AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke (ARCADIA)

Hooman Kamel, MD on behalf of the ARCADIA Investigators

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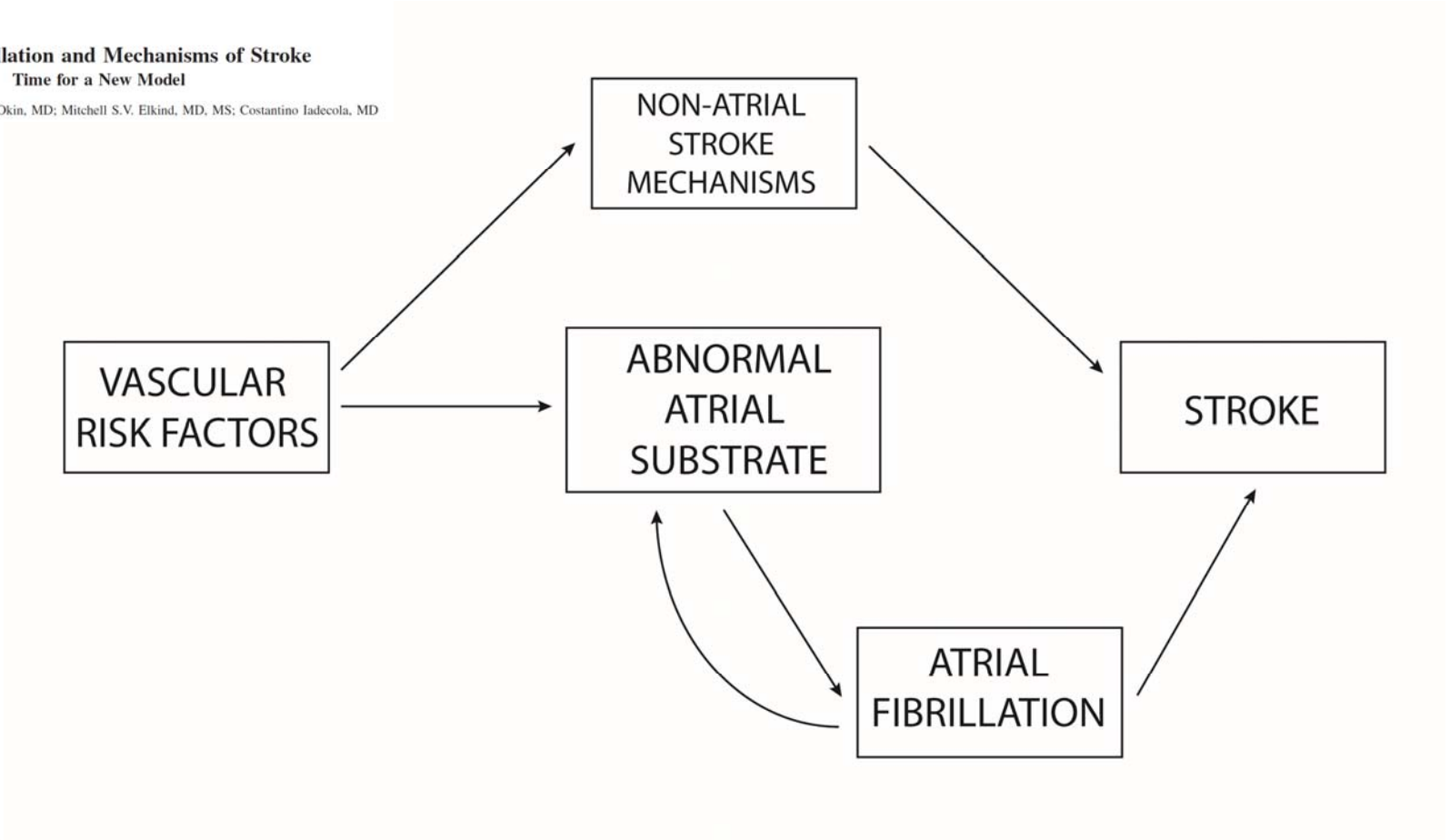
Comments and Opinions

Atrial Fibrillation and Mechanisms of Stroke
Time for a New Model

Hooman Kamel, MD; Peter M. Okin, MD; Mitchell S.V. Elkind, MD, MS; Costantino Iadecola, MD



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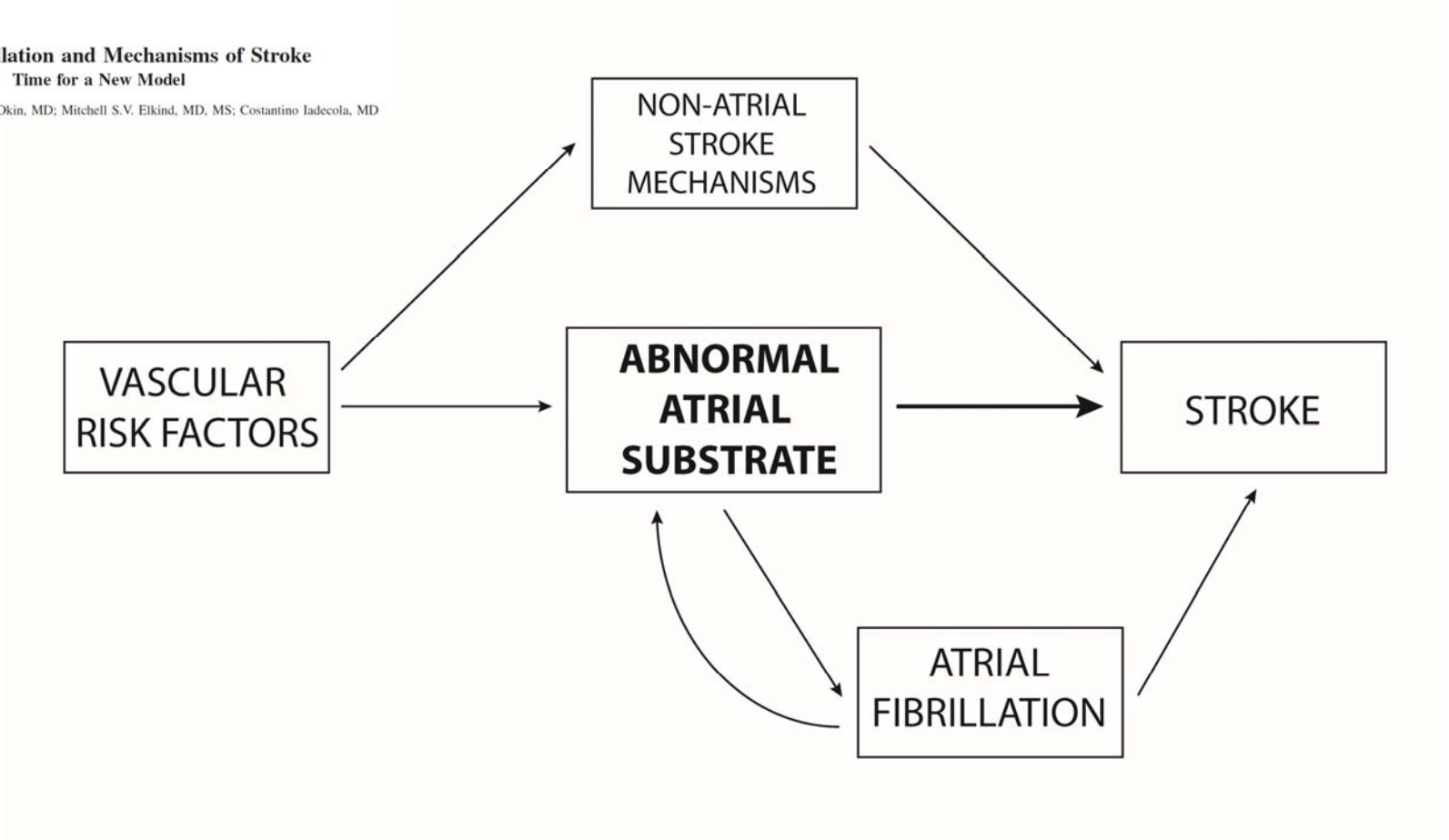

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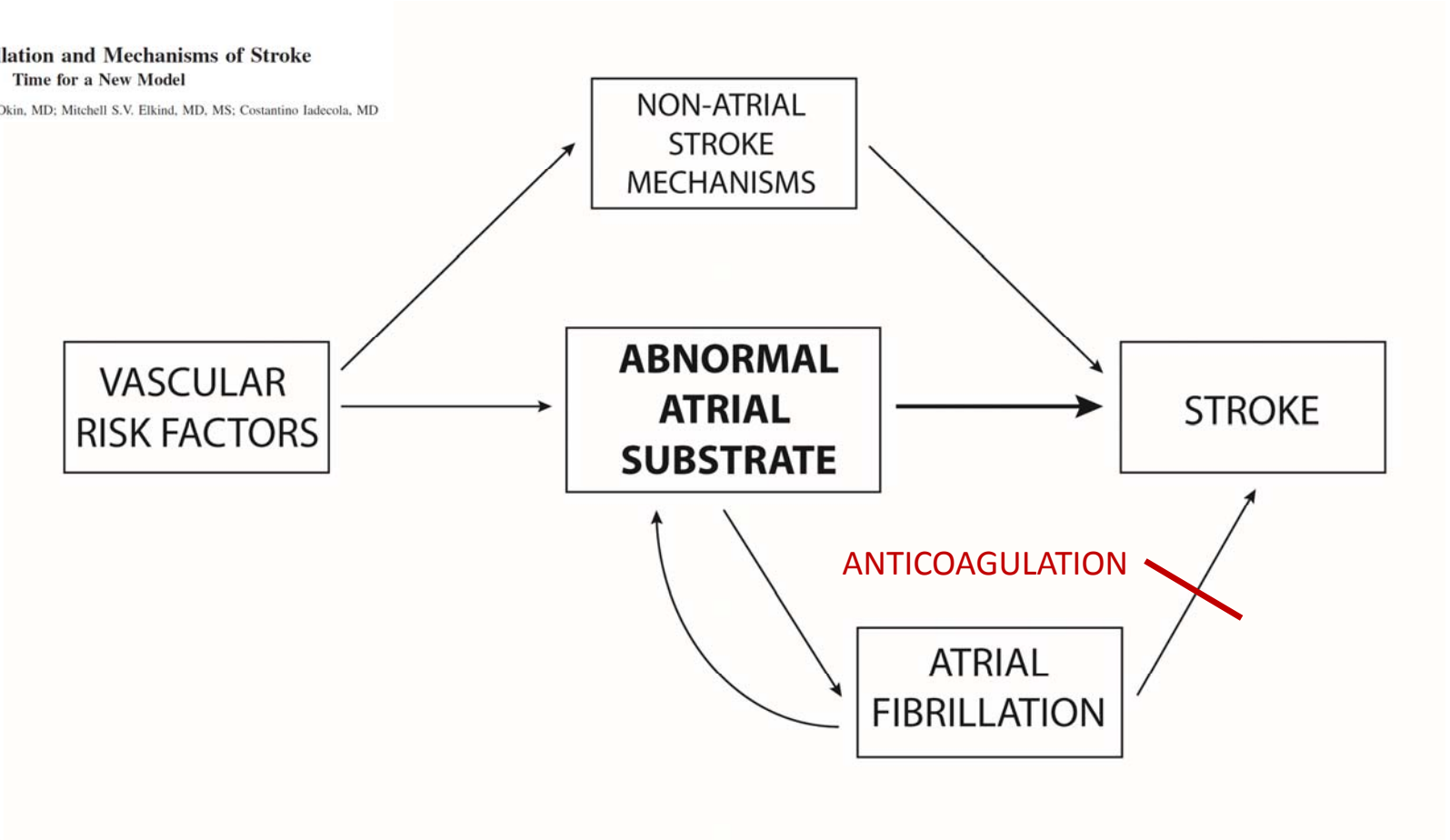

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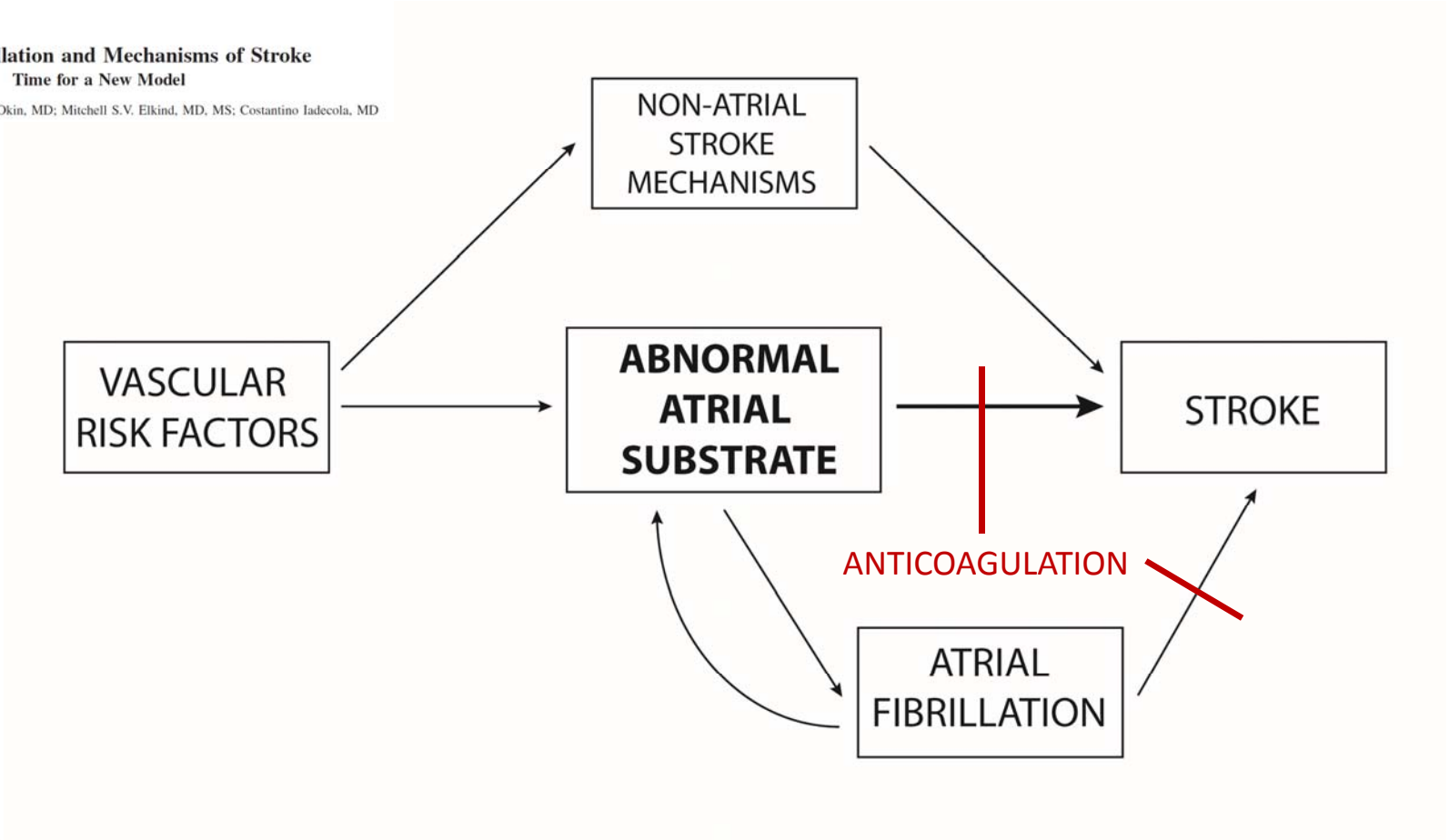

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ARCADIA: Only [ESUS + atrial cardiopathy]

AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke

- Hypothesis: apixaban is superior to aspirin for prevention of recurrent stroke in patients with ESUS and atrial cardiopathy

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Multiple biomarkers of atrial cardiopathy

Atrial cardiopathy defined as ≥1 marker:

- $PTFV_1$ >5000 μV*ms on 12-lead ECG
- Left atrial size index ≥3 cm/m^2 on echocardiogram (mod-to-severe LAE)
- Serum NT-proBNP >250 pg/mL

Site startup

- 115 CIRB submissions
- 106 CIRB approvals
- 98 readiness calls
- 98 sites released to enroll
- 41 sites with at least one randomization
- 76 sites with at least one consented patient

Top enrolling sites

	Randomized	Consented
Iowa	9	19
United	8	23
OHSU	7	20
Cincinnati	7	16
Penn	4	10
Intercoastal	3	13
OSU	3	10
UF Shands	3	9
Memorial Hermann	3	8
Univ. Illinois	3	6

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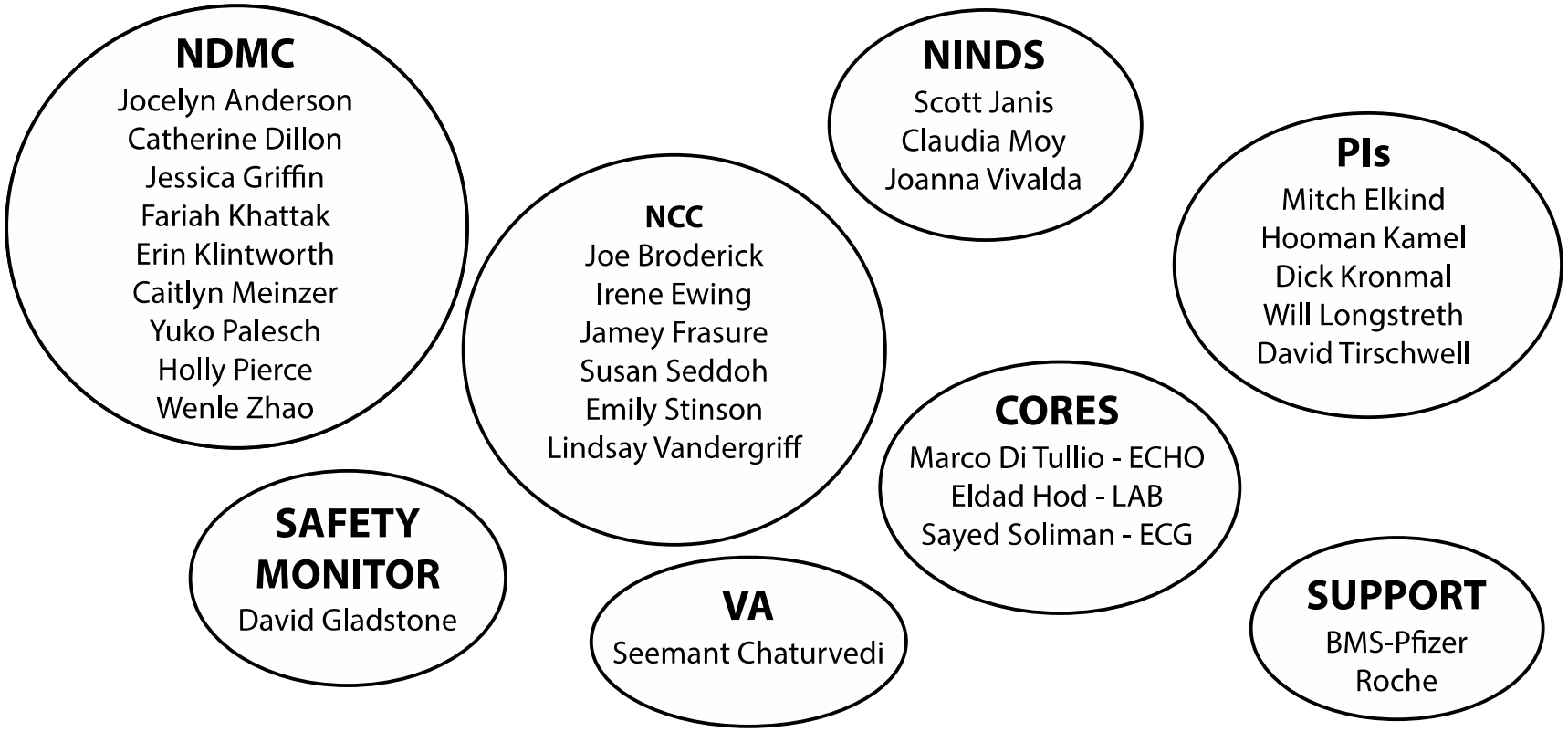
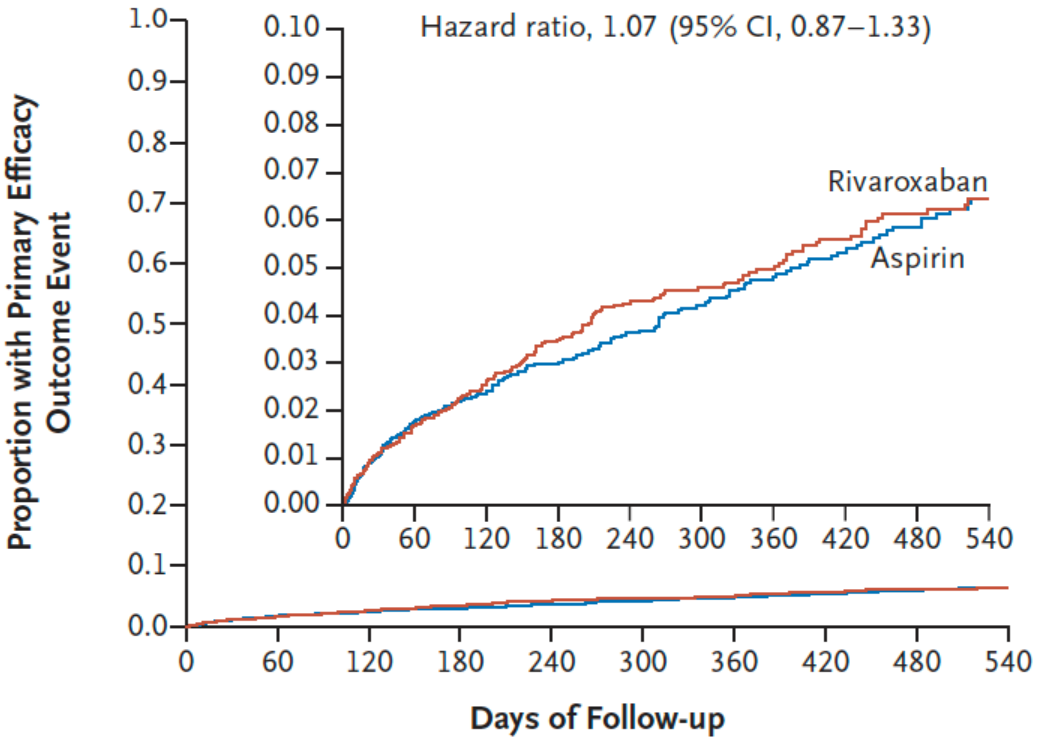
Recruitment initiatives

- Monthly webinars
- Newsletters
- Email updates
- Recruitment Innovation Center
- Brochure
- Video
- Website


NDMC
Jocelyn Anderson
Catherine Dillon
Jessica Griffin
Fariah Khattak
Erin Klintworth
Caitlyn Meinzer
Yuko Palesch
Holly Pierce
Wenle Zhao
NINDS
Scott Janis
Claudia Moy
Joanna Vivalda
PIs
Mitch Elkind
Hooman Kamel
Dick Kronmal
Will Longstreth
David Tirschwell
NCC
Joe Broderick
Irene Ewing
Jamey Frasure
Susan Seddoh
Emily Stinson
Lindsay Vandergriff
CORES
Marco Di Tullio - ECHO
Eldad Hod - LAB
Sayed Soliman - ECG
SAFETY MONITOR
David Gladstone
VA
Seemant Chaturvedi
SUPPORT
BMS-Pfizer
Roche

A Kaplan–Meier Curves for Time to Event in the Primary Efficacy Outcome



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source

R.G. Hart, M. Sharma, H. Mundl, S.E. Kasner, S.I. Bangdiwala, S.D. Berkowitz, B. Swaminathan, P. Lavados, Y. Wang, Y. Wang, A. Davalos, N. Shamalov, R. Mikulik, L. Cunha, A. Lindgren, A. Arauz, W. Lang, A. Czlonkowska, J. Eckstein, R.J. Gagliardi, P. Amarenco, S.F. Ameriso, T. Tatlisumak, R. Veltkamp, G.J. Hankey, D. Toni, D. Bereczki, S. Uchiyama, G. Ntaios, B.-W. Yoon, R. Brouns, M. Endres, K.W. Muir, N. Bornstein, S. Ozturk, M.J. O'Donnell, M.M. De Vries Basson, G. Pare, C. Pater, B. Kirsch, P. Sheridan, G. Peters, J.I. Weitz, W.F. Peacock, A. Shoamanesh, O.R. Benavente, C. Joyner, E. Themeles, and S.J. Connolly, for the NAVIGATE ESUS Investigators*

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B Kaplan–Meier Curves for Time to Major Bleeding Event

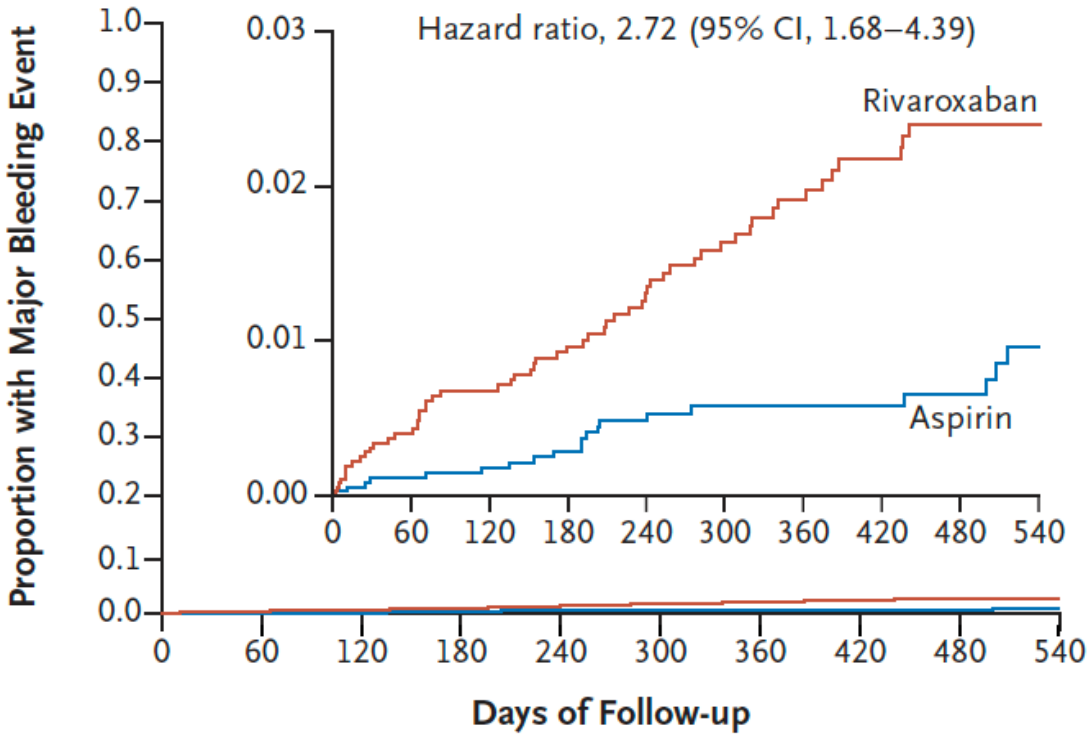

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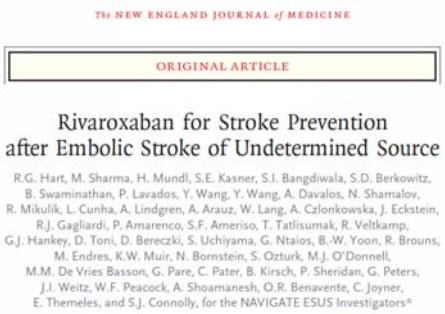
Table 2. Efficacy Outcomes.*

Outcome	Rivaroxaban Group (N=3609)	Aspirin Group (N=3604)	Hazard Ratio (95% CI)†
	no. of patients (annualized rate)		
Primary efficacy outcome: any recurrent stroke or systemic embolism	172 (5.1)	160 (4.8)	1.07 (0.87–1.33)
Secondary efficacy outcomes			
Any recurrent stroke‡	171 (5.1)	158 (4.7)	1.08 (0.87–1.34)
Ischemic stroke‡	158 (4.7)	156 (4.7)	1.01 (0.81–1.26)
Hemorrhagic stroke§	13 (0.4)	2 (0.1)	6.50 (1.47–28.8)
Systemic embolism	1 (<0.1)	2 (0.1)	0.50 (0.05–5.51)
Any recurrent stroke, myocardial infarction, death from cardiovascular causes, or systemic embolism¶	207 (6.2)	195 (5.8)	1.06 (0.87–1.29)
Any disabling stroke	41 (1.2)	29 (0.8)	1.42 (0.88–2.28)
Myocardial infarction	17 (0.5)	23 (0.7)	0.74 (0.39–1.38)
Death from any cause	65 (1.9)	52 (1.5)	1.26 (0.87–1.81)
Death from cardiovascular causes¶	34 (1.0)	23 (0.7)	1.48 (0.87–2.52)



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Justification for ARCADIA – Part 1

- *1.20.2 Overlapping trials may announce negative results before our trial finishes.* If the ongoing industry trials (NAVIGATE-ESUS and RESPECT-ESUS) announce negative results, equipoise would remain to continue randomization in our trial because of the compelling data above that atrial cardiopathy represents a distinct stroke mechanism that will preferentially respond to anticoagulation.

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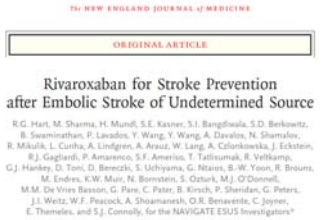
the heterogeneous underlying sources of the embolic strokes (arterial, cardiogenic, or paradoxical) with variation in the composition of emboli may have resulted in the trial enrolling a population that would not have a response to rivaroxaban.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What about RESPECT ESUS?

Protocol

Design of Randomized, double-blind, Evaluation in secondary Stroke Prevention comparing the EfficaCy and safety of the oral Thrombin inhibitor dabigatran etexilate vs. acetylsalicylic acid in patients with Embolic Stroke of Undetermined Source (RE-SPECT ESUS)

Hans-Christoph Diener[1]*, J. Donald Easton[2], Christopher B. Granger[3], Lisa Cronin[4], Christine Duffy[5], Daniel Cotton[5], Martina Brueckmann[6,7], Ralph L. Sacco[8] on behalf of the RE-SPECT ESUS Investigators

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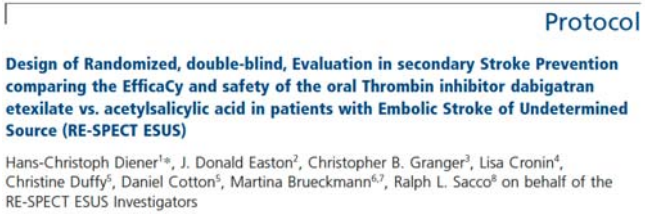
What about RESPECT ESUS?

Patient population

- absence of AF of >six-minutes in duration (11), as evidenced by cardiac monitoring for ≥20 h with automated rhythm detection



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Justification for ARCADIA – Part 2

1.20 Potential Problems and Alternative Strategies. We anticipate the possibility of several potential problems and have designed alternative strategies to manage them if they arise.

- *1.20.1 Overlapping trials may announce positive results before our trial finishes.* A positive result from one or both of the industry trials would make the execution of our trial more challenging, but would not preclude its completion. The results of the industry trials are unlikely to apply to our population. Most crucially, ***both industry trials will include many patients with AF***.

In the EMBRACE and CRYSTAL-AF randomized trials of post-stroke heart-rhythm monitoring (Gladstone 2014; Sanna 2014), 90% of neurologists in North America and Europe anticoagulated patients with even 30 seconds of AF found on monitoring. Therefore, patients with any known AF are unlikely to be enrolled in NAVIGATE-ESUS and RESPECT-ESUS sites in North America and Europe. However, practices are likely to differ in the low- and middle-income countries that will enroll many of the patients in these trials. The use of such a carefully tailored inclusion criterion suggests that the trials fully expect to enroll these patients with brief runs of AF at many sites. Given the prevalence of brief episodes of AF in patients with stroke (Sposato 2015), we can therefore expect another 10% of patients in NAVIGATE-ESUS and RESPECT-ESUS to have known AF rather than truly cryptogenic stroke. There are no publicly announced prespecified plans to perform subgroup analyses stratified by the presence or absence of baseline AF in these trials. However, if the trials are positive, most or all of the benefit may well stem from those with either known or easily diagnosable AF, who many neurologists believe have a condition for which anticoagulation has already been proven effective (Saxena 2004; Gladstone 2014; Sanna 2014).

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ARCADIA -> different question than ESUS trials

ARCADIA = No AF

- Patients with any known AF excluded
- Heart-rhythm monitoring encouraged before/after randomization

Contemporary Reviews in Cardiovascular Medicine

Evaluating the Atrial Myopathy Underlying Atrial Fibrillation

Identifying the Arrhythmogenic and Thrombogenic Substrate

Jeffrey J. Goldberger, MD, MBA; Rishi Arora, MD; David Green, MD, PhD; Philip Greenland, MD; Daniel C. Lee, MD, MSc; Donald M. Lloyd-Jones, MD, ScM; Michael Markl, PhD; Jason Ng, PhD; Sanjiv J. Shah, MD

REVIEW TOPIC OF THE WEEK

Fibrotic Atrial Cardiomyopathy, Atrial Fibrillation, and Thromboembolism

Mechanistic Links and Clinical Inferences

Benjamin J. Hirsh, MD, Robert S. Copeland-Halperin, MD, Jonathan L. Halperin, MD

EDITORIAL COMMENT

Is Atrial Fibrillation a Necessary Component of the Thrombogenic Atrium?*

Saman Nazarian, MD, PhD,[a] Tarek Zghaib, MD[b]

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VOL. 70, NO. 6, 2017

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THE PRESENT AND FUTURE

REVIEW TOPIC OF THE WEEK

Atrial Cardiomyopathy

A Useful Notion in Cardiac Disease Management or a Passing Fad?

Jean-Baptiste Guichard, MD,[a,b] Stanley Nattel, MD[a,c,d]

The possibility that atrial cardiomyopathic risk factors can be used to identify patients with sinus rhythm who might have strokes that could be prevented by OAC would need to be tested in a prospective randomized trial.

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We agree!

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Promised Benefits of ARCADIA

- Establish biologically plausible, novel subset of ESUS
- Allow personalized treatment for preventing recurrent stroke
- Advance understanding of stroke pathogenesis
- Set stage for primary prevention trial in patients with atrial cardiopathy

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@ARCADIA_trial

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Protocol

International Journal of Stroke WSO

International Journal of Stroke
0(0) 1–8

DOI: 10.1177/1747493018799981
journals.sagepub.com/home/wso
SAGE

The AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke randomized trial: Rationale and methods

Hooman Kamel[1], WT Longstreth Jr[2,3,4], David L Tirschwell[2], Richard A Kronmal[5], Joseph P Broderick[6], Yuko Y Palesch[7], Caitlyn Meinzer[7], Catherine Dillon[7], Irene Ewing[6], Judith A Spilker[6], Marco R Di Tullio[8], Eldad A Hod[9], Elsayed Z Soliman[10], Seemant Chaturvedi[11], Claudia S Moy[12], Scott Janis[12] and Mitchell SV Elkind[13,14]; on behalf of the ARCADIA Investigators

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