Top 10 Updates in Primary Care

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Disclosure

I have no financial interests or relationships to disclose.

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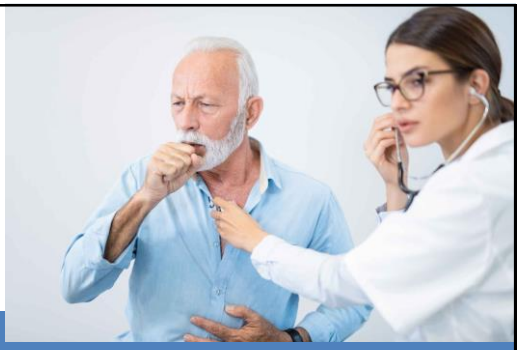
Learning Objectives

1. Consider using the Blood eosinophil count (BET) to guide choice to use oral steroids in the treatment of COPD exacerbation
2. When medically and financially possible, choose tirzepatide for treating T2DM and obesity.
3. In treating diabetic peripheral neuropathic pain, consider amitriptyline, duloxetine, or pregabalin and first and second line therapy.

How I Choose my Top 10

- I review the Journal Watch "Guideline Watch" for each year.
  - Published in January – lists highlights from the previous year
- I review the "Top 20 Research Studies" article published in the American Family Physician each year
- I subscribe to the daily Journal Watch emails and then select those studies that I deem most meaningful for family medicine
- I read on latest technologies that may impact our family medicine practice over the next 2-3 years.



Question #1:
Do Steroids Help All Patients with COPD Exacerbations or Only Those with Eosinophilia?

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Steroids for all COPD Exacerbations?

- GOLD guidelines recommend prednisone 40 mg daily x 5 days, + oral Abx for excessive cough and purulent sputum. (Standard of care)
- Trial design, 308 patients enrolled, 93 had 1 or more exacerbations
  - Group #1: **Blood eosinophil-directed treatment (BET) > 2%** or placebo
  - Group #2: 14 days of oral steroids for all patients
- BET group → 66% received steroids vs 100% of standard arm
- BET nonsignificantly fewer treatment failures 19% and 32%, respectively
  - Failure defined as re-treatment, hospital admission, or death at 30 days.
  - No differences were noted in symptom scores, lung function, or adverse effects (e.g., glycosuria, hospital admission).

1. Ramakrishnan S et al. Blood eosinophil-guided oral prednisolone for COPD exacerbations in primary care in the UK (STARR2): A non-inferiority, multicentre, double-blind, placebo-controlled, randomised controlled trial. *Lancet Respir Med* 2024 Jan; 12:67.
2. Comellas AP and Fortis S. Blood eosinophil-guided therapy for COPD exacerbations. *Lancet Respir Med* 2024 Jan; 12:9.

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Take Away #1: Consider Using the Blood Eosinophil Count (BET) to Guide Choice to Use Oral Steroids

Benefits to Primary Care Health Care Providers:

1. No worsening in outcomes with one less medication to take
2. Less side effects from oral steroids

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Question #2: Does Invasive Monitoring Benefit Patients with Heart Failure (HFrEF)?

Historical question – how many in the room have placed a Swan-Ganz catheter?

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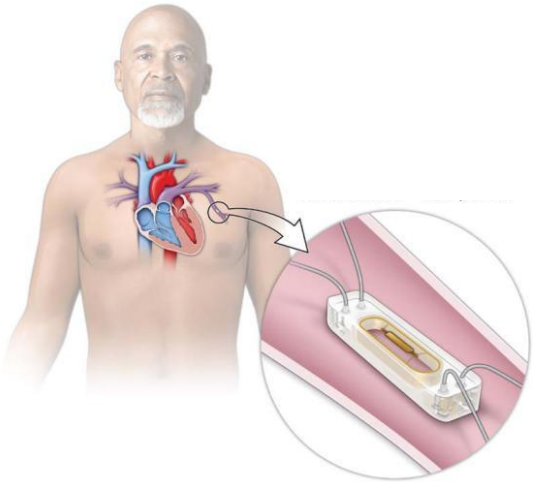
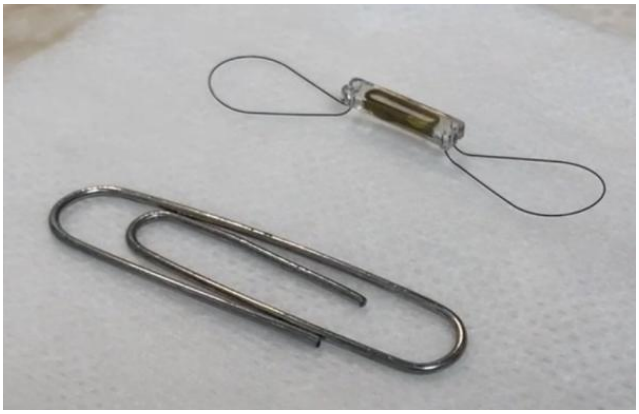
HFrEF and Invasive Monitoring with Pulmonary Artery Pressure Device





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Implantable Hemodynamic Monitors for Heart Failure with Reduced Ejection Fraction

- Meta-analysis including 1350 patients with HFrEF
  - Mean EF = 25%; 25% Black; 25% female; > 50% with NYHA class III symptoms
- Patients randomized to implantable hemodynamic monitoring or GDMT
- Median follow up 12 months
- Patients with implantable hemodynamic monitoring:
  - Decreased all-cause mortality, HR 0.75 (95% CI: 0.57-0.99); *P* = 0.043.
  - Decreased HF hospitalization, HR 0.64 (95% CI: 0.55-0.76); *P* < 0.0001.

Lindenfeld J et al. Implantable hemodynamic monitors improve survival in patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol* 2024 Feb 13; 83:682.

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Take Home #2: Implantable Hemodynamic Monitoring Is of Benefit for HFrEF

Benefits to Primary Care Health Care Providers:

1. As this device becomes more readily available, anticipate patients having questions and being able to recommend this in the hands of an experienced operator.

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Question 3: Which GLP-1 Is the Best for Weight Loss in Diabetic Patients?

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GLP-1's in the Drinking Water…

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GLP-1's, Diabetes, and Weight Loss

- GLP-1's:
  - Semaglutide
  - Tirzepatide (GLP-1 and GIP agonists)
  - Liraglutide
  - Dulaglutide
  - Exenatide
  - Others

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Most Efficacious GLP-1

- Meta-analysis of 76 randomized trials of GLP-1 receptor agonists compared with placebo or each other; 39,000 adults with type 2 diabetes, followed for ≥12 weeks, were included.
- **Tirzepatide**: Combined GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist

  −2.1% in glycosylated hemoglobin (HbA_{1c}), −56 mg/dL in fasting blood glucose

  −8.5 kg in body weight compared with placebo.
- **Semaglutide**: Straight GLP-1 agonist

  −1.4% in HbA_{1c}, −36 mg/dL in fasting blood glucose

  −3.1 kg in body weight.
- Most available agents had similar adverse effect profiles, with gastrointestinal effects predominating.

Yao H et al. Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: Systematic review and network meta-analysis. *BMJ* 2024 Jan 29; 384:e076410.

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Take Home #3: Tirzepatide Is the Most Efficacious GLP-1

(William Bryon
2024 Daytona 500 Champion)

Benefits to Primary Care Health Care Providers:

1. Effective diabetic and weight loss medication
2. Once weekly … nice and convenient for many patients
3. Still a challenge due to cost and some patients declining injections
4. GLP-1's may have CV benefits

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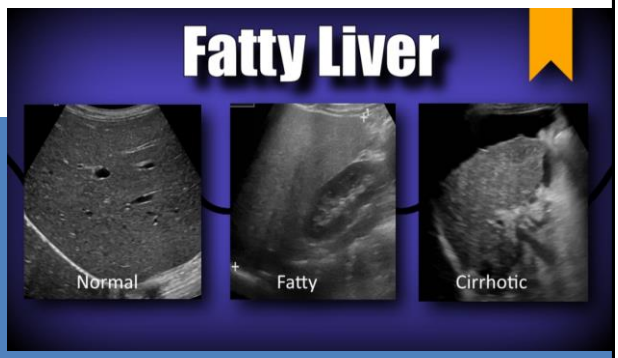
Question #4: What Treatments Are Readily Available for NAFLD/NASH in Diabetic Patients?



What can I do as a Primary Care Health Care Provider, especially if GI/hepatology is not readily available?

I see this condition weekly, sometimes daily.

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Words Are Important "LFTs" versus "Liver Enzymes"

Liver function tests: total protein, albumin, prealbumin, total bilirubin, prothrombin time

Liver enzymes: AST, ALT, GGT

Having a bump in your LFTs, your true LFTs, suggests liver dysfunction

Having a mild elevation in the AST or ALT is common and often self-healing

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New Term Is MASLD and MASH
NAFLD = Nonalcoholic Fatty Liver DZ
MASLD = Metabolic Dysfunction Associated Steatotic Liver Disease

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NAFLD Treatments in Diabetic Patients

- Korean study of 80,000 pts followed on average for 4 years.
- 4000 experienced regression of NAFLD. (1 in 20 or 5%)
- All patients were treated with metformin and a combination of one of these three medications:
  - SGLT-2, thiazolidinedione (TZD), or DPP-4
- The hazard ratios compared with sulfonylureas were:
  - SGLT-2 = 1.99 (99%)
  - TZD = 1.70 (70%)
  - DPP-4 = 1.45 (45%)
- GLP-1s not included in study

Jang H et al. Outcomes of various classes of oral antidiabetic drugs on nonalcoholic fatty liver disease. *JAMA Intern Med* 2024 Feb 12; [e-pub]

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Take Home #4: SGLT-2's, TZD's, and DPP-4's Improve NAFLD/MASLD

Benefits to Primary Care Health Care Providers:

1. We can treat this in primary care, both with weight loss and medications
2. Consider using the FIB-4 calculator to guide need of ultrasound elastography to assess for cirrhosis
3. NAFLD is now renamed metabolic-dysfunction associated fatty liver disease, MAFLD or MASH.
4. Consider bedside ultrasound to assess for fatty liver

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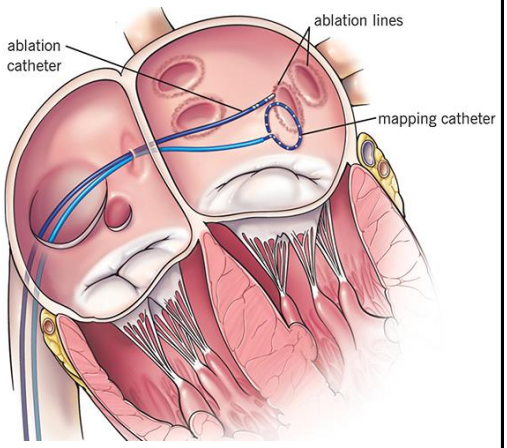
Question #5: Who Should Continue Anticoagulation Postablation in A Fib?



PCPs don't perform cardiac ablations for atrial fibrillation but we are asked frequently about this from our patients.

Answer in evolution over the past 5-10 years

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Standard of Care: Three Months Anticoagulation (AC) Post Ablation

- Observational study from Japan, 230,000 patients
- Thromboembolic and hemorrhagic outcomes from insurance claims
- The CHADS2 score is used in Japan as the CHADS2-VASC has not shown additional benefit there.

	Risk of thrombus	Risk of hemorrhage
CHADS2 ≤ 1	0.39/100 person-yrs	HR = 1.5 vs no AC (Significant)
CHADS2 ≥ 3	1.27/100 person-yrs, HR 0.6 vs no AC	HR = 1.1 vs no AC (NS)

Kanaoka K et al. Oral anticoagulation after atrial fibrillation catheter ablation: Benefits and risks. *Eur Heart J* 2023 Dec 20; [e-pub].

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Take Home #5: Continue Anticoagulation After Three Months Post Ablation Only in High-risk Patients

Benefits for Primary Care Health Care Providers:

1. We are asked about this routinely…Why did I get an ablation if I have to keep taking the same AC medicine?
2. Work with cardiology.
3. Consider deprescribing AC in patients with low risk by CHADS2/CHADS2-VASC (≤1)

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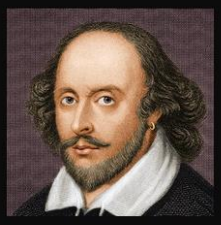

To hold, or not to hold, that is the question.

~ William Shakespeare

Question #6: Should We Continue ACEI/ARBs Around the Time of an Operation?

We prescribe these medications every day.
We perform perioperative risk assessments for our patients.
How should we best care for our patients with CV disease and perioperative risk?

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ACEI/ARBs Perioperative – To Hold or Continue, That Is the Question

- POISE-3 trial: 110 hospitals, 22 countries, ~7500 patients
- Randomized to hypotension-averse or hypertension-averse groups
- Hypotension-averse:
  - ACEI/ARB held day before surgery until POD #3
  - Intra-op MAP 80 mmHg or higher
  - BP meds restarted when BP SYS > 130
- Hypertension-averse
  - ACEI/ARB given on day of surgery
  - Intra-op MAP 60 mmHg or higher

Marcucci M et al. Hypotension-avoidance versus hypertension-avoidance strategies in noncardiac surgery: An international randomized controlled trial. *Ann Intern Med* 2023 Apr 25; 176:605.

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ACEI/ARBs Perioperative – To Hold or Continue, That Is the Question

- Intraoperative hypotension:
  - Hypotension-averse 23% vs hypertension-averse 28%
- No difference in 30-day composite outcome (14% in each group):
  - Vascular death, Nonfatal MI, Stroke, Cardiac arrest
- Recommendations:
  - Consider holding ACEI/ARB when anticipating volume shifts
  - Consider continuing ACEI/ARB with high CV risk patient (HF, ASCVD)

Marcucci M et al. Hypotension-avoidance versus hypertension-avoidance strategies in noncardiac surgery: An international randomized controlled trial. *Ann Intern Med* 2023 Apr 25; 176:605.

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Take Home #6: For Noncardiac Surgeries in Low Risk Patients, Continuing ACEI/ARB Is an Option

Benefits for Primary Care Health Care Providers:

1. We often complete pre-operative risk assessments (not “clearance”).
2. We can confidently continue ACEI/ARBs for noncardiac surgeries.

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Question #7: Are There Bone Health Benefits for Vitamin D Supplementation for Primary Prevention?

This question has been around for 2-3 decades.
Perhaps we have a good answer now…

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Vitamin D for Primary Prevention of Fracture…in Patients with Low Vitamin D

- U.S. Preventive Services Task Force (USPSTF) found insufficient evidence to recommend screening in asymptomatic individuals.
- A trial randomized 25,871 men 50 years or older and women 55 years or older
- Receive 2,000 IU of vitamin D or placebo daily for a median of five years.
- No difference between groups **in any type of fracture**, ***even in patients with low baseline vitamin D levels*** (hazard ratio = 1.04; 95% CI, 0.80 to 1.36) or a previous fracture.
- Wait, what? Let's read that again.

LeBoff MS, Chou SH, Ratliff KA, et al. Supplemental vitamin D and incident fractures in midlife and older adults. *N Engl J Med.* 2022;387(4):299-309

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Take Home #7: No Benefit to Screen for Vitamin D Deficiency for Primary Prevention

Benefit to Primary Care Health Care Providers:

1. I do not screen for vitamin D levels in general. One less thing to do, especially when the level comes back low and now you have to spend time convincing the patient/family that nothing is wrong, even though the lab is in RED!!! on the portal
2. PCP vs the Media/Pop culture.
3. By itself, supplementing with vitamin D is not beneficial…nor harmful. If patients want to take a supplement, perhaps encourage them as it is a health investment…***their*** health investment

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Question #8: What Is the Best Medication to Treat Diabetic Neuropathy (DN)?

"Don't get diabetes, right?!!" **Primary prevention and primary care are still primary.**

A story: DN is not always subtle

Several choices, let's see what the evidence shows…

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Treatments for Diabetic Neuropathy

- OPTION-DM trial in the UK of 130 randomized patients with diabetic peripheral neuropathic pain (DPNP). 16 week trial.
- Monotherapies (titrated max dose):
  - **Amitriptyline (75 mg), duloxetine(120 mg), pregabalin (600 mg)**
- Monotherapy given for 6 weeks then supplemented if pain reduction goal not met:
  - Amitriptyline→Pregabalin; Pregabalin→Amitriptyline; Duloxetine→Pregabalin
- Outcome – the numerical rating scale for pain (0-10) decreased from 6.6 at baseline to 3.3 in all three pathways.
- Patients on combination therapy had greater NRS reduction (1.0 vs 0.2)

Tesfaye S, Sloan G, Petrie J, et al. Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM): a multicentre, double-blind, randomised crossover trial [published correction appears in *Lancet*. 2022; 400(10355): 810]. *Lancet*. 2022;400(10353):680-690

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Take Away #8: There Are Three Equally Efficacious Options to Treat DN: Amitriptyline, Duloxetine, Pregabalin

Benefits to Primary Care Health Care Providers:

1. This study showed a 50% decrease in pain → that's great!
2. I will choose based on side effect profiles and cost

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Question #9: What Is the Best Treatment for Mild-moderate Acne Vulgaris?

We see this weekly, if not daily depending on our patient population

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Best Treatment for Mild-Moderate Acne

- The authors of this study defined "best" as patient perception of:
  - Effectiveness
  - Proportion of patients who reported at least moderate improvement
  - Tolerability
  - Proportion who withdrew/stopped medication due to adverse events
- Best options:
  - Adapalene/benzoyl peroxide
  - Clindamycin/benzoyl peroxide
  - Adapalene alone

Stuart B, Maund E, Wilcox C, et al. Topical preparations for the treatment of mild-to-moderate acne vulgaris: systematic review and network meta-analysis. *Br J Dermatol.* 2021;185(3):512-525.

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Take home #9:
OTC Adapalene/Benzoyl Peroxide Is an Excellent Choice for Mild-Moderate Acne.

Benefits for Primary Care Health Care Providers:

1. Excellent OTC and online options
2. Adapalene is less irritating than tretinoin

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Question #10:
In Patients with Acute Severe Depression or Depression Not Responding to Monotherapy, What Is the Next Best Step?

This is a common condition Primary Care Health Care Providers encounter in clinic.

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Best Treatment for Depression in Nonresponders

- Meta-analysis of 39 RCTs with 6751 patients
- Combination treatment statistically significantly better than monotherapy
  - Reuptake inhibitors (SSRI, SNRI, and TCA) + presynaptic α2 inhibitor (mirtazapine or trazodone)
- Bupropion combinations were not superior to monotherapy
- Number of dropouts and dropouts due to side effects did not differ between treatments
- Did not compare augmentation therapy with 2nd Gen antipsychotic

Henssler J, Alexander D, Schwarzer G, et al. Combining antidepressants vs antidepressant monotherapy for treatment of patients with acute depression: a systematic review and meta-analysis. *JAMA Psychiatry.* 2022;79(4):300-312.

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Take Home #10: Consider Mirtazapine or Trazodone for Combination Therapy for Treatment Resistant Depression

Benefits for Primary Care Health Care Providers:

1. Many physicians use 2nd generation atypical antipsychotics for augmentation.
2. This meta-analysis provides other options with mirtazapine or trazodone, which may better align with physician experience/comfort level.
3. Further benefits: mirtazapine → appetite stimulation
   trazodone → improved sleep initiation

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Best Practice

1. Steroids only in COPD exacerbations and elevated eosinophil counts
2. HFrEF and PA pressure monitoring shows benefit
3. GLP-1s: all are expensive at present
   - Consider tirzepatide and semaglutide for weight loss in T2DM
4. In treating NAFLD(MAFLD) consider use of SGLT-2 and TZDs
5. Continue A Fib anticoagulation post ablation in only the highest risk pts

Best Practice

6. Continue ACEI/ARBS perioperatively in all low-moderate risk patients
7. Vitamin D screening and asymptomatic treatment … perhaps Vit D is done? (Vitamin D still indicated in patients with osteoporosis)
8. For painful diabetic neuropathy, combination treatment with any of the two (amitriptyline, duloxetine, or pregabalin) is better than monotherapy.
9. For mild-moderate acne, initially consider adapalene in combination with either benzoyl peroxide or clindamycin as first line therapy
10. For acute severe depression resistant to monotherapy, consider SSRI/ SNRI/TCA in combination with mirtazapine or trazodone