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Forum in review

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FEATURED ARTICLES FROM THE 2018 FORUM FOR EVIDENCE-BASED MEDICINE

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Forum in review, revisits previously published articles from our 2018 OptumCare Evidence-Based Medicine Forum newsletters. If you missed it the first time, here is another opportunity to read and discuss information relevant to optimal care. The articles have not changed, but offer you the chance to claim CME credit and recall content from last year. We will create three volumes of the Forum in Review in 2019.

Claiming credit	CME/CNE credit is available. For more information, visit optumhealtheducation.com/ebm-forum
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	At the end of this educational activity, participants should be able to: • Explore the educational content surrounding testosterone replacement therapy in older males as a means to advance optimal care outcomes. • Recall pharmaceutical recommendations for the management of PCSK9 inhibitors and cost effectiveness with the new classes of diabetes medications using evidence-based literature. • Apply medical management principles grounded in evidence-based medicine that could help modify and improve treatment and clinic guidelines for fall prevention, Type 2 diabetes insulin, new versus old, and an algorithm for diagnosis predictions for benign paroxysmal positional vertigo management.

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Testosterone replacement in the older male

Testosterone use has increased over ten fold in the last decade, without a clear picture of the risks and benefits. Although areas of research are still incomplete, data are emerging that begin to answer some of the questions surrounding the use of testosterone replacement in older men. In response to an Institute of Medicine request, the NIH designed the "Testosterone Trials", a series of seven randomized, placebo based trials of testosterone replacement using a single patient population[1]. Each trial addressed one of the following key issues:

- Sexual function
- Physical function
- Vitality
- Cognitive function
- Anemia
- Bone density
- Cardiovascular status

Many of the results were published in the NEJM[2] and JAMA (2/21/17)[3,4], and are detailed here. Overall, about 800 men over age 65 with low testosterone (<275 mg/dl) were studied for 12 months. The average age was 72. This was a high vascular risk population. 63% were obese, 72% were hypertensive, and one third had diabetes. They were treated to the mid normal range for young adults using topical testosterone.

Sexual Function Trial – Both sexual desire and sexual function improved during the trial with about a 42% improvement over placebo. The benefits began to wane in the last quarter of the year. The magnitude of the effect was correlated with the testosterone level and included both increased desire and erectile function. Erectile function increased less than that seen in the PDE5 trials with specific ED drugs.

Physical Function Trial – Using the six minute walking distance, about 75% more men increased their walking distance by 50 meters and 50% more men scored higher on the Physical Function 10 scale. These results were statically significant but of fairly small magnitude.

Vitality Trial – Using the SF36, as well as a mood/depression scale, and a fatigue scale, there were statistically significant but clinically small benefits in vitality.

Cognitive Function Trial – Using four sophisticated tools to measure cognitive function, there were no improvements in memory or cognitive function with testosterone replacement.

Anemia Trial – Of the 788 men enrolled in the trial, 126 had anemia diagnosed based on a hemoglobin level <12.7 g/dl. At one year, 54% of the testosterone replacement group had at least a 1 g/dl increase in hemoglobin level compared to 15% in the placebo group. At the end of one year, 58% of the replacement group had resolution of mild anemia compared with only 22 % of the placebo group. Both measures reached statistical significance.

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Bone Density Trial – 211 men participated in the bone density trial. After one year of testosterone replacement, when compared to placebo, bone density at the spine increased 7.5% vs 0.8% and bone density at the hip improved 10.8% vs 2.5%. Both of these reached statistical significance. The trial was not powered to evaluate improvement in fracture risk.

Cardiovascular Risk Trial – This trial looked at a smaller subset of the original trial and enrolled only 170 patients. The study looked at the changes in the volume of non-calcified coronary artery plaque seen on coronary CTA in treated versus placebo patients after one year of treatment. Remember that this was a group of high CV risk patients. There was a large random baseline difference in the two groups (204 cubic mm of total non-calcified coronary plaque in the treated versus 317 cubic mm in the placebo group). The treated group had a greater increase in total non-calcified plaque volume at 28 cubic mm, versus an 8 cubic mm increase in the placebo group at one year. There were no adverse CV outcomes in either group which is not unexpected given the small size of the trial. There are other data looking at the potential CV risk of testosterone replacement. In a prior randomized trial of over 300 middle aged and older men, testosterone replacement for three years had no effect on CIMT or coronary calcium score[5]. Likewise, another trial in 114 men also showed no change in CIMT measures over two years[6]. As we have learned from studying other drug classes, cardiovascular risk may only truly be quantified by a large prospective randomized event driven CV outcomes trial. The same situation also exists regarding the potential risk of prostate cancer with prolonged therapy. This trial is currently under way and results should be available in 3-4 years. It will evaluate both the potential for increased risk of CV events and prostate cancer. The NWP research center is participating in this trial. In the interim, there exists only the above conflicting short term data in small populations. So where does this leave us with respect to testosterone use in older men? We now have documented small to modest benefits across a variety of clinical measures. There are also a wide range of responses within each of these trials with some men exhibiting a much larger benefit and some deriving no benefit. There were no signals, nor were the trials powered to see a signal, with respect to CV events or prostate cancer risk. With respect to potential CV risk, this most recent trial was in a very high risk group with over 50% of participants having a baseline coronary calcium score over 300. Nonetheless, it is significant that plaque volume increased with testosterone treatment at one year. Until reliable CV risk and prostate cancer risk data become available, a shared decision making approach is mandatory. This needs to include a discussion of the wide range of responses seen in older men with testosterone replacement. It also should include discussing the wisdom of continued therapy only in the setting of meaningful clinical benefit. Lastly, it needs to include a discussion of the potential for accelerated coronary plaque development in high risk individuals and the as of yet unknown potential risk of prostate cancer development. If men with age related hypogonadism choose testosterone replacement, there next is the issue of cost. The topical branded agents have a cost in excess of $7,000 yearly. Economic methods of testosterone replacement include injections of depo-testosterone at ~$10/month, or compounded formulations which will cost anywhere from $60-$120 monthly depending on the required dose. Therapy through the compounding pharmacies can be initiated at 200 mg/g, 0.5 gm daily with 60 grams dispensed. The dose can then be titrated based upon the individual's testosterone level on therapy. The 60 gm quantity will last from one to four months using this approach.

1. Snyder, P. J., Ellenberg, S. S., Cunningham, G. R., Matsumoto, A. M., Bhasin, S., Barrett-Connor, E., . . . Resnick, S. M. (2014). The testosterone trials: Seven coorinated trials of testosterone treatment in elderly men. Clinical Trials, 11, 362-375. doi:10.1177/1740774514524032

2. Snyder, P. J., Bhasin, S., Cunningham, G. R., Matsumoto, A. M., Stephens-Shields, A., Cauley, J. A., . . . Ellenberg, S. S. (2016). Effects of testosterone treatment in older men. The New England Journal of Medicine, 374(7), 611-624.

3. Budoff MJ, Ellenberg SS, Lewis CE, Mohler ER, Wenger NK, Bhasin S, Barrett-Connor E,. Testosterone treatment and coronary artery plaque volume in older men with low testosterone. JAMA. 2017;317(7):708–716. doi:10.1001/jama.2016.21043

4. Resnick SM, Matsumoto AM, Stephens-Shields AJ, Ellenberg SS, Gill TM, Shumaker SA, Pleasants DD, Barrett-Connor E,. Testosterone treatment and cognitive function in older men with low testosterone and age-associated memory impairment. JAMA. 2017;317(7):717–727. doi:10.1001/jama.2016.21044

5. Basaria S, Harman SM, Travison TG, Hodis H, Tsitouras P, Budoff M, Pencina KM,. Effects of testosterone administration for 3 years on subclinical atherosclerosis progression in older men with low or low-normal testosterone levels: A randomized clinical trial. JAMA. 2015;314(6):570–581. doi:10.1001/jama.2015.8881

6. Ensrud KE. Review: Calcium supplements increase risk for myocardial infarction but not mortality or stroke in adults. Ann Intern Med. 2010;153:JC5–7. doi: 10.7326/0003-4819-153-10-201011160-02007

Cost effectiveness of the PCSK9 inhibitors based upon the FOURIER Trial[7]

This is the first trial looking at PCSK9 inhibition on a background of statin therapy to evaluate for incremental reductions in cardio-vascular (CV) outcomes in a high risk cohort.

The FOURIER trial looked at over 27,000 patients, 81% of whom had a prior MI. They were on background statin therapy and began the trial with an average LDL of 92 mg/dl. Treated patients completed the trial after an average of 2.2 years, with an average LDL of 30 mg/dl, representing a 59% LDL reduction. The absolute CV risk reduction in the treated group was 1.5% with 62 fewer events per year in the treated group. This equates to a cost to prevent one event of $930,000 per year. Assuming a Quality Adjusted Life Year, (QALY) of $75,000, the PCSK9 inhibitors would need to be priced at ~$1,200/year, or less than one seventh of their current cost, in order to be considered cost effective. Unfortunately, this modestly effective drug class is not priced in the range that would justify use in this population. In response to lagging sales, Amgen reduced the price of its drug by 60%, which nonetheless is still almost five times above its value based price. The only other drug to be similarly studied is ezetimibe.

The IMPROVE-IT Trial[8], published in 2015, looked at patients following an acute coronary syndrome on a background of statin therapy and looked at the benefit of added ezetimibe. After 6 years, there was an absolute risk reduction of 2% with the addition of ezetimibe. The ending LDL in the ezetimibe group was 54 mg/dl and the NNT to prevent one event per year was 91. Although now generic, the price is still about $2,400/year, resulting in a cost to prevent one event of $218,000, also out of the range of accepted cost effectiveness.

7. Kazi DS, Penko J, Coxson PG, et al. Updated Cost-effectiveness Analysis of PCSK9 Inhibitors Based on the Results of the FOURIER Trial. Jama. 2017;318(8):748. doi:10.1001/jama.2017.9924.

8. Watkins E. IMPROVE-1 Research Trial. http://isrctnorg/>. 2013. doi:10.1186/isrctn14333261.

Cost effectiveness of the CV risk reduction with the new classes of diabetes medications

Beginning with the concern that rosiglitazone increased CV mortality; the FDA has mandated long-term CV outcome trials for all new drugs used to treat Type 2 DM.

Several recent publications[9] have examined the CV outcomes of the new drug classes. Neither the DPP-IV class nor the new extended basal insulins have demonstrated any improvement in CV outcomes. The SGLT2 inhibitors and the GLP1 agonists on the other hand were shown to slightly improve CV and renal outcomes compared to placebo. These studies had large sample sizes which allowed very small differences in outcomes to reach statistical significance. Keep in mind that these studies were done in patients at high CV risk (on average, about 75% of these patients had prior MI or stroke). This suggests little or no benefit in individuals at lower CV risk. These drugs are now being heavily marketed for cardio protection based upon this benefit. The very important question in this author's opinion, therefore, is what is the cost to prevent one vascular event in this high risk cohort?

The results are as follows:

- Canagliflozin/Invokana - $1.5 million per saved vascular event
- Empagliflozin/Jardiance - $475,000 per saved vascular event
- Liraglutide/Victoza - $2.1 million per saved vascular event

When considering the cost effectiveness of these drugs for cardio protection, they are priced anywhere from 6 fold (empagliflozin) to 28 fold too high (liraglutide). In other words, when considering the choices for treatment of Type 2 DM, this new data should have minimal to no impact on choice of therapies.

The ACC/AHA recently released primary prevention of CAD guidelines and suggested that these drugs be used for primary prevention in selected patients with DM2. The above studies document that the cost to prevent one CV event with these drugs is anywhere from 6-28 times more expensive than its value based price in a population of patients with either established vascular disease or very high vascular risk. Using these drugs in the lower risk primary prevention population would likely result in cost effectiveness figures which are considerably more expensive than the above estimates.

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9. Smith RJ, Goldfine AB, Hiatt WR. Evaluating the Cardiovascular Safety of New Medications for Type 2 Diabetes: Time to Reassess? Diabetes Care. 2016;39(5):738-742. doi:10.2337/dc15-2237

Fall Prevention

28% of community dwelling adults over age 65 suffer a fall in any given year, resulting in over 29 million falls. Injury occurs in over one third of cases and results in 2.8 million ER visits annually. The most common reasons for falls include lower extremity muscular weakness and osteoarthritis, neuropathy with decreased balance, vision loss, cognitive decline, home hazards, and drugs. The USPSTF recently examined the literature on interventions to prevent falls[10]. Although complex multifactorial intervention strategies showed a small benefit, the most significant benefit was seen with supervised exercise programs which resulted in reductions of fall related injuries in the range of 40-60%. Most of our patients have access to fall prevention exercise programs though physical therapy, Silver Sneakers, or local community recreation centers. The key to fall prevention is the proper identification of patients susceptible to falls, mitigation of any correctible causes, and referral for a fall prevention exercise program. The screening process is simple and should be performed by the medical assistant or nurse at the time of the yearly health examination in all seniors. It consists of one question followed by the "timed get up and go test" for those with a positive response (or those exhibiting frailty or balance difficulty at the time of the examination). The test is performed by timing how long it takes for a patient to rise from a hardback chair, walk ten feet, return to the chair and sit down. A time longer than 14 seconds is associated with an increased fall risk. Attached to the forum are three pieces from a review on fall prevention[11]: https://www.mdedge.com/sites/default/files/issues/articles/Beegan_FallsintheElderly.pdf

- The screening protocol algorithm [Figure 1]
- A list of the most frequent drug classes associated with increased fall risk [Table 1]
- A list of evidence based recommendations for interventions to reduce fall risk [Table 2]

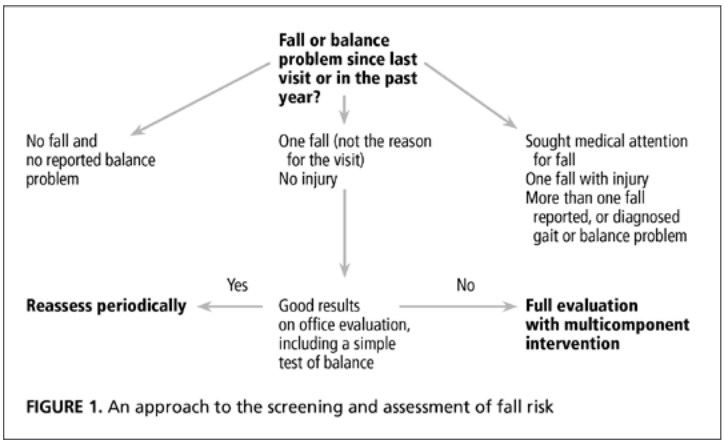

FIGURE 1. An approach to the screening and assessment of fall risk

TABLE 1

Drug classes associated with falls

Drug	Odds ratio
Any psychotropic	1.73
Any antidepressant	1.66
Type 1a antiarrhythmics	1.59
Sedative-hypnotics	1.54
Tricyclic antidepressants	1.51
Neuroleptics	1.50
Benzodiazepines	1.48
Digoxin	1.22
Nitrates	1.13
Antihypertensives[a]	NS

[a] Calcium channel blockers, diuretics, loop diuretics, angiotensin-converting enzyme inhibitors, beta-blockers.

DATA FROM LEIPZIG RM, CUMMING RG, TINETTI ME. DRUGS AND FALLS IN OLDER PEOPLE: A SYSTEMATIC REVIEW AND META-ANALYSIS: I. PSYCHOTROPIC DRUGS. J AM GERIATR SOC 1999; 47:30–39.

TABLE 2

Interventions to prevent falls in older community-dwelling adults

Rating level A (strongly recommended)

Exercise for balance, gait, and strength; includes tai chi; customized to the patient

Interventions targeted to all fall risk factors

Vitamin D ≥ 800 units/day for proven vitamin D deficiency

Home environment assessment by healthcare professional with modification as needed

Rating level B (recommended)

Stopping or minimizing psychoactive and antipsychotic medications

Review of medications and reduction of the total number

Exercise, with group or at home

Expedited surgery for older women with cataracts

Assessment and treatment of postural hypotension

Dual-chamber cardiac pacing for cardioinhibitory carotid sinus hypersensitivity

Vitamin D 800 U/day for suspected vitamin D deficiency or high risk of falls

Rating level C (no recommendation for or against)

Management of footwear and foot problems

Noncataract vision interventions

Change of eyewear from multifocal to single corrective lens

Wearing shoes with low heels and a wide base

BASED ON INFORMATION IN: PANEL ON PREVENTION OF FALLS IN OLDER PERSONS, AMERICAN GERIATRICS SOCIETY AND BRITISH GERIATRICS SOCIETY. SUMMARY OF THE UPDATED AMERICAN GERIATRICS SOCIETY/BRITISH GERIATRICS SOCIETY CLINICAL PRACTICE GUIDELINE FOR PREVENTION OF FALLS IN OLDER PERSONS. J AM GERIATR SOC 2011; 59:148–157.

10. US Preventive Services Task Force. (2018). Interventions to prevent falls in community-dwelling older adults: US Preventive Services Task Force recommendation statement. JAMA, 319(16), 1696-1704. doi:10.1001/jama.2018.3097

11. Beegan, L., & Messinger-Rapport, B. J. (215). Stand by me! Reducing the risk in injurious falls in older adults. Cleveland Clinic Journal of Medicine, 82(5), 301-307. doi:10.3949/ccjm.82a.14041

Cost effective management of Type 2 diabetes: Insulin Analogs – The "New" versus the "Old"

The "new" basal insulin analogs have largely replaced the use of NPH insulin at more than ten times the cost. New data suggests that there are not substantial benefits to these insulins despite the exorbitant costs, which challenge our patients' ability to pay for them.

The first study[12] was a retrospective study of the large Kaiser Health plan data base and looked at the risk of an ER visit for hypoglycemia as well as overall levels of A1c control within one year of initiating either a new insulin analog or NPH insulin in over 25,000 patients. The rate of severe hypoglycemia necessitating ER visit or admission was lower in the NPH group by about 25%, although the absolute risk was low in both groups. Likewise, the overall A1c control was better in the NPH group (8.1% in the new analog group and 7.9% in the NPH group).

The second study[13] was a meta-analysis of Thirty-nine trials in over 26,000 patients. Comparing all new basal analogs with NPH showed equivalent glucose lowering effects, no significant differences in the rate of severe hypoglycemia and only a mild reduction in the rate of nocturnal hypoglycemia with the longer acting newer insulin analogs compared to the older basal analogs and NPH.

Given the new ACP guideline suggesting a lowering of treatment intensity in most adults with Type 2 DM, the data from these two trials suggests that our patients may do just as well and perhaps better, using generic NPH insulin at one tenth the cost of the newer agents. **Each CDO may want to consider a systematic approach for converting the appropriate patients to generic NPH at a cost of $25/vial, which would be about one twentieth the cost compared to a branded agent for a patient on 50 units of basal insulin daily.**

Benign Paroxysmal Positional Vertigo (BPPV) – Algorithm for Prediction of Diagnosis

BPPV is the most common form of vertigo and may be misdiagnosed as vertigo of central origin or due to vertebrobasilar insufficiency. This may result in unnecessary referrals, ER evaluations or imaging of the posterior circulation. Since isolated vertigo is a symptom of vertebrobasilar insufficiency in under 1% of cases, it would be useful to have a highly accurate diagnostic algorithm to help establish the diagnosis of BPPV such that ENT/neurology referrals, ER evaluations and unnecessary imaging may be avoided. Such a diagnostic algorithm was developed in 2016 and recently prospectively tested in 200 patients presenting to a university ENT department for dizziness or vertigo.[14] Use of the algorithm was 75% sensitive and 100% specific such that no patient diagnosed using the algorithm had an alternative etiology for their symptoms. As expected, the features which correlated with BPPV were:

- Vertigo described as lasting seconds as opposed to minutes, or longer
- Vertigo triggered by lying down or rolling over in bed
- The absence of tinnitus, hearing loss, or headache associated with the vertigo

Vertigo symptoms meeting these criteria should be treated with Canalith Repositioning and/or vestibular rehabilitation prior to referral or imaging.

12. Lipska, K. J., Parker, M. M., & Moffet, H. H. (2018). Association of initiation of basal insulin analogs vs neutral protamine hagedorn insulin with hypoglycemia-related emergency department visits or hospital admissions and with glycemic control in patients with type 2 diabetes. JAMA, 320(1), 53-62. doi:10.1001/jama.2018.7993

13. Madenidou, A.-V., Paschos, P., Karagiannis, T., Katsoula, A., Athanasiadou, E., Kitsios, K., . . . Tsapas, A. (2018). Comparative benefits and harms of basal insulin analogues for type 2 diabetes: A systematic review and network meta-analysis. Annals of Internal Medicine, 169(3), 165-174. doi:10.7326/M18-0443

14. Britt, C. J., Ward, B. K., & Owusu, Y. (2018). Assessment of a statistical algorithm for the prediction of benign paroxysmal positional vertigo. JAMA Otolaryngology Head and Neck Surgery. doi:10.1001/jamaoto.2018.1657

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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 has successfully developed and reported numerous clinical quality studies in primary care, including tobacco cessation, osteoporosis, asthma, diabetes, hypertension, and ischemic vascular disease. 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 OptumCare. He has served as Chief Medical Officer since 1995. 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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