Update: Prevention after Stroke

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Disclosures

Speaker fees/Advisory Boards/Research support

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Agenda

Atrial fibrillation
- Aspirin for AF patients?
- NOAC or VKA?
- SAME-TTR to select oral anticoagulant?
- When to restart OAC after ischemic stroke?
- Is there a role for left atrial appendage occlusion?
- Carotid filter for stroke prevention?

Heart failure with sinus rhythm
- Is there a role for OAC?

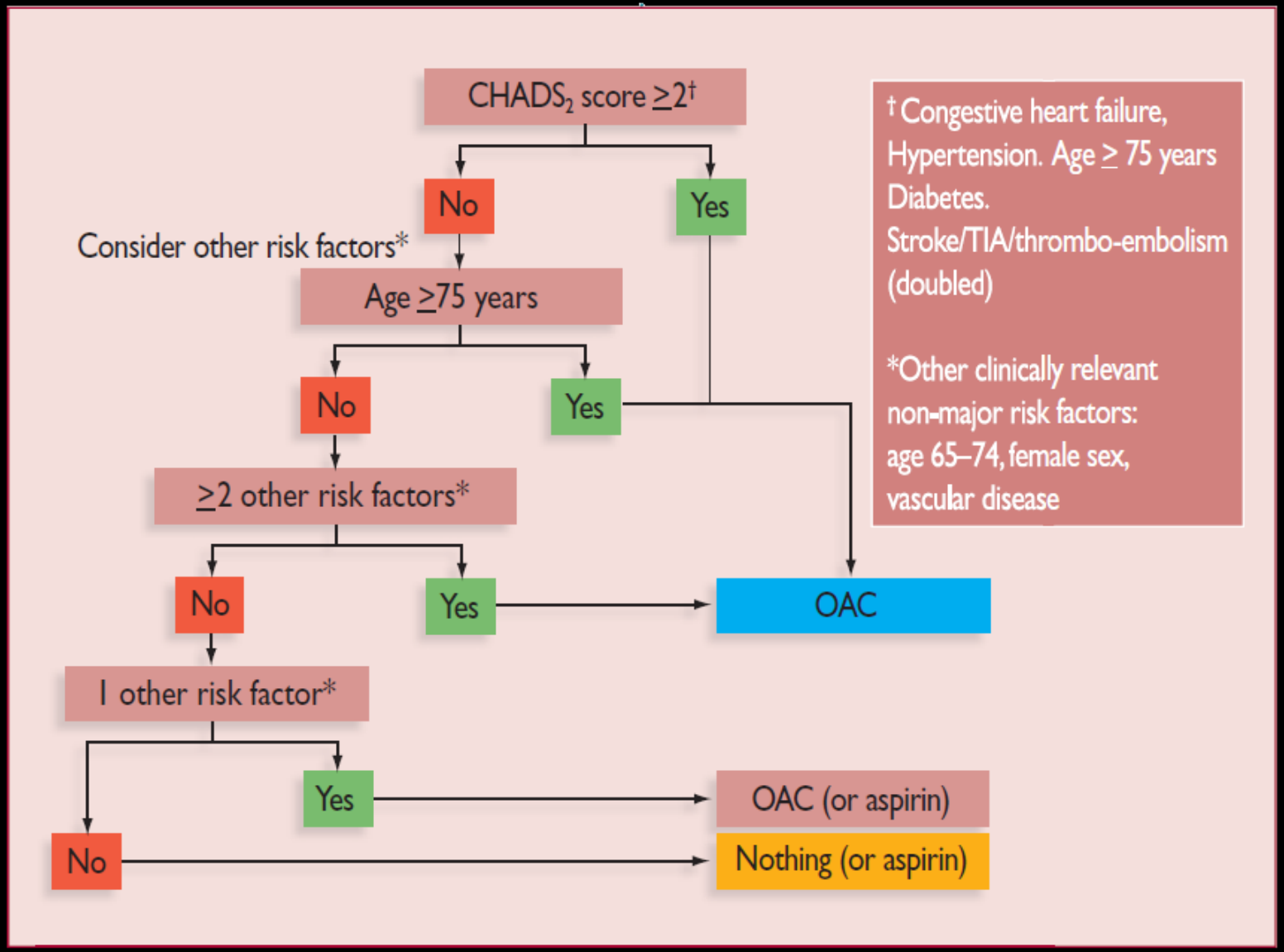
Atherosclerotic stroke
- low-dose rivaroxaban & aspirin
- LDL targets

Minor strokes
- Dual antiplatelet treatment: for how long?

PFO
- Closure or medical treatment?
- OAC or aspirin in non-closed PFOs?

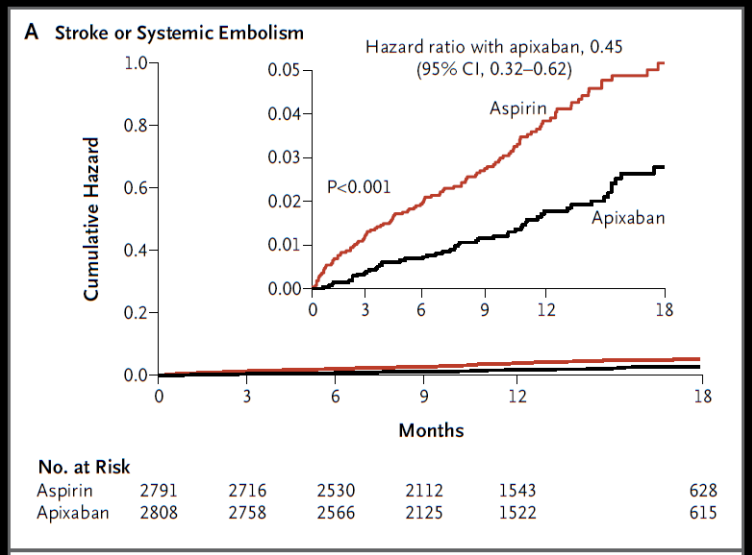
ESUS
- ESUS vs. cryptogenic
- NAVIGATE ESUS and RE-SPECT ESUS results
- Potential explanation and implications for future research

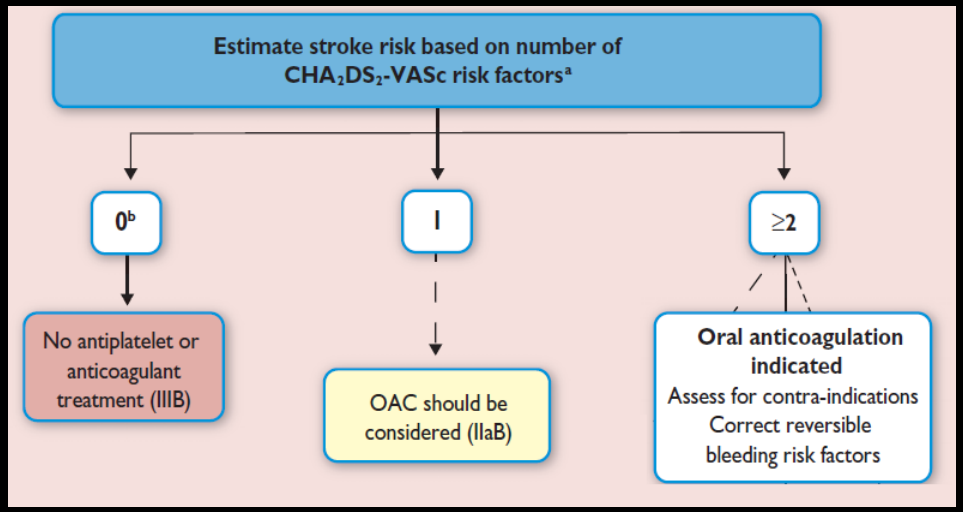
Aspirin for AF patients? -ESC Guidelines 2010

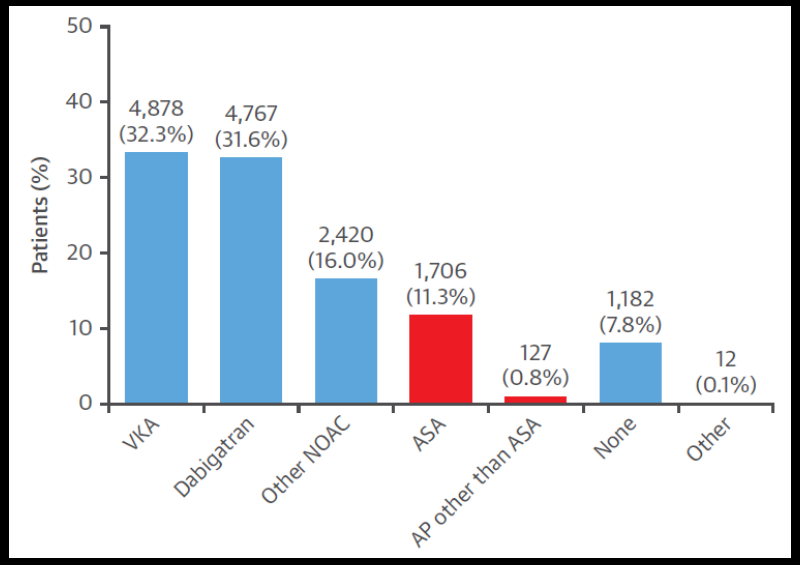


Kirchhoff, et al. Eur Heart Journal 2016

Aspirin for AF patients? –AVERROES & ESC Guidelines 2016





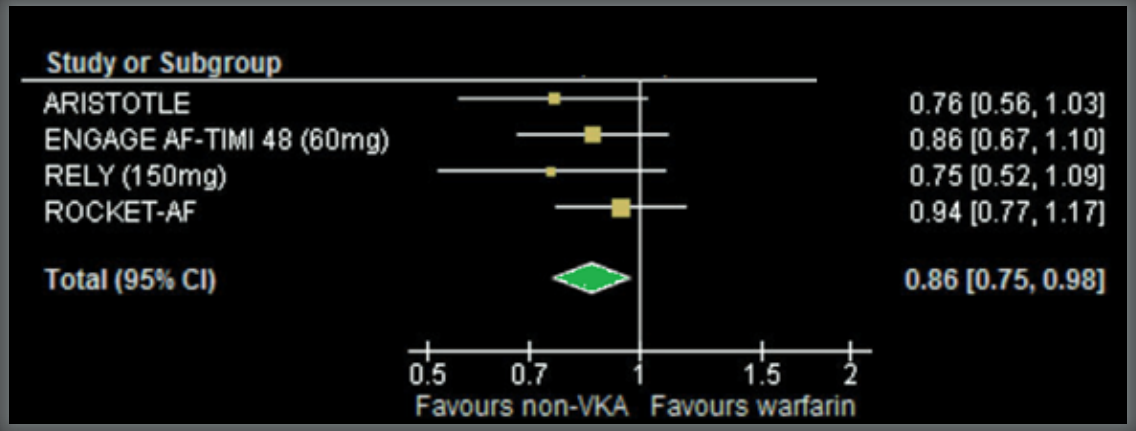


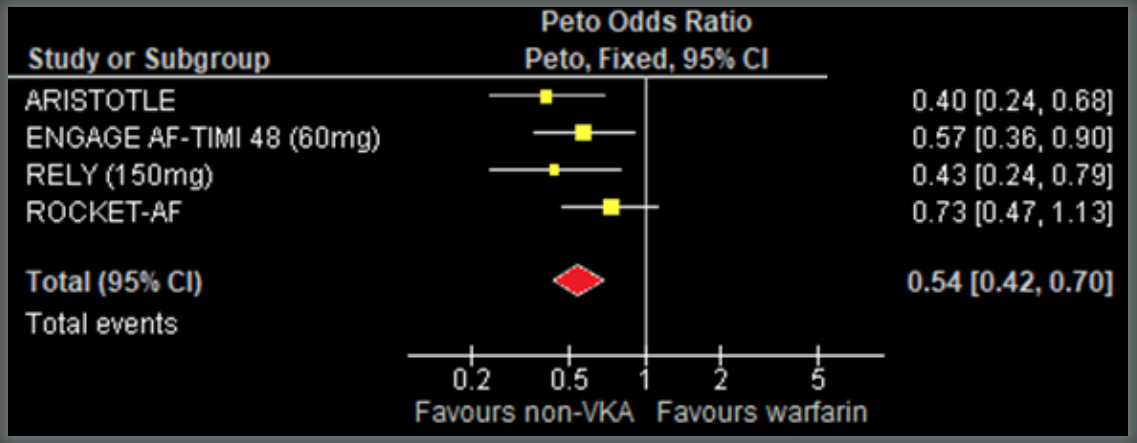
Kirchhoff, et al. Eur Heart Journal 2016

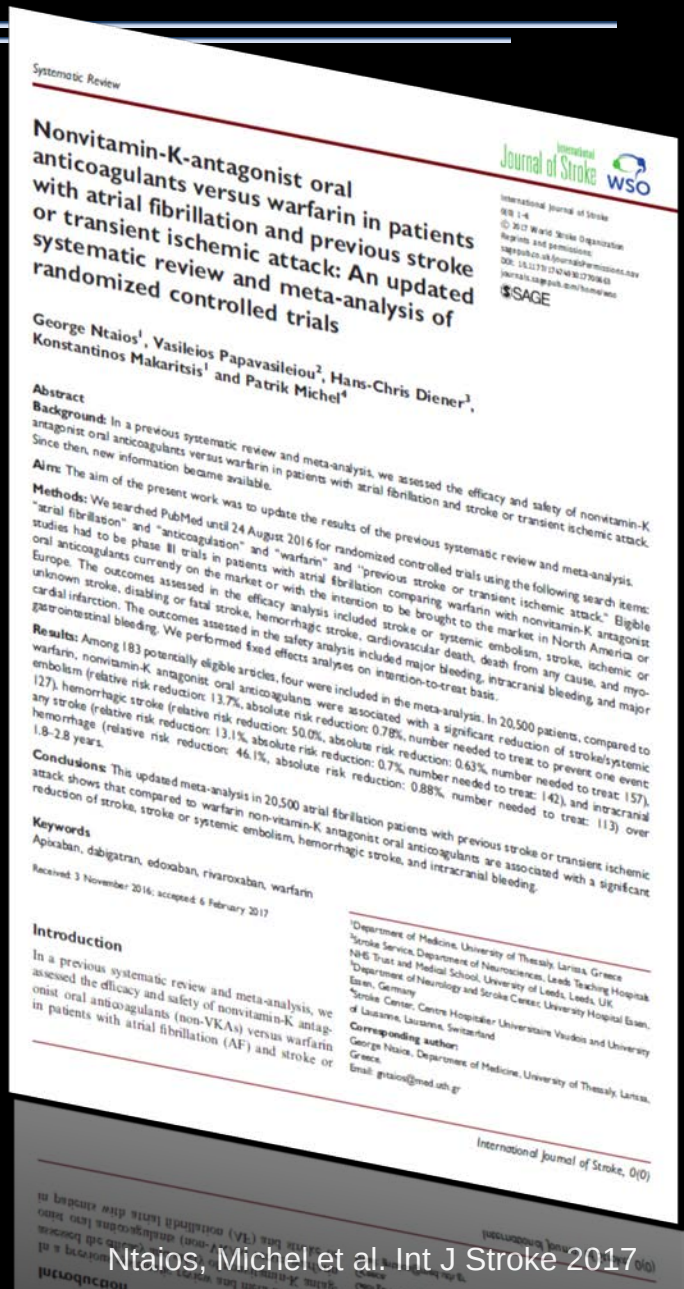
Connolly, et al. NEJM 2011

Huisman, et al. JACC 2017

NOAC vs. VKA?







Systematic Review

Nonvitamin-K-antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and previous stroke or transient ischemic attack: An updated systematic review and meta-analysis of randomized controlled trials

Journal of Stroke WSO

SAGE

George Ntaios[1], Vasileios Papavasileiou[2], Hans-Chris Diener[3], Konstantinos Makaritsis[1] and Patrik Michel[4]

Abstract

Background: In a previous systematic review and meta-analysis, we assessed the efficacy and safety of nonvitamin-K antagonist oral anticoagulants versus warfarin in patients with atrial fibrillation and stroke or transient ischemic attack. Since then, new information became available.

Aim: The aim of the present work was to update the results of the previous systematic review and meta-analysis.

Methods: We searched PubMed until 24 August 2016 for randomized controlled trials using the following search items: "atrial fibrillation" and "anticoagulation" and "warfarin" and "previous stroke or transient ischemic attack." Eligible studies had to be phase III trials in patients with atrial fibrillation comparing warfarin with nonvitamin-K antagonist oral anticoagulants currently on the market or with the intention to be brought to the market in North America or Europe. The outcomes assessed in the efficacy analysis included stroke or systemic embolism, stroke, ischemic or unknown stroke, disabling or fatal stroke, hemorrhagic stroke, cardiovascular death, death from any cause, and myocardial infarction. The outcomes assessed in the safety analysis included major bleeding, intracranial bleeding, and major gastrointestinal bleeding. We performed fixed effects analyses on intention-to-treat basis.

Results: Among 183 potentially eligible articles, four were included in the meta-analysis. In 20,500 patients, compared to warfarin, nonvitamin-K antagonist oral anticoagulants were associated with a significant reduction of stroke/systemic embolism (relative risk reduction: 13.7%, absolute risk reduction: 0.78%, number needed to treat to prevent one event: 127), hemorrhagic stroke (relative risk reduction: 50.0%, absolute risk reduction: 0.63%, number needed to treat: 157), any stroke (relative risk reduction: 13.1%, absolute risk reduction: 0.7%, number needed to treat: 142), and intracranial hemorrhage (relative risk reduction: 46.1%, absolute risk reduction: 0.88%, number needed to treat: 113) over 1.8–2.8 years.

Conclusions: This updated meta-analysis in 20,500 atrial fibrillation patients with previous stroke or transient ischemic attack shows that compared to warfarin non-vitamin-K antagonist oral anticoagulants are associated with a significant reduction of stroke, stroke or systemic embolism, hemorrhagic stroke, and intracranial bleeding.

Keywords
Apixaban, dabigatran, edoxaban, rivaroxaban, warfarin

Received: 3 November 2016; accepted: 6 February 2017

Introduction

In a previous systematic review and meta-analysis, we assessed the efficacy and safety of nonvitamin-K antagonist oral anticoagulants (non-VKAs) versus warfarin in patients with atrial fibrillation (AF) and stroke or

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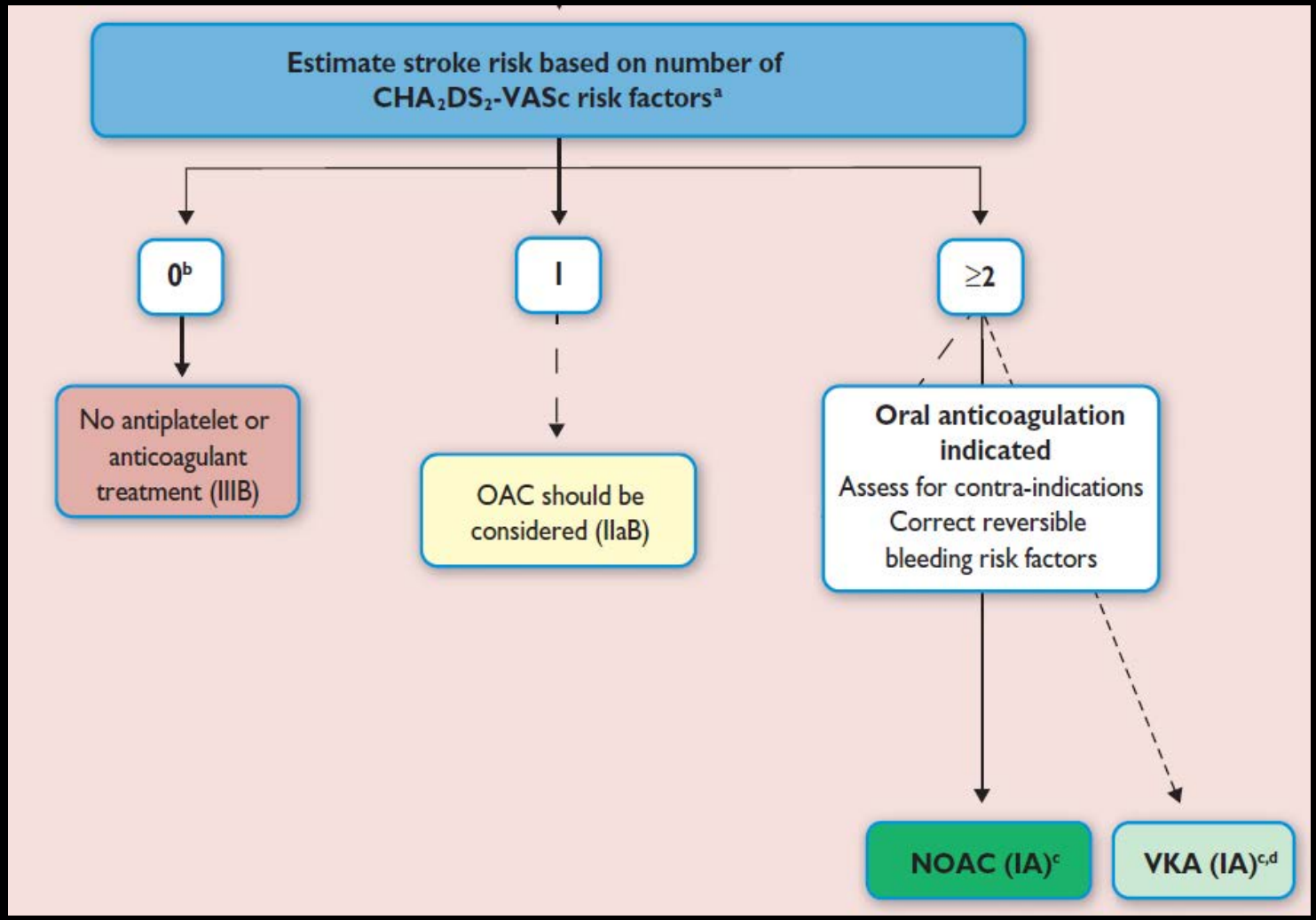
Ntaios, Michel et al. Int J Stroke 2017

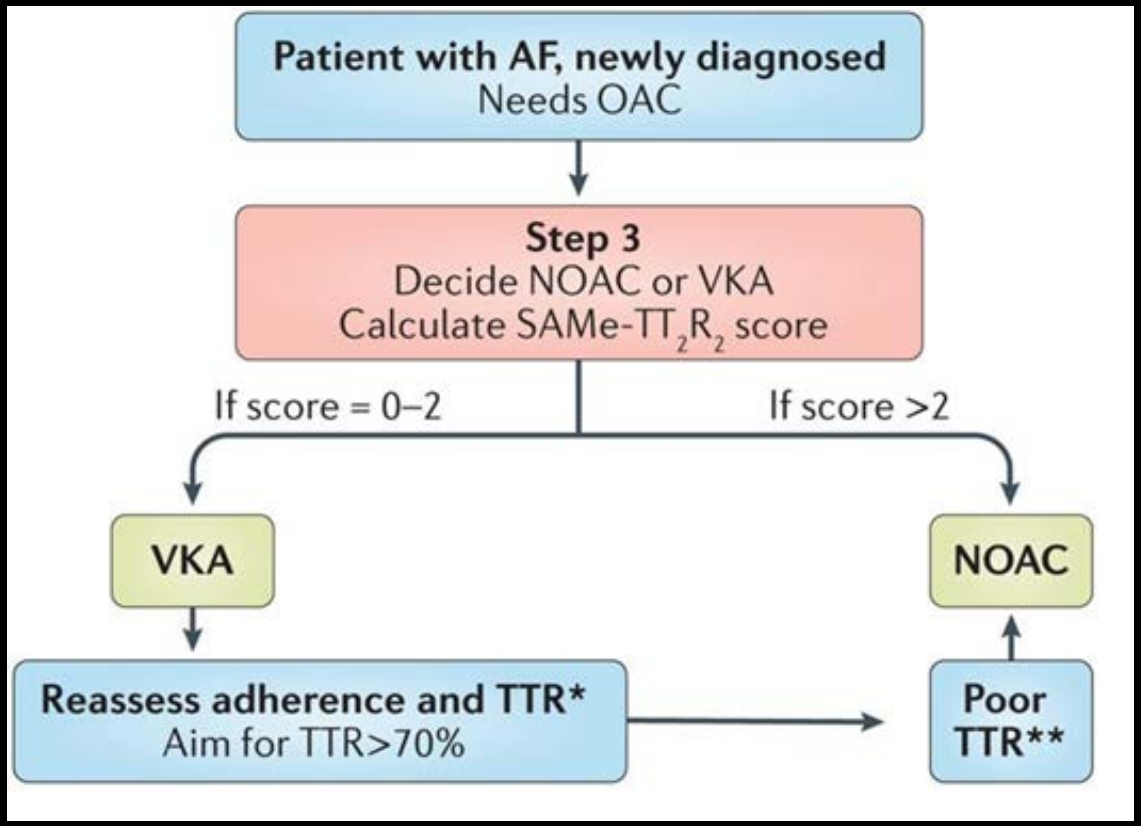
NOAC vs. VKA? – ESC Guidelines 2016



Kirchhoff, et al. Eur Heart Journal 2016

SAME-TT_2R_2 for OAC selection

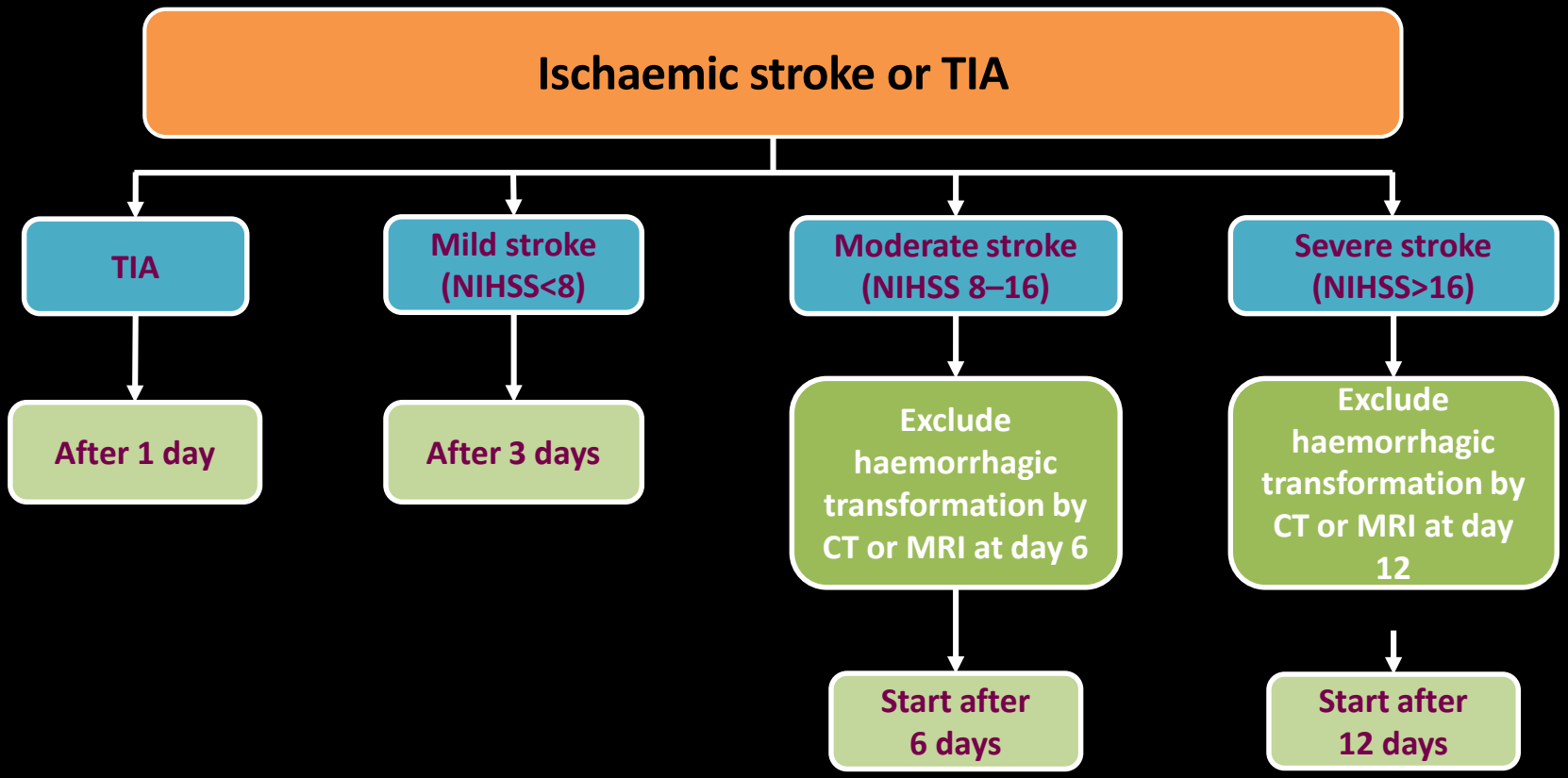
Condition/influencing factor	Points
Sex (female)	1
Age (<60 years)	1
Medical history (history of more than two of the following: hypertension, diabetes, CAD, PAD, heart failure, stroke; pulmonary, hepatic, or renal disease)	1
Treatment (interacting medications e.g. amiodarone)	1
Tobacco use (within 2 years)	2
Race (non-Caucasian)	2



Lip, et al. Nature Reviews 2018

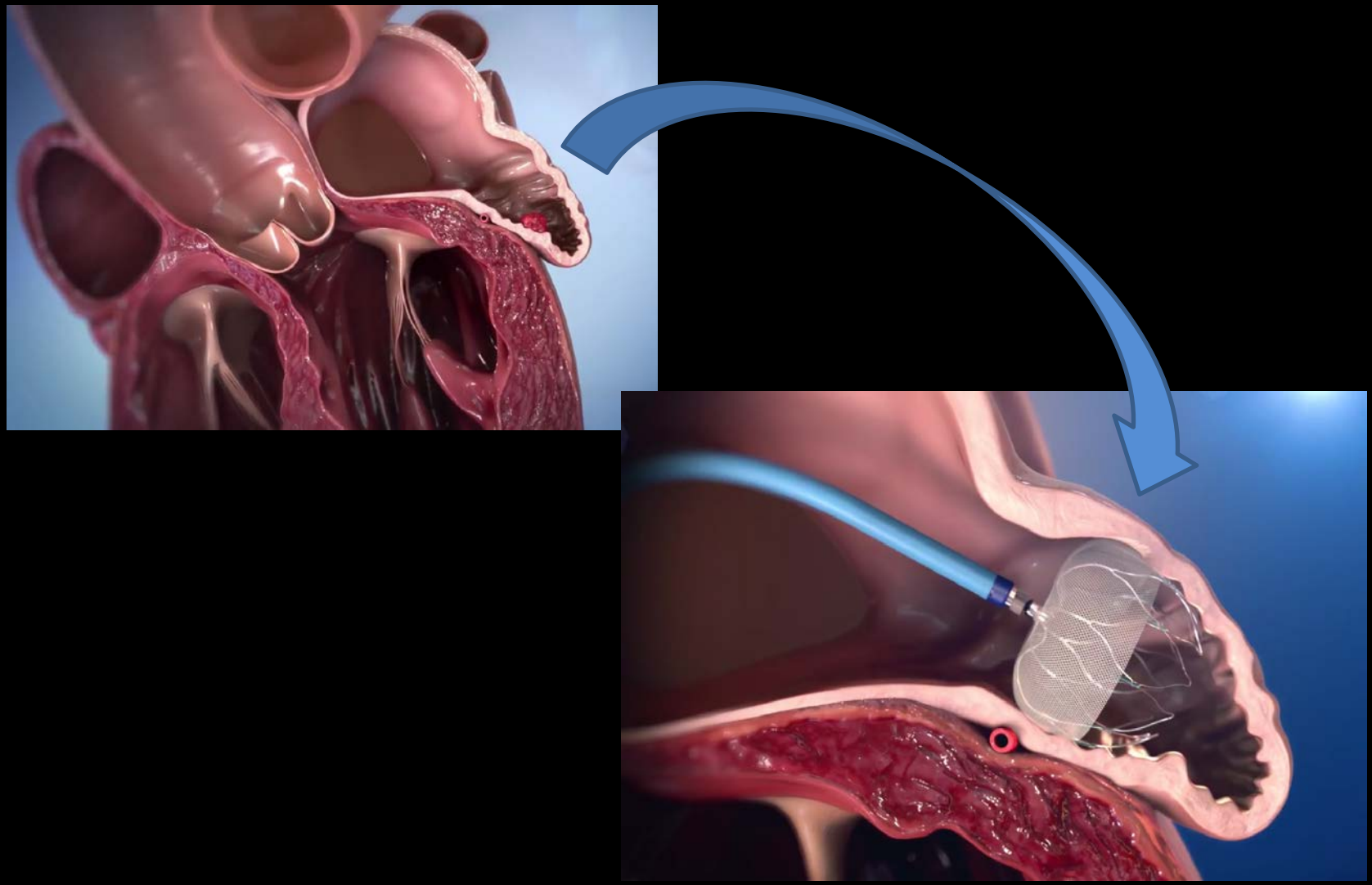
Start anticoagulants - how soon (or late)?

Start anticoagulants - how soon (or late)? / 1-3-6-12

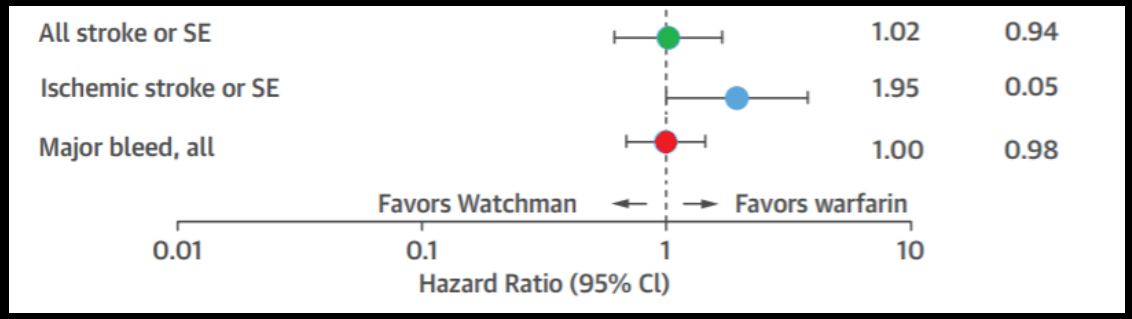


Kirchhoff, et al. Eur Heart Journal 2016

Left atrial appendage occlusion



Left atrial appendage occlusion vs. OAC



Left Atrial Appendage Closure as an Alternative to Warfarin for Stroke Prevention in Atrial Fibrillation

A Patient-Level Meta-Analysis

David R. Holmes, Jr, MD,* Shephal K. Doshi, MD,† Saibal Kar, MD,‡ Matthew J. Price, MD,§ Jose M. Sanchez, MD,‖ Horst Sievert, MD,¶ Miguel Valderrabano, MD,# Vivek Y. Reddy, MD**

ABSTRACT

BACKGROUND The risk-benefit ratio of left atrial appendage closure (LAAC) versus systemic therapy (warfarin) for prevention of stroke, systemic embolism, and cardiovascular death in nonvalvular atrial fibrillation (NVAF) requires continued evaluation.

OBJECTIVES This study sought to assess composite data regarding left atrial appendage closure (LAAC) in 2 randomized trials compared to warfarin for prevention of stroke, systemic embolism, and cardiovascular death in patients with nonvalvular AF.

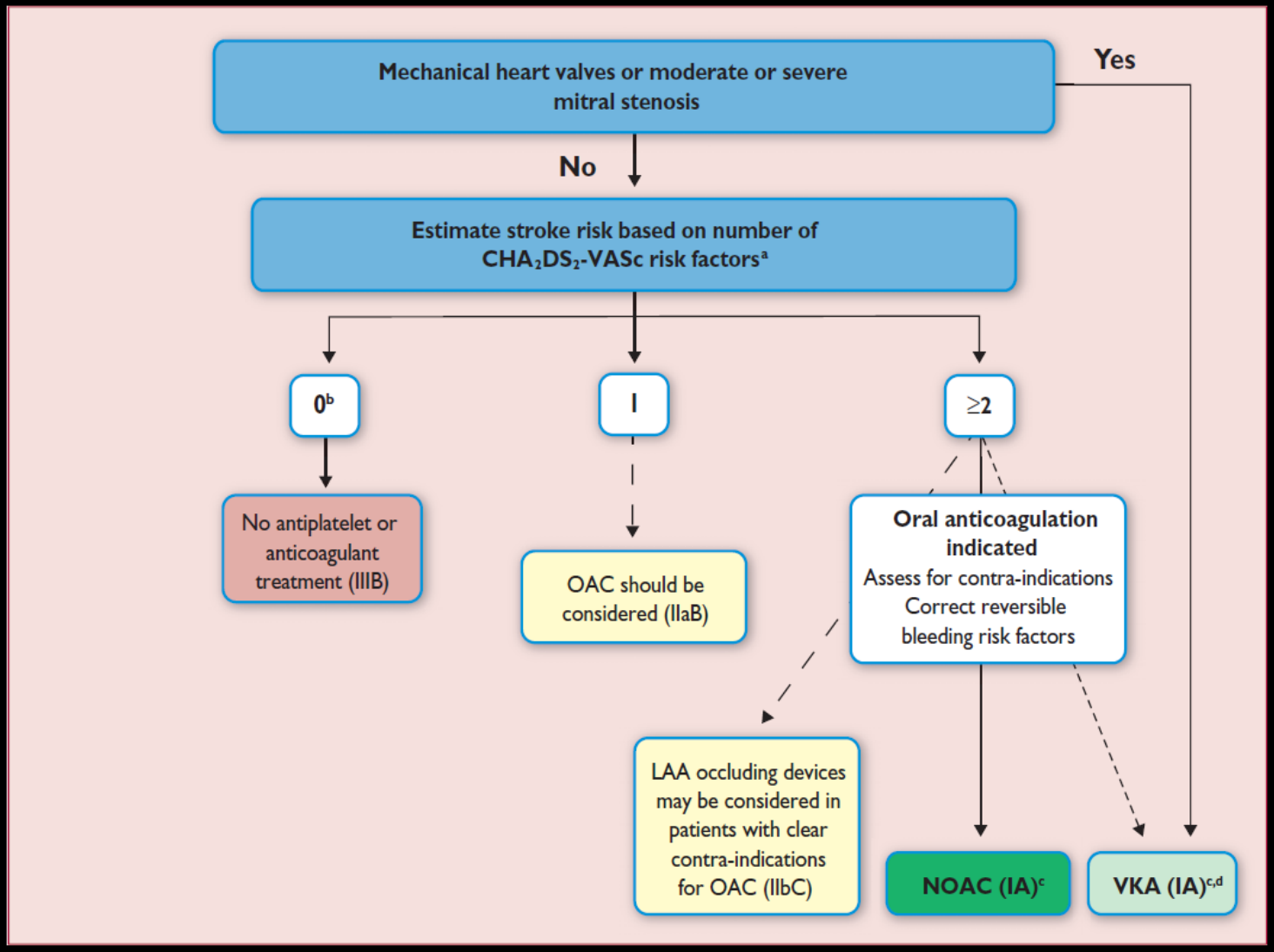
METHODS Our meta-analysis included 2,406 patients with 5,931 patient-years (PY) of follow-up from the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) and PREVAIL (Prospective Randomized Evaluation of the Watchman LAA Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) trials, and their respective registries (Continued Access to PROTECT AF registry and Continued Access to PREVAIL registry).

RESULTS With mean follow-up of 2.69 years, patients receiving LAAC with the Watchman device had significantly fewer hemorrhagic strokes (0.15 vs. 0.96 events/100 patient-years [PY]; hazard ratio [HR]: 0.22; p = 0.004), cardiovascular/unexplained death (1.1 vs. 2.3 events/100 PY; HR: 0.48; p = 0.006), and nonprocedural bleeding (6.0% vs. 11.3%; HR: 0.51; p = 0.006) compared with warfarin. All-cause stroke or systemic embolism was similar between both strategies (1.75 vs. 1.87 events/100 PY; HR: 1.02; 95% CI: 0.62 to 1.7; p = 0.94). There were more ischemic strokes in the device group (1.6 vs. 0.9 and 0.2 vs. 1.0 events/100 PY; HR: 1.95 and 0.22, respectively; p = 0.05 and 0.004, respectively). Both trials and registries identified similar event rates and consistent device effect in multiple subsets.

CONCLUSIONS In patients with NVAF at increased risk for stroke or bleeding who are candidates for chronic anticoagulation, LAAC resulted in improved rates of hemorrhagic stroke, cardiovascular/unexplained death, and nonprocedural bleeding compared to warfarin. (J Am Coll Cardiol 2015;65:2614–23) © 2015 by the American College of Cardiology Foundation.

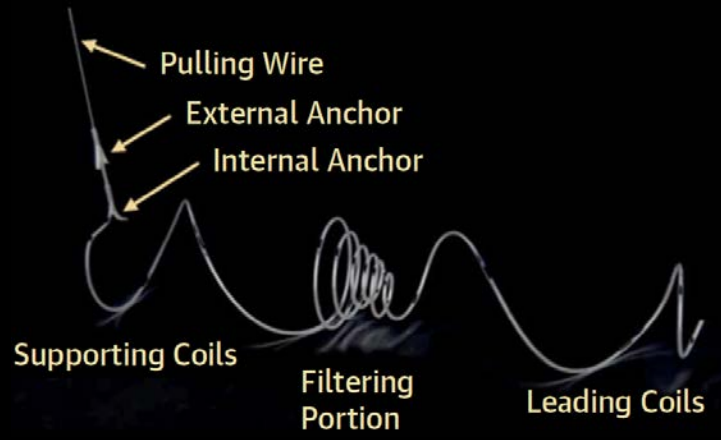
Holmes, et al. JACC 2015

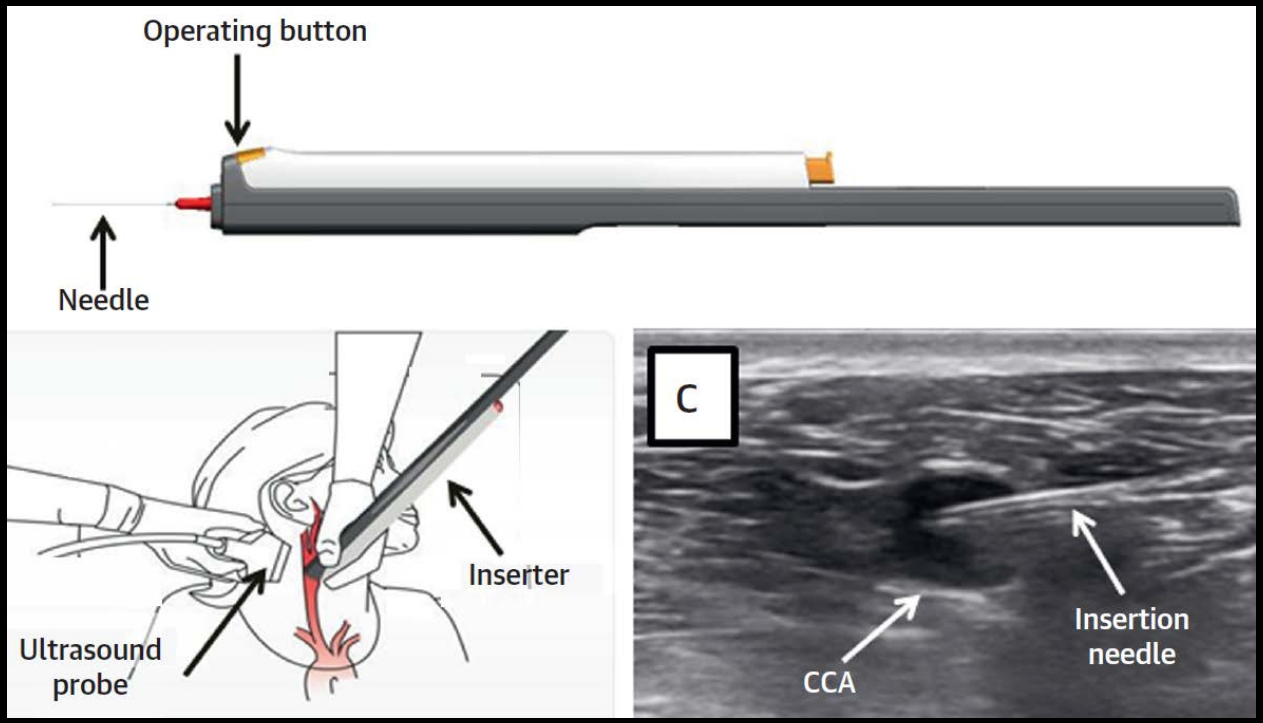
Left atrial appendage occlusion – ESC Guidelines 2016

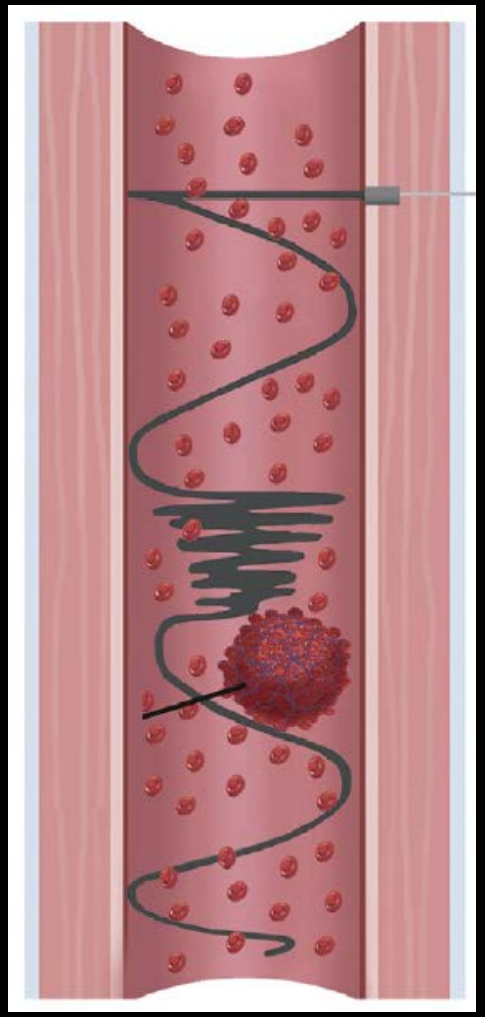


Kirchhoff, et al. Eur Heart Journal 2016

Carotid filter for stroke prevention







Reddy, et al. JACC 2019

Agenda

Atrial fibrillation

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- NOAC or VKA?
- SAME-TTR to select oral anticoagulant?
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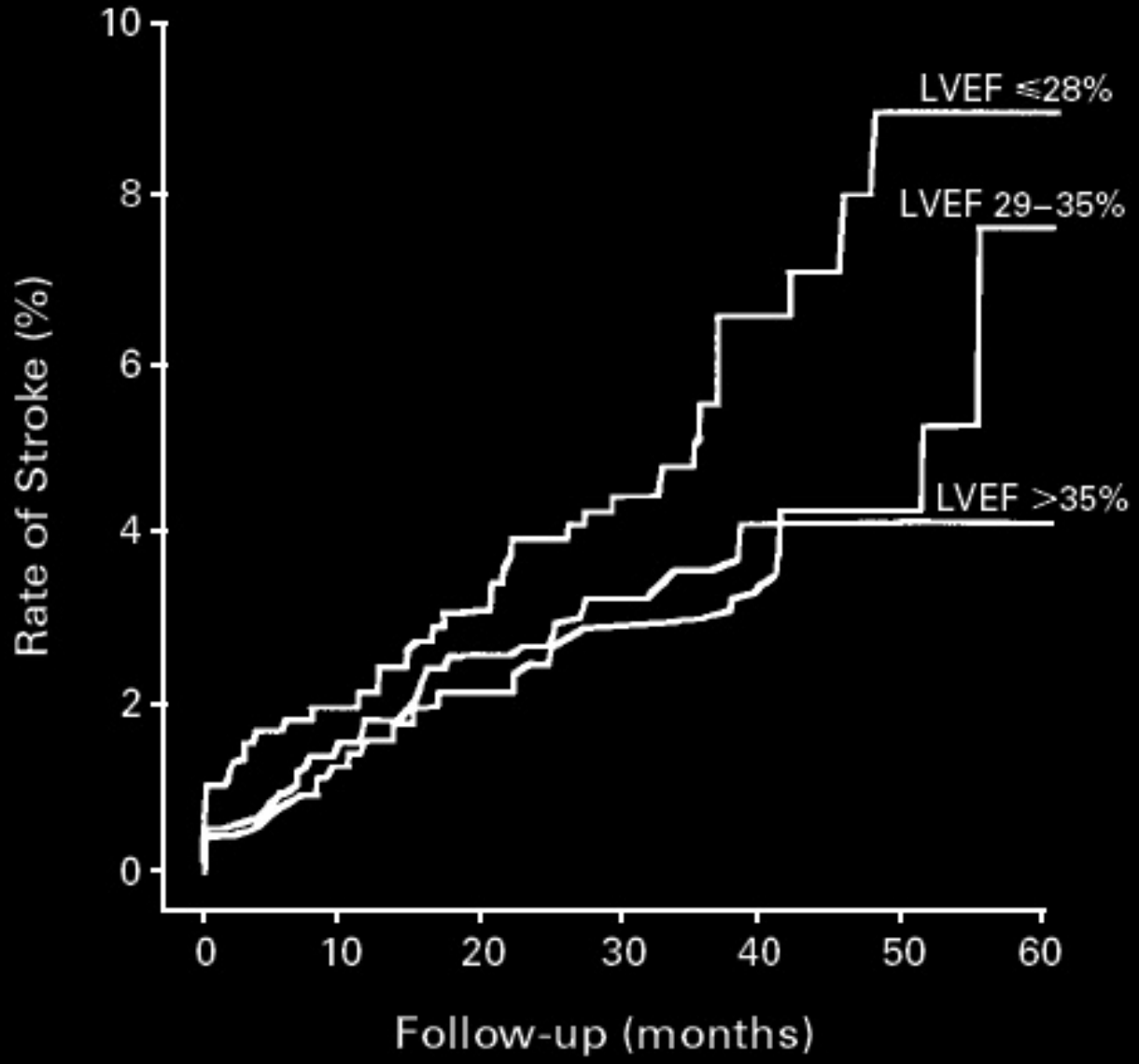
Heart failure with sinus rhythm

- Is there a role for OAC?

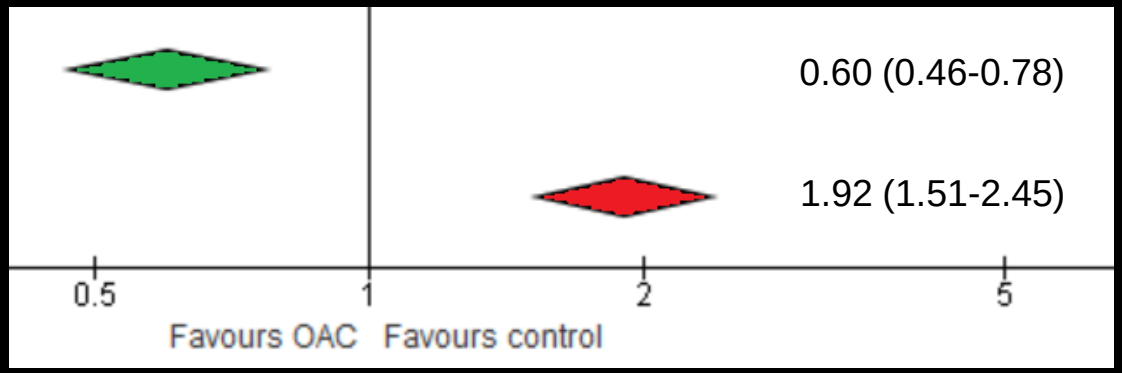
Heart failure with sinus rhythm: a prothrombotic condition

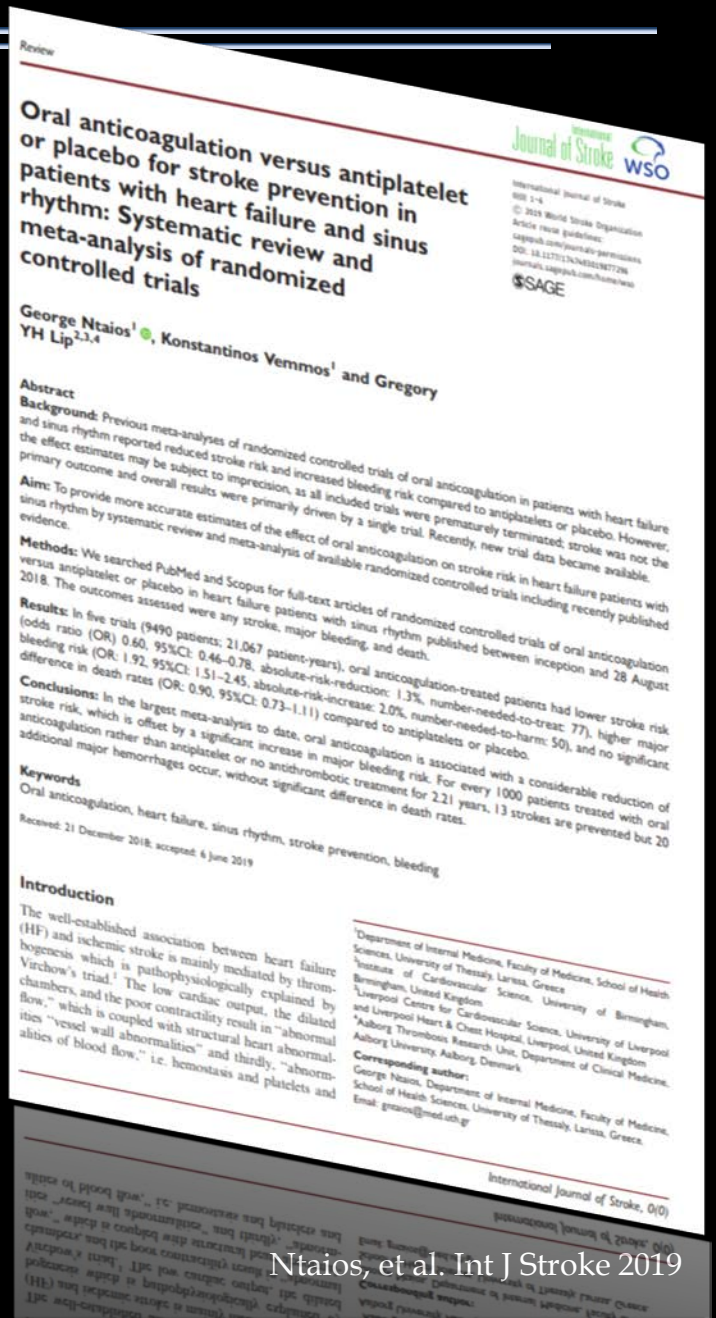


N Engl J Med 1997; 336:251-7

Heart failure with sinus rhythm: is there a role for OAC?

Green: stroke reduction
Red: hemorrhage risk





Review

Oral anticoagulation versus antiplatelet or placebo for stroke prevention in patients with heart failure and sinus rhythm: Systematic review and meta-analysis of randomized controlled trials

Journal of Stroke WSO

SAGE

George Ntaios[1], Konstantinos Vemmos[1] and Gregory YH Lip[2,3,4]

Abstract

Background: Previous meta-analyses of randomized controlled trials of oral anticoagulation in patients with heart failure and sinus rhythm reported reduced stroke risk and increased bleeding risk compared to antiplatelets or placebo. However, the effect estimates may be subject to imprecision, as all included trials were prematurely terminated; stroke was not the primary outcome and overall results were primarily driven by a single trial. Recently, new trial data became available.

Aim: To provide more accurate estimates of the effect of oral anticoagulation on stroke risk in heart failure patients with sinus rhythm by systematic review and meta-analysis of available randomized controlled trials including recently published evidence.

Methods: We searched PubMed and Scopus for full-text articles of randomized controlled trials of oral anticoagulation versus antiplatelet or placebo in heart failure patients with sinus rhythm published between inception and 28 August 2018. The outcomes assessed were any stroke, major bleeding, and death.

Results: In five trials (9490 patients; 21,067 patient-years), oral anticoagulation-treated patients had lower stroke risk (odds ratio (OR) 0.60, 95%CI: 0.46–0.78, absolute-risk-reduction: 1.3%, number-needed-to-treat: 77), higher major bleeding risk (OR: 1.92, 95%CI: 1.51–2.45, absolute-risk-increase: 2.0%, number-needed-to-harm: 50), and no significant difference in death rates (OR: 0.90, 95%CI: 0.73–1.11) compared to antiplatelets or placebo.

Conclusions: In the largest meta-analysis to date, oral anticoagulation is associated with a considerable reduction of stroke risk, which is offset by a significant increase in major bleeding risk. For every 1000 patients treated with oral anticoagulation rather than antiplatelet or no antithrombotic treatment for 2.21 years, 13 strokes are prevented but 20 additional major hemorrhages occur, without significant difference in death rates.

Keywords
Oral anticoagulation, heart failure, sinus rhythm, stroke prevention, bleeding

Received: 21 December 2018; accepted: 6 June 2019

Introduction

The well-established association between heart failure (HF) and ischemic stroke is mainly mediated by thrombogenesis which is pathophysiologically explained by Virchow's triad.[1] The low cardiac output, the dilated chambers, and the poor contractility result in "abnormal flow," which is coupled with structural heart abnormalities "vessel wall abnormalities" and thirdly, "abnormalities of blood flow," i.e. hemostasis and platelets and

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[4]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

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Ntaios, et al. Int J Stroke 2019

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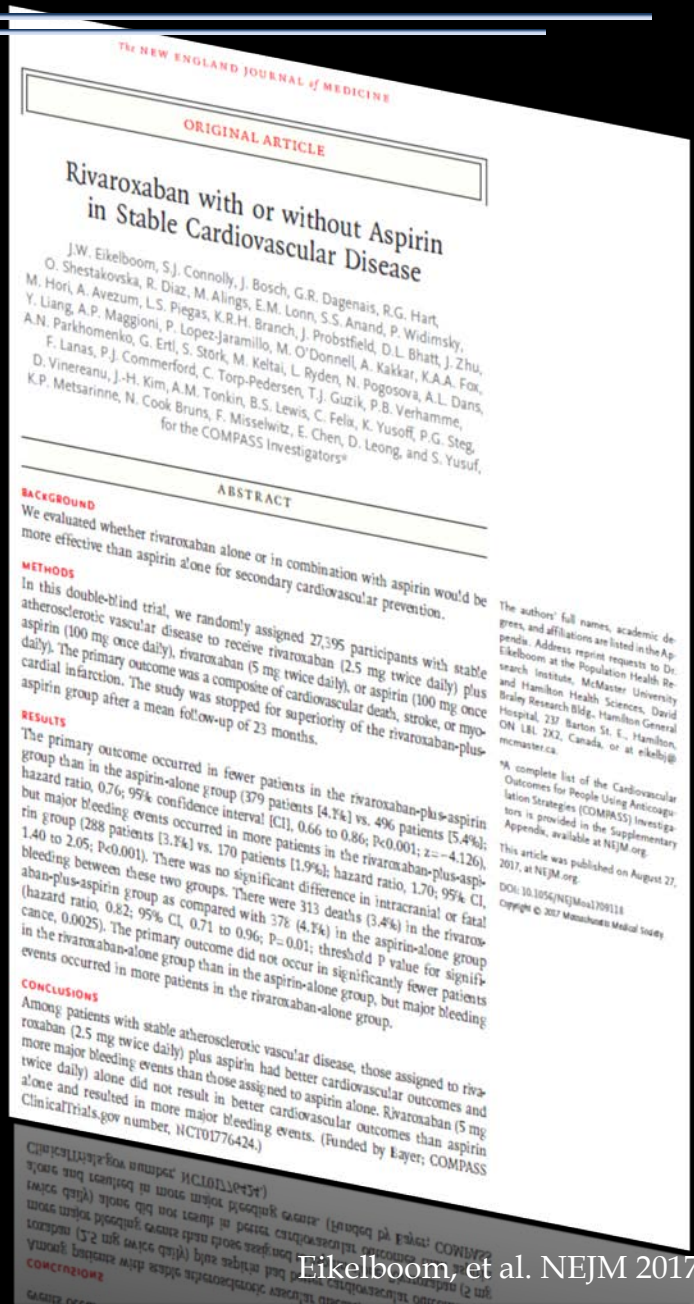
Atherosclerotic stroke

- low-dose rivaroxaban & aspirin
- LDL targets

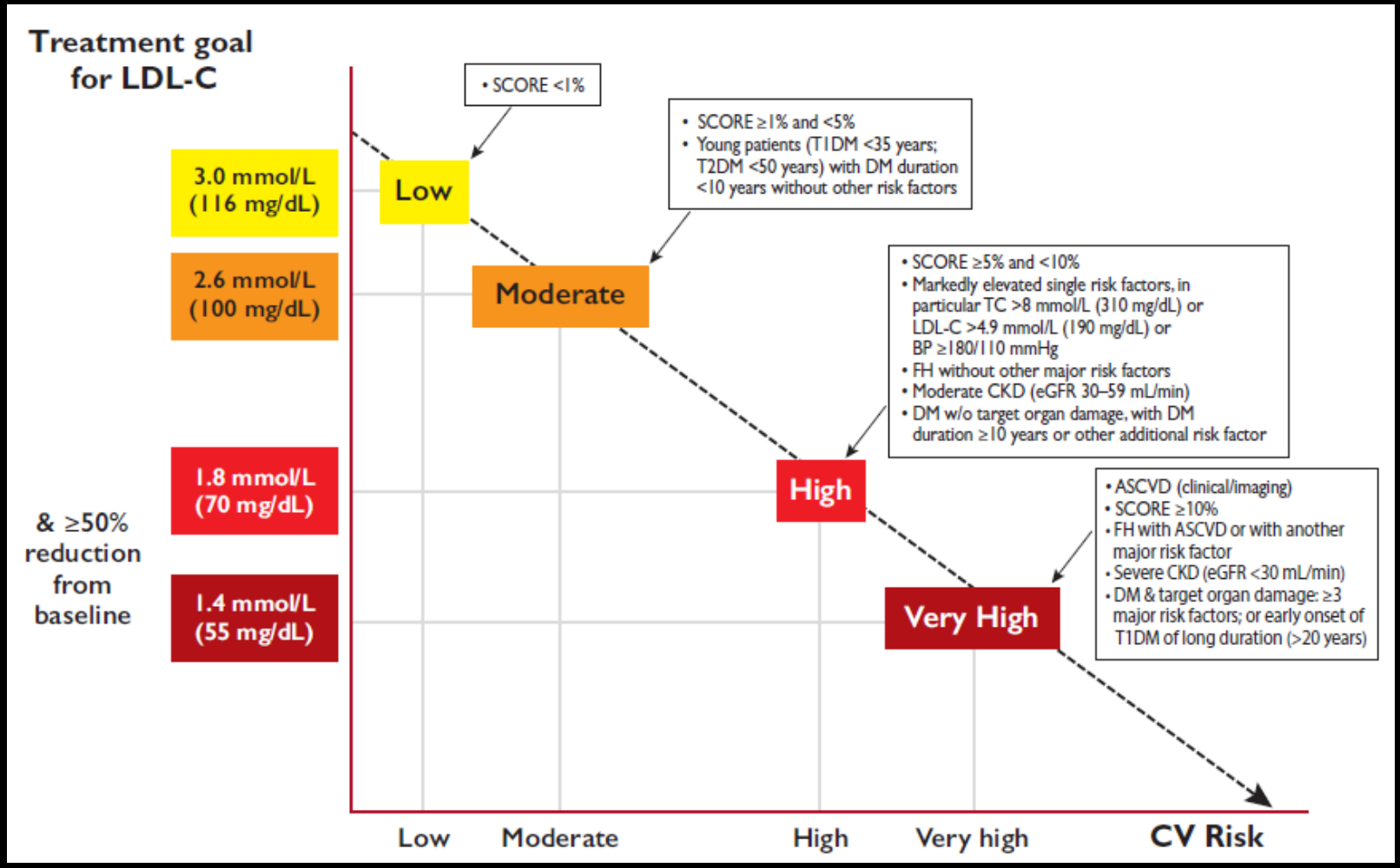
Atherosclerotic strokes: COMPASS

	Hazard Ratio (95% CI)	P Value
Ischemic or uncertain type	0.51 (0.38–0.68)	<0.001
Major bleeding	1.70 (1.40–2.05)	<0.001
Net-clinical-benefit outcome: CV death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into critical organ	0.80 (0.70–0.91)	<0.001



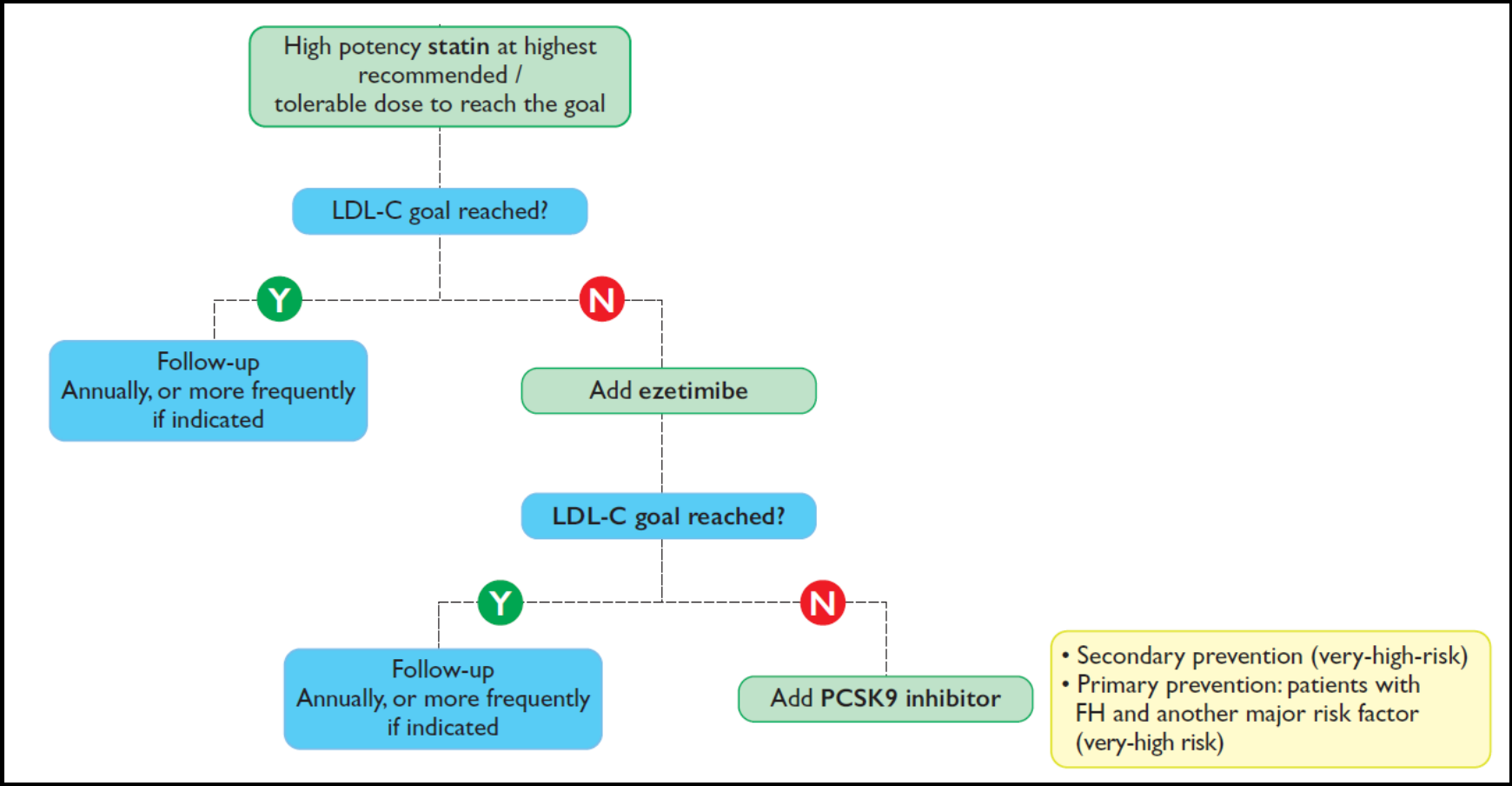
Eikelboom, et al. NEJM 2017

Atherosclerotic strokes: LDL targets



ESC/EAS Guidelines, Eur Heart Journal 2019

Algorithm for LDL management



ESC/EAS Guidelines, Eur Heart Journal 2019

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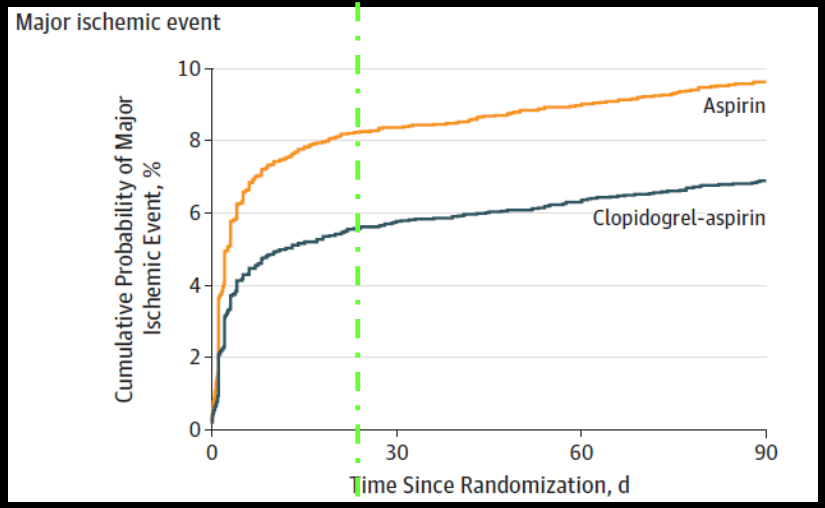
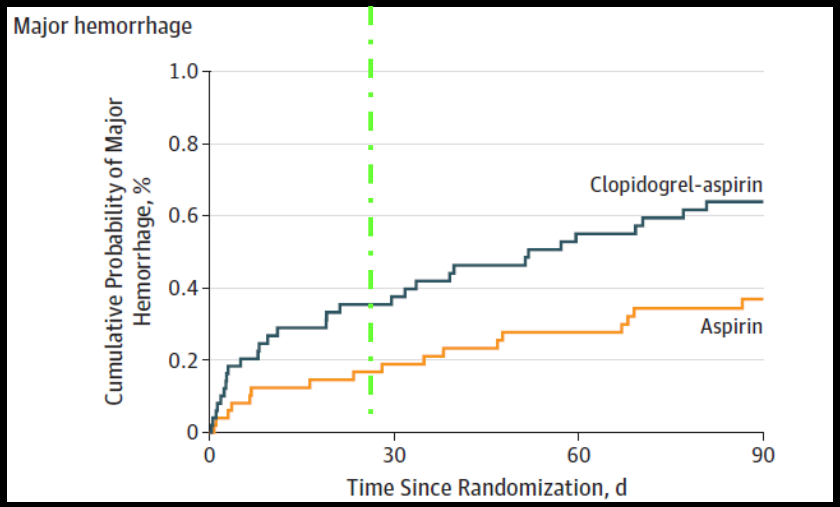
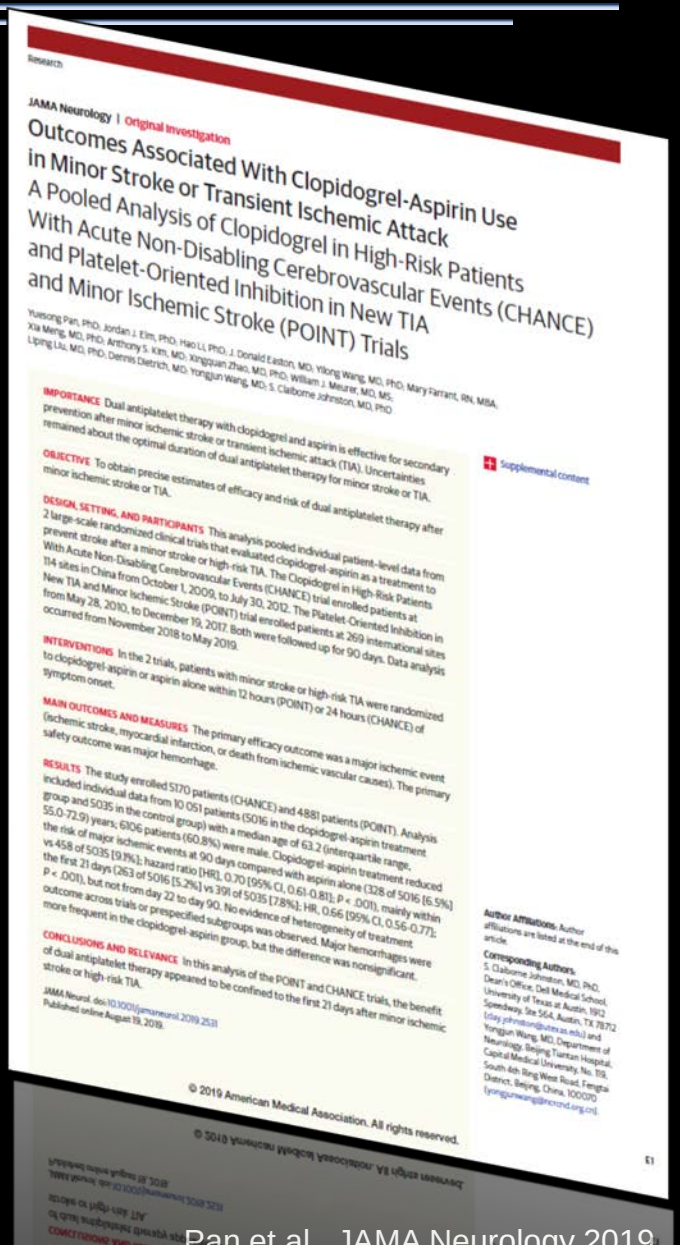
- LDL targets

Minor strokes
- Dual antiplatelet treatment: for how long?

Dual antiplatelet in the early phase of minor stroke






Research

JAMA Neurology | Original Investigation

Outcomes Associated With Clopidogrel-Aspirin Use in Minor Stroke or Transient Ischemic Attack
A Pooled Analysis of Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events (CHANCE) and Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) Trials

Yuesong Pan, PhD; Jordan J. Elm, PhD; Hao Li, PhD; J. Donald Easton, MD; Yilong Wang, MD, PhD; Mary Farrant, RN, MBA; Xia Meng, MD, PhD; Anthony S. Kim, MD; Xingquan Zhao, MD, PhD; William J. Meurer, MD, MS; Liping Liu, MD, PhD; Dennis Dietrich, MD; Yongjun Wang, MD; S. Claiborne Johnston, MD, PhD

Supplemental content

IMPORTANCE Dual antiplatelet therapy with clopidogrel and aspirin is effective for secondary prevention after minor ischemic stroke or transient ischemic attack (TIA). Uncertainties remained about the optimal duration of dual antiplatelet therapy for minor stroke or TIA.

OBJECTIVE To obtain precise estimates of efficacy and risk of dual antiplatelet therapy after minor ischemic stroke or TIA.

DESIGN, SETTING, AND PARTICIPANTS This analysis pooled individual patient-level data from 2 large-scale randomized clinical trials that evaluated clopidogrel-aspirin as a treatment to prevent stroke after a minor stroke or high-risk TIA. The Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events (CHANCE) trial enrolled patients at 114 sites in China from October 1, 2009, to July 30, 2012. The Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial enrolled patients at 269 international sites from May 28, 2010, to December 19, 2017. Both were followed up for 90 days. Data analysis occurred from November 2018 to May 2019.

INTERVENTIONS In the 2 trials, patients with minor stroke or high-risk TIA were randomized to clopidogrel-aspirin or aspirin alone within 12 hours (POINT) or 24 hours (CHANCE) of symptom onset.

MAIN OUTCOMES AND MEASURES The primary efficacy outcome was a major ischemic event (ischemic stroke, myocardial infarction, or death from ischemic vascular causes). The primary safety outcome was major hemorrhage.

RESULTS The study enrolled 5170 patients (CHANCE) and 4881 patients (POINT). Analysis included individual data from 10 051 patients (5016 in the clopidogrel-aspirin treatment group and 5035 in the control group) with a median age of 63.2 (interquartile range, 55.0-72.9) years; 6106 patients (60.8%) were male. Clopidogrel-aspirin treatment reduced the risk of major ischemic events at 90 days compared with aspirin alone (328 of 5016 [6.5%] vs 458 of 5035 [9.1%]; hazard ratio [HR], 0.70 [95% CI, 0.61-0.81]; $P < .001$), mainly within the first 21 days (263 of 5016 [5.2%] vs 391 of 5035 [7.8%]; HR, 0.66 [95% CI, 0.56-0.77]; $P < .001$), but not from day 22 to day 90. No evidence of heterogeneity of treatment outcome across trials or prespecified subgroups was observed. Major hemorrhages were more frequent in the clopidogrel-aspirin group, but the difference was nonsignificant.

CONCLUSIONS AND RELEVANCE In this analysis of the POINT and CHANCE trials, the benefit of dual antiplatelet therapy appeared to be confined to the first 21 days after minor ischemic stroke or high-risk TIA.

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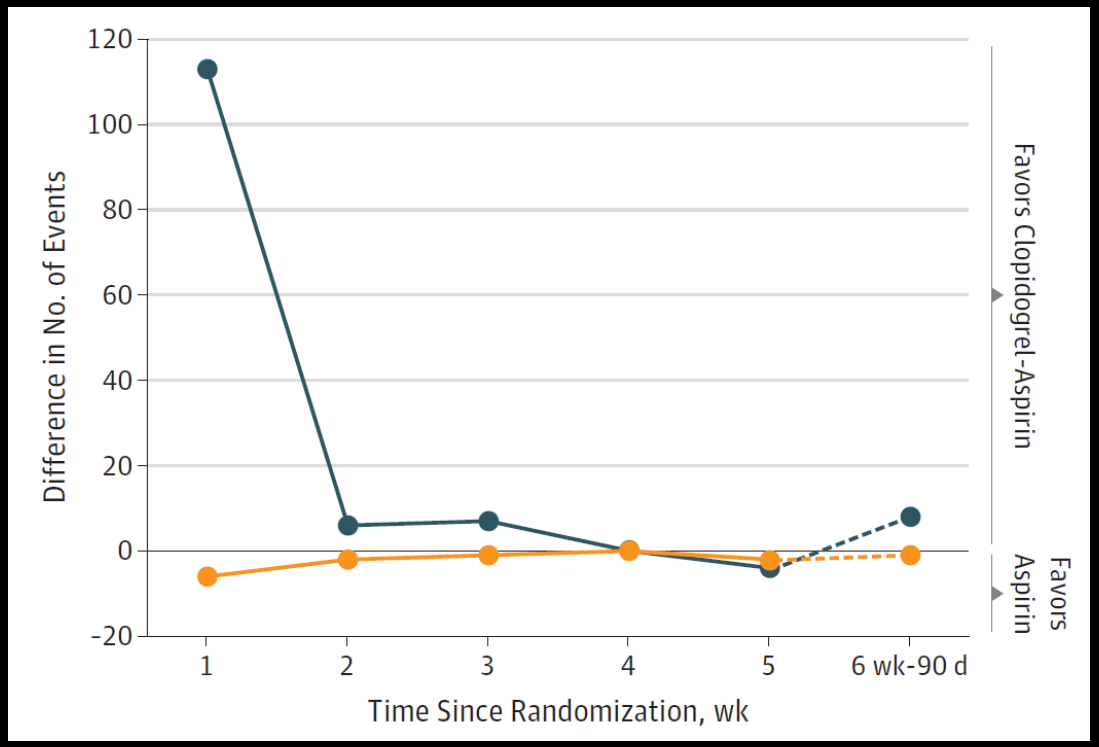
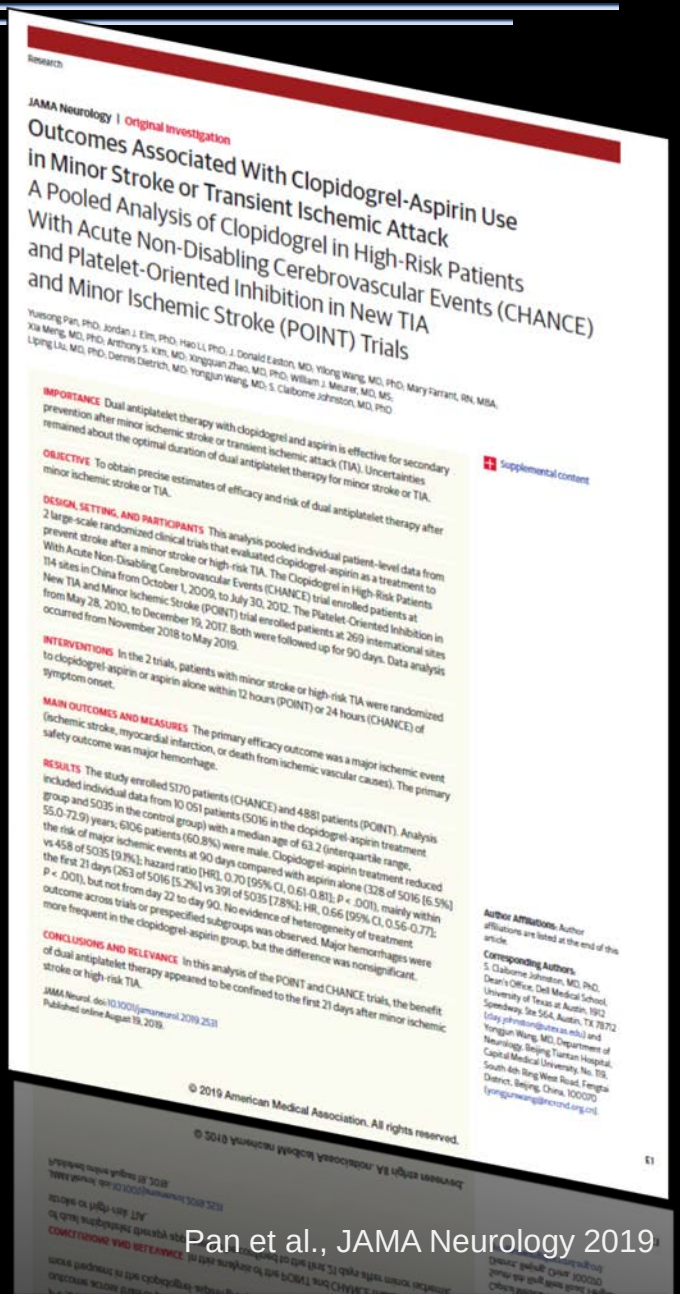
Pan et al., JAMA Neurology 2019

Dual antiplatelet in the early phase of minor stroke




Research

JAMA Neurology | Original Investigation

Outcomes Associated With Clopidogrel-Aspirin Use in Minor Stroke or Transient Ischemic Attack
A Pooled Analysis of Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events (CHANCE) and Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) Trials

Yuesong Pan, PhD; Jordan J. Elm, PhD; Hao Li, PhD; J. Donald Easton, MD; Yilong Wang, MD, PhD; Mary Farrant, RN, MBA; Xia Meng, MD, PhD; Anthony S. Kim, MD; Xingquan Zhao, MD, PhD; William J. Meurer, MD, MS; Liping Liu, MD, PhD; Dennis Dietrich, MD; Yongjun Wang, MD; S. Claiborne Johnston, MD, PhD

Supplemental content

IMPORTANCE Dual antiplatelet therapy with clopidogrel and aspirin is effective for secondary prevention after minor ischemic stroke or transient ischemic attack (TIA). Uncertainties remained about the optimal duration of dual antiplatelet therapy for minor stroke or TIA.

OBJECTIVE To obtain precise estimates of efficacy and risk of dual antiplatelet therapy after minor ischemic stroke or TIA.

DESIGN, SETTING, AND PARTICIPANTS This analysis pooled individual patient-level data from 2 large-scale randomized clinical trials that evaluated clopidogrel-aspirin as a treatment to prevent stroke after a minor stroke or high-risk TIA. The Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events (CHANCE) trial enrolled patients at 114 sites in China from October 1, 2009, to July 30, 2012. The Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial enrolled patients at 269 international sites from May 28, 2010, to December 19, 2017. Both were followed up for 90 days. Data analysis occurred from November 2018 to May 2019.

INTERVENTIONS In the 2 trials, patients with minor stroke or high-risk TIA were randomized to clopidogrel-aspirin or aspirin alone within 12 hours (POINT) or 24 hours (CHANCE) of symptom onset.

MAIN OUTCOMES AND MEASURES The primary efficacy outcome was a major ischemic event (ischemic stroke, myocardial infarction, or death from ischemic vascular causes). The primary safety outcome was major hemorrhage.

RESULTS The study enrolled 5170 patients (CHANCE) and 4881 patients (POINT). Analysis included individual data from 10 051 patients (5016 in the clopidogrel-aspirin treatment group and 5035 in the control group) with a median age of 63.2 (interquartile range, 55.0-72.9) years; 6106 patients (60.8%) were male. Clopidogrel-aspirin treatment reduced the risk of major ischemic events at 90 days compared with aspirin alone (328 of 5016 [6.5%] vs 458 of 5035 [9.1%]; hazard ratio [HR], 0.70 [95% CI, 0.61-0.81]; $P < .001$), mainly within the first 21 days (263 of 5016 [5.2%] vs 391 of 5035 [7.8%]; HR, 0.66 [95% CI, 0.56-0.77]; $P < .001$), but not from day 22 to day 90. No evidence of heterogeneity of treatment outcome across trials or prespecified subgroups was observed. Major hemorrhages were more frequent in the clopidogrel-aspirin group, but the difference was nonsignificant.

CONCLUSIONS AND RELEVANCE In this analysis of the POINT and CHANCE trials, the benefit of dual antiplatelet therapy appeared to be confined to the first 21 days after minor ischemic stroke or high-risk TIA.

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Pan et al., JAMA Neurology 2019

Agenda

Atrial fibrillation
- Aspirin for AF patients?
- NOAC or VKA?
- SAME-TTR to select oral anticoagulant?
- When to restart OAC after ischemic stroke?
- Is there a role for left atrial appendage occlusion?
- Carotid filter for stroke prevention?

Heart failure with sinus rhythm
- Is there a role for OAC?

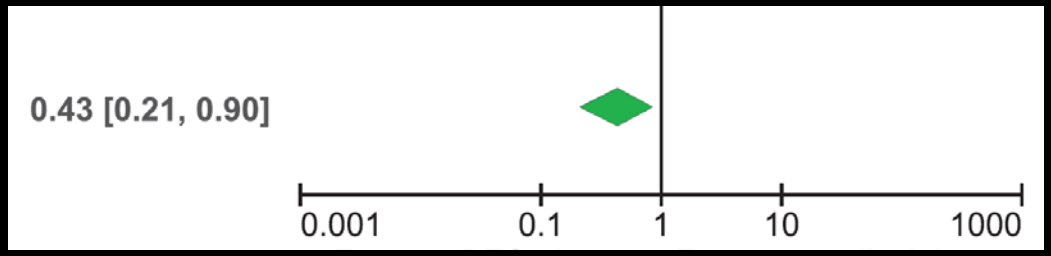
Atherosclerotic stroke
- low-dose rivaroxaban & aspirin
- LDL targets

Minor strokes
- Dual antiplatelet treatment: for how long?

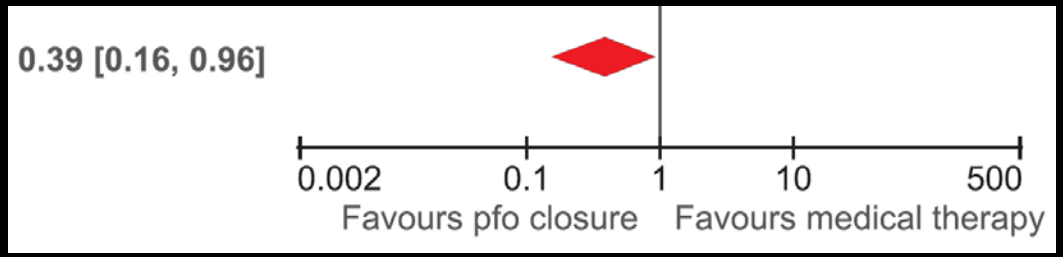
PFO
- Closure or medical treatment?
- OAC or aspirin in non-closed PFOs?

PFO closure

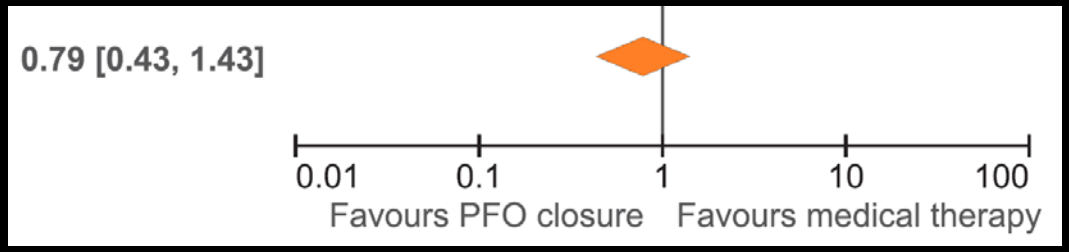
Green: stroke reduction all patients

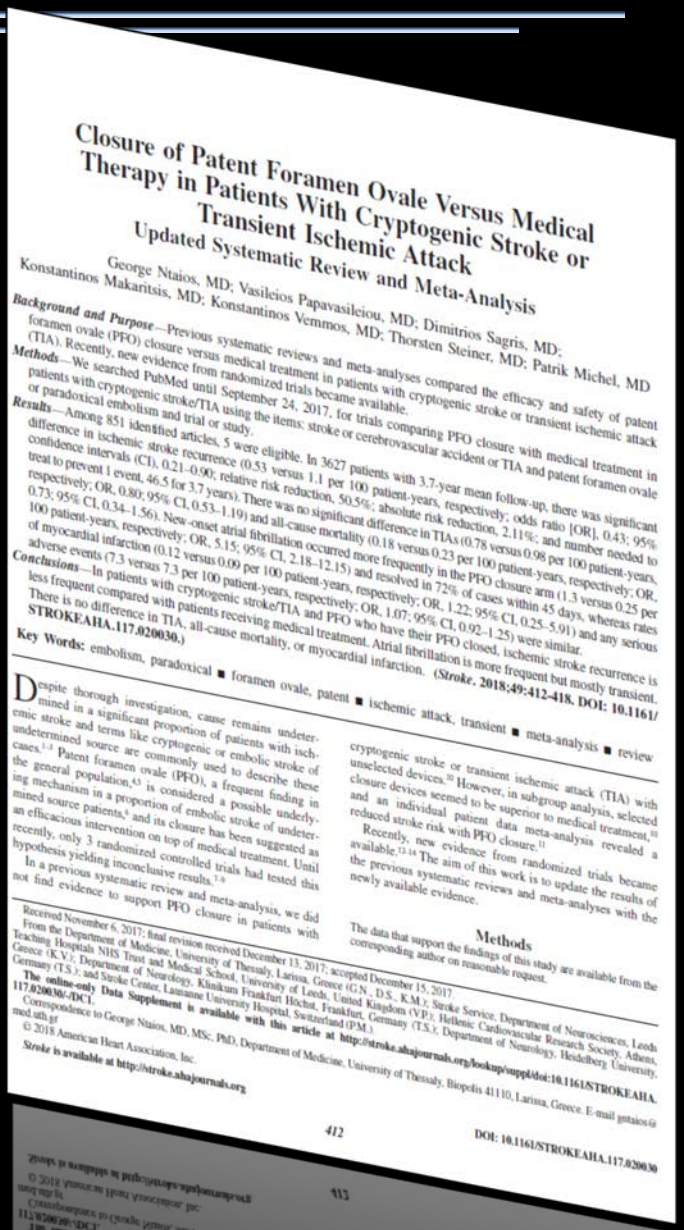


Red: stroke reduction high risk PFOs



Orange: stroke reduction low risk PFOs





Closure of Patent Foramen Ovale Versus Medical Therapy in Patients With Cryptogenic Stroke or Transient Ischemic Attack

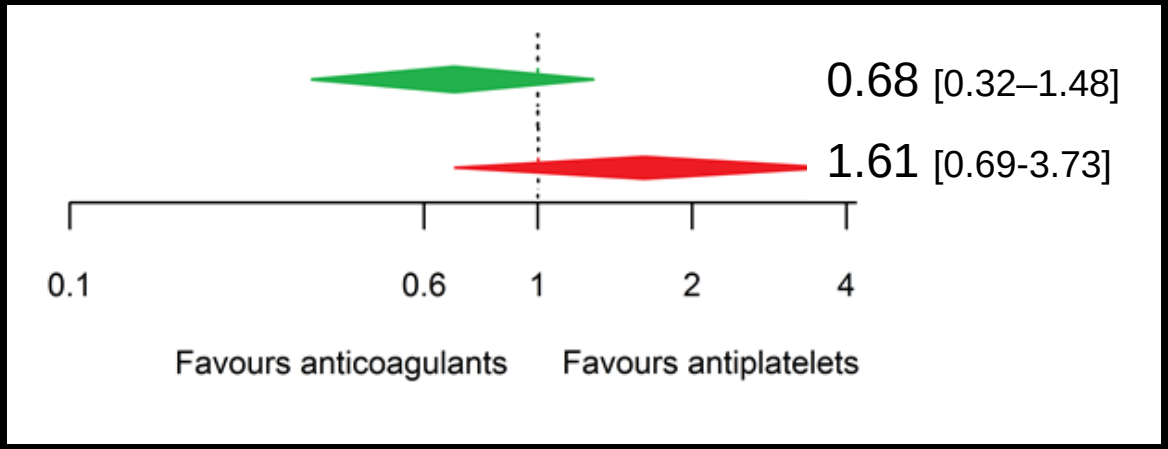
Updated Systematic Review and Meta-Analysis

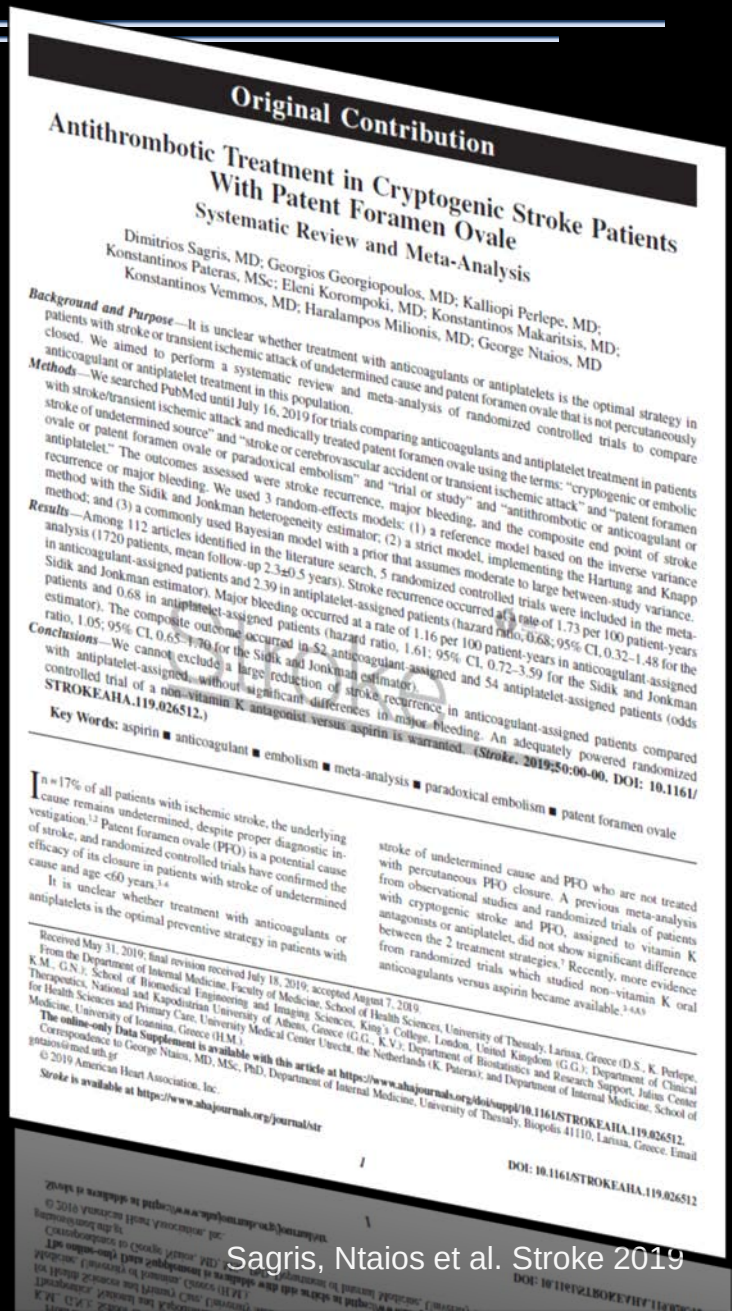
George Ntaios, MD; Vasileios Papavasileiou, MD; Dimitrios Sagris, MD; Konstantinos Makaritsis, MD; Konstantinos Vemmos, MD; Thorsten Steiner, MD; Patrik Michel, MD

Ntaios, Michel et al. Stroke 2018

OAC vs aspirin for non-closed PFO

Green: stroke reduction
Red: hemorrhage risk





Original Contribution

Antithrombotic Treatment in Cryptogenic Stroke Patients With Patent Foramen Ovale

Systematic Review and Meta-Analysis

Dimitrios Sagris, MD; Georgios Georgiopoulos, MD; Kalliopi Perlepe, MD; Konstantinos Pateras, MSc; Eleni Korompoki, MD; Konstantinos Makaritsis, MD; Konstantinos Vemmos, MD; Haralampos Milionis, MD; George Ntaios, MD

Sagris, Ntaios et al. Stroke 2019

Agenda

Atrial fibrillation
- Aspirin for AF patients?
- NOAC or VKA?
- SAME-TTR to select oral anticoagulant?
- When to restart OAC after ischemic stroke?
- Is there a role for left atrial appendage occlusion?
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PFO
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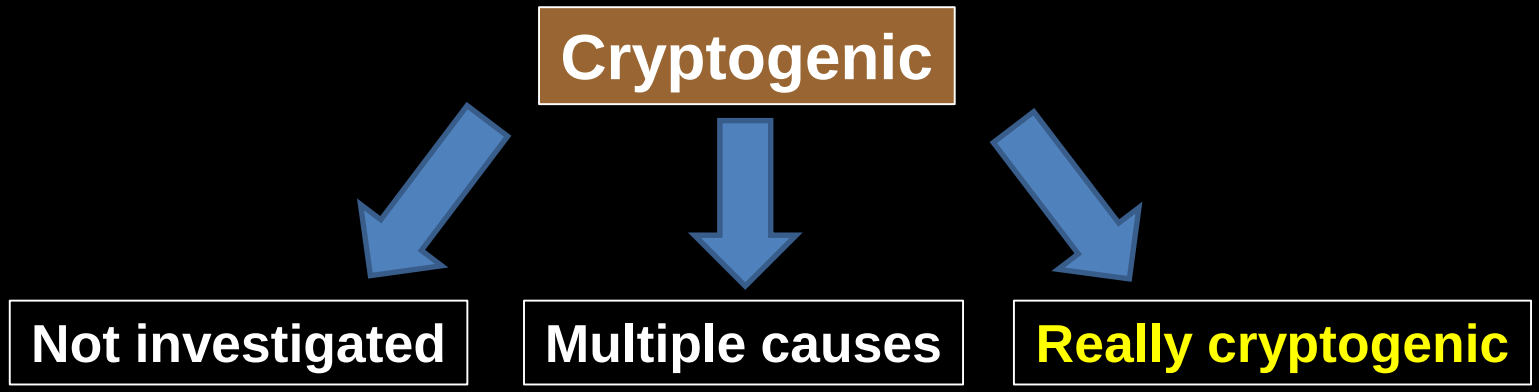
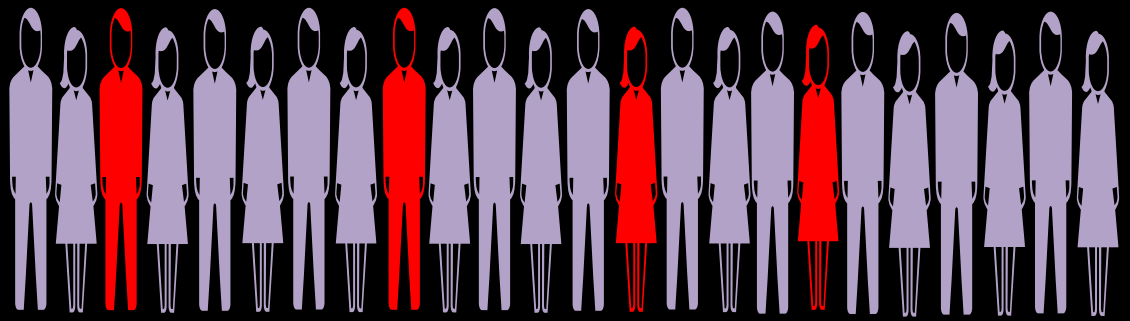
- OAC or aspirin in non-closed PFOs?

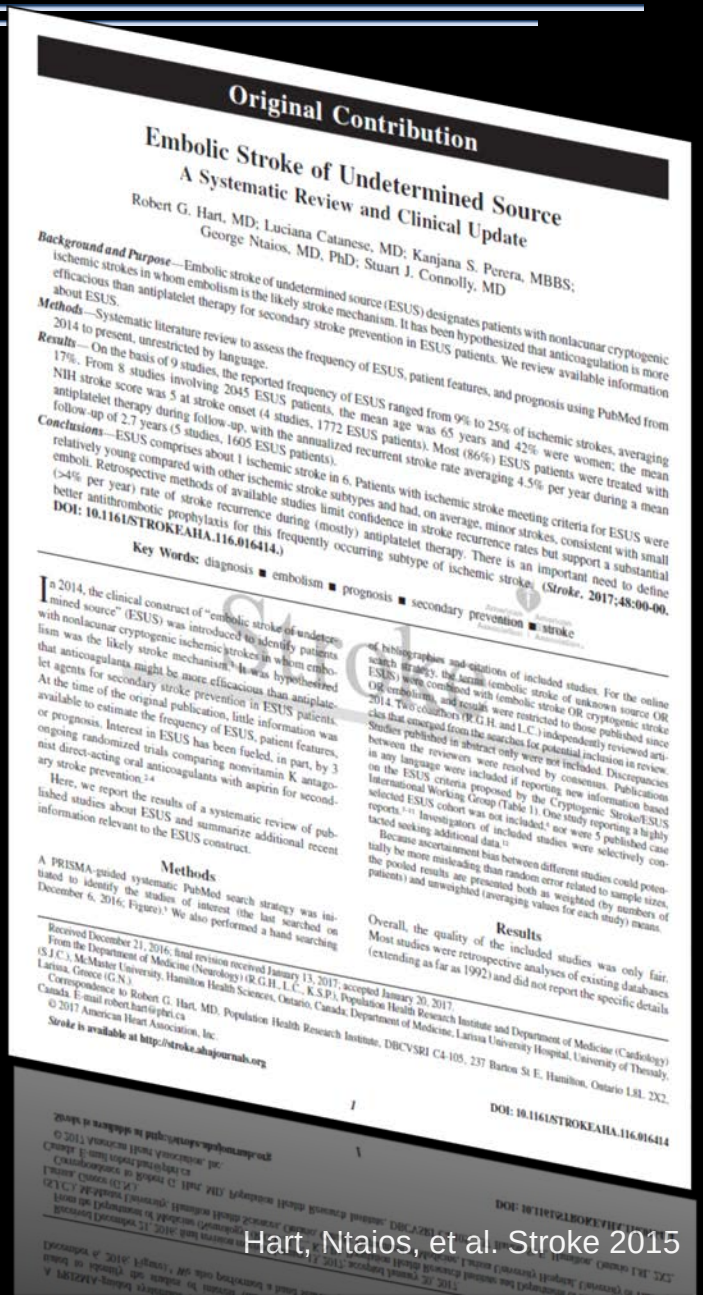
ESUS
- ESUS vs. cryptogenic
- NAVIGATE ESUS and RE-SPECT ESUS results
- Potential explanation and implications for future research

ESUS vs. cryptogenic



ESUS are frequent





Original Contribution

Embolic Stroke of Undetermined Source
A Systematic Review and Clinical Update

Robert G. Hart, MD; Luciana Catanese, MD; Kanjana S. Perera, MBBS; George Ntaios, MD, PhD; Stuart J. Connolly, MD

Background and Purpose—Embolic stroke of undetermined source (ESUS) designates patients with nonlacunar cryptogenic ischemic strokes in whom embolism is the likely stroke mechanism. It has been hypothesized that anticoagulation is more efficacious than antiplatelet therapy for secondary stroke prevention in ESUS patients. We review available information about ESUS.

Methods—Systematic literature review to assess the frequency of ESUS, patient features, and prognosis using PubMed from 2014 to present, unrestricted by language.

Results—On the basis of 9 studies, the reported frequency of ESUS ranged from 9% to 25% of ischemic strokes, averaging 17%. From 8 studies involving 2045 ESUS patients, the mean age was 65 years and 42% were women; the mean NIH stroke score was 5 at stroke onset (4 studies, 1772 ESUS patients). Most (86%) ESUS patients were treated with antiplatelet therapy during follow-up, with the annualized recurrent stroke rate averaging 4.5% per year during a mean follow-up of 2.7 years (5 studies, 1605 ESUS patients).

Conclusions—ESUS comprises about 1 ischemic stroke in 6. Patients with ischemic stroke meeting criteria for ESUS were relatively young compared with other ischemic stroke subtypes and had, on average, minor strokes, consistent with small emboli. Retrospective methods of available studies limit confidence in stroke recurrence rates but support a substantial (>4% per year) rate of stroke recurrence during (mostly) antiplatelet therapy. There is an important need to define better antithrombotic prophylaxis for this frequently occurring subtype of ischemic stroke. (***Stroke***. **2017;48:00-00.**)

DOI: 10.1161/STROKEAHA.116.016414.)

Key Words: diagnosis ■ embolism ■ prognosis ■ secondary prevention ■ stroke

In 2014, the clinical construct of "embolic stroke of undetermined source" (ESUS) was introduced to identify patients with nonlacunar cryptogenic ischemic strokes in whom embolism was the likely stroke mechanism.[1] It was hypothesized that anticoagulants might be more efficacious than antiplatelet agents for secondary stroke prevention in ESUS patients. At the time of the original publication, little information was available to estimate the frequency of ESUS, patient features, or prognosis. Interest in ESUS has been fueled, in part, by 3 ongoing randomized trials comparing nonvitamin K antagonist direct-acting oral anticoagulants with aspirin for secondary stroke prevention.[2-4]

Here, we report the results of a systematic review of published studies about ESUS and summarize additional recent information relevant to the ESUS construct.

Methods

A PRISMA-guided systematic PubMed search strategy was initiated to identify the studies of interest (the last searched on December 6, 2016; Figure).[5] We also performed a hand searching of bibliographies and citations of included studies. For the online search strategy, the terms (embolic stroke of unknown source OR ESUS) were combined with (embolic stroke OR cryptogenic stroke OR embolism), and results were restricted to those published since 2014. Two coauthors (R.G.H. and L.C.) independently reviewed articles that emerged from the searches for potential inclusion in review. Studies published in abstract only were not included. Discrepancies between the reviewers were resolved by consensus. Publications in any language were included if reporting new information based on the ESUS criteria proposed by the Cryptogenic Stroke/ESUS International Working Group (Table 1). One study reporting a highly selected ESUS cohort was not included,[6] nor were 5 published case reports.[7-11] Investigators of included studies were selectively contacted seeking additional data.[12]

Because ascertainment bias between different studies could potentially be more misleading than random error related to sample sizes, the pooled results are presented both as weighted (by numbers of patients) and unweighted (averaging values for each study) means.

Results

Overall, the quality of the included studies was only fair. Most studies were retrospective analyses of existing databases (extending as far as 1992) and did not report the specific details

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From the Department of Medicine (Neurology) (R.G.H., L.C., K.S.P.), Population Health Research Institute and Department of Medicine (Cardiology) (S.J.C.), McMaster University, Hamilton Health Sciences, Ontario, Canada; Department of Medicine, Larissa University Hospital, University of Thessaly, Larissa, Greece (G.N.).

Correspondence to Robert G. Hart, MD, Population Health Research Institute, DBCVSRI C4-105, 237 Barton St E, Hamilton, Ontario L8L 2X2, Canada. E-mail robert.hart@phri.ca

***Stroke* is available at http://stroke.ahajournals.org**

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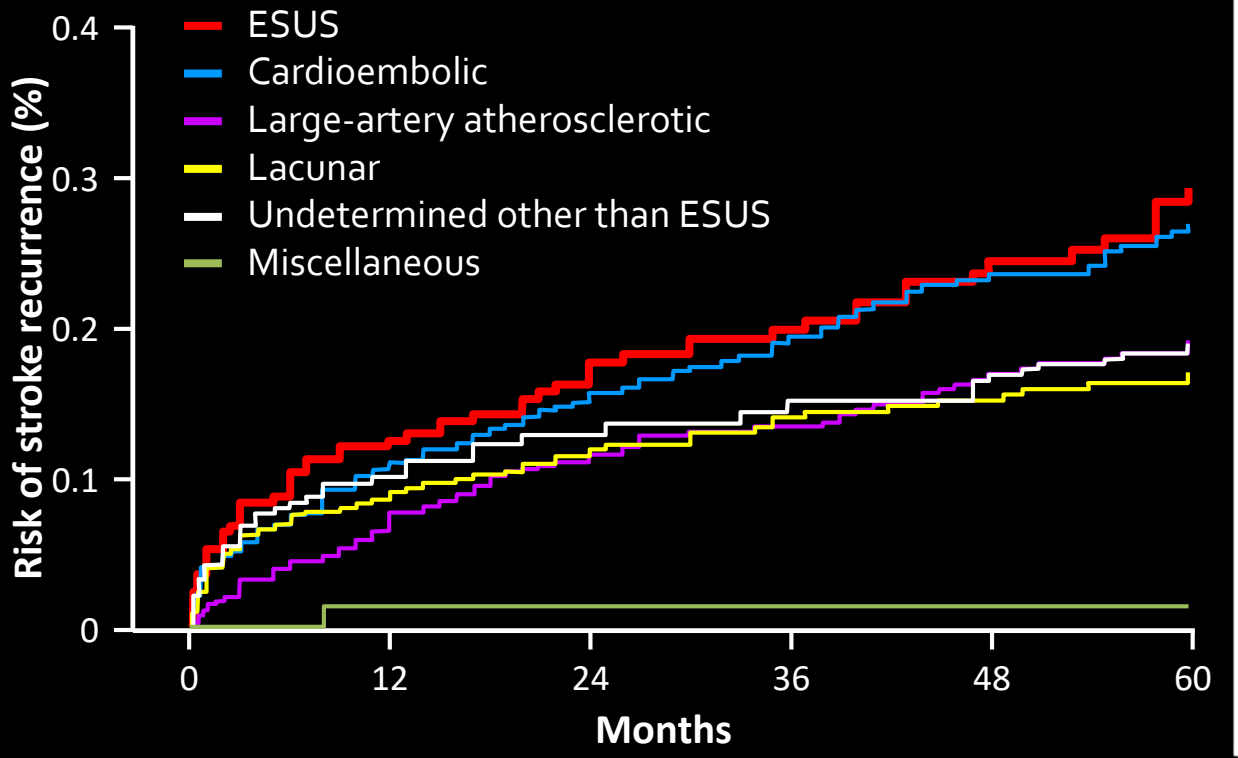
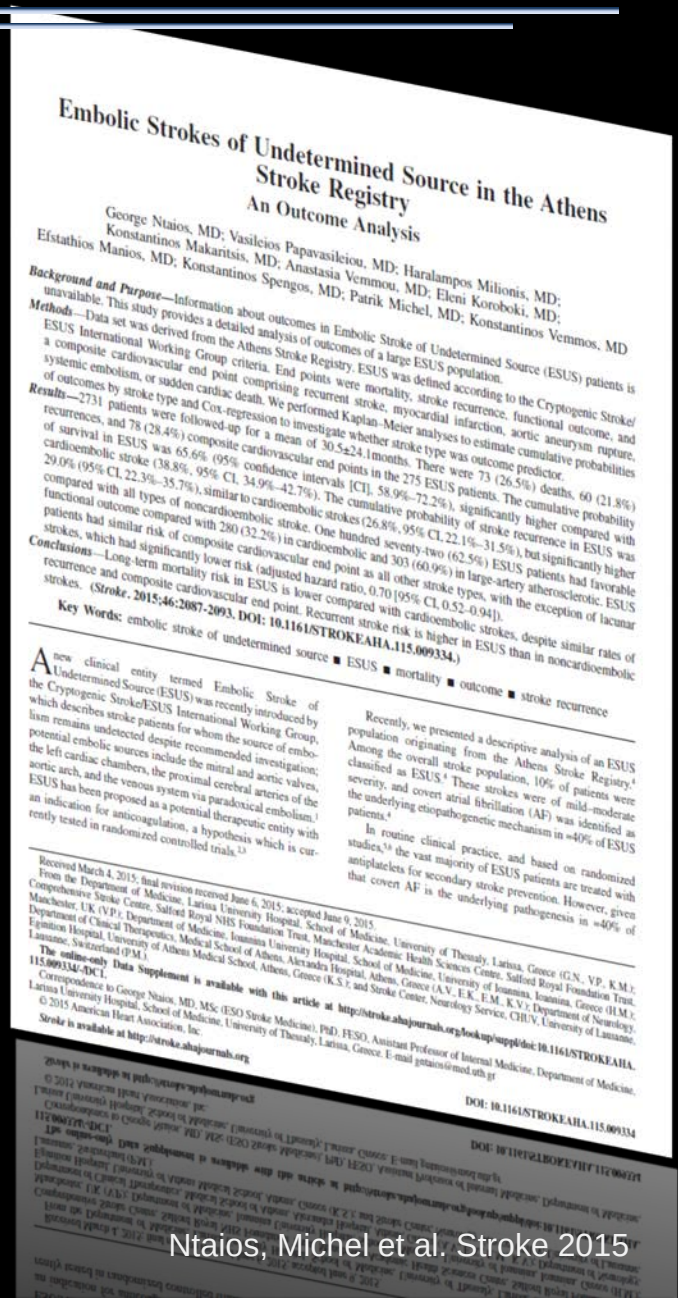
DOI: 10.1161/STROKEAHA.116.016414

Hart, Ntaios, et al. Stroke 2015

ESUS: high recurrence rate





Embolic Strokes of Undetermined Source in the Athens Stroke Registry

An Outcome Analysis

George Ntaios, MD; Vasileios Papavasileiou, MD; Haralampos Milionis, MD; Konstantinos Makaritsis, MD; Anastasia Vemmou, MD; Eleni Koroboki, MD; Efstathios Manios, MD; Konstantinos Spengos, MD; Patrik Michel, MD; Konstantinos Vemmos, MD

Background and Purpose—Information about outcomes in Embolic Stroke of Undetermined Source (ESUS) patients is unavailable. This study provides a detailed analysis of outcomes of a large ESUS population.

Methods—Data set was derived from the Athens Stroke Registry. ESUS was defined according to the Cryptogenic Stroke/ESUS International Working Group criteria. End points were mortality, stroke recurrence, functional outcome, and a composite cardiovascular end point comprising recurrent stroke, myocardial infarction, aortic aneurysm rupture, systemic embolism, or sudden cardiac death. We performed Kaplan–Meier analyses to estimate cumulative probabilities of outcomes by stroke type and Cox-regression to investigate whether stroke type was outcome predictor.

Results—2731 patients were followed-up for a mean of 30.5±24.1months. There were 73 (26.5%) deaths, 60 (21.8%) recurrences, and 78 (28.4%) composite cardiovascular end points in the 275 ESUS patients. The cumulative probability of survival in ESUS was 65.6% (95% confidence intervals [CI], 58.9%–72.2%), significantly higher compared with cardioembolic stroke (38.8%, 95% CI, 34.9%–42.7%). The cumulative probability of stroke recurrence in ESUS was 29.0% (95% CI, 22.3%–35.7%), similar to cardioembolic strokes (26.8%, 95% CI, 22.1%–31.5%), but significantly higher compared with all types of noncardioembolic stroke. One hundred seventy-two (62.5%) ESUS patients had favorable functional outcome compared with 280 (32.2%) in cardioembolic and 303 (60.9%) in large-artery atherosclerotic. ESUS patients had similar risk of composite cardiovascular end point as all other stroke types, with the exception of lacunar strokes, which had significantly lower risk (adjusted hazard ratio, 0.70 [95% CI, 0.52–0.94]).

Conclusions—Long-term mortality risk in ESUS is lower compared with cardioembolic strokes, despite similar rates of recurrence and composite cardiovascular end point. Recurrent stroke risk is higher in ESUS than in noncardioembolic strokes. (***Stroke.*** **2015;46:2087-2093. DOI: 10.1161/STROKEAHA.115.009334.)**

Key Words: embolic stroke of undetermined source ■ ESUS ■ mortality ■ outcome ■ stroke recurrence

A new clinical entity termed Embolic Stroke of Undetermined Source (ESUS) was recently introduced by the Cryptogenic Stroke/ESUS International Working Group, which describes stroke patients for whom the source of embolism remains undetected despite recommended investigation; potential embolic sources include the mitral and aortic valves, the left cardiac chambers, the proximal cerebral arteries of the aortic arch, and the venous system via paradoxical embolism.[1] ESUS has been proposed as a potential therapeutic entity with an indication for anticoagulation, a hypothesis which is currently tested in randomized controlled trials.[2,3]

Recently, we presented a descriptive analysis of an ESUS population originating from the Athens Stroke Registry.[4] Among the overall stroke population, 10% of patients were classified as ESUS.[4] These strokes were of mild–moderate severity, and covert atrial fibrillation (AF) was identified as the underlying etiopathogenetic mechanism in ≈40% of ESUS patients.[4]

In routine clinical practice, and based on randomized studies,[5,6] the vast majority of ESUS patients are treated with antiplatelets for secondary stroke prevention. However, given that covert AF is the underlying pathogenesis in ≈40% of

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The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.115.009334/-/DC1.

Correspondence to George Ntaios, MD, MSc (ESO Stroke Medicine), PhD, FESO, Assistant Professor of Internal Medicine, Department of Medicine, Larissa University Hospital, School of Medicine, University of Thessaly, Larissa, Greece. E-mail gntaios@med.uth.gr

Stroke **is available at http://stroke.ahajournals.org**

DOI: 10.1161/STROKEAHA.115.009334

Ntaios, Michel et al. Stroke 2015

ESUS: Potential embolic sources

Covert Atrial Fibrillation

Cancer associated

- Covert non-bacterial thrombotic endocarditis
- Tumour emboli from occult cancer

Arteriogenic emboli

- Aortic arch atherosclerotic plaques
- Cerebral artery non-stenotic plaques with ulceration

Paradoxical embolism

- Patent foramen ovale
- Atrial septal defect
- Pulmonary arteriovenous fistula

Minor-risk potential cardioembolic sources

Mitral or Aortic valve

- Myxomatous valvulopathy with prolapse
- Mitral annular calcification
- Aortic valve stenosis or Calcific aortic valve

Non-AF atrial dysrhythmias and stasis

- Atrial asystole and sick-sinus syndrome
- Atrial high-rate episodes
- Atrial appendage stasis with reduced flow velocities or spontaneous echodensities

Atrial structural abnormalities

- Atrial septal aneurysm or Chiari network

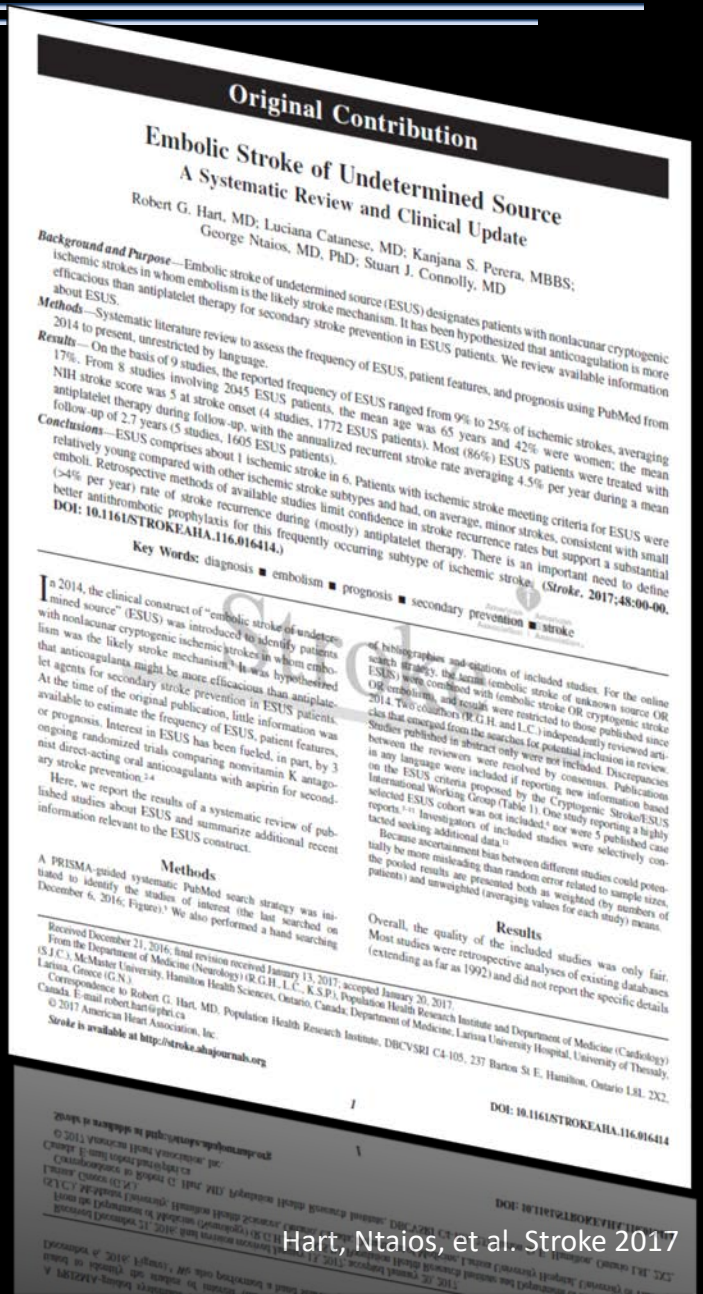
Left ventricle

- Moderate systolic or diastolic dysfunction (global or regional)
- Ventricular non-compaction or Endomyocardial fibrosis

Hart, et al. Lancet Neurol. 2014

ESUS: 90% are treated with antiplatelets

Study	Antithrombotic Therapy	AF During Follow-Up†	Stroke (Est Annualized Rate)†
Ntaios et al[13,26]‡	74% APT only, 22% OAC	80 (29%)	6.8%/y
Li et al[15]	NR	NR	≈5%/y
Putaala et al[16]‡	85% APT, 11% OAC	NR	5.1%/y
Ntaios et al[24]‡	87% APT only, 12% OAC	NR	4.8%/y‖
Masina et al[12]¶	99% APT	NR	2.3%/y
Ueno et al[22]#	72% APT, 29% OAC	NR	3.9%/y
Arauz et al[23]††	91% APT, 5% OAC	NR	2.3%/y
Pooled – unweighted average‡,††	87% APT, 12% OAC	…	4.0%/y
Pooled – weighted average‡,††	86% APT, 13% OAC	…	4.5%/y


Original Contribution

Embolic Stroke of Undetermined Source

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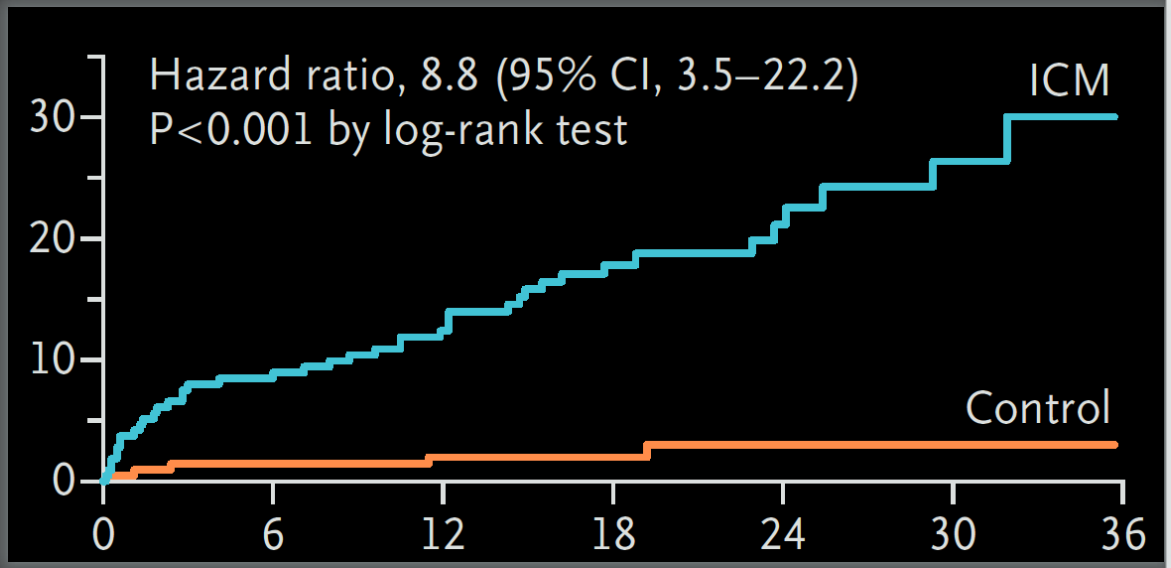
Hart, Ntaios, et al. Stroke 2017

New AF after stroke without cause (CRYSTAL – AF)



THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cryptogenic Stroke and Underlying Atrial Fibrillation

Tommaso Sanna, M.D., Hans-Christoph Diener, M.D., Ph.D., Rod S. Passman, M.D., M.S.C.E., Vincenzo Di Lazzaro, M.D., Richard A. Bernstein, M.D., Ph.D., Carlos A. Morillo, M.D., Marilyn Mollman Rymer, M.D., Vincent Thijs, M.D., Ph.D., Tyson Rogers, M.S., Frank Beckers, Ph.D., Kate Lindborg, Ph.D., and Johannes Brachmann, M.D., for the CRYSTAL AF Investigators*

ABSTRACT

BACKGROUND

Current guidelines recommend at least 24 hours of electrocardiographic (ECG) monitoring after an ischemic stroke to rule out atrial fibrillation. However, the most effective duration and type of monitoring have not been established, and the cause of ischemic stroke remains uncertain despite a complete diagnostic evaluation in 20 to 40% of cases (cryptogenic stroke). Detection of atrial fibrillation after cryptogenic stroke has therapeutic implications.

METHODS

We conducted a randomized, controlled study of 441 patients to assess whether long-term monitoring with an insertable cardiac monitor (ICM) is more effective than conventional follow-up (control) for detecting atrial fibrillation in patients with cryptogenic stroke. Patients 40 years of age or older with no evidence of atrial fibrillation during at least 24 hours of ECG monitoring underwent randomization within 90 days after the index event. The primary end point was the time to first detection of atrial fibrillation (lasting >30 seconds) within 6 months. Among the secondary end points was the time to first detection of atrial fibrillation within 12 months. Data were analyzed according to the intention-to-treat principle.

RESULTS

By 6 months, atrial fibrillation had been detected in 8.9% of patients in the ICM group (19 patients) versus 1.4% of patients in the control group (3 patients) (hazard ratio, 6.4; 95% confidence interval [CI], 1.9 to 21.7; P<0.001). By 12 months, atrial fibrillation had been detected in 12.4% of patients in the ICM group (29 patients) versus 2.0% of patients in the control group (4 patients) (hazard ratio, 7.3; 95% CI, 2.6 to 20.8; P<0.001).

CONCLUSIONS

ECG monitoring with an ICM was superior to conventional follow-up for detecting atrial fibrillation after cryptogenic stroke. (Funded by Medtronic; CRYSTAL AF ClinicalTrials.gov number, NCT00924638.)

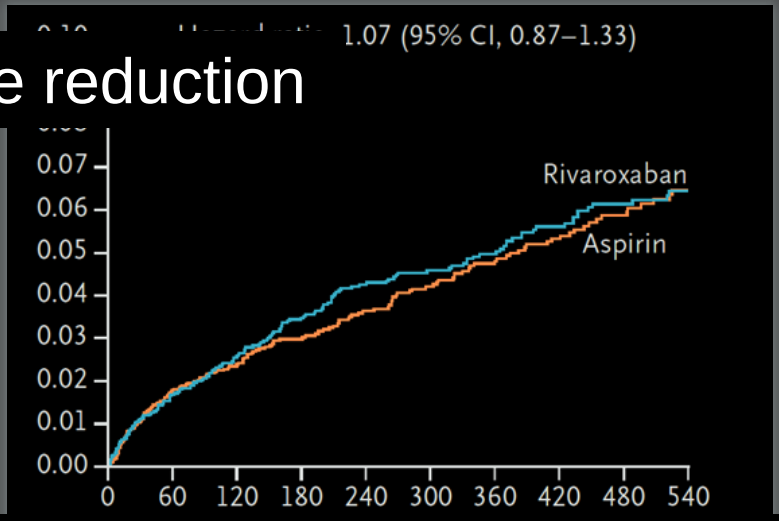
From the Catholic University of the Sacred Heart, Institute of Cardiology (T.S.), and Institute of Neurology, Campus Bio-Medico University (V.D.L.) — both in Rome; the Department of Neurology and Stroke Center, University Hospital Essen, Essen (H.-C.D.), and Hospital Klinikum Coburg, Coburg (J.B.) — both in Germany; Teaching Hospital of the University of Würzburg, Würzburg (R.A.B.), Bluhm Cardiovascular Institute (R.S.P.) and Dawee Department of Neurology (R.A.B.), Northwestern University Feinberg School of Medicine, Chicago; Population Health Research Institute, McMaster University, Hamilton, ON, Canada (C.A.M.); University of Kansas Medical Center, Kansas City (M.M.R.); the KU Leuven Department of Neurosciences, the VIB-Vesalius Research Center, and the Department of Neurology, University Hospitals Leuven — all in Leuven, Belgium (V.T.); Medtronic, Mounds View, MN (T.R., K.L.); and Medtronic, Maastricht, the Netherlands (F.B.). Address reprint requests to Dr. Sanna at the Institute of Cardiology, Catholic University of the Sacred Heart, Largo A. Gemelli 8, 00168 Rome, Italy, or at tommaso.sanna@rm.unicatt.it.

*A complete list of the Cryptogenic Stroke and Underlying AF (CRYSTAL AF) trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

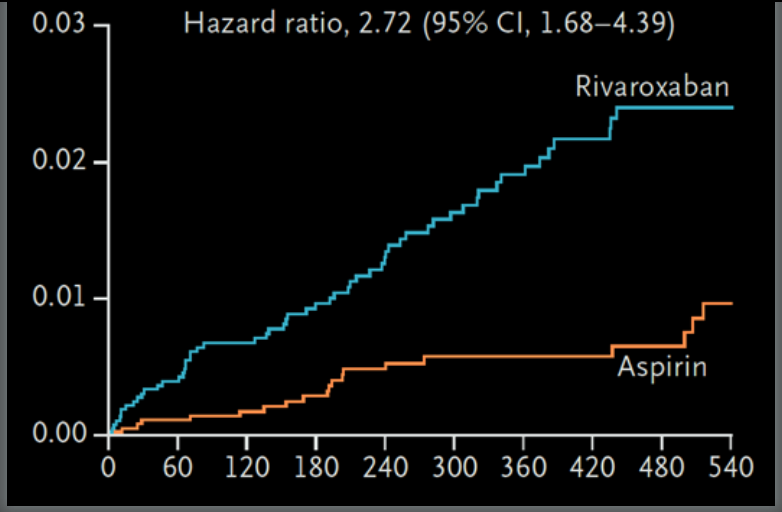
N Engl J Med 2014;370:2478-86.
DOI: 10.1056/NEJMoa1313600

NAVIGATE ESUS

Stroke reduction



Hemorrhage risk



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*

ABSTRACT

BACKGROUND

Embolic strokes of undetermined source represent 20% of ischemic strokes and are associated with a high rate of recurrence. Anticoagulant treatment with rivaroxaban, an oral factor Xa inhibitor, may result in a lower risk of recurrent stroke than aspirin.

METHODS

We compared the efficacy and safety of rivaroxaban (at a daily dose of 15 mg) with aspirin (at a daily dose of 100 mg) for the prevention of recurrent stroke in patients with recent ischemic stroke that was presumed to be from cerebral embolism but without arterial stenosis, lacune, or an identified cardioembolic source. The primary efficacy outcome was the first recurrence of ischemic or hemorrhagic stroke or systemic embolism in a time-to-event analysis; the primary safety outcome was the rate of major bleeding.

RESULTS

A total of 7213 participants were enrolled at 459 sites; 3609 patients were randomly assigned to receive rivaroxaban and 3604 to receive aspirin. Patients had been followed for a median of 11 months when the trial was terminated early because of a lack of benefit with regard to stroke risk and because of bleeding associated with rivaroxaban. The primary efficacy outcome occurred in 172 patients in the rivaroxaban group (annualized rate, 5.1%) and in 160 in the aspirin group (annualized rate, 4.8%) (hazard ratio, 1.07; 95% confidence interval [CI], 0.87 to 1.33; P=0.52). Recurrent ischemic stroke occurred in 158 patients in the rivaroxaban group (annualized rate, 4.7%) and in 156 in the aspirin group (annualized rate, 4.7%). Major bleeding occurred in 62 patients in the rivaroxaban group (annualized rate, 1.8%) and in 23 in the aspirin group (annualized rate, 0.7%) (hazard ratio, 2.72; 95% CI, 1.68 to 4.39; P<0.001).

CONCLUSIONS

Rivaroxaban was not superior to aspirin with regard to the prevention of recurrent stroke after an initial embolic stroke of undetermined source and was associated with a higher risk of bleeding. (Funded by Bayer and Janssen Research and Development; NAVIGATE ESUS ClinicalTrials.gov number, NCT02313909.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Hart at the Population Health Research Institute, David Braley Cardiac, Vascular, and Stroke Research Institute, Hamilton, ON L8L 2X2, Canada, or at robert.hart@phri.ca.

*A complete list of the NAVIGATE ESUS Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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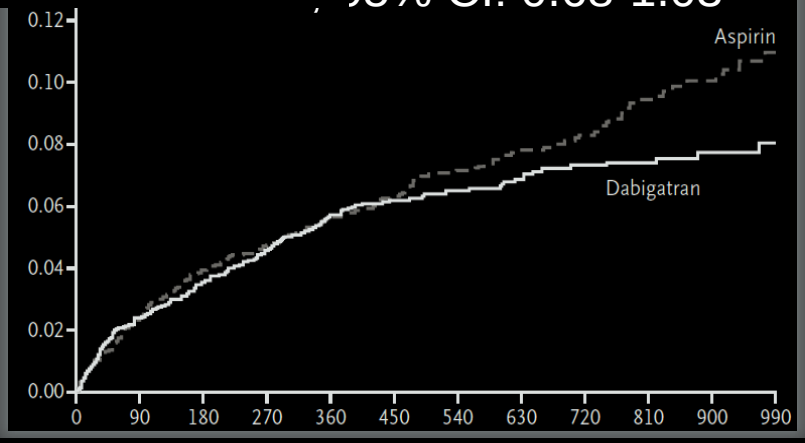
Hart, et al. NEJM 2018

RE-SPECT ESUS

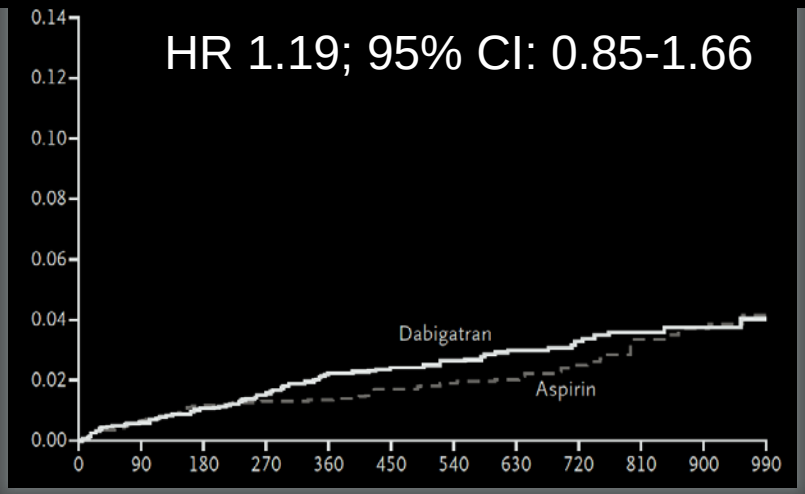
Stroke reduction

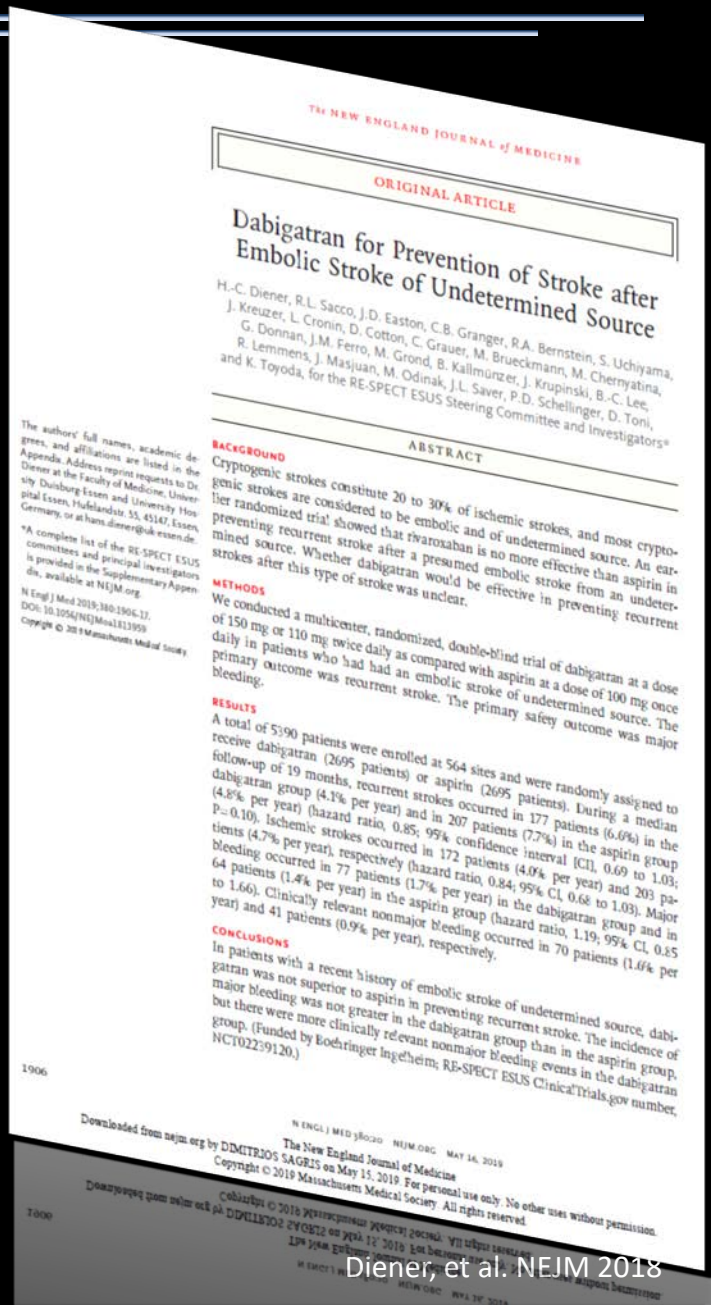
95% CI: 0.68-1.03



Hemorrhage risk

HR 1.19; 95% CI: 0.85-1.66





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dabigatran for Prevention of Stroke after Embolic Stroke of Undetermined Source

H.-C. Diener, R.L. Sacco, J.D. Easton, C.B. Granger, R.A. Bernstein, S. Uchiyama, J. Kreuzer, L. Cronin, D. Cotton, C. Grauer, M. Brueckmann, M. Chernyatina, G. Donnan, J.M. Ferro, M. Grond, B. Kallmünzer, J. Krupinski, B.-C. Lee, R. Lemmens, J. Masjuan, M. Odinak, J.L. Saver, P.D. Schellinger, D. Toni, and K. Toyoda, for the RE-SPECT ESUS Steering Committee and Investigators*

ABSTRACT

BACKGROUND

Cryptogenic strokes constitute 20 to 30% of ischemic strokes, and most cryptogenic strokes are considered to be embolic and of undetermined source. An earlier randomized trial showed that rivaroxaban is no more effective than aspirin in preventing recurrent stroke after a presumed embolic stroke from an undetermined source. Whether dabigatran would be effective in preventing recurrent strokes after this type of stroke was unclear.

METHODS

We conducted a multicenter, randomized, double-blind trial of dabigatran at a dose of 150 mg or 110 mg twice daily as compared with aspirin at a dose of 100 mg once daily in patients who had had an embolic stroke of undetermined source. The primary outcome was recurrent stroke. The primary safety outcome was major bleeding.

RESULTS

A total of 5390 patients were enrolled at 564 sites and were randomly assigned to receive dabigatran (2695 patients) or aspirin (2695 patients). During a median follow-up of 19 months, recurrent strokes occurred in 177 patients (6.6%) in the dabigatran group (4.1% per year) and in 207 patients (7.7%) in the aspirin group (4.8% per year) (hazard ratio, 0.85; 95% confidence interval [CI], 0.69 to 1.03; P=0.10). Ischemic strokes occurred in 172 patients (4.0% per year) and 203 patients (4.7% per year), respectively (hazard ratio, 0.84; 95% CI, 0.68 to 1.03). Major bleeding occurred in 77 patients (1.7% per year) in the dabigatran group and in 64 patients (1.4% per year) in the aspirin group (hazard ratio, 1.19; 95% CI, 0.85 to 1.66). Clinically relevant nonmajor bleeding occurred in 70 patients (1.6% per year) and 41 patients (0.9% per year), respectively.

CONCLUSIONS

In patients with a recent history of embolic stroke of undetermined source, dabigatran was not superior to aspirin in preventing recurrent stroke. The incidence of major bleeding was not greater in the dabigatran group than in the aspirin group, but there were more clinically relevant nonmajor bleeding events in the dabigatran group. (Funded by Boehringer Ingelheim; RE-SPECT ESUS ClinicalTrials.gov number, NCT02239120.)

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*A complete list of the RE-SPECT ESUS committees and principal investigators is provided in the Supplementary Appendix, available at NEJM.org.

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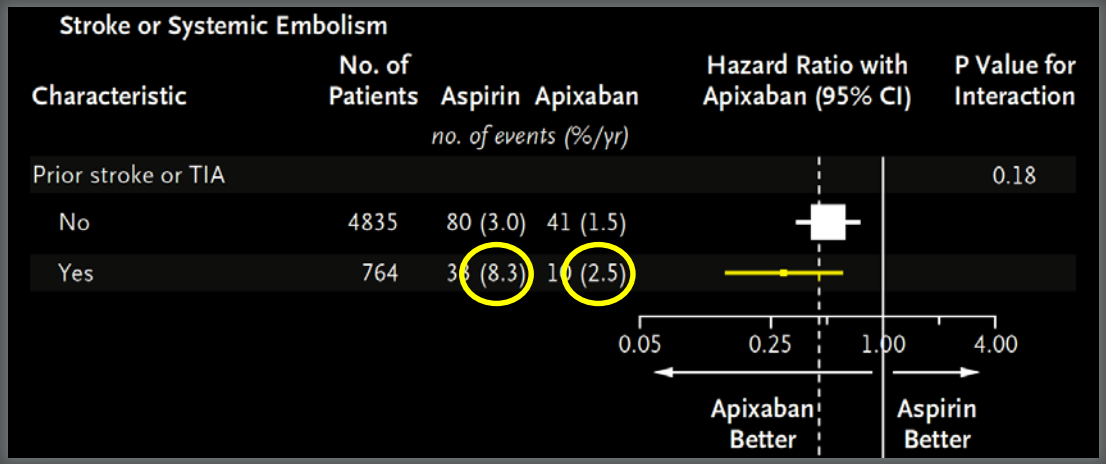
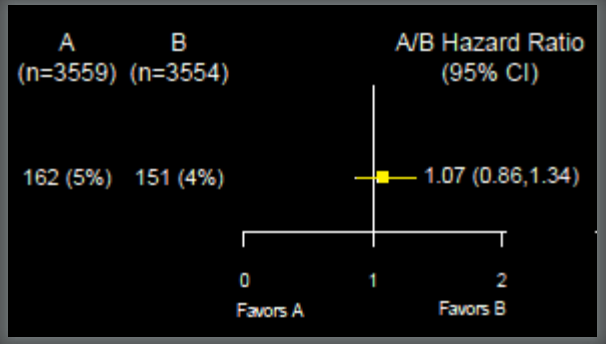
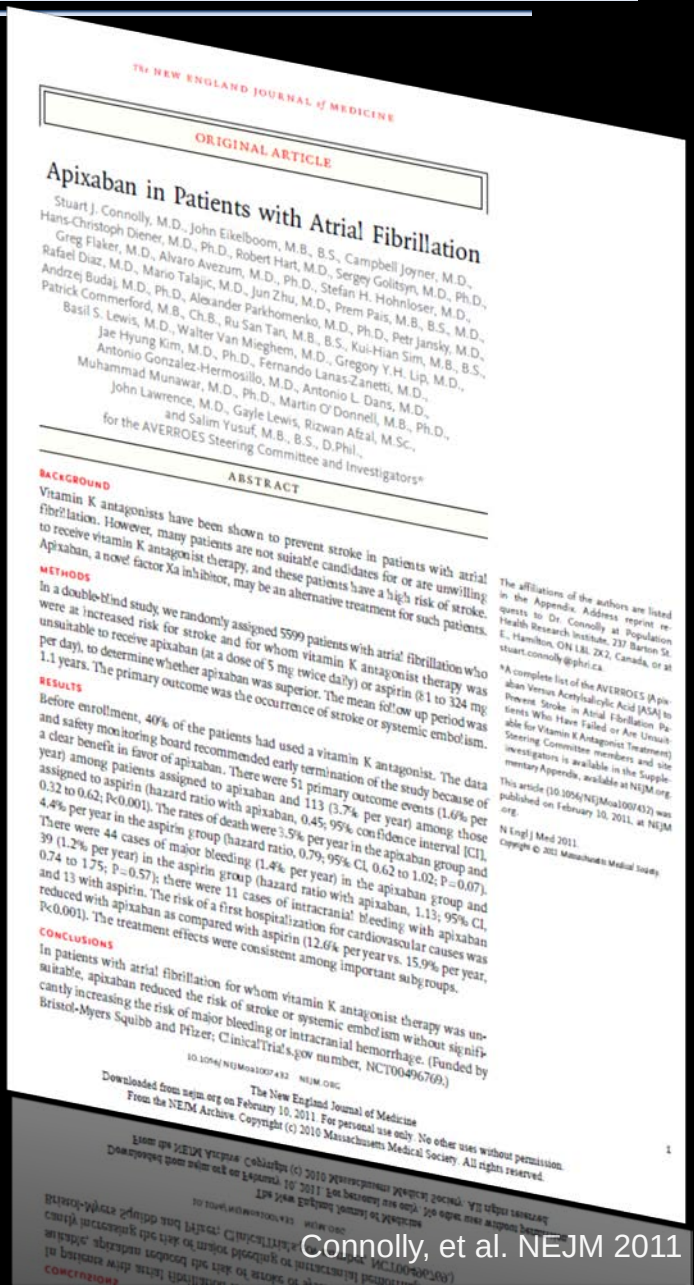
N ENGL J MED 380;20 NEJM.ORG MAY 16, 2019

Diener, et al. NEJM 2018

AVERROES






THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apixaban in Patients with Atrial Fibrillation

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ABSTRACT

BACKGROUND

Vitamin K antagonists have been shown to prevent stroke in patients with atrial fibrillation. However, many patients are not suitable candidates for or are unwilling to receive vitamin K antagonist therapy, and these patients have a high risk of stroke. Apixaban, a novel factor Xa inhibitor, may be an alternative treatment for such patients.

METHODS

In a double-blind study, we randomly assigned 5599 patients with atrial fibrillation who were at increased risk for stroke and for whom vitamin K antagonist therapy was unsuitable to receive apixaban (at a dose of 5 mg twice daily) or aspirin (81 to 324 mg per day), to determine whether apixaban was superior. The mean follow-up period was 1.1 years. The primary outcome was the occurrence of stroke or systemic embolism.

RESULTS

Before enrollment, 40% of the patients had used a vitamin K antagonist. The data and safety monitoring board recommended early termination of the study because of a clear benefit in favor of apixaban. There were 51 primary outcome events (1.6% per year) among patients assigned to apixaban and 113 (3.7% per year) among those assigned to aspirin (hazard ratio with apixaban, 0.45; 95% confidence interval [CI], 0.32 to 0.62; P<0.001). The rates of death were 3.5% per year in the apixaban group and 4.4% per year in the aspirin group (hazard ratio, 0.79; 95% CI, 0.62 to 1.02; P=0.07). There were 44 cases of major bleeding (1.4% per year) in the apixaban group and 39 (1.2% per year) in the aspirin group (hazard ratio with apixaban, 1.13; 95% CI, 0.74 to 1.75; P=0.57); there were 11 cases of intracranial bleeding with apixaban and 13 with aspirin. The risk of a first hospitalization for cardiovascular causes was reduced with apixaban as compared with aspirin (12.6% per year vs. 15.9% per year, P<0.001). The treatment effects were consistent among important subgroups.

CONCLUSIONS

In patients with atrial fibrillation for whom vitamin K antagonist therapy was unsuitable, apixaban reduced the risk of stroke or systemic embolism without significantly increasing the risk of major bleeding or intracranial hemorrhage. (Funded by Bristol-Myers Squibb and Pfizer; ClinicalTrials.gov number, NCT00496769.)

The affiliations of the authors are listed in the Appendix. Address reprint requests to Dr. Connolly at Population Health Research Institute, 237 Barton St. E., Hamilton, ON L8L 2X2, Canada, or at stuart.connolly@phri.ca.

*A complete list of the AVERROES (Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) Steering Committee members and site investigators is available in the Supplementary Appendix, available at NEJM.org.

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The New England Journal of Medicine

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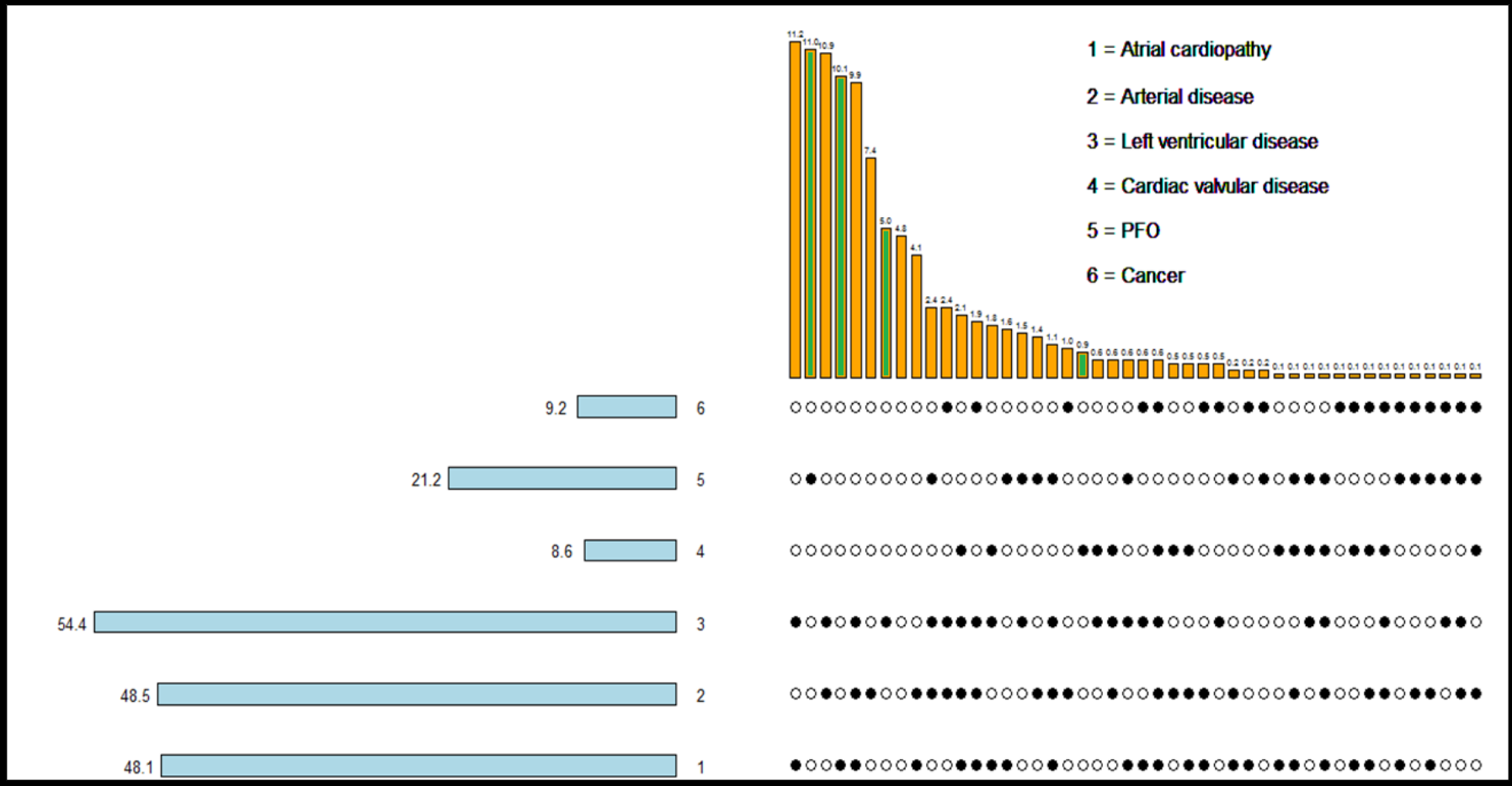
Connolly, et al. NEJM 2011

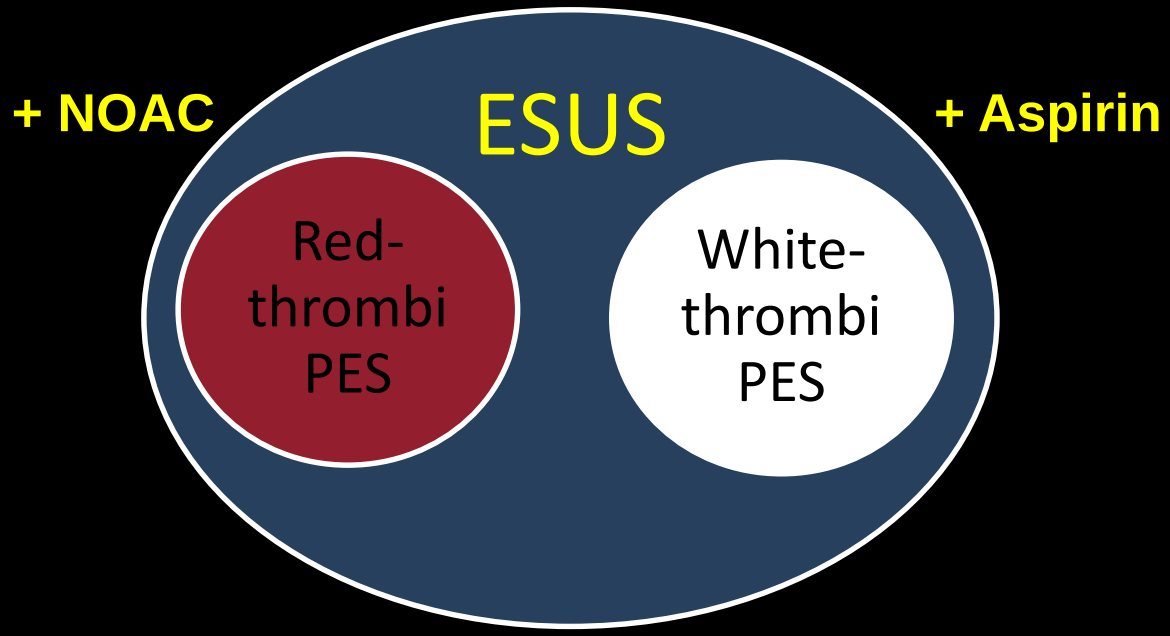
ESUS: red & white thrombi

ESUS: Overlap of potential embolic sources

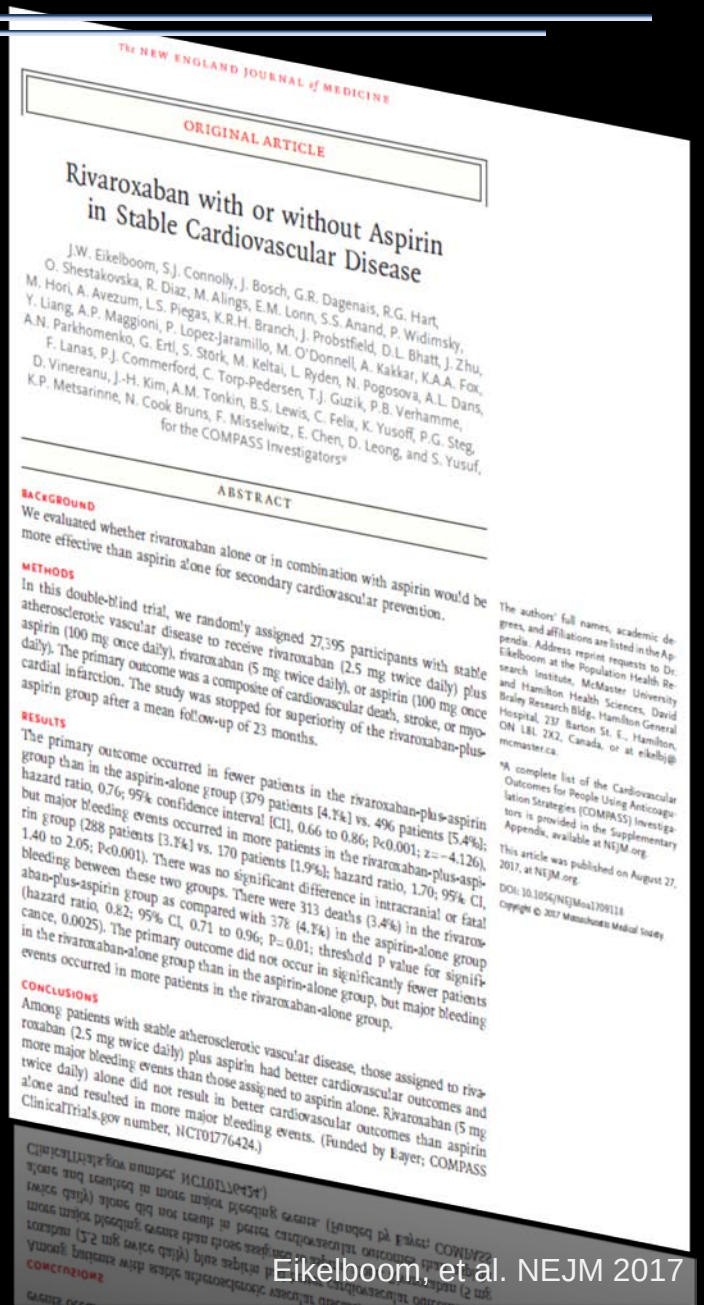


Ntaios, Michel, et al. JAHA 2019

ESUS: Implications for future research



	Hazard Ratio (95% CI)	P Value
Ischemic or uncertain type	0.51 (0.38–0.68)	<0.001
Major bleeding	1.70 (1.40–2.05)	<0.001
Net-clinical-benefit outcome: CV death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into critical organ	0.80 (0.70–0.91)	<0.001


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

J.W. Eikelboom, S.J. Connolly, J. Bosch, G.R. Dagenais, R.G. Hart, O. Shestakovska, R. Diaz, M. Alings, E.M. Lonn, S.S. Anand, P. Widimsky, M. Hori, A. Avezum, L.S. Piegas, K.R.H. Branch, J. Probstfield, D.L. Bhatt, J. Zhu, Y. Liang, A.P. Maggioni, P. Lopez-Jaramillo, M. O'Donnell, A. Kakkar, K.A.A. Fox, A.N. Parkhomenko, G. Ertl, S. Störk, M. Keltai, L. Ryden, N. Pogosova, A.L. Dans, F. Lanas, P.J. Commerford, C. Torp-Pedersen, T.J. Guzik, P.B. Verhamme, D. Vinereanu, J.-H. Kim, A.M. Tonkin, B.S. Lewis, C. Felix, K. Yusoff, P.G. Steg, K.P. Metsarinne, N. Cook Bruns, F. Misselwitz, E. Chen, D. Leong, and S. Yusuf, for the COMPASS Investigators*

ABSTRACT

BACKGROUND
We evaluated whether rivaroxaban alone or in combination with aspirin would be more effective than aspirin alone for secondary cardiovascular prevention.

METHODS
In this double-blind trial, we randomly assigned 27,395 participants with stable atherosclerotic vascular disease to receive rivaroxaban (2.5 mg twice daily), or aspirin (100 mg once daily), rivaroxaban (5 mg twice daily), or aspirin (100 mg once daily). The primary outcome was a composite of cardiovascular death, stroke, or myocardial infarction. The study was stopped for superiority of the rivaroxaban-plus-aspirin group after a mean follow-up of 23 months.

RESULTS
The primary outcome occurred in fewer patients in the rivaroxaban-plus-aspirin group than in the aspirin-alone group (379 patients [4.1%] vs. 496 patients [5.4%]; hazard ratio, 0.76; 95% confidence interval [CI], 0.66 to 0.86; P<0.001; z=−4.126), but major bleeding events occurred in more patients in the rivaroxaban-plus-aspirin group (288 patients [3.1%] vs. 170 patients [1.9%]; hazard ratio, 1.70; 95% CI, 1.40 to 2.05; P<0.001). There was no significant difference in intracranial or fatal bleeding between these two groups. There were 313 deaths (3.4%) in the rivaroxaban-plus-aspirin group as compared with 378 (4.1%) in the aspirin-alone group (hazard ratio, 0.82; 95% CI, 0.71 to 0.96; P=0.01; threshold P value for significance, 0.0025). The primary outcome did not occur in significantly fewer patients in the rivaroxaban-alone group than in the aspirin-alone group, but major bleeding events occurred in more patients in the rivaroxaban-alone group.

CONCLUSIONS
Among patients with stable atherosclerotic vascular disease, those assigned to rivaroxaban (2.5 mg twice daily) plus aspirin had better cardiovascular outcomes and more major bleeding events than those assigned to aspirin alone. Rivaroxaban (5 mg twice daily) alone did not result in better cardiovascular outcomes than aspirin alone and resulted in more major bleeding events. (Funded by Bayer; COMPASS ClinicalTrials.gov number, NCT01776424.)

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*A complete list of the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Eikelboom, et al. NEJM 2017

Take-home messages

Atrial fibrillation
- Aspirin for AF patients? → NO
- NOAC or VKA? → NOACs
- SAME-TTR to select oral anticoagulant? → Maybe, but not sure if improves outcomes
- When to restart OAC after ischemic stroke? → 1-3-6-12
- Is there a role for left atrial appendage occlusion? → If OAC is contraindicated, perhaps
- Carotid filter for stroke prevention? → Too premature

Heart failure with sinus rhythm
- Is there a role for OAC? → No

Atherosclerotic stroke
- low-dose rivaroxaban & aspirin → Significant net clinical benefit
- LDL targets → <55mg/dl (1.42mmol/l)

Minor strokes
- Dual antiplatelet treatment: for how long? → ~3 weeks

PFO
- Closure or medical treatment? → Closure for <60years, especially if higher risk PFOs
- OAC or aspirin in non-closed PFOs? → Aspirin

ESUS
- ESUS vs. cryptogenic → ESUS
- NAVIGATE ESUS and RE-SPECT ESUS results → Negative
- Potential explanation and implications for future research → overlap of red & white thrombi