EDITORIAL

# Atrial fibrillation and stroke: more than a story of a villain and a victim

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Atrial fibrillation (AF) is the main cardiogenic cause of acute ischemic stroke (AIS), with AIS risk in non-anticoagulated patients (under aspirin only) reaching 2.1%, 3.0%, and 4.2% per year for paroxysmal, persistent, and permanent AF, respectively.[1] Although vitamin K antagonists (VKAs; warfarin or coumadin) reduce the AIS risk in AF by approximately 65%, obtaining optimal therapeutic range is challenging.[2,3] While direct oral anticoagulants (DOAC) dismiss the need of a therapeutic range monitoring and are 15%–20% more effective than VKAs in preventing AIS and systemic thromboembolism, they are more expensive (that may be particularly relevant in systems with none or only partial reimbursement) and may cause more gastrointestinal bleedings than VKAs.[2,3] With an increased risk of bleeding on anticoagulants, clinicians and patients facing stroke prevention and treatment in AF are in a constant juggle between 2 calamities: thrombosis and bleeding.[4] To further complicate matters, evidence is emerging that a high residual risk of AIS remains despite appropriate dose-adjusted anticoagulation in AF patients. In the current issue of *Pol Arch Intern Med*, a study by Lasek-Bal et al[5] evaluating the impact of AF in 108 patients with AIS treated with mechanical thrombectomy (MT) reported that 76.3% of them were anticoagulated, of which 1 in every 3 patients were on therapeutic-level anticoagulation. In landmark clinical trials evaluating different DOAC agents against warfarin among patients with AF, the residual risk of stroke or systemic embolism despite anticoagulation treatment was between 1.11% and 2.40% per year, while higher rates (reaching nearly 3% per year) were reported in real-world studies.[2,3] Large-scale data show the risk of major bleeding (including hemorrhagic strokes) on VKA or DOAC of 2.84%.[2] These high risks must not be underestimated because the threshold for consideration of oral anticoagulation in AF is approximately 0.9%, corresponding to the $CHA_2DS_2$-VASc score of 1.[3] These reports signify the concerning and highly clinically relevant role of residual stroke risk even in appropriately (by today's criteria) anticoagulated AF patients and the challenges of AIS management in the AF population.

Thromboembolism in AF patients may lead to AIS due to occlusion of a single intracranial large artery by a sizeable thrombus, an event called large vessel occlusion (LVO), or occlusion of multiple smaller branches, a phenomenon named an embolic shower. These 2 patterns are highly relevant for the treatment of AIS in AF patients. The first has a worse natural history and is more amenable to endovascular intervention (MT) with established benefits of only 5 to 7 patients needed-to-treat to prevent 1 permanent functional dependence, making it one of the most effective interventions in medicine today.[6] MT is currently performed by retrieval of clots with an aspiration catheter or a capture device (stent retriever, stentriever) or both techniques combined.[5-8] The current indications for MT are LVO in patients with cerebral tissue viability, regardless of administration of intravenous thrombolysis (IVT). IVT administration should not delay treatment with MT as significantly better clinical outcomes occur with shorter times from onset of symptoms to MT.[9] This is extremely important for clinicians, as AF patients on therapeutic anticoagulation are excluded from IVT, and they should be promptly evaluated for MT.

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**Received:** January 31, 2022.
**Accepted:** February 1, 2022.
**Published online:** February 28, 2022.
Pol Arch Intern Med. 2022; 132 (2): 16213
doi:10.20452/pamw.16213

The study by Lasek-Bal et al[5] evaluated 417 LVO patients treated with MT, and compared the characteristics and outcomes of AF (n = 108) and AF-free patients. Two-thirds of the AF cohort patients were previously diagnosed with AF. This real-life group was naturally heterogeneous with regards to anticoagulation: over 75% were anticoagulated, with a roughly 50/50 spread between VKA and DOACs. The rate of poor outcomes at 10, 30, and 90 days was higher in the AF group but the AF patients were significantly older and had more comorbidities.[5] On multivariate analysis, age, stroke severity, and cerebral recanalization grade were the strongest predictors of functional outcomes.[5] The conclusion that AF has a neutral effect on the outcomes of MT[5] is a rather simplistic interpretation given the limitations, such as moderate sample size, non-assessment of pre-stroke functional status of the patients and lack of comparison between "drip-and-ship" (admission to primary hospital and then transfer to MT center) and "mothership" (direct admission to MT center), which significantly affects timely access to MT and thus MT clinical efficacy.[9] Nevertheless, the authors should be commended on their endeavor, as their study is a large one for a single-center, particularly in a country where MT needs remain largely unmet. Furthermore, the findings[5] reinforce attention to several fundamental issues that remain unresolved with regard to AF and stroke.

Several other studies reported the opposite, with AF patients undergoing MT having worse outcomes than non-AF patients, of which some were attributed to a higher risk of hemorrhagic transformation in anticoagulated AF patients treated with MT.[10] However, this increased risk was refuted in a recent meta-analysis of major randomized trials from the HERMES collaboration.[6] Contrary to AF-free population, in patients with AF the rate of symptomatic intracranial hemorrhage after MT may be reduced due to higher presence of anticoagulation and consequently reduced rates of IVT administration.[6] Interestingly, AF patients were associated with shorter times to puncture and better recanalization times and rates than AF-free patients due to a skipping of IVT and a potentially greater ease of the thrombus removal.[6] The latter may be explained by differences in clot composition, with cardiogenic source associated with a softer consistency than other sources (eg, atherosclerosis) due to differences in red blood cell and fibrin content. We must emphasize that, despite MT being the best acute treatment option for AF patients with AIS due to LVO, the residual recurrent stroke risk remains high in properly anticoagulated patients[2,3] and this population can have a high recurrence rate.[11] Therefore, optimization of AIS prevention in AF patients, including timely (re-) introduction of anticoagulation after stroke to prevent the stroke recurrence (again, in a juggle between the risk of embolism and recent stroke bleeding risk[4]—an area where several currently ongoing studies may offer some further insight) is particularly important with regard to the best time-point of starting anticoagulation in recent ischemic stroke.

Though the scenario for acute treatment of AF patients with LVOs seems reasonably well-defined, the same may not be true for the other pattern of AIS. Shower emboli may lead to multiple distal occlusions not amenable to routine MT armamentarium. The presence of anticoagulation in these patients would preclude administration of IVT, leaving them with seemingly limited options. While in advanced MT centers new catheters for access to more distal occlusions are being developed and evaluated along with progress in other stroke prevention and intervention devices,[8,12] an older tool of the neurointervention armamentarium, the intra-arterial infusion of thrombolytic drugs (intra-arterial thrombolysis, IAT) through a microcatheter, may be an interesting alternative for such cases. This modality was abandoned as a first-line one for large occlusions due to better efficacy of modern MT devices, and is currently used predominantly as a "rescue" therapy where MT fails. According to recent surveys, 40% (Germany) to 60% (USA) interventionalists administer IA fibrinolytics during or after MT on a case-by-case basis, with post-IVT patients constituting approximately 50% of the group allocated the additional IAT treatment.[13] Data suggest that IAT may constitute a reasonable supplement to achieve thrombolysis in cerebral infarction grade 2b/3 in the absence of an increase in symptomatic intracranial hemorrhage, but more evidence is needed.[13] Apart from its role in distal occlusions that cannot be reached with thrombectomy devices[13] and the role in AF patients with a "shower" of (micro)emboli, IAT reperfusion may play a role as a rescue therapy in IVT nonresponders. Unfortunately, we do not learn from the current report[5] the proportion of these patients in their series. Evidence from the PROACT (Prolyse in Acute Cerebral Thromboembolism) showed approximately a 3-fold increase in recanalization and also better rates of functional independence, while a meta-analysis of IAT studies demonstrated favorable clinical outcomes of IAT, but with a borderline increase in a symptomatic intracranial hemorrhage.[14]

The risk of intracranial hemorrhage with IAT needs a systematic assessment in anticoagulated patients and in non-anticoagulated patients. In the meanwhile, the need for optimization of AIS prevention algorithms in AF patients is once again emphasized. Novel risk stratification tools may help to calculate residual 1-year absolute stroke risk in anticoagulated AF patients, triggering a more thorough patient work-up and personalized adjustments in anticoagulant dosage,[3] along with other approaches, such as a left atrial appendage exclusion or a patent foramen ovale closure.[7] To optimize clinical outcomes, a multispecialty approach (increasingly highlighted)[5,7] is warranted.

All in all, the story of AF and AIS is more complex than that of a villain and a victim. This is an exciting area of a major clinical progress and a very active, high-level basic research.[15] It is also one of the leading fields of personalized patient-centered pharmacological approaches (with likely new breakthroughs, similar to the DOAC arrival, expected to follow the recent progress in knowledge)[16] and new, better targeted therapies to reduce the stroke risk. Better understanding of the key physiological players, and their interactions, will enable improved tailoring of stroke prevention strategies. What will remain is the need for the educated clinical judgment, as clinical trial patients will never fully reflect those in routine practice.[3,16]

With the emerging new knowledge[15] and personalized risk stratification,[3,16] the clinical juggle between the evils of thromboembolism and bleeding may get somewhat alleviated. However, clinical judgment and expertise will continue to play a fundamental role in applying the old and new evidence-based cohorts data in stroke prevention and treatment in individual patients.[16]

## ARTICLE INFORMATION

**DISCLAIMER** The opinions expressed by the author(s) are not necessarily those of the journal editors, Polish Society of Internal Medicine, or publisher.

**CONFLICT OF INTEREST** PM is the Representative of the Polish Cardiac Society Board for Stroke and Vascular Interventions; served as a Proctor or Advisory Board Member for Abbott Vascular, InspireMD, and Medtronic; and is a global Co-Principal Investigator in the CGUARDIANS FDA IDE Trial. AM has no conflicts to declare. AHS is Past Secretary of the Board of the Society of NeuroInterventional Surgery (2020-2021) and Chair of the Cerebrovascular Section of the AANS/CNS. He has received consulting fees from Amnis Therapeutics, Apellis Pharmaceuticals, Inc., Boston Scientific, Canon Medical Systems USA, Inc., Cardinal Health 200, LLC, CerebrotechMedical Systems, Inc., Cerenovus, Cerevatech Medical, Inc., Cordis, Corindus, Inc., Endostream Medical, Ltd, Imperative Care, Integra, IRRAS AB, Medtronic, MicroVention, Minnetronix Neuro, Inc., Penumbra, Q'Apel Medical, Inc., Rapid Medical, Serenity Medical, Inc., Silk Road Medical, StimMed, LLC, Stryker Neurovascular, Three Rivers Medical, Inc., VasSol, Viz.ai, Inc., W.L. Gore & Associates. Stock or stock options: Adona Medical, Inc., Amnis Therapeutics, Bend IT Technologies, Ltd., BlinkTBI, Inc, Buffalo Technology Partners, Inc., Cardinal Consultants, LLC, CerebrotechMedical Systems, Inc, Cerevatech Medical, Inc., Cognition Medical, CVAID Ltd., E8, Inc., Endostream Medical, Ltd, Imperative Care, Inc., Instylla, Inc., International Medical Distribution Partners, Launch NY, Inc., NeuroRadialTechnologies, Inc., Neurotechnology Investors, Neurovascular Diagnostics, Inc., PerFlow Medical, Ltd., Q'Apel Medical, Inc., QAS.ai, Inc., Radical Catheter Technologies, Inc., Rebound Therapeutics Corp. (Purchased 2019 by Integra Lifesciences, Corp), Rist Neurovascular, Inc. (Purchased 2020 by Medtronic), Sense Diagnostics, Inc., Serenity Medical, Inc., Silk Road Medical, Adona Medical, Inc., Amnis Therapeutics, Bend IT Technologies, Ltd., BlinkTBI, Inc, Buffalo Technology Partners, Inc., Cardinal Consultants, LLC, Cerebrotech Medical Systems, Inc, Cerevatech Medical, Inc., Cognition Medical, CVAID Ltd., E8, Inc., EndostreamMedical, Ltd, Imperative Care, Inc., Instylla, Inc., International Medical Distribution Partners, Launch NY, Inc., NeuroRadialTechnologies, Inc., Neurotechnology Investors, Neurovascular Diagnostics, Inc., PerFlow Medical, Ltd., Q'Apel Medical, Inc., QAS.ai, Inc., Radical Catheter Technologies, Inc., Rebound Therapeutics Corp. (Purchased 2019 by Integra Lifesciences, Corp), Rist Neurovascular, Inc. (Purchased 2020 by Medtronic), Sense Diagnostics, Inc., Serenity Medical, Inc., Silk Road Medical, SongBird Therapy, Spinnaker Medical, Inc., StimMed, LLC, Synchron, Inc., Three Rivers Medical, Inc., Truvic Medical, Inc., Tulavi Therapeutics, Inc., Vastrax, LLC, VICIS, Inc., Viseon, Inc. AHS has served as National PI or on Steering Committees in a number of trials including Cerenovus EXCELLENT and ARISE II Trial; Medtronic SWIFT PRIME, VANTAGE, EMBOLISE and SWIFT DIRECT Trials; MicroVention FRED Trial & CONFIDENCE Study; MUSC POSITIVE Trial; Penumbra 3D Separator Trial, COMPASS Trial, INVEST Trial, MIVI neuroscience EVAQ Trial; Rapid Medical SUCCESS Trial; InspireMD C-GUARDIANS IDE Pivotal Trial.



**HOW TO CITE** Musiałek P, Monteiro A, Siddiqui AH. Atrial fibrillation and stroke: more than a story of a villain and a victim. Pol Arch Intern Med. 2022; 132: 16213. doi:10.20452/pamw.16213

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