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Forum for Evidence-Based Medicine

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Activity description	Practicing evidence-based medicine (EBM) is important in today's health care environment because this model of care offers clinicians a way to enrich quality, provide patient satisfaction, reduce costs and improve outcomes. A common implementation of EBM involves the use of clinical practice algorithms during medical decision-making to encourage optimal care. This widely recognized practice is designed to address the persistent problem of clinical practice variation with the help of actionable information at the point of care. These e-newsletters will enable health care professionals (HCPs) to put new EBM into practice.
Target audience	This activity is designed to meet the educational needs of physicians, PAs, nurses, nurse practitioners and other HCPs who have an interest in EBM.
Learning objectives	• Examine the management of low value care in cardiology. • Review pharmacological evidence for sacubitril/valsartan vs. valsartan in HF, urate-lowering medications allopurinol/febuxostat, and promising treatment of non-alcoholic fatty liver disease. • Discuss studies regarding pain relief in individuals with chronic back pain, breast cancer screenings, sinus polyps and evidence to help risk-stratify those with high LDL.

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Low value care in cardiology

Contemporary cardiology care offers a wide breadth of diagnostic testing and therapeutic intervention. Although this has significantly improved the care of our patients, it has also resulted in a large burden of wasted and harmful care. The American Heart Association recently published in Circulation a position paper aimed at reducing low value care (LVC) in cardiology practices.[1] There are a paucity of data studying low value care (LVC) metrics at the level of the individual cardiologist. To that end, the editors of Circulation are to be applauded for beginning to highlight this issue. Several published studies and this position paper on LVC in cardiology provided the material for this review.

Diagnostic tests in cardiology are prone to overuse because they are broadly available, potentially lucrative and generally low risk. Patients may be accepting of testing because of low out-of-pocket costs and the false belief in many cases that normal tests assure a good long-term prognosis. A major problem that can arise when patients at low risk are subject to testing is that as the prevalence of disease in the population decreases, the rate of false positive test results increases. This can then lead to a diagnostic cascade and invasive interventions which may not be indicated. Conservative estimates from a meta-analyses of noninvasive testing indicate that up to 20% of echocardiograms and up to 50% of all stress tests performed in the United States are rated as "rarely appropriate."[2]

Coronary artery disease - With respect to CAD, this cascade drives a high utilization of cardiac catheterization and percutaneous coronary interventions (PCI). As has been discussed with respect to the new Optimal Care "clean cath" metric, nearly 70% of patients referred for invasive coronary angiography are found to have nonobstructive disease.[3] The CONSERVE study randomized over 16,000 patients with suspected CAD to coronary artery computed tomographic angiography (CCTA) with fractional flow reserve (FFR) when indicated, compared to usual care including ischemia testing and showed a 78% reduction in unnecessary catheterizations and a 48% reduction in unnecessary PCI.[4] A more recent study compared initial CCTA with initial cardiac catheterization in 3,561 patients with suspected stable CAD and showed a 30% reduction in major adverse cardiac events (MACE) with the CCTA strategy, and an almost four-fold increase in procedural complication rate in the catheterization group.[5]

Echocardiogram - Two studies have focused on the overuse of echocardiograms and associated this with measures of care quality. The first looked at 35 cardiologists treating 4,000 patients with CAD.[6] The cardiologists were broken into three groups based on frequency of echocardiogram ordering. The patients of the cardiologists in the highest ordering group, compared with the lowest ordering group, had a significantly lower odds of receiving labs to look at cholesterol and HbA1c, and lower rates of beta blocker and aldosterone receptor antagonist use. Those patients seen by the highest echo ordering group also had a higher all-cause mortality at one year (OR 1.54). The second study focused on 1,667 patients being managed for CHF and looked at the same 35 cardiologists, again dividing them into three groups based on frequency of echocardiogram use.[7] In this study, the cardiologists with the highest ordering frequency had the lowest rate of outpatient visits (OR 0.61), and had the lowest odds of receiving guideline-directed medical therapy (OR 0.62).

Atrial fibrillation (AF) screening - Another important area of potential overuse is screening for occult AF. The rationale for a potential screening benefit is that treatment of screen detected AF with DOAC therapy might reduce the incidence of AF related embolic stroke. However, it is likely that <20% of strokes are related to AF. The USPSTF in 2022 published a statement that the current evidence is insufficient to recommend screening for AF.[8] A recent editorial in JAMA IM also reviewed the new data around screening.[9] Adding to the studies reviewed by the USPSTF, the authors reviewed an important new study, the LOOP trial, which has also been reviewed in a prior edition of this Forum. In the LOOP trial, 6,000 older individuals were randomized to an implantable cardiac loop recorder (ILR) compared to standard of care, and followed for over five years.[10] Oral anticoagulation was encouraged if > 6 minutes of AF was detected. Screen detected AF was found in 32% of the ILR group and 12% of the control group, resulting in a nearly 3-fold higher rate of anticoagulation in the ILR group. The ILR group had a nonsignificant 1.1% decrease in stroke or systemic embolism and a non-significant 0.8% increase in the rate of major hemorrhage. The cost of an ILR is approximately $20,000 yearly with a monthly monitoring bill that is partially borne by the patient. The cost therefore to achieve this negative trial result would be approximately $120 million. In conclusion, the authors stated "recent data support the finding that AF screening among asymptomatic individuals has no net benefit on outcomes. Moreover, nonbeneficial interventions that add cost are not helpful for patients and create a net harm to

society." As patient home monitoring devices such as the Apple Watch® increase in use, we will be faced with more frequent diagnoses of screen detected AF, as well as increased medical utilization as a result of the frequent false positive results seen with these devices.

AF ablation – Data on the cost effectiveness of AF ablation are limited. ICER conducted a comprehensive review in 2010, before DOAC therapy was widely in use.[11] Based on the age and CHA_2DS_2-VASc score of the patient, the quality adjusted life year (QALY) varied between $38k in a 60 yo with paroxysmal AF up to $97k in a 75 yo with persistent AF. It could therefore be considered modestly cost-effective up to cost-ineffective depending upon the population studied. Due to the significant increasing utilization and high cost of the procedure, ablation should be reserved for symptomatic patients failing medical therapy or those with an EF<35% after a careful shared decision-making discussion with the patient.

There are other unrecognized areas of LVC in cardiology including lack of hospice referral for end stage CHF, and inappropriate placement of implantable cardioverter defibrillators and dual chamber pacemakers, among others. PCP's play an important role in the management of CVD both in terms of understanding the indications for referral and carefully choosing cardiologists who practice evidence-based high value care when referral is indicated. Using a shared decision-making approach with our patients will help align referrals with their goals and preferences.

Sacubitril/valsartan vs. valsartan alone in the treatment of advanced heart failure

The PARADIGM-HF trial in ambulatory patients with reduced ejection fraction showed that compared to an ACE inhibitor alone (enalapril) combination therapy with an angiotensin receptor-neprilysin inhibitor (sacubitril/valsartan) reduced the relative risk of cardiovascular mortality and CHF hospitalizations by 20% (absolute risk reduction 4.7%).[12] Almost all of the patients in the PARADIGM-HF trial were NYHA Stage II and III; very few patients in that trial had NYHA class IV CHF.

Therefore, the use of sacubitril/valsartan vs. valsartan alone was evaluated in patients with NYHA Stage IV CHF the double-blinded trial reviewed here.[13] NT-proBNP area under the curve (AUC) was used as a marker of effectiveness of treatment. The median NT-proBNP for the 168 patients in the valsartan-alone arm was 1.19 (IQR 0.91-1.64) and for the 167 patients in the sacubitril/valsartan arm was 1.08 (IQR 0.75-1.60). There was also no significant difference in clinical outcomes of number of days alive, out of hospital or free from heart failure events. Importantly, patients in both arms of the study had difficulty tolerating the medications (29% in the sacubitril/valsartan and 21% in the valsartan arm had to discontinue the study drug).

Medical treatment options are limited in patients with NYHA Stage IV CHF. Medication tolerance is often difficult. The addition of a neprilysin inhibitor does not seem to provide incremental benefit to valsartan in this difficult group of patients.

Allopurinol is noninferior to febuxostat in achieving serum urate goals and controlling gout flares

Population data suggest that gout is undertreated; an appropriate medication is either not used or is not advanced to a therapeutic dose.[14] Given the clinical impact of gout and its strong associations with hypertension, diabetes mellitus, obesity, renal and cardiovascular disease, and accelerated mortality, understanding the efficacy and safety of urate-lowering medications is important. Accordingly, a recent randomized double-blind clinical trial compared the relative efficacy and safety of two urate-lowering medications, allopurinol and febuxostat.[15]

A total of 950 patients with gout and hyperuricemia were recruited from 21 study sites and randomized; 20.1% withdrew before completing the protocol. The primary outcome was ≥1 gout flares. Secondary outcomes included achieving a pre-defined serum urate level, serious adverse events, and efficacy and safety among patients with chronic kidney disease.

Among patients treated with allopurinol, 36.5% reported gout flares compared to 43.5% who received febuxostat ($p<0.001$ for noninferiority of allopurinol). Target serum urate levels did not differ between groups, with approximately 80% of all participants achieving the target. Similarly, there were no differences in adverse events between groups. Febuxostat was not associated with increased cardiovascular morbidity or overall mortality.

Febuxostat costs ~$3,300 per year. Since allopurinol is noninferior to febuxostat and is a low-cost generic, it is strongly recommended as the initial treatment for gout, a recommendation supported by the American College of Rheumatology.[16]

Allopurinol is not associated with increased mortality among patients with gout and chronic kidney disease

The pooled data from two previous randomized clinical trials showed that allopurinol did not preserve renal function among patients with chronic kidney disease (CKD), without gout.[17,18] In addition, there was an unexpected two-fold increased risk of death in the allopurinol-treated patients. A recent population-based study sought to answer the question: Does allopurinol increase mortality in patients with CKD and concurrent gout?[19]

Patients 40-89 years of age, who had both CKD and gout, were identified from an electronic health records database (The Health Improvement Network, THIN). Propensity scoring was used to match cohorts

with and without allopurinol initiation. The first allopurinol prescription was used as the index date for allopurinol initiators, and all-cause mortality rates over the five years following the index date were compared between cohorts.

Mortality was lower among allopurinol initiators compared to non-initiators (4.9 versus 5.8 per 100 person-years). Comparing patients who achieved a target serum urate level (<0.36 mmol/L) versus those who did not achieve a target level, the hazard ratio of mortality was 0.87. Additionally, the hazard ratio of mortality was 0.88 for those with allopurinol escalation compared to those without allopurinol escalation.

In summary, allopurinol initiation and escalation does not appear to be associated with increased mortality among patients with gout and chronic kidney disease. There are limitations with propensity scoring as residual confounding cannot be excluded.

Systematic review of promising medications for treatment of non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is a growing epidemic worldwide and encompasses both simple liver steatosis as well as non-alcoholic steatohepatitis (NASH) that can result in significant morbidity and mortality. Various aspects, including an overview of this disease, have been covered in previous issues of the Forum.[20, 21, 22] While lifestyle modification and weight loss are the cornerstones of therapy, medications also may have a role. A recent systematic review by Mantovani et. al., highlights effectiveness of three classes of anti-hyperglycemic medications.[23] The review included active or placebo-controlled randomized studies of peroxisome proliferator-activated receptor (PPAR) agonists, glucagon-like peptide-1 receptor (GLP-1R) agonists, or sodium-glucose cotransporter-2 (SGLT2) inhibitors used to treat NAFLD or NASH in adults in phase two trials. Twenty-five trials conducted in numerous countries met inclusion criteria, with a combined pool of 2597 subjects. The authors found that PPAR agonists such as pioglitazone and GLP1-R agonists such as liraglutide and semaglutide improved histological features of NASH. The SGLT2 inhibitors such as empagliflozin and dapagliflozin reduced liver fat content, but these studies did not look at liver histology and are therefore inconclusive. Findings should not be generalized to every drug in each class, nor to all patients with NAFLD, but do provide robust evidence to consider use in appropriate cases. Use of these drugs to treat NAFLD, including NASH, is considered 'off-label' as they are not currently FDA-approved for this indication.

Pain reprocessing therapy may provide substantial and durable pain relief in individuals with chronic back pain

In approximately 85% of individuals with chronic back pain, a specific cause for pain cannot be found. Patient fears about the cause of pain are thought to contribute to pain persistence. Animal models and human studies have implicated certain brain regions – including the somatosensory and insular cortices, amygdala, and nucleus accumbens – in the chronicity of pain and pain modulation. Chronic pain can lead to changes in these brain regions, demonstrated by functional MRI (fMRI).

Pain reprocessing therapy (PRT) is a psychological intervention that focuses on the reappraisal of pain as non-dangerous. PRT aims to reduce or eliminate chronic back pain by changing how patients perceive the cause of their pain and the threat value related to pain. The efficacy of PRT was recently demonstrated in a randomized clinical trial that compared the psychological intervention to two control groups: open-label placebo and usual care.[24] The control group is described as follows:

(1) With the open-label placebo, the concept of placebo treatments was described in two videos and patients received a subcutaneous saline injection that they were told represented a placebo.

(2) With usual care, there were no additional treatments given.

The open-label placebo intervention has been shown to be as effective or nearly as effective as traditional (deceptive) placebo interventions for chronic back pain.

Using a 0-10 pain scale, patients in the PRT arm had significantly lower pain intensity scores following intervention than patients in the placebo and usual care arms (mean pain scores of 1.18, 2.84, and 3.13, respectively).[24] Thirty-three of 50 participants in the PRT group reported being pain free or nearly pain free, compared with 10 of 51 participants in the placebo group and 5 of 50 in the usual care group. Treatment effects were maintained at 1-year follow up. Additionally, longitudinal fMRI showed differences between PRT and control groups. These differences included reduced responses to evoked back pain and increased resting connectivity in the brain regions attributed to chronic pain.

Many studies support the use of cognitive-behavioral therapy as an effective psychological intervention for patients with chronic back pain. PRT may provide a similarly effective and durable treatment for these patients.

Breast cancer screening: Detection is not always beneficial

An ongoing concern with any screening test is detection of abnormalities which would, if left unaddressed, not harm the patient and when addressed can cause harm. Overdiagnosis of breast lesions is specifically a concern. Overdiagnosis in the case of breast cancer would include detection of an indolent or nonprogressive lesion that would not progress to cancer, or detection of a slowly progressive cancer that would not have manifest as clinical disease prior to the patient dying of other causes.

In an effort to better define the incidence of overdiagnosis of breast cancer 35,986 women ages 50 to 74 years old were identified at first mammography between 2000 and 2018.[25] These women underwent 82,677 mammograms over this period. Each woman had on average 2.3 screening tests and 92.1% had five or fewer tests. 718 breast cancers were diagnosed. Of these cancers, 79% were invasive and 21% were cancer in situ. The overdiagnosis rate increased from 11.5% at first screen at age 50 to 23.6% at last screen at age 74. The overall rate of overdiagnosis of screen-detected cancer was 15.4% (95% PI, 9.4 to 26.5%). Diagnosis of indolent cancer accounted occurred in 6.1% and detection of preclinical cancer in women who would have died of an unrelated cause accounted for 9.3% of the cases.

In women 50 to 74 years of age, overdiagnosis of cancer occurs 1 in 7 of cancers detected. This information is important to include in shared decision-making discussions with women.

Sinus polyps: Does their removal improve outcomes in chronic rhinosinusitis?

A recent multicenter trial randomized patients with chronic rhinosinusitis with nasal polyps to medical therapy with endoscopic sinus surgery (ESS) or medical therapy alone.[26] The medical therapy was at the discretion of the otorhinolaryngologist and could include, but was not limited to, nasal corticosteroids, nasal rinsing, systemic corticosteroids or systemic antibiotics. Adult patients, 18 years of age and older, eligible for ESS were included for randomization.

Over four years, 371 patients were screened for participation and 234 were entered into the trial; 118 in ESS plus medical therapy and 116 in the medical therapy alone. Baseline characteristics of the ESS plus medical therapy and medical therapy groups were not statistically different. Twenty-three patients in the medical therapy only arm crossed over to the surgical plus medical therapy arm. Patients were followed for 12 months with an additional 12 months of follow up planned. The primary study outcome was the score on the Sinonasal Outcome test (SNOT-22), a validated scale which rates health related outcomes. Scores on each item of the SNOT-22 range from 0 to 5 with 5 being most severe, the worst outcome. Scores can range from 0 to 110. The minimally clinically important difference for this scale is nine points.

After 12 months, the SNOT-22 score of the ESS plus medical therapy was 27.9 (SD 20.2) and for medical therapy 31.1 (SD 20.4). The adjusted mean difference between the ESS plus medical group and the medical treatment alone group was -4.9 (95% CI -9.4 to -0.4) in favor of the ESS group. This is below the clinically important threshold for this scale. There was not a compelling difference in treatment outcomes for patients with chronic rhinosinusitis with nasal polyps with or without sinus surgery. This trial will look at longer term outcomes to see if this result is different over a longer follow up period.

Evidence to help risk-stratify those with high low-density lipoproteins (LDL)

When considering primary prevention for CVD risk reduction, evidence-based guidelines for treatment of elevated levels of cholesterol and LDL-C are well established, with a strong recommendation to treat based on risk profile.[27] However, patients may decline therapy or not reach goals with a generic regimen. Mortensen and colleagues recently reported results of a cohort study of over 23,000 adult patients without a previous diagnosis of coronary artery disease who underwent CCTA as part of their work-up for symptoms with a suspected cardiac etiology. Coronary artery calcium (CAC) was routinely measured as part of the CCTA study. They examined rates of myocardial infarction, ischemic stroke, and all-cause death, and correlated these with LDL-C levels and the presence of calcified and non-calcified coronary artery plaques.[28] Outcomes were assessed over a median follow-up of 4.2 years and correlated with LDC-C levels and plaque phenotype profile as indicated by CAC score.

CAC was absent (i.e., zero) in roughly half of the participants, and the majority of those patients had no detectable plaque on CCTA. Among all of those with a CAC score of zero, the event rate per 1,000 person-years was 6.3 (95% CI, 5.6-7.0), and even those with LDL levels ≥190 mg/dL, the rate was only 6.9 (95% CI, 4.0-11.9). This is much lower than those with CAC scores of between 1-99 (rate of 11.1 [95% CI, 10.0-12.5]), and those with a CAC score ≥100 (rate of 21.9 [95% CI, 19.9-24.4]). One of the striking findings from this study was the low event rate in those with a CAC of zero and no noncalcified plaque, even in patients with LDL-C ≥190 mg/dL. However, an important caveat is that there is a small subset of patients with a CAC score of zero who have obstructive non-calcified plaque. Therefore, in the presence of potential anginal symptoms or high clinical suspicion of plaque, CCTA is preferred over CAC without CCTA.

These findings support a shared decision-making approach in cases of patients with elevated LDL cholesterol who decline treatment or who cannot easily achieve LDL reductions with conventional therapy. In these cases, CAC and plaque assessment via CCTA may be useful in further risk stratification to guide therapy intensity or help determine which statin-avoidant patients might forgo therapy.

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Dr. Kenneth Cohen is an experienced physician leader, practicing internist, and researcher who has attained national recognition for health care quality improvement. He was one of the founding physicians of New West Physicians, which is the largest primary care group practice in Colorado and now part of Optum Care. He served as Chief Medical Officer from 1995 - 2020. He now serves as the Executive Director of Clinical Research for UHG R&D and Senior National Medical Director for Optum Care. Dr. Cohen has received awards of recognition and distinction for teaching, including the Lutheran Medical Center Physician of the Year award in 2011. Under his stewardship New West Physicians was awarded the AMGA Acclaim award in 2015 and the Million Hearts Hypertension Champion Award in 2017. He is a Clinical Associate Professor of Medicine and Pharmacy at the University of Colorado School of Medicine. Dr. Cohen holds degrees from Dickinson College and Hahnemann University. He is a Fellow of the American College of Physicians and a member of the Phi Beta Kappa and Alpha Omega Alpha honor societies.

John Hitt, MD, MBA

Dr. Hitt is the Evidence-Based Medicine Implementation Sage and Senior National Medical Director for Optimal Care. He has been a physician executive for more than 25 years. Prior to joining Optum, he was Chief Medical Officer at Maricopa Integrated Health System (MIHS) in Phoenix Arizona. Dr. Hitt was a key member of the senior leadership team at MIHS having responsibility for Medical Staff Services, Grants and Research, Academic Affairs, Risk Management, physician contracted services and coordinated the activity of Residency Program Directors, Clinical Department Chairs, and Medical Staff.

He served as the Chief Medical Quality Officer for Hennepin Health System. He was a physician leader for VHA (now Vizient), Medical Director at Caremark International and the Vice President of Medical Affairs at the University of Minnesota Hospital.

Dr. Hitt graduated from the University of Virginia where he played division one soccer. He received his Medical Doctorate from the Medical College of Georgia (AOA honors), completed his Internal Medicine and Infectious Disease Fellowship at the University of Minnesota Hospital and Clinics and his MBA at the Carlson School of Management at the University of Minnesota. He is the proud father of seven children.

Geoffrey Heyer, MD

Dr. Heyer is board certified in neurology with special certification in child neurology and in headache medicine. Prior to joining our team, Dr. Heyer was an associate professor of neurology and pediatrics at The Ohio State University and Columbia University Medical Center, specializing in autonomic disorders, headache, and pain management. He has published over 50 peer-reviewed research papers and numerous editorials, clinical reviews, and textbook chapters. He also co-authored a textbook on childhood stroke and cerebrovascular disorders.

Dr. Heyer received his medical degree from Columbia University, College of Physicians and Surgeons. He completed his neurology and child neurology residencies at Columbia-Presbyterian Medical Center. He has additional research training from the Mailman School of Public Health, Columbia University.

Joshua Jacobs, MD, FAAFP

Dr. Jacobs is a Fellow of the American Academy of Family Physicians and an educator with over 20 years of clinical, academic, and leadership experience regionally, nationally, and internationally. He currently serves as National Medical Director for Provider Intelligence within Clinical Performance at Optum Care. In his various roles, he has established new organizational systems to empower clinicians, administrators, researchers, students and staff to thrive and succeed. Examples prior to joining Optum include establishing a new US LCME-accredited medical school; moving the national dialog at the Association of American Medical Colleges (AAMC) medical education services to be more student-centric and evidence-informed using principles of design thinking; helping the country of Singapore transition, accredit and modernize its medical educational model; consulting for the Japanese government on national patient safety initiatives; and creation and oversight of a successful medical device start-up company's research arm culminating in successful FDA clearance. He also has extensive experience in designing and presenting curricula and training sessions, editing, publishing, and grant writing in medical fields.

Dr. Jacobs is a Clinical Professor at the Washington State University College of Medicine. He graduated from Pomona College with honors and from the John A. Burns School of Medicine as a member of the Alpha Omega Alpha honor society.

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