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Atrial Fibrillation Anticoagulation Management – CHEST® Updated Guideline

CHEST® has recently updated its guidelines for oral anticoagulation (OAC) management in atrial fibrillation (AF). https://journal.chestnet.org/article/S0012-3692(18)32244-X/fulltext

This is an extensive 81 page review. Of the 60 recommendations, many apply to specialized circumstances where the management decisions will be made by cardiology, neurology, or in the emergency room.

The following are the most important evidence-based recommendations that pertain to situations where primary care has a key role in management of the AF. The last AHA/ACC guideline was published in 2014 and in several key areas, this is discordant with the new CHEST® guideline[1]. This will be noted in the discussion. The newer anticoagulants are referred to as Novel Oral Anticoagulants, (NOAC) or Direct Acting Oral Anticoagulants, (DOAC). In this review, they will be referred to as DOAC's.

- CHA_2DS_2VASc should be used to guide initiation of therapy. In the new CHEST® guideline2, Oral Anticoagulant, (OAC) therapy is indicated for a score of ≥1 in men and ≥2 in women. A score of 0 in men and 1 in women should not generally be treated with an OAC. This is important since as many as a quarter of patients who have AF with a 0-1 score are on anticoagulation and might not benefit from therapy. Although any score >0 may confer some increased risk of stroke, the key decision around anticoagulation is identifying the situations where the stroke risk exceeds the risk of major bleeding. **The AHA/ACC guideline recommends treatment for a score of 2 or greater in either sex, and allows discretion and shared decision making for a score of 1. This is one of the key differences between the two guidelines.**

  To help make the decision in borderline situations, it is helpful to look at a study published in the 2011 British Medical Journal[3] which looked at the entire database of Denmark from 1997-2006 and identified patients who presented with non valvular AF and were not anticoagulated. They then calculated the stroke risk based upon the parameters of the CHA_2DS_2VASc scoring system. Two important points emerge:

  - Women have a higher risk of stroke than men. However, in some studies, the increased risk is confined to women above age 65 and not younger ages. The CHEST® guideline ignores this age factor since a woman with one additional risk factor would reach a score of 2 irrespective of age. For example, women under the age of 65 with no other risk factors, except a history of vascular disease might not benefit from OAC.

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- Not all of the parameters of the scoring system have an equal risk of stroke and therefore there is a range of stroke risks in patients with a score of 1. In the table, note that female sex or a history of vascular disease, has a lower stroke risk than advanced age or diabetes.

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.

- Atrial flutter should not be viewed differently from AF with respect to the decision to initiate OAC.
- Anti-platelet therapy with aspirin or with dual therapy is not recommended for stroke prophylaxis in AF.
- For the first time, DOAC therapy is listed as preferred over warfarin. This is based on the results of the pivotal trials of the DOACs which were conducted internationally and had a broad range of time in therapeutic range (TTR). **This is another key difference between the guidelines in that AHA/ACC recommends treatment with either warfarin or a DOAC.**

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A large Swedish study published in JAMA Cardiology[4] studied over 40,000 patients with non-valvular AF treated with warfarin over a five year course. The average TTR (INR2.0-3.0) of the cohort was an excellent 68.6% which was higher than any of the pivotal DOAC trials. Among the over 50% of patients who had a TTR of >70%, the all cause yearly mortality was 1.3%, the major bleeding risk was 1.6% and the thromboembolism risk was 1.4%. All of these compare very favorably with DOAC therapy. It is therefore important that TTR be monitored for patients on warfarin, with transition to DOAC therapy if TTR cannot be maintained at >70%. Patients who are well controlled on warfarin with a TTR of >70% have the option of remaining on warfarin.

- The HAS-BLED score is useful to determine risk of bleeding. Although increased risk (≥3) is not an indication to withhold OAC, it is used to intensify the search for modifiable causes of bleeding and a reason for more frequent follow up. Modifiable bleeding causes include; uncontrolled HTN, NSAID use, excessive alcohol intake, hazardous occupations or hobbies, and extreme frailty. https://www.mdcalc.com/has-bled-score-major-bleeding-risk
- In patients with AF and stable CAD, or following carotid revascularization, OAC alone is recommended without concomitant aspirin therapy. If aspirin therapy is indicated, it should be used at a dose of 75-100 mg with concomitant PPI therapy to reduce the risk of gastrointestinal hemorrhage.
- There are not adequate data to inform the decision of when to consider OAC therapy when AF is found on monitoring. The consensus is to consider OAC when the AF episode is >24 hours and possibly with shorter episodes when they are present for hours but not minutes. This is an important area of ongoing research to determine the AF burden that would benefit from OAC therapy.
- Left atrial occlusion is indicated for patients with a high risk of ischemic stroke and an absolute contraindication to anticoagulation.
- Warfarin remains the drug of choice in patients with AF and a mechanical heart valve.
- Preoperative bridging therapy is indicated in warfarin treated patients who have a mechanical heart valve, but not in most other circumstances.
- In patients where sinus rhythm has been restored either through pharmacotherapy or ablation, OAC should be continued as there are significant rates of recurrent atrial fibrillation with both pharmacotherapy and ablation.

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Rivaroxaban to lower CV risk

The OCFEBM previously reviewed the data on CV risk reduction with the PCSK-9 inhibitors and the GLP-1 agonists. Both these drug classes have data suggesting an absolute reduction in CV risk of about 2% with no decrease in mortality. Looking at the cost to prevent a single CV event, the range of costs is $900,000 up to $2.1 million, representing 9 to 21 times the accepted QALY of $100,000. These studies have very large sample sizes in common, allowing for statistically significant results that are of small magnitude in terms of absolute risk reduction.

The currently discussed study looked at adding rivaroxaban (2.5 mg BID), to low dose aspirin in 27,000 patients with established CAD or PAD, who were at high risk of recurrent CV events. This most recent study follows suit with the above studies. In this high risk population, the low dose rivaroxaban/low dose aspirin combination reduced CV risk by 1.3% with an increased bleeding risk of 1.2% compared to aspirin alone. There was a small mortality reduction of 0.7%. **The cost to prevent one CV event is estimated to be ~$1 million and a cost to prevent one CV death is $1.4 million.**

In the author's opinion, this small benefit is offset by the increased bleeding risk and very high cost of therapy and should not routinely be employed. It is also likely that the risk of bleeding would exceed any benefit in patients who were not at high risk of recurrent CV events.

Antibiotics to prevent COPD exacerbation[5]

Despite our major initiative to limit antibiotic use, there may be a role for prophylactic antibiotic therapy for a subset of patients with COPD.

A recent Cochrane Data Base Review looked at 14 studies in almost 4,000 patients. Regimens included daily and three times weekly regimens, and most studies looked at macrolides or doxycycline. Studied patients were mostly over age 65 with moderate to severe COPD and frequent exacerbations. The relative risk of exacerbations was reduced by 43% with an absolute reduction of 14%, and a NNT for one year to prevent an exacerbation of 8. Hospitalization rates, lung function, and mortality were not affected by antibiotic use. Because macrolides have an anti-inflammatory effect in addition to their antibiotic effect, they might be preferred over doxycycline.

Overall, this represents a significant but not profound benefit, and could be considered in the subset of patients with moderate to severe COPD and frequent exacerbations, particularly if in a given patient the exacerbations have led to frequent hospitalizations.

Avoidance of antibiotics for acute diverticulitis – addendum[6]

The American Gastroenterology Guidelines have been updated to reflect the data from the two large trials reviewed in that article. The new guideline recommends abstaining from antibiotic use in acute uncomplicated diverticulitis unless accompanied by:

- Signs of sepsis
- Immunocompromised status
- Evidence of free air or abscess on CT scanning

This is a more forceful statement than expressed in the prior Oct/Nov OCFEBM article and is supported by the trial findings.

Allopurinol – Should be titrated to a urate level <6.0 mg/dl. Does it worsen renal function?

Only one third of patients with symptomatic gout receive urate lowering therapy. Average uric acid levels have doubled in the past 80 years making hyperuricemia more difficult to treat. In addition to preventing acute gout attacks, lowering uric acid levels also prevents chronic joint and soft tissue damage. Also, there is a growing body of evidence that treatment of hyperuricemia may be renal protective, as well as reducing the risk of DM2 and ischemic vascular disease.[7] CKD 3 is present in about 20% of patients with gout, likely related to the frequent comorbidities of HTN, DM2, and NSAID and diuretic use. However, there are no data that point to allopurinol being nephrotoxic.

A recent cohort study[8] of over 4700 patients with normal kidney function starting allopurinol at a dose of at least 300 mg. daily for gout were matched with a similar number of hyperuricemic patients who did not initiate allopurinol. Both groups were followed for five years and the allopurinol group had a 13% lower risk of developing CKD-3. Because of concerns over allopurinol affecting renal function, providers often fail to titrate doses and therefore do not achieve gout control. Patients remain at risk for gout recurrences when uric acid level remains >6 mg/dl. In patients with moderately severe gout, doses of 400-600 mg daily may be required and doses can be titrated to 800 mg daily.

A recent study in The Lancet[9] showed that 95% of patients achieved urate levels <6.0 mg/dl when allopurinol doses were up-titrated. The mean allopurinol dose required for control was 460 mg/day. Only 14% of patients required Fexubostat, which at a cost of $5,000 yearly should be reserved for patients not controlled with or intolerant of allopurinol.

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Rotator cuff tear management

Shoulder pain accounts for 4.5 million patient visits per year in the United States. Rotator cuff tears account for a large portion of these visits, which can result in life altering clinical symptoms. It has been estimated that 20-22% of people in the United States will experience a rotator cuff disorder in their lifetime and that 220,000 rotator cuff repairs are performed annually. Others have shown that the prevalence of pathology can be stratified by age: tears can be seen in 30% of patients age 60-69; 40% in age 70-79, and 50% in age greater than 80. Considering a large portion of these repairs are done in people of working age, rotator cuff pathology can have an enormous impact on one's quality of life.

This is not to suggest that all rotator cuff tears need to be fixed. Indeed, Kuhn[10] has demonstrated that 85% of patients, average age 62, with **atraumatic** tears, will respond to a nonoperative program, the results of which may last up to five years. Therefore, in these degenerative types of lesions, it is reasonable to begin with a cortisone injection and physical therapy for 6 to 8 weeks. Surgery may be offered for intractable symptoms, or if increased pain or new onset weakness is experienced, as this may be indicative of enlargement of the tear. **Traumatic** tears, however, seem not to fare as well, especially in a younger population. Maman[11] has shown that 48% of symptomatic rotator cuff tears can enlarge over 18 months. Considering smaller tears fare better than larger ones and some can progress to an irreparable state, early diagnosis and treatment will result in a better functional outcome in this population

There is a physiological explanation for this progression. When a rotator cuff tendon tears, it retracts medially away from its attachment. Subsequently, the muscle fibers are gradually replaced by irreversible adipose tissue rendering them stiff and less functional. Unfortunately, this process can proceed as quickly as a few months and is progressive. A recent meta-analysis[12] has shown that when the musculotendon junction retracts medial to the glenoid face, the humeral head elevates due to lack of muscle interposition. When greater than 50% atrophy occurs and fatty infiltration occurs, there is less than a 25% chance of obtaining a good result from a repair. Unfortunately, the result can be a poor clinical outcome or a more expensive arthroplasty or allograft reconstruction.

In sum, **atraumatic** rotator cuff tears, especially in an older population, can respond well to a thoughtful nonoperative physical therapy program and surgery for unresponsive symptoms. **Traumatic** tears, however, tend to do better if diagnosed early and repaired in the appropriate patient. This can result in a better quality of life for the patient and improved societal cost savings.

Special thanks to Mitch Seeman MD for the contribution to this article. Dr. Seeman is from the Panorama Orthopedic and Spine Center.

Postmenopausal bleeding and the risk of endometrial carcinoma

Endometrial cancer is the most common gynecologic cancer. Unlike ovarian cancer, it is most often diagnosed at an early stage which has a 95% cure rate with surgery alone. A woman presenting with postmenopausal bleeding, (PMB) wants to know what the likelihood is that this could be due to endometrial cancer.

A recent review and meta-analysis[13] helps answer this question. It looked at 34,000 women with PMB, of whom 6300 had endometrial cancer. From this data, it is estimated that the risk of endometrial carcinoma being present in a woman with PMB in the US is 5%. Within this overall 5% risk, it will be higher in women not using HRT since in the HRT treated women, many cases of PMB are related to the HRT induced changes in the endometrium, and not due to an underlying cancer. The available modalities for evaluation include:

- Trans-Vaginal Ultrasonogram (TVUS)
- Hysteroscopy
- Endometrial biopsy
- Methylation assay

The specificity of TVUS was 35%, however the sensitivity was 98%. Given the low cost, safety, and high sensitivity, TVUS should be the initial screening test in women with PMB.

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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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