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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	• Evaluate post-acute sequelae of SARS-CoV-2 infection • Review medication harm that results in ER visits and review polypharmacy in dementia patients. • Discuss the following: optimal management of intermittent claudication; cardiovascular risks associated with fatty liver disease; ineffectiveness of preoperative stress testing in asymptomatic patients.

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Post-acute sequelae of SARS-CoV-2 infection

Post-acute sequelae of SARS-CoV-2 (PASC) infection is defined by the NIH consensus group[1] as symptoms persisting greater than 30 days following the onset of COVID-19. SARS-CoV-2 has now infected over 254 million persons globally and 48 million persons in the United States.[2,3,4] This is an underestimate of total cases with a significant percent of cases either asymptomatic or mildly symptomatic and often undetected.[5] Survivors of infection with SARS-CoV-2 are experiencing a spectrum of post-infection outcomes. We are just beginning to understand the nature and extent of these outcomes.

SARS-CoV-2 is primarily a respiratory pathogen and this is reflected in the high percentage of patients presenting with primarily respiratory symptoms. The only symptom that predicts hospitalization is dyspnea or shortness of breath. Cough, fever and shortness of breath were present in 45% of all patients and 68% of those hospitalized.[6] However, SARS-CoV-2 also manifests unusual symptoms with greater frequency compared to other pathogens, notably anosmia and dysgeusia present in over 50% of patients and more commonly in ambulatory patients.[7] The large variety of presenting symptoms is one of the diagnostic challenges of COVID-19.

PASC will generally present as one of two syndromes. The first is serious persistent organ dysfunction in those who had critical illness. This can include pulmonary fibrosis, cardiomyopathy, sequelae of thrombosis, and neurocognitive symptoms. The second syndrome is seen in outpatients with milder disease and the most common symptoms are fatigue, myalgias, dyspnea, anxiety, sleep disturbances, and residual taste/smell dysfunction.[6] While duration of symptoms is often more prolonged in patients with more severe disease even younger patients and those with milder disease can have prolonged symptoms.[8]

A recent meta-analysis was conducted to characterize PASC.[9] The 57 included studies comprised a group of 250,351 survivors of COVID-19; 140,196 (56%) were male; 197,777 were hospitalized (79%). Symptoms were frequent both acutely (up to one month) after infection and distantly (> 5months) after infection (Table 1).

Table 1. Patients with at least one PASC (median and interquartile range, (IQR))

Symptom duration (Months)	Median (%)	IQR	Number of studies
1 (short term)	54	45–69	13
2-5 (intermediate term)	55	35–65	38
6 or longer (long term)	54	31–67	9

Like symptoms were clustered into categories and the most common symptoms fell into the categories of pulmonary, neurologic, mental health, functional mobility impairments and general/constitutional. The most common abnormalities in each category were chest imaging abnormality (62%), difficulty concentrating (24%), general anxiety disorder (30%), general functional impairments (44%) and fatigue or muscle weakness (37%). These high sequelae rates were likely skewed by the high rate of hospitalization in this cohort of patients.

Several additional meta-analyses have looked at PASC. Many of the analyses have been limited by the lack of an agreed upon definition of post-acute sequelae as they were published before the consensus definition of PASC. There has also been great variability in how symptoms are reported or assessed post-infection.

Nasserie et al. reviewed 92 studies reporting on 9751 patients (Table 2, Row 1).[10] Researchers considered persistent symptoms to be those lasting longer than 60 days after diagnosis, symptom onset, or hospitalization or at least 30 days after hospital discharge. Neurocognitive symptoms were common (25%) but only recorded in four studies.

Lopez-Leon et al reported on almost 50,000 patients and included patients as soon as two weeks after disease onset as having persistent symptoms (Table 2, Row 2).[11] There were limited data on disease severity. With the early definition of persistence, 80% of patients had at least one symptom. Inclusion of patients as early as 14 days after symptom onset likely overestimating prevalence of persistent symptoms.

A Swiss group used self-reported symptom assessment to characterize symptoms seven to nine months post COVID-19 infection.[12] Patients requiring hospitalization were excluded. In this patient group of 410 patients, 39% continued to have symptoms seven to nine months post-infection. Persistent symptoms increased with age and were more common in females (Table 2, Row 3).

Table 2. Representative studies looking at PASC

Reference	# Studies	# Patients (% male)	Median age (yrs)	Persistent definition range (days)	At least 1 symptom persistent (%)	Hospitalized (%)	Most common symptoms (%)
Nasserie	92	9751 (54)	NR	30 after d/c 60 after recovery	72.5	23–80	D (36); F (40) Sl (29)
Lopez-Leon	15	47910 (NR)	NR	14-110	80	NR	F (58); H (44); AD (27); HL (25); D (24)
Nehme	1	410 (33)	43	210-270	39	none	F (21); A (8); H (10)

D = Dyspnea; F= Fatigue; Sl= Sleep disturbance; AD= Attention disorder; HL= Hair loss; H= Headache; A=Anosmia NR=not reported

Complicating the understanding of symptom persistence after COVID-19 is the well described post-intensive care syndrome.[13] Post-intensive care syndrome includes the cognitive, psychological, physical and other consequences that plague ICU survivors. This syndrome occurs after ICU stays from any number of causes. Most common sequelae in some cases lasting for years after an ICU stay include cognitive impairment (30-80%), psychiatric illness (8-57%), frequent exercise intolerance and pulmonary function abnormalities.

A significant portion of the United States population will be affected by COVID-19 with some portion of these going on to have PASC. This is not persistent infection; it is the aftermath of an acute infection. We are early in our understanding of how these patients should be best managed. Patients who experience persistent dyspnea three months post COVID-19 may benefit from pulmonary evaluation and echocardiography due to the known sequelae of pulmonary fibrosis and myocarditis.[8] Currently, there are no pharmacologic interventions recommended for PASC, other than early observational trials of steroids in patients with ongoing interstitial lung inflammation.[6] Optimal diagnostic evaluation and treatment of PASC is critical to avoid excessive low value diagnostic testing and non-evidenced based treatments. A coordinated rehabilitation program may be needed for some persons recovering from COVID-19 to meet specific patient needs. Multidisciplinary management may be needed in many cases.

In summary, most patients with SARS-CoV-2 infection will recover with symptom resolution in a week or less. An unknown number of patients will have minimal symptoms or asymptomatic infection. A small but significant number of patients will have persistent symptoms lasting more than 30 days and meet diagnostic criteria for PASC. The NIH is coordinating a multidisciplinary task force in an attempt to quickly define optimal diagnostic and management strategies for PASC.

Medication harm resulting in ER visits

The recent article by Budnitz et al. highlights the dangers and relative frequency of inappropriate prescribing.[14] In this cross-sectional study, authors examined records from U.S. emergency department (ED) visits from a nationally representative sample during the period between 2017-2019 to determine how many visits were primarily related to harm from medication management. Interestingly and disappointingly, the data from the 2017-2019 time-period shows higher rates of harm from medications compared with four years earlier as reported for the 2013-2014 timeframe.[15] Harms attributable to medications that were used as directed were higher in those age ≥ 65 years compared to younger patients, estimated at 11.6 per 1000 people seen in the ED. Of cases identified in all age groups, roughly 38.6% needed to be hospitalized, with even higher proportions in the ≥ 65 years age groups. In those ≥ 65 years of age, the most common medication categories associated with harm were anticoagulants and agents used to treat diabetes mellitus. These two categories were also the top causes of medication-related harms seen in the ED in the 45–65-year age group, although at lower rates. Over half of harms relating to anticoagulants involved the use of warfarin, although direct oral anticoagulants (DOACs) were also implicated. Almost all harms from anti-diabetic medications involved the use of insulin. There are additional and important findings pertaining to the appropriate use of psychoactive medications and of antibiotics in younger age groups.

These findings underscore the importance of appropriate use of all medications, highlighting the risks of drifting outside of the therapeutic window when using anticoagulants or anti-diabetic medications particularly in older populations. Previous issues of the Forum outline appropriate use of newer anticoagulants and, if put into widespread practice, should result in fewer harms. Based on safety and cost-effectiveness, **apixaban is the preferred DOAC.**[16,17]

Recall that over 50% of seniors on insulin or sulfonylureas have an A1c<7% and are therefore overtreated, significantly increasing the risk of ER and hospital admission. Regarding treatment drugs and targets for patients with Type 2 diabetes mellitus as described in this Forum previously, therapeutic targets in patients should be adjusted according to age and comorbidities to minimize risk of harms. **HgbA1c in the range of 7.5-8.5% should be the target in older adults. Use of generic NPH insulin over new basal insulin analogs is more cost effective and possibly safer.**[18,19,20]

Although associated costs have not been clearly quantified for all conditions, the cascade of treatment and patient harms stemming from inappropriate prescribing are evident, and can be mitigated with appropriate medical management.

Polypharmacy more likely among patients with dementia

Polypharmacy, defined as the use of multiple medications or more medications than are medically necessary, is common among older adults, with the highest number of medications taken by those residing in nursing homes.[21] Polypharmacy increases risks of drug reactions, falls, cognitive decline, and mortality. Among patients with dementia, polypharmacy may not align with overall treatment goals and may cause harm. A recent study evaluated rates of polypharmacy among adults with dementia compared to adults without dementia.[22]

Researchers conducted an observational study of survey data from the National Ambulatory Medical Care Survey (NAMCS) from 2014-2016.[22] The NAMCS is a probability sample survey of patient visits to office-based physicians. The study definition of polypharmacy was ≥5 continued or newly prescribed medications (including all prescriptions and over-the-counter medications and vitamins). A secondary analysis compared the use of ≥10 medications between cohorts.

There were 918 sampled visits for patients with dementia and 26,543 sampled visits for patients without dementia, corresponding nationally to 29 million and 780 million visits, respectively. Patients with dementia were older than the patients without dementia, were more likely to be female, and had more comorbidities. Patients with dementia had a median number of eight medications compared to a median of three medications among patients without dementia ($p<0.001$). The adjusted odds that patients with dementia had ≥5 medications were three-fold higher compared to patients without dementia (adjusted OR 3.0; 95% CI: 2.1-4.3). The adjusted odds of having ≥10 medications were similarly higher (adjusted OR 2.8; 95% CI: 2.0-4.2). Additionally, patients with dementia were more likely to receive at least one sedating or anticholinergic medication.

Use of the NAMCS has some limitations, including:

- Potential under coding of patients with milder forms of dementia and cognitive impairment
- A lack of granular data about disease severity and chronicity
- Possible inconsistencies in medication reporting and listing

However, none of these are likely to have caused extensive inflation of the numbers of medications used. Thus, polypharmacy appears to be more among older patients with dementia than patients without dementia, which may be discordant with overall treatment goals and can cause harm. This once again underscores the important role of the primary care provider in deprescribing unnecessary and harmful drugs in the elderly.

Optimal management of intermittent claudication is maximal medical therapy

Many of our Optum Care CDO's have recognized the value of vascular plaque assessment to identify individuals who may benefit from maximizing CVD guideline directed medical therapy (GDMT). There are three predominant options for plaque assessment: carotid intima media thickness (CIMT), coronary artery calcium (CAC) scoring, and peripheral artery disease (PAD) assessment. Because it can be done quickly in the primary care office, PAD screening is now frequently used.

With increased PAD screening comes increased diagnosis of patients with both asymptomatic disease and intermittent claudication. One of the risks of increasing PAD diagnosis is overtreatment with revascularization. The Society for Vascular Surgery and the American Heart Association recommend supervised exercise therapy, smoking cessation, and optimal medical management as first-line treatment.[23,24] Revascularization procedures are controversial.

To this end, an important study was recently published in the Journal of Vascular Surgery.[25] It looked at over 1,000 patients who presented with intermittent claudication and studied the outcomes in the one third that were surgically treated compared to the two thirds that were medically treated. Propensity score methods were used to reduce confounding. The group that received revascularization was slightly younger, reported more tobacco use within the past 90 days, had higher rates of Type 2 diabetes (32.3% versus 16.3%), and higher rates of COPD (4.3% versus 1.7%), but otherwise matched similarly with the non-revascularized group in terms of sex and comorbidities.

The key outcome was progression to chronic limb threatening ischemia (CLTI). During the 15-year study period, patients who received revascularization were significantly more likely to progress to chronic limb-threatening ischemia (hazard ratio, 2.9) and a significantly greater number required ipsilateral limb amputation (hazard ratio, 4.5). Specific differences in chronic limb-threatening ischemia among patients with and without revascularization were 13% versus 6% at 3 years, 18% versus 8% at 5 years, and 27% versus 10% at 10 years (all $p<0.01$). Specific differences in limb amputations were 3% versus 1% at 3 years, 6% versus 1% at 5 years, and 11% versus 2% at 10 years (all $p<0.001$).

Although this was a single institution retrospective study, it underscores the importance of following our current algorithm for the management of PAD. Patients with intermittent claudication should not undergo surgical evaluation but rather be treated with maximal GDMT unless there is evidence of critical limb ischemia.

The cardiovascular risks associated with fatty liver disease

A recent and robust meta-analysis by Mantovani et al.[28] provides updates since previous articles in this Forum about non-alcoholic fatty liver disease (NAFLD) (Nov/Dec 2018; March 2021; July 2021). Recall the burden of disease is quite high, with some estimates as high as 46% in the United States.[29] Associations with other metabolic derangements including diabetes mellitus, hyperlipidemia,[30] and cancers such as hepatocellular carcinoma and some extrahepatic cancers are well described,[31] and NAFLD has at times been referred to as the liver manifestation of the metabolic syndrome. Findings of the Mantovani et al. meta-analysis clarify how the magnitude of cardiovascular disease risk increases with severity of NAFLD. This study aggregated data from over 5.8 million adults with median follow-up of 6.5 years and demonstrated that risk of fatal and non-fatal CVD events was higher in those with NAFLD (HR 1.45, 95% CI 1.31-1.62). This risk was even higher for those with more advanced forms of NAFLD, such as non-alcoholic steatohepatitis (NASH) (HR 2.5, 95% CI 1.68-3.72). NAFLD is not a static disease but rather a spectrum of fatty liver diseases with multisystem involvement that can progress from simple steatosis to NASH with fibrosis and, at its extreme, cirrhosis with liver failure. The findings from the meta-analysis were independent of co-morbidities such as diabetes mellitus, age, sex, smoking, hypertension, and other cardiovascular risk factors, indicating that NAFLD itself is a potential independent risk factor for poor cardiovascular outcomes.

This article adds to the scientific evidence of disease burden associated with this condition. This further highlights the importance of appropriate diagnosis and aggressive management of NAFLD to prevent progression and worsening CVD risk, as well as progression to DM2 and liver fibrosis. Evidence-based interventions previously described include weight loss through behavioral intervention, pharmacotherapy or bariatric surgery.[32]

- Behavior modification for weight loss must be intensive and sustained to be effective in slowing or stopping NAFLD progression.
- Bariatric surgery is highly effective and has proven cost effectiveness.
- The GLP1-RA's and the newer GLP1-RA/GIP drugs are also highly effective but very expensive, and cost-effectiveness data are not yet available for these drug classes.

Futility of preoperative stress testing in asymptomatic patients

In 2004, a landmark study was published in the NEJM.[26] It looked at over 500 patients with known high-grade CAD based on preoperative catheterization. Patients were undergoing two of the highest risk surgeries: abdominal aortic aneurysm resection and surgery for occlusive peripheral arterial disease. Half the patients were sent to the OR without revascularization and the other half had either stenting or bypass surgery. At three months, six months, and two years postoperatively, there was no reduction in CV events in the revascularized groups. This study moved the needle somewhat away from routine preoperative stress testing, but these continued to occur at a high enough rate that it ranks in the top ten "wasted care" interventions as defined by Medicare.

We now have new data from a recent study looking at surgeons participating in the Vascular Quality Initiative.[27] They looked at over 52,000 patients undergoing abdominal aortic aneurysm surgery via either the endovascular aneurysm repair (EVAR) or open (OAR) approach. The median proportion of stress test usage across centers before EVAR was 35.9% and before OAR was 58%. There was a striking 7-fold variation in the use of preoperative stress testing among the surgeons. There was no difference in perioperative CV risk between those who did and did not undergo preoperative stress testing. Importantly, there was also no difference in CV risk in high testing centers compared to low testing centers.

The rate of major adverse cardiac events (MACE) was 1.8% after EVAR and 11.6% after OAR. The 1-year mortality was 4.6% for EVAR and 6.6% for OAR. Interestingly, the centers in the highest quintile of stress testing had a higher adjusted likelihood of MACE after both EVAR (OR 1.78) and OAR (OR 1.99). This is the opposite of what would be expected if preoperative stress testing positively impacted perioperative CV events. The 1-year mortality was similar across all quintiles and therefore not impacted by the rate of preop stress testing.

These data once again suggest the futility of preoperative stress testing in patients who do not have symptoms of active coronary artery disease. An algorithm created by the Optum Care algorithm committee is available that could help triage patients who may benefit from preoperative cardiac evaluation.

Pre-operative cardiac risk assessment for non-cardiac surgery

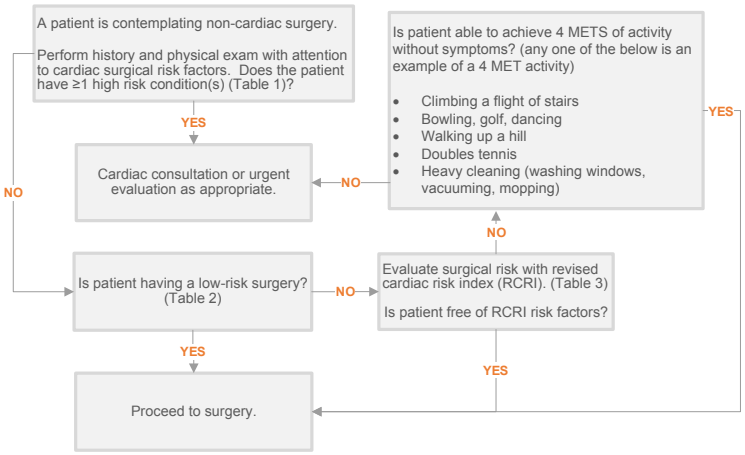

Table 1: Examples of High-Risk Surgical Conditions

- Moderate or greater valvular stenosis or regurgitation (particularly aortic)
- Cardiac implantable device
- Moderate or severe pulmonary hypertension
- Congenital heart disease
- Decompensated heart failure
- Unstable angina or MI within 60 Days
- High-grade arrhythmias

Table 2: Examples of Low-Risk Surgical Procedures

- Dermatology procedure
- Arthroscopic procedures
- Simple mastectomy (complete breast)
- Ophthalmologic surgery
- Endoscopic procedures

Table 3: Revised Cardiac Risk Index

- High-risk site (any vascular, intraperitoneal, or intrathoracic site)
- History of ischemic heart disease
  - Previous myocardial infarction or a positive exercise test
  - Current complaint of chest pain considered to be secondary to myocardial ischemia
  - Use of nitrate therapy
  - ECG with pathological Q waves
  - Coronary revascularization procedures (DO NOT COUNT unless at least one other criterion for ischemic heart disease is present)
- History of heart failure
- History of cerebrovascular disease
- Diabetes requiring insulin therapy
- Preoperative serum creatinine > 2 mg/dl

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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 chronic low back pain. • Review pharmacological evidence for bisphosphonate therapy for women with osteoporosis and first do no harm applied to persons with hypertension. • Discuss studies regarding the role of implantable loop recorders for atrial fibrillation and stroke, Omicron testing, and platelet-rich plasma for treatment options in knee, ankle or Achilles tendinopathy.

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Management of chronic low back pain

Source of review

This article is an expansion of a JAMA article I was asked to write for their "Evidence to Practice" series, published in 12/21.[1] It was based on our Optimal Care model of care for chronic low back pain (CLBP). Over the past several years, multiple randomized controlled trials (RCTs) and meta-analyses have examined important therapeutic options in the management of CLBP. These data have been supplemented by two recent systematic reviews examining both pharmacologic and non-pharmacologic treatments for CLBP.

Background

Over 10% of the population has CLBP, defined as back pain lasting more than 12 weeks. It is the sixth most costly condition in the U.S. with an annual expenditure of over $90 billion. Many interventions provided to patients lack Level I or II evidence of benefit and rely instead on observational studies and consensus recommendations. Moreover, for many patients the care model provides invasive and pharmacotherapeutic interventions but does not actively engage them in a coordinated behavioral and rehabilitative model shown to improve long term outcomes.

Summary of findings: Therapies found to produce clinically meaningful benefits

- **Noninvasive, nonpharmaceutical interventions:** A 2017 review detailed 114 studies of noninvasive treatments for acute and chronic LBP. Small improvements were seen with mindfulness-based stress reduction and chiropractic manipulation. Moderate improvements were seen with core strengthening exercises such as Pilates, Tai Chi, and yoga, as well as with acupuncture. Cognitive behavioral therapy and patient education around pain management skills have both shown clinically meaningful reductions in pain intensity and improved PROMIS scales; validated measures of physical, mental, and social health. Combining these exercise regimens and behavioral approaches through a comprehensive multi-disciplinary rehabilitation model has also shown clinically significant improvements, including lower long-term pain intensity, improved function, and a greater likelihood of returning to work compared with non-multidisciplinary rehabilitation.
- **Specific pharmacotherapies:** NSAID's have consistently shown small-to-modest benefit in CLBP, with smaller benefits in chronic radicular pain. The SNRI antidepressant duloxetine has shown small improvements in pain and function in CLBP. No other medications have consistently shown benefit in CLBP.
- **Lumbar decompression and fusion:** The SPORT (Spine Pain Outcomes Research Trial) was a large randomized controlled trial (RCT) of non-surgical care versus lumbar decompression surgery for lumbar spinal stenosis, and decompression with or without fusion for degenerative spondylolisthesis. Both the spinal stenosis and spondylolisthesis arms of the trial showed significant clinical improvements in pain, disability, and function for up to four years following surgery, at which point surgical improvements began to decline towards the non-surgical group. By year four, the improvements were no longer clinically significant.

Treatments lacking a significant evidence of support

- Apart from the therapies above, many pharmacological and invasive procedures lack sufficient evidence of effectiveness (summarized in Table 1). Gabapentinoids and opioids deserve focused attention due to their high frequency of use, lack of evidence of benefit, and high rate of adverse effects. Between 2000 and 2015, gabapentinoid use increased 15-fold in the treatment of osteoarthritis, including CLBP. Pregabalin and gabapentin have now been well studied with most data suggesting no benefit and a highly significant burden of cognitive side effects. The most robust study was a one-year RCT of pregabalin vs. placebo in acute and chronic sciatica in 209 patients. Although pregabalin did not improve pain or disability, 57% of patients had neurological side effects, including dizziness in 40%, which increases fall risk. Despite the widespread use and known serious harms of opioid treatment, there is a striking absence of data showing any benefit to opioid use in CLBP. A recent systematic review of opioid therapy for CLBP identified 14 studies that enrolled a total of 6,457 participants and compared opioid therapy to placebo or non-opioid analgesics. The duration of the longest trial was 12 weeks. Overall, compared to placebo or non-opioid analgesics, there was a clinically insignificant 0.9 decrease in the 10-point visual-analog scale (VAS) score.
- Other areas where evidence of benefit is lacking include epidural steroid injection (ESI), vertebroplasty, and spinal cord stimulators. With respect to ESI, the Agency for Healthcare Research and Quality commissioned a technology assessment in 2015 examining the totality of data on the use of ESI in the management of low back pain. ESI was not found to be of benefit for the management of CLBP. The only statistically significant effect

was in short term (5–14 day) pain relief of radicular pain, but this did not meet the threshold of a clinically important benefit. ESIs were not shown to be of benefit in CLBP, spinal stenosis, non-radicular back pain, or chronic radicular back pain, and did not reduce the likelihood of undergoing surgery.

- An additional issue is the overuse of lumbar fusion when routinely added to decompression among patients with degenerative spondylolisthesis at one or two adjacent spinal levels in the absence of significant instability. A meta-analysis published in 2020 examined six RCTs including 650 patients that compared these two approaches. There were no statistically significant differences in any outcome, including VAS score for LBP or leg pain, Oswestry Disability Index (a validated instrument to quantify disability for low back pain), or multiple quality-of-life indices. A more recent randomized trial of microdecompression versus decompression plus fusion in 570 patients again showed no statistically significant benefit to fusion in this population of patients. These studies are of importance as the rate of lumbar fusion in the Medicare population increased 15-fold between 2002 and 2007 and continues to rise. Every year 1.2 million lumbar fusions are performed at an average commercial health plan cost of $60,000-$110,000.
- **Limitations on the evidence:** Most studies have been of short-to-intermediate duration. Many studies are subject to bias by small sample sizes, methodological limitations, industry funding, and study heterogeneity. Additionally, many comparative efficacy interventions did not use a placebo or sham study design, rendering the results difficult to interpret due to the large placebo response seen in studies of chronic pain.

Conclusions

When examined in total, evidence suggests that many of the therapies commonly used to treat CLBP lack a strong evidence-base of support. The routine use of these approaches should be questioned. This is most relevant when the intervention is associated with significant harm, such as the use of gabapentinoids and opioids in CLBP, and the routine addition of fusion to lumbar decompression in degenerative spondylolisthesis.

Treatment modalities may be considered "passive", such as ESI and pharmacotherapies, versus "active," such as CBT, core strengthening exercise programs, and multi-disciplinary rehabilitation. Overall, the evidence supports active modalities, yet the majority of patients with CLBP have not had a robust trial of these interventions to treat their pain. This underscores the need to improve patient engagement and education, along with shared decision-making, to maximize clinical improvements. Patients need to be educated that these interventions can be successful, but often require three to six months to be maximally effective. When patients understand the real-world outcomes associated with active therapies compared to invasive management, they choose active therapies more frequently.

Importantly, physician reimbursement and long-term patient outcomes are often not aligned. Many of the highly reimbursed modalities such as ESI, lumbar fusion, spinal cord stimulator implantation, and vertebroplasty lack robust evidence of improved outcomes. In contrast, many of the active interventions which have proven to be effective, safe, and inexpensive—such as multi-disciplinary rehabilitation, CBT, yoga, Pilates, along with others— may have out-of-pocket costs that deter utilization. As an example, our fee-for-service reimbursement model has transformed physiatry and pain management specialties to be highly procedure-oriented.

Sophisticated care coordination with care navigation is paramount in the management of CLBP but typically unavailable to most patients with CLBP. This coordination responsibility typically falls to the primary care provider, who is often overburdened and lacking the needed resources and infrastructure. Value-based insurance designs can provide a revenue stream to support multi-disciplinary rehabilitation and care navigation, therefore helping to transition to a new model of care for CLBP. This is particularly true when the provider organization is at risk for the cost of care of these patients. As we progress along the value-based care continuum, increasing our use of evidence-based therapies can improve long-term patient outcomes while reducing the total cost of care for patients with CLBP.

Table 1. Interventions with limited evidence of benefit in the treatment of CLBP

Intervention type	Evidence overview	Evidence-base	Place in therapy
Pharmacotherapy			
SSRI antidepressants	No benefit	Systematic review	Not indicated
Tricyclic antidepressants	No benefit	Systematic review	Not indicated
Acetaminophen	No benefit	Systematic review	Non indicated
Systemic glucocorticoids	No benefit	Systematic review	Not indicated
Benzodiazepines	Minimal to no benefit	Systematic review	Infrequently indicated
Skeletal muscle relaxants	Minimal to no benefit	Systematic review	Infrequently indicated
Gabapentinoids	No benefit; significant neurological and cognitive side effects	One-year RCT of pregabalin vs. placebo	Not indicated
Opioids	No benefit	Systematic review of trials up to 16 weeks	Infrequently indicated
Pain management injection procedures (ESI and facet injections)	No benefit	CMS technology assessment, including a systematic review and randomized trials from multiple sources	Indicated for acute radiculopathy only where a small benefit is noted
Lumbar decompression for spinal stenosis and decompression with or without fusion for degenerative spondylolisthesis	Benefit of decompression surgery for spinal stenosis vs. non-surgical care for up to four years Benefit of decompression surgery with or without fusion for up to four years	Large RCT	Indicated for failure of rehabilitative modalities or progressive neurological deficits
Lumbar fusion for 1 or 2 level degenerative spondylolisthesis in the absence of significant instability	No additional benefit from fusion when combined with decompression surgery	Meta-analysis of six RCTs RCT comparing microdecompression vs. decompression plus fusion	Generally fusion indicated for >2 level decompression or marked spinal instability
Vertebroplasty	Minimal to no clinical benefit	Meta-analysis finding based on four out of five RCTs	Infrequently indicated
Spinal cord stimulation	Minimal to no clinical benefit	Meta-analysis of eight studies of SCS on neuropathic pain	Infrequently indicated

At least 12 months of bisphosphonate therapy are needed to improve bone mineral health among women with osteoporosis

The U.S. Preventive Services Task Force recommends screening for osteoporosis in women 65 years and older and postmenopausal women younger than 65 years, but with osteoporosis risk factors.[2] A recent meta-analysis explored the time to benefit from bisphosphonate therapy among postmenopausal women with osteoporosis.[3] The authors analyzed data from 10 randomized clinical trials or subsequently published pooled analyses comparing a first-line bisphosphonate (alendronate, risedronate, or zoledronic acid) to placebo. The 10 studies comprised 23,384 women, aged 63-74 years, with osteoporosis, defined as a T-score of -2.5 or lower on bone mineral density testing.

Pooled analyses demonstrated that 12.4 months of bisphosphonate therapy were needed to prevent one non-vertebral fracture per 100 women treated (absolute risk reduction [ARR] of 0.01). Bisphosphonate therapy of 20.3 months was needed to prevent one hip fracture per 200 women treated (ARR of 0.005). To prevent one vertebral fracture, 200 women would need bisphosphonate therapy for 12.1 months (ARR of 0.005).

At least 12 months of bisphosphonate therapy are needed to achieve benefit. These results have two important implications. First, when starting treatment, the patient should be counseled about the time course for bisphosphonate therapy to become effective. Second, early fractures among patients with osteoporosis who are treated with a first-line bisphosphonate do not indicate a therapeutic failure and therefore may not warrant a medication change.

Additionally, since it takes at least two years to demonstrate improvements in bone density on DEXA (dual-energy X-ray absorptiometry) scanning, repeating the DEXA scan earlier than two years is not recommended.

First do no harm: As applied to persons with hypertension

The majority of patients with hypertension are not well controlled.[4] The American College of Cardiology in their 2017 guidelines provide a list of medications that can lead to hypertension.[5] Researchers from Beth Israel Deaconess Hospital used the National Health and Nutrition Examination Survey (NHANES) to determine how often medications that can lead to hypertension (MBP↑) are used in persons with hypertension (HTN).[6]

NHANES is a biannual survey of noninstitutionalized persons in the United States. This study looked at five survey cycles of NHANES from 2009 to 2018. Prescription medication use was self-reported to the NHANES interviewers as part of the survey. Hypertension was defined as average systolic BP of 130 mm Hg or higher, average diastolic BP of 80 mm Hg or higher, or answering "yes" to the question, "Have you ever been told by a doctor or other health professional that you had hypertension, also called high blood pressure?" Data from 27,599 individuals at least 18 years of age was included. The prevalence of MBP↑ was assessed. A logistic regression model was constructed to determine any relationship between HTN and MBP↑ and the use of MBP↑ was studied relative to the number of antihypertensive medications used.

The use of MBP↑ was reported by 14% of all persons and 18.5% of persons with HTN. The most common MBP↑ were NSAIDS, steroids, and estrogens. The relationship between MBP↑ in persons with HTN is summarized in the table.

Relationship examined	Effect	Odds ratio (95% confidence interval)
Use of MBP↑ on risk of uncontrolled HTN* in persons **NOT** taking HTN medication	Present	1.24 (95% CI, 1.08-1.43)
Use of MBP↑ on risk of uncontrolled HTN in persons **taking** HTN medication	Not present	Not reported
Use of MBP↑ on the number of HTN medications use in those with **controlled** HTN	Present	1.27 (95% CI, 1.11-1.44)
Use of MBP↑ on the number of HTN medications use in those with **uncontrolled** HTN	Present	1.13 (95% CI, 1.03-1.25)

* Uncontrolled hypertension was defined as an average systolic BP reading of 130mmHg or higher or an average diastolic BP reading of 80mmHg or higher.

Polypharmacy is a well-recognized problem for many patients, increasing medication side-effects and drug interactions as illustrated by this study. In many cases MBP↑ may be discontinued or replaced by an alternative medication. There is an opportunity for heightened awareness of the negative influence that MBP↑ have on HTN management.

Table 1. Prevalence of Use of Medications That May Raise Blood Pressure (BP) Among US Adults, 2009-2018

	Survey participants, % (95% CI)		
		Adults with	
	US adult population	Hypertension[a]	Uncontrolled hypertension[b]
Unweighted No.	27 599	14 629	10 696
Weighted No.	225 284 279	111 056 498	79 921 633
Use of medications that may raise BP			
Any	14.8 (13.9-15.8)	18.5 (17.5-19.5)	17.4 (16.3-18.5)
1	12.3 (11.7-12.9)	14.9 (14.1-15.8)	14.1 (13.1-15.1)
≥2	2.5 (2.2-2.9)	3.6 (3.1-4.1)	3.3 (2.7-3.8)
Use of classes of medications that may raise BP			
Antidepressants	6.7 (6.2-7.3)	8.7 (8.0-9.5)	7.9 (7.0-8.8)
NSAIDs	4.9 (4.4-5.3)	6.5 (5.8-7.2)	6.2 (5.4-6.9)
Steroids	1.4 (1.2-1.6)	1.9 (1.6-2.1)	1.7 (1.4-2.0)
Estrogens	1.4 (1.2-1.6)	1.7 (1.4-2.0)	1.6 (1.3-1.9)
Stimulants	1.1 (0.9-1.4)	0.9 (0.6-1.1)	1.0 (0.7-1.4)
Testosterones	0.4 (0.2-0.5)	0.4 (0.2-0.6)	0.4 (0.2-0.6)
Antiobesity agents	0.2 (0.1-0.3)	0.2 (0.1-0.3)	0.1 (0.1-0.3)
Decongestants	0.2 (0.1-0.4)	0.4 (0.2-0.6)	0.4 (0.1-0.7)
Antipsychotics	0.1 (0.1-0.2)	0.2 (0.1-0.3)	0.2 (0.1-0.4)
Immunosuppressants	0.1 (0.0-0.1)	0.2 (0.1-0.3)	0.2 (0.1-0.3)
α Agonists	<0.01	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Antirheumatics	<0.01	0.1 (0.0-0.1)	0.1 (0.0-0.1)
Use of antihypertensives			
1	13.2 (12.5-13.9)	23.3 (22.2-24.4)	19.8 (18.8-20.9)
2	8.9 (8.3-9.4)	17.0 (16.0-18.0)	13.0 (12.1-14.0)
>3	4.9 (4.5-5.3)	9.8 (9.1-10.6)	7.9 (7.2-8.6)

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

[a] Hypertension was defined as an average systolic BP reading of 130 mmHg or higher, average diastolic BP reading 80mmHg or higher, or answering "yes" to a hypertension questionnaire.

[b] Uncontrolled hypertension was defined as an average systolic BP reading of 130mmHg or higher or an average diastolic BP reading of 80mmHg or higher.

Atrial fibrillation and stroke: What is the role of implantable loop recorders?

Although subclinical atrial fibrillation (AF) is associated with increased stroke risk, previous studies have shown that most strokes are not preceded by a recent episode of AF.[7,8] This finding begs the question: Is AF a risk factor or a risk marker for stroke?

Using Optum and CareLink databases, a recent study evaluated the temporal relationship of AF (detected by implantable device) and stroke.[9] Patients with a stroke and at least 120 days of monitoring prior to the event were included. An AF episode was defined as ≥5.5 hours AF. The main outcome measure was the odds ratio (OR) for stroke comparing AF during days 1-30 (control period) versus days 90-120 (case period) prior to stroke.

891 patients met inclusion criteria. Most patients (76.5%) did not have an AF episode in either the control or case periods. AF episodes were present during both the control and case periods in 16% of patients. Among the remaining 7.5% of patients, 52 had AF during the case period only versus 14 (1.5%) with AF during the control period only (OR 3.71). Stroke risk was increased most within five days of the AF episode (OR 5). AF >23 hours duration had the highest associated stroke risk (OR 5). These data support AF as a direct, temporal stroke risk factor. It is worth noting that in this large cohort of patients with stroke, 17.5% of strokes were related to AF that was present within the 30-day period prior to the stroke.

Additionally, a meta-analysis of three randomized controlled trials evaluated the AF detection rates with implantable loop recorder (ILR) versus usual care following ischemic or hemorrhagic stroke.[10] Stroke types were stratified as cryptogenic, small- or large-vessel, or embolic. Pooled data from 1,233 patients were analyzed. The AF detection rate was 13% with ILR versus 2% with usual care over a 12-month study period. Stroke or transient ischemic attack occurred in 7% of the ILR patients and 9% of the usual care patients. Patients with previous cryptogenic or embolic stroke and detected AF were more likely to receive oral anticoagulants (97% and 100%, respectively) compared to patients with strokes attributed small- or large-vessel disease (68%). Although ILR was superior to usual care in AF detection, AF was relatively rare across patients, and there was no significant reduction in stroke or TIA rate with ILR monitoring.

COVID testing in the Omicron era

Over the course of the SARS-CoV-2 pandemic we have come to understand a great deal about the infectivity, incubation period, clinical presentation, duration of symptoms, viral shedding, and immunologic response to SARS-CoV-2. We now understand how these characteristics differ from ancestral strains to most recently Delta and Omicron variants. We have also developed multiple tests to detect SARS-CoV-2. Antigen tests (Ag) have lower sensitivity and specificity for SARS-CoV-2 but are low cost and have rapid turnaround. Nucleic acid amplification tests (NAAT), also known as PCR tests, have remarkable sensitivity but remain positive well past a person's infectious period. Antibody tests and viral cultures are also now readily available, but their use should be restricted to special circumstances. This interplay between disease, viral presence and persistence, symptoms, infectivity, test choice and public health policy is a complex, partially choreographed, and still developing dance. Peeling et. al do a remarkable job of discussing and reviewing this information and present succinct testing recommendations.[11]

Characteristics of SARS-CoV-2 that influence test choice in a particular setting:

- SARS-CoV-2 typically is present and infectious two days before symptoms onset.
- Viral load peaks just before or around the time of symptom onset and rapidly decreases after symptoms begin.
- Virus is rarely present beyond eight days after symptom onset in normal hosts with mild disease.
- Unlike most diseases, IgM and IgG antibody responses to SARS-CoV-2 both peak almost at the same time 11-14 days after symptom onset.
- 106 viral genome copies/ml is estimated to be the viral load needed for transmission to occur.

Characteristics of tests that impact recommended utilization at various stages of SARS-CoV-2 infection:

- In patients with a high pretest probability of infection, Ag tests alone reliably confirm COVID-19.
- The limit of detection of Ag test are 105 to 106 viral genome copies/ml.
- The limit of detection of NAAT is 102 to 103 viral genome copies/ml.
- NAAT can detect SARS-CoV-2 RNA well after active infection has passed.

Taken together these characteristics highlight several key testing considerations. First, Ag tests with a high pre-test probability (i.e. exposed, symptomatic individuals) do not need verification of a positive test with a NAAT. Second, Ag tests level of detection roughly correlates with the viral load associate with infectivity, therefore those with a negative Ag test are not likely to be infectious. Therefore, Ag tests have an advantage over NAAT in following

a patient's recovery and giving clearance for return to work. Third, NAAT with the high sensitivity they provide are excellent in confirming a diagnosis and detecting disease more than five days post symptom onset, when an antigen test may already be negative. Finally, persistent NAAT after infection can occur based on the exquisite sensitivity of the tests and does not necessarily correlate with ongoing clinical disease or infectivity.

The authors outline when testing should be considered for asymptomatic screening including health care facilities, workplaces, schools and mass gatherings (e.g., religious, sports, music). This review outlines how knowledge of SARS-CoV-2 clinical presentation and viral dynamics coupled with understanding individual test performance characteristics inform testing decisions.

Platelet-rich plasma not effective for knee, ankle osteoarthritis or Achilles tendinopathy

ODespite mixed evidence of effectiveness and conflicting guidelines from different medical societies, platelet-rich plasma (PRP) is sometimes used in clinical practice to treat degenerative conditions such as knee or ankle osteoarthritis (OA), or Achilles tendinopathy. Recent high-quality evidence highlights the **lack of effectiveness** for most patient-oriented measures.[12]

In the prospective, double-blinded, randomized controlled RESTORE trial in Australia, Bennell and colleagues administered a series of three PRP or placebo knee injections to 288 community-based patients >49 years of age with symptomatic medial knee OA.[13] There were no significant differences in the two primary outcomes at 12 months; a patient-reported knee pain score, and a quantitative measure of cartilage volume in the knee as measured with MRI.

Kearney and colleagues demonstrated a similar lack of significant effectiveness of using PRP in treating midportion Achilles tendinopathy.[14] This study was a prospective blinded randomized controlled trial of a single PRP injection versus a subcutaneous sham dry needle procedure and involved 240 adults in the United Kingdom with Achilles tendon pain for more than three months. Difference in the primary outcome of symptom score on a validated survey instrument was not statistically significant between the two groups at six months.

In a third recent study, Paget and colleagues observed similar results for the condition of ankle OA.[15] This prospective double-blinded randomized controlled trial done in the Netherlands examined the difference in symptom scores using a validated survey instrument in 100 adults with symptomatic ankle OA. Two injections to the ankle were administered six weeks apart with the study group receiving PRP and the control group receiving normal saline. There was no significant difference in the primary outcome.

Previous issues of this Forum and the Optimal Care algorithm have addressed various aspects of treatment for knee and for shoulder dysfunction. To summarize:

- Neither arthroscopic meniscectomy[16,17] nor viscosupplementation[18] are routinely indicated for knee OA.
- Physical therapy typically yields better patient-oriented outcomes than glucocorticoid injection for knee OA,[19] although both have documentation of effectiveness and may be used in combination.
- Physical therapy is as effective as surgery for frozen shoulder.[20]

With the additional evidence summarized above, PRP should be added to the list of 'do not routinely use', not only for knee OA, but also for ankle OA and for Achilles tendinitis.

Even subsegmental pulmonary embolism may need anticoagulation treatment

Acute pulmonary embolism (PE) of segmental, or proximal, arteries has a clear indication for anticoagulation to treat the event and avoid recurrence. Embolism of more distal, subsegmental arteries does not have such a clear indication. Diagnosis of PE has been covered in a previous issue of the Forum,[21] and an algorithm is available to help guide diagnostic decision-making.[22] For patients diagnosed with subsegmental PE and no risk factors for PE including no ultrasound evidence of proximal lower extremity deep vein thrombosis, the risk of recurrence was thought to be low and clinical guidelines recommended surveillance over anticoagulation in these patients.[23] The recent publication of the SSPE study by Le Gal et al.[24] examining this population of patients, should have us re-examine this approach.

This multinational prospective cohort study of patients with subsegmental pulmonary embolism (SSPE) who were managed with surveillance and not with anticoagulation showed an incidence of recurrent PE of 3.1% (CI, 1.6% to 6.1%) within 90 days from the diagnosis of the initial PE. This is a higher rate than expected, and suggests anticoagulation be strongly considered as a management strategy in these patients to prevent recurrence.

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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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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	• Understand the risk and assessment of COPD in patients that have never smoked compared to patients who smoke or have been smokers with and without COPD. • Review pharmacological evidence for proton pump inhibitors and gastric cancer risks and selective serotonin reuptake inhibitors (SSRIs) for treating panic disorder. • Discuss medical management studies regarding meniscal tears in younger patients, cognitive behavioral therapy for major depressive disorder, self-administered adult tests for cognitive function and prediction models for pulmonary embolism.

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COPD in never-smokers

COPD has historically been the third leading cause of death both in the U.S. and worldwide, behind cardiovascular disease and cancer. Annually, it causes over 150,000 deaths in the U.S. and over 3 million deaths worldwide. The prevalence of COPD in the U.S. is ~13.5% of the adult population. Unless otherwise referenced, the information in this article is derived from a symposium published in *The Lancet Respiratory Medicine* which included four papers on various aspects of COPD in never-smokers. [1-4]

Most clinicians believe that COPD is almost always associated with longstanding tobacco use, however worldwide this is true in less than 50% of cases. The Social Deprivation Index (SDI) is a composite average of the rankings of the incomes per capita, average educational attainment, and fertility rates of all countries in the Global Burden of Disease study. In countries of middle and lower SDI, air pollution, indoor pollution from poorly ventilated cooking and heating methods, and occupational exposures add up to over 50% of cases, including up to 70% of cases at the low end of the SDI measure.

Even in the U.S., where indoor pollution is less frequent and occupational exposures are regulated more closely than middle and lower SDI countries, over a quarter of COPD cases occur in never-smokers. It is therefore important to have a high index of suspicion and understand the factors that can contribute to COPD in never-smokers. The four major risk factors are asthma, outdoor air pollution, occupational exposures and passive smoking.

The 2022 GOLD Strategy report highlights that asthma "may be a risk factor for the development of chronic airflow limitation and COPD."[5] Asthma may increase the risk for COPD as much as 12-fold compared with those without asthma, after adjusting for smoking. In high SDI countries, asthma is the most common risk factor for COPD in never-smokers, accounting for about 25%-30% of cases in never-smokers. A subset of patients with chronic asthma have persistent airways inflammation rendering them more susceptible to chronic airway remodeling. Potential reasons for COPD developing in an asthmatic include thickening of the basement membrane of the bronchial epithelium, increased airway smooth muscle mass, an increase in mucus-producing cells and subepithelial fibrosis.

Outdoor air pollution contributes to the development of COPD even in high SDI countries. A study from the UK Biobank which controlled for tobacco use in over 300k individuals, showed that about a third of COPD could be attributed to high concentrations of particulate air pollutants.[6] Similar data in the U.S. points to an association of chronic bronchitis in never-smokers and long-term exposure to particulate matter and nitrogen dioxide (NO2).[7] Occupational exposures to vapors, gases, dusts, and fumes is a significant risk factor for COPD in never-smokers. The list of occupational exposures that can lead to COPD is extensive, but the initial screen can be at the level of job "category", with a more extensive occupational history obtained where appropriate. The important job categories that have been linked to occupational asthma and COPD include people working in agriculture, industrial manufacturing and processing, mining, jobs with concentrated exposure to diesel exhaust fumes from machinery and vehicles, and warehouse workers.

Other than the major risk factors noted above, there are accumulating data that at least three other risk factors may contribute to the development of COPD in never-smokers. First, sex may be an important risk factor. Females seem to be at higher risk of COPD than males. High levels of COPD in never-smokers were seen in the third US National Health and Nutrition Examination Survey (NHANES III).[8] Among people with COPD, of the 25% of those with mild-to-moderate COPD who had never smoked, the majority were female (83%). In a study from Rotterdam, the proportion of female participants with COPD who were lifelong never-smokers was 27%, compared with 7% for male never-smokers. One reason could be that females may be more susceptible to COPD due to passive tobacco exposure. Among patients with incident COPD who had never smoked, the proportion of people exposed to passive smoking was 51% and the majority (77%) of those with passive smoke exposure were female.[9] Next, early life exposures may be a significant contributor to COPD in never-smokers. Lung growth continues in the first two decades of life and common conditions that may impair the attainment of maximal lung capacity include premature birth, malnutrition, maternal smoking and severe childhood pneumonia. Because lung function begins to decline in the third decade, nonsmoking individuals with baseline low lung capacity are more at risk for COPD later in life. Lastly, genetics have a significant impact on the future development of COPD. Although alpha one antitrypsin deficiency is widely recognized, it is rare and accounts for only a small fraction of COPD cases. On the other hand, the available data support a model in which the largest contribution to COPD risk arises not from rare variants with large disease impact, but from the combined effect of many common variants with smaller

but combined disease impact. Using a polygenic risk score, those at the highest decile of risk have a 7.5-fold increase risk (European ancestry) or a 4.5 fold increase risk (non-European ancestry) of COPD compared to the lowest decile.[10] Heritability of COPD may be as high as 40%.[11]

So how best can this information be put into clinical practice? Consider the following:

- Counsel patients with a family history of COPD that they may be at increased risk and therefore should avoid not only tobacco use, but also other potential exposures as noted above.
- Clinical presentations of COPD in never-smokers are different than in smokers, with overall milder disease (Table 2). There will often be a younger age at onset, milder airways obstruction, and less exertional dyspnea. Awareness of this different presentation can trigger spirometry assessment in never-smokers who might have COPD presenting with milder symptoms.
- Given the markedly elevated risk of COPD in chronic asthma, persistent asthma should be treated with an inhaled corticosteroid (ICS) as part of the regimen. Additionally, it is prudent to follow patients who have persistent asthma with periodic spirometry to evaluate for subclinical declines in lung function, which could trigger an up-step in therapy. The frequency of spirometry should be guided by the severity of the asthma.
- Never-smokers with COPD may have less severe emphysema, but a higher degree of small airways disease. COPD exacerbations appear to be equally prevalent. They should be treated per the GOLD or COPD Foundation guidelines.
- The risk of lung cancer in never-smokers with COPD is as high as that in smokers who do not have COPD, but somewhat lower than in the population of smokers with COPD. The USPSTF guidelines do not currently recommend CT screening of never-smokers.

	COPD in ever-smokers	COPD in never-smokers
Typical age of onset	>40 years	>30 years
Sex	More males than females affected	Males and females affected equally, or more females than males affected (especially in LMICs)
Symptoms	More cough and dyspnoea (relatively less sputum production)	More cough (relatively less dyspnoea and sputum production)
Respiratory exacerbations	Frequent (and potentially severe)	Frequent (and potentially severe)
Comorbidities	Prevalent	Generally less prevalent
Risk of lung cancer	High	High
Lung physiology	More severe airflow obstruction; greater increase in RV/TLC (hyperinflation); increase in airway resistance; less small airways obstruction; reduced DLCO	Milder airflow obstruction; increase in RV/TLC (hyperinflation); greater increase in airway resistance; more small airways obstruction; normal DLCO
FEV1 decline	Can be rapid	Usually normal
Lung CT imaging	Less air trapping due to small airways obstruction; more emphysema	More air trapping due to small airways obstruction; less emphysema
Sputum inflammatory cells	Greater increase in neutrophils	Increase in neutrophils; relatively greater increase in eosinophils
Pharmacological responses	Long-acting bronchodilators favoured over inhaled corticosteroids in terms of safety and effectiveness, especially among those with predominant emphysema	Not known

COPD=chronic obstructive pulmonary disease. DLCO=diffusing capacity of the lung for carbon monoxide. RV=residual volume. TLC=total lung capacity.

Table 2: Clinical characteristics of COPD in never-smokers compared with ever-smokers[1]

Proton pump inhibitors and risk of gastric cancer

Proton pump inhibitors (PPI) are now commonly used to manage symptoms or treat several gastric conditions. There have been concerns over side effects from PPI agents including infection with resistant pathogens, Clostridium difficile and gastric cancers. Previous studies have suggested an association with gastric cancer but had limitations based on methodologic shortcomings.

Researchers utilized the UK Clinical Practice Research Datalink (CPRD) to look more carefully at the risk of gastric cancer associated with PPI use.[12] The CPRD is a primary care database which contains complete records from 15 million patients. Patients using PPIs were compared with those using histamine-2 receptor antagonists (HR2A) using a new-user active comparator design. Cox proportional hazards models were used to estimate the estimated increased risk for gastric cancer. PPI use was found to have a greater risk of gastric cancer compared to patients using HR2As (see table).

Table: Gastric cancer risk associated with PPI

Agent	New users	Years of follow-up	Gastric cancer cases	Fully adjusted hazard ratio
PPI	973,281	5.1	1,166	1.45
HR2A	198,306	4.2	244	1.0

Kaplan-Meier estimates suggest that the number to harm after five years was 2,121 but only 1,191 after ten years of PPI use. The risk of gastric cancer associated with PPI use is small, but this risk should be considered in evaluating the need for ongoing treatment with PPIs and in creating evidence-based guidelines. Particularly in patients with GERD, PPI's are often continued long term when slow weaning is often
well tolerated

SSRIs likely best for treating panic disorder

A recent systematic review and network meta-analysis suggests several drug classes are more effective than placebo in treating panic disorder with or without agoraphobia.[13] Many of these classes are associated with increased risk of adverse events. The drug class that maximizes efficacy while minimizing risk of adverse events is selective serotonin reuptake inhibitors (SSRIs). The remission risk ratio for this class vs placebo was 1.38 (95% CI 1.26-1.50) while adverse event risk ratio was 1.19 (95% CI 1.01 to 1.41). Specifically, sertraline and escitalopram prescribed at therapeutic doses are the two drugs with the highest remission rate and lowest risk of adverse events in the studies included in
the meta-analysis.

The meta-analysis included 87 studies and over 12,800 participants. However, since the available studies were of moderate to very low certainty level of evidence, the synthesized findings should be interpreted with caution.

Meniscal tears in younger patients: New evidence does not support early surgery

It is critical to understand the benefit of the one million knee arthroscopies performed in the United States each year. Previous studies in patients over 40 years of age have shown there to be no additional clinically meaningful outcomes for patients undergoing surgery for partial meniscectomy compared to exercise therapy. [14,15] Most of the meniscal injuries in this older group of patients are thought to be related to degenerative disease which have not been shown to benefit from meniscectomy.

A recent trial examined the effectiveness of meniscal surgery in patients 18 to 40 years of age.[16] Three quarters of patients had a specific traumatic event. This Danish trial was conducted across seven recruitment sites. Of the 546 patients clinically suspected of having a meniscal tear, 121 had an MRI confirmed meniscal tear and were randomized to surgery or exercise therapy. The type of surgery was determined by the operating surgeon. Surgery was followed by at least a minimal level of postoperative rehabilitation. For patients randomized to exercise, they underwent a specially designed 12-week program with sessions twice a week at one of 19 specific sites. The physical therapists involved in the exercise arm were specially trained and also provided 30-45 minutes of education. Of the 61 patients in the exercise group, 59% completed 18 or more of the possible 24 sessions.

The primary outcome was the between-group difference in change in Knee Injury and Osteoarthritis Outcome Score (KOOS4) from baseline to 12 months. This validated tool has scores that range from 0 to 100 across four domains: pain, symptoms, function in sport and recreation, and quality of life. The minimally clinically significant difference in the KOOS4 is 10 points. Outcomes were collected via online surveys at 3, 6, and 12 months (see table).

Exercise vs surgical outcomes measured by KOOS4

Intervention	# patients	Completed 12 months	Surgery in 12 months	KOOS4 improvement at 12 months		
				Mean	>20%	>50%
Exercise	61	58	16.4 (26%)	16.4	64%	57%
Surgery	60	49	52 (87%)	19.2	76%	38%

In this group of younger patients, 74 % of meniscal injuries were from a specific (traumatic) incident. This trial of exercise vs early surgery for mostly traumatic meniscal tears in younger patients, suggests that a strategy of early surgery was not superior to a strategy of exercise and education with the option of later surgery in improving pain, function, and quality of life at 12 months in young, active adults.

Outcomes do not differ between parathyroidectomy and observation for patients with mild primary hyperparathyroidism

A 2014 guideline recommended surgical parathyroidectomy in eligible patients with primary hyperparathyroidism who meet certain criteria including elevated serum calcium, signs of osteoporosis, or abnormal renal function;[17] although, evidence demonstrating improved clinical outcomes with surgery was lacking.

Given that there are no clear outcome data supporting surgery versus observation in those with mild hyperparathyroidism, authors of a recent study compared surgical parathyroidectomy (n=95 patients) versus observation (n=96 patients) for patients with mild, asymptomatic primary hyperparathyroidism.[18] The primary outcome of the randomized trial was mortality, and various morbidities (cardiovascular events, cerebrovascular events, cancer, bone fractures, and kidney stones) were assessed as secondary outcomes.

After 10 years, outcomes from parathyroidectomy and observation did not differ. A total of 44 deaths and 101 morbidities occurred and were equally distributed between study groups. The authors concluded that parathyroidectomy did not appear to reduce morbidity or mortality.[2] The authors of an editorial about the study wrote that these results provide a strong rationale for the nonoperative management of patients with mild primary parathyroidism.[19]

However, some study limitations deserve mention. Only 68% of randomized patients completed the study. Twenty-three patients in the parathyroidectomy group and 27 in the observation group withdrew. Cross-over also occurred with 18% of the patients randomized to the observation group having surgical treatment during the study period. Lastly, male patients and younger patients were underrepresented, so these results may not be broadly generalizable.

Cognitive behavioral therapy for major depressive disorder is cost-effective in adults

The global burden of disease from major depressive disorder is substantial, causing an estimated 63.2 million disability adjusted life-years lost in 2010 alone.[20] Treatment of this disorder varies, with pharmacotherapy the mainstay in the United States. Cognitive behavioral therapy (CBT) is a form of psychotherapy that focuses on the role of cognitive framing to help influence emotion and behavior to treat major depression. CBT can be delivered in person or via technology (e.g., via the internet) in a guided or unguided manner. It is an attractive adjunct, and a possible first-line alternative for those reticent to being on long-term medication for major depression treatment. A recent systematic review of cost utility analyses for this type of therapy either alone or in combination with usual care suggests this is a cost-effective approach in adults with major depression, when compared to usual care alone.[21] Included studies of adolescent and pediatric populations were inconclusive regarding cost utility.

The authors followed well-established methodologies for selecting studies in both English and Chinese that were published between 2004-2020 for inclusion in their review. Of the 3,306 studies initially identified, 38 qualified for inclusion. The quality of 26 of the studies were characterized as high and 12 as fair. When considering economic evaluations, it is important to state what perspective the cost-benefit is viewed from. In this systematic review, only two of the 38 studies were conducted from the payer perspective, with the remainder from the perspective of society, the health system, or both. Duration of the studies varied, averaging 21 months with a maximum up to five years. Reported costs included both direct costs of major depression care, and indirect costs such as lost productivity, etc. For treatment of major depression in adults, cognitive behavior therapy, either alone or in conjunction with usual care including pharmacotherapy, should be strongly considered.

Can a self-administered test reliably detect changes in cognitive function among adults with cognitive complaints?

Several brief clinical instruments are available for the office-based assessment of cognitive function when adults present with subjective cognitive decline (SCD), mild cognitive impairment (MCI), or dementia. Since approximately two-thirds of patients who present with cognitive symptoms score in the dementia range with office-based testing, it is possible that a self-administered instrument would detect cognitive impairments earlier in the course of disease. As newer treatments become available for Alzheimer's disease and other forms of dementia, earlier detection of cognitive impairment and progression may become relevant for treatment outcomes. In that vein, the Self-Administered Gerocognitive Examination (SAGE) was developed for the patient to self-assess cognitive function.

In a retrospective study, changes in SAGE scores were compared with changes in the office-based Mini-Mental Status Exam (MMSE).[22] Among 424 patients who completed both instruments during the study period, both SAGE and MMSE scores appropriately declined over time when the initial diagnosis was dementia or MCI that later converted to dementia, and the scores appropriately stabilized over time with SCD and MCI without conversion to dementia. A significant decline in SAGE scores occurred at least six months earlier than MMSE scores for MCI converting to Alzheimer's dementia (14.4 versus 20.4 months) and for MCI converting to non-Alzheimer's dementia (14.4 versus 32.9 months). The authors advocated use of the SAGE to detect cognitive decline more rapidly when it occurs.

SAGE can be downloaded for free from SAGE - Memory Disorders | Ohio State Medical Center (osu.edu): https://wexnermedical.osu.edu/brain-spine-neuro/memory-disorders/sage#SAGETest.

However, there are study limitations. Most importantly, this was a retrospective study of patients who completed both instruments in the office setting during at least two visits. A psychometrician administered the MMSE and then handed the patient the SAGE to complete on his/her own. The authors noted that patients with vision problems and lower reading levels may not be able to self-administer the instrument. Unfortunately, it is not known if patients can reliably self-administer the instrument from home or when patients with progressive cognitive decline can no longer self-administer the instrument, regardless of office or home environment.

Prediction models for pulmonary embolism

Multiple studies have attempted to identify the ideal combination of clinical decision rules (CDR) (the Wells criteria, Geneva score or YEARS algorithm) and D-dimer testing to aid in the evaluation of suspected pulmonary embolism. In a perfect world the correct combination of a CDR and D-dimer would identify with 100% accuracy those patients that do not have a pulmonary embolism from those that need further testing to aid in the diagnosis.

A recent meta-analysis of 16 studies looked at diagnostic strategies to identify patients with pulmonary embolism.[23] The review included a total of 20,553 patients and evaluated the efficacy defined as the proportion of individuals classified by the strategy as "PE considered excluded" without imaging tests. It also evaluated the safety of the approach, by looking at the diagnostic failure rate. The authors defined this as the predicted 3-month VTE incidence after exclusion of PE without imaging at baseline. Evaluation strategies generally traded off safety vs efficacy, meaning that the strategies with the fewest missed PE's also had the smallest reduction in unneeded imaging. All strategies had acceptable safety levels. Overall, best performing was the Wells rule combined with an age adjusted D-dimer, yielding a low failure rate of 1.1% (CI 0.8% to 1.5%). The efficacy (PE considered excluded) was also high at 47% (CI 42% to 52%) outperforming Geneva and YEARS (although CI for all three overlapped).[24] All of the models are less accurate in ruling out pulmonary embolism in patients over age 80 or with cancer. We continue to advocate for the clinical use of the age adjusted D-dimer combined with Wells criteria for the evaluation of possible PE.

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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.

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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.

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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.
Learning objectives	• Examine the Choosing Wisely® program at 10 years and Optimal Care's progress in eliminating low value care. • Evaluate the cost effectiveness of SGLT-2 inhibitors as first-line pharmacotherapy in adults with Type 2 diabetes mellitus. • Apply pharmacological evidence regarding gabapentin and overdose deaths, hyaluronic acid for osteoarthritis, and recognize when the use of PCSK9 inhibitors or ezetimibebe of value. • Discuss medical management concerning adjuvant chemotherapy, and asymptomatic patients with severe carotid artery stenosis and stroke rate.

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Choosing Wisely® at 10 years and Optimal Care - Are we making progress in eliminating low value care?

This article takes the occasion of the 10th anniversary of the Choosing Wisely® campaign to discuss the program within the context of the Optimal Care model. Choosing Wisely is a partnership between the American Board of Internal Medicine Foundation and the specialty societies. [1] It now comprises 626 measures contributed by 93 specialty societies and has expanded to over 20 countries. [2] It has generated a large volume of literature with 634 articles published last year alone.

Choosing Wisely seeks to minimize patient harm through the use of shared decision-making, discouraging tests and treatments with little benefit, and recognizing the impact of the costs of care on patients and their families. We now understand that this is not simply wasted care, but commonly care that is directly harmful. A recent analysis found that 87.5% of the services the campaign addressed carried a high or moderate risk of direct harm or starting an unnecessary cascade of care. [2] The campaign therefore may have helped keep patients safe. However, critics of the program point to the fact that it has had only a small effect on reducing low value care (LVC).[3] A recent study examining measures of LVC in 556 health systems, encompassing over 11 million Medicare beneficiaries, showed that over a third of patients received LVC tests or procedures.[4] Some of the most highly prevalent LVC medications included opiate use for back pain, antipsychotic use in patients with dementia, and antibiotics for upper respiratory infections. Important invasive LVC procedures included the use of vertebroplasty, epidural steroid injections and coronary artery interventions in asymptomatic individuals.

By allowing the individual societies to establish their own priorities, many of the recommendations largely target services with low impact on cost of care. They also often focus on procedures that are infrequently done and therefore do not have significant impact on the revenue generated by members of the recommending societies. Perhaps most importantly, because Choosing Wisely recommendations must focus on easily definable services, they may miss many tests and procedures that constitute wasteful care and harmful care but cannot be measured with simple claims analyses. For example. over 50% of Choosing Wisely measures are laboratory or imaging tests and only 18% are surgical procedures.

The Optimal Care (OC) model extends the ability to impact LVC beyond that addressed by the Choosing Wisely campaign in several key areas. The OC model is predicated on the fact that up to one third of the health care delivered in the U.S. does not improve health outcomes or quality of life and is therefore either wasted or harmful care. [5,6] It does not require the specialty societies to suggest their recommendations for LVC, but rather examines the clinical outcomes of tests, drugs, and procedures in high-quality evidenced-based literature to determine their effectiveness. As the standard of care has improved for many of the conditions we treat, new drugs, devices, and interventions may show only small increments in effect. Industry sponsors may overemphasize incremental improvements by enrolling large clinical trials where small differences in effect may be statistically significant but may or may not be clinically meaningful. Also, these results are often expressed in relative risk reduction as opposed to absolute risk reduction. To address these trends in clinical trials, OC uses tools such as incremental cost effectiveness, number needed to treat to achieve a given outcome (NNT), number needed to harm with any given intervention (NNH), and comparative effectiveness analyses to examine various treatment options based on metrics and outcomes that are available in the published literature. The goal is to establish the clinically meaningful positive and/or negative effect of any given intervention and deploy this information at the bedside. Finally, the OC team then uses all of the available data to create algorithms that are designed to drive improvements in clinical outcomes while minimizing potential patient harm. Some recent examples of the Optimal Care model that do not exist within the Choosing Wisely framework include:

- Comparative pharmacoeconomic analysis of the two new classes of drugs for chronic migraine showing that the cost to reduce a single monthly migraine day is ~$300 with a CGRP antagonist such as erenumab (Aimovig®), but ~$2,100 with rimegepant (Nurtec®), a “gepant” drug that is being heavily marketed for the treatment of chronic migraine.

- Algorithm development for stable chest pain using the comparative analysis of the new literature comparing the use of coronary artery CTA (with fractional flow reserve) to ischemia testing with nuclear or echo imaging. These studies suggest a 78% reduction in unnecessary heart catheterizations in patients with stable chest pain using the CCTA approach, with improved long-term rates of major adverse cardiovascular events (MACE).[7]
- Analysis of the literature documenting the overtreatment of low-risk prostate cancer and subsequent development of a clinical algorithm and shared decision-making platform (in process) to reduce the unnecessary treatment of many of these patients.[8]
- Analysis of the excess use of non-evidenced drugs and procedures and overuse of lumbar fusion for chronic low back pain (CLBP) to foster the development of a new physiatrist-based model of CLBP to improve outcomes and reduce cost of care for this condition.[9]

Often the available literature is insufficient to determine the efficacy, potential harms, and cost effectiveness of a given treatment or procedure. In these cases, the data science team at the Optum Center for Research and Innovation (OCRI), in collaboration with academic partners, can utilize the extensive data assets within Optum and Optum Care to design "synthetic" randomized controlled trials to test new hypotheses. Results are used to further inform Optimal Care program components to effect change at the bedside to reduce LVC. Studies currently in progress include:

- Comparative analysis of spinal cord stimulator placement and conventional medical management in the treatment of CLBP (submitted for publication).
- Examination of the change in clinical outcomes and cost effectiveness of the placement of implantable loop recorders compared to 30-day event monitoring in patients with cryptogenic stroke.
- Comparative analysis of the efficacy of zoledronic acid and denosumab for the prevention of osteoporotic fracture in women with osteoporosis who have failed oral bisphosphonate therapy.

The ultimate success of the OC model will be measured by documenting not only reductions of LVC and total cost of care, but most importantly, by improvements in patient outcomes. To that end, we have launched our patient reported outcome (PRO) platform and have begun to directly measure the performance of the OC model. It will take several years to scale the PRO initiative and then collect data sufficient for measurement of OC outcomes. These results will then feed back into our shared decision-making modules to inform our patients of the real-world outcomes of their care options. This last important step will ensure that our patients are partnering with their health care team to choose the best care that aligns with their values and preferences.

Preliminary examination of whether using SGLT-2 inhibitors as first-line pharmacotherapy in adults with Type 2 diabetes mellitus is cost effective

A recent large cohort study of adult patients with Type 2 diabetes mellitus (T2DM) who were started on an SGLT-2 inhibitor (SGLT-2i) as first-line pharmacotherapy compared cardiovascular and mortality outcomes in propensity-matched patients to those started on metformin as first-line therapy. [10] Findings demonstrated lower risk in one of the two primary outcome measures in favor of the SGLT-2i group. This was the composite of hospitalization for heart failure (HHF) and all-cause mortality (HHF/mortality). The other primary outcome measure was a composite of hospitalization for acute myocardial infarction (MI), stroke, or all-cause mortality (MI/stroke/mortality). This composite outcome was similar between the two groups. Secondary outcomes measured (HHF alone, all-cause mortality alone) and sub-group analysis showed lower risk of HHF compared with those started on metformin in those patients without previous history of cardiovascular disease (CVD). An additional sub analysis demonstrated those patients with a history of CVD in the SGLT-2i group had a lower risk of MI. The SGLT-2i group had higher rates of genital infections, but other measures of adverse events were similar between groups.

The methodology was robust, but as this is a cohort study, causation cannot be confirmed. That said, based on the data from this study, the number needed to treat (NNT) using SGLT-2 inhibitors instead of metformin as first-line pharmacotherapy for T2DM in patients with no previous history of CVD to prevent hospitalization for heart failure is 37. The NNT for those with a history of CVD to prevent one MI is 11. Using an average annual SGLT-2 inhibitor drug cost of $4,993 per year [11] compared with $156 for metformin, the estimated incremental cost per year to prevent one hospitalization from heart failure using an SGLT-2i as first line pharmacotherapy for T2DM in those without previous CVD is $179,000, which would not be considered cost effective. On the other hand, the cost to prevent one MI in those with previous CVD is $53,200, which may be considered cost effective. Therefore, based on accepted cost effectiveness metrics, the preferred initial therapy for those adults with DM2 but no underlying CVD continues to be metformin. For those patients newly starting drug therapy for DM2 with an existing diagnosis of CVD, SGLT-2 therapy may be considered as initial therapy in those patients where the additional cost is not prohibitive.

There is a higher risk of genital infections using this drug class compared with metformin. Therefore, if an SGLT-2 inhibitor is used, increased surveillance for this treatable complication is indicated.

Gabapentin implicated in overdose deaths

In 2019, the U.S. Food and Drug Administration warned that medicines used to treat nerve pain, gabapentin and pregabalin, can cause serious breathing problems for patients with respiratory disease and those who combine the medicine with opioids. [12] Since gabapentinoids can amplify the effects of illicit opioids, the two drug types are often combined. As a result, gabapentin has been found in nearly 10% of U.S. overdose deaths between 2019 and 2020.[13] Medical examiners have attributed the cause of death to gabapentin in about half of these cases. Data from the State Unintentional Drug Overdose Reporting System suggest that the role of gabapentin in overdose deaths may be growing. [13]

Importantly, care must be taken when prescribing gabapentinoids, particularly since the off-label use of this drug class has dramatically increased, often without an evidence base to support improved outcomes. Patients should be counseled about the added respiratory risks. When patients using prescribed opioids are have known illicit opioid use, gabapentanoid use should be avoided.

Hyaluronic acid for osteoarthritis: Recommendations against its use has not decreased utilization

The use of hyaluronic acid (HA) injections to treat osteoarthritis (OA) has been discouraged as the evidence has not supported benefit over sham injection. In 2013, the American Academy of Orthopedic Surgeons clinical practice guideline recommended against the use of HA. New clinical evidence has not suggested a need to alter this recommendation.

Despite the recommendation against the use of HA, HA utilization has increased from 2012 to 2018. [14] HA use was determined from the Medicare Fee-for-Service Provider Utilization and Payment Public Use Files. HA utilization has increased from 1,090,503 instances in 2012 to 1,209,489 in 2018. This was associated with overall costs for HA use increasing from $290 to

$325 million (2012 and 2018 respectively). The use among orthopedic surgeons remained essentially unchanged over the period. Use among nurse practitioners and physician assistants has increased by 220% and 169% respectively. In contrast, use among rheumatologists has decreased by 26%. Utilization seems to be driven by a desire to avoid or delay total knee arthroplasty, although it is difficult to measure if the revenue associated with its use plays an additional role in utilization. This study demonstrates the difficulty in implementing evidence-based practices or discontinuing practices not supported by evidence when treatment options are limited, clinical trials do not provide compelling evidence of efficacy and recommendations are counter to established norms.

Beyond statins – When may PCSK9 inhibitors or ezetimibe be of value?

Statin therapy is a mainstay in the primary and secondary prevention of cardiovascular disease (CVD), the leading cause of death in the U.S. In some patients, the therapeutic ceiling of statin therapy provides suboptimal risk reduction for adverse cardiovascular outcomes. In other patients, statin therapy is not an option due to intolerance of adverse effects. In these patients, ezetimibe and proprotein convertase subtilisn/kexin type 9 inhibitors (PCSK9i) have been recommended to further reduce LDL-C levels and thereby reduce cardiovascular risk. [15]

A recent systematic review and network meta-analysis of over 83,000 patients by Khan et al. sheds light on the cost-benefit use of these adjunctive medications. [16] The authors quantified the risk reduction of CVD with these agents over a 5-year period for the outcomes of non-fatal myocardial infarction (MI), non-fatal stroke, all-cause mortality, and cardiovascular mortality. The data suggest that when looking at the broad population, adding PCSK9i, ezetimibe or both to those on maximal statin therapy or using them in patients who are statin-intolerant had no significant effect on all-cause or cardiovascular mortality. They then sub-stratified the populations and looked at those with low, moderate, high and very high risk of CVD. Moderate risk was defined as patients with three or four cardiovascular risk factors (median risk of MACE over five years is 7%). High risk was defined as patients with five or more cardiovascular risk factors or a hereditary lipid disorder with no other CV risks (the median risk of major adverse cardiovascular event (MACE) over five years is 18%). Very high risk was defined as patients with established cardiovascular disease or hereditary lipid disorder (median risk of MACE over 5 years is 24%). In the high and very high CV risk populations, there was a small benefit observed in reduction of non-fatal MI and stroke.

From these data we calculated the number needed to treat (NNT) to prevent each outcome in various risk subgroups. Using cost data for these drugs estimated at ~$1,421 per year for ezetimibe and ~$7,056 for PCSK9i;[17] we derived the cost to avoid one event in Table 1.

Table 1. Estimated cost to avoid 1 non-fatal myocardial infarction or non-fatal stroke over 5-year period using PCSK9i and/or ezetimibe in high and very high cardiovascular risk patients.

	NNT adding ezetimibe	Cost to avoid 1 event	NNT adding PCSK9i	Cost to avoid 1 event	NNT adding PCSK9i to those already on ezetimibe	Cost to avoid 1 event	NNT adding ezetimibe to those already on PCSK9i	Cost to avoid 1 event
High risk patients on max statin – non-fatal MI	Did not exceed MID*	N/A	83	$2.93M	Did not exceed MID	N/A	Did not exceed MID	N/A
Very high-risk patients on max statin – non-fatal MI	Did not exceed MID	N/A	63	$2.22M	71	$2.50M	Did not exceed MID	N/A
High risk patients statin intolerant – non-fatal stroke	Did not exceed MID	N/A	63	$2.22M	77	$2.72M	Did not exceed MID	N/A
Very high-risk patients statin intolerant – non-fatal stroke	71	$504,455	48	$1.69M	59	$2.08M	Did not exceed MID	N/A
High risk patients statin-intolerant – non-fatal MI	83	$589,715	59	$2.93M	67	$2.36M	Did not exceed MID	N/A
Very high-risk patients statin- intolerant – non-fatal MI	63	$447,615	43	$1.52M	50	$1.76M	77	$547,085
High risk patients statin-intolerant – non-fatal stroke	77	$547,085	56	$1.98M	67	$2.36M	Did not exceed MID	N/A
Very high-risk patients statin- intolerant – non-fatal stroke	59	$419,195	42	$1.48M	50	$1.76M	77	$547,085

*MID= "minimal important difference" as defined by authors of 12 per 1000 for non-fatal MI, 10 per 1,000 for non-fatal stroke, and 8 per 1,000 for both all-cause and cardiovascular mortality

As can be seen from the results, the costs to prevent one MI or stroke are very high in all situations. For most of the above categories, the reduction in event rates were between 1-2 per 100 patients over five years, hence the high NNT's. Directionally, the results were consistent, small, and only of benefit to patients with high and very high-risk of CV morbidity. Although the absolute reduction in stroke and MI in the high and very high-risk populations was greater with the PCSK9 inhibitors, due to their higher cost, the cost to avoid one event was much higher in this group, far exceeding the Institute for Clinical and Economic Review (ICER) accepted QALY target of $100,000. The cost-benefit ratio for ezetimibe is more favorable though the cost is still above the accepted ICER QALY targets and again, only of benefit for high and very-high risk patients. There was no benefit with either agent in low or moderate risk CVD. These results can help inform our decisions about the costs and benefits of adding PCSK9i's or ezetimibe to maximally tolerated statin doses, and when it may be of benefit to use these drugs in statin intolerant patients.

Adjuvant chemotherapy: Can society afford the cost?

Adjuvant chemotherapy is offered to many patients after chemotherapy treatment. A subset of patients treated with adjuvant chemotherapy benefit, others do not and suffer the adverse consequences of additional chemotherapy. The cost of adjuvant chemotherapy is high and the cost to avert one negative outcome even higher.

To understand the cost of adjuvant chemotherapy, 11 clinical trials reporting outcomes of agents used for adjuvant chemotherapy in the treatment of solid tumors were reviewed over a four-year period.[18] Monthly costs of the agents were obtained from the Micromedex RED BOOK database. Original clinical trial data was reviewed to determine the success of the agent in achieving the primary trial end point. Trials varied in the primary endpoint and included disease progression, relapse-free survival, or the occurrence of a disease related event. From each clinical trial, the number needed to treat to avert one negative outcome was determined. The drug cost per patient was defined as the cost to complete one adjuvant treatment per patient. The overall survival benefit has yet to be shown for any of the agents reviewed.

The total median drug cost of adjuvant chemotherapy was $158,000. The median cost per event averted was $1,610,000.

Improved identification of patients at risk for recurrence is needed to identify the subset of patients most likely to benefit from adjuvant chemotherapy. The current cost to avert a single event is extraordinarily high using current methods to identify patients recommended to receive adjuvant chemotherapy.

Adjuvant chemotherapy for colorectal cancer targeted use

Adjuvant chemotherapy is utilized in many cancers following initial treatment. As noted in the above review, a method to target who might benefit from adjuvant therapy is clearly needed. Ideally, only patients most likely to benefit from adjuvant chemotherapy would be offered this additional treatment. To improve patient selection, the use of adjuvant chemotherapy in patients with stage II colon cancer was directed by the presence or absence of circulating tumor DNA (ctDNA). ctDNA is well known to predict recurrence (>80%) when present after curative-intent therapy.[19] A trial involving 455 patients from 23 Australian centers compared standard management to ctDNA directed therapy.[20] Patients with a performance status of 0-2, without macroscopic evidence of metastatic disease and medically able to receive adjuvant chemotherapy were included. They were randomized 2:1 to the ctDNA group (n=302) and standard therapy (n=153). In the ctDNA group the presence of ctDNA guided recommendation for adjuvant chemotherapy. In the standard therapy group usual criteria to determine high-risk was used. There was no difference in observed survival or recurrence between the groups (see ctDNA table).

Table: ctDNA vs standard therapy outcomes

Parameter	ctDNA guided		Standard therapy		Relative risk (RR)(95% CI)
	ctDNA positive	ctDNA negative	High risk	Not high risk	or hazard ratio (HR)
Received AC	44 of 45	1 of 236	41	182	
% receiving AC	15		28		RR 1.82(1.25-2.65)
2-year RFS	93.5%		92.4 %		RR 1.1% (-4.1-6.2)
3-year RFS	86.4%	92.5	-	-	HR 1.83 (0.79-4.27)
3-year RFS	91.7		92.4		HR 0.96 (0.51-1.82)

AC = adjuvant chemotherapy RFS = recurrence free survival

Importantly, of the 302 patients in the ctDNA randomized group, only 15% required adjuvant therapy, compared with almost twice that number (28%) in the standard therapy group. Importantly, recurrence rates and survival did not differ. This study represents a major step forward in the selection of the subset of patients most likely to benefit from adjuvant chemotherapy. The 13% patients (28% less 15%) who did not receive adjuvant chemotherapy in the ctDNA guided group avoided the complications and side effects accompanying chemotherapy and the added costs of additional therapy without adversely effecting outcomes.

Asymptomatic patients with severe carotid artery stenosis and no surgical intervention had a low annual stroke rate of <1%

As medical and surgical therapies for carotid artery stenosis have evolved, optimal treatment for asymptomatic patients with severe stenosis(es) of 70% to 99% have been questioned. In a recent study, researchers retrospectively evaluated a cohort of community-based patients with severe stenosis of one or both carotid arteries.[21] Between 2008 and 2012, 3,737 study eligible patients were identified from the Kaiser Permanente health system. Of these, 2,314 had not yet had a surgical intervention. The mean duration of follow-up was 4.1 years.

Prior to surgical intervention, there were 133 ipsilateral strokes consistent with a carotid artery distribution, an annual stroke rate estimated at 0.9% per year (95% CI, 0.7%-1.2%). [21] The unadjusted rate of all-cause mortality during the study period was 51.4%. Statin therapy was the most common medical intervention with 74% of patients prescribed a statin at baseline.

The authors list several limitations related to the retrospective nature of the study including the inability to assess aspirin use as it is sold without prescription, the difficulties determining why surgical interventions would be performed in some patients and not others, and the well-published dilemma related to poor documentation of transient ischemic attacks (TIAs). An additional limitation includes the high rate of all-cause deaths and the potential lack of comorbid stroke diagnoses. Overall, in a community-based cohort, there was a relatively low stroke rate among asymptomatic patients with severe carotid artery stenosis(es) and without surgical intervention. Medical therapy is an appropriate option for these patients.

In contrast, a recent systematic review and network meta-analysis examined the results of seven RCT's of surgery compared to stenting for asymptomatic carotid artery stenosis.[22] As has previously been documented, the short-term stroke rate was higher with carotid artery stenting than with surgery. However, relevant to the above results seen with medical management, in those patients who underwent carotid endarterectomy for asymptomatic stenosis in these seven trials, the 30-day combined endpoint of stroke, MI, and death was over 3%. The results of the first contemporary trial of medical management versus surgery for asymptomatic carotid artery stenosis are due at the end of this year and may influence the current recommendation for medical management of asymptomatic carotid artery stenosis.

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Learning objectives	• Examine thyroid nodules and the varying degrees of importance and active surveillance in low-risk papillary thyroid carcinoma. • Apply pharmacological evidence to evaluate the use of aspirin compared with enoxaparin following hip and knee arthroplasty, treatment of actinic keratosis, and 5 alpha-reductase inhibitors and prostate cancer. • Discuss medical management concerning Medicare Shared Savings Program (MSSP) and Medicare Advantage (MA), functional cardiac testing after PCI, physical activity and depression and long-term oxygen therapy with moderate hypoxemia from COPD.

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Thyroid nodules: Focus on high value care

Thyroid cancer is one of the most over diagnosed and over treated cancers. In the last 25 years, the diagnosis of thyroid cancer has tripled and most of these cases reflect the detection of small papillary thyroid cancers.[1] The rate of thyroid lobectomy or total thyroidectomy during this same time increased almost six-fold, yet the mortality of thyroid cancer did not change, suggesting that most of these cases represent over diagnosis.

It has been estimated that at least one third of adults harbor small indolent papillary thyroid cancers, the vast majority of which will not produce symptoms during a person's lifetime.[2] A recent survey of 439 endocrinologists and surgeons who regularly treat thyroid cancer compared their recommendations to those of the American Thyroid Association's (ATA). Their recommendations represented overdiagnosis 64% of the time and over treatment 40% of the time when compared to the ATA guidelines.[3] The key issue for PCP's is differentiating between the infrequent, significant thyroid cancers and the frequent ones that are indolent, and not likely to cause clinical disease in the patient's lifetime. When diagnosed, these latter cancers should be managed with active surveillance, as per the ATA recommendations. The goal of assessing a thyroid nodule is therefore to identify those that represent cancers that could cause harm to the patient, and avoid diagnostic workups and treatment of those that would not cause harm.

Fifty percent of adults have thyroid nodules of which only 15% are clinically relevant.[4] Using patient characteristics and known risk factors along with imaging, particularly ultrasound, can help determine which nodules need follow-up. Nodules 1.5 to 2 cm in size can be followed with ultrasound without the need for FNA when there are minimal or no suspicious features. [5,6] Small (under 1-2 cm in diameter) papillary cancers can be safely followed. [7] This conservative approach avoids unnecessary and potentially harmful surgery.[1]

Patient risk factors for thyroid cancer are well appreciated. A thyroid nodule in a male has a 20-30% risk of malignancy; for a female the risk is 10-20%. For patients 50 years of age or younger, 20-30% of nodules are malignant; for those over 50 the figure drops to 10-20%. Thyroid nodularity increases with age, but does not increase the likelihood of cancer in an individual patient.[8] Following assessment of the patient, additional factors known to increase the risk of malignancy include: [5]

- Younger age
- A solid nodule
- Persistent new cervical lymphadenopathy
- Permanent voice hoarseness with evidence of laryngeal nerve compromise
- A family history of medullary thyroid cancer
- Rapid growth of the nodule
- Childhood exposure to ionizing radiation

Ultrasound should not be used to screen for thyroid nodules or thyroid cancer. However, ultrasound is very useful in characterizing significant thyroid nodules discovered on physical exam or incidentally on an imaging study and is the initial imaging test of choice to characterize a thyroid nodule. The incidence of thyroid cancer confirmed with ultrasound guided FNA is between 7 and 15%.[9] The ultrasonic characteristics that help determine the risk of malignancy in a thyroid nodule can be found in Table 1.

Ultrasound characteristics should be coupled with the other risk factors described above to fully characterize an individual's risk of malignancy. Very low-risk nodules (i.e., nodules with a cancer risk of <5%) should be managed only with periodic monitoring. Decision aids are available to assist in discussions with patients about the advantages of monitoring nodules with low-risk cancers.[10] Nodules with intermediate risk (i.e., those with variable risk of malignancy, but without high-risk features or signs of metastasis) in older patients or in patients with substantial comorbid illness may be managed with periodic imaging without the need for FNA. [5,11]

Table 1. [12,13]

Sonographic feature		TIRADS scoring	ATA Scoring (malignant risk)	Malignancy risk (%)
Not worrisome feature	Cystic nodule (CN)	1–2 points	Benign	<2%
	Iso-hyperechogenicity or Hyperechogenicity (HE)			Low risk
Single high-risk feature	Irregular Borders (IB)	3–4 points	Very low to intermediate risk	Low to intermediate risk
	Microcalcifications (MC)			
	Hypoechogenicity (Hypo)			
Multiple high-risk features	Hypo and MC	5 or more points	High risk	Intermediate to high risk
	Hypo and IB			

TIRADS=Thyroid Imaging Reporting and Data Systems ATA=American Thyroid Association

TIRADS grading seems to have a higher diagnostic accuracy [11]

The strategy for management of a thyroid nodule can be guided by a combination of size and sonographic characteristics. Almost all nodules smaller than 1 cm can be followed conservatively without the need for FNA regardless of finding on sonogram.[14] Nodules between 1.5 to 2.0 cm in size and low-risk features on ultrasound (Table 1) can be monitored and those with higher-risk features should be evaluated with FNA. Consideration of comorbid conditions is important in patients over 70 years of age in deciding if a FNA is warranted.

For nodules requiring further evaluation, FNA is the initial gold standard.[5] FNA accurately diagnoses 70% of lesions as benign. [14] Cytologic analysis of the FNA sample is critical. Pathologic categories are outlined in the Table 2, indicating risk of malignancy for each category. A growth rate of more than 2-4 mm (in the nodules largest dimension) per year should be suspicious for malignancy.[15]

Table 2. FNA cytology classification and malignant potential [12]

Cytologic classification	Occurrence in FNA (% of aspirated)	Malignancy overall estimated risk (%)
Non diagnostic or unsatisfactory	2–24	1–10
Benign	55–74	<4
Atypia of undetermined significance	1–18	15–30
Follicular neoplasm	2–25	20–35
Suspicious for malignancy	1–6	60–75
Malignancy	2–8	>97

Use of molecular analysis should be reserved for clinically relevant thyroid nodules when surgery is recommended based on indeterminant FNA cytology.[5] Molecular analysis has no role in routine screening.

Summary: Thyroid cancer is one of the most over diagnosed and over treated cancers. Screening for thyroid nodules is not recommended; thyroid nodules are frequent, increase with age and most are benign. The next most common category are those that represent indolent papillary carcinomas, which are present in up to one third of the population. These are predominantly the ones that fall into the over diagnosis category, in which case treatment can potentially result in patient harm. Small thyroid nodules should not be ultrasonographically followed or indiscriminately evaluated, rather the use of the Optimal Care thyroid nodule algorithm is recommended. (Click the Clinician/Patient Content link on page 10 for algorithm search.) Very low risk and low risk nodules under 1.5-2 cm can safely be followed without FNA as per the ATA guidelines. Ultrasound along with individual patient risk factors can help define which nodules need pathologic examination using FNA. Most patients with small papillary thyroid cancers should be offered active surveillance as the primary course of action.

Active surveillance is a viable treatment option for low-risk papillary thyroid carcinoma

An oft-used example of wasted care is the impact of the South Korean population-based screening program for papillary thyroid carcinoma and resultant impact on diagnosis (vastly increased) and mortality from the carcinoma (unchanged at near zero).[16] For when this most common type of thyroid cancer is diagnosed, active surveillance (AS), rather than surgery, is a viable treatment option. A study recently published in JAMA Oncology[17] and accompanying editorial[18] reinforce this approach. The study furthermore extends the parameters of inclusion for consideration of AS from the current standard of tumor size of 10mm or less and growth of no more than 3mm, to instead be used for patients with low-risk tumors up to 20mm, if growth was less than 5mm and total volume of the nodule did not double (respective yearly incidences were 1.2% and 2.2%). Surgery indications in the study included exceeding these parameters, development of biopsy-confirmed metastatic disease, or patient decision.

In the study, 222 patients with low-risk papillary thyroid CA seen in a California-based health system during the 2014-2021 timeframe were enrolled. 50.5% chose AS whereas the remaining 49.5% chose immediate surgery. Active surveillance consisted of thyroid ultrasound every six months for two years, then annually for the duration of the study if no growth was identified. Mean follow-up was 37.1 months. 90.1% of those in the AS group remained on AS, with 7.1% crossing over to have delayed surgery (half with an indication of 5mm or more of tumor growth, and half due to patient or provider preference). All patients (AS, immediate surgery, and delayed surgery) remain disease free at the latest follow up. There was no significant correlation between initial tumor size and subsequent tumor growth, nor between younger age and subsequent increase in tumor size.

Study authors also examined patient anxiety scores as part of the protocol and determined patients who opted for immediate surgery had higher scores at baseline compared to those who opted for AS, and this difference persisted over time. Anxiety remained high in the immediate surgery group and decreased from baseline in the AS group. After baseline measures, anxiety scores were not assessed in the small subset (8 patients) who underwent delayed surgery.

Although sample size was small and the study was not randomized, findings support consideration of expanded criteria for use of AS in low-risk papillary thyroid CA, and further reinforces the need for shared decision-making to account for patient anxiety levels. Ideally, this SDM conversation should take place at the time of FNA and prior to the diagnosis of thyroid cancer, as this has been shown to markedly increase the use of AS. Of note, more than 70% of diagnosed thyroid cancers in the US are smaller than the 20mm cut-off used in this study of AS.[19]

Aspirin is less effective than enoxaparin in preventing symptomatic venous thromboembolism after hip or knee arthroplasty

Routine use of thromboprophylaxis following total hip and knee arthroplasty improves post-operative morbidity and mortality from thromboembolic events such as pulmonary embolism. Aspirin has been prescribed for thromboprophylaxis, but its efficacy has not been well-studied. Recently, investigators compared aspirin monotherapy with enoxaparin monotherapy following hip and knee arthroplasty and found that aspirin was inferior.[20]

The study used a cluster-randomized, crossover methodology. Hospitals were randomized to administer aspirin (100 mg/d) or enoxaparin (40 mg/d) for 35 days following total hip arthroplasty and for 14 days following total knee arthroplasty. Patients were followed for 90 days to evaluate the primary outcome of symptomatic venous thromboembolism. A noninferiority margin was set at 1%.

Enrollment was stopped after interim analysis. Among 9,203 patients who completed the trial, 256 developed at least one form of symptomatic venous thromboembolism: pulmonary embolism (n=79), above-knee DVT (n=18), and below-knee DVT (n=174). The rate of venous thromboembolism was 3.45% with aspirin prophylaxis versus 1.82% with enoxaparin prophylaxis, which led to early termination of the trial. [20]

Based on this study, monotherapy with aspirin is not as effective as monotherapy with enoxaparin in preventing venous thromboembolic events following hip or knee replacement. This is relevant to primary care as we should recommend enoxaparin prophylaxis to appropriate patients as part of our preoperative evaluations for patients planned for hip or knee arthroplasty.

Treatment of actinic keratosis

A recent study in JAMA Dermatology [21] looked at the incidence of treatment for actinic keratoses (AK's) in patients over age 65 from Medicare claims data. Of five million patients examined, 29% had one or more treatments for AK's over a five year period. 79% of these treatments were by dermatologists, and 79% of patients were treated with liquid nitrogen. If left untreated, AK's can develop into squamous cell carcinoma. Importantly, fluorouracil, which has recently been shown to decrease the incidence of squamous cell carcinoma,[22] was used less than 3% of the time. Randomized trials on the effectiveness of "field therapy" treatment of AK's are limited. A NEJM study [23] compared four different approaches to field therapy in 624 patients, including the three most commonly used in the US: fluorouracil, imiquimod, and photodynamic therapy. Of these three, fluorouracil was effective in 75% of patients compared to 54% with imiquimod and 38% with photodynamic therapy. Patient satisfaction and increase in health-related quality of life were also highest with fluorouracil. Fluorouracil is available as an inexpensive generic. This information is important as treatment of uncomplicated AK's using liquid nitrogen for isolated lesions and topical fluorouracil for field therapy is easily accomplished in the primary care setting.

5 alpha-reductase inhibitors and prostate cancer mortality

5 alpha-reductase inhibitors (5-ARIs), the standard treatment for benign prostatic hyperplasia, are associated with a reduced risk of prostate cancer. Two prospective randomized trials demonstrated that 5-ARIs reduced the incidence of low and intermediate risk prostate cancer. [24,25] There appeared a concern over possible increased rate of high-risk prostate cancer, however this was felt to likely be a detection bias within the trials. 18-year follow up of one of the trials showed no difference in all-cause mortality and a non-significant reduction in prostate cancer specific mortality. Overall, there are a paucity of data looking at the association of 5-ARI use with prostate cancer mortality. To help address this, a population-based study was conducted in Sweden, looking at ~349,000 men who had a PSA test done between 2007 and 2018, and for whom data were analyzed in 2021. [26] Approximately 26,000 of these men were 5-ARI users.

With a median follow-up of 8.2 years, and a median exposure to 5-ARIs of 4.5 years, there were 852 deaths from prostate cancer. There were no differences in all-cause mortality related to 5-ARI use, however 5-ARI use was associated with a lower prostate cancer mortality and this mortality improvement increased with duration of use. For those using a 5-ARI for over 8 years, prostate cancer mortality was 56% lower compared to non-users. Overall, the 5-ARI users had larger prostates, higher PSA's, and a higher rate of PSA testing and biopsy. Therefore, it is still unclear if 5-ARIs inherently suppress or slows the growth of prostate cancer, or if the survival difference is caused by increased monitoring in this population. The authors concluded that 5-ARI treatment does not increase the risk of prostate cancer and may decrease the risk of prostate cancer mortality.

MSSP spending is 23-30% higher than MA spending across four clinical conditions

Several studies have previously documented that Medicare Advantage (MA) provides care that is less expensive than FFS Medicare. However, CMS intended the Medicare Shared Savings Program (MSSP) to be an ACO based care model that could compete with MA in terms of reduced costs. Currently about 47% of Medicare beneficiaries are enrolled in MA and about a third in MSSP. Researchers from the Perelman School of Medicine at U. Penn performed a retrospective economic evaluation using data from 15,763 beneficiaries who were continuously enrolled in MA or MSSP from January 1, 2014, to December 31, 2018, with diabetes, congestive heart failure (CHF), chronic kidney disease (CKD), or hypertension.[27] All participants received care at a single large academic health care system (Ochsner). Propensity matching accounted for variables in demographic characteristics, clinical variables, and socioeconomic variables.

For disease-specific cohorts over the study follow-up period, mean unadjusted per-member per-year (PMPY) spending differences between MSSP and MA were $2,159 (diabetes), $4,074 (CHF), $2,560 (CKD), and $2,335 (hypertension). Adjusted MSSP spending remained 23% to 30% higher than MA spending across the follow-up period in all disease cohorts. Primary care was the only category where spending was higher in the MA population compared to the MSSP population. Outpatient hospital spending contributed the most to higher MSSP overall spending, but inpatient spending was also significantly higher for MSSP in all disease cohorts. Specialist spending was not significantly different between MSSP and MA beneficiaries across all disease cohorts. Quality metrics were similar across both groups.

The drivers of this spending difference are likely multifactorial and complex. These include improved utilization management in MA, differences in benefit design, differences in site of service of outpatient services, and unmeasured socioeconomic factors, to name but a few. This study is one of a growing body of literature demonstrating improvements in the cost of care related to the MA model.

Functional cardiac testing after PCI shows no benefit compared with usual care alone

Evidence is clear that, in stable coronary artery disease in most patients, medical management is as effective as catheter-based therapy for the prevention of major adverse cardiovascular event (MACE), and therefore evaluation with functional testing (e.g., nuclear stress tests) is not indicated.[28,29,30] Indeed, this type of testing may result in unnecessary cardiac catheterization. A recent study titled the POST-PCI trial further shows that functional testing even among high-risk patients after percutaneous coronary intervention (PCI) provides no benefit.[31] This randomized controlled multi-center study examined 1,706 patients who had undergone PCI (96.4% of whom received a drug-eluting stent) and deemed 'high-risk' by anatomical or clinical characterization. This definition of 'high risk' included those with left main disease, bifurcation disease, multivessel disease, diffuse long lesions, chronic renal failure or hemodialysis and diabetes mellitus. Those randomized to functional testing received standard care and underwent a routine nuclear stress test, exercise ECG, or stress echocardiogram roughly one year after randomization. The other group received standard care with no routine functional testing. All patients had routine follow-up every six months for two years after randomization. The primary outcome at two years was a composite of death from any cause, myocardial infarction, or hospitalization for unstable angina. There was no significant difference between the two groups for the primary outcome, nor for the secondary outcomes that were each a component of the primary composite outcome.

Even looking at the secondary outcomes of coronary angiography and repeat revascularization, the differences between groups was small, and directionally suggest that those who undergo routine functional testing at one year are more likely to have repeat testing later, with subsequent higher rates of revascularization, yet without any significant improvement in outcomes. At the two-year follow-up, 12.3% of the functional testing group and 9.3% in the standard care group had angiography, with 8.1% and 5.8% undergoing revascularization, respectively. In summary, this is another study that provides evidence that in stable coronary artery disease, even in high-risk patients with previous PCI, functional testing is not typically indicated and may lead to additional unnecessary and potentially dangerous procedures.

Does physical activity decrease the risk of depression?

Previous studies have shown that increased physical activity is associated with lower rates of depression. A recently published meta-analysis aimed to establish a dose-response between the levels of self-reported activity and incident depression.[32] The meta-analysis included prospective cohort studies that (1) reported at least three levels of activity with corresponding risk estimates of depression, (2) included at least 3,000 adults, and (3) provided at least three years of follow-up. A total of 15 studies met inclusion criteria. The 15 studies comprised 191,130 participants, 2,110,588 person-years.

In this analysis, activity volumes were converted to mMET (marginal metabolic equivalents) hours per week. Investigators used mMET midpoints for activity ranges and multiplied the midpoint values by the hours of activity per week reported by study participants. Light activities (e.g., light housework, light gardening) have a range of 0.5-2 mMETs, so a midpoint value of 1.5 mMET was used. Moderate activity was assigned a midpoint value of 3.5 mMET, and vigorous activity was assigned a value of 7 mMET. The World Health Organization advises 150-300 minutes of moderate activity or 75-150 minutes of vigorous activity per week,[33] which represents ~9-18 mMET-hours per week.

Study participants with half the World Health Organization recommended activity (4.4 mMET-h/wk) had 18% lower risk of depression compared to participants who reported no activity. Adults with 8.8 mMET-h/w had 25% lower risk of depression. Activity levels beyond 8.8 mMET-h/w led to diminishing addition potential benefits and greater uncertainty.

Limitations of the studies include self-reports of activity, which can be biased, and observational methodologies, which cannot establish causality. Confounders could affect both the inclination to be sedentary and the risk of depression.

Although we cannot assume causality, it is reasonable to promote physical activity as one of the potential treatments when patients present with depression. Given that exercise improves general health, has few potential harms, and has minimal, if any, costs, health care providers should promote exercise broadly, regardless of the presence or absence of depression.

Long-term oxygen therapy provides no mortality benefit for patients with moderate hypoxemia from COPD

Long-term oxygen therapy (LTOT) has demonstrated mortality benefit in patients with chronic obstructive pulmonary disease (COPD) and severe persistent hypoxemia . The use of LTOT in other populations has been prescribed based on the assumption of benefit, but limited evidence. A recent systematic review and meta-analysis looked at the mortality benefit of LTOT compared with usual care or ambient air via sham concentrators over a three-year treatment period for patients with COPD who had hypoxemia that wasn't severe and persistent.[34] The investigators included studies that examined patients with COPD and moderate hypoxemia, nocturnal hypoxia with desaturations, or both. They used a cut-off of a PaO2 of 56 mm Hg or higher (roughly SaO2 of 89% or higher) as a marker that the hypoxemia was not 'severe', but rather fell in the 'moderate' range. For nocturnal desaturations, they used the European and American cut-offs of ≥30% nighttime recording with SpO2 of <90% or SpO2 of <90% for ≥5 min with a nadir of ≤85% during the night , respectively. For this study, LTOT was defined as the prescription of low-flow oxygen therapy for 15-18h per day or delivered during sleep time only (nocturnal oxygen therapy).

The authors identified five high-quality trials of LTOT with a combined total of 1,002 patients. They defined a minimally important clinical difference in mortality reduction with LTOT during 3 years of follow up as a 30-40% reduction. The results demonstrated a relative risk of death in the LTOT group of 0.91 (a relative risk reduction of 9%), with the 95% confidence intervals crossing (0.72-1.16). This means that even with reporting results in terms of relative risk, which tends to exaggerate differences compared with reporting using absolute risk reduction, the difference between the LTOT group and the group that did not receive LTOT was not clinically meaningful, if indeed it was present at all. Additional analyses in the paper suggested that quality of life, COPD exacerbation rates or hospitalizations were not different between LTOT and non-LTOT groups, although the data was not as complete as it was for the findings of the lack of mortality risk reduction.

At the population level, prescribing LTOT to patients with COPD and moderate daytime hypoxemia or isolated nocturnal hypoxemia or both, appears to be wasted care in terms of mortality prevention, and may also be wasted care for other measures. As always when interpreting population-level studies, individual factors, complications, comorbidities and disease severity must be considered when making patient-specific decisions.

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