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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	At the end of this educational activity, participants should be able to: <ul style="list-style-type: none"> • Explore the educational content surrounding syncope as a means to advance optimal care outcomes. • Review pharmaceutical recommendations for the management of type 2 diabetes and high cardiovascular risk from the CAROLINA Trial. • Apply medical management principles grounded in evidence-based medicine in regards to Cancer prevention from the human papillomavirus (HPV) vaccine, risk of clinical stroke in elective surgical procedures, and preoperative ECG's.

Accreditation statement



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Credit designation statements

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The participant will be awarded up to 1.00 contact hour(s) of credit for attendance and completion of supplemental materials.

Nurse practitioners

The American Academy of Nurse Practitioners Certification Program (AANPCP) accepts credit from organizations accredited by the ACCME and ANCC.

Physicians

OptumHealth Education designates this enduring activity for a maximum of 1.00 AMA *PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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Attendance

A certificate of attendance will be provided to learners upon completion of activity requirements, enabling participants to register with licensing boards or associations that have not been pre-approved for credits. To apply for credit types not listed above, participants should use the procedure established by the specific organization with which they wish to obtain credit.

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Syncope¹



Syncope is commonly encountered in both the primary care and emergency room setting. Excessive evaluation, including hospitalization and unnecessary testing is often seen with low risk forms of syncope. Most often the etiology and subsequent management can be ascertained from a careful history, exam and ECG. The three primary causes of syncope in order of decreasing frequency are neurally mediated, orthostatic, and cardiac. These first two forms of syncope are of low risk and benign. Studies have shown that the long term survival is normal in patients with syncope who have no structural heart disease.

Neurally Mediated Syncope accounts for two thirds of all cases. The majority of these can be diagnosed based solely on the history of the event. Premonitory symptoms include lightheadedness, diaphoresis, nausea, malaise, and tunnel vision. Palpitations may occur. What is often not appreciated is that if syncope is prolonged, brief tonic/clonic movements and urinary incontinence may be seen. Seizure evaluation is not needed in the setting of the above typical history. Post syncope malaise is common. Episodes may occur while seated or standing, but rarely when supine. Common forms of this are vasovagal, carotid hypersensitivity, and post exercise syncope (as opposed to syncope **during** exercise which may be cardiac). The mechanism of neurally mediated syncope is strong contractions in an “under filled heart” which results in a paradoxical reflex causing both bradycardia and hypotension. Typical etiologies include prolonged standing, emotional stress, micturition, weight lifting, hot environments, and carotid sinus stimulation, among others. Carotid sinus massage should always be done as part of the evaluation as it may unmask the underlying conduction system block often seen with this form of syncope. It is not however, diagnostic, as about 40% of the elderly will have some degree of carotid hypersensitivity. Neurally mediated syncope can be confirmed with tilt table testing, although this is not usually necessary. The specificity of tilt table testing is 90%, the sensitivity 80%, and the false positive rate 10%. When considering this diagnosis, think of the “3P’s”:

1. Posture – prolonged standing
2. Prodrome – sweating, pallor, sensation of warmth, tunnel vision
3. Provocation – blood draw, pain, micturition, exercise, emotional stress

Orthostatic Hypotension accounts for about 10% of all syncope but is the most common form of syncope in the elderly. The primary mechanisms are autonomic dysfunction, volume depletion, and drug induced. Autonomic dysfunction results in the inability to constrict splanchnic and peripheral vessels and appropriately increase heart rate upon standing, resulting in hypotension and syncope. A typical meal causes major sequestration of blood in the splanchnic circulation and therefore, syncope occurring within one hour after eating is often orthostatic. Orthostatic hypotension may also be seen in young, otherwise healthy women, often tall and thin. They have autonomic dysfunction causing reduced peripheral vasoconstriction, but preserved cardiac receptors, resulting in symptomatic tachycardia and occasionally near syncope and syncope. Treatment is with vigorous volume support, particularly for athletes and if needed, beta blocker therapy to prevent the reflex tachycardia.

Cardiac Syncope occurs in 10-20% of patients with syncope. The goal of emergency evaluation of syncope is to ascertain which patients fall into this category. These patients have an increased risk of sudden death and require hospital admission. The history in these cases is almost always abrupt syncope without warning, often with injury related to falling. There are three major categories of cardiac syncope:

1. Structural heart disease with obstruction results in abrupt hypotension and syncope due to the inability to compensate for an increased cardiac output. Examples of this include severe aortic stenosis, obstructive hypertrophic cardiomyopathy, and severe pulmonary hypertension. Acute pulmonary hypertension may be a presentation of massive pulmonary embolus.
2. Ventricular tachycardia is usually associated with structural heart disease, typically CAD, but may also occur with pure electrical syndromes such as familial prolonged QT syndromes and Wolf-Parkinson-White (WPW).
3. Bradyarrhythmias may occur with or without structural heart disease and are often related to degenerative disease of the conduction system in the elderly, and may be exacerbated by medications.

Of note, there are two neurological syndromes which may be confused with syncope. Posterior circulation cerebrovascular disease very rarely causes syncope in the absence of focal neurological signs and symptoms. Seizure may mimic syncope but can usually be differentiated by the following characteristics:

- Seizure is usually of much longer duration, often as long as five minutes. If tonic/clonic movement is seen in syncope it is usually less than 30 seconds in duration
- Postictal confusion or paralysis is usually present with seizure
- Tongue biting strongly suggests seizure

(continued on page 2)

Syncope

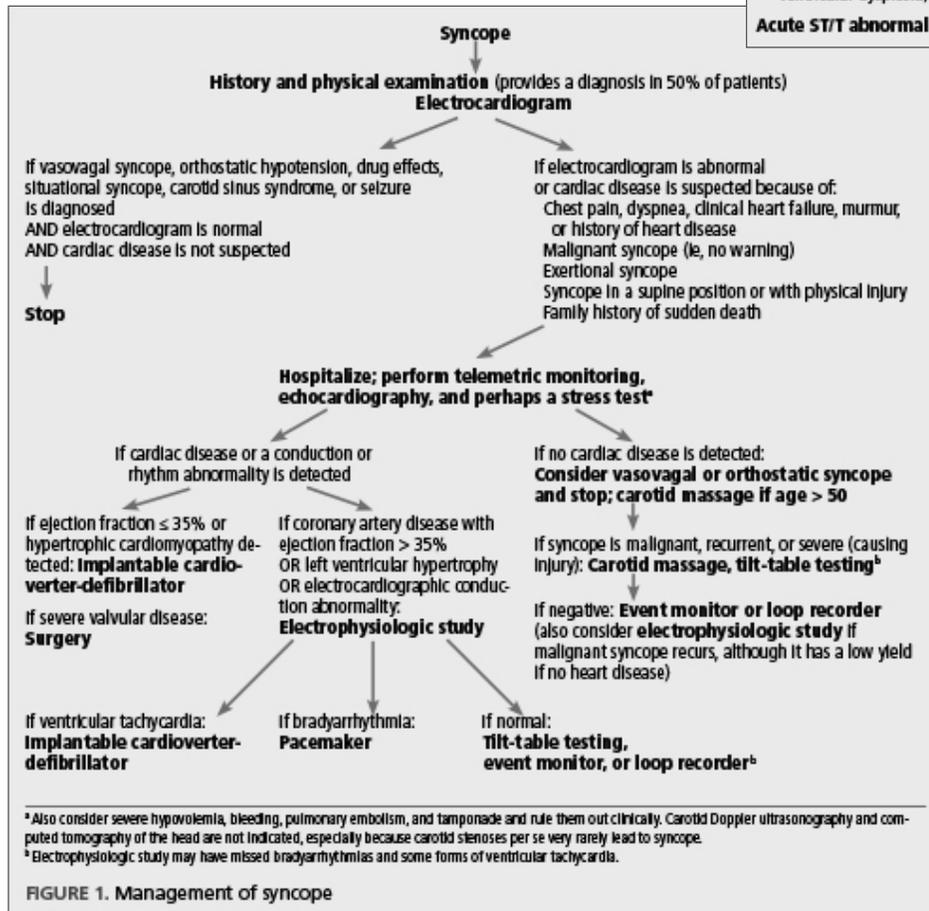
(continued from page 1)

Diagnostic Evaluation – The suggested evaluation is attached, as well as a table looking at the major ECG and Holter findings to support a diagnosis of arrhythmic syncope. Orthostatic BP measurements are indicated in all cases of syncope, as is bedside carotid massage. Indications for hospitalization include:

- History of CHF, low EF or CAD
- ECG suggestive of high risk arrhythmia
- Family history of sudden death
- Lack of prodromal symptoms, exertional syncope, syncope while supine, or syncope associated with dyspnea or chest pain

Although stress testing appears on the diagnostic algorithm, the yield on finding a cause of syncope is only ~5% and therefore, should be done selectively in patients with exertional syncope (following an echocardiogram) to evaluate for “obstructive syncope”, or active angina. Unexplained syncope in the setting of a right or left bundle branch block may be related to either high grade block or ventricular tachycardia and is an indication for cardiology referral.

TABLE 3 Electrocardiographic or Holter findings that suggest cardiac syncope
Bradyarrhythmia-related syncope is established with any of the following: Sinus bradycardia (< 40 beats per minute) or sinus pauses > 3 seconds while awake Mobitz II, high-grade, or complete atrioventricular block Alternating left or right bundle branch block on the same electrocardiogram or on electrocardiograms obtained on separate occasions
Bradyarrhythmia-related syncope is suggested with: Isolated right or left bundle branch block (ventricular tachycardia also possible depending on the underlying cardiac disease) Mobitz I atrioventricular block
Tachyarrhythmia-related syncope is established with: Sustained ventricular tachycardia or fast supraventricular tachycardia (>160 beats per minute)
Underlying heart disease and ventricular tachycardia are suggested with: Q waves Left bundle branch block, right bundle branch block, QRS > 0.11 seconds Left ventricular hypertrophy, right ventricular hypertrophy Large R wave in V ₁
Primary electrical disorders are suggested with: Long QTc Pre-excitation Right bundle branch block with Brugada pattern T-wave inversion in V ₁ -V ₃ or epsilon waves (arrhythmogenic right ventricular dysplasia)
Acute ST/T abnormalities



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New data on the cardiovascular safety of sulfonylureas

Beginning in 2008 with the study of pioglitazone and rosiglitazone, the FDA mandated long term cardiovascular (CV) outcomes studies in all new classes of medications for diabetes. Metformin had established its CV safety through the UK Prospective Diabetes Study (UKPDS) trial which was published in 1998.² The sulfonylureas were therefore the only major class of diabetes medication which had not been subjected to a long term prospective CV outcomes trial. There were concerns about possible increased CV risk from retrospective analyses and data base studies, although these types of analyses are known to be inaccurate in predicting CV outcomes.

Last month, the CAROLINA Trial³ was published in JAMA. It randomized over 6,000 patients with type 2 diabetes and high cardiovascular risk to either glimepiride or linagliptin and followed them for a mean of 6.3 years. The cardiovascular outcomes were statically the same with the primary outcome occurring in 11.8% versus 12.0%. Although hypoglycemia was seen with sulfonylurea therapy, rates of severe hypoglycemia were low at 0.45 per 100 patient-years in the glimepiride group. At the trial conclusion, weight gain from sulfonylurea treatment was 1.54 kg. The accompanying editorial⁴ commented "Further evidence on the comparative effectiveness of glimepiride compared to a DPP-4 inhibitor, a GLP-1 receptor agonist, and basal insulin, each added to metformin, is expected with the publication of the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness (GRADE) Study in 2022. In the meantime, clinicians can continue to use low-cost sulfonylureas added to metformin for management of hyperglycemia in type 2 diabetes with confidence in their effectiveness for reduction of microvascular complications as well as their cardiovascular safety"

With this new information, it is timely to review strategies to minimize hypoglycemia with sulfonylurea use. 62% of patients over age 65 are treated to an A1c level <7% in conflict with recent guidelines⁵ that recommend an A1c target between 7.5%-8.5% based upon clinical judgment. 54% of these patients are treated with insulin or a sulfonylurea, the two drugs with the highest risk of hypoglycemia. A large Kaiser database analysis⁶ showed that when sulfonylurea therapy is used in patients under the age of 77 who do not have stage 3 or 4 chronic kidney disease (CKD), the annual risk of severe hypoglycemia is under 1%.



Addendum to Pevnar 13[®] (PCV13) article in the September/October Forum

The ACIP changed their recommendations from their preliminary statement to their final statement, with final CDC approval pending.⁷ They had initially favored two equal statements:

1. No longer recommending PCV13 for adults ≥ 65 years who do not have an immunocompromising condition.
2. Recommending PCV13 based on shared decision-making for adults 65 years or older who do not have an immunocompromising condition and who have not received PCV13 before.

In the final recommendation, they chose only the shared decision making statement. The data upon which to base a shared decision making conversation includes the following:

- In the 5 years since the 13-valent conjugate vaccine (PCV13; Prevnar) was first recommended for all older adults, it has had no discernable further direct effect on risks for either nonbacteremic pneumonia or invasive disease (i.e., bacteremic pneumonia or meningitis) in this population. In fact, as is now the case in many countries, most pneumococcal disease in the U.S. is caused by serotypes not covered by the conjugate vaccine.
- The "number needed to vaccinate" to prevent 1 case of invasive pneumococcal disease is estimated to be 26,000 annually; the estimated number to prevent 1 case of pneumonia ranges from 2600 to 14000.
- The CDC estimates its price tag at between US\$200,000 and >\$500,000 per quality-adjusted life-year.

This data clearly suggests that PCV 13 is not cost effective when used in the general population over age 65. In our hectic daily workflow, having an extensive shared decision making conversation around a vaccine that is not cost effective in the general population is not practical, although it is an option. PCV 13 could be considered, albeit without supporting clinical trial evidence, for patients with diabetes or serious liver, lung, or heart disease; and for frail elders. It should continue to be used in immunocompromised populations over age 19 as noted below.

The CDC's ACIP recommends Pevnar 13[®] in series with Pneumovax 23[®] for immunocompromised patients aged 19 and older with the following medical conditions:⁸

- Congenital or aquired immunodeficiencies
- Human immunodeficiency virus (HIV)
- Chronic renal failure
- Nephrotic syndrome
- Leukemia
- Lymphoma
- Hodgkin disease
- Generalized malignancy
- Iatrogenic immunosuppression
- Solid organ transplant
- Multiple myeloma
- Functional or anatomic asplenia (including sickle cell disease/ other hemoglobinopathies and congenital or aquired asplenia)
- Cerebrospinal fluid leaks
- Cochlear implants

2. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) Lancet. 1998;352:837-853.
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Cancer prevention from HPV vaccination

The first human papillomavirus (HPV) vaccine was introduced a decade ago. Introduction and administration of this vaccine has not been without controversy. In *Lancet*⁹, Drolet and colleagues conducted a study and meta-analysis of the effect the papillomavirus vaccine has had on HPV infection, anogenital warts, and cervical intraepithelial neoplasia (CIN). Earlier studies showed the vaccine effective in reducing HPV infection. Now more than 60 million persons have received the vaccine in 99 countries. The vaccine has been in use for enough time (more than eight years) to now see the effect on CIN.

This study had important findings:

- Reductions in HPV infection, anogenital warts, and CIN continue to be observed
- When vaccine coverage covers multi-age cohorts and is gender neutral, broader coverage and herd immunity occurs

The reductions in HPV infection in women ranged from 66% to 83% in different age cohorts. Expected reduction in anogenital wart diagnosis ranged from 31% to 67%. Five to nine years post vaccination CIN rates dropped by 31 to 51% in different cohorts. This study emphasizes the positive public health effects of the focused vaccination campaign. The World Health Organization recently updated its HPV vaccination recommendations to include multiple age cohorts of girls. Cervical cancer elimination might be possible if sufficient population health vaccination coverage can be obtained.

A related study in *JAMA*¹⁰ used the NHANES (National Health and Nutrition Examination Survey) database to gain an understanding of vaccination rates and the effects in the US. Chaturvedi and coauthors also showed a 37% reduction in vaccine-type oral HPV infections in unvaccinated US men supporting the occurrence of herd immunity. The prevalence in non-vaccine type HPV remained unchanged. This decrease was observed despite an overall relative low vaccination rate in woman of 15.3% and 5.8% in men. These two studies emphasize the importance of continuing to expand utilization of HPV vaccination.

Special thanks to John Hitt, MD, MBA, for his contribution to this article. Dr. Hitt has recently joined OptumCare and will become a regular contributor to the Forum in 2020.



Consequences of unnecessary preoperative ECG's

Preoperative ECG's in the setting of a low risk surgical procedure are a recognized low value care procedure, even in patients with underlying cardiovascular disease. Low risk surgeries include endoscopic procedures, skin and subcutaneous surgeries, breast surgery, and most ambulatory surgeries. The AHA Guidelines¹¹ state:

Preoperative resting 12-lead ECG is not useful for patients undergoing low-risk surgeries including those with known coronary artery disease, significant arrhythmia, peripheral

arterial disease, cerebrovascular disease, or other significant structural heart disease.

We have been largely successful in eliminating preoperative ECG's in patients undergoing cataract surgery, but less so in other low risk surgical procedures. A recent study looked at the downstream costs of the index unnecessary ECG. The study group was 110,000 patients undergoing cataract surgery in which 11% had a preoperative ECG. Abnormalities on the ECG triggered additional testing in 16% of this group, most frequently additional cardiac testing (85%) and cardiology visits (48%). The cumulative cost equated to an average expenditure of \$1700 for each patient who underwent a preoperative ECG. This resulted in an excess Medicare expenditure of \$35 million in the cataract surgery group alone. This should serve as a useful reminder that ECGs in the setting of a low risk surgical procedure add cost but not value.¹²



Risk of covert perioperative stroke in elective surgery over age 65

The risk of clinical stroke in elective surgical procedures that are non-vascular and non-brain surgery is estimated to be 0.7%. These are associated with a high mortality (32%) and disability (59%). The risk of covert stroke is unknown. Covert stroke is defined as an acute stroke by MRI but without clear signs or symptoms of focal neurologic impairment. The NeuroVISION study¹³ was a prospective cohort study of 1100 patients age 65 and older undergoing elective surgery. The surgeries were expected to be associated with a two day inpatient stay. Most procedures were orthopedic, urologic, gynecologic or general surgical. Most anesthetics were either general or spinal. Patients were followed closely and had an MRI 2-9 days postoperatively. Strikingly, 7% of patients were diagnosed with a new acute brain infarction by MRI. In the stroke group, there was twice the risk of cognitive decline at one year, defined as a two point drop in the Montreal Cognitive Assessment. The absolute increased risk of cognitive decline was 13%. From a patient perspective, loss of cognitive function is one of the most feared surgical complications. A Canadian study found that 36% of patients feared brain damage or memory loss from a surgical procedure. The risk of covert stroke should be discussed with seniors undergoing significant surgical procedures under general or spinal anesthesia.

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Chief Medical Officer

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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