Level A evidence

**Importance:** The joint American College of Cardiology (ACC), American Heart Association (AHA), and Heart Rhythm Society (HRS) guidelines on the management of atrial fibrillation (AF) are used extensively to guide patient care.

**Objective:** To describe the evidence base and changes over time in the AHA/ACC/HRS guidelines on AF with respect to the distribution of recommendations across classes of recommendations and levels of evidence.

**Data Sources:** Data from the AHA/ACC/HRS guidelines on AF from 2001, 2006, 2011, and 2014 were abstracted. A total of 437 recommendations were included.

**Data Extraction and Synthesis:** The number of recommendations and distribution of classes of recommendation (I, II, and III) and levels of evidence (A, B, and C) were determined for each guideline edition. Changes in recommendation class and level of evidence were analyzed using the 2001 and 2014 guidelines.

**Results:** From 2001 to 2014, the total number of AF recommendations increased from 95 to 113. Numerically, there was a nonsignificant increase in the use of level of evidence B (30.5% to 39.8%; $P = .17$) and a nonsignificant decrease in the use of level of evidence C (60.0% to 51.3%; $P = .21$), with limited changes in the use of level A evidence (8.4% to 8.8%; $P = .92$). In the 2014 guideline document, 10 of 113 (8.8%) recommendations were supported by level of evidence A, whereas 58 of 113 (51.3%) were supported by level of evidence C. Most recommendations were equally split among class I (49/113; 43.4%) and class IIa/IIb (49/113; 43.4%), with the minority (15/113; 13.3%) assigned as class III. Most class I recommendations were supported by level of evidence C (29/49; 59.2%), whereas only 6 of 49 (12.2%) were supported by level of evidence A. No rate control category recommendations were supported by level of evidence A.

**Conclusions and Relevance:** Some aspects of the quality of evidence underlying AHA/ACC/HRS AF guidelines have improved over time. However, the use of level of evidence A remains low and has not increased since 2001. These findings highlight the need for focused and pragmatic randomized studies on the clinical management of AF.


**#13: PubMed:** NOACs | As good as warfarin in AF

**Objective:** To study the effectiveness and safety of the non-vitamin K antagonist oral anticoagulants (novel oral anticoagulants, NOACs) dabigatran, rivaroxaban, and apixaban compared with warfarin in anticoagulant naïve patients with atrial fibrillation.

**Design:** Observational nationwide cohort study.

**Setting:** Three Danish nationwide databases, August 2011 to October 2015.

**Participants:** 61678 patients with non-valvular atrial fibrillation who were naïve to oral anticoagulants and had no previous indication for valvular atrial fibrillation or venous thromboembolism. The study population was distributed according to treatment type: warfarin (n=35436, 57%), dabigatran 150 mg (n=12701, 21%), rivaroxaban 20 mg (n=7192, 12%), and apixaban 5 mg (n=6349, 10%).

**Main Outcome Measures:** Effectiveness outcomes defined a priori were ischaemic stroke; a composite of ischaemic stroke or systemic embolism; death; and a composite of ischaemic stroke, systemic embolism, or death. Safety outcomes were any bleeding, intracranial bleeding, and major bleeding.

**Results:** When the analysis was restricted to ischaemic stroke, NOACs were not significantly different from warfarin. During one year follow-up, rivaroxaban was associated with lower annual rates of ischaemic stroke or systemic embolism (3.0% v 3.3%, respectively) compared with warfarin: hazard ratio 0.83 (95% confidence interval 0.69 to 0.99). The hazard ratios for dabigatran and apixaban (2.8% and 4.9% annually, respectively) were non-significant compared with warfarin. The annual risk of death was significantly lower with apixaban (5.2%) and dabigatran (2.7%) (0.65, 0.56 to 0.75 and 0.63, 0.48 to 0.82, respectively) compared with warfarin (8.5%), but not with rivaroxaban (7.7%). For the combined endpoint of any bleeding, annual rates for apixaban (3.3%) and dabigatran (2.4%) were significantly lower than for warfarin (5.0%) (0.62, 0.51 to 0.74). Warfarin and rivaroxaban had comparable annual bleeding rates (5.3%).

**Conclusion:** All NOACs seem to be safe and effective alternatives to warfarin in a routine care setting. No significant difference was found between NOACs and warfarin for ischaemic stroke. The risks of death, any bleeding, or major bleeding were significantly lower for apixaban and dabigatran compared with warfarin.

**Reference:** Larsen TB et al. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. BMJ. 2016 Jun 16;353:i3189
BACKGROUND: Therapeutic decisions in atrial fibrillation (AF) are often influenced by assessment of bleeding risk. However, existing bleeding risk scores have limitations.

OBJECTIVES: We sought to develop and validate a novel bleeding risk score using routinely available clinical information to predict major bleeding in a large, community-based AF population.

METHODS: We analysed data from Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF), a prospective registry that enrolled incident and prevalent AF patients at 176 US sites. Using Cox proportional hazards regression, we identified factors independently associated with major bleeding among patients taking oral anticoagulation (OAC) over a median follow-up of 2 years (interquartile range = 1.6-2.5). We also created a numerical bedside risk score that included the five most predictive risk factors weighted according to their strength of association with major bleeding. The predictive performance of the full model, the simple five-item score, and two existing risk scores (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly, HAS-BLED, and anticoagulation and risk factors in atrial fibrillation, ATRIA) were then assessed in both the ORBIT-AF cohort and a separate clinical trial population, Rivaroxaban Once-daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET-AF).

RESULTS: Among 7411 ORBIT-AF patients taking OAC, the rate of major bleeding was 4.0/100 person-years. The full continuous model (12 variables) and five-factor ORBIT risk score (older age [75+ years], reduced haemoglobin/haematocrit/history of anaemia, bleeding history, insufficient kidney function, and treatment with antiplatelet) both had good ability to identify those who bled vs. not (C-index 0.69 and 0.67, respectively). These scores both had similar discrimination, but markedly better calibration when compared with the HAS-BLED and ATRIA scores in an external validation population from the ROCKET-AF trial.

CONCLUSIONS: The five-element ORBIT bleeding risk score had better ability to predict major bleeding in AF patients when compared with HAS-BLED and ATRIA risk scores. The ORBIT risk score can provide a simple, easily remembered tool to support clinical decision making.

<table>
<thead>
<tr>
<th>Orbit Variables</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older Age (&gt; 74)</td>
<td>1</td>
</tr>
<tr>
<td>Reduced hemoglobin (men &lt; 13 g/dL</td>
<td>women &lt; 12 g/dL)</td>
</tr>
<tr>
<td>Bleeding tendency/predisposition*</td>
<td>2</td>
</tr>
<tr>
<td>Insufficient kidney function (GFR &lt; 60)</td>
<td>1</td>
</tr>
<tr>
<td>Treatment with antiplatelets</td>
<td>1</td>
</tr>
</tbody>
</table>

Low risk (0 – 2) | 2.4 bleeds/100 patient-years
Medium risk (3) | 4.7 bleeds/patient-years
High risk (≥ 4) | 8.1 bleeds/patient-years


<table>
<thead>
<tr>
<th>HAS-BLED</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (systolic blood pressure &gt;160 mm Hg)</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal renal and liver function*</td>
<td>1 or 2</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding tendency/predisposition*</td>
<td>1</td>
</tr>
<tr>
<td>Labile INRs (if on warfarin)*</td>
<td>1</td>
</tr>
<tr>
<td>Elderly (e.g., age &gt;65 y)</td>
<td>1</td>
</tr>
<tr>
<td>Drugs or alcohol (1 point each)*</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

Maximum score: 9

Abnormal renal function is classified as the presence of chronic dialysis, renal transplantation, or serum creatinine ≥2.3 mg/dl. Abnormal liver function is defined as chronic hepatic disease (eg, cirrhosis) or biochemical evidence of significant hepatic derangement (bilirubin 2 to 3 times the upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase 3 times the upper limit normal, etc), history of bleeding or predisposition (anemia), labile INR (ie, time in therapeutic range <60%), concomitant antiplatelets or nonsteroidal anti-inflammatory drugs, or excess alcohol.

High risk for bleeding > 3


#15: PubMed: NOACs | ~12% of US patients given off label doses → worse outcomes

**BACKGROUND:** Although non-vitamin K antagonist oral anticoagulants (NOACs) do not require frequent laboratory monitoring, each compound requires dose adjustments on the basis of certain clinical criteria.

**OBJECTIVES:** This study assessed the frequency of off-label NOAC doses among AF patients and the associations between off-label dose therapy and clinical outcomes in community practice.

**METHODS:** We evaluated 5,738 patients treated with a NOAC at 242 ORBIT-AF II (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation phase II) sites. NOAC doses were classified as either underdosed or overdosed, consistent with Food and Drug Administration labeling. Longitudinal outcomes (median follow-up: 0.99 years) included stroke or systemic embolism, myocardial infarction, major bleeding (International Society of Thrombosis and Haemostasis criteria), cause-specific hospitalization, and all-cause mortality.

**RESULTS:** Overall, 541 NOAC-treated patients (9.4%) were underdosed, 197 were overdosed (3.4%), and 5,000 were dosed according to U.S. labeling (87%). Compared with patients receiving the recommended dose, those who were receiving off-label doses were older (median: 79 and 80 years of age vs. 70 years of age, respectively; p < 0.0001), more likely female (48% and 67% vs. 40%, respectively; p < 0.0001), less likely to be treated by an electrophysiologist (18% and 19% vs. 27%, respectively; p < 0.0001), and had higher CHA2DS2-VASc scores (96% and 97% ≥2 vs. 86%, respectively; p < 0.0001) and higher ORBIT bleeding scores (25% and 31% >4 vs. 11%, respectively; p < 0.0001). After dose adjustment, NOAC overdosing was associated with increased all-cause mortality compared with recommended doses (adjusted hazard ratio: 1.91; 95% confidence interval [CI]: 1.02 to 3.60; p = 0.04). Underdosing was associated with increased cardiovascular hospitalization (adjusted hazard ratio: 1.26; 95% CI: 1.07 to 1.50; p = 0.007).

**CONCLUSIONS:** A significant minority (almost 1 in 8) of U.S. patients in the community received NOAC doses inconsistent with labeling. NOAC over- and underdosing are associated with increased risk for adverse events. (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II [ORBIT-AF II]; NCT01701817).


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#16: Center for Medical Education: Monitoring NOACs

The authors, coordinated at the University of Toronto, present a practical evidence-based checklist for monitoring direct oral anticoagulants (DOACs) applied for stroke prevention in atrial fibrillation, such as apixaban, dabigatran, edoxaban, and rivaroxaban. The checklist for safety monitoring and risk factor modification contains the key categories A (adherence), B (bleeding), C (creatinine clearance), D (drug interactions), E (examination), and F (follow-up), and a reference table. In particular, concomitant use of aspirin or NSAIDs can increase risk of bleeding. Benefits vs. bleeding risk of concomitant antiplatelet therapy need to be evaluated, and the addition of aspirin to warfarin is discouraged. As low patient adherence can increase stroke risk, a target adherence rate of greater than 80% is suggested, and adherence should be checked and supported by patient education, and problem solving or counseling, as indicated. At a creatinine clearance between 30 and 50mL/min/1.73m2, oral factor Xa inhibitors are preferred over dabigatran due to its lower renal elimination rate, and DOACs should be avoided at a creatinine clearance below 30mL/min/1.73m2. Creatinine levels and glomerular filtration rate should be assessed at least every six to twelve months, and more often in those with dehydrating illnesses and a baseline borderline low creatinine clearance. Hypertension treatment and fall prevention aids should be provided as indicated. Follow-up and reassessment are recommended every six months, or every three months for high-risk patients. A useful monitoring checklist is available (free of charge) at http://thrombosiscanada.ca/?p=1400.

**REFERENCE:** Gladstone DJ, et al. How to Monitor Patients Receiving Direct Oral Anticoagulants for Stroke Prevention in Atrial Fibrillation: A Practice Tool Endorsed by Thrombosis Canada, the Canadian Stroke Consortium, the Canadian Cardiovascular Pharmacists Network, and the Canadian Cardiovascular Society. Ann Intern Med. 2015 Sep 1;163(5):382-5 PMID: 26121536 Copyright 2016 by Primary Care Medical Abstracts – All Rights Reserved

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### Monitoring Patients on Direct Oral Anticoagulants

<table>
<thead>
<tr>
<th>Monitoring Patients on Direct Oral Anticoagulants</th>
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<tbody>
<tr>
<td><strong>Adherence</strong></td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
</tr>
<tr>
<td><strong>Creatinine clearance</strong></td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
</tr>
<tr>
<td><strong>Examination</strong></td>
</tr>
</tbody>
</table>
### Background
The Valsalva manoeuvre is an internationally recommended treatment for supraventricular tachycardia, but cardioversion is rare in practice (5-20%), necessitating the use of other treatments including adenosine, which patients often find unpleasant. We assessed whether a postural modification to the Valsalva manoeuvre could improve its effectiveness.

### Methods
We did a randomised controlled, parallel-group trial at emergency departments in England. We randomly allocated adults presenting with supraventricular tachycardia (excluding atrial fibrillation and flutter) in a 1:1 ratio to undergo a modified Valsalva manoeuvre (done semi-recumbent with supine repositioning and passive leg raise immediately after the Valsalva strain), or a standard semi-recumbent Valsalva manoeuvre. A 40 mm Hg pressure, 15 s standardised strain was used in both groups. Randomisation, stratified by centre, was done centrally and independently, with allocation with serially numbered, opaque, sealed, tamper-evident envelopes. Patients and treating clinicians were not masked to allocation. The primary outcome was return to sinus rhythm at 1 min after intervention, determined by the treating clinician and electrocardiogram and confirmed by an investigator masked to treatment allocation. This study is registered with Current Controlled Trials (ISRCTN67937027).

### Findings
We enrolled 433 participants between Jan 11, 2013, and Dec 29, 2014. Excluding second attendance by five participants, 214 participants in each group were included in the intention-to-treat analysis. 37 (17%) of 214 participants assigned to standard Valsalva manoeuvre achieved sinus rhythm compared with 93 (43%) of 214 in the modified Valsalva manoeuvre group (adjusted odds ratio 3·7 (95% CI 2·3-5·8; p<0·0001). We recorded no serious adverse events.

### Interpretation
In patients with supraventricular tachycardia, a modified Valsalva manoeuvre with leg elevation and supine positioning at the end of the strain should be considered as a routine first treatment, and can be taught to patients.

### Funding
National Institute for Health Research.

### Reference

### Key Points
1. The ARN inhibitor Valsartan/sacubitril combination has received a Class 1 recommendation from the ACC/AHA in the treatment of Stage 3 (NYHA Class II or III) CHF with reduced ejection fraction (HFrEF)
2. In patients with coronary artery disease, heart failure, and severe left ventricular systolic dysfunction, CABG plus medical therapy is associated with better outcomes than medical therapy
3. Vitamin D is not associated with any patient orientated outcomes in patients with CHF
4. NSAIDS increase risk of hospitalization for CHF
5. NOACs are as good as warfarin in AF, but are given in off label doses ~ 12% of the time
6. The ORBIT risk score can provide a simple, easily remembered tool to support clinical decision making.
7. A modified Valsalva is effective in terminating SVT ~50% of the time

### Appendix 1: Doses of HF meds achieved in clinical trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean Doses Achieved in Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Daily Dose</td>
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<tr>
<td>-----------------</td>
<td>------------</td>
</tr>
<tr>
<td>Captopril</td>
<td>122 mg/d</td>
</tr>
<tr>
<td>Enalapril</td>
<td>16 mg/d</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>35 mg/d</td>
</tr>
<tr>
<td>Candesartan</td>
<td>24 mg/d</td>
</tr>
<tr>
<td>Losartan</td>
<td>129 mg/d</td>
</tr>
<tr>
<td>Valsartan</td>
<td>254 mg/d</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>37 mg/d</td>
</tr>
<tr>
<td>Metoprolol succinate</td>
<td>159 mg/d</td>
</tr>
</tbody>
</table>

Adapted from J Cardiac Failure 2017;23:628
Appendix 2:

ACC/AHA AF 2014 Guidelines on Atrial Fibrillation

“The ACC/AHA practice guidelines are intended to assist clinicians in clinical decision making by describing a range of generally acceptable approaches to the diagnosis, management, and prevention of specific diseases or conditions. The guidelines attempt to define practices that meet the needs of most patients in most circumstances ... situations may arise in which deviations from these guidelines may be appropriate.” The ACC/AHA recommendations are associated with various recommendation strengths:

Class of Recommendation Table

- **Class I (Benefit >>> Risk):** Should be done
- **Class IIa (Benefit >> Risk):** Reasonable to do
- **Class IIb (Benefit > Risk):** May be considered
- **Class III (No benefit or harm):** Not helpful or harmful

Estimate of certainty of treatment effect

- **Level A:** Multiple populations evaluated, Multiple RCTs or meta-analyses
- **Level B:** Limited populations evaluated, Single RCT or nonrandomized trials
- **Level C:** Very limited populations evaluated; Consensus opinion, Standard of care

<table>
<thead>
<tr>
<th>Anticoagulant Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation</strong></td>
</tr>
<tr>
<td>In patients with AF, antithrombotic therapy should be individualized based on shared decision making after discussion of the absolute and relative risks of stroke and bleeding and the patient’s values and preferences.</td>
</tr>
<tr>
<td>Selection of antithrombotic therapy should be based on the risk of thromboembolism irrespective of whether the AF pattern is paroxysmal, persistent, or permanent</td>
</tr>
<tr>
<td>In patients with nonvalvular AF, the CHA2DS2-VASc score is recommended for assessment of stroke risk</td>
</tr>
<tr>
<td>For patients with nonvalvular AF with prior stroke, transient ischemic attack (TIA), or a CHA2DS2-VASc score of 2 or greater, oral anticoagulants are recommended. Options include:</td>
</tr>
<tr>
<td>- warfarin (INR 2.0 to 3.0)</td>
</tr>
<tr>
<td>- dabigatran</td>
</tr>
<tr>
<td>- rivaroxaban</td>
</tr>
<tr>
<td>- apixaban</td>
</tr>
<tr>
<td>Among patients treated with warfarin, the INR should be determined at least weekly during initiation of antithrombotic therapy and at least monthly when anticoagulation (INR in range) is stable</td>
</tr>
<tr>
<td>For patients with nonvalvular AF unable to maintain a therapeutic INR level with warfarin, use of a direct thrombin or factor Xa inhibitor (dabigatran, rivaroxaban, or apixaban) is recommended</td>
</tr>
<tr>
<td>Renal function should be evaluated before initiation of direct thrombin or factor Xa inhibitors and should be reevaluated when clinically indicated and at least annually</td>
</tr>
</tbody>
</table>
Pediatric Potpourri 2018

John Hickner, MD, MSc
Written by: Steven R. Brown, MD

Objectives

1. Summarize clinical approaches to fever in a pediatric patient
2. Discuss updates in well-child preventive care including vision screening and screening for hip dysplasia
3. Review evidence for use of tympanostomy tubes

What is a reasonable approach to the febrile infant? Is clinical diagnosis reliable? Are any blood tests helpful?

#1: Clinical diagnosis of serious infection in children is difficult

Clinical question: How reliable is the history and physical in determining if a child has a serious infection?
Study design: Meta-analysis (other)
Setting: Various (meta-analysis)
Synopsis: These authors searched several databases looking for studies in ambulatory settings that evaluated clinical features of children (1 month to 18 years of age) with suspected serious infection. The studies had to include an appropriate spectrum of illness severity and a reference standard. The authors defined serious infection as sepsis (including bacteremia), meningitis, pneumonia, osteomyelitis, cellulitis, gastroenteritis with dehydration, complicated urinary tract infection (positive urine culture and systemic signs such as fever), and viral respiratory tract infections complicated by hypoxia (eg, bronchiolitis). One can argue about whether some of these are truly serious. Two authors independently assessed the quality of each study, finding most only fair to poor. They found 30 studies evaluating clinical features. The studies included from 72 to 3981 children! The positive likelihood ratios (LR+) for individual elements of the history ranged from 1 to 23 and the negative likelihood ratios (LR-) ranged from 0.26 to 1.3. (Remember: Tests with likelihood ratios of 1 provide no useful information and that an LR+ near 10 and an LR- near 0.1 have the greatest discriminatory capacity.) In most of the studies, the value of the history and physical ranged widely on the basis of the rate of illness in the sick children (less than 5%, 5% to 20%, or more than 20%). Among all of the tested history and physical findings, 4 were predictive for serious infections: cyanosis (LR+ range = 2.66 - 52.2); rapid breathing (LR+ range = 1.26 - 9.78); poor peripheral perfusion (LR+ range = 2.39 - 38.8); and petechial rash (LR+ range = 6.18 - 83.7). In one primary care study, parental concern and clinician instinct were also strong red flags. The negative likelihood ratios, however, were too high to be useful to rule out serious infection. Clinical decision rules, such as the Yale Observational Scale, were also quite variable with the LR+ ranging from 1.1 to 7 and the LR- from 0.2 to 1. There are a couple of "Aunt Fannie" findings in this study (everyone has an Aunt Fannie who can be recognized from 100 feet away because of her easily recognized and eccentric manner of dress). For example, the presence of petechiae, nuchal rigidity, or coma had a LR+ of 395. I think most of us would recognize that a comatose child is seriously ill!
Bottom line: In this systematic review, each element of the history and physical has a wide enough range of reliability that they should not be used independently to evaluate sick children. Specifically, they are not reliable enough to rule out serious infection. (LOE = 1a-)

#2: Pediatric SIRS criteria not accurate for predicting which children will require critical care

Clinical question: How useful are pediatric SIRS vital signs in predicting which children require critical care resuscitation?
Study design: Cohort (retrospective)
Setting: Emergency department
Synopsis: Pediatric SIRS vital signs require the presence of 2 or more of the following criteria, one of which must be abnormal temperature or leukocyte count: Core temperature less than 36C or greater than 38.5C, tachycardia (or bradycardia in infants), tachypnea, abnormal leukocyte count for age, or greater than 10% immature neutrophils. Despite consensus agreement on these criteria, their effectiveness as a screening test for detecting critically ill children is unknown. These investigators retrospectively analyzed data from all visits by patients younger than 18 years to the emergency department (ED) of a tertiary academic pediatric hospital between April 2011 and March 2012. Eligible patients (N = 40,356) included those presenting to the ED for the first time within the preceding 72 hours with nontrauma-related diagnoses and for whom SIRS vital signs were recorded. A temperature-heart rate correction was performed: For each 1 degree Celsius above 38.5C, 10 beats per minute was subtracted from the heart rate. Outcomes included requirement for critical care within 24 hours of ED arrival, intensive care unit admission, 30-day in-hospital mortality, 72-hour readmission, ED laboratory evaluation, and ED intravenous therapy. A total of 6122 patients (15.2%) met SIRS criteria. Of these, 4993 (81.6%) were discharged from the ED without the need for intravenous therapy and without 72-hour readmission. Only 99 children (0.25%) required critical care within the first 24 hours, including 23 patients with and 76 without SIRS vital signs. Those children meeting SIRS criteria had a significantly increased risk of critical care requirement, intensive care unit admission, and intravenous therapy, but the sensitivity of meeting the SIRS criteria for critical care requirement was only 23.2% (95% CI 15.3%-32.8%). The pair of SIRS vital signs with the highest positive likelihood ratio was temperature and corrected heart rate (LR+ = 2.74; 95% CI 1.87-4.01). Positive likelihood ratios of less than 5 are generally felt to be clinically useful. No differences in results were detected in any specific age subgroups.
Bottom line: Pediatric systemic inflammatory response syndrome (SIRS) vital signs are minimally, if at all, accurate in predicting which acutely ill children will require critical care resuscitation. (LOE = 2c)

#3: Useful signs and symptoms for diagnosing pneumonia in children younger than 5 years

Clinical question: Are there useful signs and symptoms for diagnosing pneumonia in children younger than 5 years?
Study design: Other Funding source: Unknown/not stated
Setting: Population-based
Synopsis: These investigators sourced MEDLINE and Embase, as well as pertinent references for articles evaluating the accuracy of the medical history and physical examination for the diagnosis of pneumonia in children younger than 5 years. Additional eligibility criteria included the use of chest radiography as the reference standard for diagnosis. Two individuals evaluated potential articles for study inclusion and assessed methodologic quality using a standard scoring tool. Disagreements were resolved by consensus discussion with a third reviewer. Only studies of medium or high quality were included. A total of 23 prospective cohort studies (N = 13,833 patients) met inclusion criteria. The presence of chest pain was the only symptom with a positive likelihood ratio approximating at least 2.0 (LR+ = 1.9; 95% CI 1.1 - 3.4). Cough, difficulty breathing, vomiting, and diarrhea all had positive likelihood ratios that were not useful (95% CI that included 1.0). Absence of cough was the only finding with a negative likelihood ratio of less than 0.5 (LR- = 0.47; 0.24 - 0.70). The finding of hypoxemia varied with oxygen saturation thresholds: hypoxemia at 96% or less (LR+ = 2.8; 2.1 - 3.6) and hypoxemia at 95% or less (LR+ = 3.5; 2.0 - 6.4). More severe hypoxemia (oxygen saturation < 90%) was actually less useful (LR+ = 1.5; 1.1 - 1.9). A normal oxygenation saturation (> 96%) was useful for ruling out pneumonia (LR- = 0.47; 0.32 - 0.67). The presence of fever was not useful for ruling in pneumonia, but the absence of fever decreased the likelihood of pneumonia (LR- range = 0.17 - 0.37). Tachypnea (respiratory rate at least 40 breaths per minute), the physicians general assessment of the presence or absence of tachypnea, and tachypnea defined by age-specific rates all had positive likelihood ratios of less than 2.0 or with 95% CI that included 1.0 or less. However, a respiratory rate less than or equal to 40 breaths per minute decreased the likelihood of pneumonia (LR- = 0.41; 0.17 - 0.99). No auscultatory findings—including crackles, rales, crepitations, wheeze and rhonchi—were useful in ruling pneumonia in or out. Signs of increased work of breathing were the most useful physical examination findings, including grunting (LR+ = 2.7; 1.5 - 5.1), nasal flaring (LR+ = 2.2; 1.3 - 3.1), and chest retractions (LR+ = 1.9; 1.2 - 2.5).
Bottom line: No single symptom or physical examination finding is reliably useful (positive likelihood ratio [LR+] > 10.0; negative likelihood ratio [LR-] < 0.1) for diagnosing pneumonia in children younger than 5 years. Hypoxia (oxygen saturation < 96%) and physical findings of increased work of breathing (grunting, nasal flaring, and chest retractions) are the most useful for the diagnosis of pneumonia. Tachypnea and auscultation are not useful. (LOE = 3a)

#4: Clinical signs and symptoms of pneumonia unreliable in children

Clinical question: Which clinical features are useful for the accurate diagnosis of pneumonia in children younger than 5 years?
Study design: Systematic review Funding source: Government
Setting: Various (meta-analysis)
Synopsis: These investigators searched multiple databases including MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews, as well as performed manual searches of reference lists from eligible articles, for studies evaluating the diagnostic accuracy of clinical signs and symptoms of pneumonia in children aged between 2 months and 6 years. Studies included otherwise healthy children with acute respiratory infections from both the ambulatory and inpatient hospital settings. No language restrictions were applied. Two reviewers used standard risk of bias assessment tools to independently assess articles for inclusion criteria and methodological quality. Disagreements were resolved by consensus discussion. Chest radiography served as the reference standard for the diagnosis of pneumonia. Of the 18 studies that met the inclusion criteria, most were of low to moderate risk of bias. No clinical signs or symptoms reached the level for commonly accepted clinical usefulness (positive likelihood ratio [LR+] > 5 or negative likelihood ratio [LR-] < 0.2). The most useful signs and symptoms for ruling in pneumonia included respiratory rate higher than 50 breaths per minute (LR+ = 1.90; 95% CI 1.45-2.48); grunting (LR+ = 1.78; 1.10-2.88), chest retractions (LR+ = 1.76; 0.86-3.58), and nasal flaring (LR+ = 1.75; 1.20-2.56). The most useful signs and symptoms (when absent) for excluding the diagnosis of pneumonia included cough (LR? = 0.30; 0.09-0.96), history of fever (LR? = 0.53; 0.41-0.69), and respiratory rate higher than 40 breaths per minute (LR? = 0.43; 0.23-0.83).
Bottom line: Standard clinical signs and symptoms are minimally useful in accurately diagnosing pneumonia in children younger than 5 years. The most useful signs and symptoms for ruling in pneumonia included a respiratory rate higher than 50 breaths per minute, grunting, chest retractions, and nasal flaring. The most useful signs and symptoms (when absent) for excluding the diagnosis of pneumonia included cough, history of fever, and a respiratory rate higher than 40 breaths per minute. (LOE = 2a)

#5: Gut feelings have good negative predictive value for serious infection in children

Clinical question: What is the accuracy of a clinician’s gut feelings about the seriousness of illness in children without overt symptoms of serious infection?
Study design: Diagnostic test evaluation  
Funding source: Foundation  
Setting: Outpatient (primary care)  
Synopsis: Cognitive researchers have found that experienced clinicians make diagnoses using 2 different approaches: either a slow, logical, step-by-step reasoning process, or (more often) a fast, intuitive approach based on recognition of patterns of illness seen in previous cases. This study, conducted in Belgium, evaluated the role of the latter approach, which they called "gut feeling," in the diagnosis of children with possible serious infections. The researchers evaluated 3890 consecutive children aged 0 to 16 years presenting to primary care physicians with acute illness. For each child the doctors recorded clinical features along with their overall clinical impression and whether the doctor had a gut feeling, based on intuition, suggesting the child had something more serious than was suggested by the clinical features. The report doesn't tell us anything about the clinicians but they all seem to be practicing in primary care. After this initial assessment the children were cared for in the usual manner. Serious infection -- defined as requiring hospitalization for pneumonia, sepsis, meningitis, or other infections -- occurred in 21 children (0.54%). Physicians' gut feeling of seriousness was present in 62% of these children but also in 2.7% of children without a serious illness, resulting in a sensitivity of 61.9% and a specificity of 97%. Given the low likelihood of serious infection in the group, though, the positive predictive value was only 10.8% and the negative predictive value was 99.8%. An accurate gut feeling of seriousness was present for 2 of the 6 seriously ill children whose clinical features suggested a nonserious illness (positive predictive value = 4.4%; negative predictive value = 99.8%). Individual clinical features strongly associated with a gut feeling of serious illness were the child's lack of responsiveness, abnormal breathing, weight loss, convulsions, and parents' concern.  
Bottom line: An intuitive feeling that the objective clinical assessment of a sick child misrepresents the seriousness of his or her illness usually overidentifies serious infection. But, in some cases, this gut feeling is correct. In this study, a parent's concern and nonspecific symptoms in the child (such as drowsiness, abnormal breathing, weight loss, and convulsions) were linked to clinicians' gut feelings of a more serious illness. The authors suggest that you can hone the accuracy of these gut feelings by reflecting on the triggers in the clinical presentation that make you suspicious of something more serious. (LOE = 1c)  

#6: CRP and procalcitonin best for dx in febrile children

Clinical question: What is the diagnostic value of laboratory tests for the diagnosis of serious infections in febrile children?  
Study design: Meta-analysis (other)  
Funding source: Government  
Setting: Outpatient (any)  
Synopsis: To conduct this systematic review, the authors searched 4 databases, including DARE, to find studies that evaluated the diagnostic accuracy of tests in febrile outpatient children at least 30 days of age. They identified 14 studies, all of moderate quality or low quality. The prevalence of serious infection ranged from 4.5% to 29.3%. The tests best at ruling in serious infection were C-reactive protein, using a cut-off of 80 mg/L (positive likelihood ratio [LR+] = 8.4; 95% CI, 5.1 - 14.1), and procalcitonin greater than 2 ng/mL (LR+ [from 2 studies] = 3.6 and 13.7; 95% CIs, 7.4 - 25.3 and 1.4 - 8.9). Using a C-reactive protein cutoff of 20 mg/L (negative likelihood ratio [LR-] = .19 - .25) and a procalcitonin cutoff of .5 ng/mL (LR- = .08 - .25) is effective in ruling out serious infection. An elevated white blood cell count is not effective at ruling in or ruling out disease. Combinations of tests did not appreciably improve diagnostic accuracy.  
Bottom line: C-reactive protein and procalcitonin are the most effective laboratory tests for ruling in or ruling out serious infections in febrile children. Both tests are better at ruling out than ruling in disease. A white blood cell count is not useful, and other markers of inflammation do not provide good sensitivity or specificity. (LOE = 2a)  

From the authors:

What this study adds  
C reactive protein and procalcitonin may be useful measures, but different cut-off values should be used for ruling in or ruling out serious infections  
White blood cell counts are less useful  

MAJOR CAVEATS:  
No evidence from primary care was identified  
No studies of high methodologic quality
#7: Risk-based use of CRP preferred for acutely ill children

**Clinical question:** Should C-reactive protein be used for all acutely ill children, or only for those at high risk of serious infection?

**Study design:** Randomized controlled trial (nonblinded)

**Funding source:** Government

**Allocation:** Unconcealed

**Setting:** Outpatient (primary care)

**Synopsis:** CRP is an inflammatory biomarker available as a rapid point-of-care test in many countries (it is not CLIA-waived in the United States, though). It has been shown in previous studies to be a good predictor of pneumonia, acute sinusitis, and other bacterial infections. In this study, 133 general practitioners in 78 practices in Belgium were randomized to use universal or selective CRP for acutely ill children. Children aged 1 month to 16 years were eligible for the study if they had been sick for less than 5 days, and if the illness was not due to a traumatic, neurologic, or psychiatric condition, or to poisoning or intoxication. The universal group always ordered a CRP, while the selective group only ordered a CRP when one of the following was present: shortness of breath, fever 40 °C or higher, diarrhea (in children 12 to 30 months old), or "physician concern." The primary outcome was whether the child was hospitalized for a serious infection between 1 and 5 days after the index visit. In the selective testing group, 285 of 1417 patients met the criteria for testing, of whom 30 were referred to the hospital and 4 had a serious infection. In the comparison group, 50 were referred to the hospital, of whom 7 had a serious infection. These small differences between groups were not statistically significant. In the selective testing group, a cutoff of 5 mg/L or higher would not have missed any serious infections, but would have resulted in a 57% false positive rate. Among the 24 children who met these criteria and had a CRP level of less than 5 mg/L who were referred to the hospital, 13 received a final diagnosis of viral upper respiratory tract infection, 3 had a urinary tract infection, and 8 had viral gastroenteritis. Only one of these 24 children were admitted.

**Bottom line:** Restricting the use of C-reactive protein (CRP) to children with shortness of breath, fever of 40 °C or higher, or diarrhea (in 12- to 30-month-olds), or because of "physician concern" is a safe strategy. Of the 24 children who met these criteria and had a CRP level of less than 5 mg/L, 3 had a urinary tract infection and the remainder had a self-limited viral infection. (LOE = 1b-)


What’s new with the well child exam?

#8: American Academy of Pediatrics guidelines for hip dysplasia screening and treatment

**Clinical question:** How should infants be screened and treated for hip dysplasia?
Supplementation. In both cases—benefit and harm—absence of proof is not proof of absence. It would be great to have research that good research showing a benefit to iron supplementation in identified children. Limited evidence does not show significant harm with children without risk factors. Evaluation for possible hip dislocation should be performed by an orthopedist. The authors also suggest counseling parents to swaddle the infant in a way that does not restrict hip motion. The guideline developers acknowledge these guidelines are very conservative and err on the side of overdiagnosis; the US Preventive Services Task Force has concluded there is insufficient evidence to support screening. If you find a click or clunk on examination, remember that only 1 in 8 children with positive findings will have dysplasia (Arch Dis Child Fetal Neonatal Ed 2005;90:F25-30).

**Bottom line:** The American Academy of Pediatrics continues to recommend universal ultrasonography for the screening of newborns for developmental hip dysplasia, reserving ultrasound screening for infants at "high risk." A video showing an abnormal Barlow-Ortolani test result can be downloaded at www2.aap.org/sections/ortho/BarlowOrtolani.avi. The authors also suggest counseling parents to swaddle infants in a way that does not restrict hip motion. (LOE = 5)


### #9: USPSTF 2017 recommends vision screening for all children aged 3 years to 5 years

**Clinical question:** Should primary care clinicians screen for vision abnormalities in children younger than 6 years?

**Study design:** Practice guideline

**Setting:** Population-based

**Synopsis:** In this updated review the USPSTF evaluated current evidence that assessed the accuracy of vision screening tests and the benefits and harms of vision screening and treatment in children younger than 6 years. The prevalence of amblyopia or its risk factors in this age group is 1% to 6%. No eligible randomized clinical trials directly compared screening with no screening. In addition, no studies evaluated patient-oriented outcomes, such as school performance or quality of life. The task force found adequate evidence that vision-screening tools are accurate for detecting vision abnormalities. Treatment of amblyopia is associated with improved visual acuity in children aged 3 to 5 years. Potential harms of screening include psychosocial problems due to labeling and anxiety (eg, if wearing a patch or eyeglasses is necessary), unnecessary referrals due to false-positive results, and unnecessary treatments. Overall, the task force considered the potential harms of screening and subsequent treatment as small. Trials that examined the benefits and harms of treatment did not enroll children younger than 3 years. The Academy of Pediatrics and Ophthalmology recommend vision assessment in children aged 6 months to 3 years. The American Academy of Family Physicians recommends vision screening in all children at least once between the age of 3 years and 5 years.

**Bottom line:** The US Preventive Services Task Force (USPSTF) recommends that primary care clinicians perform visual screening at least once for all children aged 3 to 5 years to detect amblyopia or its risk factors (B recommendation). Current evidence is insufficient to assess the benefits and harms of vision screening in children younger than 3 years (I statement). This updated recommendation is essentially unchanged from the previous recommendation in 2011. (LOE = 2b)


### #10: Screening for and treating iron deficiency in children: no evidence of benefit or harm

**Clinical question:** Is there a benefit to screening for iron deficiency in infants and children and in subsequently giving supplements to those found to be deficient?

**Study design:** Systematic review

**Funding source:** Government

**Setting:** Various (meta-analysis)

**Synopsis:** Here's the logic trail: Iron deficiency can be identified in approximately 8% of infants and toddlers in the United States; approximately one-third of these children (and 1% to 2% of all children) will have iron-deficiency anemia. However, there is no research that demonstrates either the harm or the benefit of treating iron deficiency or anemia. The researchers searched Medline and the Cochrane databases, as well as reference lists of systematic reviews, to identify English-language clinical trials and observational studies performed in developed countries regarding the screening for iron deficiency and the benefits and harms of iron supplementation in children aged 6 to 24 months. Two investigators evaluated identified studies for inclusion and 2 investigators evaluated included research for quality. They found no studies that evaluated the effect of screening on growth, development, mortality, or quality of life. Iron supplementation had an inconsistent effect on hematologic measures (10 studies). No studies of iron supplementation evaluated the effect on neurodevelopment. Five of 6 weak studies found no clear benefit on growth. No studies have evaluated the harm of iron supplementation.

**Bottom line:** There is no evidence to support screening for iron deficiency or iron-deficiency anemia in infants and toddlers, and no good research showing a benefit to iron supplementation in identified children. Limited evidence does not show significant harm with supplementation. In both cases—benefit and harm—absence of proof is not proof of absence. It would be great to have research that explores these common interventions in children. (LOE = 1a)

#11: USPSTF: Prevention of dental caries in children

**DESCRIPTION:** Update of the 2004 US Preventive Services Task Force (USPSTF) recommendation on prevention of dental caries in preschool-aged children.

**METHODS:** The USPSTF reviewed the evidence on prevention of dental caries by primary care clinicians in children 5 years and younger, focusing on screening for caries, assessment of risk for future caries, and the effectiveness of various interventions that have possible benefits in preventing caries.

**POPULATION:** This recommendation applies to children age 5 years and younger.

**RECOMMENDATION:** The USPSTF recommends that primary care clinicians prescribe oral fluoride supplementation starting at age 6 months for children whose water supply is deficient in fluoride. (B recommendation) The USPSTF recommends that primary care clinicians apply fluoride varnish to the primary teeth of all infants and children starting at the age of primary tooth eruption. (B recommendation) The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of routine screening examinations for dental caries performed by primary care clinicians in children from birth to age 5 years. (I Statement).


#12: USPSTF: Screening for speech and language delay and disorders

**BACKGROUND:** This report is an update of the US Preventive Services Task Force (USPSTF) 2006 recommendation on screening for speech and language delay in preschool-aged children.

**METHODS:** The USPSTF reviewed the evidence on screening for speech and language delay and disorders in children aged 5 years or younger, including the accuracy of screening in primary care settings, the role of surveillance by primary care clinicians, whether screening and interventions lead to improved outcomes, and the potential harms associated with screening and interventions.

**POPULATION:** This recommendation applies to asymptomatic children aged 5 years or younger whose parents or clinicians do not have specific concerns about their speech, language, hearing, or development.

**RECOMMENDATION:** The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for speech and language delay and disorders in children aged 5 years or younger (I statement).


#13: USPSTF: Screening for autism spectrum disorder in young children

**DESCRIPTION:** New US Preventive Services Task Force (USPSTF) recommendation on screening for autism spectrum disorder (ASD) in young children.

**METHODS:** The USPSTF reviewed the evidence on the accuracy, benefits, and potential harms of brief, formal screening instruments for ASD administered during routine primary care visits and the benefits and potential harms of early behavioral treatment for young children identified with ASD through screening.

**POPULATION:** This recommendation applies to children aged 18 to 30 months who have not been diagnosed with ASD or developmental delay and for whom no concerns of ASD have been raised by parents, other caregivers, or health care professionals.

**RECOMMENDATION:** The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for ASD in young children for whom no concerns of ASD have been raised by their parents or a clinician. (I statement).


#14: Editorial: What to Do at Well-Child Visits: The AAFP's Perspective

Evidence supports the following clinical interventions:

- **Newborns**
  - Congenital hypothyroidism, screening
  - Hearing loss, screening
  - Ocular gonorrhea infection, preventive medication
  - Phenylketonuria, screening
  - Sickle cell disease, screening

- **Children six months and older**
  - Fluoride supplementation in areas where the primary water source is deficient in fluoride

- **Children three to five years of age**
  - Visual impairment, screening
School-aged children  Tobacco use, counseling to prevent initiation

Children six years and older  Obesity, screening

Children 10 years and older  Skin cancer, counseling to reduce risk

Children 12 years and older  Depression, screening

Sexually active adolescents  Sexually transmitted infections, counseling to reduce risk

Sexually active adolescent females  Gonorrhea and chlamydia infections, screening

Children at high risk of infection  Hepatitis B virus, screening

“The current AAP Bright Futures guideline includes three screening tests that were not recommended for all children in previous versions: autism screening at 18 and 24 months of age, cholesterol screening between nine and 11 years of age, and annual screening for high blood pressure beginning at three years of age.”

“Time is a precious clinical resource. Clinicians who spend time delivering unproven or ineffective interventions at health maintenance visits risk “crowding out” effective services. For example, a national survey of family and internal medicine physicians regarding adult well-male examination practices found that physicians spent an average of five minutes discussing prostate-specific antigen screening (a service that the AAFP and the USPSTF recommend against because the harms outweigh the benefits), but one minute or less each on nutrition and smoking cessation counseling. Similarly, family physicians have limited time at well-child visits and therefore should prioritize preventive services that have strong evidence of net benefit.”


When are tympanostomy tubes recommended for otitis media with effusion? How strong is the evidence they are beneficial?

#15: AHRQ: Otitis Media With Effusion: Comparative Effectiveness of Treatments

Objectives: To compare benefits and harms of strategies currently in use for managing otitis media with effusion (OME). Treatment for OME may include single approaches alone or combinations of two or more approaches. We compared benefits and harms among these treatments: tympanostomy tubes (TT), myringotomy (myr), adenoidectomy (adenoid), autoinflation (auto), oral or nasal steroids, complementary and alternative medicine (CAM), and watchful waiting (WW). We included comparisons of treatment effectiveness in subgroups of patients with OME, and whether outcome differences were related to factors affecting health care delivery or the receipt of pneumococcal vaccine inoculation.

Data sources: We identified five recent systematic reviews a priori and searched MEDLINE, Embase, the Cochrane Library, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL), from root through August 13, 2012, for additional studies. Eligible studies included randomized controlled trials (RCTs), nonrandomized trials, and cohort studies.

Review methods: Eligible studies included at least two arms comparing the treatments described above. Pairs of reviewers independently selected, extracted data from, and rated the risk of bias of relevant studies; they graded the strength of evidence using established criteria. We incorporated meta-analyses from the earlier reviews and synthesized additional evidence qualitatively.

Results: We identified 59 studies through the earlier reviews and our independent searches. Generally, studies examined interventions in otherwise healthy, noninfant children. We did not find any eligible studies covering CAM. Findings are reported for clinical and functional outcomes, and harms. Variation in length of TT retention corresponded to whether TT were designed to be short versus long term, but variation in TT type was not related to improved OME and hearing outcomes. TT decreased OME for 2 years compared with WW or myr, and improved hearing for 6 months compared with WW. OME resolution was more likely with adenoid than no treatment at 12 months. Adenoid and myr were superior to myr alone in relation to OME and hearing outcomes at 24 months. Adenoid and TT were superior to WW for hearing outcomes at 24 months. Auto was superior to standard treatment at improving OME at 1 month. We found no benefits from oral steroids at 2 months, or topical steroids at 9 months. In relation to functional outcomes, TT and WW did not differ in long-term language, cognitive or academic outcomes. Tymanosclerosis and otorrhea were more common in ears with TT. Adenoid increased the risk of postsurgical hemorrhage. In one study of a subgroup, adults receiving auto were more likely to recover from OME than those in the control group at one month. We found no studies examining the influence of any health care factors on treatment effectiveness.

Conclusions: There is evidence that both TT and adenoid reduce OME and improve hearing in the short term, but both treatments also have associated harms. Large, well-controlled studies could help resolve the risk-benefit ratio by measuring AOM recurrence, functional outcomes, quality of life measures, and long-term outcomes. Finally, additional research is needed to support treatment decisions in subpopulations, particularly those with comorbidities and those who have received a pneumococcal vaccine inoculation.
#16: Clinical practice guideline: Tympanostomy tubes in children.

Objective: Insertion of tympanostomy tubes is the most common ambulatory surgery performed on children in the United States. Tympanostomy tubes are most often inserted because of persistent middle ear fluid, frequent ear infections, or ear infections that persist after antibiotic therapy. Despite the frequency of tympanostomy tube insertion, there are currently no clinical practice guidelines in the United States that address specific indications for surgery. This guideline is intended for any clinician involved in managing children, aged 6 months to 12 years, with tympanostomy tubes or being considered for tympanostomy tubes in any care setting, as an intervention for otitis media of any type.

Purpose: The primary purpose of this clinical practice guideline is to provide clinicians with evidence-based recommendations on patient selection and surgical indications for and management of tympanostomy tubes in children. The development group broadly discussed indications for tube placement, perioperative management, care of children with indwelling tubes, and outcomes of tympanostomy tube surgery. Given the lack of current published guidance on surgical indications, the group focused on situations in which tube insertion would be optional, recommended, or not recommended. Additional emphasis was placed on opportunities for quality improvement, particularly regarding shared decision making and care of children with existing tubes.

Action statements: The development group made a strong recommendation that clinicians should prescribe topical antibiotic ear drops only, without oral antibiotics, for children with uncomplicated acute tympanostomy tube otorrhea. The panel made recommendations that (1) clinicians should not perform tympanostomy tube insertion in children with a single episode of otitis media with effusion (OME) of less than 3 months’ duration; (2) clinicians should obtain an age-appropriate hearing test if OME persists for 3 months or longer (chronic OME) or prior to surgery when a child becomes a candidate for tympanostomy tube insertion; (3) clinicians should offer bilateral tympanostomy tube insertion to children with bilateral OME for 3 months or longer (chronic OME) and documented hearing difficulties; (4) clinicians should reevaluate, at 3- to 6-month intervals, children with chronic OME who did not receive tympanostomy tubes until the effusion is no longer present, significant hearing loss is detected, or structural abnormalities of the tympanic membrane or middle ear are suspected; (5) clinicians should not perform tympanostomy tube insertion in children with recurrent acute otitis media (AOM) who do not have middle ear effusion in either ear at the time of assessment for tube candidacy; (6) clinicians should offer bilateral tympanostomy tube insertion to children with recurrent AOM who have unilateral or bilateral middle ear effusion at the time of assessment for tube candidacy; (7) clinicians should determine if a child with recurrent AOM or with OME of any duration is at increased risk for speech, language, or learning problems from otitis media because of baseline sensory, physical, cognitive, or behavioral factors; (8) in the perioperative period, clinicians should educate caregivers of children with tympanostomy tubes regarding the expected duration of tube function, recommended follow-up schedule, and detection of complications; (9) clinicians should not encourage routine, prophylactic water precautions (use of earplugs, headbands; avoidance of swimming or water sports) for children with tympanostomy tubes. The development group provided the following options: (1) clinicians may perform tympanostomy tube insertion in children with unilateral or bilateral OME for 3 months or longer (chronic OME) and symptoms that are likely attributable to OME including, but not limited to, vestibular problems, poor school performance, behavioral problems, ear discomfort, or reduced quality of life and (2) clinicians may perform tympanostomy tube insertion in at-risk children with unilateral or bilateral OME that is unlikely to resolve quickly as reflected by a type B (flat) tympanogram or persistence of effusion for 3 months or longer (chronic OME).


#17: Prompt tympanostomy tube insertion doesn’t improve 9 yr outcomes

Clinical question: Does the delayed insertion of tympanostomy tubes impair the long-term outcomes in children with persistent middle-ear effusion?

Study design: Randomized controlled trial (single-blinded) Setting: Outpatient (any)

Synopsis: Many parents and clinicians still believe that there is a significant risk of permanent harm if tympanostomy tubes are not promptly inserted for children with persistent middle-ear effusion. In this study, which is a follow-up to a previously published POEM (N Engl J Med 2005;353:576), 429 children between the ages of 2 months and 3 years with middle-ear effusion for at least 90 days (bilateral) or 135 days (unilateral) were randomized to receive either prompt or delayed tympanostomy tube insertion. The delay was 6 months for bilateral effusion and 9 months for unilateral effusion. Allocation was concealed, groups were balanced at the start of the study, and analysis was by intention to treat. The researchers did an excellent job of following up: 195 of 216 in the early treatment group and 196 of 213 in the delayed treatment group underwent developmental testing between the ages of 9 years and 11 years. At the time of this final evaluation, 86% in the early treatment group had received tympanostomy tubes compared with only 49% in the delayed treatment group. There was no differences between groups in the results of a broad range of tests including evaluation of hearing, reading, oral fluency, auditory processing, phonological processing, behavior, or intelligence. There was also no difference between these groups and a group of children with ear problems that weren’t bad enough to qualify them for the study.

Bottom line: Delayed tympanostomy tube insertion successfully helps many children avoid tubes and does not result in any developmental or other impairment. (LOE = 1b)

There is evidence that tympanostomy tubes are substantially overused. According to a 2008 cohort study in the BMJ (Keyhani, et al, Oct 3 2008), only 30% of tube insertions met criteria based on any guideline in the New York City metropolitan area. The authors concluded:

“A significant majority of tympanostomy tube insertions in the largest and most populous metropolitan area in the United States were inappropriate according to the explicit criteria and not recommended according to both guidelines. Regardless of whether current practice represents a substantial overuse of surgery or the guidelines are overly restrictive, the persistent discrepancy between guidelines and practice cannot be good for children or for people interested in improving their health care.”

#18: Tubes ineffective for treating otitis media in children

**Clinical question:** In children with recurrent otitis media or chronic effusion, do tympanostomy tubes decrease further episodes, improve hearing, or improve language acquisition?

**Study design:** Meta-analysis (other)  
**Funding source:** Government

**Setting:** Various (meta-analysis)

**Synopsis:** These researchers searched 4 databases, including Cochrane CENTRAL, to find randomized controlled trials and other comparative research studies that evaluated the effectiveness of tympanostomy tubes. They included research written in any language. Citations were selected by 2 independent researchers. Study details were abstracted by one researcher and checked by a second researcher. In 16 randomized controlled trials of treating children with otitis media with effusion, the insertion of tubes with or without adenoidectomy decreased (improved) hearing threshold within the first 1 month to 3 months by an average 9.1 dB to 10.0 dB as compared with no treatment. However, there was no effect on hearing thresholds at 12 months to 24 months for tympanostomy alone or combined with adenoidectomy, prophylactic antibiotic treatment, or myringotomy as compared with no treatment. Overall, there was no effect on cognitive, language, and behavioral outcomes. In 3 small studies of children with recurrent acute otitis media the effect of tympanostomy tubes was inconsistent regarding recurrences. This analysis was a Bayesian network analysis, a statistical approach that still has some kinks in it, and the study report itself was somewhat incomplete, as is the evidence base for this common intervention.

**Bottom line:** Tympanostomy tubes, with or without other interventions, do not produce sustained improved hearing as compared with no treatment, and has not been shown to improve language acquisition, cognitive development, or behavior measures. There might be a small reduction in the recurrence of acute otitis media, but there is little research in this area. Another study of tubes found no long-term (6 years to 9 years) benefit on development (N Engl J Med 2007;356:248-261). (LOE = 1a)


#19: Surface swimming all right with tympanostomy tubes

**Clinical question:** What precautions, if any, are required to decrease the incidence of otorrhea in children with tympanostomy tubes?

**Study design:** Non-randomized controlled trial  
**Setting:** Outpatient (any)

**Synopsis:** Five hundred thirty-three children who were undergoing placement of tympanostomy tubes were enrolled in the study. Of those enrolled, only 399 had comprehensive follow-up. Clinical examination occurred two weeks after the procedure and then every 3 months until the tubes were extruded. Parents were asked to recall the number of episodes of otorrhea for their children and the relationship of otorrhea to swimming, bathing, and upper respiratory infections (URIs). The authors report only the total percentage of subjects who developed otorrhea. A child who swam once and developed otorrhea was counted the same as a child who went swimming on multiple occasions and developed otorrhea once. It was not possible therefore to calculate the risk of otorrhea based on the amount of exposure. Parents self-selected one of four interventions for their children: 1) swimming allowed with no precautions, 2) swimming allowed with no precautions, but on days with water exposure three drops of a suspension of polymyxin B sulfate, neomycin sulfate, and hydrocortisone were instilled into each ear before bedtime, 3) swimming allowed only with custom-molded ear plugs, and 4) swimming not allowed. Diving or swimming more than 180 cm (approximately 6 feet) below the surface was discouraged for all subjects. The groups differed by age (mean age of 29, 31, 60, and 26 months for groups 1, 2, 3, and 4, respectively). No other comparisons between the groups were given such as gender or the performance of simultaneous tonsillectomy or adenoidectomy. No reason was given for subjects that were lost to follow-up (25%). There were no comparisons between those in the study and those lost to follow-up. No power calculations were performed so it is uncertain if there were sufficient subjects in each group to show a statistically significant difference between the groups, if one truly existed. Most episodes of otorrhea were related to URIs and not to swimming. There was no difference between the three swimming groups with respect to swimming-related URIs-related or bathing-related otorrhea. Although not statistically significant, swimming children using ear molds were nearly twice as likely to report otorrhea compared with children using no precautions (20 percent vs. 11 percent). Nonswimmers had a lower overall incidence of otorrhea (59%) than the swimming groups (68%), but this difference was not statistically significant. The place of swimming (pool, ocean, lake, river) did not make a significant difference on the incidence of swimming-related otorrhea.

**Bottom line:** Preventing children from swimming during the hot summer months may cause considerable family strife and should not be mandated without clear evidence of harm. Allowing surface swimming without specific precautions for children with tubes is a reasonable approach until there is evidence to the contrary. (LOE = 3b)


#20: Antibiotic/steroid drops best treatment for otorrhea in afebrile kids with tympanostomy tubes
Clinical question: In children with tympanostomy tubes, what is the best treatment for acute otorrhea?

Study design: Randomized controlled trial (double-blinded) Setting: Outpatient (any)

Synopsis: These researchers identified children with TT who had at least 7 days of otorrhea symptoms; excluded were any kids with temperature > 38.5 C, and any with recent TT placement, recent episode of otorrhea, recent antibiotics, or secondary cause such as immunodeficiency or craniofacial abnormality. Patients were recruited, and either immediately enrolled in the trial if currently symptomatic or the parents were asked to call in if the child became symptomatic. Of 1133 children who were registered for the study, 886 did not report an episode of otorrhea and 247 had home visits for otorrhea. After excluding those with fever, 230 children were randomized to 1 of 3 groups: (1) hydrocortisone-bacitracin-colistin eardrops -- 5 drops given 3 times daily for 7 days; (2) oral amoxicillin-clavulanate -- 30 mg/7.5 mg per kilogram divided into 3 daily doses for 7 days; or (3) observation only for 2 weeks. The patients' mean age was 4.5 years, 58% were male, and 17% had bilateral symptoms. Patients or parents kept a symptom diary for 6 months, and the children were examined in their home by a study physician at 2 weeks and at 6 months. Adherence to the assigned treatment, or lack thereof, was best for eardrops (93%), then for oral antibiotics (88%), and least for observation (79%); analysis was by intention to treat. The primary outcome was persistent otorrhea at 2 weeks, and was much less common with the eardrops than with oral antibiotics or observation (5% vs 44% vs 55%; P < .05; number needed to treat = 2). The median duration of otorrhea was 4 days with eardrops, 5 days with antibiotics, and 12 days with observation. There was also a median of 1 fewer recurrence in the eardrop group than in the oral antibiotic group (P = 0.03). Gastrointestinal symptoms were fairly common in children receiving an oral antibiotic, and pain with eardrop administration was also common. No complications or serious adverse events were reported. Note that the specific antibiotic combination studied is only available in Europe. Also, the dose of amoxicillin used was lower than typically used in the United States (30 mg/kg divided 3 times a day instead of 80 to 90 mg/kg divided 3 times a day).

Bottom line: For nonfebrile children aged 1 year to 10 years with tympanostomy tubes (TT) and at least 1 week of otorrhea symptoms, a combination hydrocortisone-bacitracin-colistin eardrop is the best initial therapy. (LOE = 1b)


Bottom Lines

1. Clinical signs and symptoms of serious infection can be unreliable in children; your “gut feeling” may be the most useful
2. There may be a limited role for CRP in diagnosing serious infection in children, but there are no high quality studies in primary care settings.
3. Well child exams should be evidence based; there is insufficient evidence for many interventions currently recommended by experts
4. Evidence to support tympanostomy tubes in children with otitis media with effusion is weak, but they may be indicated in children with effusion and 3 months of hearing loss.
Learning objectives | Understand:

1. The results of the Systolic Blood Pressure Intervention Trial (SPRINT) trial compared to the ACCORD BP Trial, and its relevance to cardiovascular disease prevention.
2. The results of the HOPE – 3 hypertension trial and its relevance to cardiovascular disease prevention.
3. Recent AAFP and ACP guidelines on intensive BP treatment for those > 60
4. Recent 2017 AHA ACC guideline on HTN

**Blood pressure and macrovascular disease in the post–SPRINT era**

**#1: PubMed: The SPRINT Trial**

**BACKGROUND:** The most appropriate targets for systolic blood pressure to reduce cardiovascular morbidity and mortality among persons without diabetes remain uncertain.

**METHODS:** We randomly assigned 9361 persons 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). The primary composite outcome was myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes.

**RESULTS:** At 1 year, the mean systolic blood pressure was 121.4 mm Hg in the intensive-treatment group and 136.2 mm Hg in the standard-treatment group. The intervention was stopped early after a median follow-up of 3.26 years owing to a significantly lower rate of the primary composite outcome in the intensive-treatment group than in the standard-treatment group (1.65% per year vs. 2.19% per year; hazard ratio with intensive treatment, 0.75; 95% confidence interval [CI], 0.64 to 0.89; P<0.001). All-cause mortality was also significantly lower in the intensive-treatment group (hazard ratio, 0.73; 95% CI, 0.60 to 0.90; P=0.003). 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.

**CONCLUSIONS:** Among patients at high risk for cardiovascular events but without diabetes, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause, although significantly higher rates of some adverse events were observed in the intensive-treatment group.


**#2: PubMed: The ACCORD BP Trial**

**BACKGROUND:** There is no evidence from randomized trials to support a strategy of lowering systolic blood pressure below 135 to 140 mm Hg in persons with type 2 diabetes mellitus. We investigated whether therapy targeting normal systolic pressure (i.e., <120 mm Hg) reduces major cardiovascular events in participants with type 2 diabetes at high risk for cardiovascular events.

**METHODS:** A total of 4733 participants with type 2 diabetes were randomly assigned to intensive therapy, targeting a systolic pressure of less than 120 mm Hg, or standard therapy, targeting a systolic pressure of less than 140 mm Hg. The primary composite outcome was nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The mean follow-up was 4.7 years.

**RESULTS:** After 1 year, the mean systolic blood pressure was 119.3 mm Hg in the intensive-therapy group and 133.5 mm Hg in the standard-therapy group. The annual rate of the primary outcome was 1.87% in the intensive-therapy group and 2.09% in the standard-therapy group (hazard ratio with intensive therapy, 0.88; 95% confidence interval [CI], 0.73 to 1.06; P=0.20). The annual rates of death from any cause were 1.28% and 1.19% in the two groups, respectively (hazard ratio, 1.07; 95% CI, 0.85 to 1.35; P=0.55). The annual rates of stroke, a prespecified secondary outcome, were 0.32% and 0.53% in the two groups, respectively (hazard ratio, 0.59; 95% CI, 0.39 to 0.89; P=0.01). Serious adverse events attributed to antihypertensive treatment occurred in 77 of the 2362 participants in the intensive-therapy group (3.3%) and 30 of the 2371 participants in the standard-therapy group (1.3%) (P<0.001).

**CONCLUSIONS:** In patients with type 2 diabetes at high risk for cardiovascular events, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events. (ClinicalTrials.gov number, NCT00000620.)


**#3: PubMed: The Hope-3 Trial**

**BACKGROUND:** Antihypertensive therapy reduces the risk of cardiovascular events among high-risk persons and among those with a systolic blood pressure of 160 mm Hg or higher, but its role in persons at intermediate risk and with lower blood pressure is unclear.
#4: PubMed: Baseline predicted CV risk equations for DP lowering decisions

**BACKGROUND:** We aimed to investigate whether the benefits of blood pressure-lowering drugs are proportional to baseline cardiovascular risk, to establish whether absolute risk could be used to inform treatment decisions for blood pressure-lowering therapy, as is recommended for lipid-lowering therapy.

**METHODS:** This meta-analysis included individual participant data from trials that randomly assigned patients to either blood pressure-lowering drugs or placebo, or to more intensive or less intensive blood pressure-lowering regimens. The primary outcome was total major cardiovascular events, consisting of stroke, heart attack, heart failure, or cardiovascular death. Participants were separated into four categories of baseline 5-year major cardiovascular risk using a risk prediction equation developed from the placebo groups of the included trials (<11%, 11-15%, 15-21%, >21%).

**FINDINGS:** 11 trials and 26 randomised groups met the inclusion criteria, and included 67,475 individuals, of whom 51,917 had available data for the calculation of the risk equations. 4167 (8%) had a cardiovascular event during a median of 4.0 years (IQR 3.4-4.4) of follow-up. The mean estimated baseline levels of 5-year cardiovascular risk for each of the four risk groups were 6.0% (SD 2.0), 12.1% (1.5), 17.7% (1.7), and 26.8% (5.4). In each consecutive higher risk group, blood pressure-lowering treatment reduced the risk of cardiovascular events relatively by 18% (95% CI 7-27), 15% (4-25), 13% (2-22), and 15% (5-24), respectively (p=0.30 for trend). However, in absolute terms, treating 1000 patients in each group with blood pressure-lowering treatment for 5 years would prevent 14 (95% CI 8-21), 20 (8-31), 24 (8-40), and 38 (16-61) cardiovascular events, respectively (p=0.04 for trend).

**INTERPRETATION:** Lowering blood pressure provides similar relative protection at all levels of baseline cardiovascular risk, but progressively greater absolute risk reductions as baseline risk increases. These results support the use of predicted baseline cardiovascular disease risk equations to inform blood pressure-lowering treatment decisions.

**FUNDING:** None.


#5: PubMed: Meta-analysis: Intensive treatment for patients > 60

**Background:** Recent guidelines recommend a systolic blood pressure (SBP) goal of less than 150 mm Hg for adults aged 60 years or older, but the balance of benefits and harms is unclear in light of newer evidence.

**Purpose:** To systematically review the effects of more versus less intensive BP control in older adults.

**Data Sources:** Multiple databases through January 2015 and MEDLINE to September 2016.

**Study Selection:** 21 randomized, controlled trials comparing BP targets or treatment intensity, and 3 observational studies that assessed harms.

**Data Extraction:** Two investigators extracted data, assessed study quality, and graded the evidence using published criteria.

**Data Synthesis:** Nine trials provided high-strength evidence that BP control to less than 150/90 mm Hg reduces mortality (relative risk [RR], 0.90 [95% CI, 0.83 to 0.98]), cardiac events (RR, 0.77 [CI, 0.68 to 0.89]), and stroke (RR, 0.74 [CI, 0.65 to 0.84]). Six trials yielded low- to moderate-strength evidence that lower targets (<140/85 mm Hg) are associated with marginally significant decreases in cardiac events (RR, 0.82 [CI, 0.64 to 1.00]) and stroke (RR, 0.79 [CI, 0.59 to 0.99]) and nonsignificantly fewer deaths (RR, 0.86 [CI, 0.69 to 1.06]). Low- to moderate-strength evidence showed that lower BP targets do not increase falls or cognitive impairment.

**Limitation:** Data relevant to frail elderly adults and the effect of multimorbidity are limited.

**Conclusion:** Treatment to at least current guideline standards for BP (<150/90 mm Hg) substantially improves health outcomes in older adults. There is less consistent evidence, largely from 1 trial targeting SBP less than 120 mm Hg, that lower BP targets are beneficial for high-risk patients. Lower BP targets did not increase falls or cognitive decline but are associated with hypotension, syncope, and greater medication burden.


**Primary Funding Source:** U.S. Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative. (PROSPERO 2015: CRD42015017677)
#6: Pubmed: AAFP/ACP: Practice guideline Intensive treatment for patients > 60

**Description:** The American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP) jointly developed this guideline to present the evidence and provide clinical recommendations based on the benefits and harms of higher versus lower blood pressure targets for the treatment of hypertension in adults aged 60 years or older.

**Methods:** This guideline is based on a systematic review of published randomized, controlled trials for primary outcomes and observational studies for harms only (identified through EMBASE, the Cochrane Database of Systematic Reviews, MEDLINE, and ClinicalTrials.gov), from database inception through January 2015. The MEDLINE search was updated through September 2016. Evaluated outcomes included all-cause mortality, morbidity and mortality related to stroke, major cardiac events (fatal and nonfatal myocardial infarction and sudden cardiac death), and harms. This guideline grades the evidence and recommendations using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) method.

**Target Audience and Patient Population:** The target audience for this guideline includes all clinicians, and the target patient population includes all adults aged 60 years or older with hypertension.

**Recommendation 1:** ACP and AAFP recommend that clinicians initiate treatment in adults aged 60 years or older with systolic blood pressure persistently at or above 150 mm Hg to achieve a target systolic blood pressure of less than 150 mm Hg to reduce the risk for mortality, stroke, and cardiac events. (Grade: strong recommendation, high-quality evidence). ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on a periodic discussion of the benefits and harms of specific blood pressure targets with the patient.

**Recommendation 2:** ACP and AAFP recommend that clinicians consider initiating or intensifying pharmacologic treatment in adults aged 60 years or older with a history of stroke or transient ischemic attack to achieve a target systolic blood pressure of less than 140 mm Hg to reduce the risk for recurrent stroke. (Grade: weak recommendation, moderate-quality evidence). ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on a periodic discussion of the benefits and harms of specific blood pressure targets with the patient.

**Recommendation 3:** ACP and AAFP recommend that clinicians consider initiating or intensifying pharmacologic treatment in some adults aged 60 years or older at high cardiovascular risk, based on individualized assessment, to achieve a target systolic blood pressure of less than 140 mm Hg to reduce the risk for stroke or cardiac events. (Grade: weak recommendation, low-quality evidence). ACP and AAFP recommend that clinicians select the treatment goals for adults aged 60 years or older based on a periodic discussion of the benefits and harms of specific blood pressure targets with the patient.

**Reference:** Qaseen A et al. Pharmacologic Treatment of Hypertension in Adults Aged 60 Years or Older to Higher Versus Lower Blood Pressure Targets: A Clinical Practice Guideline From the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med. doi:10.7326/M16-1785 Published online January 17 2017

2107 ACC AHA Guidelines on HTN

In November of 2017 the American College of Cardiology/American Heart Association published a new guideline on the prevention, detection, evaluation, and management of high blood pressure in adults. The article was published online and is 401 pages, however the "meat" of the guideline was covered in only ~ 89 pages. Also the COI declarations covered 22 pages (on a quick review however most authors had no COI with industry). This guideline was heavily influenced by results of the SPRINT study. Broad sections included the following:

- BP and CVD risk
- Classification of the BP
- Measurement of BP
- Causes of HTN
- Patient Evaluation
- Treatment of High BP
- Hypertension in patients with comorbidities
- Special patient groups
- Other considerations (e.g. resistant HTN, hypertensive crises etc)

I'm including my determination of the items that most likely will have the highest impact on primary care providers. My Summary of key aspects of the New BP guidelines are below the numbering and emphases are mine

The New Normal
1. BP should be categorized as normal, elevated, or stage 1 or 2 hypertension to prevent and treat high BP (Table 6) (COR I | LOE B-NR)

The new normal is < 120 / < 80. In addition, a new category of “Elevated Blood Pressure” is included (and if present, non-pharmacological therapy is recommended). Hypertension is defined now as > 130 / > 80. Also returned from previous guidelines are stages of hypertension (Stage 1 and Stage 2). Note the checklist for accurate BP measurement from this guideline is in the appendix.

<table>
<thead>
<tr>
<th>BP Category</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 120 and &lt; 80</td>
<td></td>
</tr>
<tr>
<td>Elevated</td>
<td>120-129 and &lt; 80</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>130-139 or 80 - 89</td>
<td></td>
</tr>
<tr>
<td>Stage 2</td>
<td>&gt; 140 or &gt; 90</td>
<td></td>
</tr>
</tbody>
</table>

Out-of-office BP measurements recommended

2. Out-of-office BP measurements are recommended to confirm the diagnosis of hypertension and for titration of BP-lowering medication, in conjunction with telehealth counseling or clinical interventions. (COR I | LOE A)

Take at least 2 readings 1 min apart in morning before taking medications and in evening before supper. Optimally, measure and record BP daily. Ideally, obtain weekly BP readings beginning 2 weeks after a change in the treatment regimen and during the week before a clinic visit. BP should be based on an average of readings on ≥2 occasions for clinical decision-making. The information above may be reinforced with videos available online: Monitoring Your Blood Pressure at Home

Treatment recommendations are a bit more nuanced

3. Use of BP-lowering medications is recommended for secondary prevention of recurrent CVD events in patients with clinical CVD and an average SBP of 130 mm Hg or higher or an average DBP of 80 mm Hg or higher, and for primary prevention in adults with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of 10% or higher and an average SBP 130 mm Hg or higher or an average DBP 80 mm Hg or higher. (COR I | LOE A for SBP)

4. Use of BP-lowering medication is recommended for primary prevention of CVD in adults with no history of CVD and with an estimated 10-year ASCVD risk < 10% and an SBP of 140 mm Hg or higher or a DBP of 90 mm Hg or higher. (COR I | LOE C-LD)

Use the ACC/AHA Pooled Cohort Equation to estimate 10-year risk of atherosclerotic CVD. However – with one exception (as noted below) treatment should be initiated with a confirmed BP of ≥ 130 / ≥ 80. You will note that for most patients we are asked to calculated the 10-year ASCVD risk (much like we are asked to do for determining candidacy for statin therapy) to determine if the patients 10-year risk is > or < 10%
### Summary of BP Thresholds and Goals for Pharmacologic Treatment

<table>
<thead>
<tr>
<th>Clinical Condition(s)</th>
<th>BP Threshold, mm</th>
<th>Hg BP Goal, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical CVD or 10-year ASCVD risk ≥10%</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>No clinical CVD and 10-year ASCVD risk &lt;10%</td>
<td>≥140/90</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Older persons (≥65 years of age; noninstitutionalized)</td>
<td>≥130 (SBP)</td>
<td>&lt;130 (SBP)</td>
</tr>
<tr>
<td><strong>Specific comorbidities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Chronic kidney disease after renal transplantation</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Heart failure</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Stable ischemic heart disease</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Secondary stroke prevention</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Secondary stroke prevention (lacunar)</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
</tbody>
</table>

5. For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, CCBs, and ACE inhibitors or ARBs. (COR I | LOE A)

6. Initiation of antihypertensive drug therapy with 2 first-line agents of different classes, either as separate agents or in a fixed-dose combination, is recommended in adults with stage 2 hypertension and an average BP more than 20/10 mm Hg above their BP target. (COR I | LOE C-EO)

### Special Circumstances

**Stable ischemic Heart Dz (SIHD)**

7. Adults with SIHD and hypertension (BP ≥130/80 mm Hg) should be treated with medications (e.g., GDMT beta blockers, ACE inhibitors, or ARBs) for compelling indications (e.g., previous MI, stable angina) as first-line therapy, with the addition of other drugs (e.g., dihydropyridine CCBs, thiazide diuretics, and/or mineralocorticoid receptor antagonists) as needed to further control hypertension

Heart Failure with Preserved Ejection Fraction
8. Adults with HFpEF and persistent hypertension after management of volume overload should be prescribed ACE inhibitors or ARBs and beta blockers titrated to attain SBP of less than 130 mm Hg. (COR I | C-LD)

Note that GDMT beta-blockers for BP control or relief of angina include carvedilol, metoprolol tartrate, metoprolol succinate, nadolol, bisoprolol, propranolol, and timolol. Avoid beta-blockers with intrinsic sympathomimetic activity (e.g. pindolol, acebutolol). The beta-blocker atenolol should not be used because it is less effective than placebo in reducing cardiovascular events.

Diabetes

9. In adults with DM and hypertension, all first-line classes of antihypertensive agents (i.e., diuretics, ACE inhibitors, ARBs, and CCBs) are useful and effective (COR I | LOE A)
10. In adults with DM and hypertension, ACE inhibitors or ARBs may be considered in the presence of albuminuria (COR Iib | LOE B-NR)

African-Americans

11. In black adults with hypertension but without HF or CKD, including those with DM, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. (COR I | B-R)
12. Two or more antihypertensive medications are recommended to achieve a BP target of less than 130/80 mm Hg in most adults with hypertension, especially in black adults with hypertension. (COR I | C-LD)

Elderly (> 65)

13. Treatment of hypertension with a SBP treatment goal of less than 130 mm Hg is recommended for noninstitutionalized ambulatory community dwelling adults (≥65 years of age) with an average SBP of 130 mm Hg or higher (COR I | LOE A)
14. For older adults (≥65 years of age) with hypertension and a high burden of comorbidity and limited life expectancy, clinical judgment, patient preference, and a team-based approach to assess risk/benefit is reasonable for decisions regarding intensity of BP lowering and choice of antihypertensive drugs. (COR Iib | LOE C-EO)

#7: PubMed: 13.7% more people in the US are now classified as having HTN

BACKGROUND: The 2017 American College of Cardiology/American Heart Association (ACC/AHA) Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults provides recommendations for the definition of hypertension, systolic and diastolic blood pressure (BP) thresholds for initiation of antihypertensive medication and BP target goals.


METHODS: We analyzed data from the 2011-2014 National Health and Nutrition Examination Survey (N=9,623). NHANES participants completed study interviews and an examination. For each participant, blood pressure was measured three times following a standardized protocol and averaged. Results were weighted to produce US population estimates.

RESULTS: According to the 2017 ACC/AHA and JNC7 guidelines, the overall crude prevalence of hypertension among US adults was 45.6% (95% confidence interval [CI] 43.6%,47.6%) and 31.9% (95%CI 30.1%, 33.7%), respectively, and antihypertensive medication was recommended for 57.2% (95%CI 54.4%, 60.0%) and 37.5% (35.0%, 39.9%) of US adults, respectively. Compared to US adults recommended antihypertensive medication by JNC7, those recommended treatment by the 2017 ACC/AHA guideline had higher CVD risk. Non-pharmacological intervention is advised for the 9.4% of US adults with hypertension according to the 2017 ACC/AHA guideline who are not recommended antihypertensive medication. Among US adults taking antihypertensive medication, 53.4% (95%CI 49.9%, 56.8%) and 39.0% (95%CI 36.4%, 41.6%) had BP above the treatment goal according to the 2017 ACC/AHA
and JNC7 guidelines, respectively. Overall, 103.3 (95%CI 92.7, 114.0) million US adults had hypertension according to the 2017 ACC/AHA guideline of whom 81.9 (95%CI 73.8, 90.1) million were recommended antihypertensive medication.

**CONCLUSION:** Compared with the JNC 7 guideline, the 2017 ACC/AHA guideline results in a substantial increase in the prevalence of hypertension but a small increase in the percentage of U.S. adults recommended antihypertensive medication. A substantial proportion of US adults taking antihypertensive medication is recommended more intensive BP lowering under the 2017 ACC/AHA guideline.


**Key Points**

1. The SPRINT trial demonstrated that targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, in *non-diabetic high risk patients*, resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause.
2. The HOPE-3 trial demonstrated that in average risk patients with a mean baseline BP of 136/82; the addition of candesartan PLUS hydrochlorothiazide for ~5.6 years was not associated with better macrovascular outcomes.
3. The ACP and AAFP recommend that clinicians initiate blood pressure treatment in adults aged 60 years or older with systolic blood pressure persistently at or above 150 mm Hg.
4. The ACP and AAFP recommend that clinicians consider initiating or intensifying pharmacologic treatment in adults aged 60 years or older with a history of stroke or transient ischemic attack to achieve a target systolic blood pressure of less than 140 mm Hg.
5. The new ACC AHA guidelines are “hot off the press” and could have a dramatic effect on BP management in the next several years.
6. As a result of these new guidelines, 13.7% more people in the US are now classified as having HTN.
Intelligent Imaging: What should I order? By Steven R. Brown, MD, FAAFP

Objectives

1. Review the harms of imaging including radiation exposure and incidentalomas
2. Discuss evidence-based use of imaging for abdominal pain, headache, and head trauma

Can imaging be harmful? Radiation

Table: Exposure by type of study. World wide average for naturally occurring background radiation: 2.4 mSv/year

<table>
<thead>
<tr>
<th>Imaging study</th>
<th>Dose (mSv)</th>
<th>CXR</th>
<th>Imaging study</th>
<th>Dose (mSv)</th>
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<tr>
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<td>950</td>
<td>Coronary angiography</td>
<td>7</td>
<td>350</td>
</tr>
</tbody>
</table>

Source: Nature Reviews Cardiology 6, 436-438 (June 2009)

Table 4. Estimated Number of Patients Undergoing Computed Tomography (CT) That Would Lead to the Development of 1 Radiation-Induced Cancer, by Type of CT Examination and Age at the Time of Exposure, Based on the Median and Interquartile Radiation Dose Observed

Image gently: Why we should talk to parents about CT in children (Am J Roent 2009;1176) “even low-level radiation exposure can be harmful…” Helpful handouts at http://www.pedrad.org

#1: Use of medical imaging procedures with ionizing radiation in children: a population-based study

Objective: To determine population-based rates of the use of diagnostic imaging procedures with ionizing radiation in children, stratified by age and sex.

Design: Retrospective cohort analysis.

Setting: All settings using imaging procedures with ionizing radiation.


Main Outcome Measures: Number and type of diagnostic imaging procedures using ionizing radiation in children.

Results: A total of 355 088 children were identified; 436 711 imaging procedures using ionizing radiation were performed in 150 930 patients (42.5%). The highest rates of use were in children older than 10 years, with frequent use in infants younger than 2 years as
well. Plain radiography accounted for 84.7% of imaging procedures performed. Computed tomographic scans-associated with substantially higher doses of radiation-were commonly used, accounting for 11.9% of all procedures during the study period. Overall, 7.9% of children received at least 1 computed tomographic scan and 3.5% received 2 or more, with computed tomographic scans of the head being the most frequent.

**Conclusions:** Exposure to ionizing radiation from medical diagnostic imaging procedures may occur frequently among children. Efforts to optimize and ensure appropriate use of these procedures in the pediatric population should be encouraged.


“It has been estimated that 48% of total exposure to ionizing radiation for persons in the US involves medical tests and procedures, and that 1.5-2.0% of all future cancers in the US population might be attributable to CT scanning.” There is a growing movement that not only should we be using CT scans more judiciously, but we also need to discuss risks with patients. (Baerlocher MO, et al. Discussing radiation risks associated with CT scans with patients. JAMA 2010;304(19):2170.) According on one study while 47% of patients getting CT scans are aware it is a source of radiation, only 3% are aware of the relative dose, 2% are aware of the cancer risk, and only 9% are aware this risk is worse in younger than older patients. (Caoili EM, et al. Medical decision making regarding computed tomographic radiation dose and associated risk: The patient’s perspective. Arch Intern Med 2009;169(11):1070.)

**Can imaging be harmful? Incidentalomas**

CT scans often reveal incidental findings, or ‘incidentalomas’. These results are not related to the symptom that led to the ordering of the diagnostic test, are usually asymptomatic, and are unlikely to impact the health of the patient. However, incidental findings often lead to a costly and potentially harmful cascade of further testing.

The rate of incidental findings varies by type of imaging performed. Chest CT scans reveal incidental findings requiring further evaluation in up to 41.5% of tests. After two chest CT scans for lung cancer screening in high risk smokers, 1 in 3 patients has a false-positive test leading 7% of patients overall to have surgical or invasive procedures. Approximately 30% of abdominal CTs and 6% of head CTs demonstrate incidental findings requiring follow up among trauma patients. Adrenal lesions, among the most common incidental findings, are found in 4.2% of CT scans, though more than 90% are of no clinical importance.

The reporting and further evaluation of incidental findings on imaging has important ethical implications and poses medicolegal risks. In one study of trauma patients only 27% of incidental findings were communicated at discharge. In addition, while primary care clinicians often look to the reading radiologist for follow-up recommendations, interrater reliability is highly variable even in settings with standardized training and rigid definitions. These and other uncertainties have led some professional medical societies to create guidelines to assist clinicians in the management of incidental findings.

In summary, while it appears that 1 in roughly 2-3 CT examinations will result in an incidental finding, approximately 1 in 4 will lead to a finding that requires follow-up.


**One of the best POEMs ever**

**Clinical question:** Do negative test results reassure patients?

**Study design:** Systematic review  
**Setting:** Various (meta-analysis)

**Synopsis:** These authors searched several databases, including the Cochrane Library, to find randomized controlled trials comparing the effectiveness of diagnostic testing with no testing for symptomatic patients with a low probability of serious disease based on clinical features. They included articles written in any language but excluded unpublished research. Two authors independently selected studies for inclusion. They identified 14 studies of 3828 patients. Most of the studies evaluated the effectiveness of endoscopy and radiology for dyspepsia; other studies included imaging for back pain, electrocardiogram and blood tests for chest pain, event recording for palpitations, and MRI for chronic headache. Three studies showed no overall effect of diagnostic testing on illness worry and 2 showed no effect on nonspecific anxiety. Eleven studies showed no overall long-term effect on the persistence of symptoms (ie, “therapeutic testing”). There was significant heterogeneity among some of the studies. Excluding outlying studies, a meta-analysis showed a small reduction in primary care visits (odds ratio = 0.77; 95% CI, .62-.96). This effect translates into 1 less visit for every 16 patients with dyspepsia and 1 less visit for every 26 patients with back pain who undergoes diagnostic testing.

**Bottom line:** Diagnostic testing does not reassure patients with low probability of serious disease. It also does not decrease their chronic symptoms. It may, however, decrease their likelihood of returning to the office. (LOE = 1a-)
What is the best approach to imaging in abdominal pain?

#3: Ultrasound preferred as initial imaging study for abdominal pain

**Purpose:** To perform a meta-analysis to evaluate the diagnostic performance of ultrasonography (US) and computed tomography (CT) for the diagnosis of appendicitis in pediatric and adult populations.

**Methods:** Medical literature (from 1986 to 2004) was searched for articles on studies that used US, CT, or both as diagnostic tests for appendicitis in children (26 studies, 9356 patients) or adults (31 studies, 4341 patients). Prospective and retrospective studies were included if they separately reported the rate of true-positive, true-negative, false-positive, and false-negative diagnoses of appendicitis from US and CT findings compared with the positive and negative rates of appendicitis at surgery or follow-up. Clinical variables, technical factors, and test performance were extracted. Three readers assessed the quality of studies.

**Results:** Pooled sensitivity and specificity for diagnosis of appendicitis in children were 88% (95% confidence interval [CI]: 86%, 90%) and 94% (95% CI: 92%, 95%), respectively, for US studies and 94% (95% CI: 92%, 97%) and 95% (95% CI: 94%, 97%), respectively, for CT studies. Pooled sensitivity and specificity for diagnosis in adults were 83% (95% CI: 78%, 87%) and 93% (95% CI: 90%, 96%), respectively, for US studies and 94% (95% CI: 92%, 95%) and 94% (95% CI: 94%, 96%), respectively, for CT studies.

**Conclusion:** From the diagnostic performance perspective, CT had a significantly higher sensitivity than did US in studies of children and adults; from the safety perspective, however, one should consider the radiation associated with CT, especially in children.

(c) RSNA, 2006.


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<td>CT</td>
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#4: Ultrasound, followed by CT if negative, best for acute abdomen

**Clinical question:** In patients with nontraumatic acute abdominal pain, what is the best strategy for detecting urgent conditions?

**Setting:** Emergency department

**Study design:** Cohort (prospective)

**Synopsis:** These investigators enrolled 1021 patients with nontraumatic abdominal pain lasting 2 hours to 5 days who presented to 1 of 6 university emergency departments in the Netherlands. Pregnant women and patients in hemorrhagic shock or with a ruptured aortic aneurysm were excluded. The final diagnosis of an urgent condition -- acute appendicitis, diverticulitis, bowel obstruction, and so forth -- was present in 65% of the patients. After giving medical histories and undergoing physical examinations and laboratory studies, all patients received upright and supine abdominal plain x-rays, abdominal ultrasound, and CT. Interpretation of the ultrasound and CT were performed with a knowledge of the clinical information but without knowing the results of either of these tests (ie, physicians reading the CT were unaware of ultrasound findings, and vice versa). The gold standard used in this study was interpretation by an expert panel 6 months following presentation using follow-up data collected over that period. Sensitivity -- the ability to identify an urgent condition so as to rule it out if it is not present -- was high with clinical diagnosis (88%) and was not dramatically improved with plain radiographs (88%) or CT (89%) and was worsened, because of many false-positives, with ultrasound (70%). Specificity, the percentage of true-negatives, was low with clinical diagnosis (41%) and not improved with radiographs (43%) or ultrasound (70%). Combining these results, the best strategy for ruling out urgent conditions (highest sensitivity) is to perform an ultrasound in all patients and perform a CT if the ultrasound is negative or inconclusive (94%); this approach decreases CT use by almost half and is more effective than going straight to CT.

**Bottom-line:** Urgent conditions -- acute appendicitis, bowel obstruction, and so forth -- in patients with acute abdominal pain presenting to an emergency department are best ruled out by clinical examination and ultrasound of all patients, followed by computed tomography (CT) of those whose ultrasound is negative or inconclusive. Using this approach, 94% of urgent conditions will be correctly ruled out if the CT is negative, and it will avoid unnecessary cost and radiation in almost half the patients presenting with acute abdominal pain. Going straight to CT actually results in a lower sensitivity (89%).


#5: PubMed: A simple way to rule out appendicitis in patients with nondiagnostic ultrasound results

**OBJECTIVES:** The objective was to identify a set of clinical features that can rule out appendicitis in patients with suspected acute appendicitis and nondiagnostic ultrasound (US) results, allowing safe discharge and next-day reevaluation without initial computed tomography (CT) or magnetic resonance imaging (MRI)

**METHODS:** Data on clinical and US evaluation, including a number of prespecified variables potentially associated with acute appendicitis, were prospectively collected in two diagnostic accuracy studies of imaging. These studies included patients with
suspected appendicitis seen in the emergency department (ED). For development and validation of the clinical decision rule (CDR), only patients with inconclusive or negative US results were included. There were 199 (of 422) patients in the development cohorts and 120 (of 211) patients in the validation cohort. Logistic regression analysis was used for data from patients with inconclusive or negative US results, and profiles were created of all possible combinations of predictors retained in the multivariable model. A final diagnosis was assigned by an expert panel based on perioperative data, histopathology, and clinical follow-up of at least 3 months.

**RESULTS:** The CDR selected patients after negative or inconclusive US for discharge and next-day reevaluation without initial CT or MRI if fewer than two of the following predictors were present: male sex, migration of pain to the right lower quadrant, vomiting, and white blood cell (WBC) count higher than 12.0 × 10^9 /L. Applying the CDR in the development set selected 126 of 199 (63%) patients with negative or inconclusive US results for discharge without further imaging. This rule reduced the probability of appendicitis from 26% (51 of 199) in the total group of patients with negative or inconclusive US results to 12% (15 of 126) in the group that would be discharged based on the rule (p = 0.001). In the validation set (n = 120), the decision rule selected 72 (60%) patients for discharge and next-day reevaluation and reduced the probability of appendicitis from 20% (24 of 120) in the total group to 6% (4 of 72) in the patients selected on the rule (p = 0.001). The negative predictive value of the decision rule in the validation set was 94% (95% confidence interval [CI] = 87% to 98%). In comparison, the negative predictive value of CT in the same group was 99% (95% CI = 93% to 100%, p = 0.14), and that of MRI was 99% (95% CI = 94% to 100%, p = 0.12). Alternative decision rules based on combinations of the present decision rule with C-reactive protein (CRP) results did not improve selection.

**CONCLUSIONS:** This newly developed CDR significantly reduces the probability of appendicitis in a large subgroup of patients with negative or inconclusive US results. These patients can be safely discharged for outpatient reevaluation without further initial imaging if proper follow-up is available. This could assist in lowering the number of ED imaging investigations in patients with suspected appendicitis.


**#6: PubMed: A serial ultrasound clinical diagnostic pathway in suspected appendicitis**

**OBJECTIVES:** The primary objective was to determine the diagnostic accuracy of a serial ultrasound (US) clinical diagnostic pathway to detect appendicitis in children presenting to the emergency department (ED). The secondary objective was to examine the diagnostic performance of the initial and interval US and to compare the accuracy of the pathway to that of the initial US.

**METHODS:** This was a prospective cohort study of 294 previously healthy children 4 to 17 years old with suspected appendicitis and baseline pediatric appendicitis scores of ≥2, who were managed with the serial US clinical diagnostic pathway. This pathway consisted of an initial US followed by a clinical reassessment in each patient and an interval US and surgical consultation in patients with equivocal initial US and persistent concern about appendicitis. The USs were interpreted by published criteria as positive, negative, or equivocal for appendicitis. Children in whom this pathway did not rule in or rule out appendicitis underwent computed tomography (CT). Cases with missed appendicitis, negative operations, and CTs after the pathway were considered inaccurate. The primary outcome was the diagnostic accuracy of the serial US clinical diagnostic pathway. The secondary outcomes included the test performance of the initial and interval US imaging studies.

**RESULTS:** Of the 294 study children, 111 (38%) had appendicitis. Using the serial US clinical diagnostic pathway, 274 of 294 children (93%, 95% confidence interval [CI] = 90% to 96%) had diagnostically accurate results: 108 of the 111 (97%) appendicitis cases were successfully identified by the pathway without CT scans (two missed and one CT), and 166 of the 183 (91%) negative cases were ruled out without CT scans (14 negative operations and three CTs). The sensitivity of this pathway was 108 of 111 (97%, 95% CI = 94% to 100%), specificity 166 of 183 (91%, 95% CI = 87% to 95%), positive predictive value 108 of 125 (86%; 95% CI = 79% to 92%), and negative predictive value 166 of 169 (98%, 95% CI = 96% to 100%). The diagnostic accuracy of the pathway was higher than that of the initial US alone (274 of 294 vs. 160 of 294; p < 0.0001). Of 123 patients with equivocal initial US, concern about appendicitis subsided on clinical reassessment in 73 (no surgery and no missed appendicitis). Of 50 children with persistent symptoms, 40 underwent interval US and 10 had surgical consultation alone. The interval US confirmed or ruled out appendicitis in 22 of 40 children (55.0%) with equivocal initial US, with one false-positive interval US.

**CONCLUSIONS:** The serial US clinical diagnostic pathway in suspected appendicitis has an acceptable diagnostic accuracy that is significantly higher than that of the initial US and results in few CT scans. This approach appears most useful in children with equivocal initial US, in whom the majority of negative cases were identified at clinical reassessment and appendicitis was diagnosed by interval US or surgical consultation in most study patients.


**AAP #ChoosingWisely**
When is neuroimaging indicated in patients with headache?

#7: Does this patient with headache have a migraine or need neuroimaging?

CONTEXT: In assessing the patient with headache, clinicians are often faced with 2 important questions: Is this headache a migraine? Does this patient require neuroimaging? The diagnosis of migraine can direct therapy, and information obtained from the history and physical examination is used by physicians to determine which patients require neuroimaging.

OBJECTIVE: To determine the usefulness of the history and physical examination that distinguish patients with migraine from those with other headache types and that identify those patients who should undergo neuroimaging.

DATA SOURCES AND STUDY SELECTION: A systematic review was performed using articles from MEDLINE (1966-November 2005) that assessed the performance characteristics of screening questions in diagnosing migraine (with the International Headache Society diagnostic criteria as a gold standard) and addressed the accuracy of the clinical examination in predicting the presence of underlying intracranial pathology (with computed tomography/magnetic resonance imaging as the reference standard).

DATA EXTRACTION: Two authors independently reviewed each study to determine eligibility, abstract data, and classify methodological quality using predetermined criteria. Disagreement was resolved by consensus with a third author.

DATA SYNTHESIS: Four studies of screening questions for migraine (n = 1745 patients) and 11 neuroimaging studies (n = 3725 patients) met inclusion criteria. All 4 of the migraine studies illustrated high sensitivity and specificity if 3 or 4 criteria were met. The best predictors can be summarized by the mnemonic POUNDing (Pulsating, duration of 4-72 hOurs, Unilateral, Nausea, Disabling). If 4 of the 5 criteria are met, the likelihood ratio (LR) for definite or possible migraine is 24 (95% confidence interval [CI], 1.5-388); if 3 are met, the LR is 3.5 (95% CI, 1.3-9.2), and if 2 or fewer are met, the LR is 0.41 (95% CI, 0.32-0.52). For the neuroimaging question, several clinical features were found on pooled analysis to predict the presence of a serious intracranial abnormality: cluster-type headache (LR, 10.7; 95% CI, 2.2-52); abnormal findings on neurologic examination (LR, 5.3; 95% CI, 2.4-12); undefined headache (ie, not cluster-, migraine-, or tension-type) (LR, 3.8; 95% CI, 2.0-7.1); headache with aura (LR, 3.2; 95% CI, 1.6-6.6); headache aggravated by exertion or a valsalva-like maneuver (LR, 2.3; 95% CI, 1.4-3.8); and headache with vomiting (LR, 1.8; 95% CI, 1.2-2.6). No clinical features were useful in ruling out significant pathologic conditions.

CONCLUSIONS: The presence of 4 simple historical features can accurately diagnose migraine. Several individual clinical features were found to be associated with a significant intracranial abnormality, and patients with these features should undergo neuroimaging.

REFERENCE: Detsky ME, McDonald DR, Baerlocher MO, Tomlinson GA, McCrory DC, Booth CM. Does this patient with headache have a migraine or need neuroimaging? JAMA. 2006 Sep 13;296(10):1274-83.

The American College of Radiology Appropriateness Criteria (2013) for headache:

‘Chronic headache: No new features. Normal neurological exam:
• MRI “may be appropriate.” (4)
• CT “usually not appropriate.” (3)

“Chronic headache with new features or neurologic deficit:”
• MRI with and without contrast “usually appropriate.” (8)
• CT without contrast “usually appropriate.” (7)

Sudden onset of severe headache “worst headache of my life” “thunderclap headache”:
• CT head without IV contrast “usually appropriate.” (9)
• MRA head with and without contrast “usually appropriate.” (7)
• CT head with IV contrast “usually not appropriate.” (3)

New headache. Focal neurologic deficit or papilledema
• MRI without contrast “usually appropriate” (8)
American Headache Society #ChoosingWisely

1. Don’t perform neuroimaging studies in patients with stable headaches that meet criteria for migraine.
   Numerous evidence-based guidelines agree that the risk of intracranial disease is not elevated in migraine. However, not all severe headaches are migraine. To avoid missing patients with more serious headaches, a migraine diagnosis should be made after a careful clinical history and an examination that documents the absence of any neurologic findings such as papillaeadema. Diagnostic criteria for migraine are contained in the International Classification of Headache Disorders.

2. Don’t perform computed tomography (CT) imaging for headache when magnetic resonance imaging (MRI) is available, except in emergency settings.
   When neuroimaging for headache is indicated, MRI is preferred over CT, except in emergency settings when hemorrhage, acute stroke or head trauma are suspected. MRI is more sensitive than CT for the detection of neoplasm, vascular disease, posterior fossa and cervicomedullary lesions and high and low intracranial pressure disorders. CT of the head is associated with substantial radiation exposure which may elevate the risk of later cancers, while there are no known biologic risks from MRI.

When is imaging indicated after head trauma?

#8: Useful signs and symptoms of severe intracranial injury after minor head trauma

Clinical question: What clinical signs and symptoms are useful in accurately diagnosing a severe intracranial injury after minor head trauma in adults?
Study design: Systematic review
Setting: Various (meta-analysis)
Synopsis: Adults who appear well and have a Glasgow Coma Scale (GCS) of 13 or higher after traumatic brain injury (TBI) are defined as having minor head trauma. These investigators searched MEDLINE and the Cochrane Library, as well as pertinent references from retrieved articles, for English-language studies of adults (18 years or older) with head trauma who presented for evaluation with GCS scores ranging from 13 to 15. Inclusion criteria included diagnostic accuracy studies focusing on severe intracranial injuries requiring prompt intervention. A total of 14 studies (N = 23,079) met inclusion criteria with a severe intracranial injury prevalence of 7.1% (95% CI 6.8% - 7.4%) and a prevalence of injuries leading to death or requiring neurosurgical intervention of 0.9% (0.78% - 1.0%). The highest risk factors included pedestrians struck by motor vehicles (positive likelihood ratio [LR+] = 95% CI 3.0 - 4.3), age at least 65 years (LR+ = 2.3; 1.8 - 3.1), and age at least 60 years (LR+ = 2.2; 1.6 - 3.2). Useful symptoms included the presence of vomiting, especially at least 2 episodes (LR+ = 3.6; 3.1 - 4.1), or posttraumatic seizures (LR+ = 2.5, 1.3 - 4.3). Likelihood ratios for loss of consciousness or the presence of headache were minimally, if at all, useful for predicting adverse outcomes. Useful physical signs included features suspicious for skull fractures: visible open skull fracture, palpable depressed skull fracture, postauricular ecchymosis (Battle sign), hemotympanum, cerebrospinal fluid otorrhea, or raccoon eyes (LR+ = 16; 3.1 - 59). A GCS score of 13 (LR+ = 4.9; 2.8 - 8.5), a GCS score of less than 15 at 2 hours after injury (LR+ = 1.6 - 7.6), any decline in GCS score (LR+ range = 3.4 - 16) or a focal neurologic deficit (LR+ range = 1.9 - 7.0) also increased the likelihood of severe intracranial injury. Two clinical decision rules, including the Canadian CT Head Rule and the New Orleans Criteria, were also evaluated. The absence of all features on the Canadian CT Head Rule lower the probability of a severe injury to 0.31% (0% - 4.7%), with the corresponding absence of any of the New Orleans Criteria lowering the risk to 0.61% (0.08% - 6.0%).
Bottom line: Specific individual risk factors, clinical signs, and symptoms (see Synopsis) are useful in identifying adults with minor head trauma who are at risk of severe intracranial injury. The absence of all features of the Canadian CT Head Rule and New Orleans Criteria are also highly accurate for identifying adults at low risk of severe injury. (LOE = 1b)
#### #9: Clinical factors identify children at low risk of traumatic brain injury

**Clinical question:** Can clinical factors identify children with head injury who are at low risk for clinically important traumatic brain injury?

**Study design:** Cohort (prospective)  
**Setting:** Emergency department

**Synopsis:** This team of researchers systematically evaluated more than 42,000 children presenting to emergency departments within 24 hours of sustaining head trauma. The researchers excluded children with trivial injuries (eg, trip and fall, walking into stationary objects) and children with penetrating injuries or pre-existing neurologic disorders. Each child underwent a standardized clinical assessment. The researchers defined clinically important brain injuries as those that resulted in death, neurosurgical intervention, intubation, or more than 2 days in the hospital. A pediatric radiologist unaware of the child’s clinical characteristics interpreted radiographs whenever CT was performed. The decision to perform CT was left to the discretion of the emergency department physician. To identify children with clinically important brain injuries missed during the initial assessment, a researcher contacted the child’s parents between 7 days and 90 days of discharge from the emergency department. The researchers also split children into 2 age groups: younger than 2 years and 2 years and older. The researchers used data from the first 2 years of the study to derive clinical prediction rules. These were subsequently validated on children during the last 6 months of the study. Approximately one third of the children had CT, of whom 5% had radiographic signs of traumatic brain injury and 1% had clinically important brain injuries. For children younger than 2 years, the presence of any of the following clinical factors were useful in identifying children with clinically important brain injuries: altered mental status, occipital/parietal/temporal scalp hematoma, loss of consciousness for longer than 5 seconds, severe mechanism of injury, palpable skull fracture, or parent report of not acting normally. The researchers defined severe mechanism of injury as: motor vehicle crash with ejection of the child, death of another passenger, or rollover; pedestrian or bicyclist without helmet struck by a motorized vehicle; falls of more than 1.5 meters (5 feet) for children 2 years and older and more than 0.9 meter (3 feet) for those younger than 2 years; or head struck by a high-impact object. In the validation set, the presence of any of these factors was 100% sensitive (95% CI, 86.3% - 100%), but only 54% specific (51.6% - 55.8%). In other words, a child having none of these factors is very unlikely to have a serious injury and does not need CT. For children 2 years and older, the presence of any of the following clinical factors helps identify children with clinically important brain injuries: altered mental status, loss of consciousness, vomiting, severe mechanism of injury, clinical signs of basilar skull fracture, or severe headache. In the validation set, the presence of any of these factors was 97% sensitive (89% - 99.6%), but only 60% specific (58.6% - 61%). A child having none of these factors is very unlikely to have a serious injury and does not need CT.

**Bottom line:** In this large study, clinical factors identified which children with head injuries were unlikely to have a serious brain injury. Since computed tomography (CT) uses enormous amounts of radiation and children are especially vulnerable to potential adverse effects of radiation exposure, these factors can help reduce the use of CTs. (LOE = 1b-)


#### #10: Clinical decision rules useful for evaluating minor head injury

**Clinical question:** Which clinical decision rule -- the Canadian CT Head Rule or the New Orleans Criteria -- is the most useful in evaluating adults with minor head injury?

**Study design:** Decision rule (validation)  
**Setting:** Emergency department

**Synopsis:** Two clinical rules -- the CCHR and the New Orleans Criteria -- are currently used to identify adults with blunt head injury at increased risk and in need of cranial CT. To compare accuracy of the 2 rules the investigators consecutively enrolled 1822 eligible and consenting adults with blunt head trauma and a Glasgow Coma Scale score of 15 (normal). Emergency medicine attendings and residents trained to use both tools assessed all patients. Another emergency physician randomly assessed some patients to judge interobserver agreement. Eighty percent of the patients underwent emergency CT and the remaining patients were clinically followed up for 14 days. An independent committee reviewed all outcomes and made the final determination of all diagnoses. Individuals blinded to clinical data interpreted all CT scans. Of the 1822 patients with blunt head injury, 8 (0.4%) required neurosurgical intervention and 97 (5.3%) had "clinically important" brain injury. "Clinically important" brain injury was defined as any acute finding revealed on CT that would, in an independent formal survey of 125 academic neurosurgeons and emergency physicians, require hospitalization and neurological follow-up. Both the NOC and CCHR had 100% sensitivity for predicting the need for neurosurgical intervention and clinically important brain injury (no cases were missed by either rule). The CCHR had a significantly higher specificity (patients without either outcome are more accurately identified) for both events (76.3% vs 12.1% and 50.6% vs 12.7%, respectively). CT rates would be significantly lower with the use of the CCHR than with NOC (52.1% vs 88%). Physician agreement for interpretation of the rules is significantly higher for the CCHR, meaning the CCHR is easier to interpret. A second study in the same journal (Smits M, Dippel DW, de Haan GG, et al. JAMA 2005;294:1519-25) found that the CCHR has a lower sensitivity than the NOC for identifying all cases of neurocranial trauma, but supported that fact that the CCHR identified all cases requiring neurosurgical intervention. In addition, the CCHR had a greater potential for reducing the need for CT.

**Bottom line:** Both the New Orleans Criteria (NOC) and the Canadian CT Head Rule (CCHR) are equally accurate for identifying patients with clinically important brain injury requiring neurosurgical intervention and/or close follow-up. However, patients presenting with blunt head injury and a Glasgow Coma Scale score of 15 who have any intracranial injury are more accurately identified using the NOC. The CCHR has a significantly higher specificity for important clinical outcomes and a greater potential for reducing the need for computed tomography (CT). Concerns of litigation will likely determine which rule is applied in specific clinical situations. A study in
which patients are randomly assessed to either rule and measures long-term morbidity and mortality is needed to definitively answer this clinical question. (LOE = 1b)


Neurosurgery #ChoosingWisely

Don’t routinely obtain CT scanning of children with mild head injuries.
A mild traumatic brain injury is a temporary loss of neurologic function resulting from a blunt blow to the head or an acceleration/deceleration injury. There are predictors that a more severe injury has occurred and CT scanning may be appropriate. In patients younger than age two, a persistent altered mental status, non-frontal scalp hematoma, loss of consciousness for five seconds or more, severe injury mechanism, palpable skull fracture or not acting normally according to the parent may be signs of a more serious injury. In patients older than two, prolonged abnormal mental status, any loss of consciousness, history of vomiting, severe injury mechanism, clinical signs of basilar skull fracture or severe headache may also necessitate CT imaging. Any patient with a traumatic injury to the head that has any neurologic deficits should also be imaged if no other cause can be determined.

AAP #ChoosingWisely

Computed tomography (CT) scans are not necessary in the immediate evaluation of minor head injuries; clinical observation/Pediatric Emergency Care Applied Research Network (PECARN) criteria should be used to determine whether imaging is indicated.

Key Points

1. Use of imaging, especially CT, should be minimized as scans can cause cancer. Additionally, 1 in 4 scans will reveal an incidentaloma that will require further evaluation.
2. In assessment of acute abdominal pain ultrasound is a specific test and can be used to minimize CT.
3. Imaging should only be used in headache with specific indications; imaging should not be used in chronic headache with no new features and normal neurologic exam.
4. A clinical decision rule like PECARN, New Orleans, or Canadian Head CT rule should be utilized in adults or children with minor trauma to determine if imaging is indicated.
Learning objectives: Understand:

1. USPSTF screening recommendations and the ADA recommendations for glycemic targets in type II diabetes in 2017
2. Where “tight control” is in 2017 for most patients with DM-II.
3. That empagliflozin, liraglutide and semaglutide use are associated with improved macrovascular outcomes in patients with long standing DM-II and established vascular disease
4. Understand metformin remains the primary recommended option for DM-II, and cautions on its use have been relaxed
5. Hypoglycemia remains a major limiting feature associated with diabetic medications
6. Incretin based therapies and sulphonylureas are not associated with excess CV risk
7. Replacing diet beverages with water in diabetics associated with weight loss

The USPSTF

- The USPSTF recommends screening for abnormal blood glucose as part of cardiovascular risk assessment in adults aged 40 to 70 years who are overweight or obese. Clinicians should offer or refer patients with abnormal blood glucose to intensive behavioral counseling interventions to promote a healthful diet and physical activity. (B)

#1: PLOS One | Death attributable to diabetes is severely underestimated

Objective: The goal of this research was to identify the fraction of deaths attributable to diabetes in the United States.

Research Design and Methods: We estimated population attributable fractions (PAF) for cohorts aged 30–84 who were surveyed in the National Health Interview Survey (NHIS) between 1997 and 2009 (N = 282,322) and in the National Health and Nutrition Examination Survey (NHANES) between 1999 and 2010 (N = 21,814). Cohort members were followed prospectively for mortality through 2011. We identified diabetes status using self-reported diagnoses in both NHIS and NHANES and using HbA1c in NHANES. Hazard ratios associated with diabetes were estimated using Cox model adjusted for age, sex, race/ethnicity, educational attainment, and smoking status.

Results: We found a high degree of consistency between data sets and definitions of diabetes in the hazard ratios, estimates of diabetes prevalence, and estimates of the proportion of deaths attributable to diabetes. The proportion of deaths attributable to diabetes was estimated to be 11.5% using self-reports in NHIS, 11.7% using self-reports in NHANES, and 11.8% using HbA1c in NHANES. Among the sub-groups that we examined, the PAF was highest among obese persons at 19.4%. The proportion of deaths in which diabetes was assigned as the underlying cause of death (3.3–3.7%) severely understated the contribution of diabetes to mortality in the United States.

Conclusion: Diabetes may represent a more prominent factor in American mortality than is commonly appreciated, reinforcing the need for robust population-level interventions aimed at diabetes prevention and care.


ADA Glycemic Targets 2017

- “A reasonable A1C goal for many nonpregnant adults is <7% (53 mmol/mol).” (A)
- “Providers might reasonably suggest more stringent A1C goals (such as <6.5% [48 mmol/mol]) for selected individual patients if this can be achieved without significant hypoglycemia or other adverse effects of treatment (i.e., polypharmacy). Appropriate patients might include those with short duration of diabetes, type 2 diabetes treated with lifestyle or metformin only, long life expectancy, or no significant cardiovascular disease.” (C)
- “Less stringent A1C goals (such as <8% [64 mmol/mol]) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes in whom the goal is difficult
We know that targeting an HbA1c of ~ 7% is not associated with improved macrovascular outcomes compared to an A1c of ~8% (brief review in the appendix). We also know that metformin is associated with improved macrovascular outcomes independent of HbA1c (UKPDS). To my knowledge no other class of drugs has been associated with improved macrovascular outcomes, in spite of the fact that all of them are proven to reduce A1c levels by 0.5 – 1.0%. Indeed, most of the recently approved GLP-1 agents have been approved because they have been proven to not increase major cardiovascular events.

According to the ADA “Atherosclerotic cardiovascular disease (ASCVD) …. is the leading cause of morbidity and mortality for individuals with diabetes and is the largest contributor to the direct and indirect costs of diabetes” (Diabetes Care 2017 Jan; 40(Supplement 1): S75-S87.) Since macrovascular disease (including coronary disease) is the primary process affecting diabetics, AND since glucose lowering therapies (e.g. insulin, GLP-1 agonists, DDP-IV inhibitors, sulphonylureas, glitazones, etc) have not been associated with improved macrovascular outcomes (except metformin) and several may have adverse effects on macrovascular outcomes, abstract #3 caught my eye this past year; is there a new (albeit much more expensive!) metformin for some of our diabetic patients? Given this, the industry sponsored EMPA-REG trial (Abstract #3) also deserves a more in-depth analysis. This drug was initially FDA approved for glycemic management in 2014, and in December of 2016 was approved to decrease the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and cardiovascular disease.

Pharmacologic Therapy for DM II

The updated ADA guidelines (Appendix | Figure 2) on pharmacologically treating DM – II state in part

- “Metformin … is the preferred initial pharmacologic agent for the treatment of type 2 diabetes.”
  - “...periodic measurement of vitamin B12 levels should be considered in metformin-treated patients...”
  - “Metformin may be safely used in patients with estimated glomerular filtration rate (eGFR) as low as 30 mL/min/1.73 m2”
“In patients with long-standing suboptimally controlled type 2 diabetes and established atherosclerotic cardiovascular disease, empagliflozin or liraglutide should be considered as they have been shown to reduce cardiovascular and all-cause mortality when added to standard care. Ongoing studies are investigating the cardiovascular benefits of other agents in these drug classes.”

Note that the patient populations in studies demonstrating improved macrovascular outcomes of all three drugs were older, predominantly male with long standing diabetes AND established vascular disease (Appendix)

The EMPA-Reg, Leader and Sustain-3 trials | Abstracts 3 – 5

Baseline characteristics of patients enrolled in the EMPA-Reg, Leader and Sustain-3 trials

<table>
<thead>
<tr>
<th>Patient Features</th>
<th>Empaglifozin</th>
<th>Liraglutide</th>
<th>Semaglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>Empa-Reg</td>
<td>Leader</td>
<td>Sustain-6</td>
</tr>
<tr>
<td>Mean Follow up (yrs)</td>
<td>3.1</td>
<td>3.8</td>
<td>2.1</td>
</tr>
<tr>
<td>Mean age</td>
<td>63</td>
<td>64</td>
<td>65</td>
</tr>
<tr>
<td>Male</td>
<td>70%</td>
<td>64%</td>
<td>60%</td>
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<tr>
<td>Race</td>
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</tr>
<tr>
<td>White</td>
<td>72%</td>
<td>NR</td>
<td>83%</td>
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<tr>
<td>Asian</td>
<td>21%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Black/African-American</td>
<td>5%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>DM Duration</td>
<td>57% &gt; 10 yrs</td>
<td>13 yrs</td>
<td>14 yrs</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>75%</td>
<td>81%</td>
<td>60%</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>47%</td>
<td></td>
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</tr>
<tr>
<td>CVA</td>
<td>23%</td>
<td>16%</td>
<td>14%</td>
</tr>
<tr>
<td>PAD</td>
<td>20%</td>
<td></td>
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</tr>
<tr>
<td>Cabg</td>
<td>25%</td>
<td>39%</td>
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<tr>
<td>MI hx</td>
<td>46%</td>
<td>34%</td>
<td>32%</td>
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<tr>
<td>Microalbuminuria</td>
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<tr>
<td>Macroadalbuminuria</td>
<td>10%</td>
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<tr>
<td>Heart failure</td>
<td>10%</td>
<td>18%</td>
<td>23%</td>
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<tr>
<td>Average HbA1c</td>
<td>8%</td>
<td>8.7</td>
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<td>92%</td>
<td>94%</td>
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<td>Lipid lowering therapy</td>
<td>80%</td>
<td>75%</td>
<td>76%</td>
</tr>
<tr>
<td>Anti-coagulants (mostly antiplatelet agents)</td>
<td>90%</td>
<td>67%</td>
<td>75%</td>
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## EMPA-Reg Trial Results | 3.1 year follow up

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<tr>
<th></th>
<th>Placebo (n=2333)</th>
<th>Empa (n=4687)</th>
<th>ARR</th>
<th>NNT</th>
<th>p-value</th>
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<tr>
<td><strong>Primary outcome (composite)</strong></td>
<td></td>
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<td></td>
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<tr>
<td>CV death</td>
<td>12.1%</td>
<td>10.5%</td>
<td>1.6</td>
<td>62</td>
<td>.04</td>
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<tr>
<td>Nonfatal MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal CVA</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>ARR</strong></td>
<td></td>
<td></td>
<td>1.6</td>
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<td><strong>NNT</strong></td>
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<td>62</td>
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<tr>
<td><strong>p-value</strong></td>
<td></td>
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<td>.04</td>
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<tr>
<td><strong>All-cause mortality</strong></td>
<td>8.3</td>
<td>5.7</td>
<td>2.6</td>
<td>38</td>
<td>&lt;.001</td>
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<td><strong>CV mortality</strong></td>
<td>5.9</td>
<td>3.7</td>
<td>2.2</td>
<td>45</td>
<td>&lt;.001</td>
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<td><strong>Hosp for heart failure</strong></td>
<td>4.1</td>
<td>2.7</td>
<td>1.4</td>
<td>71</td>
<td>.003</td>
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<tr>
<td><strong>Hosp for heart failure or CV death (excluding fatal CVA)</strong></td>
<td>30.1</td>
<td>19.7</td>
<td>1.4</td>
<td>71</td>
<td>.003</td>
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<tr>
<td><strong>End-of-study HbA1c</strong></td>
<td>~8.1</td>
<td>~7.7</td>
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<table>
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<tr>
<th></th>
<th>Placebo (n=4672)</th>
<th>Liraglutide (n=4668)</th>
<th>ARR</th>
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<th>p-value</th>
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<tr>
<td>Primary outcome (composite)</td>
<td>14.9</td>
<td>13.0</td>
<td>1.9</td>
<td>53</td>
<td>0.01</td>
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<tr>
<td>CV death</td>
<td>6.3</td>
<td>7.3</td>
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<td>100</td>
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<tr>
<td>Nonfatal MI</td>
<td>9.6</td>
<td>8.2</td>
<td>1.4</td>
<td>71</td>
<td>0.02</td>
</tr>
<tr>
<td>Nonfatal CVA</td>
<td>6.0</td>
<td>4.7</td>
<td>1.3</td>
<td>77</td>
<td>0.007</td>
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<tr>
<td>MI</td>
<td>4.7</td>
<td>5.3</td>
<td>0.14</td>
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<tr>
<td>All-cause mortality</td>
<td>6.0</td>
<td>4.7</td>
<td>1.3</td>
<td>77</td>
<td>0.007</td>
</tr>
<tr>
<td>CV mortality</td>
<td>3.9</td>
<td>2.9</td>
<td>1.1</td>
<td>90</td>
<td>0.04</td>
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<tr>
<td>Hosp for heart failure</td>
<td>3.6</td>
<td>3.8</td>
<td>0.79</td>
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<tr>
<td>End of study HbA1c</td>
<td>8.3</td>
<td>7.3 – 7.6%</td>
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<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=1649)</th>
<th>Semaglutide (n=1648)</th>
<th>ARR (%)</th>
<th>NNT</th>
<th>p-value</th>
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<tr>
<td>Primary Composite Outcome</td>
<td>8.9%</td>
<td>6.6%</td>
<td>2.3</td>
<td>43</td>
<td>0.02</td>
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<tr>
<td>CV Death</td>
<td>3.6</td>
<td>3.8</td>
<td>0.12</td>
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<tr>
<td>Non-fatal MI</td>
<td>3.9</td>
<td>2.9</td>
<td>0.79</td>
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<tr>
<td>Non-fatal CVA</td>
<td>2.7</td>
<td>1.6</td>
<td>0.92</td>
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<tr>
<td>All-cause mortality</td>
<td>2.8</td>
<td>2.7</td>
<td>0.57</td>
<td></td>
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</tr>
<tr>
<td>CV mortality</td>
<td>3.3</td>
<td>3.6</td>
<td>8.3%</td>
<td>7.3 – 7.6%</td>
<td></td>
</tr>
<tr>
<td>Hosp for heart failure</td>
<td>8.3</td>
<td>7.3 – 7.6%</td>
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</table>


**# 3: PubMed: Empagliflozin (Jardiance®) is associated with ↓ CV events & all-cause mortality in DM-II**

**BACKGROUND:** The effects of empagliflozin, an inhibitor of sodium-glucose cotransporter 2, in addition to standard care, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high cardiovascular risk are not known.
CONCLUSIONS: Patients with type 2 diabetes at high risk for cardiovascular events who received empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome and of death from any cause when the study drug was added to standard care. (Funded by Boehringer Ingelheim and Eli Lilly; EMPA-REG OUTCOME ClinicalTrials.gov number, NCT01131676).


Two other drugs for DM-II (both GLP-1 agonists) are on the horizon (one already approved) which also ↓ macrovascular disease

#4: PubMed: Liraglutide (Victoza®) decreases cardiovascular events and all-cause mortality in DM-II

BACKGROUND: The cardiovascular effect of liraglutide, a glucagon-like peptide 1 analogue, when added to standard care in patients with type 2 diabetes, remains unknown.

METHODS: In this double-blind trial, we randomly assigned patients with type 2 diabetes and high cardiovascular risk to receive liraglutide or placebo. The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The primary hypothesis was that liraglutide would be noninferior to placebo with regard to the primary outcome, with a margin of 1.30 for the upper boundary of the 95% confidence interval of the hazard ratio. No adjustments for multiplicity were performed for the prespecified exploratory outcomes.

RESULTS: A total of 9340 patients underwent randomization. The median follow-up was 3.8 years. The primary outcome occurred in significantly fewer patients in the liraglutide group (608 of 4668 patients [13.0%]) than in the placebo group (694 of 4672 [14.9%]) (hazard ratio, 0.87; 95% confidence interval [CI], 0.78 to 0.97; P<0.001 for noninferiority; P=0.01 for superiority). Fewer patients died from cardiovascular causes in the liraglutide group (219 patients [4.7%]) than in the placebo group (278 [6.0%]) (hazard ratio, 0.78; 95% CI, 0.66 to 0.93; P=0.007). The rate of death from any cause was lower in the liraglutide group (381 patients [8.2%]) than in the placebo group (447 [9.6%]) (hazard ratio, 0.85; 95% CI, 0.74 to 0.97; P=0.02). The rates of nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group. The most common adverse events leading to the discontinuation of liraglutide were gastrointestial events. The incidence of pancreatitis was nonsignificantly lower in the liraglutide group than in the placebo group.

CONCLUSIONS: In the time-to-event analysis, the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide than with placebo. (Funded by Novo Nordisk and the National Institutes of Health; LEADER ClinicalTrials.gov number, NCT01179048.)


#5: PubMed: Semaglutide decreases cardiovascular death, MI and CVA in DM-II

Background Regulatory guidance specifies the need to establish cardiovascular safety of new diabetes therapies in patients with type 2 diabetes in order to rule out excess cardiovascular risk. The cardiovascular effects of semaglutide, a glucagon-like peptide 1 analogue with an extended half-life of approximately 1 week, in type 2 diabetes are unknown.

Methods We randomly assigned 3297 patients with type 2 diabetes who were on a standard-care regimen to receive once-weekly semaglutide (0.5 mg or 1.0 mg) or placebo for 104 weeks. The primary composite outcome was the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. We hypothesized that semaglutide would be noninferior to placebo for the primary outcome. The noninferiority margin was 1.8 for the upper boundary of the 95% confidence interval of the hazard ratio.

Results At baseline, 2735 of the patients (83.0%) had established cardiovascular disease, chronic kidney disease, or both. The primary outcome occurred in 108 of 1648 patients (6.6%) in the semaglutide group and in 146 of 1649 patients (8.9%) in the placebo group (hazard ratio, 0.74; 95% confidence interval [CI], 0.58 to 0.95; P=0.001 for noninferiority). Nonfatal myocardial infarction occurred in 2.9% of the patients receiving semaglutide and in 3.9% of those receiving placebo (hazard ratio, 0.74; 95% CI, 0.51 to 1.08; P=0.12); nonfatal stroke occurred in 1.6% and 2.7%, respectively (hazard ratio, 0.61; 95% CI, 0.38 to 0.99; P=0.04). Rates of death from cardiovascular causes were similar in the two groups. Rates of new or worsening nephropathy were lower in the semaglutide group, but rates of retinopathy complications (vitreous hemorrhage, blindness, or conditions requiring treatment with an intravitreal agent or photocoagulation) were significantly higher (hazard ratio, 1.76; 95% CI, 1.11 to 2.78; P=0.02). Fewer serious adverse events occurred in the semaglutide group, although more patients discontinued treatment because of adverse events, mainly gastrointestinal.
Conclusions In patients with type 2 diabetes who were at high cardiovascular risk, the rate of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was significantly lower among patients receiving semaglutide than among those receiving placebo, an outcome that confirmed the noninferiority of semaglutide. (Funded by Novo Nordisk; SUSTAIN-6 ClinicalTrials.gov number, NCT01720446.).


Other effects of empagliflozin …

# 6. PubMed: Empagliflozin (Jardiance®) is associated with ↓ CHF event

AIMS: We previously reported that in the EMPA-REG OUTCOME® trial, empagliflozin added to standard of care reduced the risk of 3-point major adverse cardiovascular events, cardiovascular and all-cause death, and hospitalization for heart failure in patients with type 2 diabetes and high cardiovascular risk. We have now further investigated heart failure outcomes in all patients and in subgroups, including patients with or without baseline heart failure.

METHODS AND RESULTS: Patients were randomized to receive empagliflozin 10 mg, empagliflozin 25 mg, or placebo. Seven thousand and twenty patients were treated; 706 (10.1%) had heart failure at baseline. Heart failure hospitalization or cardiovascular death occurred in a significantly lower percentage of patients treated with empagliflozin (265/4687 patients (5.7%)) than with placebo (198/2333 patients (8.5%)) [hazard ratio, HR: 0.66 (95% confidence interval: 0.55-0.79); P < 0.001], corresponding to a number needed to treat to prevent one heart failure hospitalization or cardiovascular death of 35 over 3 years. Consistent effects of empagliflozin were observed across subgroups defined by baseline characteristics, including patients with vs. without heart failure, and across categories of medications to treat diabetes and/or heart failure. Empagliflozin improved other heart failure outcomes, including hospitalization for or death from heart failure [2.8 vs. 4.5%; HR: 0.61 (0.47-0.79); P < 0.001] and was associated with a reduction in all-cause hospitalization [36.8 vs. 39.6%; HR: 0.89 (0.82-0.96); P = 0.003]. Serious adverse events and adverse events leading to discontinuation or death from heart failure [2.8 vs. 4.5%; HR: 0.61 (0.47-0.79); P < 0.001] and was associated with a reduction in all-cause hospitalization [36.8 vs. 39.6%; HR: 0.89 (0.82-0.96); P = 0.003]. Serious adverse events and adverse events leading to discontinuation were reported by a higher proportion of patients with vs. without heart failure at baseline in both treatment groups, but were no more common with empagliflozin than with placebo.

CONCLUSION: In patients with type 2 diabetes and high cardiovascular risk, empagliflozin reduced heart failure hospitalization and cardiovascular death, with a consistent benefit in patients with and without baseline heart failure.


# 7. PubMed: Empagliflozin (Jardiance®) is associated with ↓ renal events

BACKGROUND: Diabetes confers an increased risk of adverse cardiovascular and renal events. In the EMPA-REG OUTCOME trial, empagliflozin, a sodium-glucose cotransporter 2 inhibitor, reduced the risk of major adverse cardiovascular events in patients with type 2 diabetes at high risk for cardiovascular events. We wanted to determine the long-term renal effects of empagliflozin, an analysis that was a prespecified component of the secondary microvascular outcome of that trial.

METHODS: We randomly assigned patients with type 2 diabetes and an estimated glomerular filtration rate of at least 30 ml per minute per 1.73 m²(2) of body-surface area to receive either empagliflozin (at a dose of 10 mg or 25 mg) or placebo once daily. Prespecified renal outcomes included incident or worsening nephropathy (progression to macroalbuminuria, doubling of the serum creatinine level, initiation of renal-replacement therapy, or death from renal disease) and incident albuminuria.

RESULTS: Incident or worsening nephropathy occurred in 525 of 4124 patients (12.7%) in the empagliflozin group and in 388 of 2061 (18.8%) in the placebo group (hazard ratio in the empagliflozin group, 0.61; 95% confidence interval, 0.53 to 0.70; P<0.001). Doubling of the serum creatinine level occurred in 70 of 4645 patients (1.5%) in the empagliflozin group and in 60 of 2323 (2.6%) in the placebo group, a significant relative risk reduction of 44%. Renal-replacement therapy was initiated in 13 of 4687 patients (0.3%) in the empagliflozin group and in 14 of 2333 patients (0.6%) in the placebo group, representing a 55% lower relative risk in the empagliflozin group. There was no significant between-group difference in the rate of incident albuminuria. The adverse-event profile of empagliflozin in patients with impaired kidney function at baseline was similar to that reported in the overall trial population.

CONCLUSIONS: In patients with type 2 diabetes at high cardiovascular risk, empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant renal events than was placebo when added to standard care. (Funded by the Boehringer Ingelheim and Eli Lilly and Company Diabetes Alliance; EMPA-REG OUTCOME ClinicalTrials.gov number, NCT01131676.).


FDA APPROVAL ALERT: DIABETES COMBINATION APPROVED | On December 12, 2016 the FDA approved Synjardy XR (empagliflozin and metformin hydrochloride extended-release tablets; Boehringer Ingelheim and Eli Lilly) tablets for adults with type 2 diabetes. Cost for a one-month supply is $426 on googdrx.com

Note a cousin of empagliflozin (canagliflozin sold as Invokana® and Invokamet®) has an FDA warning on bone fracture risk and decreased bone mineral density.

www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm461876.htm

#8. PubMed: AAFP/ACP Guideline | Metformin for most patients with DM-II needing pharmacotherapy
Description: The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on oral pharmacologic treatment of type 2 diabetes in adults. This guideline serves as an update to the 2012 ACP guideline on the same topic. This guideline is endorsed by the American Academy of Family Physicians.

Methods: This guideline is based on a systematic review of randomized, controlled trials and observational studies published through December 2015 on the comparative effectiveness of oral medications for type 2 diabetes. Evaluated interventions included metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium–glucose cotransporter-2 (SGLT-2) inhibitors. Study quality was assessed, data were extracted, and results were summarized qualitatively on the basis of the totality of evidence identified by using several databases. Evaluated outcomes included intermediate outcomes of hemoglobin A1c, weight, systolic blood pressure, and heart rate; all-cause mortality; cardiovascular and cerebrovascular morbidity and mortality; retinopathy, nephropathy, and neuropathy; and harms. This guideline grades the recommendations by using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system.

Target Audience and Patient Population: The target audience for this guideline includes all clinicians, and the target patient population includes adults with type 2 diabetes.

Recommendation 1: ACP recommends that clinicians prescribe metformin to patients with type 2 diabetes when pharmacologic therapy is needed to improve glycemic control. (Grade: strong recommendation; moderate-quality evidence)

Recommendation 2: ACP recommends that clinicians consider adding either a sulfonylurea, a thiazolidinedione, an SGLT-2 inhibitor, or a DPP-4 inhibitor to metformin to improve glycemic control when a second oral therapy is considered. (Grade: weak recommendation; moderate-quality evidence.) ACP recommends that clinicians and patients select among medications after discussing benefits, adverse effects, and costs.


#9. PubMed: Metformin is safe in patients who historically had contraindications

Background: Recent changes to the U.S. Food and Drug Administration boxed warning for metformin will increase its use in persons with historical contraindications or precautions. Prescribers must understand the clinical outcomes of metformin use in these populations.

Purpose: To synthesize data addressing outcomes of metformin use in populations with type 2 diabetes and moderate to severe chronic kidney disease (CKD), congestive heart failure (CHF), or chronic liver disease (CLD) with hepatic impairment.


Study Selection: English-language studies that: 1) examined adults with type 2 diabetes and CKD (with estimated glomerular filtration rate less than 60 ml/min/1.73 m2), CHF, or CLD with hepatic impairment; 2) compared diabetes regimens that included metformin with those that did not; and 3) reported all-cause mortality, major adverse cardiovascular events, and other outcomes of interest.

Data Extraction: 2 reviewers abstracted data and independently rated study quality and strength of evidence.

Data Synthesis: On the basis of quantitative and qualitative syntheses involving 17 observational studies, metformin use is associated with reduced all-cause mortality in patients with CKD, CHF, or CLD with hepatic impairment, and with fewer heart failure readmissions in patients with CKD or CHF.

Limitations: Strength of evidence was low, and data on multiple outcomes of interest were sparse. Available studies were observational and varied in follow-up duration.

Conclusion: Metformin use in patients with moderate CKD, CHF, or CLD with hepatic impairment is associated with improvements in key clinical outcomes. Our findings support the recent changes in metformin labeling.

Primary Funding Source: U.S. Department of Veterans Affairs. (PROSPERO: CRD42016027708).


#10: PubMed: 5 diabetic agents among 15 most common drugs → ED visits

Importance: The Patient Protection and Affordable Care Act of 2010 brought attention to adverse drug events in national patient safety efforts. Updated, detailed, nationally representative data describing adverse drug events can help focus these efforts.

Objective: To describe the characteristics of emergency department (ED) visits for adverse drug events in the United States in 2013-2014 and describe changes in ED visits for adverse drug events since 2005-2006.

Design, Setting, and Participants: Active, nationally representative, public health surveillance in 58 EDs located in the United States and participating in the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project.

Exposures: Drugs implicated in ED visits.

Main Outcomes and Measures: National weighted estimates of ED visits and subsequent hospitalizations for adverse drug events.

Results: Based on data from 42,565 cases, an estimated 4.0 (95% CI, 3.1-5.0) ED visits per 1000 individuals annually in 2013 and 2014 and 27.3% (95% CI, 22.2%-32.4%) of ED visits for adverse drug events resulted in hospitalization. An estimated 34.5% (95% CI, 30.3%-38.8%) of ED visits for adverse drug events occurred among adults aged 65 years or older in 2013-2014 compared with an estimated 25.6% (95% CI, 21.1%-30.0%) in 2005-2006; older adults experienced 11% highest hospitalization rates (43.6%; 95% CI, 36.6%-50.5%). Anticoagulants, antibiotics, and diabetes agents were implicated in an estimated 46.9% (95% CI, 44.2%-49.7%) of ED visits for adverse drug events, which included clinically significant adverse events, such as hemorrhage (anticoagulants), moderate to severe allergic reactions (antibiotics), and hypoglycemia with moderate to severe neurological effects (diabetes agents). Since 2005-2006, the proportions of ED visits for adverse drug events from anticoagulants and diabetes agents have increased, whereas the proportion from antibiotics has decreased. Among children aged 5 years or younger,
antibiotics were the most common drug class implicated (56.4%; 95% CI, 51.8%-61.0%). Among children and adolescents aged 6 to 19 years, antibiotics also were the most common drug class implicated (31.8%; 95% CI, 28.7%-34.9%) in ED visits for adverse drug events, followed by antipsychotics (4.5%; 95% CI, 3.3%-5.6%). Among older adults (aged ≥65 years), 3 drug classes (anticoagulants, diabetes agents, and opioid analgesics) were implicated in an estimated 59.9% (95% CI, 56.8%-62.9%) of ED visits for adverse drug events; 4 anticoagulants (warfarin, rivaroxaban, dabigatran, and enoxaparin) and 5 diabetes agents (insulin and 4 oral agents) were among the 15 most common drugs implicated. Medications to always avoid in older adults according to Beers criteria were implicated in 1.8% (95% CI, 1.5%-2.1%) of ED visits for adverse drug events.

Conclusions and Relevance: The prevalence of emergency department visits for adverse drug events in the United States was estimated to be 4 per 1000 individuals in 2013 and 2014. The most common drug classes implicated were anticoagulants, antibiotics, diabetes agents, and opioid analgesics.


#11: PubMed: Prevalence of hypoglycemia in diabetic patients not on insulin

IMPORTANCE: Intensive glucose-lowering treatment among patients with non-insulin-requiring type 2 diabetes may increase the risk of hypoglycemia.

OBJECTIVES: To estimate the prevalence of intensive treatment and the association between intensive treatment, clinical complexity, and incidence of severe hypoglycemia among adults with type 2 diabetes who are not using insulin.

DESIGN, SETTING, AND PARTICIPANTS: Retrospective analysis of administrative, pharmacy, and laboratory data from the OptumLabs Data Warehouse from January 1, 2001, through December 31, 2013. The study included nonpregnant adults 18 years or older with type 2 diabetes who achieved and maintained a hemoglobin A1c (HbA1c) level less than 7.0% without use of insulin and had no episodes of severe hypoglycemia or hyperglycemia in the prior 12 months.

MAIN OUTCOMES AND MEASURES: Risk-adjusted probability of intensive treatment and incident severe hypoglycemia, stratified by patient clinical complexity. Intensive treatment was defined as use of more glucose-lowering medications than recommended by practice guidelines at specific index HbA1c levels. Severe hypoglycemia was ascertained by ambulatory, emergency department, and hospital claims for hypoglycemia during the 2 years after the index HbA1c test. Patients were categorized as having high vs low clinical complexity if they were 75 years or older, had dementia or end-stage renal disease, or had 3 or more serious chronic conditions.

RESULTS: Of 31 542 eligible patients (median age, 58 years; interquartile range, 51-65 years; 15 483 women [49.1%]; 18 188 white [57.7%]), 3910 (12.4%) had clinical complexity. The risk-adjusted probability of intensive treatment was 25.7% (95% CI, 25.1%-26.2%) in patients with low clinical complexity and 20.8% (95% CI, 19.4%-22.2%) in patients with high clinical complexity. In patients with low clinical complexity, the risk-adjusted probability of severe hypoglycemia during the subsequent 2 years was 1.02% (95% CI, 0.87%-1.17%) with standard treatment and 1.30% (95% CI, 0.98%-1.62%) with intensive treatment (absolute difference, 0.28%; 95% CI, -0.10% to 0.66%). In patients with high clinical complexity, intensive treatment significantly increased the risk-adjusted probability of severe hypoglycemia from 1.74% (95% CI, 1.28%-2.20%) with standard treatment to 3.04% (95% CI, 1.91%-4.18%) with intensive treatment (absolute difference, 1.30%; 95% CI, 0.10%-2.50%).

CONCLUSIONS AND RELEVANCE: More than 20% of patients with type 2 diabetes received intensive treatment that may be unnecessary. Among patients with high clinical complexity, intensive treatment nearly doubles the risk of severe hypoglycemia.

REFERENCE: McCoy RG et al. Intensive Treatment and Severe Hypoglycemia Among Adults With Type 2 Diabetes. JAMA Intern Med. 2016 Jul 1;176(7):969-78

#12: PubMed: Hypoglycemia risk ↑ 50% with DPP-IV inhibitors and sulphonylureas

OBJECTIVE: To quantify the risk of hypoglycaemia associated with the concomitant use of dipeptidyl peptidase-4 (DPP-4) inhibitors and sulphonylureas compared with placebo and sulphonylureas.

DESIGN: Systematic review and meta-analysis.

DATA SOURCES: Medline, ISI Web of Science, SCOPUS, Cochrane Central Register of Controlled Trials, and clinicaltrial.gov were searched without any language restriction.

STUDY SELECTION: Placebo controlled randomised trials comprising at least 50 participants with type 2 diabetes treated with DPP-4 inhibitors and sulphonylureas.

REVIEW METHODS: Risk of bias in each trial was assessed using the Cochrane Collaboration tool. The risk ratio of hypoglycaemia with 95% confidence intervals was computed for each study and then pooled using fixed effect models (Mantel Haenszel method) or random effect models, when appropriate. Subgroup analyses were also performed (eg, dose of DPP-4 inhibitors). The number needed to harm (NNH) was estimated according to treatment duration.

RESULTS: 10 studies were included, representing a total of 6546 participants (4020 received DPP-4 inhibitors plus sulphonylureas, 2526 placebo plus sulphonylureas). The risk ratio of hypoglycaemia was 1.52 (95% confidence interval 1.29 to 1.80). The NNH was 17 (95% confidence interval 11 to 30) for a treatment duration of six months or less, 15 (9 to 26) for 6.1 to 12 months, and 8 (5 to 15) for more than one year. In subgroup analysis, no difference was found between full and low doses of DPP-4 inhibitors: the risk ratio related to full dose DPP-4 inhibitors was 1.66 (1.34 to 2.06), whereas the increased risk ratio related to low dose DPP-4 inhibitors did not reach statistical significance (1.33, 0.92 to 1.94).

CONCLUSIONS: Addition of DPP-4 inhibitors to sulphonylurea to treat people with type 2 diabetes is associated with a 50% increased risk of hypoglycaemia and to one excess case of hypoglycaemia for every 17 patients in the first six months of treatment. This highlights the need to respect recommendations for a decrease in sulphonylurea dose when initiating DPP-4 inhibitors and to assess the effectiveness of this risk minimisation strategy.

REFERENCE: Salvo F et al. Addition of dipeptidyl peptidase-4 inhibitors to sulphonylureas and risk of hypoglycaemia: systematic review and meta-analysis. BMJ. 2016 May 3;353:i2231
Glucagon like peptide–1 (GLP-1) acts to increase insulin secretion in response to food. GLP-1 is an incretin based therapy [i.e. Intestinal secretion of insulin (Incretin). GLP-1 is diminished or absent in many with DM-II. GLP-1 agonists act as "replacement therapy" whereas Dipeptidyl peptidase-4 inhibitors (DPP-IV inhibitors) inhibit the endogenous enzyme that breaks down endogenous GLP-1 (thereby increasing endogenous GLP-1)

#13: PubMed: Incretin based therapies not associated with risk of hospitalization for CHF

**BACKGROUND:** There is concern that antidiabetic incretin-based drugs, including dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide 1 (GLP-1) analogues, can increase the risk of heart failure. Ongoing clinical trials may not have large enough samples to effectively address this issue.

**METHODS:** We applied a common protocol in the analysis of multiple cohorts of patients with diabetes. We used health care data from four Canadian provinces, the United States, and the United Kingdom. With the use of a nested case-control analysis, we matched each patient who was hospitalized for heart failure with up to 20 controls from the same cohort; matching was based on sex, age, cohort-entry date, duration of treated diabetes, and follow-up time. Cohort-specific hazard ratios for hospitalization due to heart failure among patients receiving incretin-based drugs, as compared with those receiving oral antidiabetic-drug combinations, were estimated by means of conditional logistic regression and pooled across cohorts with the use of random-effects models.

**RESULTS:** The cohorts included a total of 1,499,650 patients, with 29,741 hospitalized for heart failure (incidence rate, 9.2 events per 1000 persons per year). The rate of hospitalization for heart failure did not increase with the use of incretin-based drugs as compared with oral antidiabetic-drug combinations among patients with a history of heart failure (hazard ratio, 0.86; 95% confidence interval [CI], 0.62 to 1.19) or among those without a history of heart failure (hazard ratio, 0.82; 95% CI, 0.67 to 1.00). The results were similar for DPP-4 inhibitors and GLP-1 analogues.

**CONCLUSIONS:** In this analysis of data from large cohorts of patients with diabetes, incretin-based drugs were not associated with an increased risk of hospitalization for heart failure, as compared with commonly used combinations of oral antidiabetic drugs. (Funded by the Canadian Institutes of Health Research; ClinicalTrials.gov number, NCT02456428.)


#14: PubMed: Sulphonylureas are not associated with risk of all-cause/CV mortality

**BACKGROUND:** Sulfonylureas are an effective and inexpensive treatment for type 2 diabetes. There is conflicting data about the safety of these drugs regarding mortality and cardiovascular outcomes. The objective of the present study was to evaluate the safety of the sulfonylureas most frequently used and to use trial sequential analysis (TSA) to analyze whether the available sample was powered enough to support the results.

**METHODS AND FINDINGS:** Electronic databases were reviewed from 1946 (Embase) or 1966 (MEDLINE) up to 31 December 2014. Randomized clinical trials (RCTs) of at least 52 wk in duration evaluating second- or third-generation sulfonylureas in the treatment of adults with type 2 diabetes and reporting outcomes of interest were included. Primary outcomes were all-cause and cardiovascular mortality. Additionally, myocardial infarction and stroke events were evaluated. Data were summarized with Peto odds ratios (ORs), and the reliability of the results was evaluated with TSA. Forty-seven RCTs with 37,650 patients and 890 deaths in total were included. Sulfonylureas were not associated with all-cause (OR 1.12 [95% CI 0.96 to 1.30]) or cardiovascular mortality (OR 1.12 [95% CI 0.87 to 1.42]). Sulfonylureas were also not associated with increased risk of myocardial infarction (OR 0.92 [95% CI 0.76 to 1.12]) or stroke (OR 1.16 [95% CI 0.81 to 1.66]). TSA could discern an absolute difference of 0.5% between the treatments, which was considered the minimal clinically significant difference. The major limitation of this review was the inclusion of studies not designed to evaluate safety outcomes.

**CONCLUSIONS:** Sulfonylureas are not associated with increased risk for all-cause mortality, cardiovascular mortality, myocardial infarction, or stroke. Current evidence supports the safety of sulfonylureas; an absolute risk of 0.5% could be firmly discarded.

**REVIEW REGISTRATION:** PROSPERO CRD42014004330.


#15: PubMed: Sulphonylureas are associated with risk of all-cause/CV mortality

**AIM:** To conduct a systematic review and meta-analysis to determine the risk of cardiovascular events and all-cause mortality associated with sulphonylureas (SUs) vs other glucose lowering drugs in patients with T2DM (T2DM).

**MATERIALS AND METHODS:** A systematic review of Medline, Embase, Cochrane and clinicaltrials.gov was conducted for studies comparing SUs with placebo or other antihyperglycaemic drugs in patients with T2DM. A cloglog model was used in the Bayesian framework to obtain comparative hazard ratios (HRs) for the different interventions. For the analysis of observational data, conventional fixed-effect pairwise meta-analyses were used.

**RESULTS:** The systematic review identified 82 randomized controlled trials (RCTs) and 26 observational studies. Meta-analyses of RCT data showed an increased risk of all-cause mortality and cardiovascular-related mortality for SUs compared with all other treatments combined (HR 1.26, 95% confidence interval [CI] 1.10-1.44 and HR 1.46, 95% CI 1.21-1.77, respectively). The risk of myocardial infarction was significantly higher for SUs compared with dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose co-transporter-2 inhibitors (HR 2.54, 95% CI 1.14-6.57 and HR 41.80, 95% CI 1.64-360.4, respectively). The risk of stroke was significantly higher for SUs than for DPP-4 inhibitors, glucagon-like peptide-1 agonists, thiazolidinediones and insulin.
CONCLUSIONS: The present meta-analysis showed an association between SU therapy and a higher risk of major cardiovascular disease-related events compared with other glucose lowering drugs. Results of ongoing RCTs, which should be available in 2018, will provide definitive results on the risk of cardiovascular events and all-cause mortality associated with SUs vs other antihyperglycaemic drugs.


#16: PubMed: Moderate alcohol improves cardiometabolic risk

BACKGROUND: Recommendations for moderate alcohol consumption remain controversial, particularly in type 2 diabetes mellitus (T2DM). Long-term randomized, controlled trials (RCTs) are lacking.

OBJECTIVE: To assess cardiometabolic effects of initiating moderate alcohol intake in persons with T2DM and whether the type of wine matters.


SETTING: Ben-Gurion University of the Negev-Soroka Medical Center and Nuclear Research Center Negev, Israel.

PATIENTS: Alcohol-abstaining adults with well-controlled T2DM.

INTERVENTION: Patients were randomly assigned to 150 mL of mineral water, white wine, or red wine with dinner for 2 years. Wines and mineral water were provided. All groups followed a Mediterranean diet without caloric restriction.

MEASUREMENTS: Primary outcomes were lipid and glycemic control profiles. Genetic measurements were done, and patients were followed for blood pressure, liver biomarkers, medication use, symptoms, and quality of life.

RESULTS: Of the 224 patients who were randomly assigned, 94% had follow-up data at 1 year and 87% at 2 years. In addition to the changes in the water group (Mediterranean diet only), red wine significantly increased high-density lipoprotein cholesterol (HDL-C) level by 0.05 mmol/L (2.0 mg/dL) (95% CI, 0.04 to 0.06 mmol/L [1.6 to 2.2 mg/dL]; P < 0.001) and apolipoprotein(a)1 level by 0.03 g/L (CI, 0.01 to 0.06 g/L; P = 0.05) and decreased the total cholesterol-HDL-C ratio by 0.27 (CI, -0.52 to -0.01; P = 0.039). Only slow ethanol metabolizers (alcohol dehydrogenase alleles [ADH1B*1] carriers) significantly benefited from the effect of both wines on glycemic control (fasting plasma glucose, homeostatic model assessment of insulin resistance, and hemoglobin A1c) compared with fast ethanol metabolizers (persons homozygous for ADH1B*2). Across the 3 groups, no material differences were identified in blood pressure, adiposity, liver function, drug therapy, symptoms, or quality of life, except that sleep quality improved in both wine groups compared with the water group (P = 0.040). Overall, compared with the changes in the water group, red wine further reduced the number of components of the metabolic syndrome by 0.34 (CI, -0.68 to -0.001; P = 0.049).

LIMITATION: Participants were not blinded to treatment allocation.

CONCLUSION: This long-term RCT suggests that initiating moderate wine intake, especially red wine, among well-controlled diabetics as part of a healthy diet is apparently safe and modestly decreases cardiometabolic risk. The genetic interactions suggest that ethanol plays an important role in glucose metabolism, and red wine's effects also involve nonalcoholic constituents.

PRIMARY FUNDING SOURCE: European Foundation for the Study of Diabetes.


#17: PubMed: Replacing diet beverages with water associated with weight reduction in diabetics

AIMS: To compare the effect of replacing diet beverages (DBs) with water or continuing to drink DBs in patients with type 2 diabetes during a 24-week weight loss program. The primary endpoint was the effect of intervention on weight over a 24-week period. The main secondary endpoints included anthropometric measurement and glucose and fat metabolism during the 24-week period.

METHODS: A total of 81 overweight and obese women with type 2 diabetes, who usually consumed DBs in their diet, were asked to either substitute water for DBs or continue drinking DBs five times per week after lunch for 24 weeks (DBs group) during a weight loss program.

RESULTS: Compared with the DBs group, the water group had a greater decrease in weight (-6.40 ± 2.42 kg; DBs, -5.25 ± 1.60 kg; P = .006), in BMI (water, -2.49 ± 0.92 kg/m(2); DBs, -2.06 ± 0.62 kg/m(2); P = .006), in FPG (water, -1.63 ± 0.54 mmol/L; DBs, -1.29 ± 0.48 mmol/L; P = .005), in fasting insulin (water, -5.71 ± 2.30 m IU/mL; DBs, -4.16 ± 1.74 m IU/mL, P = .011), in HOMA IR (water, -3.20 ± 1.17; DBs, -2.48 ± 0.99, P = 0.03) and in 2 hour postprandial glucose (water, -1.67 ± 0.62 mmol/L; DBs, -1.35 ± 0.39 mmol/L; P = 0.03) and the total cholesterol-HDL-C ratio by 0.27 (CI, -0.52 to -0.01; P = 0.039). Only slow ethanol metabolizers (persons homozygous for ADH1B*2). Across the 3 groups, no material differences were identified in blood pressure, adiposity, liver function, drug therapy, symptoms, or quality of life, except that sleep quality improved in both wine groups compared with the water group (P = 0.040). Overall, compared with the changes in the water group, red wine further reduced the number of components of the metabolic syndrome by 0.34 (CI, -0.68 to -0.001; P = 0.049).

LIMITATION: Participants were not blinded to treatment allocation.

CONCLUSION: This long-term RCT suggests that initiating moderate wine intake, especially red wine, among well-controlled diabetics as part of a healthy diet is apparently safe and modestly decreases cardiometabolic risk. The genetic interactions suggest that ethanol plays an important role in glucose metabolism, and red wine's effects also involve nonalcoholic constituents.

PRIMARY FUNDING SOURCE: European Foundation for the Study of Diabetes.


Bottom Lines

1. Diabetes related mortality is estimated to be ~12% in the US
2. A 9 year follow up to the ACCORD trial continue to demonstrate no mortality benefit AND an increase in CV related deaths
3. For appropriately selected patients, empagliflozin therapy is associated with improved macrovascular outcomes and decreased all-cause mortality.
4. Liraglutide and semaglutide use is also associated with improved macrovascular outcomes in DM-II
5. Metformin is safe in patients who historically had contraindications
6. The prevalence of hypoglycemia in patients with DM-II is not insubstantial
7. The association between Sulfonylureas and macrovascular outcomes amongst patients with DM-II is still not known
8. Moderate alcohol intake (red wine) in well controlled diabetics is associated with a slight improvement in metabolic risk
9. Replacing diet beverages with water associated with weight reduction in diabetics

Appendix 1

References


Appendix 2

Tight Control

Brief Overview of the major trials testing the hypothesis on targeting and A1c ~ 7 vs and A1c ~8

- The ACCORD trial tested this hypothesis in about 10,000 patients with a mean age of 62 with already established cardiovascular disease (35% of the study population) or those with risk factors for CV disease. Within 4 months the authors noted
  - A 1.1% separation in the target an A1C between the intervention group (6.4%) and the control group (7.5%).
  - At the end of 3.5 years, death from any cause was 5% in the intervention group and 4% in the control group. The study was terminated early.

- The ADVANCE trial tested this hypothesis in about 11,000 patients with a mean age of 66, 32% of whom had macrovascular disease. The authors noted:
  - A 0.8% separation in the targeted A1C between the treatment group (6.5%) and the control group (7.3%).
  - After 5 years, the major outcome in the study were:
    - Slightly lower risk of developing macroalbuminuria (2.9% in the intervention group vs. 4.1% in the control group).
    - So you'd have to treat 83 patients to an A1C of 6.5% for 5 years to prevent a single case of macroalbuminuria.
    - No between group differences in macrovascular outcomes were noted.

- The VDAT trial tested this hypothesis in about 1,800 patients with a mean age of 60 (40% with known ASCVD). The authors noted:
  - A 1.5% separation (6.9% vs. 8.4%) in A1c levels.
  - After 5.6 years of follow up, no between group differences were noted in any macrovascular outcome.
What each of these studies did demonstrate was an excess of hypoglycemia in the “intensive” group (3.2x higher in ACCORD; 1.4X higher in ADVANCE; and 3.6 x higher in the VDAT trial) an outcome that is associated with a higher risk of dementia in diabetics over the age of 65. Taken in sum, these studies suggest that targeting an A1C of ~7.0 (vs. ~8.0) for 3 – 5 years is at best associated with a slightly lower risk of albuminuria, at the cost of a slightly higher risk of mortality and much higher risk of hypoglycemia.

You may remember the UKPDS study from the late 1980’s. This 15-year study also assessed the effect of intensive glycemic control in newly diagnosed type II diabetics. This non-blinded study produced a between group A1C difference of 0.9% (7.0 v 7.9%) and demonstrated that intensive treatment (either insulin or sulfonylurea or, in obese patients, metformin) vs. diet, lowered diabetes-related endpoints ~12%, almost all due to a decreased need for retinal photocoagulation (it should be noted that there were no between group differences in visual acuity, blindness or other markers of microvascular disease including microabluminuria). Also, as in the above-mentioned studies, the intensive treatment group demonstrated no between group differences in macrovascular disease, death from CVD or all-cause mortality, and hypoglycemia was much more common in the intensive treatment group vs. diet (11-36% vs. 1.2%). Subgroup analysis demonstrated that within the intensive treatment group, those obese patients taking metformin alone had a reduction in mortality and myocardial infarction, an effect not seen in the intensive treatment group receiving insulin or sulfonylureas, suggesting a beneficial effect of metformin, and not of “intensive treatment” per se.

A follow up to the UKPDS was published in 2008. About three quarters of the original patients were followed for 10 years after the study finished (note this is ~25 years after the study started). No attempt was made to keep the previously randomized treatments (the differences in A1C levels were lost within a year). Patients originally randomized to the insulin-sulfonylurea group demonstrated a 2.8% absolute risk reduction in MI and a 3.5% decrease in overall mortality, patients in the metformin group demonstrated an absolute decrease of 6.3% in MI and a 7.2% decrease in all-cause mortality. These results raise the possibly of a legacy effect (a delayed effect of early glucose control).

Recall the results of 3 major randomized controlled trails published over the past few years concluded tight (A1C target 6–7%) vs less tight (A1c 7-8%) demonstrated no benefit on macrovascular outcomes, minimal benefit on microvascular outcomes, and higher rates of hypoglycemia.

Also as part of their annual update, the ADA published “Standards of medical care in diabetes – 2015” (Diabetes Care 2015;38(suppl 1):S33-S40)

Among their recommendations/statement on tight control include verbatim:

- “Mortality findings in ACCORD and subgroup analyses of the VADT suggested that the potential risks of intensive glycemic control may outweigh its benefits in some patients.”
- “Those with long duration of diabetes, known history of severe hypoglycemia, advanced atherosclerosis, or advanced age/frailty may benefit from less aggressive targets.”
- “Severe hypoglycemia was significantly more likely in participants in all three trials randomized to the intensive glycemic control arm.”
  o "Severe or frequent hypoglycemia is an absolute indication for the modification of treatment regimens, including setting higher glycemic goals."
- “Less stringent A1C goals (such as < 8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advance microvascular or macrovascular complications and extensive co-morbid conditions …”
• “...individualization of treatment is the cornerstone of success”
• “Our recommendations are less prescriptive than and not as algorithmic as prior guidelines”
• “Importantly, utilizing the percent of diabetic patients who are achieving an HbA1c < 7.0% as a quality indicator, as promulgated by various health care organizations, is inconsistent with the emphasis on individualization of treatment goals”
Appendix 3

Clinical Decision making for glycemic targets in DM - II
General Recommendations: The order in the chart was determined by historical availability and the route of administration, with injectables to the right; it is not meant to denote any specific preference.
Appendix 5

Bonus Abstracts

PubMed: ASA for primary prevention in diabetics, not all upside

AIMS: To evaluate the benefits and harms of aspirin for the primary prevention of cardiovascular disease and all-cause mortality events in people with diabetes by conducting a systematic review and meta-analysis.

METHODS: Randomized controlled trials of aspirin compared with placebo (or no treatment) in people with diabetes with no history of cardiovascular disease were identified from MEDLINE, EMBASE, Web of Science, the Cochrane Library and a manual search of bibliographies to November 2015. Study-specific relative risks with 95% CIs were aggregated using random effects models.

RESULTS: A total of 10 randomized trials were included in the review. There was a significant reduction in risk of major adverse cardiovascular events in groups taking aspirin compared with placebo or no treatment. Limited subgroup analyses suggested that the effect of aspirin on major adverse cardiovascular events differed by baseline cardiovascular disease risk, medication compliance and sex (P for interaction for all > 0.05). There was no significant reduction in the risk of myocardial infarction, coronary heart disease, stroke, cardiovascular mortality or all-cause mortality. Aspirin significantly reduced the risk of myocardial infarction for a treatment duration of ≤ 5 years. There were differences in the effect of aspirin by dosage and treatment duration on overall stroke outcomes (P for interaction for all < 0.05). There was an increase in risk of major or gastrointestinal bleeding events, but estimates were imprecise and not significant.

CONCLUSIONS: The emerging data do not clearly support guidelines that encourage the use of aspirin for the primary prevention of cardiovascular disease in adults with diabetes who are at increased cardiovascular disease risk.


PubMed: Excessive testing for A1c → over treatment

STUDY QUESTION: What is the extent and effect of excessive testing for glycated hemoglobin (HbA1c) among adults with controlled type 2 diabetes?

METHODS: A retrospective analysis of data from a national administrative claims database included commercially insured individuals in the USA, 2001-13. Study patients were aged 18 years or older, had type 2 diabetes with stable glycemic control (two consecutive HbA1c tests showing HbA1c<7.0% within 24 months), did not use insulin, had no history of severe hypoglycemia or hyperglycemia, and were not pregnant. HbA1c testing frequency was measured within 24 months after the second (index) HbA1c test, and classified as guideline recommended (≤ 2 times/year), frequent (3-4 times/year), and excessive (≥ 5 times/year). Changes in treatment regimen were ascertained within three months of the index test.

STUDY ANSWER AND LIMITATIONS: Of 31,545 patients in the study cohort (mean age 58 years; mean index HbA1c 6.2%), HbA1c testing frequency was excessive in 6% and frequent in 55%. Despite good glycemic control at baseline, treatment was further intensified by addition of glucose lowering drugs or insulin in 8.4% of patients (comprising 13%, 9%, and 7% of those tested excessively, frequently, and per guidelines, respectively; P<0.001). Compared with guideline recommended testing, excessive testing was associated with treatment intensification (odds ratio 1.35 (95% confidence interval 1.22 to 1.50)). Excessive testing rates remained unchanged in 2001-08, but fell significantly after 2009. The odds of excessive testing was 46% lower in 2011 than in 2001-02. The study population is not representative of all US patients with type 2 diabetes because it was restricted to commercially insured adults with stable and controlled diabetes not receiving insulin treatment. The study design did not capture the underuse of HbA1c testing.

WHAT THIS STUDY ADDS: In this US cohort of adults with stable and controlled type 2 diabetes, more than 60% received too many HbA1c tests, a practice associated with potential overtreatment with hypoglycemic drugs. Excessive testing contributes to the growing problem of waste in healthcare and increased patient burden in diabetes management.

FUNDING, COMPETING INTERESTS, DATA SHARING: NDS and RGM are funded partly by the Agency for Healthcare Research and Quality (R18HS18339) and AcademyHealth Delivery System Science Fellowship (2013), respectively. No competing interests declared. Additional data are available from mccoy.rozalina@mayo.edu.


Poem: Older patients with diabetes have higher fall risk, especially if using insulin

Clinical question: Are older patients with diabetes at increased risk of falls?

Study design: Meta-analysis (other)

Setting: Various (meta-analysis)

Synopsis: Because of inconsistent findings in individual studies, these authors searched two databases to identify prospective cohort studies that evaluated falls in patients older than 60 years with diabetes. In addition to the databases, the authors supplemented the search by combing through the reference lists of included studies and relevant reviews. They dont describe searching registries for unpublished studies. Two reviewers independently extracted data and assessed the quality of the studies. Ultimately, they included 6
studies with nearly 15,000 patients followed from 10 months to 10 years. Two of the studies included only women, and 3 reported whether patients received insulin. The range of quality scores of the studies ranged from 6 to 8 (of a maximum of 9). Over the course of the studies, the overall rate of falls was 25% in patients with diabetes and 18% in patients without diabetes (relative risk [RR] 1.64; 95% CI 1.27 - 2.11). Although the increased risk persisted across many subgroups (eg, follow-up duration, sex, and body weight), the rate was especially higher in patients using insulin (32% vs 21%; RR 1.94; 1.42 - 2.63). The authors don't report on the annual rate of falls nor did they formally assess the potential for publication bias. Finally, the authors reported significant heterogeneity in the rate of falls across the studies.

**Bottom line:** This limited meta-analysis of high-quality prospective cohort studies found that older patients with diabetes, especially those using insulin, have a higher rate of falls than older patients without diabetes and those not using insulin.

Vitamins: to take or not to take, that is the question

John Hickner MD, MSc

Objectives

1. Know the value of a variety of vitamins for prevention and disease treatment
2. Know the conditions for which Vitamin D supplementation is effective or ineffective or unknown

Vitamin supplementation other than Vitamin D

Vitamins are a multi-billion dollar business. Unfortunately, solid evidence from RCTs for effectiveness of vitamin therapy is scarce. Here are a few studies about vitamins published in the past few years. There is not a whole lot that is new, other than Vitamin D, which is the current darling child of vitamin researchers.

1. B vitamins produce small increase in sustained depression remission

Clinical question: Does B vitamin supplementation enhance response to antidepressants?

Study design: Randomized controlled trial (double-blinded)

Setting: Outpatient (any)

Synopsis: Drawing on epidemiologic research that found a relationship between B vitamin deficiency and anemia with depression, the authors of this Australian study tested a B vitamin supplement on 153 patients. The patients were referred by their primary care physician or were drawn from a survey of adults who were found to have moderate depression but were not yet being treated. The patients were randomly assigned, using concealed allocation, to treatment with citalopram plus a combination of 0.5 mg vitamin B12, 2 mg folic acid, and 25 mg vitamin B6, or to citalopram plus placebo. Citalopram doses were adjusted to a maximum of 40 mg daily. Citalopram was continued, or the antidepressant was changed, for 9 months in patients who achieved remission, at the discretion of the treating physician, and B vitamin or placebo was continued. Remission (resolution of depression scores) within 3 months occurred in approximately 78% of patients in both groups. However, more patients who were taking the supplement were in remission after 1 year (85.5% vs 75.8%). A few caveats: The study was small, patients had more severe depression than typically seen in primary care, and the response to the antidepressant in both groups was higher than is typical.

Bottom line: The addition of B vitamins -- cyanocobalamin, thiamine, and folate -- to antidepressant medication in patients with moderate depression does not improve the initial response rate but increases the percentage of patients in remission after 1 year. This effect was more pronounced in patients with higher baseline homocysteine levels, a marker of low B vitamin status. The effect in this study was small, but given their low expense and low risk B vitamin supplements could be tried in some patients.


2. Nicotinamide reduces recurrent non-melanoma skin cancers in high-risk patients

Clinical question: Does nicotinamide reduce the likelihood of new nonmelanoma skin cancers in high-risk patients?

Study design: Randomized controlled trial (double-blinded)

Setting: Outpatient (specialty)

Synopsis: Previous studies have shown that nicotinamide (vitamin B3) may improve cell repair and can reduce the likelihood of actinic keratoses. In this Australian study (Australia, with its combination of pale inhabitants and lots of sun, is the epicenter of skin cancer), 386 adults with at least 2 previous nonmelanoma skin cancers (NMSC) were randomized to receive nicotinamide 500 mg twice daily or matching placebo. Patients who were immunosuppressed, pregnant, who had significant comorbidities, or were currently taking medications for actinic keratosis (eg, fluorouracil) were excluded. The patients' mean age at enrollment was 66 years, 63% were men, and 47% were never smokers. These folks had a lot of skin cancers: a mean of 8 NMSC (6 basal cell and 2 squamous cell) in the previous 5 years. Clearly, this was a very high-risk group. They were evaluated every 3 months by dermatologists masked to treatment assignment, and followed up for 12 months. The mean number of new NMSC during the year of active treatment was lower with nicotinamide (1.8 vs 2.4; P = .02), with a trend toward both fewer basal cell cancers (1.3 vs 1.7; P = .12) and squamous cell cancers (0.5 vs 0.7; P = .05). The relative reduction was 23%. During the 6 months after the intervention the benefit went away, with no differences between groups. There was no difference between groups in melanomas or serious adverse events.

Bottom line: For patients at very high risk of nonmelanoma skin cancers (NMSC), with a mean of 8 such cancers in the previous 5 years, nicotinamide 500 mg twice daily provides a modest reduction of 0.6 fewer lesions in 12 months of treatment.


3. Carotenoids and omega-3 fatty acids do not effect rate of cognitive function decline
Clinical question: Can an increased dietary intake of carotenoids (lutein plus zeaxanthin), omega-3 fatty acids, or both, reduce the rate of cognitive function decline in adults with age-related macular degeneration?

Study design: Systematic review

Setting: Outpatient (specialty)

Synopsis: Previous studies from the Age-Related Eye Disease Study (AREDS) reported that adding the carotenoids lutein and zeaxanthin and/or omega-3 fatty acids as daily oral supplements to standard antioxidant vitamins and minerals did not further reduce the risk of advanced AMD. As part of the AREDS these investigators identified adults, aged 50 to 85 years, at high risk for progression to advanced AMD with either bilateral large drusen or large drusen in one eye and advanced AMD in the other eye. Consenting patients (N = 3741) eligible for an add-on cognitive function study randomly received assignment (concealed allocation assignment) to 1 of 4 treatment groups: (1) omega-3 fatty acids (1g), (2) the carotenoids lutein (10 mg) and zeaxanthin (2 mg), (3) both the omega-3s and the carotenoids, or (4) matched placebo. All patients were also given varying combinations of vitamins C, E, beta carotene, and zinc. Individuals who assessed outcomes using a standard cognitive function battery test remained masked to treatment group assignment. Testing occurred 3 months after randomization and then approximately every 2 years. Follow-up with at least 2 interviews occurred for 93% of participants. Using intention-to-treat analysis, the authors found no significant differences between the treatment groups in the rate of cognitive function decline for a mean of 4.9 years. Similarly, no significant difference in cognitive function decline occurred in high-zinc versus low-zinc groups nor in groups with or without beta carotene. Multiple analyses were performed to adjust for potential confounding factors, including age, sex, race, education, depression, and history of hypertension. No clinically significant differences in reported serious adverse events occurred. The study was adequately powered to have a 85% chance of detecting a pre-determined clinically significant difference between the treatment groups.

Bottom line: Adding the carotenoids lutein and zeaxanthin and/or omega-3 fatty acids as daily oral supplements to standard antioxidant vitamins and minerals did not reduce the rate of cognitive function decline in adults with advanced age-related macular degeneration (AMD). A similar study in the same issue also found no benefit to moderate-intensity physical activity in reducing cognitive function decline in the elderly.


4. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration: Cochrane

Background: It has been proposed that antioxidants may prevent cellular damage in the retina by reacting with free radicals that are produced in the process of light absorption. Higher dietary levels of antioxidant vitamins and minerals may reduce the risk of progression of age-related macular degeneration (AMD).

Objectives: The objective of this review was to assess the effects of antioxidant vitamin or mineral supplementation on the progression of AMD in people with AMD.

Search methods: We searched CENTRAL (2017, Issue 2), MEDLINE Ovid (1946 to March 2017), Embase Ovid (1947 to March 2017), AMED (1985 to March 2017), OpenGrey (System for Information on Grey Literature in Europe), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/icrtp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 29 March 2017.

Selection criteria: We included randomised controlled trials (RCTs) that compared antioxidant vitamin or mineral supplementation (alone or in combination) to placebo or no intervention, in people with AMD.

Data collection and analysis: Both review authors independently assessed risk of bias in the included studies and extracted data. One author entered data into RevMan 5; the other author checked the data entry. We graded the certainty of the evidence using GRADE.

Main results: We included 19 studies conducted in USA, Europe, China, and Australia. We judged the trials that contributed data to the review to be at low or unclear risk of bias. Nine studies compared multivitamins with placebo (7 studies) or no treatment (2 studies) in people with early and moderate AMD. The duration of supplementation and follow-up ranged from nine months to six years; one trial followed up beyond two years. Most evidence came from the Age-Related Eye Disease Study (AREDS) in the USA. People taking antioxidant vitamins were less likely to progress to late AMD (odds ratio (OR) 0.72, 95% confidence interval (CI) 0.58 to 0.90; 2445 participants; 3 RCTs; moderate-certainty evidence). In people with very early signs of AMD, who are at low risk of progression, this would mean that there would be approximately 4 fewer cases of progression to late AMD for every 100 people taking vitamins (3 fewer to 13 fewer). In one study of 1206 people, there was a lower risk of progression for both neovascular AMD (OR 0.62, 95% CI 0.47 to 0.82; moderate-certainty evidence) and geographic atrophy (OR 0.75, 95% CI 0.51 to 1.10; moderate-certainty evidence) and a lower risk of losing 3 or more lines of visual acuity (OR 0.77, 95% CI 0.62 to 0.96; 1791 participants; moderate-certainty evidence). Low-certainty evidence from one study of 110 people suggested higher quality of life scores (National Eye Institute Visual Function Questionnaire) in treated compared with the non-treated people after 24 months (mean difference (MD) 12.30, 95% CI 4.24 to 20.36). Six studies compared lutein (with or without zeaxanthin) with placebo. The duration of supplementation and follow-up ranged from six months to five years. Most evidence came from the AREDS2 study in the USA. People taking lutein or zeaxanthin may have similar or slightly reduced risk of progression to late AMD (RR 0.94, 95% CI 0.87 to 1.01; 6656 eyes; low-certainty evidence), neovascular AMD (RR 0.92, 95% CI 0.84 to 1.02; 6891 eyes; low-certainty evidence), and geographic atrophy (RR 0.92, 95% CI 0.80 to 1.05; 6891 eyes; low-certainty evidence). A similar risk of progression to visual loss of 15 or more letters was seen in the lutein and control groups (RR 0.98, 95% CI 0.91 to 1.05; 6656 eyes; low-certainty evidence). Quality of life (measured with Visual Function Questionnaire) was similar between groups in one study of 108 participants (MD 1.48, 95% -5.53 to 8.49, moderate-certainty evidence). One study, conducted in Australia, compared vitamin E with placebo. This study randomised 1204 people to vitamin E or placebo, and followed up for four years. Participants were enrolled from the general population; 19% had AMD.
The number of late AMD events was low (N = 7) and the estimate of effect was uncertain (RR 1.36, 95% CI 0.31 to 6.05, very low-certainty evidence). There were no data on neovascular AMD or geographic atrophy. There was no evidence of any effect of treatment on visual loss (RR 1.04, 95% CI 0.74 to 1.47, low-certainty evidence). There were no data on quality of life. Five studies compared zinc with placebo. The duration of supplementation and follow-up ranged from six months to seven years. People taking zinc supplements may be less likely to progress to late AMD (OR 0.83, 95% CI 0.70 to 0.98; 3790 participants; 3 RCTs; low-certainty evidence), neovascular AMD (OR 0.76, 95% CI 0.62 to 0.93; 2442 participants; 1 RCT; moderate-certainty evidence), geographic atrophy (OR 0.84, 95% CI 0.64 to 1.10; 2442 participants; 1 RCT; moderate-certainty evidence), or visual loss (OR 0.87, 95% CI 0.75 to 1.00; 3791 participants; 2 RCTs; moderate-certainty evidence). There were no data reported on quality of life. Very low-certainty evidence was available on adverse effects because the included studies were underpowered and adverse effects inconsistently reported.

**Authors' conclusions:** People with AMD may experience some delay in progression of the disease with multivitamin antioxidant vitamin and mineral supplementation. This finding was largely drawn from one large trial, conducted in a relatively well-nourished American population. We do not know the generalisability of these findings to other populations. Although generally regarded as safe, vitamin supplements may have harmful effects. A systematic review of the evidence on harms of vitamin supplements is needed. Supplements containing lutein and zeaxanthin are heavily marketed for people with age-related macular degeneration but our review shows they may have little or no effect on the progression of AMD.


5. Vitamin E for Alzheimer's dementia and mild cognitive impairment

**Background:** Vitamin E occurs naturally in the diet. It has several biological activities, including functioning as an antioxidant to scavenge toxic free radicals. Evidence that free radicals may contribute to the pathological processes behind cognitive impairment has led to interest in the use of vitamin E supplements to treat mild cognitive impairment (MCI) and Alzheimer's disease (AD). This is an update of a Cochrane Review first published in 2000, and previously updated in 2006 and 2012.

**Objectives:** To assess the efficacy of vitamin E in the treatment of MCI and dementia due to AD.

**Search methods:** We searched the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group (ALOIS), the Cochrane Library, MEDLINE, Embase, PsycINFO, CINAHL, LILACS as well as many trials databases and grey literature sources on 22 April 2016 using the terms: "Vitamin E", vitamin-E, alpha-tocopherol.

**Selection criteria:** We included all double-blind, randomised trials in which treatment with any dose of vitamin E was compared with placebo in people with AD or MCI.

**Data collection and analysis:** We used standard methodological procedures according to the Cochrane Handbook for Systematic Reviews of Interventions. We rated the quality of the evidence using the GRADE approach. Where appropriate we attempted to contact authors to obtain missing information.

**Main results:** Four trials met the inclusion criteria, but we could only extract outcome data in accordance with our protocol from two trials, one in an AD population (n = 304) and one in an MCI population (n = 516). Both trials had an overall low to unclear risk of bias. It was not possible to pool data across studies owing to a lack of comparable outcome measures. In people with AD, we found no evidence of any clinically important effect of vitamin E on cognition, measured with change from baseline in the Alzheimer's Disease Assessment Scale - Cognitive subscale (ADAS-Cog) over six to 48 months (mean difference (MD) -1.81, 95% confidence interval (CI) -3.75 to 0.13, P = 0.07, 1 study, n = 272; moderate quality evidence). There was no evidence of a difference between vitamin E and placebo groups in the risk of experiencing at least one serious adverse event over six to 48 months (risk ratio (RR) 0.86, 95% CI 0.71 to 1.05, P = 0.13, 1 study, n = 304; moderate quality evidence), or in the risk of death (RR 0.84, 95% CI 0.52 to 1.34, P = 0.46, 1 study, n = 304; moderate quality evidence). People with AD receiving vitamin E showed less functional decline on the Alzheimer's Disease Cooperative Study/Activities of Daily Living Inventory than people receiving placebo at six to 48 months (mean difference (MD) 3.15, 95% CI 0.07 to 6.23, P = 0.04, 1 study, n = 280; moderate quality evidence). There was no evidence of any clinically important effect on neuropsychiatric symptoms measured with the Neuropsychiatric Inventory (MD -1.47, 95% CI -4.26 to 1.32, P = 0.30, 1 study, n = 280; moderate quality evidence). We found no evidence that vitamin E affected the probability of progression from MCI to probable dementia due to AD over 36 months (RR 1.03, 95% CI 0.79 to 1.35, P = 0.81, 1 study, n = 516; moderate quality evidence). Five deaths occurred in each of the vitamin E and placebo groups over the 36 months (RR 1.01, 95% CI 0.30 to 3.44, P = 0.99, 1 study, n = 516; moderate quality evidence). We were unable to extract data in accordance with the review protocol for other outcomes. However, the study authors found no evidence that vitamin E differed from placebo in its effect on cognitive function, global severity or activities of daily living. There was also no evidence of a difference between groups in the more commonly reported adverse events.

**Authors' conclusions:** We found no evidence that the alpha-tocopherol form of vitamin E given to people with MCI prevents progression to dementia, or that it improves cognitive function in people with MCI or dementia due to AD. However, there is moderate quality evidence from a single study that it may slow functional decline in AD. Vitamin E was not associated with an increased risk of serious adverse events or mortality in the trials in this review. These conclusions have changed since the previous update, however they are still based on small numbers of trials and participants and further research is quite likely to affect the results.


6. Multivitamins in the prevention of cancer in men: the Physicians' Health Study II randomized controlled trial

**CONTEXT:** Multivitamin preparations are the most common dietary supplement, taken by at least one-third of all US adults. Observational studies have not provided evidence regarding associations of multivitamin use with total and site-specific cancer incidence or mortality.

**OBJECTIVE:** To determine whether long-term multivitamin supplementation decreases the risk of total and site-specific cancer events
among men.

**DESIGN, SETTING, AND PARTICIPANTS:** A large-scale, randomized, double-blind, placebo controlled trial (Physicians’ Health Study II) of 14,641 male US physicians initially aged 50 years or older (mean [SD] age, 64.3 [9.2] years), including 1312 men with a history of cancer at randomization, enrolled in a common multivitamin study that began in 1997 with treatment and follow-up through June 1, 2011.

**INTERVENTION:** Daily multivitamin or placebo.

**MAIN OUTCOME MEASURES:** Total cancer (excluding nonmelanoma skin cancer), with prostate, colorectal, and other site-specific cancers among the secondary end points.

**RESULTS:** During a median (interquartile range) follow-up of 11.2 (10.7-13.3) years, there were 2669 men with confirmed cancer, including 1373 cases of prostate cancer and 210 cases of colorectal cancer. Compared with placebo, men taking a daily multivitamin had a statistically significant reduction in the incidence of total cancer (multivitamin and placebo groups, 17.0 and 18.3 events, respectively, per 1000 person-years; hazard ratio [HR], 0.92; 95% CI, 0.86-0.998; P=.04). There was no significant effect of a daily multivitamin on prostate cancer (multivitamin and placebo groups, 9.1 and 9.2 events, respectively, per 1000 person-years; HR, 0.98; 95% CI, 0.88-1.09; P=.76), colorectal cancer (multivitamin and placebo groups, 1.2 and 1.4 events, respectively, per 1000 person-years; HR, 0.89; 95% CI, 0.68-1.17; P=.39), or other site-specific cancers. There was no significant difference in the risk of cancer mortality (multivitamin and placebo groups, 4.9 and 5.6 events, respectively, per 1000 person-years; HR, 0.88; 95% CI, 0.77-1.01; P=.07). Daily multivitamin use was associated with a reduction in total cancer among 1312 men with a baseline history of cancer (HR, 0.73; 95% CI, 0.56-0.96; P=.02), but this did not differ significantly from that among 13,329 men initially without cancer (HR, 0.94; 95% CI, 0.87-1.02; P=.15; P for interaction=.07).

**CONCLUSION:** In this large prevention trial of male physicians, daily multivitamin supplementation modestly but significantly reduced the risk of total cancer.


7. **Vitamin, mineral, and multivitamin supplements for the primary prevention of cardiovascular disease and cancer: U.S. Preventive services Task Force recommendation statement**

**DESCRIPTION:** Update of the 2003 U.S. Preventive Services Task Force (USPSTF) recommendation on vitamin supplementation to prevent cardiovascular disease and cancer.

**METHODS:** The USPSTF reviewed the evidence on the efficacy of multivitamin or mineral supplements in the general adult population for the prevention of cardiovascular disease and cancer.

**POPULATION:** This recommendation applies to healthy adults without special nutritional needs (typically aged 50 years or older). It does not apply to children, women who are pregnant or may become pregnant, or persons who are chronically ill or hospitalized or have a known nutritional deficiency.

**RECOMMENDATION:** The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of multivitamins for the prevention of cardiovascular disease or cancer. (I statement). The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of single- or paired-nutrient supplements (except β-carotene and vitamin E) for the prevention of cardiovascular disease or cancer. (I statement). The USPSTF recommends against β-carotene or vitamin E supplements for the prevention of cardiovascular disease or cancer. (D recommendation).


**Vitamin D as a Medication**

Vitamin D’s popularity as a therapy is booming. A PubMed search of “vitamin D supplementation” in December of 2017 yielded 5,776 clinical studies and 683 systematic reviews. The good news is that, although the benefits are small, there is evidence that Vitamin D therapy is useful for more than bone health. Following are some of the new findings, both positive and negative. These studies are not so much about achieving an adequate vitamin D level (“adequate level” is controversial) but about using vitamin D as a medication to improve outcomes of specific conditions. There is hardly an affliction that affects humans for which Vitamin D has not been tested. I have not included all the negative trials, such as those for liver disease (no effects). Vitamin D therapy for vascular disease and cancer has not yet been adequately studied, but most RCTs to date have been negative. The very large trial underway should have definitive results in about 5 years. Vitamin D combined with calcium has very modest effects on fracture prevention, but we will not present data about bones in this chapter.

**Respiratory Tract Infections and Asthma**
8. Bolus dosing of Vitamin D does not prevent ARTI or asthma exacerbation in vitamin D–deficient patients

Clinical question: Does vitamin D supplementation improve asthma symptoms?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (any)
Synopsis: Ah, vitamin D. You are such a good marker of bad health, yet supplementing you seems to have so little effect. For example, lots of observational studies have found an association between low vitamin D levels and a high rate of acute respiratory tract infections (ARTI). This is the first randomized trial to test the hypothesis that vitamin D supplementation would reduce the likelihood of ARTI or asthma exacerbation in adults with corticosteroid-treated asthma. The authors identified 590 patients with asthma: 297 were then screened for inclusion and 250 met the inclusion criteria. All were between the ages of 16 and 80 years, had smoked less than 15 pack-years, were using an inhaled corticosteroid, and had evidence of reversible airway obstruction. The 250 participants were randomized to receive either 120,000 IU vitamin D every 2 months for 1 year, or matching placebo. The mean age of participants was 48 years, 44% were male, most had received a flu vaccine, and most had moderately severe asthma. Most (82%) had a low vitamin D level at enrollment (serum 25(OH)D level < 75 nmol/L [30 ng/mL]). Unfortunately, the intervention had no effect. The intervention group experienced a significant increase in vitamin D levels (23 nmol/L [10 ng/mL]), but there was no difference between groups in the time to first exacerbation or time to first ARTI. The study was powered to detect a 60-day difference in the time to event.
Bottom line: Vitamin D supplementation does nothing to prevent exacerbations or improve clinical outcomes in a group of adults with asthma, most of whom were also vitamin D deficient.

9. High-dose vitamin D does not reduce wintertime URIs in healthy children

Clinical question: Does high-dose vitamin D reduce the incidence of wintertime upper respiratory infections in otherwise healthy children?
Study design: Randomized controlled trial (double-blinded)
Setting: Outpatient (primary care)
Synopsis: Vitamin D increases the synthesis of antimicrobial peptides in respiratory epithelium and may thus reduce viral replication and subsequent URIs. These investigators enrolled 703 healthy children, 1 year to 5 years old, who presented for a scheduled well-child visit prior to the wintertime viral season in Toronto, Ontario, Canada. Eligible children randomly received (concealed allocation assignment) liquid vitamin D in a standard dose (400 IU daily) or a high-dose (2000 IU daily). Drops were identical in taste, volume, and color. Throughout the winter months parents completed a symptom checklist and collected viral nasal swabs for suspected URIs. The individuals who assessed outcomes remained masked to treatment group assignment. Follow-up occurred for 99.4% of participants for approximately 6 months (winter lasts a LONG time up there). Mean baseline serum 25-hydroxyvitamin D levels were comparable in the standard-dose and high-dose groups (36.9 ng/mL and 35.9 ng/mL, respectively). Using intention-to-treat analysis, no significant differences occurred between the 2 groups in the mean number of infections per child based on both parent-reported URIs and laboratory confirmed upper respiratory virus infections from nasal smears. There was a statistically significant difference in serum 25-hydroxyvitamin D levels between the standard-dose and high-dose groups after treatment (36.8 ng/mL vs 48.7 ng/mL, respectively). The study was 90% powered to detect a reduction of at least 1 URI per winter season between the 2 treatment groups.
Bottom line: Daily administration of high-dose vitamin D (2000 IU) did not reduce the incidence of wintertime upper respiratory infections (URIs) compared with standard dose vitamin D (400 IU) in otherwise healthy children residing in Toronto, Canada.

10. Vitamin D does not reduce URIs in children age 1 to 5

IMPORTANCE: Epidemiological studies support a link between low 25-hydroxyvitamin D levels and a higher risk of viral upper respiratory tract infections. However, whether winter supplementation of vitamin D reduces the risk among children is unknown.
OBJECTIVE: To determine whether high-dose vs standard-dose vitamin D supplementation reduces the incidence of wintertime upper respiratory tract infections in young children.
DESIGN, SETTING, AND PARTICIPANTS: A randomized clinical trial was conducted during the winter months between September 13, 2011, and June 30, 2015, among children aged 1 through 5 years enrolled in TARGet Kids!, a multisite primary care practice-based research network in Toronto, Ontario, Canada.
INTERVENTIONS: Three hundred forty-nine participants were randomized to receive 2000 IU/d of vitamin D oral supplementation (high-dose group) vs 354 participants who were randomized to receive 400 IU/d (standard-dose group) for a minimum of 4 months between September and May.
MAIN OUTCOME MEASURES: The primary outcome was the number of laboratory-confirmed viral upper respiratory tract infections based on parent-collected nasal swabs over the winter months. Secondary outcomes included the number of influenza infections, noninfluenza infections, parent-reported upper respiratory tract illnesses, time to first upper respiratory tract infection, and serum 25-hydroxyvitamin D levels at study termination.
RESULTS: Among 703 participants who were randomized (mean age, 2.7 years, 57.7% boys), 699 (99.4%) completed the trial. The mean number of laboratory-confirmed upper respiratory tract infections per child was 1.05 (95% CI, 0.91-1.19) for the high-dose group and 1.03 (95% CI, 0.90-1.16) for the standard-dose group, for a between-group difference of 0.02 (95% CI, -0.17 to 0.21) per child. There was no statistically significant difference in number of laboratory-confirmed infections between groups (incidence rate ratio [RR], 0.97; 95% CI, 0.80-1.16). There was also no significant difference in the median time to the first laboratory-confirmed infection: 3.95 months (95% CI, 3.02-5.95 months) for the high-dose group vs 3.29 months (95% CI, 2.66-4.14 months) for the standard-dose group.
or number of parent-reported upper respiratory tract illnesses between groups (625 for high-dose vs 600 for standard-dose groups, incidence RR, 1.01; 95% CI, 0.88-1.16). At study termination, serum 25-hydroxyvitamin D levels were 48.7 ng/mL (95% CI, 46.9-50.5 ng/mL) in the high-dose group and 36.8 ng/mL (95% CI, 35.4-38.2 ng/mL) in the standard-dose group.

**CONCLUSIONS AND RELEVANCE:** Among healthy children aged 1 to 5 years, daily administration of 2000 IU compared with 400 IU of vitamin D supplementation did not reduce overall wintertime upper respiratory tract infections. These findings do not support the routine use of high-dose vitamin D supplementation in children for the prevention of viral upper respiratory tract infections.


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**11. No Effect of Vitamin D3 Supplementation on Respiratory Tract Infections in Healthy Individuals**

**OBJECTIVE:** Vitamin D supplementation may be a simple preventive measure against respiratory tract infections (RTIs) but evidence from randomized controlled trials is inconclusive. We aimed to systematically summarize results from interventions studying the protective effect of vitamin D supplementation on clinical and laboratory confirmed RTIs in healthy adults and children.

**METHODS:** Medline, EMBASE, CENTRAL, and CINAHL were screened from inception until present (last updated in January 2016) completed by a search of the grey literature, clinical trial registers and conference abstracts. We included randomized trials comparing vitamin D versus placebo or no treatment. Two independent reviewers were responsible for study selection and data extraction. Cochrane’s risk of bias tool and the GRADE approach were used for quality assessment. Estimates were pooled with random-effects models. Heterogeneity was explored by sub-group and meta-regression analyses.

**RESULTS:** Of 2627 original hits, 15 trials including 7053 individuals were ultimately eligible. All used oral cholecalciferol. We found a 6% risk reduction with vitamin D3 supplementation on clinical RTIs, but the result was not statistically significant (RR 0.94; 95% CI 0.88 to 1.00). Heterogeneity was large (I-square 57%) and overall study quality was low. There were too few studies to reliably assess a potential risk reduction of laboratory confirmed RTI. Evidence was insufficient to demonstrate an association between vitamin D supplementation and risk of clinical RTI in sub-groups with vitamin D deficiency.

**CONCLUSIONS:** In previously healthy individuals vitamin D supplementation does not reduce the risk of clinical RTIs. However, this conclusion is based on a meta-analysis where the included studies differed with respect to population, baseline vitamin D levels and study length. This needs to be considered when interpreting the results. Future trials should focus on vitamin D deficient individuals and apply more objective and standardized outcome measurements.


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**12. Vitamin D reduces the frequency of respiratory tract infections**

**Objectives** To assess the overall effect of vitamin D supplementation on risk of acute respiratory tract infection, and to identify factors modifying this effect.

**Design** Systematic review and meta-analysis of individual participant data (IPD) from randomised controlled trials.

**Data sources** Medline, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, ClinicalTrials.gov, and the International Standard Randomised Controlled Trials Number registry from inception to December 2015.

**Eligibility criteria for study selection** Randomised, double blind, placebo controlled trials of supplementation with vitamin D3 or vitamin D2 of any duration were eligible for inclusion if they had been approved by a research ethics committee and if data on incidence of acute respiratory tract infection were collected prospectively and prespecified as an efficacy outcome.

**Results** 25 eligible randomised controlled trials (total 11 321 participants, aged 0 to 95 years) were identified. IPD were obtained for 10 933 (96.6%) participants. Vitamin D supplementation reduced the risk of acute respiratory tract infection among all participants (adjusted odds ratio 0.88, 95% confidence interval 0.81 to 0.96; P for heterogeneity <0.001). In subgroup analysis, protective effects were seen in those receiving daily or weekly vitamin D without additional bolus doses (adjusted odds ratio 0.81, 0.72 to 0.91) but not in those receiving one or more bolus doses (adjusted odds ratio 0.97, 0.86 to 1.01; P for interaction=0.05). Among those receiving daily or weekly vitamin D, protective effects were stronger in those with baseline 25-hydroxyvitamin D levels <25 nmol/L (adjusted odds ratio 0.30, 0.17 to 0.53) than in those with baseline 25-hydroxyvitamin D levels ≥25 nmol/L (adjusted odds ratio 0.75, 0.60 to 0.95; P for interaction=0.006). Vitamin D did not influence the proportion of participants experiencing at least one serious adverse event (adjusted odds ratio 0.98, 0.80 to 1.20, P=0.83). The body of evidence contributing to these analyses was assessed as being of high quality.

**Conclusions** Vitamin D supplementation was safe and it protected against acute respiratory tract infection overall. Patients who were very vitamin D deficient and those not receiving bolus doses experienced the most benefit.


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**13. Vitamin D supplementation during pregnancy does not prevent wheezing in the infant**

**Clinical question:** Does vitamin D supplementation during pregnancy reduce the risk of asthma or recurrent wheezing in children up to 3 years of age?

**Study design:** Randomized controlled trial (double-blinded)

**Setting:** Outpatient (any)

**Synopsis:** These investigators identified 623 consenting and eligible Danish women within pregnancy weeks 22 through 26 with no history of endocrine, cardiovascular, or nephrological disorders. Patients randomly received (concealed allocation assignment) a daily
Dose of 2400 IU vitamin D3 supplementation or matching placebo from pregnancy week 24 to postpartum week 1. All women also took an additional 400 IU per day of vitamin D3 supplementation. Participating clinicians masked to treatment group assignment assessed children at periodic scheduled visits for a total of 36 months. Parents, also masked to treatment group, assessed their children's daily symptom burden between scheduled visits using daily diary cards. Complete follow-up occurred for 94% of children at 3 years. The authors used intention-to-treat analysis and found that, although the intervention resulted in a significant increase in maternal serum vitamin D levels in the treatment group, no significant differences occurred between the 2 groups in the risk of the primary outcome: persistent wheeze in offspring during the first 3 years of life. No confounding effect was found after controlling for sex, season of birth, or maternal vitamin D3 level at baseline. A secondary analysis found a significant reduction in episodes of "troublesome lung symptoms" in the vitamin D group, but no significant differences occurred in the risk of asthma diagnosis, upper or lower respiratory tract infections, or eczema diagnoses. The study was underpowered (< 80%) to detect a clinically significant effect in the primary end point of wheezing.

**Bottom line:** Vitamin D supplementation (2800 IU/day) during the third trimester of pregnancy compared with a standard prenatal dose of 400 IU per day in average-risk women did not significantly reduce the risk of wheezing-related illness in offspring through the age of 3 years. A similar study of supplementation with a higher vitamin D dose (4400 IU/day) in pregnant women at high risk of allergic disease also reported no reduced risk of wheezing-related illness in offspring through age 3 years (Litonjua AA, et al. *JAMA* 2016;315(4):362-370).


### 14. Prenatal vitamin D supplementation reduces risk of asthma/recurrent wheeze in early childhood

**BACKGROUND:** We recently published two independent randomized controlled trials of vitamin D supplementation during pregnancy, both indicating a >20% reduced risk of asthma/recurrent wheeze in the offspring by 3 years of age. However, neither reached statistical significance.

**OBJECTIVE:** To perform a combined analysis of the two trials and investigate whether maternal 25-hydroxy-vitamin D (25(OH)D) level at trial entry modified the intervention effect.

**METHODS:** VDAART (N = 806) and COPSAC2010. (N = 581) randomized pregnant women to daily high-dose vitamin D3 (4,000 IU/d and 2,400 IU/d, respectively) or placebo. All women also received a prenatal vitamin containing 400 IU/d vitamin D3. The primary outcome was asthma/recurrent wheeze from 0-3yrs. Secondary end-points were specific IgE, total IgE, eczema and lower respiratory tract infections (LRTI). We conducted random effects combined analyses of the treatment effect, individual patient data (IPD) meta-analyses, and analyses stratified by 25(OH)D level at study entry.

**RESULTS:** The analysis showed a 25% reduced risk of asthma/recurrent wheeze at 0-3yrs: adjusted odds ratio (aOR) = 0.74 (95% CI, 0.57-0.96), p = 0.02. The effect was strongest among women with 25(OH)D level ≥30ng/ml at study entry: aOR = 0.54 (0.33-0.88), p = 0.01, whereas no significant effect was observed among women with 25(OH)D level <30ng/ml at study entry: aOR = 0.84 (0.62-1.15), p = 0.25. The IPD meta-analyses showed similar results. There was no effect on the secondary end-points.

**CONCLUSIONS:** This combined analysis shows that vitamin D supplementation during pregnancy results in a significant reduced risk of asthma/recurrent wheeze in the offspring, especially among women with 25(OH)D level ≥ 30 ng/ml at randomization, where the risk was almost halved. Future studies should examine the possibility of raising 25(OH)D levels to at least 30 ng/ml early in pregnancy or using higher doses than used in our studies.


### 15. Vitamin D Reduces the Risk of Asthma Exacerbations

**BACKGROUND:** A previous aggregate data meta-analysis of randomised controlled trials showed that vitamin D supplementation reduces the rate of asthma exacerbations requiring treatment with systemic corticosteroids. Whether this effect is restricted to patients with low baseline vitamin D status is unknown.

**METHODS:** For this systematic review and one-step and two-step meta-analysis of individual participant data, we searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and Web of Science for double-blind, placebo-controlled, randomised controlled trials of vitamin D3 or vitamin D2 supplementation in people with asthma that reported incidence of asthma exacerbation, published between database inception and Oct 26, 2016. We analysed individual participant data requested from the principal investigator for each eligible trial, adjusting for age and sex, and clustering by study. The primary outcome was the incidence of asthma exacerbation requiring treatment with systemic corticosteroids. Mixed-effects regression models were used to obtain the pooled intervention effect with a 95% CI. Subgroup analyses were done to determine whether effects of vitamin D on risk of asthma exacerbation varied according to baseline 25-hydroxyvitamin D (25(OH)D) concentration, age, ethnic or racial origin, body-mass index, vitamin D dosing regimen, use of inhaled corticosteroids, or end-study 25(OH)D levels; post-hoc subgroup analyses were done according to sex and study duration. This study was registered with PROSPERO, number CRD42014013953.

**FINDINGS:** Our search identified 483 unique studies, eight of which were eligible randomised controlled trials (total 1078 participants). We sought individual participant data for each and obtained it for seven studies (955 participants). Vitamin D supplementation reduced the rate of asthma exacerbation requiring treatment with systemic corticosteroids among all participants (adjusted incidence rate ratio [aIRR] 0.74, 95% CI 0.56-0.97; p=0.03; 955 participants in seven studies; high-quality evidence). There were no significant differences between vitamin D and placebo in the proportion of participants with at least one exacerbation or time to first exacerbation. Subgroup analyses of the rate of asthma exacerbations treated with systemic corticosteroids revealed that protective effects were seen in participants with baseline 25(OH)D of less than 25 nmol/L (aIRR 0.33, 0.11-0.98; p=0.046; 92 participants in three studies; moderate-quality evidence) but not in participants with higher baseline 25(OH)D levels (aIRR 0.77, 0.58-1.03; p=0.08; 764 participants in six studies; moderate-quality evidence; pinteraction=0.25). P values for interaction for all other subgroup analyses were also higher than 0.05;
therefore, we did not show that the effects of this intervention are stronger in any one subgroup than in another. Six studies were assessed as being at low risk of bias, and one was assessed as being at unclear risk of bias. The two-step meta-analysis did not reveal evidence of heterogeneity of effect ($I^2=0.0$, $p=0.56$).

**INTERPRETATION:** Vitamin D supplementation reduced the rate of asthma exacerbations requiring treatment with systemic corticosteroids overall. We did not find definitive evidence that effects of this intervention differed across subgroups of patients. Jolliffe DA, Greenberg L, Hooper RL, Griffiths CJ, Camargo CA Jr, Kerley CP, Jensen ME, Mauger D, Stelmach I, Urashima M, Martineau AR. Vitamin D supplementation to prevent asthma exacerbations: a systematic review and meta-analysis of individual participant data. Lancet Respir Med. 2017 Nov;5(11):881-890.

**Pain**

16. Vitamin D does not reduce pain in adults with symptomatic knee osteoarthritis

**Clinical question:** Does vitamin D supplementation reduce pain in adults with symptomatic knee osteoarthritis and low vitamin D levels?

**Study design:** Randomized controlled trial (double-blinded)

**Setting:** Outpatient (primary care)

**Synopsis:** These investigators identified adults, aged 50 to 79 years, in otherwise good health with at least 6 months of symptomatic knee osteoarthritis (based on standard diagnostic criteria) and a pain score of 20 mm to 80 mm on a 100-mm visual analog scale. Eligibility criteria also included a low serum 25-hydroxyvitamin D level (12.5 nmol/L to 60 nmol/L). Study patients randomly received (concealed allocation assignment) a monthly capsule of 50,000 IU vitamin D3 or identical placebo for 24 months. The primary outcomes of knee pain and tibial cartilage volume were assessed using standard evaluation tools by individuals masked to treatment group assignment. Complete follow-up occurred for 92.4% of participants at 24 months. Serum 25-hydroxyvitamin D levels increased significantly more in the vitamin D group than in the placebo group, with 79% versus 43% of patients, respectively, who reached a 25-hydroxyvitamin D level of greater than 60 nmol/L at month 3. Although pain scores significantly decreased from baseline over 24 months in both groups, there was no difference in change of pain scores from baseline to 24 months between the 2 groups using intention-to-treat and per-protocol analyses. Tibial cartilage volume loss also occurred similarly between both groups. The study was 80% powered to detect predetermined clinically significant differences in pain scores and cartilage loss.

**Bottom line:** Vitamin D supplementation did not significantly reduce pain or prevent cartilage loss compared with placebo in adults with symptomatic knee osteoarthritis and low vitamin D levels over 2 years.


17. Maintaining Vitamin D Sufficiency Is Associated with Improved Structural and Symptomatic Outcomes in Knee Osteoarthritis

**BACKGROUND:** The aim of this study was to describe whether maintaining sufficient serum vitamin D levels in people with knee osteoarthritis and baseline vitamin D insufficiency has an association with change in knee structures and symptoms over 2 years.

**METHODS:** Participants (n = 413, mean age 63.2 years) with symptomatic knee osteoarthritis and vitamin D insufficiency were enrolled in a clinical trial. In all, 340 participants (82.3%) completed the study, with 25-hydroxyvitamin D [25(OH)D] measurements at baseline and months 3 and 24. Participants were classified as consistently insufficient [serum 25(OH)D ≤50 nmol/L at months 3 and 24, n = 45], fluctuating [25(OH)D >50 nmol/L at either point, n = 48], and consistently sufficient [25(OH)D >50 nmol/L at months 3 and 24, n = 226] groups. Knee cartilage volume, cartilage defects, bone marrow lesions, and effusion-synovitis volume were assessed using MRI at baseline and month 24. Knee symptoms were assessed at baseline and months 3, 6, 12, and 24 using the Western Ontario and McMaster Universities Arthritis Index.

**RESULTS:** The consistently sufficient group had significantly less loss of tibial cartilage volume (β 2.1%; 95% confidence interval [CI], 0.3%, 3.9%), less increase in effusion-synovitis volume (β -2.5 mL; 95 CI%, -4.7, -0.2 mL), and less loss of Western Ontario and McMaster Universities Arthritis Index physical function (β -94.2; 95% CI, -183.8, -4.5) compared with the consistently insufficient group in multivariable analyses. In contrast, there were no significant differences in these outcomes between the fluctuating and consistently insufficient groups. Changes in cartilage defects, bone marrow lesions, and knee pain were similar between groups.

**CONCLUSION:** This post hoc analysis suggests beneficial effects of maintaining vitamin D sufficiency on cartilage loss, effusion-synovitis, and physical function in people with knee osteoarthritis.


18. Vitamin D for the treatment of chronic painful conditions in adults

**Background:** This review is an update of a previously published review in the Cochrane Database of Systematic Reviews (Issue 1, 2010) on 'Vitamin D for the treatment of chronic painful conditions in adults'. Vitamin D is produced in the skin after exposure to sunlight and can be obtained through food. Vitamin D deficiency has been linked with a range of conditions, including chronic pain. Observational and circumstantial evidence suggests that there may be a role for vitamin D deficiency in the aetiology of chronic painful conditions.

**Objectives:** To assess the efficacy and safety of vitamin D supplementation in chronic painful conditions when tested against placebo or against active comparators.
19. Vitamin D supplementation improves pain symptoms in patients with chronic widespread pain (aka fibromyalgia)

Chronic non-specific widespread pain (CWP) including fibromyalgia (FMS) is characterized by widespread pain, reduced pain threshold, and multiple tender points on examination, causing disability and decreased quality of life. Vitamin D has been proposed as an associated factor in CWP. This meta-analysis aimed to explore the benefit of vitamin D supplementation in the management of CWP. A comprehensive search of the CENTRAL, MEDLINE, and Embase databases was performed from inception through January 2017. The inclusion criterion was the randomized clinical trials' evaluating the effects of vitamin D treatment in adult subjects with CWP or FMS. CWP was defined as chronic recurrent musculoskeletal pain without secondary causes; FMS patients met the American College of Rheumatology criteria for FMS. Study outcome was assessed using visual analog scale (VAS) of pain intensity. Pooled analysis using a random-effects model was performed to explore the effects of change in vitamin D in the treatment group on difference in the mean of VAS. Sensitivity analysis was performed to evaluate the robustness of results. The between-study heterogeneity of effect size was quantified using the Q statistic and I².

Main results: We included six new studies (517 participants) in this review update, bringing the total of included studies to 10 (811 participants). The studies were heterogeneous with regard to study quality, the chronic painful conditions that were investigated, the dose of vitamin D given, co-interventions, and the outcome measures reported. Only two studies reported responder pain outcomes; the other studies reported treatment group average pain outcomes only. Overall, there was no consistent pattern that vitamin D treatment was associated with greater efficacy than placebo in any chronic painful condition (low quality evidence). Adverse events and withdrawals were comparatively infrequent, with no consistent difference between vitamin D and placebo (good quality evidence).

Authors' conclusions: The evidence addressing the use of vitamin D for chronic pain now contains more than twice as many studies and participants than were included in the original version of this review. Based on this evidence, a large beneficial effect of vitamin D across different chronic painful conditions is unlikely. Whether vitamin D can have beneficial effects in specific chronic painful conditions needs further investigation.


20. The Effect of Improved Serum 25-Hydroxyvitamin D Status on Glycemic Control in Diabetic Patients: A Meta-Analysis

Background: Type 2 diabetes is a global health concern, with an increased prevalence and high cost of treatment.

Objective: The aim of this systematic review and meta-analysis was to determine the effect of vitamin D supplementation and improved vitamin D status on glycemia and insulin resistance in type 2 diabetic patients.

Data Source: We searched PUBMED/Medline, Cumulative Index to Nursing and Allied Health, and Cochrane Library (until January 2017).

Study Selection: Prospective clinical trials were selected evaluating the impact of vitamin D supplementation on glycosylated hemoglobin (HbA1c), serum fasting plasma glucose (FPG), and homeostatic model assessment of insulin resistance (HOMA-IR) in diabetic patients. Data Extraction and Synthesis: We used a random-effects model to synthesize quantitative data, followed by a leave-one-out method for sensitivity analysis. The systematic review registration was CRD42017059555. From a total of 844 entries identified via literature search, 24 controlled trials (1528 individuals diagnosed with type 2 diabetes) were included. The meta-analysis indicated a significant reduction in HbA1c [mean difference: -0.30%; 95% confidence interval (CI): -0.56 to -0.04, P < 0.001], FPG [mean difference: -4.9 mg/dL (-0.27 mmol/L); 95% CI: -8.1 to -1.6 (-0.45 to -0.09 mmol/L), P = 0.003], and HOMA-IR (mean difference: -0.66; 95% CI: -1.06 to -0.26, P = 0.001) following vitamin D supplementation and significant increase in serum 25-hydroxyvitamin D levels [overall increase of 17 ± 2.4 ng/mL (42 ± 6 nmol/L)].

Conclusions: Vitamin D supplementation, a minimum dose of 100 µg/d (4000 IU/d), may significantly reduce serum FPG, HbA1c, and HOMA-IR index, and helps to control glycemic response and improve insulin sensitivity in type 2 diabetic patients.

21. Vitamin D does not improve symptoms of bipolar disorder

OBJECTIVE: Bipolar depression is difficult to treat. Vitamin D supplementation is well tolerated and may improve mood via its neurotransmitter synthesis regulation, nerve growth factor enhancement and antioxidant properties. Vitamin D adjunct reduces unipolar depression, but has not been tried in bipolar depression.

METHODS: 18-70yos with DSM IV bipolar depression and Vitamin D deficiency (<30 ng/ml) were randomized in a controlled double blind trial of 5000IU Vitamin D3 po qday supplementation versus placebo for twelve weeks. Change in Montgomery-Åsberg Depression Rating Scale (MADRS), Hamilton Anxiety Rating Scale (HAM-A), Young Mania Rating Scale (YMRS), medication, and tolerance were assessed q2weeks.

RESULTS: 16 VitD vs 17 placebo subjects did not differ in baseline characteristics (mean = 44 yo, SD = 13), VitD level (19.2 ± 65.8 g/ml vs 19.3 ± 5.5 ng/ml respectively) or mood ratings (MADRS 21.3 ± 6.4 vs 22.8 ± 6.9 respectively). At 12wks, the placebo group VitD levels remained unchanged, while the VitD group levels increased to 28 ng/ml. MADRS score decreased significantly in both placebo (mean = 6.42 (95% CI [2.28 to 10.56]) and VitD groups (mean = 9.54 (95% CI [3.51 to 15.56])) (p = 0.031), but there were no differences between treatment groups (time by treatment interaction estimate: 0.29, t(23) = 0.14, p = 0.89); VitD and placebo groups had similar reductions in YMRs and HAM-A. Vitamin D3 was well tolerated.

CONCLUSIONS: In this small study, despite a greater rise in Vitamin D levels in the VitD supplementation group, there was no significant difference reduction in depressive symptoms. However both groups’ VitD levels remained deficient. Vitamin D3 supplementation vs placebo did not improve reduction in mood elevation or anxiety symptoms.


22. Vitamin D plus calcium does not reduce cancer risk in postmenopausal women

Clinical question: Does dietary supplementation with vitamin D and calcium reduce the risk of cancer in postmenopausal women?

Study design: Randomized controlled trial (double-blinded)

Setting: Population-based

Synopsis: These investigators enrolled 2303 postmenopausal women, 55 years and older, who consented to random (concealed) allocation to either the treatment group (2000 IU vitamin D3 once daily and 500 mg calcium carbonate 3 times daily) or identical placebos. Individuals masked to treatment group assignments assessed cancer diagnosis outcomes (excluding nonmelanoma skin cancer) using medical records and death certificates. The mean baseline serum 25-hydroxyvitamin D level for all women was 32.8 ng/mL (81.8 nmol/L) and the values did not differ significantly between groups. Complete follow-up occurred for 89.6% of patients at 4 years. Using intention-to-treat analysis, the authors found no significant difference between the treatment group and the control group in the incidence of cancers diagnosed (3.89% vs 5.58%, respectively, difference not significant). In particular, there was no significant difference in the incidence of breast cancer diagnoses, with all other individual cancers occurring too infrequently to analyze separately.

The primary outcome of CVD occurred in 303 participants (11.8%) in the vitamin D group and 293 participants (11.5%) in the placebo group. The primary outcome of CVD occurred in 303 participants (11.8%) in the vitamin D group and 293 participants (11.5%) in the placebo group, yielding an adjusted hazard ratio of 1.02 (95% CI, 0.87-1.20). Similar results were seen for participants with baseline vitamin D deficiency and for secondary outcomes.

CONCLUSIONS AND RELEVANCE: Monthly high-dose vitamin D supplementation does not prevent CVD. This result does not

23. High Dose Bolus Vitamin D does NOT prevent cardiovascular disease

IMPORTANCE: Cohort studies have reported increased incidence of cardiovascular disease (CVD) among individuals with low vitamin D status. To date, randomized clinical trials of vitamin D supplementation have not found an effect, possibly because of using too low a dose of vitamin D.

OBJECTIVE: To examine whether monthly high-dose vitamin D supplementation prevents CVD in the general population.

DESIGN, SETTING, AND PARTICIPANTS: The Vitamin D Assessment Study is a randomized, double-blind, placebo-controlled trial that recruited participants mostly from family practices in Auckland, New Zealand, from April 5, 2011, through November 6, 2012, with follow-up until July 2015. Participants were community-resident adults aged 50 to 84 years. Of 47 905 adults invited from family practices and 163 from community groups, 5110 participants were randomized to receive vitamin D3 (n = 2558) or placebo (n = 2552). Two participants retracted consent, and all others (n = 5108) were included in the primary analysis.

INTERVENTIONS: Oral vitamin D3 in an initial dose of 200 000 IU, followed a month later by monthly doses of 100 000 IU, or placebo for a median of 3.3 years (range, 2.5-4.2 years).

MAIN OUTCOMES AND MEASURES: The primary outcome was the number of participants with incident CVD and death, including a prespecified subgroup analysis in participants with vitamin D deficiency (baseline deseasonalized 25-hydroxyvitamin D [25(OH)D] levels <20 ng/mL). Secondary outcomes were myocardial infarction, angina, heart failure, hypertension, arrhythmias, arteriosclerosis, stroke, and venous thrombosis.

RESULTS: Of the 5108 participants included in the analysis, the mean (SD) age was 65.9 (8.3) years, 2969 (58.1%) were male, and 4253 (83.3%) were of European or other ethnicity, with the remainder being Polynesian or South Asian. Mean (SD) baseline deseasonalized 25(OH)D concentration was 26.5 (9.0) ng/mL, with 1270 participants (24.9%) being vitamin D deficient. In a random sample of 438 participants, the mean follow-up 25(OH)D level was greater than 20 ng/mL higher in the vitamin D group than in the placebo group. The primary outcome of CVD occurred in 303 participants (11.8%) in the vitamin D group and 293 participants (11.5%) in the placebo group, yielding an adjusted hazard ratio of 1.02 (95% CI, 0.87-1.20). Similar results were seen for participants with baseline vitamin D deficiency and for secondary outcomes.

CONCLUSIONS AND RELEVANCE: Monthly high-dose vitamin D supplementation does not prevent CVD. This result does not
support the use of monthly vitamin D supplementation for this purpose. The effects of daily or weekly dosing require further study. 


*Sorry; Vitamin D did not help earthquake survivors*

**Bottom Lines**

1. Consider augmenting depression treatment with a multi-B vitamin.
2. Prescribe nicotinamide for patients with multiple non-melanoma skin cancers.
3. People with acute macular degeneration may experience some delay in progression of the disease with multivitamin antioxidant vitamin and mineral supplementation.
4. Vitamin E may slow cognitive decline in patients with Alzheimer’s dementia but does not prevent cardiovascular disease.
5. The jury is out on whether any vitamins reduce risk of cancer or cardiovascular disease. So far there is no strong evidence to support benefit.
6. Vitamin D decreases frequency of acute respiratory infections, though not in young children.
7. Vitamin D decreases asthma exacerbations requiring steroids, but not the rate of exacerbations.
8. Vitamin D does not reduce pain from knee arthritis but does decrease the pain of chronic widespread pain syndrome.
9. Vitamin D decreases A1C slightly in type 2 diabetes; the clinical significance is unknown.
10. Vitamin D does not decrease symptoms of manic depression.
**Editor’s Choice**

1. **Cost-effectiveness of confirmatory testing before treatment of onychomycosis**

**Clinical question:** Is confirmatory diagnostic testing cost-effective for the management of clinically suspected onychomycosis?

**Bottom line:** The most cost-effective approach to the patient with clinically suspected onychomycosis is empiric therapy with oral terbinafine. The chance of liver injury is estimated to be only 1 in 50,000 to 1 in 120,000, so testing to confirm the diagnosis would cost tens of millions of dollars per case of liver injury avoided. If you plan to prescribe the much more expensive topical solution efinaconazole 10% (Jublia), then confirmatory testing with periodic acid-Schiff (PAS) reduces costs (LOE = 2a)

**Study design:** Decision analysis

**Funding source:** Unknown/not stated

**Setting:** Outpatient (any)

**Synopsis:** An annoyance of clinical practice is the requirement by many insurance companies to perform confirmatory diagnostic testing prior to initiating treatment for patients with clinically suspected onychomycosis. This was based on analyses done 15 years ago, when terbinafine was significantly more expensive. Terbinafine is now affordable (approximately $10 for a full 12-week course), but the topical solution efinaconazole 10% provides a new, more expensive option (more than $500 for each 4-mL bottle in the United States). These authors performed a decision analysis that compared 3 strategies: (1) treat all patients empirically; (2) if in-office potassium hydroxide testing result is positive, treat; if negative, order PAS stain and treat if positive; or (3) order PAS stain on all patients and treat only if positive. They assumed, on the basis of previous studies, that between 65% and 95% of patients presenting with clinical nail dystrophy have a fungal infection, and that the cost of a course of treatment was $2307 for efinaconazole and $53 for terbinafine (including monitoring liver function). They concluded that if you are going to prescribe terbinafine, empiric therapy without confirmatory testing is the preferred strategy (and the least expensive overall) with a very low risk of serious adverse effects. If you are going to prescribe efinaconazole, then confirmatory testing with PAS is preferred. However, this is a much more expensive treatment option.


2. **AAN Guideline on managing patients with restless leg syndrome**

**Clinical question:** How should clinicians manage restless leg syndrome?

**Bottom line:** The American Academy of Neurology recommends using dopamine agonists to treat patients with moderate to severe restless leg syndrome (RLS). Second-line treatments include long-acting opioid/naltrexone combinations or iron supplements (in patients with a ferritin level < 75 mcg/L). For patients who prefer nonpharmaceutical treatment, pneumatic compression appears to be the most studied alternative. (LOE = 5)

**Study design:** Practice guideline

**Funding source:** Foundation

**Setting:** Outpatient (any)

**Synopsis:** This committee of the American Academy of Neurology, staffed by members who had multiple ties to industry, systematically assessed multiple studies to develop guidance on managing patients with RLS. Before reviewing the studies, the committee decided to use a change of 3 points on the International Restless Legs Syndrome Study Group rating scale (IRLS) as clinically meaningful. Additionally, the authors established criteria for meaningful findings on polysomnography (periodic leg movement index, total sleep time, sleep efficiency, sleep latency, wake after sleep onset), as well as measures of sleep outcomes. Finally, when making their treatment recommendations, the committee suggested that establishing qualifying criteria is not necessary before treating patients with moderate to severe RLS. Many of the agents in question are also used in treating Parkinson’s disease, yet the number of high-quality studies on treating patients with RLS are limited. Most studies are of short duration (approximately 12 weeks), rarely evaluate individual agents head-to-head, and I suspect from my experience in reviewing studies that they also tend to underreport the harms of treatment. Most of the existing data are on the use of dopamine agonists: ropinirole (Requip), pramipexole (Mirapex), rotigotine (Neupro), cabergoline (Cabaser, Dostinex), and levodopa. Each appears effective in managing various symptoms, though cabergoline has not been rigorously studied in RLS and the data on levodopa are mixed. Additionally, dopamine agonists have the potential problem of augmentation—gradual worsening of symptoms after treatment that often requires changing medication or adding a new agent. Gabapentin (Neurontin) and pregabalin (Lyrica) also improve the IRLS score but less clearly decrease periodic limb movements. Iron, oral and parenteral, also improves the IRLS score. Long-acting opioid/naltrexone combinations improve the IRLS score and improve sleep quality in patients with poor response to other agents. Very limited data suggest that the following clinical interventions are also likely to be effective: near-infrared spectroscopy, pneumatic compression, transcranial direct current stimulation, repetitive transcranial magnetic stimulation, and vibrating pads.


3. **Meta-analysis: alpha blockers effective for kidney stones**

**Clinical question:** In patients with kidney stones (ureteric calculi), is treatment with an alpha blocker effective in improving passage rate and decreasing pain?

**Bottom line:** Although a recent large study found no benefit to alpha blocker treatment (Lancet 2015;386:341-49), this meta-analysis of 55 studies found a benefit to using alpha blockers to increase the likelihood of stone passage, decrease surgical intervention, and decrease episodes of pain. These findings support European and US guidelines that recommend their use. Patients with larger (at least 5 mm) stones are more likely to benefit. (LOE = 1a-)

(LOE = 5)
4. Better outcomes for hospitalized patients treated by female physicians

Clinical question: Are there differences in outcomes for hospitalized patients who are treated by female physicians versus male physicians?

Bottom line: Patients hospitalized for medical conditions who are treated by female physicians are less likely to die or be readmitted within 30 days than those treated by male physicians. Although the effects shown in this study were modest, at less than a percentage point reduction for both outcomes, the difference may be clinically meaningful when applied to more than 10 million annual Medicare hospitalizations. (LOE = 2b)

Study design: Cross-sectional
Allocation: Uncertain
Setting: Inpatient (any location) with outpatient follow-up

Synopsis: These authors analyzed a 20% sample of Medicare patients who had a nonelective hospitalization for a medical condition between 2011 and 2014. The main physician caring for the patient during the hospitalization was identified as the physician who garnered the highest amount of Medicare Part B spending, which includes professional fees as well as other fees determined by the physician. The analysis was restricted only to those hospitalizations in which the main physician was identified as a general internist. More than 1.5 million hospitalizations treated by almost 58,000 physicians were included in the sample. The characteristics of patients treated by female physicians and those treated by male physicians were well-balanced, with a mean age of 81 years and similar comorbidities across the 2 groups. The overall 30-day mortality rate and 30-day readmission rates were 11.32% and 15.42%, respectively. After adjusting for patient, hospital, and physician factors, patients treated by female physicians had a lower 30-day mortality than those treated by male physicians (11.07% vs 11.49%; P < .001; number needed to treat [NNT] = 233). Similarly, 30-day readmission rates were lower in the group treated by female physicians (15.02% vs 15.57%; P < .001; NNT = 182). When the sample was restricted to patients treated by hospitalists only, the findings remained the same with lower mortality and readmission rates for patients treated by female hospitalists. Furthermore, the results were consistent when analyzed across specific medical conditions and different categories of severity of illness.


5. Type 2 diabetes: metformin first, other treatments second

Clinical question: What should we use as the primary treatment of type 2 diabetes mellitus?

Bottom line: The American College of Physicians recommends treating patients with type 2 diabetes with metformin first, then adding a second oral treatment (a sulfonfonylurea, a thiazolidinedione, an SGLT-2 inhibitor, or a DPP-4 inhibitor) if needed for glycemic control. The group saves advice about when to initiate treatment, treatment goals, use of insulin, and when to add the second treatment for another guideline. (LOE = 5)

Study design: Practice guideline
Funding source: Foundation
Setting: Various (guideline)

Synopsis: These guidelines, developed by the American College of Physicians, were based on a systematic review (doi:10.7326/M15-2650). The committee represented a single primary care specialty and members had no reported financial conflicts of interest. The recommendations focus on improving patient-oriented outcomes and are based on graded evidence, but they are a bit fuzzy. The authors recommend prescribing metformin "when pharmacologic therapy is needed to improve glycemic control" (strong recommendation, moderate-quality evidence), implying that there should be a specific goal for glycemic control but not stating what it should be. Metformin remains the cornerstone of treatment on the basis of its effectiveness in reducing cardiovascular mortality as compared with sulfonylurea treatment, its effectiveness in reducing glycemic levels, its association with weight loss, low risk of hypoglycemic, and cost. When additional glycemic control is needed (again, no guidance regarding when that would be), the authors suggest using either a sulfonfonylurea, a thiazolidinedione, an SGLT-2 inhibitor, or a DPP-4 inhibitor in addition to metformin (weak recommendation, moderate-quality evidence). The authors focused only on oral therapy here and did not give recommendations regarding insulin.

6. **No added benefit with higher doses of ketorolac for treatment of acute pain in the ED**

**Clinical question:** Are lower doses of ketorolac as effective as standard doses for acute pain control in patients presenting to the emergency department?

**Bottom line:** A 10-mg dose of ketorolac is as effective as higher doses for the short-term treatment of acute pain for emergency department (ED) patients. (LOE = 1b)

**Study design:** Randomized controlled trial (double-blinded)  
**Allocation:** Concealed  
**Funding source:** Government  
**Setting:** Emergency department  
**Synopsis:** Ketorolac is a nonsteroidal anti-inflammatory drug available in parenteral form for the treatment of acute pain. Although higher doses are often used, ketorolac may have a therapeutic ceiling of 10 mg. To investigate the efficacy of lower doses of ketorolac, these investigators used a convenience sample of patients presenting to the ED on weekdays between 8 AM and 8 PM to enroll patients with acute flank, abdominal, musculoskeletal, or headache pain rated at least 5 on a 0 to 10 numeric rating scale. The authors excluded patients with unstable vitals, active peptic ulcer disease or gastrointestinal bleeding, history of liver or renal disease, and those who were pregnant or breastfeeding. Using concealed allocation, investigators randomized 240 patients to receive either a 10-mg, 15-mg, or 30-mg dose of ketorolac. Patients who still required pain medication after 30 minutes of administration of the study drug received intravenous morphine at a dose of 0.1 mg per kg. The 3 groups were similar at baseline: They all had a mean age of approximately 40 years, two-thirds were female, and the baseline pain score was between 7 and 8. Analysis was by intention to treat. The primary outcome was a reduction of pain scores at 30 minutes after administration of the study drug. In all 3 groups, there was a significant decrease in pain scores from baseline to 30 minutes by at least 2 points. However, there were no significant differences in reduction of pain scores across the 3 groups at 30 minutes, or at subsequent time points of 60, 90, and 120 minutes. Further, there were no differences in the use of rescue morphine analgesia between the 3 groups. The most common adverse effects reported were dizziness, nausea, and headache, and again, were similar in all 3 groups.

Motov S, Yasavolian M, Likourezos A et al. Comparison of intravenous ketorolac at three single-dose regimens for treating acute pain in the emergency department. 2016 Dec 16 [Epub ahead of print].

7. **Two-year outcomes better with endovascular stroke treatment in selected patients (MR CLEAN follow-up)**

**Clinical question:** Does mechanical thrombectomy using a stent retriever improve long-term outcomes in patients with acute stroke?

**Bottom line:** Mechanical thrombectomy using a stent retriever appears to have some functional benefits, with a greater likelihood that patients have no more than slight disability (number needed to treat [NNT] = 7). There was a trend toward reduced all-cause mortality, but this was not significant, and the loss of more than 20% of patients to follow-up is concerning. (LOE = 1b-)

**Study design:** Randomized controlled trial (single-blinded)  
**Allocation:** Concealed  
**Setting:** Inpatient (any location) with outpatient follow-up  
**Funding source:** Industry + govt  
**Synopsis:** This is a follow-up study to the original MR CLEAN trial, which compared usual care with mechanical thrombectomy using a stent retriever in patients within 6 hours of the onset of acute stroke. The original trial, funded by industry and a foundation, found that the intervention improved 90-day outcomes. This follow-up study was funded by the Dutch government. Of the original 500 patients enrolled in the study, 391 were included in the follow-up study of function and quality of life. The authors evaluated function using a modified Rankin Scale (0 to 6 points, where lower scores are better) every 6 months for up to 2 years following the original intervention. The patients’ quality of life was also evaluated, and the vital status was assessed even for patients not giving consent. A modified Rankin score of 0, 1, or 2 was more likely in the intervention group (37% vs 24%, NNT = 7 over 2 years), and the quality of life score was also significantly but modestly better in the intervention group (effect size 0.1). However, all-cause mortality was not significantly different (26% vs 31%; P = .46; adjusted hazard ratio 0.9; 95% CI 0.6 - 1.2). Patients in the follow-up study were more likely to have been in the intervention group, and they had a lower incidence of atrial fibrillation and a shorter time from stroke to randomization.


8. **Children with appendicitis do fairly well with antibiotic treatment!**

**Clinical question:** Do children with appendicitis treated with antibiotics do as well as those treated with surgery?

**Bottom line:** The existing data are limited to a few small studies. While surgery is clearly better at improving short term and long-term outcomes, it is expensive and patients need to recover. Most children treated with antibiotics will do well, but about 1 in 4 will undergo surgery within a year. This is the perfect place for shared decision-making. (LOE = 2a)

**Study design:** Meta-analysis (randomized controlled trials)  
**Funding source:** Unknown/not stated  
**Setting:** Various (meta-analysis)  
**Synopsis:** These authors searched multiple databases and a trial registry to identify trials comparing antibiotics and surgery in children with acute uncomplicated appendicitis. Two authors independently evaluated each potential paper for inclusion and assessed each included paper’s risk of bias. They included five small studies with 404 children; 168 were treated with antibiotics and 236 were treated surgically. Only one of the trials was randomized. Three studies reported one year follow up and one followed the children for 4.3 years. One planned one year of follow up but only reported a median of 4.7 months. The range of patients not available after one year ranged from 0% to 23% and was similar among those treated surgically or with antibiotics. The included studies also used different diagnostic approaches. In the children treated with antibiotics, 9.5% failed initial treatment - resolution of symptoms without needing surgery within 48 hours or recurrence of appendicitis 1 month after antibiotics while all 236 of those treated surgically had confirmed appendicitis and only one needed reoperation. In other words, about 90% of children treated with antibiotics will do well initially. Forty-five of the antibiotic-treated children (26.8%), however, underwent appendectomy within the following year, 8 of whom had normal appendices on histopathology. Children treated with antibiotics had 8 days of disability compared with 21 in those treated surgically. Four studies
reported data on children with an appendicolith, three of which reported that its presence was associated with a 50% rate of antibiotic failure.


9. Medication reminder gizmos don’t help adherence

Clinical question: Do medication reminder devices improve adherence to chronic disease medication?
Bottom line: William Osler believed that "the desire to take medicine is perhaps the greatest feature which distinguishes man from animals." Well, perhaps we like the idea more than the practice. None of 3 different devices improved adherence to chronic disease medication as measured by prescription refill rates. I'm waiting for the study in which they give the participants Apple Watches to improve adherence; I'd sign up for that one. (LOE = 1b)

Study design: Randomized controlled trial (single-blinded)  
Allocation: Uncertain  
Synopsis: These researchers enrolled 53,480 participants with an average age of 45 years who were identified through a pharmacy benefits manager. The patients took 1 to 3 chronic medications but did not take them regularly. The researchers randomized patients (allocation concealment unknown) to receive 1 of 3 reminder systems: (1) a strip to be attached to a prescription bottle with toggles to keep track of dosing; (2) a digital timer cap that displays the elapsed time since the previous dose, or (3) a standard pillbox. A fourth group did not receive any device. Over 12 months, only approximately 15% of the patients in each of the 4 groups took at least 80% of their chronic medicine, according to prescription records. Similar results were found in patients who were prescribed antidepressants. Analysis was by intention to treat. The researchers simply mailed the devices to patients. Perhaps direct delivery of the device by prescribers or pharmacists would result in better results; the added aspect of "I'm watching you" might have benefit. Reminders delivered via text have been shown to be effective in studies of mixed adherers and nonadherers (JAMA Intern Med 2016;176(3):340-349).


10. Umbrellas alone do not provide adequate sun protection

Clinical question: Which provides better sun protection, sunscreen or a beach umbrella?
Bottom line: This study had a number of important limitations: industry sponsorship, small size, uncertain clinical significance of "sunburn scores," and a somewhat contrived set of study conditions (who doesn’t get in the water when you’re at the beach on a hot day?). Nevertheless, I think the authors are correct in concluding that an umbrella alone does not provide complete protection from the reflected and diffracted ultraviolet (UV) rays that reach the shaded person. This makes some sense since it isn’t pitch black under an umbrella. So, slather on that sunscreen, even if you plan to stay under an umbrella. (LOE = 2b)

Study design: Randomized controlled trial (single-blinded)  
Allocation: Uncertain  
Synopsis: These researchers recruited 81 patients, all of whom spent 3.5 hours at a beach in Texas. The participants are not described at all, an important deficiency in the study, other than that all but one had Fitzpatrick skin type II or III (moderately pale, either European Scandinavian or southern/central European). Half were randomized to receive a standard-sized beach umbrella (just over 6 feet in diameter) and half received an application of sunscreen with a sun protection factor of 100. Participants in the sunscreen group reapplied it an average of twice during the study period. Those under the umbrella were told to stay there, and could only leave it for a total of 30 minutes and only after covering up. Neither group was allowed to enter the water, which seems cruel. The investigators evaluated the exposed areas 24 hours later for the presence of redness or sunburn using a 4-point sunburn score, where 0 indicated no sunburn, 2 indicated defined redness clearly caused by UV rays, and 4 meant edema and/or blisters. The global sunburn score was more likely to increase (worsen) in the umbrella group, and there were more sunburned body sites in the umbrella group than in the sunscreen group (142 vs 17). This study was sponsored and conducted by Johnson & Johnson, the manufacturer of Neutrogena sunscreens and skin care products.


11. Treatment of subclinical hypothyroidism ineffective in older adults

Clinical question: Is there a clinical benefit to treating subclinical hypothyroidism in older adults?
Bottom line: Treatment of patients with a minimally elevated thyrotropin (thyroid-stimulating hormone) level did not result in any improvement in symptoms. If patients present with a thyrotropin level between 4.6 mIU and 10 mIU per liter, repeat the test as the levels often normalize (this occurred in 60% of the patients initially referred for the study). Only consider treatment if levels increase to above 10.0 mIU/L. (LOE = 1b)

Study design: Randomized controlled trial (double-blinded)  
Allocation: Concealed  
Synopsis: Whether to treat patients with subclinical hypothyroidism (slightly elevated thyrotropin, normal T4, and no or minimal symptoms) remains controversial. The authors of this study recruited 737 such adults, 65 years and older, and randomized them to receive thyroid replacement or matching placebo. The mean baseline thyrotropin level was 6.4 mIU/L (normal range: 0.4 to 4.59 mIU/L), and few had a value greater than 10.0 mIU/L. The groups were balanced, allocation was appropriately concealed, and analysis was by intention to treat. Patients were followed up for 1 year, and the primary outcomes were the 4-item ThyPRO thyroid symptom score and a 7-item Tiredness Score. The treatment dose of levothyroxine was started at 50 mcg daily for most patients, and gradually increased until the thyrotropin was in the normal range (the placebo group had sham titration of their "dose"). The final achieved average
thyrotropin level was just over 3.0, which is a bit higher than the target 2.5 mIU/L recommended by some guidelines (Eur Thyroid J 2013;2:215-28). At the end of the study period, there was no difference in any clinical outcomes. A subset of slightly more than half the patients in each group had extended follow-up for a median of 2 years, and at that time there was a slightly greater improvement in the Tiredness Score in the levothyroxine group, but this was of marginal clinical and statistical significance. There was no difference in harms, including cardiovascular events, although the study was not powered to detect a difference if there was one. Stott DJ, Rodondi N, Kearney PM, et al, for the TRUST Study Group. Thyroid hormone therapy for older adults with subclinical hypothyroidism. N Engl J Med 2017;376(26):2534-2544.

12. "Bendopnea"—dyspnea in heart failure patients when bending forward—predicts adverse outcomes

**Clinical question:** What is bendopnea and what does it tell us?

**Bottom line:** Unlike "'Twas brillig, and the slithy toves did gyre and gimble in the wabe," bendopnea is not a nonsense word but a neologism used to describe the shortness of breath experienced by some patients with heart failure. Bendopnea is defined as becoming dyspneic within 20 seconds of leaning forward while seated in a chair as if to tie a shoelace. It seems to be predictive of a worse prognosis; at the very least it's another marker for worsening symptoms. Patients experiencing bendopnea were more likely to have New York Heart Association (NYHA) class IV heart failure, were more likely to have a subsequent hospitalization within 3 months, and might have a worse long-term prognosis. We'll need to wait for research that compares patients with similar heart failure symptoms to determine how much additional prognosis value this has.  

**Study design:** Cohort (prospective)

**Funding source:** Self-funded or unfunded

**Setting:** Outpatient (specialty)

**Synopsis:** Don't know about bendopnea? It is a recently described observation that occurs in approximately 20% of patients with heart failure and associated with higher ventricular filling pressures, especially in patients with a low cardiac index. For this study, the researchers enrolled a convenience sample (ie, not randomized) of 179 patients in a heart failure clinic. The patients were an average 57 years old, there were slightly more men than women, and approximately 60% were white. Patients with bendopnea were more likely to have NYHA class IV heart failure. Higher body mass index was not associated with bendopnea, and other studies have not shown an association with abdominal circumference and bendopnea. The patients were followed up for 1 year. Those with bendopnea were at increased risk of experiencing death, admission for heart failure, inotrope use, left ventricular assist device implantation, and cardiac transplantation—though none of these outcomes was individually significantly more likely. Patients were more likely to be admitted for heart failure treatment within 3 months.


13. No mortality benefit and higher costs with early goal-directed therapy for septic shock

**Clinical question:** Does early goal-directed therapy improve outcomes when treating septic shock?

**Bottom line:** Early goal-directed therapy (EGDT)—a 6-hour resuscitation protocol using central venous monitoring to administer fluids, vasopressors, inotropes, and as-needed transfusions for early treatment of septic shock—does not improve mortality and can lead to longer intensive care unit stays and higher hospitalization costs. Even patients at the highest risk of mortality did not benefit from EGDT in this analysis. Notably, another study in the same journal of the timing of more basic care for septic shock in the emergency department, including drawing blood cultures, measuring lactate levels, and administering antibiotics within 3 hours, showed that longer times were associated with higher in-hospital mortality.  

**Study design:** Meta-analysis (randomized controlled trials)

**Funding source:** Government

**Allocation:** Concealed

**Setting:** Inpatient (any location)

**Synopsis:** The ProCESS, ARISE, and ProMISe trials were multicenter randomized controlled trials that compared EGDT with usual care for the management of septic shock. Each trial revealed a lack of mortality benefit with the use of EGDT. The investigators planned a prospective meta-analysis prior to the enrollment of the first patient into the first trial with the goal of pooling patient-level data from all 3 trials (N = 3723). Patients in the EGDT group and the usual care group were balanced at baseline. For the primary outcome of 90-day mortality, the 2 groups had similar mortality rates (24.9% in the EGDT group vs 25.4% in the usual care group). Additionally, the EGDT group had longer intensive care unit stays, higher costs, and required more cardiovascular support. Subgroup analyses showed no benefit of EGDT in patients with greater severity of illness or those with a higher intensity of underlying care. A separate retrospective study looked at New York's mandated emergency care for the treatment of severe sepsis and septic shock. In this study, a delay in timing of the delivery of a 3-hour bundle, consisting of obtaining blood cultures prior to starting antibiotics, measuring serum lactate, and administering broad-spectrum antibiotics, was associated with higher in-hospital mortality with each incremental hour until the completion of the 3-hour bundle (odds ratio of death until completion of 3-hour bundle: 1.04 per hour; 95% CI 1.02 - 1.05). The PRISM Investigators, Rowan KM, Angus DC, et al. Early, goal-directed therapy for septic shock—a patient-level meta-analysis. N Engl J Med 2017;376(23):2223-2234. Seymour CW, Gjesten F, Prescott HC, et al. Time to treatment and mortality during mandated emergency care for sepsis. N Engl J Med 2017;376(23):2235-2244.

14. Pathologists disagree with each other and themselves on melanoma diagnoses

**Clinical question:** How accurate are pathologists' evaluations of skin lesions for melanoma?

**Bottom line:** Pathologists use a wide variety of descriptors to report biopsy results. Even so, a diagnosis of normal (nevus or mild atypia) can be trusted most of the time. But pathologists often disagree with one another (and themselves); They disagree with one another on moderate atypia (only 25% agreement), severe atypia (40% agreement), and early melanoma (43% agreement). Approximately 8% of all cases will be overinterpreted and 9% will be underinterpreted.  

**LOE = 1c**
15. Treating sleep apnea with positive airway pressure does not reduce adverse CV outcomes or mortality

Clinical question: Does positive airway pressure for adults with sleep apnea reduce cardiovascular disease morbidity and mortality?
Bottom line: The use of positive airway pressure (PAP) for adults with sleep apnea does not reduce adverse cardiovascular events or mortality. Patients who experience daytime fatigue at baseline benefit from reduced sleepiness and improved physical and mental well-being. Order sleep testing only in patients with signs or symptoms of sleep apnea who also experience clinically significant symptoms of daytime fatigue. No one else will benefit. (LOE = 1a)

Study design: Meta-analysis (randomized controlled trials)
Funding source: Government
Setting: Various (meta-analysis)
Synopsis: These investigators thoroughly searched multiple databases including MEDLINE, EMBASE, and the Cochrane Library, as well as reference lists from clinical trials, review articles, conference abstracts, and the clinicaltrials.gov website. Eligible studies included randomized clinical trials that assessed the use of PAP compared with standard care or sham PAP among adults, 18 years or older, with either obstructive sleep apnea (OSA) or central sleep apnea (CSA). No language restrictions were applied. Two individuals independently assessed studies for inclusion criteria and for methodologic quality using a standard risk of bias assessment tool. Disagreements were resolved by consensus. A total of 10 studies that assessed the use of PAP in adults (N = 7266) with OSA and CSA met the inclusion criteria—9 evaluated continuous positive airway pressure and 1 evaluated adaptive servo-ventilation. The overall risk of bias was low to medium; all studies concealed allocation assignment and masked outcomes assessment. No significant associations occurred between the use of PAP and major adverse cardiovascular events, cardiovascular mortality, or all-cause mortality in patients with both OSA and CSA. In addition, there was no significant association with length of follow-up, adherence with using PAP, and baseline apnea-hypopnea index. The use of PAP was significantly associated with improvements in sleepiness and quality of life. A formal analysis found no evidence of publication bias and minimal heterogeneity of assessed outcomes.


16. Personal sound amplification works as well as a hearing aid for understanding speech at 20% of the cost

Clinical question: Are personal sound amplification devices useful for improving speech understanding in noisy environments?
Bottom line: The mean cost of a pair of hearing aids ($4700) is out of reach for most adults and not currently covered by Medicare. This study found that 3 of 5 commercially available personal sound amplification products (PSAPs) improved speech understanding in noisy environments as well as hearing aids. The most expensive of these is still less than one-fifth the cost of a conventional hearing aid. Hmmm... this sounds like useful information for our Medicare patients. (LOE = 2b)

Study design: Cohort (prospective)
Funding source: Foundation
Setting: Outpatient (specialty)
Synopsis: Understanding what a friend is saying from across the table in a noisy restaurant can be a frustrating experience, especially as one ages (as I know from personal experience). For most adults, the price of 2 hearing aids (mean cost $4700) is way out of their budget. These investigators identified 42 adults, aged 60 to 85 years, with mild to moderate hearing loss (20 - 55 dB HL) with no history of prior amplification use or cognitive impairment. Participants completed a standard sentence-in-noise hearing test used to measure speech understanding and functional hearing in the presence of background noise under 7 conditions: unaided, with a standard hearing aid, and with each of 5 commercially available PSAPs. The primary outcome was speech accuracy, defined as the percentage of words repeated correctly. The mean unaided accuracy was 76.5%. Hearing aids improved speech understanding accuracy to 88.4% (absolute improvement 11.9%; 95% CI 9.8 - 14.0%). Three PSAPs improved accuracy by a similar absolute improvement amount: Sound World Solutions C550+ (11%; 8.8% - 13.1%), Soundhawk (10.2%; 8.0% - 12.3%), and Etymotic BEAN (7.7%; 5.5% - 9.8%). The Tweak...
Focus improved hearing but to a lesser degree than the other 3 (4.9%; 2.8% - 7.0%). One PSAP resulted in significantly worse speech accuracy (MSA 30X, accuracy 65%; absolute difference -11.2%; -15.2 to -7.3%). Among this sample, performance correlated with price: The 2 best are $350 and the worst is $30. Reed NS, Betz J, Kendig N, Korczak M, Lin FR. Personal sound amplification products vs a conventional hearing aid for speech understanding in noise. JAMA 2017;318(1):89-90.

17. Price transparency doesn't change clinicians' ordering of inpatient lab tests (PRICE)

Clinical question: Does displaying the prices for inpatient laboratory tests in the electronic health record influence clinician ordering?

Bottom line: Displaying fees at the point of order entry did not affect the number of inpatient laboratory tests ordered. The fees displayed in this study were Medicare reimbursement rates rather than actual costs to patients. (LOE = 1b)

Study design: Randomized controlled trial (nonblinded)  
Funding source: Other

Allocation: Concealed  
Setting: Inpatient (any location)

Synopsis: To evaluate the effect of price transparency on clinical ordering, these investigators randomly assigned 60 groups of inpatient laboratory tests to either display the Medicare allowable fees in the electronic health record (intervention) or not display the fees (control). The laboratory test groups were composed of tests that could be ordered both individually or within a panel. For example, the basic metabolic panel and all its individual components were in the same group. Randomization was stratified with attention to high-volume tests and more expensive tests so that there was an equal representation in the tests that displayed fees and those that did not. Any clinician who was able to place orders in the electronic health record was able to see the prices of the intervention tests at the time of order entry during the intervention period. The primary outcome was number of tests ordered per patient-day. An adjusted analysis, which took into account patient demographics and comorbidities, showed no significant change in the number of tests ordered from either the intervention group or the control group from a 1-year pre-intervention period to a 1-year postintervention period. Additionally, there were no changes in associated laboratory fees per patient-day over time. These findings suggest that displaying prices did not alter clinician behavior when ordering tests. Alert fatigue or one-time ordering of repeat daily labs (which would eliminate the daily price reminder) may have contributed to the lack of effect.


18. Guideline on managing adults with primary Sjogren’s syndrome

Clinical question: How should clinicians manage the symptoms of adults with primary Sjogren's syndrome?

Bottom line: Primary care physicians can manage the bulk of symptoms experienced by patients with Sjogren's syndrome by using simple measures to improve local dryness: lubricants, sugar-free gum, and pilocarpine. (LOE = 5)

Study design: Practice guideline  
Funding source: Other

Setting: Various (guideline)

Synopsis: The National Institute for Health and Care Excellence accredited the process used by the British Society for Rheumatology for this study. Although the society reported they received no funding to support the guideline, several authors had ties to industry. The authors searched several databases for studies published since 1990 and then used a formal Delphi process to develop this guideline; its target audience includes rheumatologists, primary care clinicians, and other specialists. The guideline covers management of the eye and mouth manifestations, xerostomia, and systemic disease. Virtually all of the recommendations are based on expert opinion and other lower-quality evidence. Sicca syndrome is among the most bothersome of Sjogren's manifestations and all patients should be offered symptomatic treatment. Patients with mild eye symptoms can be managed with lubricants; those with moderately severe symptoms should also receive topical steroids or antibiotics (if blepharitis is present). Additionally, patients with moderate to severe symptoms benefit from punctal plugs or secretagogues such as pilocarpine. Patients with more severe eye problems should be referred to an ophthalmologist. You should not be surprised that the focus on xerostomia similarly focuses on moisture: room air humidification; the avoidance of medications that cause dry mouth; and the use of sugar-free chewing gum, anhydrous crystalline maltose, and pilocarpine. Additionally, the guideline recommends fastidious dental hygiene, the use of fluoride, and so forth because of the higher rate of dental caries associated with xerostomia. Additionally, since these patients often experience oral candida and cheilitis, the panel recommends topical antifungals when these occur. In patients who experience parotid enlargement, the panel recommends ultrasound to assess for stones, the use of massage, and treatment with systemic corticosteroids when inflamed. Systemic dryness, manifested as chronic cough and vaginal dryness, should be treated with local products, and with pilocarpine when the symptoms are more severe. The panel recommends immunomodulating agents (methotrexate, azathioprine, hydroxychloroquine, mycophenolate, biologics, and the like) and corticosteroids in patients with systemic disease. Mucosal lymphoma (salivary and gastrointestinal) occurs more frequently in patients with Sjogren's syndrome, especially those with lymphadenopathy, parotid enlargement, palpable purpura, low serum C4 levels, and cryoglobulins. The panel recommends the use of ultrasound and biopsy to evaluate patients with firm, palpable parotid swelling given the increased risk of lymphoma. Lymphoma can also be present in the orbits, thyroid, airways, and gastrointestinal tract, so symptoms in those areas may necessitate further evaluation.


19. Patent foramen ovale closure in cryptogenic stroke reduces recurrence rate compared with antiplatelet agents

Clinical question: In patients with a patent foramen ovale and a history of cryptogenic stroke, does closure followed by antiplatelet therapy improve outcomes compared with antiplatelet therapy alone?
Bottom line: After closure, patients with a patent foramen ovale (PFO) and a cryptogenic stroke and had a reduced risk of recurrent stroke over a 5.4-year mean follow-up period (number needed to treat (NNT) = 16), though atrial fibrillation was a common complication, occurring in 4.6%. A second study in the same journal compared PFO closure followed by at least 6 months of antiplatelet therapy with anticoagulation or antiplatelet therapy alone in 980 patients, and found that PFO closure was more effective than antiplatelet therapy, especially for patients with a large shunt or an atrial septal aneurysm. However, that study did not find a benefit when compared with anticoagulation. Finally, a third study that randomized 664 patients to PFO closure plus antiplatelet therapy versus antiplatelet therapy alone found similar results to this study by Mas and colleagues. (LOE = 1b)

Study design: Randomized controlled trial (nonblinded)

Allocation: Concealed

Setting: Outpatient (specialty)

Synopsis: Previous studies (http://www.essentialevidenceplus.com/content/poem/140501, http://www.essentialevidenceplus.com/content/poem/150507) have not found a benefit to PFO closure in patients with a cryptogenic stroke (that is, a stroke in patients with no clear underlying cause such as atrial fibrillation or coronary artery disease). However, these studies showed trends in favor of treatment, and they may have been underpowered. The current study identified patients aged 16 to 60 years who had suffered an acute ischemic stroke in the past 6 months, had at least 30 microbubbles in the left atrium within 3 cardiac cycles on a bubble test, and had no alternative cause of stroke based on a standardized set of tests. This study was larger than previous trials and also included patients with lower vascular risk, making a recurrent stroke due to other vascular causes less likely. The mean age of patients was 44 years and they had few cardiovascular risk factors (10% hypertension, 3% diabetes mellitus, and 14% hyperlipidemia). In the primary comparison, 524 patients were randomized to receive either PFO closure plus antiplatelet therapy (aspirin plus clopidogrel for 3 months, followed by one of the drugs from then on), to antiplatelet therapy alone, or to anticoagulation alone. Patients with a contraindication to PFO closure (n = 10) were randomized to receive antiplatelet therapy or anticoagulation, and those with a contraindication to oral anticoagulants (n = 129) were randomized to PFO closure plus antiplatelet therapy or anticoagulation alone. For the comparison of PFO closure plus antiplatelet therapy versus antiplatelet therapy alone, at 4.4 years of follow-up the likelihood of recurrent stroke was 0.0% in the former and 6.0% in the latter (hazard ratio [HR] 0.02; 95% CI 0.0 - 0.26; NNT = 16). The risk of the composite of stroke, transient ischemic stroke, or thromboembolic event was also lower in the PFO group (3.4% vs 8.9%; P = .01; NNT = 18). The risk of major or fatal complications (largely atrial fibrillation or flutter, supraventricular tachycardia, air embolism, or hypothermia) in the PFO group was 5.9%. For the comparison of anticoagulation with antiplatelet therapy, there was a nonsignificant trend favoring anticoagulation (HR 0.44; 0.11 - 1.48) for the outcome of recurrent stroke. There was only 1 death in the study (in a patient assigned to anticoagulation). Disabling strokes were rare, with no more than 1 occurring in each treatment group.


20. Care by general internists who trained outside of US superior to that of US trained physicians

Objective To determine whether patient outcomes differ between general internists who graduated from a medical school outside the United States and those who graduated from a US medical school.

Design Observational study.

Setting Medicare, USA.

Participants 20% national sample of data for Medicare fee-for-service beneficiaries aged 65 years or older admitted to hospital with a medical condition in 2011-14 and treated by international or US medical graduates who were general internists. The study sample for mortality analysis included 1 215 490 admissions to the hospital treated by 44 227 general internists.

Main outcome measures Patients’ 30 day mortality and readmission rates, and costs of care per hospital admission, with adjustment for patient and physician characteristics and hospital fixed effects (effectively comparing physicians within the same hospital). As a sensitivity analysis, we focused on physicians who specialize in the care of patients admitted to hospital (“hospitalists”), who typically work in shifts and whose patients are plausibly quasi-randomized based on the physicians’ work schedules.

Results Compared with patients treated by US graduates, patients treated by international graduates had slightly more chronic conditions. After adjustment for patient and physician characteristics and hospital fixed effects, patients treated by international graduates had lower mortality (adjusted mortality 11.2% v 11.6%; adjusted odds ratio 0.95, 95% confidence interval 0.93 to 0.96; P<0.001) and slightly higher costs of care per admission (adjusted costs $1145 (£950; €1080) v $1098; adjusted difference $47, 95% confidence interval $39 to $55, P<0.001). Readmission rates did not differ between the two types of graduates. Similar differences in patient outcomes were observed among hospitalists. Differences in patient mortality were not explained by differences in length of stay, spending level, or discharge location.

Conclusions Data on older Medicare patients admitted to hospital in the US showed that patients treated by international graduates had lower mortality than patients cared for by US graduates.


21. Scribes improve physician satisfaction and charting accuracy and efficiency: RCT

PURPOSE: Scribes are increasingly being used in clinical practice despite a lack of high-quality evidence regarding their effects. Our objective was to evaluate the effect of medical scribes on physician satisfaction, patient satisfaction, and charting efficiency.

METHODS: We conducted a randomized controlled trial in which physicians in an academic family medicine clinic were randomized to 1 week with a scribe then 1 week without a scribe for the course of 1 year. Scribes drafted all relevant documentation, which was reviewed by the physician before attestation and signing. In encounters without a scribe, the physician performed all charting duties. Our outcomes were physician satisfaction, measured by a 5-item instrument that included physicians’ perceptions of chart quality and chart accuracy; patient satisfaction, measured by a 6-item instrument; and charting efficiency, measured by time to chart close.
RESULTS: Scribes improved all aspects of physician satisfaction, including overall satisfaction with clinic (OR = 10.75), having enough face time with patients (OR = 3.71), time spent charting (OR = 86.09), chart quality (OR = 7.25), and chart accuracy (OR = 4.61) (all P values < .001). Scribes had no effect on patient satisfaction. Scribes increased the proportion of charts that were closed within 48 hours (OR = 1.18, P = .028).

CONCLUSIONS: To our knowledge, we have conducted the first randomized controlled trial of scribes. We found that scribes produced significant improvements in overall physician satisfaction, satisfaction with chart quality and accuracy, and charting efficiency without detracting from patient satisfaction. Scribes appear to be a promising strategy to improve health care efficiency and reduce physician burnout.