

Acute Respiratory Infections

John Hickner, MD, MSc

Objectives

- ▶ Summarize evidence on sore throat treatment, including use of steroids and ibuprofen lozenges
- ▶ Review new publications regarding more accurate diagnosis of bacterial sinusitis, mono, and pertussis
- ▶ Review recent studies of acute cough illness
- ▶ Learn strategies for antibiotic stewardship

Sore Throat

1. Low-dose ibuprofen throat lozenge effective for sore throat pain
 - RCT of 385 adults: 25 mg ibuprofen lozenge vs. placebo
 - Up to 6 a day, minimum of 2 hours between doses
 - Better than placebo up to 24 hr., but not impressive (NNT 8 to 11) and no better after 2 days
2. Single-dose oral dexamethasone decreases sore throat pain (Cochrane review)
 - Meta-analysis 10 studies of 1426 patients 5 years or older
 - Onset of pain relief was 4.8 hours faster with the steroid (7.4 vs 12.3 hours)
 - more than twice as many patients reporting complete resolution at 24 hours (relative risk 2.24; 95% CI 1.17 - 4.29)
 - No diff in return to work or adverse events

Sore Throat

3. Dexamethasone may reduce sore throat symptoms in adults at 48 hours
 - RCT: 565 adults; dexamethasone 10 mg oral; no immediate antibiotic, but could give delayed prescription
 - Outcome: complete resolution of sore throat
 - No diff at 24 hours, but significant diff at 48 hrs; (35.4% vs 27.1%, respectively; NNT = 12).
4. Accurate signs, symptoms, and labs for diagnosing mononucleosis
 - Systematic review of 11 studies, over 4,000 patients
 - Useful clinical signs: presence of palatine petechiae (LR+ 5.3), posterior cervical adenopathy (LR+ 3.1), and axillary or inguinal adenopathy (LR+ 3.0)
 - atypical lymphocytosis greater than or equal to 10% (LR+ = 11), (LR+ = 26 for at least 20%, and LR+ = 50 for at least 40%).
 - The absence of any lymphadenopathy was most useful for decreasing the probability of mono (LR- range = 0.23 - 0.44)

Sinusitis

5. Antibiotics for acute maxillary sinusitis in adults
 - 63 studies, but only 11 RCT (N: 1915) comparing various antibiotics to placebo
 - Antibiotics somewhat effective at 7 to 14 days outcome, but effect size small: 86% for placebo vs. 91% with antibiotic (NNT for cure or significant improvement 20)
 - All antibiotics tested equally effective; more SE with Augmentin
6. Chronic sinusitis: saline irrigation helps somewhat; steroid doesn't add more benefit
 - RCT of 80 patients with chronic sinusitis sx
 - average age 51 years; Sino-Nasal Outcome Test (SNOT-22) score of 44.1 out of a possible 110
 - 20.7 points decrease in the steroid group vs 13.6 in control
 - 79% vs 59% "clinically important benefit of 9 points"

Cough, acute bronchitis

7. Typical signs and symptoms minimally effective for the diagnosis of pertussis infection
 - Prevalence of 12.4% (1 in 8) and 18% (1 in 5.5) among adults and children, respectively, with cough longer than 7 days
 - 22 studies (n=15,909)
 - overall impression was most useful (LR+ = 3.3; LR- = 0.63)
 - Other symptoms not that helpful
8. POEM: Oral steroids not helpful for acute lower respiratory tract infection in non-asthmatic adults
 - RCT of 401 patients: 40 mg prednisolone daily vs. placebo for 5 days
 - no diff in ANY outcomes

Cough, acute bronchitis

9. POEM: Nothing works for cough associated with the common cold

- Expert panel systematic review using a thorough search
- No evidence for efficacy of OTC cough meds
- Honey probably better than placebo in kids >1 and adolescents

10. POEM: Subacute cough treatments: limited data, unclear benefits

- Systematic review for cough treatments of 8 weeks or less
- 6 trials with between 30 and 276 patients
- Montelukast, inhaled albuterol, ipratropium, gelatin, inhaled corticosteroids, and opioids
- Minimal positive effects not clinically significant

Cough, acute bronchitis

11. Cochrane: Antibiotics for acute bronchitis

- 17 trials with 5099 participants
- 11 studies with 3841 participants, no diff in overall clinical improvement, BUT,
- Less likely to have cough, NNT of 6
- Shorter cough duration on average of 0.46 days
- Decrease in days feeling ill on average of 0.64 days
- NNH of about 24 for antibiotic treated group

Antibiotic Stewardship

12. POEM: Delayed Rx for respiratory infections produces similar results and satisfaction as immediate treatment

- RCT of 398 adults in Spain: antibiotic, delayed script, none
- acute pharyngitis (46%), acute bronchitis (32%), rhinosinusitis (20%), or exacerbation of COPD (2%)
- Immediate antibiotic decreased duration by 0.5 to 1.0 days
- Equal satisfaction

13. POEM: Delayed antibiotic prescription for new-onset cough associated with decreased re-consultation

- Cohort: 28,779 patients with acute cough less than 3 weeks
- 25.5% were not treated with an antibiotic, 61.3% received a prescription for an antibiotic, and 13.3% received a prescription for delayed antibiotic
- Return visit for 14.1% with delayed antibiotic vs 19.7% with no antibiotic and 25.3%

Antibiotic Stewardship

14. POEM: Behavioral interventions reduce inappropriate antibiotic prescribing for acute RTIs

- RCT of PCP to:
 - 1. automated alternative rx suggested;
 - 2. provide justification in note for Ab;
 - 3. feedback as "top performer" or not.
- Control group decreased inappropriate antibiotics by 11%
- Intervention 1. did not work;
- intervention 2. decreased by 18% and
- intervention 3. by 16.2%

Antibiotic Stewardship

15. Short courses of antibiotics as effective as longer courses for outpatient infections

- In children:
 - 5-7 days as good as 10 days for strep
 - Community acquired pneumonia, 3d as good as 5d
 - at least 3 days for acute otitis media as good as 5-7
 - 2 to 4 days as good as 7 to 14 for UTI
- In adults:
 - 3 to 7 days was as good as 6 to 10 days for acute bacterial sinusitis,
 - 3 days was as good as 5 or more days for uncomplicated UTI in nonpregnant women, 3 to 6 days as effective as 7 to 14 days for UTI in older women, and 7 to 14 days as good as 14 to 42 days for acute pyelonephritis
 - 7 or fewer days was as good as more than 7 days for CAP

Bottom Lines

- ▶ Anti-inflammatory lozenges may be helpful for sore throat.
- ▶ Dexamethasone is of limited benefit, if any, for sore throat.
- ▶ Steroids do nothing for acute bronchitis in patients without asthma, and antibiotics decrease symptom duration about a half day on average.
- ▶ Nothing works very well for acute and subacute cough.
- ▶ Behavioral interventions and delayed prescriptions can reduce antibiotic use for acute RTI.
- ▶ When you choose to prescribe an antibiotic, use shorter courses (3 to 5 days) for acute respiratory infections and acute cystitis.

Dementia/End-of-Life Care

Gary Ferenchick, MD MS

Mild Cognitive Impairment (MCI)

Abstract 1 | Meta-analysis

1. In community-based and clinical studies the rate of reversion from MCI to normal cognition is ~ 18%.
 - Therefore MCI cannot be considered the 1st manifestation of an underlying neuro degenerative disorder

Dementia = a ↓ in cognitive function from a previously attained level which effects ADLs and social function

MCI = a ↓ in cognitive function from a previously attained level BUT can still engage in complex activities (e.g. paying bills)

Note that DSM has stopped using the word dementia (which is associated with stigma) and is now using the phrase major neurocognitive disorder)

Medications and Cognitive Decline

Abstracts 2-4 | Cohort & Prospective population based studies

2. Higher total cumulative doses of anti-cholinergic medications* associated with higher risk for dementia
3. No differences were noted in dementia risk and PPI use in a large case-control study
4. In an observation longitudinal study, PPI use was associated with a *lower* dementia risk

*1st generation TCAs, antihistamines and bladder anti-muscarinics

AHA/ASA/Lancet Reports

Abstracts 5 + 6 | "Presidential Advisory" Expert opinion

- ▶ Optimal brain health is the optimal capacity to function adaptively in the environment across the *domains* of thinking, moving and feeling and the *abilities* of learning, judging, remembering and using language
- ▶ Many brain disorders *manifest later in life* but, in fact, are *life-course illnesses*.
- ▶ Research has convincingly demonstrated that *cardiovascular risk factors* are major contributors to late-life cognitive health and risk of stroke and AD
- ▶ A high proportion of dementia risk is modifiable

Many brain disorders manifest later in life but are, in fact, life course illnesses from the cumulative exposure to vascular risk factors throughout life

AHA/ASA Report

Abstract 5

A strategy of using AHA *Life's Simple 7* helps preserve cognition

Health-Related Behaviors

1. Nonsmoking status
2. Physical activity at goal levels
3. BMI <25 kg/m²
4. Healthy diet consistent with current guidelines

Health-Related Factors

1. Untreated BP <120/<80 mm Hg
2. Untreated total cholesterol <200 mg/dL
3. Fasting blood glucose <100 mg/dL

Life's Simple Seven

Abstract 7

- ▶ Every 1 unit increase in AHA *Life's Simple 7*, associated with a 60% ↑ in odds of having healthy vascular aging (HVA)

HVA represents the lack of HTN and the lack of vascular stiffness

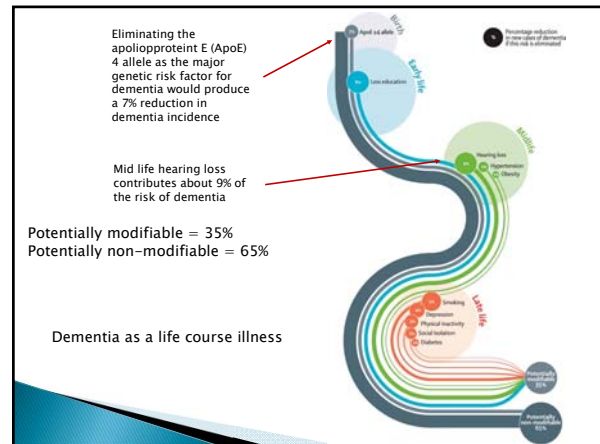
Lancet Commission Report

Abstract 6

35% of dementia risk attributable to a combination of:

- ▶ **Smoking***
- ▶ **Physical inactivity***
- ▶ **Midlife obesity***
- ▶ **Midlife hypertension***
- ▶ **Diabetes***
- ▶ Education to a maximum of age 11–12 years
- ▶ Hearing loss
- ▶ Late life depression
- ▶ Social isolation

*Also listed in Life's Simple 7



Lancet Commission Report

Abstract 6

	Relative risk for dementia (95% CI)	Prevalence	Commonality	RR†	Weighted RR†
Early life (age <18 years)					
Low education (none or primary school only)	1.5 (1.26–1.81)	40.0%	64.0%	19.0%	7.5%
Midlife (age 45–65 years)					
Hypertension	1.5 (1.16–2.04)	8.9%	17.2%	5.1%	2.0%
Obesity	1.5 (1.14–1.91)	3.4%	60.4%	2.0%	0.8%
Hearing loss	1.9 (1.18–2.77)	10.7%	40.1%	23.0%	9.1%
Late life (age >65 years)					
Smoking	1.6 (1.11–2.28)	27.4%	13.1%	13.0%	5.5%
Depression	1.5 (1.15–1.93)	33.1%	18.6%	10.4%	4.0%
Physical inactivity	1.4 (1.16–1.67)	17.7%	26.6%	6.5%	2.6%
Social isolation	1.5 (1.11–1.91)	11.0%	41.9%	5.9%	2.3%
Diabetes	1.5 (1.11–1.78)	6.4%	79.3%	3.2%	1.2%

Contribution of each factor to overall risk

PAF is the population attributable fraction (PAF) is the % reduction in new cases over a given time if a particular risk factor was eliminated

FINGER Study

Abstract 8 | RCT

- ▶ Multidomain intervention focusing on diet, exercise, cognitive training and vascular monitoring was associated with improved function on overall cognition, processing speed and executive function but not on memory

Intensive intervention with 200 meetings (300 hours) with health professionals and trainers over 2 years

FINGER = **F**innish **G**eriatric Intervention Study to Prevent Cognitive Impairment and Disability)

Mediterranean Diet

Abstract 9 | RCT

- ▶ A Mediterranean diet supplemented with olive oil or mixed nuts for 4 years is associated with improved performance on neuro psychological testing compared to a control low fat diet

RCTs on Interventions to Prevent AD

Abstracts 10–13

- ▶ In adults with normal cognition, evidence is insufficient for the effect of cognitive training regarding prevention of cognitive decline
- ▶ In adults with normal cognition or MCI:
 - Pharmacological treatments, OTC supplements or single-component physical activity interventions have not been shown to prevent cognitive decline

"Although we found some intriguing positive results ... nothing even approached the evidence level required for a USPSTF recommendation." Eric Larson

Advanced Care Planning (ACP)

Abstracts 14 | RCT

- ▶ Use of a 5-step "Prepare for Your Care" interactive website increased ACP documentation from 25 to 35%.

URL in your chapter

Melatonin

Abstract 15 | Meta-analysis

- ▶ Melatonin increases sleep efficacy in patients with dementia with no increase in ADE

PEG Placement

Abstract 16 | Retrospective analysis

- ▶ PEG placement in patients with dementia associated with worse outcomes compared to PEG placement for other reasons

Bottom Lines

- ▶ MCI appears to be reversible in some patients
- ▶ Cumulative anticholinergic use is associated with dementia risk
- ▶ No association between PPI use and dementia
- ▶ About 35% of dementia risk is potentially modifiable
- ▶ Resource intensive multi-domain interventions and the Mediterranean diet as associated with improved cognition
- ▶ No evidence that single interventions (e.g. cognitive training, exercise) improve cognitive outcomes
- ▶ ACP is facilitated with an easy to use online resource
- ▶ PEG placement in patients with dementia associated with worse outcomes compared to PEG placement for other reasons

Anxiety and Depression

John Hickner, MD, MS

Objectives

1. Review recent studies on prevention and treatment of depression
2. Review recent studies on the treatment of anxiety disorders
3. Review evidence of effectiveness for mindfulness-based therapy and internet-based therapy for mental health disorders

Depression

1. Effect of physical activity on risk for depression
 - Meta-analysis of 49 cohort studies, 266,939 men/women
 - High intensity over 150 min/week, up to 7.4 year follow up
 - Odds ratio of incident depression 0.83 in exercisers
 - Adjustment for confounders did not change conclusion
2. HRT to prevent depression in peri- and early menopause
 - RCT with 174 women age 45–60 randomized to HRT or no
 - Assessed for depressive sx 1,2,4,6,8,10,12 mo.
 - 17.3% vs 32.3%; number needed to treat = 6.6; 95% CI 3.6 – 46.5

Depression

3. Comparing CBT & light therapy for seasonal affective disorder (SAD)
 - RCT of 177 depressed individuals in Vermont
 - 10,000 LUX cool light for 30 min in am for 6 weeks or CBT 2 90-minute sessions weekly for 6 weeks
 - About half of participants in each group achieved remission
4. Light therapy for bipolar depression
 - RCT 46 adults with BPD randomized to bright light or regular light
 - Light therapy titrated upward from 15 min to 60 min by week 4
 - Remission better for bright light: 68% vs 22%; odds ratio 7.5; 95% CI 1.8 – 31.3; P = .003

Depression

5. Escitalopram reduces risk of adverse cardiac events in adults with depression and acute coronary syndrome
 - RCT of escitalopram vs. placebo
 - All 300 participants followed for a median of 8.1 years
 - MACE (major cardiac events) 40.9% vs 53.6%, respectively; number needed to treat = 7.9; 95% CI 4.2 – 71.0
6. Prevalence of unrecognized bipolar disorder in primary care patients
 - Patients taking antidepressants were recruited from UK PCP
 - 7.3% had unrecognized bipolar disorder; adjust to 10%

Social Anxiety Disorder

7. Diagnosis & treatment of social anxiety disorder
 - 6.7% lifetime prevalence
 - Offer individual CBT specifically developed to treat social anxiety disorder as first-line treatment for adults.
 - Do not offer group therapy
 - Consider drug therapy with an SSRI only after encouraging patients to try CBT first

Social Anxiety Disorder

8. Cognitive behavioral therapy best for social anxiety disorder

- 101 trials (13,164 participants) of 41 interventions
- MAOI, benzos, SSRI, SNRI, anticonvulsants somewhat effect
- SNRI and SSRI the best drugs
- CBT best overall

9. Pharmacotherapy of Social Anxiety Disorder

- Cochrane review of 66 RCTs
- Similar conclusions to the study #8
- SSRI best, but evidence not high quality for any

Other Anxiety Disorders

10. Pharmacotherapy for panic disorder

- 41 RCTs including 9377 participants
- Antidepressants NNT Benefit of 7
- Limitations: drug company sponsorship and short duration

11. CBT and SSRIs effective for childhood anxiety disorders

- 7719 patients from 115 studies
- CBT, SSRI, SNRI somewhat effective
- Tricyclics and benzos were not effective

Other Anxiety Disorders

12. Higher doses of SSRIs but not SNRIs are more effective

- Evaluation of efficacy of SSRIs and SNRIs
- Meta-analysis of 57 trials (N = 16,056)
- Both effective; best for social anxiety disorder
- Higher doses better for SSRI but not for SNRI

13. Is the effectiveness of SSRIs due largely to verbal suggestion (placebo)?

- RCT for social anxiety disorder with 47 patients randomized
- Both groups received escitalopram; overt or covert
- three times higher response rate (50% vs. 14%) in overt group

Novel treatments for mental health disorders

14. Eye movement desensitization and reprocessing (EMDR) better than CBT for PTSD

- Meta-analysis of 11 studies (n = 547) showed that EMDR is better than CBT in reducing post-traumatic symptoms [SDM (95% CI) = -0.43, p = 0.006]; no diff 3 mos.
- The EMDR was also better than CBT in reducing anxiety [SDM (95% CI) = -0.71, p = 0.005].

15. Mindfulness based cognitive therapy somewhat effective for symptoms of bipolar disorder

- Systematic review; 13 studies (N = 429)
- improvements in cognitive functioning and emotional regulation, reduction in symptoms of anxiety depression and mania symptoms

Novel treatments for mental health disorders

16. Internet-based mindfulness interventions reduce symptoms of anxiety and depression

- Systematic review of 12 studies
- Reduced symptoms of depression and anxiety
- Improved functioning and quality of life
- Did not work as well in subgroup with pure depression

17. Therapist assisted Internet-based CBT effective for obsessive-compulsive disorder

- 179 participants (117 females, 65.7%)
- iCBT vs. standard education and progressive relaxation
- iCBT was superior to control in symptom reduction, though significant symptom reduction occurred in only 50%

Bottom Lines

1. Physical activity reduces the risk of developing depression.
2. Hormone replacement therapy reduces the risk of depression in peri-menopausal and early menopausal women.
3. Light therapy reduces symptoms of seasonal affective disorder and bipolar depression.
4. Cognitive behavioral therapy is the preferred treatment for social anxiety disorder. SSRIs are also somewhat effective.

Bottom Lines

5. Higher doses of SSRIs are more effective but higher doses of SNRIs are not more effective.
6. EMDR is effective in treating post-traumatic stress disorder (PTSD).
7. Mindfulness-based interventions in person or via the web can reduce symptoms of anxiety and depression, including bipolar disorder.
8. Therapist assisted Internet-based treatment of obsessive compulsive disorder with CBT is effective.

Exercise and Rehabilitation

Gary Ferenchick, MD MS

Sedentary Time

Abstracts 1 + 2 | Retrospective and prospective cohort

1. Higher total sedentary time associated with mortality risk
 - If above the mean in moderate-to-vigorous physical activity, ↑ sedentary time not associated with increased mortality
2. Total sedentary time and accrual in bouts > 10 minutes both independently associated with mortality risk
 - Physical activity guidelines should target reducing and interrupting sedentary time

Athletic Events and Mortality

Abstracts 3 + 4 | Case series

3. Death or cardiac arrest occurs in 1.7/100,000 triathlon participants overall (2.4 men:0.7 women); 19/100,000 in men > 60.
 - Outcomes similar for short, medium and long races
 - 44% had ASCVD on autopsy
4. Cardiac arrest occurred in 0.8/100,000. Only 3 of 74 cases of cardiac arrest that occurred during a sporting event *were from structural heart disease and therefore potentially identifiable with pre-participation screening*

Wearable Technology

Abstracts 5 + 6 | RCTs

5. Pedometer ↑ number of steps per day by ~ 10% and ↑ 35 minutes/w (5 minutes/day) in exercise with no effect on weight loss
6. Wearable technology that tracks diet and exercise associated with less weight loss than standard care (3.5 kg vs 5.9 kg)

Exercise and Stable IHD

Abstracts 7 | Observational study

7. Doubling exercise time decreases all-cause mortality by 18% and CV mortality by 17% in patients with stable IHD.
 - Most benefit seen in those at highest risk of mortality

Exercise and Fall Risk

Abstracts 8 + 9 | Both Meta-analyses

8. Exercise and vision assessment and treatment was the most effective strategy for preventing falls in the elderly (> 65)
9. Tai Chi decreases short and long-term fall risk in the elderly

Exercise for Meniscal Tears

Abstract 10 | Non-blinded RCT

10. Exercise for 3 months was as effective as surgery for pain and function at 2 years in patients with meniscal tears and no OA
- 20% cross over from exercise to surgery in 2 years

Early PT for LBP

Abstract 11 | Cost effectiveness analysis

11. Early PT for acute LBP is minimally cost-effective producing a small increase in quality-adjusted life years (QALY = 0.02)
- \$29,000 per additional QALY

One QALY = one year in perfect health

PT = Standard Rx for Ankle Sprain

Abstract 12 | Non-blinded RCT

13. Acute ankle sprain outcomes (Grades 1 + 2) at 3 and 6 months no different with and without PT

Grade 1 = mild damage to ligament and no instability
Grade 2 = partial tear with some instability

Exercise + Pregnancy

Abstracts 14 - 16 | RCTs + Meta-analysis

Among pregnant women:

- 14. Thrice weekly exercise consisting of aerobic, resistance and stretching activities associated with less gestational HTN, DM, weight gain and macrosomia (NNTs = 13-35)
- 15. Exercise decreases GDM and gestational weight gain
- 16. Cycling for 30 minutes three times weekly, decreases GDM (NNT = 5) and weight gain (2 Kg Δ)

Genetic Screening for Sports Participation

Abstract 13 | Commentary

14. Ethical considerations abound for genetic testing as a "preventive strategy" for SCD prior to participation in sports
- Cardiac screening for sports participation not uncommon
 - Potential role of genetic testing | esp with a (+) Fam Hx SCD or in those with (+) screening test
 - Many conditions that predispose to SCD are genetic (e.g. HCM, Marfan's, long QT)
 - Highly variable penetrance | genotype (+) does not equate 100% to phenotype (+)
 - American and European guidelines disagree on disqualification on the basis of a (+) genetic test only
 - Ethics of disqualification and loss of opportunity - laws exist banning pre-employment genetic testing in other domains
 - Respecting patient autonomy | confidential genetic testing and counseling from practitioners external to the screening and eligibility process

Bottom Lines

- 1. Sedentary time and behavior is a risk factor for mortality independent of moderate to vigorous physical activity
- 2. SCD occurs in 1-3/100,000 participants in athletic events, and traditional screening is unlikely to be effective
- 3. Wearable technology increases number of steps and minutes of exercise, but has no (or a negative) effect on weight gain
- 4. Exercise and vision assessment and Tai Chi are effective in fall prevention

Bottom Lines

5. Exercise = arthroscopic surgery for non-traumatic meniscal tears
6. Genetic testing as part of a pre-participation screening has several complex ethical considerations
7. Regular exercise during pregnancy is associated with improved outcomes

Genitourinary Update

John Hickner, MD, MS

Objectives

1. Know the findings of recent studies regarding potential benefits and harms of screening for and treating prostate cancer
2. Review recent research regarding renal and bladder conditions pertinent to primary care practitioners.
3. Review recent evidence for the effectiveness of treatments for ureteral calculi and chronic kidney disease.

Prostate Cancer

1. Active surveillance for localized prostate CA: no increased mortality, but higher rates of clinical progression (ProtecT)
 - RCT of 2,662 men with organ confined prostate cancer
 - Active surveillance vs. surgery or radiation rx
 - 50% of active surveillance had treatment in 10 yr follow-up
 - No diff in all cause or prostate specific mortality
 - 3 more metastatic cancers and 13 more "clinical progression" per 100 men after 10 years
2. Prostatectomy for local prostate cancer does not significantly reduce mortality in up to 20 years of follow-up
 - Older RCT, follow-up less stringent
 - 5.5% absolute reduction in all-cause mortality and a 4% absolute reduction in prostate cancer mortality
 - Mortality risk reduction higher in men under 65 (12.2%)

Chronic Kidney Disease

3. No Recent Increase in the Prevalence of Chronic Kidney Disease in the United States
 - 6.9% prevalence in 2003–2004 and in 2011–2012
4. Screening for chronic kidney disease: U.S. Preventive Services Task Force recommendation
 - The USPSTF concludes that the evidence is insufficient to assess the balance of benefits and harms of routine screening for CKD in asymptomatic adults (I statement) – 2012

Chronic Kidney Disease

5. Clinical Guidelines Committee of the American College of Physicians. Screening, monitoring, and treatment of stage 1 to stage 3 chronic kidney disease: Recommendations
 - 1. No screening for chronic kidney disease in asymptomatic adults without risk factors for chronic kidney disease. (Grade: low quality evidence)
 - 2. No testing for proteinuria in adults with or without diabetes who are currently taking an angiotensin-converting enzyme inhibitor or an angiotensin II-receptor blocker. (Grade: low-quality evidence)
 - 3. for those with HTN and stage 1–3 CKD, treat with an ACE or an ARB (Grade: strong recommendation)
 - 4. Treat with a statin to manage elevated low-density lipoprotein in patients with stage 1 to 3 chronic kidney disease. (Grade: strong recommendation, moderate-quality evidence)
6. Chronic Kidney Disease: Detection and Evaluation

Renal Function

7. Intensive BP control in older patients can decrease renal function
 - RCT, SPRINT: 6662 participants, mean age 66 years, with a baseline estimated GFR of at least 60
 - Intensive (systolic <120) or standard (systolic <140)
 - Greater 30% decline in GFR with intensive rx (NNH 38) 3 yrs
8. Empagliflozin slows progression of renal disease in very high-risk patients with T2DM
 - RCT of 7020 patients, secondary renal outcomes
 - Progression to macroalbuminuria (11.2% vs 16.2%, NNT = 20), doubling of serum creatinine (1.5% vs 2.6%, NNT = 90), and, need for renal replacement (0.3% vs 0.6%, NNT = 333)

Ureteral Stones

9. Tamsulosin = placebo for rate of 1-week stone passage in patients with urolithiasis

- RCT of 127 ED patients; rx with 0.4 mg tamsulosin vs placebo
- No diff in stone passage at 7 days: 62% vs 54%
- Underpowered; did not consider stone size

10. Tamsulosin effective as expulsion therapy for 5-mm to 10-mm distal ureteric stones

- RCT; rx with 0.4 mg Tamsulosin vs. placebo
- (87% in the tamsulosin group vs 82% in the placebo group; $P = .22$).
- For stones 5 mm –10 mm, the tamsulosin group did better (83% vs 61%; $P = .03$)

Ureteral Stones

11. Tamsulosin beneficial for passage of 5-mm to 10-mm distal ureteral stones

- Meta-analysis of 8 RCTs for stones 10 mm or less
- 85% vs 66% overall, NNT
- more effective than placebo for 5-mm to 10-mm distal stones (79% vs 57%; NNT = 5), but not for smaller stones

12. Meta-analysis: alpha blockers effective for kidney stones

- Meta-analysis of 55 studies
- Stone passage, which occurs in approximately half of patients without intervention, is 50% greater with treatment (NNT = 3.74)
- Passage 4 days sooner on average (9.6 d vs 13.3 d)
- need for surgery will decrease by approximately half (NNT = 6.17)
- hospital admissions will decrease approximately 60% (NNT = 10.6)

Ureteral Stones

13. Water, medical treatments recommended to prevent kidney stones

- American College of Physicians Guidelines 2014
- Increase water intake to produce 2L urine/day (weak evidence)
- Other dietary interventions: insufficient evidence
- drug therapy
 - monotherapy with thiazide diuretics, which block calcium excretion, will halve calcium stone recurrence (moderate-quality evidence).
 - potassium, potassium-magnesium, or potassium-sodium citrate will decrease calcium stone recurrence (moderate-quality evidence).
 - Allopurinol has moderate-quality evidence that it reduces calcium oxalate stones.

Acupuncture

14. Electroacupuncture beneficial for women with stress urinary incontinence

- RCT in China
- Sham or active electroacupuncture: 18 sessions over 6 weeks
- 30 week follow up
- a 50% or more reduction in the mean number of 72-hour incontinence episodes better in active group versus sham group (25.6% difference; NNT = 3.9)

15. Acupuncture effective for chronic prostatitis/chronic pelvic pain syndrome in men

- RCT of 68 men with at least 3 mo. Chronic pelvic pain/prostatitis
- 3 sessions/wk for 8 wks of real vs. sham
- At 32 weeks, scores for active tx 7.4 lower on 43 point scale.
- 50% decrease from baseline higher in active tx (56.3% vs 0.0%, respectively; NNT = 1.9).

UTI

16. Analgesic-only treatment for UTI is an option for some

- RCT of 484 women with cystitis
- fosfomycin (Monuril) 3 g or ibuprofen 400 mg 3 tid X 3 d
- Symptom free on day 4, 56% vs. 39% favoring antibiotic
- Total symptom duration less with antibiotic (4.6 vs 5.6 days)
- Over the subsequent 28 days, 34% of analgesic-treated women received an antibiotic

17. Increased water intake decreases UTI recurrence in women

- RCT 140 women with at least 3 UTI past year
- Drink ADDITIONAL 1.5 liters water/day for 12 months
- 1.7 vs. 3.2 infections favoring water group

UTI

18. Seven days vs. 14 days of antibiotic treatment for febrile UTI

- RCT of 200 patients (men and women)
- short-term clinical cure for 7 day and 14 day treatment
 - Overall: 90% and 95%
 - Women: 94% and 93%
 - Men: 86% and 98%
- Long term cure rates, however, 91% and 92%
- Conclusion: 7 days treatment sufficient for women and most men

Bottom Lines

1. PSA screening with shared decision making is an acceptable approach to prostate cancer screening.
2. Screening the general population for chronic kidney disease is not recommended.
3. Intensive blood pressure control in older adults can lead to renal function decline over 3 years.
4. Empagliflozin slows renal function decline in patients with type 2 diabetes.
5. Alpha blockers increase the likelihood of passage of stones 5mm to 10mm only.

Bottom Lines

6. Lots of fluids, a thiazide diuretic or citrate in patients with recurrent calcium stones, and allopurinol in patients with calcium oxalate stones helps prevent recurrent kidney stones.
7. Electroacupuncture is somewhat effective for stress incontinence in women.
8. Increasing water intake by 1.5 liters a day halves the incidence of recurrent UTIs in women.
9. Simple cystitis in women resolve with no antibiotic treatment in about 40% of cases.
10. 7 days antibiotic treatment is sufficient for women and most men with febrile UTI.

MICHIGAN STATE UNIVERSITY | **College of Human Medicine**

Hypertension

Abstracts 1 – 4



■ **Advancing Knowledge.** Transforming Lives.

JNC 8 | Abstract 1
Hypertension Guidelines

- Target for treatment **150/90**
 - Age ≥ 60
- Target for treatment **140/90**
 - Age 18 - 60
 - Patients with CKD (eGFR < 60 and/or albuminuria)
 - Diabetes

The "good old days"

14 pages long

2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014 Feb 5;311(5):507-20.

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JNC 8 | Abstract 1
Hypertension Guidelines

- Initial treatment should include,
 - Thiazide-type diuretic, OR
 - Calcium channel blocker, OR
 - ACE-inhibitor, OR ARBs
- JNC 8 concluded that each of these 4 drug classes yield *comparable beneficial effects* on overall mortality and cardiovascular, cerebrovascular, and renal outcomes.

2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014 Feb 5;311(5):507-20.

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JNC 8 | Abstract 1
Hypertension Guidelines

"Setting a goal SBP of lower than 140 mm Hg in patients > 60 provides *no additional benefit* when compared with a SBP of ... 140 to 149."

2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014 Feb 5;311(5):507-20.

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SPRINT Trial | Abstract 2

Compare the outcomes of a treated systolic blood pressure targeted to < 120 mm Hg vs. a SBP targeted to < 140 among high risk persons.

19 months after JNC 8

SPRINT Research Group, Wright JT Jr, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med*. 2015 Nov 26;373(22):2103-16.

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SPRINT Trial | Inclusion Criteria

- Age ≥ 50
- SBP 130 – 180 (note: no DBP criteria)
- Increased risk of CV events (≥ 1):
 - 10-year risk of CV disease $> 15\%$ (Framingham)
 - CV disease (clinical/subclinical | other than CVA)
 - CKD (eGFR 20 – 60 ml/min)
 - Age > 75

SPRINT Research Group, Wright JT Jr, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med*. 2015 Nov 26;373(22):2103-16.

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SPRINT Trial | Exclusions

Excluded patients with:

- Diabetes
- Stroke history

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SPRINT Research Group, Wright JT Jr, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2015 Nov 26;373(22):2103-16.

SPRINT Trial

Excluded patients with:

- Diabetes
- Stroke history

Use of beta-blockers or other antihypertensives (e.g. vasodilators, alpha 2 agonists, alpha-agonists) were allowed "as appropriate for compelling reasons".

Treatment algorithm: 2 or 3 drugs, a combo of: ✓

- Thiazide diuretic (or loop-diuretic if advanced CKD), and/or
- ACE or ARB (not both), and/or
- CCB

GDMT consistent with JNC 8 recommendations

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SPRINT Research Group, Wright JT Jr, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2015 Nov 26;373(22):2103-16.

SPRINT Trial | Outcomes

Primary outcome | 5 Point MACE → Major adverse cardiovascular events

- MI
- ACS
- Stroke
- Acute decompensated CHF
- Death from CV causes

Secondary outcomes

- Individual components of the composite outcome
- Overall mortality
- Composite of primary outcome AND death
- Renal outcomes

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SPRINT Research Group, Wright JT Jr, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2015 Nov 26;373(22):2103-16.

SPRINT Trial | Subgroups

Pre specified subgroups

1. Baseline CKD
2. Gender
3. Ethnicity
4. Age (< 75 v > 75)
5. Baseline SBP (< 132; 132 – 145; > 145)

Blood pressure reading | Mean of 3 automated in-office BP measurements, patient seated after 5 minutes of rest

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SPRINT Research Group, Wright JT Jr, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2015 Nov 26;373(22):2103-16.

SPRINT Trial | Baseline characteristics

	Intensive N = 4678 (%)	Conventional N = 4683 (%)
Mean age	67.9	67.9
Age > 75	28.2	28.2
Female	36	35.2
Non-Hispanic black	29.5	30.4
Hispanic	10.8	10.3
CKD	28.4	28.1
CV Dz	22	22
Average 10-yr CV risk (Framingham)	20	20
Baseline BP	140/78	140/78
% baseline SBP < 132	33.8	33.2

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SPRINT Research Group, Wright JT Jr, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2015 Nov 26;373(22):2103-16.

SPRINT Trial | 3.2 years f/u

	Intensive N = 4678	Conventional N = 4683	Δ	NNT
SBP/DBP 3.2 yr	122/66	135/74	Δ 13/8	
Primary outcome (%)	5.2	6.8	1.6%	61
All cause mortality (%)	3.3	4.5	1.2%	90
CV death (%)	0.8	1.5	0.7%	173
CHF	1.3	2.1	0.8%	125

The results were consistent across the prespecified subgroups

Baseline CKD | Gender | Ethnicity | Age | Baseline SBP

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SPRINT Research Group, Wright JT Jr, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2015 Nov 26;373(22):2103-16.

SPRINT Trial | 3.2 years f/u

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Primary outcome (%)	5.2	6.8	1.6%	61
All cause mortality (%)	3.3	4.5	1.2%	90
CV death (%)	0.8	1.5	173	173
CHF	1.3	2.1	0.8%	125
Mean # BP meds	2.8	1.8	1	
≥ 4 drugs (%)	24	7	14%	7
Serious adverse events (%)	4.7	2.5%	2.2%	45

MICHIGAN STATE
UNIVERSITYCollege of
Human MedicineSPRINT Research Group, Wright JT Jr, et al. A Randomized Trial of
Intensive versus Standard Blood-Pressure Control.
N Engl J Med. 2015 Nov 26;373(22):2103-16.

SPRINT Trial

For every 1 patient avoiding death, 2 patients will experience an adverse event

Hypotension; Syncope, Electrolyte abnormalities, AKI/AKF

MICHIGAN STATE
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Human MedicineSPRINT Research Group, Wright JT Jr, et al. A Randomized Trial of
Intensive versus Standard Blood-Pressure Control.
N Engl J Med. 2015 Nov 26;373(22):2103-16.

SPRINT Trial

Compare the outcomes of treated systolic blood pressure to a target of < 120 mm Hg compared to a target of < 140 among high risk persons.

MICHIGAN STATE
UNIVERSITYCollege of
Human MedicineSPRINT Research Group, Wright JT Jr, et al. A Randomized Trial of
Intensive versus Standard Blood-Pressure Control.
N Engl J Med. 2015 Nov 26;373(22):2103-16.

ACCORD BP Trial | Abstract 3

Compare the outcomes of treated systolic blood pressure to a target of < 120 mm Hg compared to a target of < 140 among high-risk persons with diabetes.

4.7 years of follow-up

MICHIGAN STATE
UNIVERSITYCollege of
Human MedicineACCORD Study Group. Effects of intensive blood-pressure
control in type 2 diabetes mellitus.
N Engl J Med. 2010 Apr 29;362(17):1575-85.

SPRINT v ACCORD

	SPRINT N = 9361	ACCORD N = 4733
Mean age	67.9	62.2
Female (%)	36	48
Non-Hispanic black (%)	29	24
Hispanic (%)	11	7
CV Dz (%)	22	38
BP at baseline	140/78	139/76

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Human MedicineACCORD Study Group. Effects of intensive blood-pressure
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N Engl J Med. 2010 Apr 29;362(17):1575-85.
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CV Dz (%)	22	38
BP at baseline	140/78	139/76
BP at end of study	Δ 13/6	Δ 12/6

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Human MedicineACCORD Study Group. Effects of intensive blood-pressure
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CV Dz (%)	22	38
BP at baseline	140/78	139/76
BP at end of study	Δ 13/6	Δ 12/6
Primary outcome (MACE)	Δ 1.6%	Δ 0.22% (NS)

ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus.
N Engl J Med. 2010 Apr 29;362(17):1575-85

SPRINT Research Group. Wright JT Jr, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control.
N Engl J Med. 2015 Nov 26;373(22):2103-16

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BP at baseline	140/78	139/76
BP at end of study	Δ 13/6	Δ 12/6
Primary outcome (MACE)	Δ 1.6%	Δ 0.22% (NS)
Serious adverse events (%)	Δ 2.2%	Δ 2.0%

ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus.
N Engl J Med. 2010 Apr 29;362(17):1575-85

SPRINT Research Group. Wright JT Jr, et al. A Randomized Trial of Intensive versus Standard Blood-Pressure Control.
N Engl J Med. 2015 Nov 26;373(22):2103-16

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HOPE-3 Trial | Abstract 4

Compare the outcomes of treated systolic blood pressure with fixed dose candesartan/HCTZ in intermediate risk persons without CVDz.

5.6 years of follow up | 3 - point MACE

6 months after SPRINT published

HOPE-3 Investigators. Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease.
N Engl J Med. 2016 May 26;374(21):2009-20

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HOPE-3 Trial | Baseline characteristics

	Active Rx N = 6356 (%)	Placebo N = 6349 (%)
Mean age	66	66
Female	46	46
Non-Hispanic black	1.8	1.7
Hispanic	27	27
Chinese/Asian	50	50
Diabetes	5.8	5.8
Hx HTN	33	33
Baseline 10-yr CV risk	10%	10%
Baseline BP	138/82	138/82

Almost identical to the SPRINT Trial

HOPE-3 Investigators. Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease.
N Engl J Med. 2016 May 26;374(21):2009-20

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Mean age	66	66
Female	46	46
Non-Hispanic black	1.8	1.7
Hispanic	27	27
Chinese/Asian	50	50
Diabetes	5.8	5.8
Hx HTN	33	33
Baseline 10-yr CV risk	10%	10%
Baseline BP	138/82	138/82

SPRINT Trial baseline 10-yr risk was 20%

HOPE-3 Investigators. Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease.
N Engl J Med. 2016 May 26;374(21):2009-20

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Hope-3 Trial | 5.6 years f/u

	Intensive N = 4678	Conventional N = 4683	Δ	NNT
SBP	128/75	134/79	Δ 6/3	
Primary outcome (%)	4.1	4.4	0.3%	NS
Secondary outcomes (%)	4.9	5.2	0.3%	NS
CV death (%)	2.4	2.7	0.3%	NS
All-cause mortality	5.4	5.5	0.1%	NS

SPRINT Δ 13/6

HOPE-3 Investigators. Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease.
N Engl J Med. 2016 May 26;374(21):2009-20

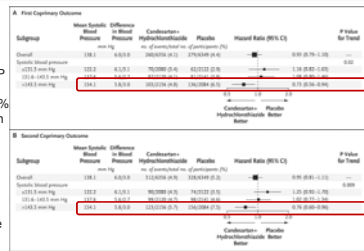
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Hope-3 Trial | 5.6 years f/u

In patients with a mean baseline SBP ~ 154, treatment associated with 27% relative decrease in MACE

NNT = 58

However based upon JNC 8 these patients would have qualified for treatment anyway



HOPE-3 Investigators. Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease. N Engl J Med. 2016 May 26;374(21):2009-20.

ACP/AAFP BP Guideline 2017 | #5

Initiate Rx in adults > 60 with a SBP persistently > 150 to a target of < 150 to ↓ risk or mortality, CVA and cardiac events (Strong Recommendation | High Quality Evidence)

Initiate or intensify pharmacological treatment in adults > 60 with a history of CVA (or TIA) to a target of < 140 to reduce the risk of recurrent CVA (Weak Recommendation | Moderate Quality Evidence)

Initiate or intensify pharmacological treatment in adults > 60 at high CV risk to a target SBP or < 140 to reduce the risk of CVA or cardiac events (Weak Recommendation | Low Quality Evidence)

16 months after SPRINT

Pharmacological Treatment of Hypertension in Adults Aged 60 Years or Older to Higher Vascular Lower Blood Pressure Targets: A Clinical Practice Guideline From the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med. 2017 March 21;166:430.

ACC AHA | COR and LOE Paradigm

- Class (Strength) of Recommendation (COR) Table**
- Class I (Strong) (A) (High Quality Evidence)
 - Class IIa (Moderate) (B) (Moderate Quality Evidence)
 - Class IIb (Weak) (C) (Low Quality Evidence)
 - Class III (No recommendation) (D) (Unknown usefulness/Weak)
- Level (Quality) of Evidence (LOE) Table**
- Level A: High quality evidence from > 1 RCT
 - Level B: Moderate quality evidence from > 1 RCT
 - Level C: Low quality evidence from > 1 RCT
 - Level D: Very low quality evidence from > 1 RCT
 - Level E: Expert opinion or consensus
- Any COR can be paired with any LOE, including LOE C, D, and E, but only the COR is weak.

ACC/AHA BP Guideline 2017 | #6

This article has

- 193 pages
- 106 recommendations
- 23 tables

JNC 8 was 14 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). Articles published through August of 2015 were included. This guideline was heavily influenced by results of the SPRINT study.

Whelton PK, et al 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASHASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017 Nov 7; pii: S0735-1097(17)41819-1

ACC/AHA BP Guideline 2017 | #6

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

BP Category	SBP		DBP
Normal	< 120	and	< 80
Elevated	120-129	and	< 80
Hypertension			
Stage 1	130-139	or	80-89
Stage 2	> 140	or	> 90

Whelton PK, et al 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASHASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017 Nov 7; pii: S0735-1097(17)41819-1

ACC/AHA BP Guideline 2017 | #6

Hypertension is now defined as > 130 / > 80

Whelton PK, et al 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASHASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017 Nov 7; pii: S0735-1097(17)41819-1

ACC/AHA BP Guideline 2017 | #6

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)

Consistent with USPSTF (see links in chapter for other information)

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Whelton PK, et al 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASHASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017 Nov 7; pii: S0735-1097(17)41519-1

ACC/AHA BP Guideline 2017 | #6

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)***

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)***

*** ACC AHA recommends the use of the ACC/AHA Pooled Cohort Equations to estimate 10-year risk of atherosclerotic CVD (ASCVD) to establish the BP threshold for treatment

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Whelton PK, et al 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASHASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017 Nov 7; pii: S0735-1097(17)41519-1

ACC/AHA BP Guideline 2017 | #6

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)***
- **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)***

*** ACC AHA recommends the use of the ACC/AHA Pooled Cohort Equations to estimate 10-year risk of atherosclerotic CVD (ASCVD) to establish the BP threshold for treatment

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Whelton PK, et al 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASHASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017 Nov 7; pii: S0735-1097(17)41519-1

ACC/AHA BP Guideline 2017 | #6

Summary of BP Thresholds and Goals for Pharmacologic Treatment

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

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Whelton PK, et al 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASHASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017 Nov 7; pii: S0735-1097(17)41519-1

ACC/AHA BP Guideline 2017 | #6

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

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)

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Whelton PK, et al 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASHASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017 Nov 7; pii: S0735-1097(17)41519-1

ACC/AHA BP Guideline 2017 | #6

Special Circumstances

SIHD and BP $\geq 130/80$ | treat with beta-blockers, ACE or ARBs

- Do not use atenolol, preference of carvedilol, metoprolol etc

DM and HTN | use any 1st line drug

DM and HTN and Albuminuria | treat with ACE or ARB

African-American patients with HTN (+/- DM BUT NO HF or CKD) | Treat with thiazide or CCB

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Whelton PK, et al 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APHA/ASHASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017 Nov 7; pii: S0735-1097(17)41519-1

Abstract 7

13.7% more people newly classified as hypertensive with the new ACC AHA guidelines

In patients < 45, prevalence of HTN ↑ 2x in women and 3x in men

Recall the SPRINT trial only enrolled patients > 50 years old

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Muntner P et al. Potential U.S. Population Impact of the 2017 American College of Cardiology/American Heart Association High Blood Pressure Guideline. J Am Coll Cardiol. 2017 Nov 6 (PMID: 29146532)

Abstract 8

CV Risk Equation may help inform blood pressure lowering decisions

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Blood Pressure Lowering Treatment Trials' Collaboration, Sundstrom J, et al. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. Lancet. 2014 Aug 16;384(9943):591-8.

Abstracts 9-11 | Cochrane Reviews

8. In predominantly healthy adults with a mean age of 50 and hypertension (> 140 / > 90) antihypertensive drugs do not effect all-cause mortality or MI risk, but decreases CVA morbidity and mortality (NNT ~ 160)
9. In adults with CV disease mean age 50 and hypertension more aggressive BP lowering (< 135/85) has no effect on total or CV mortality after 3.7 years of follow up but a slight improvement in "total CV serious events" (RR= .87)
10. In older adults (mean age 75) BP target of < 140 / < 90 of uncertain benefit

All published ~ 2 years after SPRINT

Musini VM et al. Pharmacotherapy for hypertension in adults aged 18 to 59 years. Cochrane Database Syst Rev. 2017 Aug 16;8:CD008276.

Saiz LC, et al. Blood pressure targets for the treatment of people with hypertension and cardiovascular disease. Cochrane Database Syst Rev. 2017 Oct 11;10:CD010315.

Garrison SR et al. Blood pressure targets for hypertension in older adults. Cochrane Database Syst Rev. 2017 Aug 8;8:CD011575.

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ACC/AHA BP Guideline 2017



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AAFP Decides to Not Endorse AHA/ACC Hypertension Guideline

Academy Continues to Endorse JNC8 Guideline

December 12, 2017 9:44 pm CDTs Continued - The AAFP has decided to not endorse the recent hypertension guideline from the American Heart Association (AHA), the American College of Cardiology (ACC) and other health professional organizations.

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AAFP Late 2017

David O'Gurek, M.D. | Chair of the AAFP's Commission on Health of the Public and Science (CHPS) the guideline "did not meet the Academy's criteria for endorsement or affirmation of value."

Reasons for non-endorsement included:

- The bulk of the guideline was not based on a systematic evidence review
 - A systematic review was performed for 4 key questions, although the guideline provided over 100 recommendations
 - Assessments of the quality of individual studies or systematic reviews weren't provided
 - Specifically "...the guideline offered a strong recommendation (COR: I) for using the unvalidated atherosclerotic cardiovascular disease risk assessment tool previously developed by AHA and ACC, to determine whether medications should be initiated for BP control. However, this recommendation wasn't based on evidence that using the tool in this way improves outcomes."
 - The harms of treating patients to a lower BP were not assessed in the systematic review.

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AAFP News Accessed Online December 26th 2017
<https://www.aafp.org/news/health-of-the-public/20171212notendorseaha-accguideline.html>

AAFP Late 2017

David O'Gurek, M.D. | Chair of the AAFP's Commission on Health of the Public and Science (CHPS) the guideline "didn't meet the Academy's criteria for endorsement or affirmation of value."

Other reasons for non-endorsement included:

- Substantial weight was given to the SPRINT trial, while other trials were minimized
 - "The AAFP "... commission said conflict of interest is a major concern in judging the trustworthiness of guidelines and plays a key role in the AAFP's assessment of guidelines. In the case of the AHA/ACC guideline, the guideline panel commissioned the chair of the SPRINT trial steering committee to chair its work, when, notably, the SPRINT trial served as the foundation for the guideline panel's recommendations to change BP treatment targets."
 - Additionally "... several other AHA/ACC guideline panel members had intellectual conflicts of interest, which were not considered in the guideline's preparation."
- "The AAFP chose not to participate in this guideline development given significant concerns about the guideline methodology, including the management of intellectual conflicts of interest of guideline participants"

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AAFP News Accessed Online December 26th 2017
<https://www.aafp.org/news/health-of-the-public/20171212notendorseaha-accguideline.html>

ACP 2018

The ACP does not endorse the new AHA/ACC HTN guidelines

"... the (ACC/AHA) guideline falls short in weighing the potential benefits against potential harms, costs, and anticipated variation in individual patient preferences."

"We believe that initiation of pharmacologic therapy at or above a BP of 130/80 mm Hg and treatment to targets less than 130/80 mm Hg in a broad population of older adults are not supported by evidence and may result in low-value care for several reasons."

"SPRINT provides the footing for an intensive treatment target in higher-risk populations, but the lack of consistent benefit across trials underscores the uncertainty about the actual benefit of aggressive control and highlights the need for targeted application of the SPRINT findings"

"... there is no evidence from randomized controlled trials to support a DBP target less than 80 mm Hg."

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Will T et al, for the Clinical Guidelines Committee of the American College of Physicians. Hypertension Limbo: Balancing Benefits, Harms, and Patient Preferences Before We Lower the Bar on Blood Pressure. *Annals of Internal Medicine* 2018;168

European Society of Cardiology/HTN | 2018 Guidelines

Hypertension is defined as the level of blood pressure at which the benefits of treatment (either with lifestyle intervention or drugs) unequivocally outweigh the risks of treatment as documented by clinical trials

Hypertension is defined as office SBP values greater ≥ 140 mmHg and/or diastolic blood pressure values \geq to 90 mmHg

3 years after SPRINT | 98 pages

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2018 ESC/ESH guidelines for the management of arterial hypertension, European Heart J 2018;39:3021

HTN Guidelines | JNC VIII; ACC; ACP/AAFP; ESC

	JNC VIII	ACC/AHA	ACP/AAFP	European Society of Cardiology/ HTN
BP Category				
Optimal				$< 120 / < 80$
Normal		$< 120 / < 80$	$< 140 / < 90$	$120 - 129 / 80 - 84$
Elevated***		$120 - 129 / < 80$		$130 - 139 / 85 - 89^{**}$
Hypertension	$> 140 / > 90^{*}$		$> 140 / > 90^{*}$	
Stage 1		$> 130 / > 80$		$140 - 159 / 90 - 99$
Stage 2		$> 140 / > 90$		$160 - 179 / 100 - 109$
Stage 3				$\geq 180 / \geq 110$

* $> 150 / > 90$ for those ≥ 60

** Consider drug treatment if CV risk is very high (i.e. CVD – including asymptomatic disease on imaging, DM, Grade 3 HTN, CKD)

*** Called High Normal in ECS Guideline

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HTN Guidelines | JNC VIII; ACC; ACP/AAFP; ESC

	JNC VIII	ACC/AHA	ACP/AAFP	European Society of Cardiology/ HTN
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** Consider drug treatment if CV risk is very high (i.e. CVD – including asymptomatic disease on imaging, DM, Grade 3 HTN, CKD)

*** Called High Normal in ECS Guideline

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Bottom-line

- JNC 8 recommendations are still valid for the most part*
- SPRINT results suggest that treating ~ 100 patients with a 10 year CV risk of $\geq 20\%$ (and who do not have DM or a CVA) to a target BP of 120/80 for 3 years will prevent one MACE, but create 2 adverse events
- No evidence exists that blood pressure lowering in patients with a 10 year CV risk of $< 10\%$ will prevent a MACE

* Like everything in medicine – it doesn't matter what you do there is risk. If you do something there is risk, if you do nothing there is risk. Determining with the patient what type of risk best suits the patient and their circumstances is patient centered care.

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2017 Cochrane Reviews Abstracts 8 - 10

In healthy adults mean age of 50 treating a BP of $> 140 / > 90$ associated with small net benefit (0.7% absolute decrease in CVA mortality/morbidity) with no effect on all cause mortality or CHD

In adults mean age of 50 with a history of CV Dz (MI, angina, CVA or PAD), targeting a BP $< 135/85$ decreases total CV serious events by 13%, with no effect on total or CV mortality

In adults mean age of 74 treating to a lower BP ($< 140 / < 90$) is not associated with differences in all-cause mortality, CVA or total serious CV events compared to a BP of 150 – 160/90

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Introduction to a unique style of CME

John Hickner, MD, MSc
Professor Emeritus, Michigan
State University

Welcome!

Not your usual CME...

- Few PowerPoint slides
- 30 minute talks
- Truly evidence-based
- Targeted to experienced primary care physicians
- Speakers are not industry supported

Each talk is based largely on:

- POEMs from the past 2-3 years
- Cochrane systematic reviews
- PubMed searches by faculty
- Evidence-based guidelines



The challenge of evidence-based practice: how can we find the most useful information without getting swamped?

Outcomes matter... what do your patients REALLY care about?

Basic science theory and pathophysiology

Surrogate markers in animals

Surrogate markers in humans (e.g. LDL, blood sugar)

Disease-specific clinical outcomes (e.g. CV mortality)

All-cause mortality, morbidity, and quality of life

Disease-Oriented Evidence

Patient-Oriented Evidence

Comparing POEMs and DOEs (disease oriented evidence)

Example	DOE	POEM	Comment
Avandia™	Lowers blood sugar	↑ CV mortality, CHF	POEM ≠ DOE
Metformin	Lowers blood sugar	↓ all-cause mortality	POEM = DOE
Tight blood sugar control for Type 2 DM	Lower is always better!	No change and possibly even increased mortality	POEM ≠ DOE
Diuretics for BP	Diuretic ↓ BP	Diuretic ↓ mortality	POEM = DOE
Arthroscopic surgery for OA of knee	Cleaning joint debris is good	No change in symptoms/ function	POEM ≠ DOE
Antiarrhythmics	Encanide ↓ PVCs on ECG	Encanide ↑ mortality	POEM ≠ DOE

What is the most useful medical information?



$$\text{Usefulness} = \frac{\text{Relevance} \times \text{Validity}}{\text{Work}}$$

- **Whether** to read an article, not just **how** to read an article as with original EBM teaching.
- "Usefulness" is the central concept in "Information Mastery" approach of Dave Slawson (UVA) and Allen Shaughnessy (Tufts), proposed in 1994.

Information Mastery



$$\text{Usefulness} = \frac{\text{Relevance} \times \text{Validity}}{\text{Work}}$$

- Common or important problem in your practice
- Relevant population was studied
- Patient-oriented outcomes reported (how well or long patients live)

Information Mastery



$$\text{Usefulness} = \frac{\text{Relevance} \times \text{Validity}}{\text{Work}}$$

- Was study was designed to minimize bias?
- Unintentional and intentional?
- Most physicians need an expert in critical appraisal to evaluate studies

Information Mastery



$$\text{Usefulness} = \frac{\text{Relevance} \times \text{Validity}}{\text{Work}}$$

- Concise summaries emailed to you (POEMs)
- Algorithms, tables, figures, interactive tools
- Concise bullets, not lengthy text
- Point of care access

POEMs: Patient Oriented Evidence that Matters



- **Relevant**
 - Reports improved patient-oriented outcomes
- **Valid**
 - Study designed to avoid intentional and unintentional bias
- **It Matters**
 - Would change your practice

POEMs tell you about new information that has potential to improve how long or well your patients live

POEMs as a practical filter to keep current



- Each year
 - 600,000 articles added to PubMed
 - 20,000 articles per year in top 100 English language clinical journals
 - **Only 250 meet the criteria for POEMs**

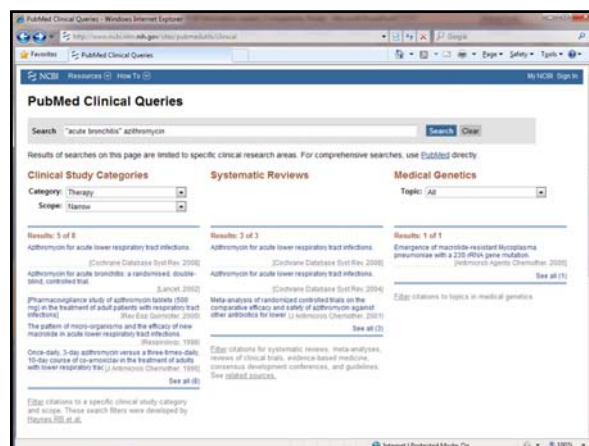
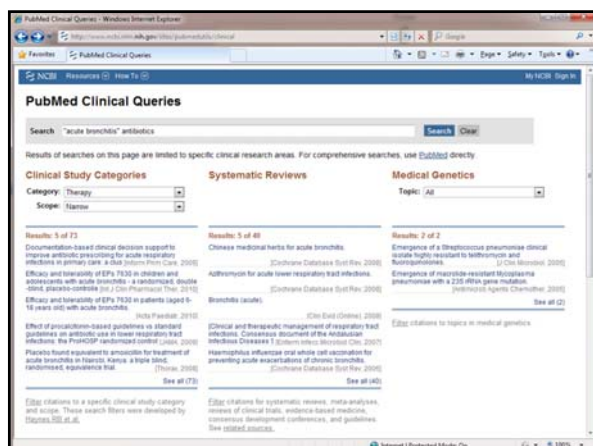
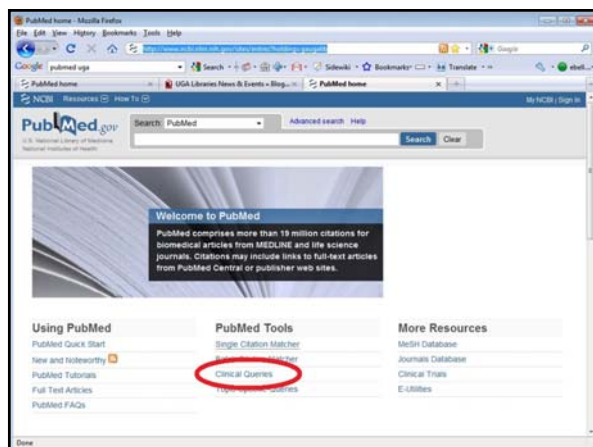
Only 1.2% of articles in top journals, and only 0.04% of articles indexed in PubMed each year

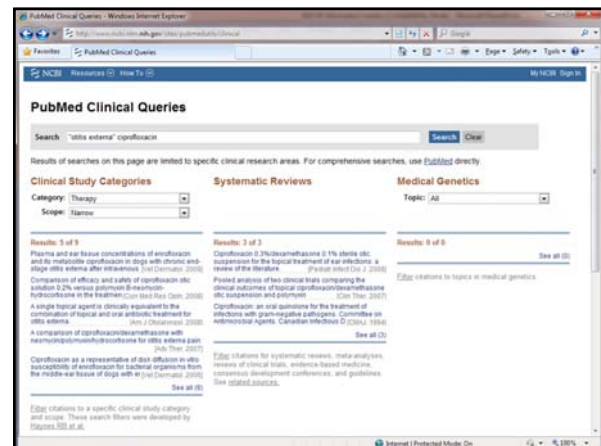
Some hints for answering questions

1. Use secondary sources first: let someone else do the searching and filtering and evidence assessment
2. Get smart about searching PubMed
3. Load up your smartphone with apps

Examples of Secondary Sources

- Essential Evidence
 - Daily InfoPOEMs via email
 - Online reference with evidence-based topic summaries, interactive decision support, Cochrane abstracts, guidelines, diagnostic test data
 - Demo: www.essentialevidence.com
 - Disclosure: I helped develop it, am editor-in-chief
- Other evidence-based secondary sources
 - National Guidelines Clearinghouse, Clinical Evidence, DynaMed, ACP PIER, UpToDate





Primary literature: Key points for PubMed searches

- Learn to use PubMed's "Clinical Queries" feature
- When you find a useful article, select "Related articles"
- Learn how to narrow searches using quotation marks
- Use the AND operator to further narrow your search
- Use "NOT" to exclude non-relevant articles

Let's Get Started!

Some Important concepts for interpreting "how much" or "how accurate"

- Number needed to treat NNT
- Number needed to harm NNH
- Number need to screen
- Odds ratio (can be misleading)
- Relative risk (ratio), relative risk reduction
- Absolute risk, absolute risk reduction
- Sensitivity, specificity, positive and negative predictive value

Lipids

Gary Ferenchick, MD MS

USPSTF | Statin Use for Adults

Abstract 1

- ▶ Low to moderate dose statin if aged 40–75 (B)
 - Adults 40–75 AND no CVD AND ≥ 1 CV risk factors AND calculated 10-year CV risk of $\geq 10\%$
- ▶ Low to moderate dose statin if aged 40–75 (C)
 - Adults 40–75 AND no CVD AND ≥ 1 CV risk factors AND calculated 10-year CV risk of **7.5–10%**
- ▶ Adults > 75 with no history of MI or CVA (I)

"Although myalgia is a commonly reported adverse effect of statin use, controlled trial data do not support any increased risk of myalgia with the use of statins compared with placebo" | More later

Table for what are "Low to Moderate Dose Statins" on page 2 of this chapter

Lipid Treatment in Elderly

Abstract 2 | Post hoc analysis of RCT

- ▶ In patients > 65 without baseline CV disease, starting pravastatin 40 mg daily for 6 years is not associated with improved outcomes

Patients over the age of 75 the hazard ratio for all cause mortality of pravastatin versus usual care was 1.34 ($P = .07$)

USPSTF | Lipid Screening for Kids

Abstract 3

- ▶ Evidence insufficient to assess the benefit–risk balance of screening for lipid disorders in persons < 20.

Inadequate evidence that pharmacotherapy or lifestyle changes substantially reduce lipids, atherosclerosis markers or premature CVD. Unclear if changes in lipid disorders or atherosclerosis parameters in those < 20 correlate with improved CV outcomes in adults

Statin Use Guidelines Differ

Abstract 4

- ▶ Guidelines for eligibility for statin use for primary prevention differ by as much as 3x; more "liberal" guidelines should *theoretically* prevent more ASCVD events

Non-fasting Lipids

Abstract 5

- ▶ Differences between fasting and non-fasting lipid profiles (1–6 hours after eating usual meals) are negligible, and are comparable in CV risk prediction

Maximum mean changes at 1 – 6 hours post usual meal

Triglycerides	26 mg/dL
Total cholesterol	8 mg/dL
Non-HDL cholesterol	8 mg/dL
LDL cholesterol	8 mg/dL
HDL	0 mg/dL

Consider fasting TG if > 440 mg/dL

Statin Associated Muscle Symptoms (SAMS)

Abstract 6

- ▶ Several strategies exist for SAMS based upon an expert working group
 - Withdrawal following by re-challenge after 4 weeks of "washout"
 - Use intermittent dosing
 - Use hydrophilic statins (pravastatin or fluvastatin, pitavastatin)
 - Consider vitamin D in Vitamin D deficient SAMS patients

ACC | [Statin Intolerance Tool](#)

Anti-inflammatory Therapy

Abstract 7

- ▶ A monoclonal antibody canakinumab decreases a 3-point MACE in high risk patients compared to placebo at 3.7 years, but was associated with higher rates of fatal infections

FDA axes bid to add CVD indication for canakinumab
October 22, 2018 | [Dariusz Adar's Healthcare Economics & Policy](#)

Raising HDL

Abstract 8

- ▶ Anacetrapib (which raises HDL ~ 2x | e.g. 40 mg/dL to 80 mg/dL) is associated with minimally improved CV outcomes

"The saga of this drug class is a cautionary tale; once thought of as the path toward extinguishing heart disease because of its remarkable effect on lipids, the story ends with a whimper and lessons about the need to validate surrogate outcomes." | Dr. Harlan Krumholz,

Merck not seeking approval for anacetrapib

PCSK9 Inhibitors

Abstract 9 – 10

9. PCSK9 inhibitors ↓ LDL by 39%, ↓ CV events by 55% and ↑ ADE by 18% compared to statins & ezetimibe with *no effect on all-cause mortality*
10. Evolocumab (Repatha®) plus a statin decreased risk of CV events (NNT=66) in high risk patients compared to placebo plus statin after 2.2 years

PCSK9 Inhibitors

Abstract 11

11. Evolocumab costs \$14,300/year and provides an additional QALY for \$337,000.

HEALTH NEWS | OCTOBER 24, 2018 / 4:10 PM / UPDATED 18 HOURS AGO

Amgen cuts price of cholesterol drug Repatha by 60 percent

Annual cost now \$5,850

Ezetimibe plus Statin

Abstract 12

- ▶ In patients with ACS, ezetimibe plus simvastatin was associated with improved CV outcomes after 6 years (NNT = 50) compared to simvastatin alone. *No effect on all-cause mortality*

Non-Statin Therapies for LDL-C Lowering

Abstract 13

ACC/AHAs Evidence Based Statin-Benefit Groups

1. Patients ≥ 21 years with stable clinical ASCVD:
 - a) Without comorbidities
 - b) With comorbidities (see end of chapter Appendix ***)
 - c) With baseline LDL-C > 190 mg/dL not due to secondary causes
2. Patients with LDL-C > 190 mg/dL, not due to secondary causes;
3. Patients aged 40 to 75 years with diabetes mellitus and LDL-C 70 – 189 mg/dL
4. Patients aged 40 to 75 years with no diabetes, but with LDL-C 70 to 189 mg/dL and predicted 10-year ASCVD risk $> 7.5\%$.

Non-Statin Therapies for LDL-C Lowering

Abstract 13

► Indicators of Efficacy

- **50% LDL-C reduction** from baseline for *high-intensity* statin doses
- **30% to 50% LDL-C reduction** from baseline for *moderate-intensity* statin doses
- ACC gives tacit endorsement of an LDL < 70 mg/dL for a high-intensity statin target or 100mg/dL for a moderate-intensity statin target for those without a baseline LDL.

• Note the strategy of "treating to target" (and these levels specifically) were not endorsed in the 2013 guideline.

Non-Statin Therapies for LDL-C Lowering

Abstract 13

1. Patient not at target AND
 - i. They are adherent
 - ii. On high-intensity statin
 - iii. Engaged in lifestyle modification (including phytosterol use)

Consider ezetimibe first and PCSK9i second for groups 1 and 2

Consider ezetimibe or bile acid sequestrants for groups 3 and 4 (no recommendation for PCSK9i in these groups)

Triglycerides

Abstract 14 | RCT

- Among patients with ASCVD or DM (and other risk factors) and already on statins, 2 grams icosapent ethyl twice daily decreased event rates (17.2% vs 22%) after 4 years

Bottom-Lines

- In patients > 65 primary prevention with pravastatin 40 mg daily for 6 years is not associated with improved outcomes
- Guidelines for statin eligibility for primary prevention differ by as much as 3x; more "liberal" guidelines theoretically prevent more ASCVD events
- The differences between fasting and non fasting lipid profiles are negligible
- Several strategies exist for statin associated muscle symptoms (SAMS)

Bottom-Lines

- Monoclonal anti-inflammatory therapies are being developed for ASCVD | Unclear efficacy
- Raising HDL with the monoclonal antibody anacetrapib is not associated with improved CV outcomes | Marketing Halted
- PCSK9i decrease CV events when added to statins in HR patients, have no effect on all-cause mortality and are expensive (ish)
- Adding ezetimibe to statin is associated with one few MACE per 50 HR patients treated for 6 years
- Icosapent ethyl use associated with lower event rates in patients with ASCVD or DM already on statins