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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: • Explore the educational content surrounding urgent management of TIA or minor strokes as a means to advance optimal care outcomes. • Recall pharmaceutical recommendations for the management of actinic keratosis, and direct oral anticoagulants therapy using evidence-based literature and observational data. • Apply medical management principles grounded in evidence-based medicine that could help modify and improve the use of the colon cancer FIT test screening, the role of catheter ablation in the management of atrial fibrillation, and Afib anticoagulation guidelines.

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Urgent management of TIA/minor stroke

With the advent of specialty stroke centers, there has been renewed emphasis on the importance of immediate evaluation of patients presenting with transient ischemic attack (TIA) and minor stroke. While it is widely appreciated that these events predict a high risk of early progression to completed stroke, it is often not appreciated that the highest risk occurs in the first 1-3 days following the index symptoms. Studies have suggested that the likelihood of progression to completed stroke can be reduced by as much as 80% with prompt evaluation and treatment. It therefore, is timely to review this topic. Importantly, this article applies only to those patients whose neurological symptoms have totally resolved by the time the patient is in contact with the PCP. If there are ongoing neurological symptoms, acute stroke in evolution is possible and the patient needs urgent evaluation, preferably at a stroke center.

Typical presenting symptoms - A NEJM study[1] looked at a registry of over 4,700 patients presenting to specialized stroke centers. The population had presented with either TIA or minor stroke within the prior seven days and the registry was designed to estimate the probability of completed stroke within the next year. The majority of patients presented with unilateral weakness and/or speech disturbance (aphasia or dysarthria). Each of these occurred in about 50% of patients. All other symptoms were less common. Unilateral numbness, monocular visual disturbances, and ataxia with or without vertigo occurred in about 15% or less of patients. Isolated vertigo is uncommonly due to stroke. These patients most often have other associated symptoms which may include ataxia, diplopia, dysarthria, and motor symptoms.[2]

Etiology of TIA/minor stroke - At the time of presentation, one third of patients had a completed stroke even though many of these patients were initially thought to have had a TIA. Only 15% had significant carotid arterial stenosis of at least 50% and 15% had atrial fibrillation. One third of these cases of atrial fibrillation (5%) were new at onset. The ABCD2 criteria were useful to predict risk of progression to stroke.[3]

ABCD2 score

Points	Age	Blood Pressure	Clinical Features	Duration of TIA	Diabetes
0	<60 yrs	Normal	No speech disturbance and not unilateral (one-sides) weakness	<10 mins	Absent
1	≥60 yrs	Raised (≥140/90 mmHg)	Speech disturbance presented but no unilateral weakness	10-59 mins	Present
2	-	-	Unilateral weakness	≥60 mins	-

For example: A person aged 60 (1 point) with normal blood pressure (0 point) and without diabetes (0 point) who experienced a TIA lasting 10 minutes (1 point) with a speech disturbance but no weakness on one side of the body (1 point) would score a total of 3 points.

Interpretation: The risk for stoke can be estimated for the ABCD2 score as follows:

Score 1-3 (low)	Score 4-5 (moderate)	Score 6-7 (high)
2 day risk = 1.0%	2 day risk = 4.1%	2 day risk = 8.1%
7 day risk = 1.2%	7 day risk = 5.9%	7 day risk = 11.7%%

Urgent diagnostic evaluation and management – Although the long term prognosis of these patients is most favorably impacted by optimal control of HTN, DM, hyperlipidemia, tobacco cessation, and the use of antiplatelet therapy, urgent evaluation within 24 hours is critical to mitigate the increased short term risk of progression to completed stroke. Efforts should be focused on the studies which will identify patients at high risk of progression to stroke for which there are rapidly correctable etiologies.

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Educational Forum: Urgent management of TIA/minor stroke

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There are three critical elements to the evaluation:

1. Brain imaging to document if there is a stroke and exclude brain hemorrhage, which would preclude use of anticoagulant or antiplatelet therapies.
2. Carotid artery ultrasound to evaluate for the 15% of patients with high grade stenosis. In the above referenced registry study, about 25% of patients with significant carotid artery stenosis had revascularization within four days of presentation, emphasizing the goal of mitigating the short term risks of progression to stroke by acting quickly in this subset of patients.
3. Stethoscope examination and ECG to evaluate for atrial fibrillation and important structural cardiac disease.

Echocardiogram, which is often done urgently, has a diagnostic yield of only about 4% with most of the relevant abnormalities also being present on stethoscope exam or ECG. Echocardiogram therefore very infrequently affects the management of these patients and does not have an evidence base to support improved outcomes with use. However many guidelines continue to include this as part of the routine order set. The exception to the above is the patient under the age of 60 with a paucity of vascular risks in whom an echocardiogram with an agitated saline injection (bubble study) is indicated to evaluate for a patent foramen ovale (PFO). This is discussed in further detail below. 30 day event monitoring to evaluate for occult atrial fibrillation is important, but not part of the urgent evaluation.

The urgent treatment should include:

1. Patients in atrial fibrillation require immediate full anticoagulation unless there are absolute contraindications.
2. Patients in sinus rhythm who do not have contraindications, should be treated with dual antiplatelet therapy (DAPT). In terms of the duration of DAPT, a recent clinical practice guideline in the BMJ noted that for every 1,000 patients treated with DAPT for 90 days, 19 strokes would be prevented and 2 major hemorrhages would be created. The guideline[4] therefore recommended DAPT for the first 10-21 days following a high risk TIA or small stroke, followed by conversion to daily aspirin therapy for long term management.
3. Patients with significant carotid artery stenosis who are acceptable surgical candidates require urgent surgical evaluation.

Using the above approach, the goal is to reduce the 90 day risk of stroke following TIA/minor stroke to the 3-5% range. If the above urgent evaluation cannot be achieved within 24 hours, ER evaluation is indicated. Urgent neurology evaluation should be obtained for any areas of diagnostic or therapeutic uncertainty.

Cryptogenic stroke and patent foramen ovale (PFO) – PFO is present in about 25% of the population but found in 40% of patients with cryptogenic stroke. Paradoxical embolus through a PFO as a cause of stroke is predominantly relevant in patients under the age of 60. Over age 60, vascular etiologies far outweigh PFO as a cause of stroke and therefore PFO closure has not been found to affect future stroke risk in this group. When stroke in the setting of PFO occurs, addressing the option of PFO closure does not need to be done urgently. However, review of the treatment options is timely as new data have influenced the management. In the last couple of years, both the CLOSE and the REDUCE trail were published and the results summarized in the American Journal of Cardiology.[5] Both of these trials used newer generation closure devices and stricter enrollment criteria. They focused on patients 60 years old or younger who had cryptogenic stroke associated with PFO and either large intra-atrial shunts or an atrial septal aneurysm. Patients were excluded if they had any significant cranial arterial stenoses. In the case of the REDUCE trial, they were also excluded if they had a lacunar stroke or uncontrolled stroke risk factors. In the CLOSE study, 6% of patients in the antiplatelet therapy group had recurrent stroke over five years compared to none in the closure group. This equated to a NNT of 20 to prevent one stroke over 5 years. In the REDUCE trial, after 3.2 years, there was a 5.4% rate of stroke in the antiplatelet therapy group compared with a 1.4% risk in the closure group. This equated to a NNT of 28 over two years to prevent one stroke. These studies had similar designs, enrolled similar patient groups, and had similar results. A cost effectiveness analysis of the recent PFO closure trials was subsequently done[6] suggesting that PFO closure may be cost effective when the patient selection criteria strictly match the enrollment criteria of the above two trials. Taken together, these trials have tilted the management towards PFO closure, although this still remains controversial.

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3. https://academic.oup.com/fampra/article/28/4/366/508539

4. Prasad, K., Siemieniuk, R., Hao, Q., Guyatt, G., O'Donnell, M., Lytvyn, L., . . . Rochwerg, B. (2018). Dual antiplatelet therapy with aspirin and clopidogrel for acute high risk transient ischemic attack and minor ischemic stroke: A clinical practice guideline. BMJ (Clinical Research Ed.), 363, k5130. doi:10.1136/bmj.k5130

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6. Leppart, M. H., Poisson, S. N., Carroll, J, D., Thaler, D. E., Kim, C. H., Orjuela, K. D., Ho, P. M., Burke, J. F., & Campbell, J. D. (2018) Cost effectiveness of patent foramen ovale closure versus medical therapy for secondary stroke prevention. Stroke 49(6); 1443-1450. Doi: https://doi.org/10.1161/STROKEAHA.117.020322

Actinic Keratosis – Important new study outlining optimal treatment

Actinic Keratoses (AKs) are the most frequent premalignant skin lesions encountered in primary care. Although solitary lesions are usually best treated with cryotherapy, multiple lesions typically require topical therapies. Current guidelines do not offer definitive recommendations as comparative studies are scarce. Increasingly, dermatologists are using photodynamic (blue light) therapy at an average cost of ~$400 per treatment and which often requires multiple treatments. A Dutch study[7] examined over 600 patients randomized to treatment with 5% fluorouracil (5-FU), 5% imiquimod, photodynamic therapy, or 0.015% ingenol mebutate. The primary endpoint was the proportion of patients with a 75% reduction in lesions at one year post treatment. The results were as follows:

Treatment type	Response rate %	Cost per treatment course
5-FU	75	~$240
Imiquimod	54	~$200
Photodynamic therapy	38	~$400
Ingenol mebutate	29	~$1,200

At the three month follow up, there were 2-3 times the number of early failures with the other three treatments courses compared to 5-FU. Adverse effects were similar across patient groups with the exception of severe pain and severe burning which were seen 3 times as frequently in the photodynamic therapy group with a frequency exceeding 60% of patients. Patient satisfaction with treatment and increased QOL scores were highest with the 5-FU treatment. This is an important study for two reasons.

1. We now have a large randomized trial showing superiority of 5-FU in all domains of outcomes.
2. 5-FU is easily managed by primary care providers and these results should inform our practices with a decrease in both dermatology referrals and total cost of care for AK.

Conversations should take place with our dermatology colleagues requesting alignment of treatment patterns with this new evidence base.

Does apixiban have a lower bleeding risk than rivaroxaban?

It is unlikely that the pharmaceutical industry will conduct head to head trials of the direct oral anticoagulants (DOAC's). We are therefore left with observational data to try and determine if there are differences in safety and efficacy between drugs within this class. Apixiban (Eliquis®) and rivaroxaban (Xarelto®) are the two most frequently prescribed drugs in this class and therefore amenable to study through large data bases. There are now three observational trials all suggesting a significantly lower risk of bleeding and possible increased efficacy with apixiban.

- In the first study[8] over 750,000 patient years of data were examined in patients with atrial fibrillation (AF) on anticoagulant treatment. The risk of hospitalization for upper GI bleeding was 50% lower with apixiban, and ~15% lower with dabigatran and warfarin, compared to rivaroxaban.
- The second study[9] looked at over 75,000 patients with AF and showed a one third lower risk of stroke and a 50% lower risk of major bleeding with apixiban compared to rivaroxaban.
- The third study[10] looked at the three month outcomes of patients with acute DVT/PE and compared treatment with apixiban to rivaroxaban. 15,000 patients were studied and the results included a 57% lower risk of recurrent DVT/PE and a 50% lower risk of major bleeding.

Although the mechanism of action of the two drugs is similar, because rivaroxaban is a dosed once daily, it has both a higher peak level and a lower trough level. This could explain both the higher bleeding risk when blood levels are at their peak, as well as lower efficacy when blood levels are at their trough. Given our current body of knowledge, assuming patients will be compliant with a twice daily regimen; apixiban is likely to be a safer and more efficacious drug.

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Sensitivity of annual fecal immunochemical test (FIT) testing

FIT testing is an effective and inexpensive test for colorectal cancer (CRC) screening. It is far more cost effective than fecal DNA testing which in most cost effective analyses, is more expensive than colonoscopy. A recent meta-analysis in the Annals of Internal Medicine[11] looked at studies involving over 120,000 patients comparing a single FIT to colonoscopy. The study reported that the sensitivity and specificity for colon cancer using a single FIT in average risk individuals is 91% and 90%. This sensitivity compares favorably with colonoscopy. The sensitivity for the detection of advanced adenomas is less with FIT at 40%. The authors point out that advanced adenomas infrequently transition to cancer and should this occur, the FIT should become positive with yearly screening. Should FIT testing routinely replace colonoscopy for initial screening? This cannot be answered as there are no studies comparing colonoscopy to FIT looking at long term CRC survival. In most other countries, FIT is used for population screening with colonoscopy reserved for patients who have positive results. In the US only 65% of eligible patients receive CRC screening which suggests that increased use of FIT could improve the US CRC screening rates. FIT can fill the following niches:

- Patients who decline colonoscopy because of cost, concern over adverse effects, unwillingness to do the prep, or personal preference.
- Patients who reach age 75 and do not wish to discontinue screening - Screening beyond age 75 does not have an evidence base of support. Data has shown that screening patients over age 75 for an 8 year period had no significant effect on reducing CRC detection (2.84% with screening vs. 2.97% without screening). This represented an additional 2 patients found to have colon cancer for every 1000 colonoscopies performed and equated to a cost to detect a single case of CRC of over $600,000. Moreover, in this age group, there were 5 serious adverse events requiring hospitalization for each discovered colon cancer. FIT therefore is an ideal option for elderly patients who do not wish to discontinue screening.

Effects of catheter ablation versus medical therapy for atrial fibrillation

Atrial fibrillation (AF) will affect over 10% of the population by age 75. Ablation is increasingly being chosen over medical therapy for management however large comparative trials are lacking. The CABANA Trial[12] prospectively randomized over 2,200 patients to either catheter ablation or medical therapy and followed them for over four years. All patients were anticoagulated based upon the CHA2DS2VASc guidelines. This was the largest trial of ablation for AF and was published in two separate papers. The first was the CV outcomes study and the second was the quality of life study. The salient findings of the study are as follows:

- The primary outcome was the composite of death, disabling stroke, serious bleeding, or cardiac arrest. There were no statistically significant differences between the two groups with the primary endpoint occurring in 8% of the ablation group and 9.2% of the medical therapy group. This would equate to a NNT of 83 and a cost of close to $1.8 million to prevent one outcome event. The stroke rate in the trial was very low at 0.7%.
- By the end of the four years, about 20% of the patients required a second ablation. Overall, the AF recurrence rate in the ablation group was 50% at four years. This figure has been consistent in multiple trials.
- In the quality of life study, scores improved from a baseline of 63 on a scale of 100, up to 86 in the ablation group versus 81 in the medical therapy group. This just met the threshold of being clinically meaningful with a five point difference.

How should these results inform daily practice?

Currently, the Optimal Care recommendation is for patients to be referred for ablation in two circumstances. The first is when there are intractable symptoms despite best medical therapy. The second recommendation follows the publication of the CASTLE-AF Trial last year.[13] This trial looked at ablation therapy for AF in the subset of patients with symptomatic CHF and an EF<35%. Although a small study, it showed a significant improvement in both mortality as well as hospital admission for CHF. Therefore, pending larger studies in this subgroup, ablation should be considered when atrial fibrillation is accompanied by an ejection fraction <35%.

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AHA/ACC updated atrial fibrillation anticoagulation guideline

The Jan/Feb edition of the Forum outlined the new Chest guideline for anticoagulation management of AF. The ACC/AHA guideline was compared to the Chest guideline in that article however it was then updated after this publication. There is one important difference between the two that should be highlighted. In the new version of the ACC/AHA guideline, the recommended threshold for anticoagulation in patients with AF has been set at ≥ 2 in men and ≥ 3 in women. This is a higher score to initiate therapy than that in the Chest guideline, making this a more conservative guideline in terms of treating fewer patients with anticoagulants. For comparison, the new Chest guideline recommends therapy for a score of ≥ 1 in men and ≥ 2 in women. **The ACC/AHA guideline allows for discretion at this lower score by stating, "Oral anticoagulants might be reasonable for men with a score of 1 and women with a score of 2."** So how should we best manage men with a score of 1 and women with a score of 2? Enlisting the below chart will allow the prediction of the actual stroke rate for any given patient by looking at which risk factors contribute to their score. This is important as the true stroke risk varies widely according to which risk factors any given patient may have. For example, vascular disease and female sex carries almost three times the stroke risk of CHF and female sex, even though both give a score of 2. Depending on the specific risk factors, the risk of stroke in a patient at these lower scores could be greater than or less than the risk of major hemorrhage. A shared decision making approach should therefore be employed.

Table 6 Event rates (95% CI) for hospital admission and death due to thromboembolism* per 100 person years by CHA_2DS_2-VASc score and by covariates

Score and covariates	1 year's follow-up	5 years' follow-up	10 years' follow-up
CHA_2DS_2-VASc score= 0	0.78 (0.58 to 1.04)	0.69 (0.59 to 0.81)	0.66 (0.57 to 0.76)
CHA_2DS_2-VASc score=1:			
Heart failure	1.50 (0.37 to 5.98)	2.35 (1.30 to 4.24)	1.78 (0.99 to 3.21)
Hypertension	2.14 (1.46 to 3.15)	1.60 (1.26 to 2.01)	1.49 (1.21 to 1.84)
Diabetes mellitus	3.47 (1.65 to 7.27)	2.28 (1.42 to 3.66)	2.02 (1.29 to 3.16)
Vascular disease	0.75 (0.24 to 2.33)	1.40 (0.91 to 2.15)	1.47 (1.01 to 2.12)
Age 65-74	2.88 (2.29 to 3.62)	2.13 (1.85 to 2.46)	2.09 (1.83 to 2.38)
Female sex	1.24 (0.89 to 1.73)	0.86 (0.70 to 1.06)	0.82 (0.68 to 1.00)
CHA_2DS_2-VASc score=2:			
Diabetes + heart failure	4.53 (0.64 to 32.17)	3.52 (1.13 to 10.91)	3.83 (1.44 to 10.21)
Diabetes + hypertension	3.29 (1.37 to 7.91)	1.79 (0.93 to 3.44)	1.94 (1.10 to 3.42)
Diabetes + age 65-74	1.49 (0.48 to 4.61)	1.92 (1.11 to 3.30)	1.98 (1.21 to 3.22)
Diabetes + vascular disease	0	1.06 (0.15 to 7.55)	1.80 (0.45 to 7.19)
Diabetes + female sex	1.11 (0.16 to 7.85)	0.62 (0.16 to 2.49)	1.23 (0.51 to 2.96)
Heart failure + hypertension	4.11 (1.96 to 8.62)	3.19 (1.98 to 5.14)	2.81 (1.79 to 4.41)
Heart failure + age 65-74	1.84 (0.69 to 4.90)	2.49 (1.55 to 4.01)	2.46 (1.59 to 3.82)
Heart failure + vascular disease	3.55 (0.50 to 25.17)	1.91 (0.48 to 7.66)	1.49 (0.37 to 5.97)
Heart failure + female sex	0	0.55 (0.08 to 3.87)	0.87 (0.22 to 3.49)
Hypertension + age 65-74	2.54 (1.74 to 3.70)	2.22 (1.79 to 2.76)	2.30 (1.89 to 2.78)
Hypertension + vascular disease	1.56 (0.70 to 3.48)	1.48 (0.96 to 2.30)	1.52 (1.02 to 2.24)
Hypertension + female sex	1.84 (1.09 to 3.11)	1.48 (1.09 to 2.02)	1.43 (1.08 to 1.89)
Age 65-74 + vascular disease	2.90 (1.72 to 4.89)	2.47 (1.82 to 3.35)	2.54 (1.93 to 3.35)
Age 65-74 + female sex	2.82 (2.21 to 3.60)	2.10 (1.81 to 2.45)	2.06 (1.80 to 2.36)
Vascular disease + female sex	2.87 (0.93 to 8.91)	1.95 (0.93 to 4.08)	2.26 (1.21 to 4.19)
Age≥75	4.75 (4.14 to 5.44)	4.37 (4.02 to 4.75)	4.27 (3.94 to 4.62)
Previous thromboembolism	16.07 (11.64 to 22.18)	7.87 (6.12 to 10.11)	6.98 (5.50 to 8.85)

*Includes peripheral artery embolism, ischaemic stroke, and pulmonary embolism.

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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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