Posttest

1. Which of the following statements is true regarding AF as a risk factor for stroke:
   
   A. Non-valvular AF increases the risk of stroke 5-fold compared to patients without AF
   B. Non-valvular AF increases the risk of stroke 3-fold compared to patients without AF
   C. Non-valvular AF increases the risk of stroke 2-fold compared to patients without AF
   D. Non-valvular AF is not an independent risk factor for stroke

   **Rationale:** Atrial fibrillation (AF) is a strong independent risk factor for stroke, with non-valvular AF increasing risk by 5-fold compared to patients without AF.86,52

2. Which of the following patients with AF is at the highest risk for stroke:
   
   A. A 65 year old female
   B. A 65 year old male
   C. An 85 year old female
   D. An 85 year old male

   **Rationale:** The risk of stroke varies greatly depending on the presence of coexisting cardiovascular disease, and the presence of additional risk factors. The most commonly identified risk factors for stroke include older age, history of previous systemic thromboembolism, hypertension, female sex, congestive heart failure or left ventricular systolic dysfunction, systolic blood pressure, and diabetes.36

3. The following are commonly recognized risk factors for stroke:
   
   A. Hypertension, diabetes, prior stroke, obesity
   B. Hypertension, diabetes, congestive heart failure, obesity
   C. Hypertension, diabetes, smoking, age > 75 years
   D. Hypertension, diabetes, age > 75 years, female sex

   **Rationale:** The most commonly identified risk factors for stroke include older age, history of previous systemic thromboembolism, hypertension, female sex,
congestive heart failure or left ventricular systolic dysfunction, systolic blood pressure, and diabetes.³⁶

4. According to the CHADS² Index, which of the following risk factors is associated with a score of 2 in patients with non-valvular AF?

A. Hypertension
B. Diabetes
C. Prior stroke or TIA
D. Heart failure

**Rationale:** The CHADS² risk score is based on a cumulative point system focusing on five major risk factors, in which two points are assigned for a history of stroke or TIA and one point each is assigned for age over 75 years, a history of hypertension, diabetes, or recent heart failure. (See Table 2)

5. A patient with a CHADS² Index of 4 is at high risk for stroke.

A. True
B. False

**Rationale:** The risk of stroke is increased with an increasing CHADS² score.³⁴ (See Table 3) A patient at low risk for stroke would have a CHADS² score of 0, a patient at moderate risk would have a score of 1-2, and a patient at high risk would have a score of 3-6.

6. The following statement is true about the CHA²DS²VASc Index:

A. CHA²DS²VASc identifies a lower risk population compared to CHADS²
B. CHA²DS²VASc is the most commonly used stroke risk stratification scheme in the US
C. CHA²DS²VASc was recently adapted by the ACC/AHA Guidelines as the only appropriate risk stratification scheme to use on AF patients
D. None of the above

**Rationale:** While widely used in the US, the CHADS² scoring system also has some limitations such as low reliability in patients with prior stroke or TIA and no other risk factors. In addition, less well-validated risk factors such as age 65 to 74 years, female gender, and vascular disease, were not included in this scoring scheme. A more recent risk stratification scheme, the CHA²DS²VASc, has been developed to overcome some of these limitations and includes these latter risk factors. The CHA²DS²VASc identifies a lower risk population and appears to have a somewhat better predictive value for stroke when compared with other risk stratification schemes.⁵⁷
7. XR is a 66 year old female with non-valvular AF, and a history of peripheral arterial disease and hypertension: The CHA₂DS₂VASc index in this patient is:

   A. 1
   B. 2
   C. 3
   D. 4

**Rationale:** The CHA₂DS₂VASc score and recommended therapy¹² (See Table 5)

8. XR is a 66 year old female with non-valvular AF, and a history of peripheral arterial disease and hypertension: The following is the recommended antithrombotic treatment option in this patient:

   A. No antithrombotic therapy is recommended
   B. ASA 325 mg daily
   C. Warfarin at an INR of 2-3
   D. Dabigatran 150 mg daily

**Rationale:** Antithrombotic Treatment Recommendations for Stroke Prevention in AF – Based on the ACC/AHA/ESC Guidelines.³² (See Table 6)

9. According to the most current updates to the American College of Cardiology/American Heart Association (ACC/AHA) treatment guidelines for management of patients with AF, which of the following stroke prevention strategies is recommended for a patient with more than one moderate risk factor or any high risk factor?

   A. Aspirin
   B. Aspirin or warfarin
   C. Warfarin
   D. Warfarin or dabigatran

**Rationale:** Antithrombotic Treatment Recommendations for Stroke Prevention in AF – Based on the ACC/AHA/ESC Guidelines.³² (See Table 6)

10. C.D., a 78-year-old male, presents to the cardiology clinic complaining of several days of fatigue and a “racing heart.” On physical examination, his pulse is irregularly irregular, and his heart rate is approximately 120 beats/minute. Using ECG, a diagnosis of atrial fibrillation is made and cardioversion planned. Four weeks after successful cardioversion, C.D. presents to the ED with chest palpitations and light-headedness. An ECG is evaluated, and atrial fibrillation is diagnosed again. The team decides that
the patient will benefit from long-term antithrombotic therapy. You recommended the following long-term therapy:

- A. ASA 325 mg daily
- B. Warfarin at INR of 2-3
- C. Dabigatran 150 mg twice daily
- D. ASA 325 mg daily OR Warfarin at INR 2-3 OR Dabigatran 150 mg twice daily

**Rationale:** Antithrombotic therapy given to patients with AF for primary prevention (before the first stroke or episode of systemic embolism) or as secondary intervention (after stroke or systemic embolism has occurred) reduces the risk of stroke. The guidelines issued by ACC/AHA/ESC and ACCP recommend antithrombotic therapy for all patients with AF to prevent stroke. As mentioned above, stroke risk is categorized as low, moderate, and high based on the presence or absence of various risk factors and therapy is guided by the predicted stroke risk. (See Tables 4 and 6) For example, patients with prior stroke or TIA, or with multiple (> 2) risk factors (age > 75, hypertension, heart failure, diabetes, left ventricular ejection fraction (LVEF) ≤ 35%) would be considered at high-risk of stroke and are candidates for warfarin therapy International Normalized Ratio (INR) target of 2.5 (range 2.0-3.0]). Patients with the presence of any risk factor would be considered at moderate risk and are candidates for either warfarin [INR target of 2.5 (range 2.0-3.0)] or aspirin therapy. More recent data favors anticoagulation over aspirin, as patients at moderate risk (CHADS2 score of 1) apparently derive a significant benefit with vitamin K antagonists and with no increase in major hemorrhage. Patients with no additional risk factors would be considered at low risk and are candidates for aspirin therapy. The most recent focused updates to the ACC/AHA/ESC guidelines also suggest the option of combination clopidogrel and aspirin therapy in patients with AF in whom oral anticoagulation with warfarin is considered unsuitable. In addition, the novel oral direct thrombin inhibitor, dabigatran is an alternative in patients for warfarin therapy but who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (creatinine clearance (CrCl) < 15 mL/min), or advanced liver disease (impaired baseline clotting function). Another important criterion to note is that the risk of stroke is the same whether the patient has permanent or intermittent AF and the same guidelines apply.

11. Aspirin is more effective then placebo but less effective then warfarin for stroke prevention in patients with non-valvular AF.

- A. True
- B. False

**Rationale:** Although more effective than placebo, aspirin is much less effective than warfarin in preventing stroke (primarily noncardioembolic stroke). Five studies compared the efficacy of aspirin with control. The Stroke
Prevention in Atrial Fibrillation (SPAF) trial, found a 42% relative risk reduction in favor of aspirin. Three trials found no significant benefit in favor of aspirin vs. control or placebo, and the Low-Dose Aspirin, Stroke, and Atrial Fibrillation (LASAF), found inconsistent effects of aspirin among various dosing regimens. Pooled data from the three largest studies resulted in a 21% (95% CI, 0 to 38%) relative risk reduction in favor of aspirin compared to placebo. Another meta-analysis of six randomized trials of aspirin vs. control reported similar results, a 22% risk reduction (95% CI, 2 to 38%), and absolute risk reduction of 1.5% per year. However, randomized trials have shown that aspirin is less effective than warfarin, except in low-risk patients. Therefore, patients with no risk factors for stroke can be given aspirin but those with one or more risk factors should be considered for anticoagulation therapy.

12. Which of the following statements regarding the effectiveness of warfarin therapy in patients with AF is consistent with current evidence?

A. Warfarin has been shown to be superior to placebo, aspirin, and aspirin plus clopidogrel for the prevention of stroke in patients with AF
B. When compared with aspirin, warfarin resulted in a lower risk for ischemic stroke and also a lower risk of major bleeding
C. Warfarin was shown to be less efficacious compared to aspirin and clopidogrel combination therapy
D. Ninety percent (90%) of patients on warfarin therapy have an international normalized ratio in the therapeutic range

Rationale: Warfarin has been shown to be superior to placebo, aspirin, and aspirin plus clopidogrel for the prevention of stroke in patients with AF in several trials. Compared with placebo, warfarin reduces the relative risk of stroke by nearly 70%. The absolute reduction in stroke risk by warfarin ranges from 2.5% per year to 4.7% per year in primary prevention studies and was 8.4% per year in the secondary intervention studies. This implies that 22-40 patients would need to be treated with warfarin to prevent one first time stroke or systemic embolism per year. Prevention of one secondary event per year would require warfarin therapy in only 12 patients. Anticoagulation was found to be effective in preventing strokes of all severities, and the beneficial effect of warfarin on outcomes was maintained across all patient subgroups.

13. The following are characteristics of novel oral anticoagulants developed for stroke prevention if AF:

A. No monitoring required, limited drug interactions, fast onset of action
B. No drug interactions, fast onset of action, no monitoring required
C. Fixed daily doses, low cost, no monitoring
D. All of the above

**Rationale:** Novel anticoagulants have been developed to overcome the limitations of traditional anticoagulants such as warfarin leading to improved patient management. These novel agents ideally would have a predictable dose response with the potential to be given at a fixed dose with no monitoring or dose adjustment, limited or no drug/food interactions, a fast onset and offset of action, removing the need for bridging therapy, thus being more convenient for patients and physicians. Several novel oral anticoagulants are available or currently in development including: direct thrombin inhibitors (DTIs), Factor-Xa inhibitors, Factor-IX inhibitors and tissue factor inhibitors. (See Table 7)

14. Which of the following is a direct thrombin inhibitor:
   A. Apixaban
   B. **Dabigatran**
   C. Edoxaban
   D. Rivaroxaban

**Rationale:** Thrombin is a serine protease that converts fibrinogen to fibrin in the final steps of the coagulation cascade. Since thrombin amplifies its own generation, limiting its activity becomes a vital mechanism to achieve effective anticoagulation. DTIs inactivate clot-bound thrombin, as well as fluid-phase thrombin. DTIs are not metabolized by the cytochrome P-450 (CYP) system and have limited binding to plasma proteins and cellular elements. To date, two oral DTIs have been studied in AF: ximelagatran and dabigatran.

15. The lower 75 mg dose of dabigatran is indicated for which of the following patient subpopulations?
   A. All patients with AF
   B. Patients with creatinine clearance 15-30 mL/min
   C. Patients with creatinine clearance >30 mL/min
   D. Patients with creatinine clearance <15 mL/min

**Rationale:** Approximately 80% of dabigatran is eliminated in the urine and a dose adjustment (75 mg twice daily) has been recommended in patients with severe renal impairment (CrCl < 30 ml/min). The use of dabigatran is contraindicated in patients with a CrCl < 15 ml/min.

16. The dose of rivaroxaban and dabigatran should be reduced in patients with renal impairment.
   A. True
   B. False

**Rationale:** Approximately 80% of dabigatran is eliminated in the urine and a dose adjustment (75 mg twice daily) has been recommended in patients with severe renal impairment (CrCl < 30 ml/min). The use of dabigatran is contraindicated in patients with a CrCl < 15 ml/min.
severe renal impairment (CrCl < 30 ml/min). The use of dabigatran is contraindicated in patients with a CrCl < 15 ml/min. Approximately two-thirds of rivaroxaban is excreted renally and use in patients with decreased renal function has led to increases in rivaroxaban exposure. Therefore, rivaroxaban should be used with caution in patients with moderate renal dysfunction (CrCl 30-49 ml/min) and contraindicated in patients with severe renal impairment (CrCl < 30 ml/min).

17. The efficacy and safety results of the RE-LY trial, comparing dabigatran with warfarin for stroke prevention in patients with AF, support which of the following statements?

A. Dabigatran 150 mg bid is noninferior to warfarin for stroke prevention and is associated with higher rates of major bleeding.
B. Dabigatran 150 mg bid is noninferior to warfarin for stroke prevention and is associated with similar rates of major bleeding.
C. Dabigatran 150 mg bid is superior to warfarin for stroke prevention and is associated with higher rates of major bleeding.
D. Dabigatran 150 mg bid is superior to warfarin for stroke prevention and is associated with similar rates of major bleeding.

Rationale: Dabigatran was evaluated in the phase III, multicenter, randomized, non-inferiority trial Randomized Evaluation of Long-term anticoagulation therapy (RE-LY). RE-LY evaluated the efficacy and safety of 2 fixed doses of dabigatran etexilate (110 mg and 150 mg twice per day [bid]), in a blinded fashion, compared with open-label warfarin in patients with AF at increased risk of stroke. A total of 18,113 patients who had AF and were at a risk of stroke were enrolled. Dabigatran 150 mg bid was found to be superior to warfarin for the primary efficacy outcome of stroke and systemic embolism (1.11% vs. 1.69% per year, \(P < .001\)), with a similar rate of major bleeding (3.11% vs. 3.36% per year, \(P = .31\)), whereas dabigatran 110 mg bid was non-inferior to warfarin for the primary efficacy outcome (1.53% vs. 1.69% per year, \(P = .34\)), with a significantly lower rate of major bleeding (2.71% vs. 3.36% per year, \(P = .003\)).

18. The efficacy and safety results of the ROCKET trial, comparing rivaroxaban with warfarin for stroke prevention in patients with AF, support which of the following statements?

A. Rivaroxaban is noninferior to warfarin for stroke prevention and is associated with lower rates of major bleeding.
B. Rivaroxaban is noninferior to warfarin for stroke prevention and is associated with similar rates of major bleeding.
C. Rivaroxaban is superior to warfarin for stroke prevention and is associated with lower rates of major bleeding.
D. Rivaroxaban is superior to warfarin for stroke prevention and is
associated with similar rates of major bleeding.

**Rationale:** Rivaroxaban has been evaluated in the phase III Rivaroxaban Once daily oral direct FXa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF).67 ROCKET-AF was a randomized, double-blind, double-dummy, multicenter, event-driven study to test the non-inferiority of rivaroxaban (20 mg/d or 15 mg/d in patients with renal impairment [CrCl of 30-49 mL/min]) compared with adjusted dose warfarin in 14,264 patients with nonvalvular atrial fibrillation who were at moderate to high risk for stroke. The per-protocol, as-treated primary analysis was designed to determine whether rivaroxaban was noninferior to warfarin for the primary end point of stroke or systemic embolism. The primary safety outcome was the composite of major and non-major clinically relevant bleeds. In the primary analysis, the primary end point occurred in 188 patients in the rivaroxaban group (1.7% per year) and in 241 in the warfarin group (2.2% per year) (hazard ratio in the rivaroxaban group, 0.79; 95% confidence interval [CI], 0.66 to 0.96; P<0.001 for noninferiority). In the intention-to-treat analysis, the primary end point occurred in 269 patients in the rivaroxaban group (2.1% per year) and in 306 patients in the warfarin group (2.4% per year) (hazard ratio, 0.88; 95% CI, 0.74 to 1.03; P<.001 for noninferiority; P=0.12 for superiority). Major and nonmajor clinically relevant bleeding occurred in 1475 patients in the rivaroxaban group (14.9% per year) and in 1449 in the warfarin group (14.5% per year) (hazard ratio, 1.03; 95% CI, 0.96 to 1.11; P=0.44), with significant reductions in intracranial hemorrhage (0.5% vs. 0.7%, P=0.02) and fatal bleeding (0.2% vs. 0.5%, P=0.003) in the rivaroxaban group. ROCKET-AF demonstrated that rivaroxaban was noninferior to warfarin and that there was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.

19. Based on the RE-LY study, both dosing regimens of dabigatran 110 mg po bid and 150 mg po bid were approved by the FDA for stroke prevention in AF.

   A. True
   B. False

**Rationale:** The findings of the RE-LY trial led to the approval of dabigatran for stroke prevention in AF by the Food and Drug Administration (FDA) at the dosage of 150 mg bid.

20. In the AVERROES trial, which compared the direct factor Xa inhibitor apixaban with aspirin therapy for stroke prevention in patients with AF, apixaban therapy was associated with which of the following safety and efficacy results compared with aspirin?

   A. Reduced risk of stroke and systemic embolism and higher rate of
major bleeding

B. Reduced risk of stroke and systemic embolism and similar rate of major bleeding

C. Similar risk of stroke and systemic embolism and higher rate of major bleeding

D. Similar risk of stroke and systemic embolism and similar rate of major bleeding

Rationale: Apixaban has been assessed in the phase III Study of Apixaban in Patients with Atrial Fibrillation (AVERROES), a randomized, double-blind, double-dummy study to assess the superiority of apixaban 5 mg bid vs. aspirin (81-324 mg/d) for the prevention of stroke in 5,600 patients with atrial fibrillation and at least one additional risk factor for stroke, who had failed or were considered unsuitable for vitamin K antagonist treatment. The primary efficacy outcome was the time to first ischemic stroke, hemorrhagic stroke, or systemic embolism. The study was terminated early due a clear benefit in favor of apixaban. The primary outcome was stroke or systemic embolism. There were 52 primary outcome events in those randomized to apixaban (1.6%/year) and 112 primary outcome events in those randomized to aspirin (3.5%/year) (HR 0.46; 95% CI, 0.33-0.64; P < .001). Mortality rates were 3.4%/year for those randomized to apixaban and 4.4%/year for those randomized to aspirin (HR 0.79; 95% CI, 0.61-1.01; P = .06). There were 46 major bleeds (1.4%/year) in the apixaban group and 43 major bleeds (1.3%/year) in the aspirin group (HR 1.08; 95% CI, 0.71-1.63; P = .73). There were 13 intracranial bleeds in the apixaban group and 12 intracranial bleeds in the aspirin group. Thus, superiority of apixaban over aspirin was shown in terms of efficacy and comparable safety.