The “BEST and BRIGHTEST” Address the 130 “TRICKIEST and TOUGHEST” Questions, Issues, and Clinical Dilemmas in Stroke Prevention in Atrial Fibrillation

World Authorities Answer Questions You and Other Cardiovascular Specialists Have Posed About Landmark Trials, Clinical Strategies, Cross-Trial Comparisons, and Real World Challenges Cardiologists and Clinical Specialists Face at the Front Lines of Practice

Question # 1:
Dr. Goldhaber, why have you assembled this distinguished group of international thrombosis, EP, and cardiovascular experts to focus on stroke prevention in AF (SPAF)? Please give us a “State of the Art and Science” for SPAF as you see it.

Question # 2:
What about the temptation to make cross-trial comparisons among ARISTOTLE, ROCKET AF, and RE-LY? What is your position? And what will the discussions focus on?

Question # 3:
What can we expect to learn in this iQ&A Medical Intelligence Zone focused on SPAF?

Question # 4:
What are some of the vexing clinical dilemmas we are likely to face when assessing stroke risk in AF; and, as important, when applying the results of ARISTOTLE, ROCKET AF and RE-LY to the front lines of patient-focused, cardiovascular practice.

Question # 5:
In the face of such robust trial-based evidence in favor of NMOACs for SPAF, which patient types and/or subgroups do you feel are most eligible for initiating treatment with rivaroxaban, apixaban, or dabigatran?

Question # 6:
From a public health and societal perspective, how do these SPAF trial help clinicians overcome the barriers we’ve had in treating AF patients in guideline-consistent fashion and using anticoagulation when warranted?

Question # 7:
What is your interpretation of the ARISTOTLE trial and how do the results direct us toward optimal management of stroke prevention in AF? And how do the new agents compare to warfarin?

Question # 8:
Even though cross-trial comparisons are difficult if not impossible, how do we begin aligning specific factor Xa or thrombin inhibitors with specific AF patient types? With individual patients?

Supported by an educational grant from Janssen Pharmaceuticals, Inc., administered by Janssen Scientific Affairs, LLC, and an educational grant from the Bristol-Myers Squibb/Pfizer Partnership
Question # 9: Total mortality was reduced in ARISTOTLE, but not cardiovascular mortality. Why? Can you drill down to the trial design and explain this?

Question # 10: How do we use these trials—ROCKET AF, ARISTOTLE, and RE-LY—to help us align NMOACs with specific patient sub-populations and CHADS2 risk scores with AF?

Question # 11: Does this mean that in patients with CHADS2 scores of 2 or less, it would be more desirable to use apixaban, whereas in patients with CHADS2 scores of 3 or more, rivaroxaban would be preferable?

Question # 12: How much of translating the results from these SPAF trials to the front lines of practice is “science” and how much will require practicing the “art” of medicine?

Question # 13: Why are so many AF patients at risk for stroke, who are eligible for anticoagulation, undertreated, even if their CHADS2 risk scores support treatment? How can the new factor Xa and direct thrombin inhibitors help?

Question # 14: What part of the “warfarin means worry” perspective you just shared represents, in your view, the greatest deterrent to its guideline-driven use? Is it bleeding? Something else?

Sana M. Al-Khatib, MD, MHS, FACC
Assistant Professor of Medicine
Director of Clinical Electrophysiology Research
Duke University Medical Center
Durham, North Carolina

Question # 15: Can you summarize the findings recently reported at the ESC for the ARISTOTLE trial for SPAF?

Question # 16: Why are AF patients at risk for stroke based on CHADS2 risk score stratification not treated more consistently with oral anticoagulation?

Deepak L. Bhatt, MD, MPH, FACC, FAHA,
Chief of Cardiology, VA Boston Healthcare System
Director, Integrated Interventional Cardiovascular Program
Brigham and Women’s Hospital and the VA Boston Healthcare System
Senior Investigator, TIMI Group
Harvard Medical School

Question # 17: How do we make sense and apply the results of at least three landmark trials—ARISTOTLE, ROCKET AF, and RE-LY—focused on SPAF?

Question # 18: How do we translate data from the published SPAF trials to a patient with CHADS2 risk score of 2?

Question # 19: Are these new anticoagulants, including rivaroxaban, apixaban, and dabigatran, really “breakthrough” agents for SPAF as so many experts are saying?

Question # 20: Are there any reasons, speculative or otherwise, for why dabigatran might be associated with a higher bleeding risk than other NMOACs?

Question # 21: Which AF patients are the ideal candidates for either initiating therapy or switching to NMOACs? De novo patients?

Question # 22: How long should a patient with chronic AF be continued on anticoagulation after they have been converted to sinus rhythm?

Question # 23: How should we approach a patient with AF in terms of employing a rate control vs rhythm restoration strategy?

Sana M. Al-Khatib, MD, MHS, FACC
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Question # 24: From an EP perspective, what are some cautionary notes you can provide for use of anti-arrhythmic drugs for rhythm-based management of AF?

Question # 25: What is the current status for the use of dronedarone in AF?

Question # 26: What questions about new therapies for SPAF still need to be answered, even after publication of ARISTOTLE, ROCKET AF, and RE-LY?

Deepak L. Bhatt, MD, MPH, FACC, FAHA,
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Question # 27: Can we say about how apixaban performs in patients with higher CHADS2 risk scores of 2-3 or greater?

Question # 28: What is your approach to triple therapy in the AF patient who requires a stent for ACS? What specific agents would you use and for what duration? What trials may help shed light on this?

Question # 29: Given the complexity and flux around triple therapy approaches to patients with AF, ACS, and stent, what should the clinician do, today, prior to completion on ongoing studies?

Question # 30: Given the success of NMOACs for SPAF, can we extrapolate the data from the pivotal trials to other patient populations, including those with ACS, stent, and AF? Or do we need to wait?

Question # 31: While cross trial comparisons among ARISTOTLE, ROCKET AF, and RE-LY are difficult, how would you recommend we undertake “cross patient” comparisons to identify AF patient subgroups that might optimally respond to apixaban, rivaroxaban, or dabigatran?

Question # 32: How do you see the results of the results of apixaban in the ARISTOTLE trial, specifically, as compared to other trials?

Question # 33: Where does the AVERROES trial fit into the mix of SPAF trials?

Question # 34: From a practical patient perspective, how do we align specific AF patient populations with specific agents such as rivaroxaban, apixaban, and dabigatran?

Christopher P. Cannon, MD
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Question # 35: Why are these novel NMOACs so much more effective than warfarin for SPAF? And how do they fare in ACS?

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YOUR QUESTIONS

EXPERT ANALYSIS
**Question # 36:**
What is the role of NMOACs in patients with AF and ACS and who might require triple therapy for management of SPAF and post-stent insertion?

**Question # 37:**
Your approach to the AF patient who requires a stent would include what specific agents and for what duration? And how does the type of stent influence your regimen?

**Question # 38:**
Given that patients in ARISTOTLE benefited from stroke reduction and bleeding reduction at all TTR levels, is there any reason not to switch patients from warfarin to apixaban, should it become available, for SPAF?

**Question # 39:**
How do we reconcile the results of the SPAF trials and the ACS trials using NMOACs as the third agent for a three-drug regimen in patients with ACS, stent, and AF?

**Question # 40:**
How should the trial designs for the landmark ARISTOTLE, ROCKET AF, and RE-LY SPAF trials impact our drug selection strategies for NMOACs? Especially in patients with renal dysfunction?

**Question # 41:**
How do we approach AF patients with high-risk CHADS2 scores of 3 and greater? All the trials included these patients, but are some trials more robust in their study design and analysis than others?

**Question # 42:**
What is the translational implication of ROCKET AF evaluating high-risk AF patients with an average CHADS2 score of about 3.4? How do apply this information to the front lines of CV practice?

**Question # 43:**
Given that IC hemorrhage with NMOACs is reduced in all the SPAF trials, how should we approach AF patients already on warfarin who appear to be stable with INRs in the therapeutic range? Should we switch these patients?

**Question # 44:**
If I am practicing in a center with an excellent TTR, how should that impact on how I apply the results of the SPAF trials?

**Question # 45:**
Can these new agents be used in AF patients or other patients with prosthetic valves?

**Question # 46:**
How much of a factor should once-daily vs. twice-daily therapy be when selecting NMOACs?

**Question # 47:**
How would you apply the data reported from the SPAF trials to an AF patient with a CHADS2 risk score of 0, 1, and 2?

**Question # 48:**
How would you apply the data reported from the SPAF trials to an AF patient with a CHADS2 risk score of 3, 4, or 5?

**Question # 49:**
What signals are we, as cardiologists, going to be looking for in the post-approval period to reassure and/or guide our use of these new NMOACs?

**Question # 50:**
As one of the principal investigators of the ARISTOTLE trial with apixaban, can you share with us the rationale, design strategies, and take-home findings of this landmark SPAF trial?

**Question # 51:**
What was responsible for the reduction in all-cause mortality that you observed in the apixaban-based ARISTOTLE trial?

**Question # 52:**
What differences did you observe in ARISTOTLE results related to the site of the trial and with regard to institutional TTR times? What do you make of these findings?

**Question # 53:**
What explains the difference between high-performing vs. low-performing centers with respect to TTR metrics? And what does it say about regimen adherence in these studies, in general?

**Question # 54:**
What does the TTR reflect about the institutional center or patient population being evaluated in the SPAF trials?

**Question # 55:**
What are the advantages and disadvantages of warfarin vs the NMOACs with respect to adherence of these medications?

**Question # 56:**
With respect to quartile studies for ARISTOTLE, were the end points increased for both the warfarin and apixaban groups in centers with poor TTRs?

**Question # 57:**
With respect to all-cause mortality reduction in ARISTOTLE, is there any evidence that apixaban has pleiotropic effects that might explain this finding?

**Question # 58:**
How should the clinician apply results of the pivotal SPAF trials—ROCKET AF, ARISTOTLE, and RE-LY—to help them align specific factor Xa and direct thrombin inhibitors with specific patient sub-populations requiring SPAF?

**Question # 59:**
Specifically for AF patients with high-risk CHADS2, scores of 3 or greater, how should the cardiologist apply results of the pivotal SPAF trials to the front lines of anticoagulation management?

**Question # 60:**
Considering the success of the ARISTOTLE, ROCKET AF, AVERROES, and RE-LY trials, where do we go from here in terms of optimizing management for SPAF?

**Question # 61:**
What is your take-home message as it relates to the ARISTOTLE trial?
Question # 62: What unique features of the ARISTOTLE trial caught your attention as you reviewed the data and compared it to other SPAF trials?

Question # 63: Even though cross-trial comparisons are difficult if not impossible, how do we begin aligning specific factor Xa or thrombin inhibitors with specific AF patient types? Is this possible? What factors should we consider when making these choices?

Question # 64: Are there some patient populations with AF that are uniquely suited for specific NMOACs? What about high-risk patients in ROCKET AF?

Question # 65: Since IC hemorrhage is reduced by all the NMOACs—apixaban, rivaroxaban, and dabigatran—how would you approach AF patients already on warfarin who appear to be stable with INRs in the therapeutic range?

Question # 66: Should we be using institutional TTR metrics to determine whether we should be using novel anticoagulants for SPAF?

Question # 67: What is the relationship, if any, between inflammation and thrombosis?

Question # 68: Can you articulate the process by which thrombosis can precipitate inflammation? And the nature of this feedback loop?

Question # 69: Going beyond the specific breakthroughs ushered in by the SPAF trials, what can we do to break the cycle between thrombosis and inflammation?

Question # 70: With the ARISTOTLE trial for SPAF, as well as RE-LY and ROCKET AF, what is the best way for us to communicate this information to the cardiologist and other clinicians?

Question # 71: Prior to the ARISTOTLE trial, we have never achieved a reduction in all-cause mortality in a SPAF trial. Any thoughts about why?

Question # 72: What is your perspective on the global cardiovascular community? Is there a convergence in progress?

Question # 73: How can the CHADS2 score assist us in aligning AF patients with specific therapies, based on the results of the ARISTOTLE, ROCKET AF, and RE-LY SPAF trials?

Question # 74: Do the results of the trials provide a prescriptive approach to selecting a specific agent, whether it be apixaban, rivaroxaban, or dabigatran, for an individual patient with AF?

Question # 75: Can you provide guidance for parsing out the factor Xa and direct thrombin inhibitors based on the results of landmark SPAF trials?

Question # 76: How might the differences in trial design and risk group focus for ROCKET AF, ARISTOTLE, and RE-LY affect our thinking about and choices for NMOACs in patients requiring SPAF?

Question # 77: Considering that CHADS2 has been the gold standard risk score tool for the ROCKET AF, ARISTOTLE, and RE-LY trials, how might the introduction of CHADS-VASC or HAS-BLED alter our clinical approach to risk scoring for AF?

Question # 78: How do we balance thrombotic (stroke) risk with bleeding risk in patients requiring anticoagulation for AF? Can the HAS-BLED risk score play a role in drug selection and determining net clinical benefit for factor Xa and DT inhibitors?

Question # 79: How should the cardiologist employ HAS-BLED, even though it wasn’t part of risk assessment protocol for the major SPAF trials?

Question # 80: Why are so many AF patients at risk for stroke who are eligible for anticoagulation undertreated, despite CHADS2, risk scores that mandate thromboprophylaxis against stroke?

Question # 81: How might availability of such agents as apixaban, rivaroxaban, and dabigatran increase guideline-consistent mandates for oral anticoagulation in patients requiring SPAF?

Question # 82: How good are our scoring assessment tools for identifying patients who are at risk for stroke in patients with AF? Who are at risk for hemorrhage?

Question # 83: What consistent safety and efficacy findings across the SPAF trials do you feel are most important in terms of their translational aspect to the front lines of cardiovascular practice?

Question # 84: Based on the consistency of efficacy findings in ROCKET AF, ARISTOTLE, and RE-LY, i.e. a minimum bar of non-inferiority vs warfarin, what should our approach to these agents be for SPAF?

Question # 85: How can clinicians utilize the CHADS2 or CHADS-VASC risk scores to optimize their selection of specific anticoagulants for SPAF?

Question # 86: How would you optimize stroke prevention in an 81-year old woman, who is warfarin, has new onset AF, and a CHADS2 score of 3? What choices and considerations, including bleeding, go through your mind?
Question # 87: What advances in the area of risk stratification tools for SPAF will help us in future decision-making? What new variables, such as biomarkers, should we consider?

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Question # 88: Assuming all three NMOACs become available for clinical use, how would you use the findings of ROCKET AF, ARISTOTLE, and RE-LY to help select agents for specific subgroups of patients with AF?

Question # 89: What is it about the ROCKET AF trial that explains why it has special relevance for the high CHADS2 risk score subgroup?

Question # 90: How does the ROCKET AF trial shed light on the role of NMOACs for secondary prevention of stroke and other high-risk features?

Question # 91: How are these new trials, including ROCKET AF, ARISTOTLE, and RE-LY, likely to impact the under-treatment of patients with AF in who guidelines would mandate anticoagulation as a primary strategy?

Question # 92: Given that NMOACs reduce ICH in all the SPAF trials, how should we approach AF patients already on warfarin and who appear to be stable with INRs in the therapeutic range?

Question # 93: What advances in risk stratification for AF patients do you see coming down the road?

Question # 94: In terms of patients who have renal dysfunction, how should we approach selecting among and dosing strategies for apixaban, rivaroxaban, and dabigatran?

Christian T. Ruff, MD, MPH
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Instructor of Medicine
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Question # 95: Is there any controversy about whether it’s optimal or preferable to use a factor Xa inhibitor or a direct thrombin inhibitor for SPAF?

Question # 96: What is your perspective, as an investigator and cardiologist, on what changes are occurring on the landscape of SPAF? And the impact of NMOACs such as rivaroxaban, apixaban, and dabigatran?

Question # 97: Given that patients may be stable on warfarin, because IC hemorrhage is reduced by all the NMOACs, how do we decide which AF patients might nevertheless be better off switched to a factor Xa or direct thrombin inhibitor? Triggers?

Question # 98: Based on ROCKET AF, ARISTOTLE, and RE-LY, how do we analyze the factors that might induce us to switch an AF patient who has been stable on warfarin, with a consistent INR, to one of the factor Xa or direct thrombin inhibitors?

Manesh R. Patel, MD
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Question # 99: What signals are we going to be looking for in post-marketing surveillance data to reassure and/or guide our use of new NMOACs?

Question # 100: Why has there been a systemic failure in undertreating so many AF patients at risk for stroke who are eligible for anticoagulation? And how might the new factor Xa and direct thrombin inhibitors help improve guideline-directed treatment for SPAF?

Question # 101: Based on data published in the pivotal SPAF trials—ROCKET AF, ARISTOTLE, and RE-LY—how will you likely align specific factor Xa and direct thrombin inhibitors with specific patient sub-populations, based on risk, requiring SPAF?

Meyer-Michel Samama, MD
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Paris, France

Question # 102: Is there any controversy about whether it’s optimal or preferable to use a factor Xa inhibitor or a direct thrombin inhibitor for SPAF?

Question # 103: What do we make of the slight increase in ACS and MI in the RE-LY trial with the direct thrombin inhibitor dabigatran?

Question # 104: How should clinicians transition from warfarin to NMOACs in AF patients being managed for SPAF?

Question # 105: Can you summarize the differences in renal metabolism for the factor Xa and direct thrombin inhibitors and what the implications might be based on this parameter?

Question # 106: What steps should we take to develop consensus around SPAF management, in light of these new trials?

Question # 107: Should all AF patients currently taking warfarin be switched to a NMOAC, based on the positive results from multiple SPAF trials?

Question # 108: Why are the novel NMOACs so much more successful for SPAF than they are for VTE prophylaxis and/or treatment?

Christian T. Ruff, MD, MPH
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Question # 109: With ARISTOTLE, do you think its success is a result of achieving a sweet spot as far as its dosing profile and pharmacokinetic modeling, or because of some intrinsic biochemical property of apixaban?

Meyer-Michel Samama, MD
Professor Emeritus of Hematology
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Question # 110: Why is the altered (improved) benefit-to-risk ratio of the new oral agents lowering the barriers to guideline-endorsed anticoagulation of AF patients with CHADS2 risk scores of 1 or greater?

Meyer-Michel Samama, MD
Professor Emeritus of Hematology
Faculty of Medicine
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Paris, France

Question # 111: Given that patients may be stable on warfarin, because IC hemorrhage is reduced by all the NMOACs, how do we decide which AF patients might nevertheless be better off switched to a factor Xa or direct thrombin inhibitor? Triggers?

Question # 112: Based on data published in the pivotal SPAF trials—ROCKET AF, ARISTOTLE, and RE-LY—how will you likely align specific factor Xa and direct thrombin inhibitors with specific patient sub-populations, based on risk, requiring SPAF?

Christian T. Ruff, MD, MPH
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Question # 113: Is there any controversy about whether it’s optimal or preferable to use a factor Xa inhibitor or a direct thrombin inhibitor for SPAF?

Question # 114: What do we make of the slight increase in ACS and MI in the RE-LY trial with the direct thrombin inhibitor dabigatran?

Question # 115: How should clinicians transition from warfarin to NMOACs in AF patients being managed for SPAF?

Question # 116: Can you summarize the differences in renal metabolism for the factor Xa and direct thrombin inhibitors and what the implications might be based on this parameter?

Question # 117: What steps should we take to develop consensus around SPAF management, in light of these new trials?

Question # 118: Should all AF patients currently taking warfarin be switched to a NMOAC, based on the positive results from multiple SPAF trials?

Question # 119: Why are the novel NMOACs so much more successful for SPAF than they are for VTE prophylaxis and/or treatment?

Question # 120: With ARISTOTLE, do you think its success is a result of achieving a sweet spot as far as its dosing profile and pharmacokinetic modeling, or because of some intrinsic biochemical property of apixaban?
Alexander G.G. Turpie, MD
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Question # 110: How do factor X and direct thrombin inhibitors differ in their mode of action and, based on ARISTOTLE, ROCKET AF, and RE-LY, what are the practical issues that should impact our choice of these agent for SPAF?

Question # 111: Are there “off-target” effects associated with the NMOACs that have shown to be safe and effective for SPAF?

Question # 112: While cross trial comparisons among ARISTOTLE, ROCKET AF, and RE-LY are difficult, how would you recommend we undertake “cross patient” comparisons to identify AF patient subgroups that might optimally respond to apixaban, rivaroxaban, or dabigatran?

Question # 113: How do we approach anticoagulation in AF patients with impaired renal clearance?

Question # 114: How should an institution’s TTR metric influence the decision to switch and/or start a patient on a novel oral anticoagulant in the setting of SPAF? Who should we start and/or switch from warfarin?

Freek Verheugt, MD, PhD
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Onze Lieve Vrouwe Gasthuis
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Question # 115: Which AF patients are the ideal candidates for either initiating therapy or switching to NMOACs? Do novo patients with AF? AF patients on warfarin? Who are not candidates for the novel agents?

Question # 116: Given that IC hemorrhage is reduced by all the NMOACs—apixaban, rivaroxaban, and dabigatran—how should we approach AF patients already on warfarin who appear to be stable with INRs in the therapeutic range?

Question # 117: Considering that CHADS2 has been the gold standard risk score tool for the ROCKET AF, ARISTOTLE, and RE-LY trials, how might the introduction of CHADS-VASC or HAS-BLED alter our clinical approach to risk scoring for AF?

Question # 118: Has the ESC taken a position on the usefulness of the CHADS-VASC score?

Alexander G.G. Turpie, MD
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Question # 119: How do we make sense and apply the results of the three latest landmark trials—ARISTOTLE, ROCKET AF, and RE-LY—focused on SPAF? And how will they shape our thinking moving forward?

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Canada Research Chair in Thrombosis
Heart and Stroke Foundation
J.F. Mustard Chair in Cardiovascular Research

Question # 120: How do we approach AF patients with high-risk CHADS2 scores of 3 and greater? All the trials included these patients, but aren’t some SPAF trials more robust in their study design and inclusionary criteria for these patients than others?

Question # 121: At what point in the clinical presentation of AF should a patient be referred to a cardiologist or electrophysiologist?

Question # 122: How do we use the pivotal SPAF trials—ROCKET AF, ARISTOTLE, and RE-LY—to help us align specific factor Xa and direct thrombin inhibitors with specific patient sub-populations requiring SPAF?

Question # 123: There has been some controversy about the lack of the 110 mg dabigatran dose in the U.S. As a Canadian, who has access an approved 110 mg dose of dabigatran, can you shed light on this?

Question # 124: What about bleeding as a deterrent to using NMOACs and the role of the 110 mg dose of dabigatran? And how does apixaban in the ARISTOTLE trial shed light on the issue of bleeding?

Question # 125: For whom might the 110 mg BID dose of dabigatran be useful if available, and when are you using it in Canada?

Question # 126: What aspects of monitoring (PT, aPTT) or vigilance should we be aware of when using such agents as apixaban, rivaroxaban, and dabigatran, if and/or when they become approved for SPAF?

Question # 127: Given that IC hemorrhage is reduced by all the NMOACs—apixaban, rivaroxaban, and dabigatran—how should we approach AF patients already on warfarin who appear to be stable with INRs in the therapeutic range?

Question # 128: In your assessment, based on the data from ROCKET AF, ARISTOTLE, and RE-LY, what are the most compelling reasons for switching from warfarin to a NMOAC?

Question # 129: What is your interpretation for why the results of the ARISTOTLE trial appeared to produce optimal results across the range of important end points, i.e., stroke risk reduction, reduction in IC and major hemorrhage, and mortality?

Question # 130: Assuming all three NMOACs become available for clinical use, how would you use the findings of ROCKET AF, ARISTOTLE, and RE-LY to help select agents for specific subgroups of patients with AF? In your assessment, based on the data from ROCKET AF, ARISTOTLE, and RE-LY, what are the most compelling reasons for switching from warfarin to a NMOAC?