Update: Prevention after Stroke

George Ntaios

Department of Internal Medicine

University of Thessaly, Larissa, Greece







Disclosures

Speaker fees/Advisory Boards/Research support

Amgen; Bayer; BMS/Pfizer; Boehringer-Ingelheim; Elpen; European Union;

Galenica; Sanofi; Winmedica

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?

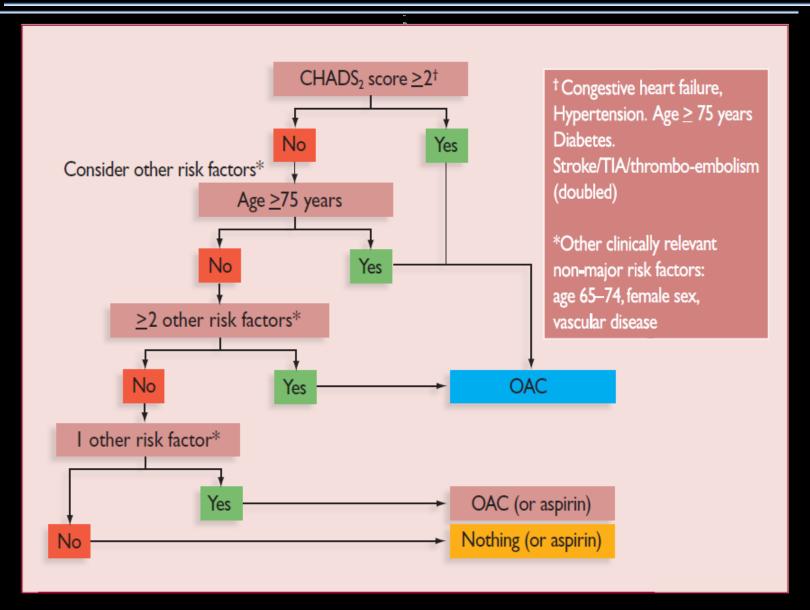
PFO

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

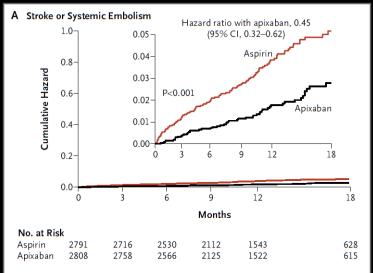
ESUS

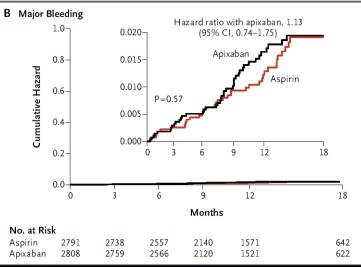
- ESUS vs. cryptogenic
- NAVIGATE ESUS and RE-SPECT ESUS results
- Potential explanation and implications for future research

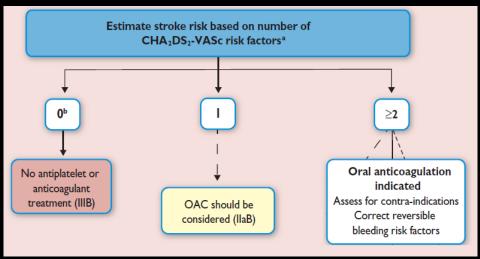
Aspirin for AF patients? -ESC Guidelines 2010

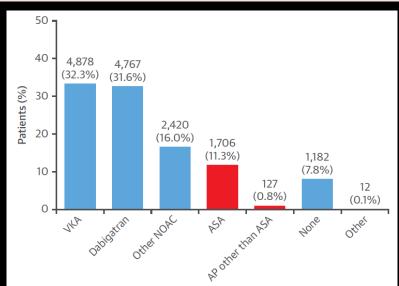


Aspirin for AF patients? –AVERROES & ESC Guidelines 2016

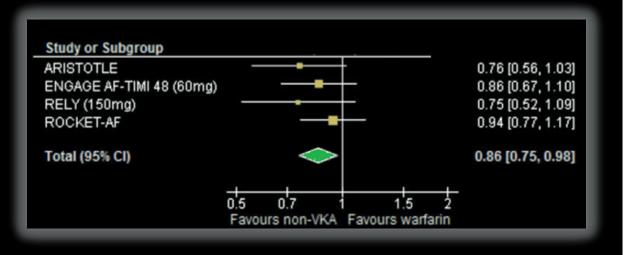


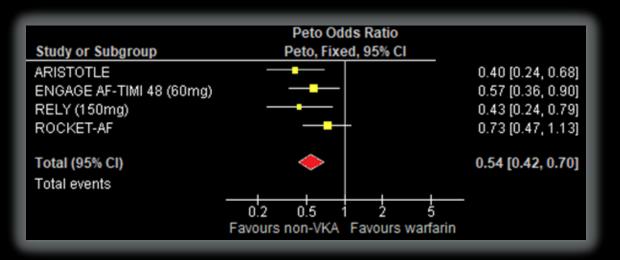






NOAC vs. VKA?







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

(C) Still Motid Strake Ordanization Region and person OR STILLINGSHALLINGS craft tamput con/bond/an SAGE

George Ntaios¹, Vasileios Papavasileiou², Hans-Chris Diener³,

Abstract
Background: In a previous systematic review and meca-analysis, we assessed the efficacy and safety of nonvitamin-K
assaurates and areasonal-bree versus worthin in oxionit with serial febrillation and stroke or transient inchemic attack. Background: In a previous systematic review and meta-analysis, we assessed the efficacy and safety of nonwtamin-K arraignists oral anexcoagulates. Versus warfarin in pazients with atrial fibrillation and stroke or transient is chemic attack.

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: Methods: We searched PubMed until 24 August 2016 for randomized controlled trait using the following search generations and "anticopylation" and "warfarm" and "previous stroke or transient ischemic attack." Bigble usides had to be obese ill reals in pasents with atrial far-libation companies warfarin with nonvitamin. R. angeolegy. "arrial fibrillation" and "anticoagulation" and "warfarin" and "previous stroke or transient ischemic attack." Bigble under a superconductor of the marker or with the supersion on he because to the marker in Morth Armarion or he because to the marker in Morth Armarion or he because to the marker in Morth Armarion or he marker in Morth Armarion or he was a supersion or he because to the marker in Morth Armarion or he was a supersion or h studies had to be phase III trials in patients with atrial fibrillation comparing warfarin with nonvitamin-K artagonist forces. The outcomes assessed in the efficacy analysis included stroke or systemic embodism. Stroke bethere or systemic embodism. Stroke bethere or oral anticoagulants currendy on the market or with the intersion to be brought to the market in North America or Europe. The outcomes assessed in the efficacy analysis included stroke or systemic embolism, stroke, itchnical currence, cardiovascular death, death from any cause, sand more cardiovascular death, death from any cause, sand more cardiovascular death, death from any cause, sand more cardiovascular death. Europe. The outcomes assessed in the efficacy analysis included stroke or systemic embolism, stroke, technic or unknown stroke, disabling or fatal stroke, hemorrhagic stroke, cardiovascular death, death from any cause, and myone acceptance accepted in the cases and procedure included major blanders are accepted and major blanders.

unknown stroke, disabling or fatal stroke, hemorrhagic stroke, cardiovascular death, death from any cause, and myo-cardial infarction. The outcomes assessed in the safety analysis included major bleeding, intracranial bleeding, and major assessment of the safety analysis on intension-to-treat basis. Results: Anong 183 potentially eligible articles, four were included in the meta-analysis. In 20,500 patients, compared to use a service of which a standard reduction of a meta-analysis and a meta-analysis. Results: Among 183 potentially eighle articles, four were included in the meta-analysis. In 20,500 patients, compared to warfarin, nonvicamin-K, antagonist oral anticoagulants were associated with a significant reduction of stroke/systemic ambolism (relative risk reduction; 13.7%, absolute risk reduction; 0.78%, number needed to treat to prevent one events. warfarin, nonvitamin-K anagonist oral articologulans 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 of the should be absolute and reduction 0.78%, number needed to treat to prevent one event of the should be absolute and reduction 0.78% or number of the should be absolute and reduction 0.78% or number of the should be absolute and reduction 0.78% or number of the should be absolute and reduction 0.78% or number of the should be absolute and reduction 0.78% or number of the should be absolute and reduction 0.78% or number of the should be absolute as the reduction 0.78% or number of the should be absolute as the reduction 0.78% or number of the should be absolute as the reduction 0.78% or number of the should be absolute as the reduction 0.78% or number of the should be absolute as the reduction 0.78% or number of the should be absolute as the reduction 0.78% or number of the should be absolute as the reduction 0.78% or number of the should be absolute as the reduction 0.78% or number of the should be a should be absolute as the reduction 0.78% or number of the should be absolute as the reduction 0.78% or number of the should be a should be as the reduction 0.78% or number of the should be a should be as the reduction 0.78% or number of the should be a should be as the reduction 0.78% or number of the should be a should be as the reduction 0.78% or number of the should be a should be as the reduction 0.78% or number of the should be a should be a should be a should be a should be as the reduction 0.78% or number of the should be a should be

embolism (relative risk reduction: 13.7%, absolute risk reduction: 0.78%, number needed to treat to prevent one event.

127), hemorrhapic twoise (relative risk reduction: 50.0%, absolute risk reduction: 0.63%, number needed to treat to prevent one event.

228, hemorrhapic risk enduction: 13.1%, absolute risk reduction: 0.7%, number needed to treat to prevent one event.

239, sumber needed to treat 1570, number needed 1570, n 127), hemorrhagic stroke (relative risk reduction: 50.0%, absolute risk reduction: 0.63%, number needed to treat 157), and stroke (relative risk reduction: 0.1%, number needed to treat 157), hemorrhage (relative risk reduction: 0.88%, number needed to treat 143), and stratarial relative risk reduction: 0.88%, number needed to treat 143), and stratarial relative risk reduction: 0.88%, number needed to treat 157). any stroke (relative risk reduction: | 3,1% absolute risk reduction: 0,7% number needed to treat: | 42), and intracranial | 1,8-2,8 years | 1,

Conclusions: This updated meta-analysis in 20,500 arrial fibrillation patients with previous stroke or transfer inches associated an approximation of an approximation of an approximation of a second of the approximation of th Conclusions: This updated meta-analysis in 20,500 atrial for littion patients with previous tricks or transfer exchemic attack shows that compared to worker non-vitament. Anagonist oral anticoagulants are associated with a significant conclusion of etroks, stroke or switemic embeliant, hemorrhapic stroke, and intracranial bleeding.

Received: 3 November 2016; accepted: 6 February 2017

Introduction

In a previous systematic review and meta-analysis, we in a previous systematic review and meta-analysis, we assessed the officacy and safety of nonvitamin-k arriage anassess are energy and source of nonvironment amage onist oral anticologidants (non-VKAs) versus warfarm onist oral anticoaguiants (non-vr-Ass) versus warrarin in patients with atrial fibrillation (AF) and stroke or

Department of Medicine, University of Thesaly, Larina Grace Other make or Prescrip, University of Thesatoy, Larina, Grance Stroke Service, Department of Nanococierces, Leads Techniq Hospital, NAS Trust and Prescriptions, Leads Techniq Hospital, Nasaccas, Advanced Conference and Leads Conference (Leads Links, UK). here is no reason school, there are or Least Least Un.
Department of Neurology and Stroke Center, University Hospital Baser

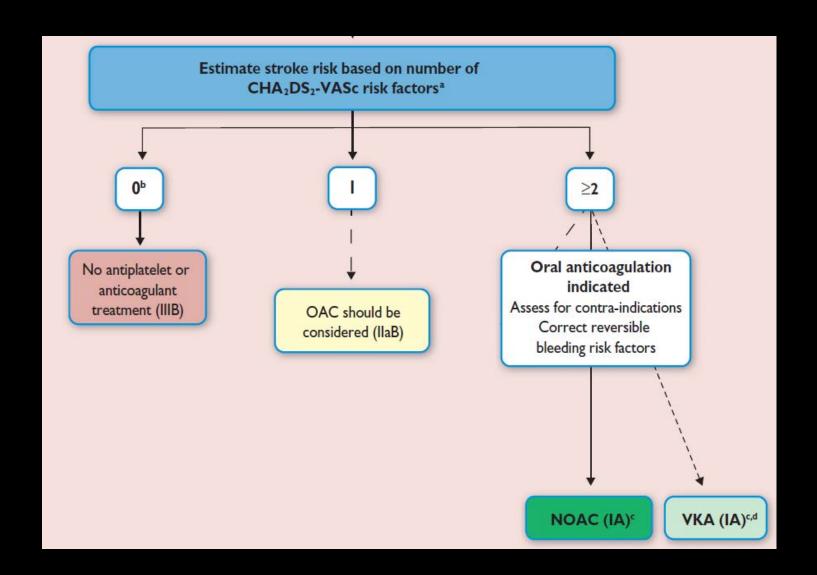
tases, cermany
Stocks Center Centre Hospitalier Universitate Vasidos and University

Corresponding author: George Nasce, Department of Medicine, University of Thessaly, Lanssa.

International Journal of Stroke, 0(0)

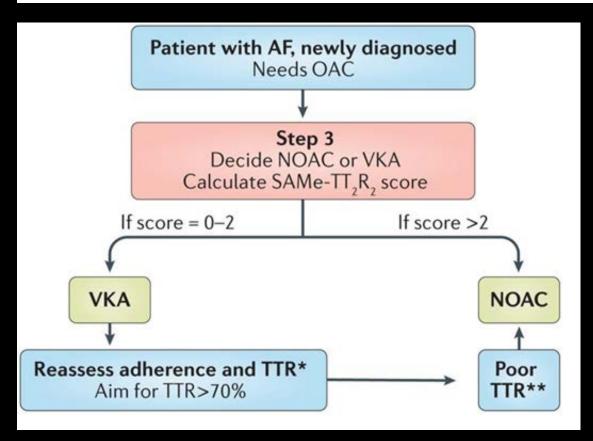
Ntaios, Michel et al. Int J Stroke 2017

NOAC vs. VKA? – ESC Guidelines 2016

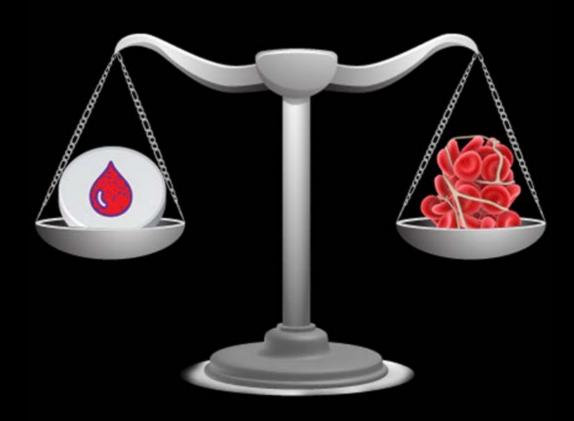


SAME-TT₂R₂ for OAC selection

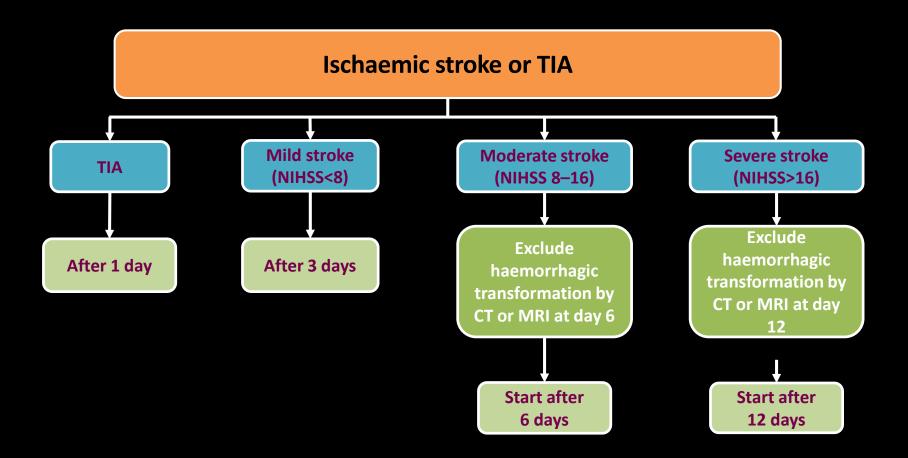
Condition/influencing factor	Points
Sex (female)	1
Age (<60 years)	1
Medical history (history of more than two of the following: hypertension, diabetes, CAD, PAD, heart failure, stroke; pulmonary, hepatic, or renal disease)	1
Treatment (interacting medications e.g. amiodarone)	1
Tobacco use (within 2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



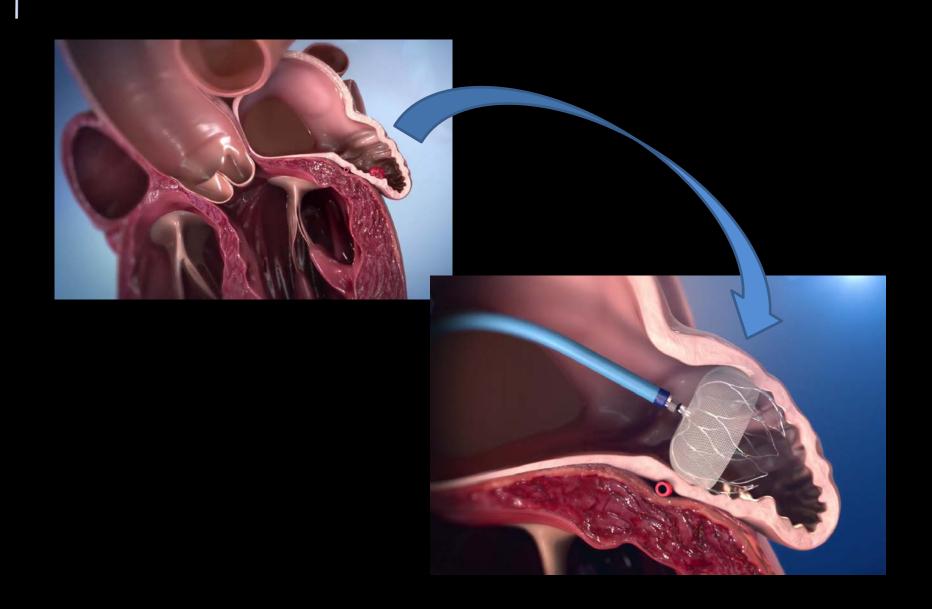
Start anticoagulants - how soon (or late)?



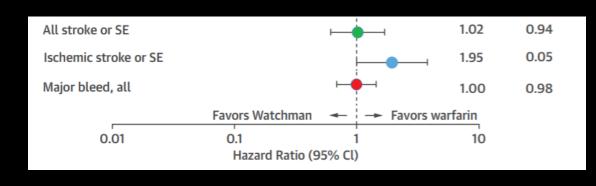
Start anticoagulants - how soon (or late)? / 1-3-6-12



Left atrial appendage occlusion



Left atrial appendage occlusion vs. OAC



ADERNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY FORWARD OF THE AMERICAN COLLEGE OF CANDIDLOUP

8 2005 BY THE AMERICAN COLLEGE OF CANDIDLOUP

CANDIDLOU

VOL. 65, NO. 24, 2015 MIN // de der out les MIN / 1840 5015 ON 552 15 SN 07 25-10 97/\$56.00

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



David R. Holmes, Js., MD.* Shephal K. Doshi, MD. | Saibal Kar, MD.; Matthew I. Price, MD.; Jose M. Sanchez, MD.

BACKGROUND The risk-benefit ratio of left atrial appendage closure (LAAC) versus systemic therapy (warfarin) for 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 nonvalvatar atrial fibrillation (NVAF) requires

OBJECTIVES This study sought to assess composite data regarding left atrial appendage closure (LAAC) in 2 ran-OBJECTIVES This study sought to assess composite data regarding left atrial appendage closure ILAAC) as 2 ran-domitted trials. Compared to worthin for prevention of stroke, systemic embolism, and cardiovascular death in potents

METHODS Our meta-analysis included 2,406 patients with 5,939 patient-years (PV) of follow-up from the PROTECT AF METHODS Our meta-analysis included 2,406 patients with 5,931 patient-years (PY) of follow-up from the PROTECT.

(Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fortilation) and PREVAR. (Vestchman Left Atrial Appendage System for Embolic Protection in Patients with Afrike Fibribation) and PREVAIK

(Prospective Randomized Evaluation of the Watchman LAA Closure Device in Patients With Afrike Fibribation) and PREVAIK

Facility States of States and States of Sta (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

RESULTS With mean follow-up of 2.69 years, putients receiving LAAC with the Watchmundevice had significantly fewer RESULTS With mean follow-up of 2.69 years, patients receiving UAXC with the Watchman device had significantly fewer benchmans strokes (0.75 vs. 0.96 events/100 patient-years [PV]; hazard ratio [Hit]: 0.22; p = 0.004); card oxiously fewer consensations of the consensation of the consens bencomagic strokes (0.15 vs. 0.96 events/100 pittent-years [PY]: bazard rato [HR]: 0.22; p = 0.004), cardiovascular/
unexplained death (1.1 vs. 2.3 events/100 PY; HR: 0.48; p = 0.006), and neutrocedural bleeding (6.0% vs. 11.3%; HR: unexplained death (1.1 vs. 2.3 eventy/100 PY; HE: O.AR; p = 0.006), and nonprocedural bleeding (6.0% vs. 11.3%; HR: 0.31; p = 0.006) compared with warfarin. All-clause stroke or systemic embodism was similar between both strategies. 0.31; p = 0.006) compared with warfaro. All-cause stroke or systems: embolism was similar between both strategies (1.75 vs. 1.87 evers.n/00 pY; HR: 1.02; 95% CI: 0.52 to 1.7; p = 0.94). There were more ischemic strokes in the dryke (1.75 VE. 1.87 events/100 PY; HR: 102; 95% CI: 0.62 to 1.7; p = 0.94). There were more licherisc strokes in the device grap (1.6 VE. 0.9) and 0.2 VE. 1.0 events/100 PY; HR: 1.95 and 0.22, respectively; p = 0.05 and 0.004, respectively).

CONCLUSIONS In patients with NVAF at increased risk for stroke or bleeding who are candidates for chronic antico-

CONCLUSIONS In patients with INVAF at increased risk for stroke or biseding who are candidates for clinoxic analogs agalation, LAAC residited in improved rates of hemorrhogic stroke, cardiovascular/unexplained death, and nonprocedural structure for the cardiovascular for the agulation, LAAC resided in improved rates of hemorrhagic stroke, cardiova scular/unexplained death, and nonprocedural bleeding compared to warfarin. (J Am Coll Cardiol 2015;65:2614-23) to 2015 by the American College of Cardiology

From the *Mayo Clinic, Roches ter, Minnesonia; 102, John 's Health Genere, 'Batta Monica, California; (Octava Simul Medical Genere, Los Angelia, California; (Octava Simul Medical Genere, Harring, St. Lean, Manager, California; (Octava Simul Medical Genere, St. Lean, Manager, C From the 'Mayo Claix, Roches Br., Manesota; Dr. John's Health Genter, Surra Monko, California; (Colars Strait Medical Content.)

Los Angeles, California; (Surpeys Claic, La Solta, California; (Mercy Hoopera, St. Lossa, Manoure, Scard ownershall content.)

Furt, Sarat Kalbarreno, Frankfurt, Gennaly; Scheduckie Housea, Housea, Texac; and the "Monte Sinca School of Markota." Los Angeles, California; (Scrippe Clear, La John, California; (Mercy Hospita), 28. Liota, Manouri, Cardiovesculai Gener Frank-furt, Sanit Katharren, Frankfurt, Generary; &tentidae Hospita, Houseon, Trixer and the "salous tima tichool of Mariana. New York, New York, Dr. Holmes and the Mayo Clear have a featural intension in technology solubed to the remarks the sector. furt, Sankt Kaburnen, Frankfurt, Gernany, disebudist Hospiral, Housino, Tricari and the "Mosine Sinai School of Medicine New York, New York, Dr. Helmes and the Mayo Clinic have a featural intense in Inchesionary missed to distributed, the nations has been licensed to Roston Schoolfiel. Dr. Dodd has received meanth grants and consultant feat from such the sect-New York, New York, Dr. Belma and the Mayo Chric have a fearcial intense in including shaded to the emerged and one of the Common Sciences. Dr. Books has received mountain principal fearest and emeasure fear from the second value of the Commons Access from Books Namedo, nology has been beened to Boston Scientific Dr. Dodd has treed ved measure gravits and consultant fees from Boston Scientific.

22. July Marical, Coheste, and Septemberry, and is the Justical promptyd investigator of the Community Research Scientific Sc st, Judé Malkal, Cobern, and SenteHeart, and is the hadonal principal Investigator of the Communis Acean Registry EAP2.

Dr. Kar has received research genera from Boston Scientific, 12. Judé Modecal, and Abbort Vaccular; is a Rember of Sente Acean Registry EAP2.

Description of the Acean Registry EAP2.

The Acean Registry EAP2 and Configurate Acean Registry EAP2.

The Acean Registry EAP2 and Configurate Acean Registry EAP2.

The Acean Registry EAP2 and Configurate Acean Registry EAP2.

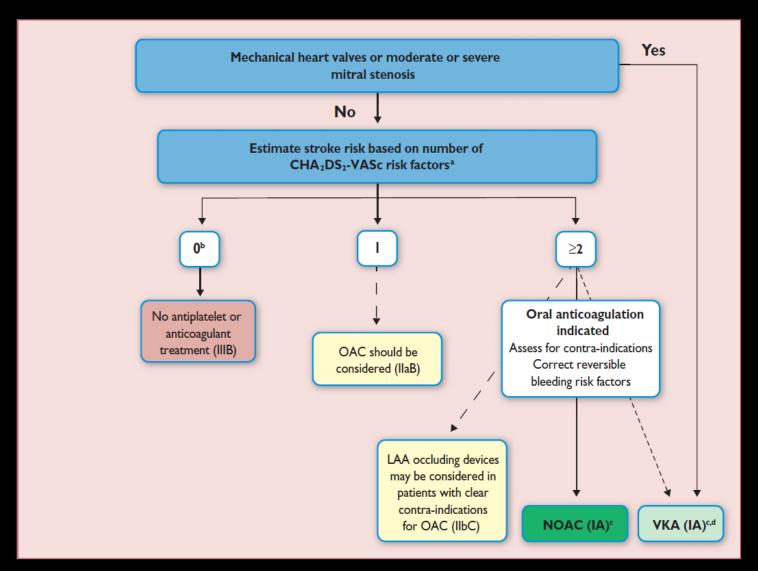
The Acean Registry EAP2 and Configurate Acean Registry EAP2. Dr. Kar has received resourch general from Boston Indentific, St. Jude Mederal, and Abbest Vaccular, in a member of the abstract particle and a process for Boston Scientific owns quarry to Cohenit, and is a consultant for Abbest Vaccular. In Price has board for left axial appendage doming is the national principal investigator of the Continuous Acress Sequences (EAP and CAP7).

In served as a Procur for Somes Assemble, to west squary to Cohema; and is a commission for Abbon Vaccular, the Price And Sequences (EAP and CAP7).

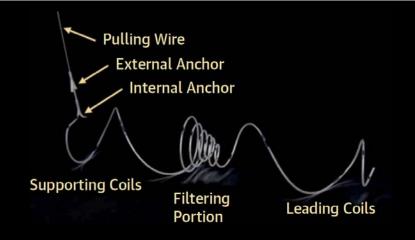
Received consulting bosonicaris from Board Naturals, 2s. hade Mod.cl. laterate Planta as for Abbon Vaccular, the Price And Sequences (EAP and CAP7). has served at a process for Romen Scientific, owns equity to Cohemes and it a considerer for Abbote Vaccidar, the Price bit received containing homeway from Romen Viertific, 32, hade Medical, homeon Pharmacheck, thinksh Saringo, Tremes, but License and his tenthsten Romens required a timo certifien Romen Scientific, 32, hade Medical, and Medical and Me received consulting knowards from Roston Scientife, St. Julie Medical, Jameses Flasmac at Real, Datch Analysis, Terrano, and W.J., Gores and the tentilition received research support from Roston Scientific, St. Julie Medical, and Sentralizari Dr. Rosson James Base accessed consultant from Society James Base accessed consultant from Society James Base accessed code before Society Society Scientific, St. Julie Medical, and Sentralizari Dr. Rosson James Base accessed code before Society Socie W.L. Gores and his institution mentions transach support from Boston Sciencelic, St., Jude Medical, and SectorMeart, Dr. Natocher. Dr. Nature has necessed study honoraris, stravel on process, committing free

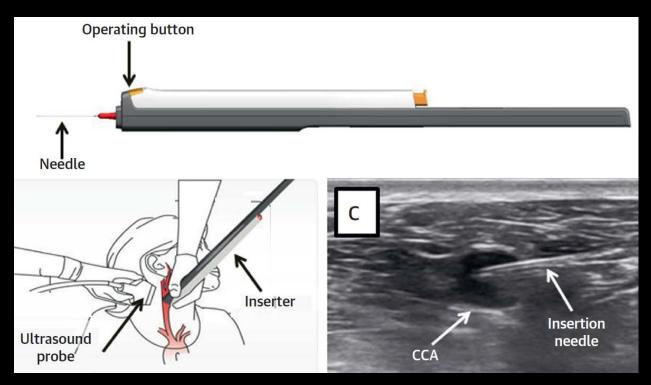
Holmes, et al. JACC 2015

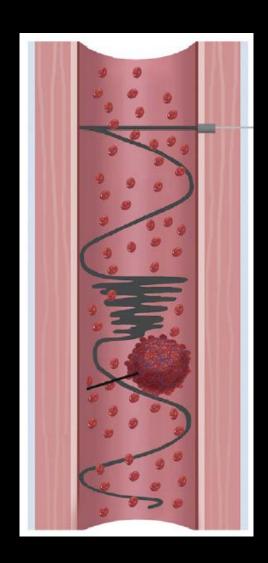
Left atrial appendage occlusion – ESC Guidelines 2016



Carotid filter for stroke prevention







Agenda

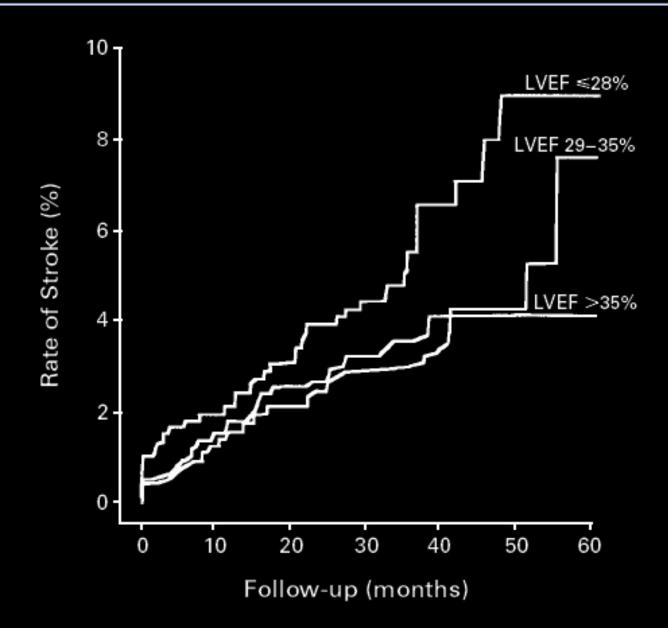
Atrial fibrillation

- 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

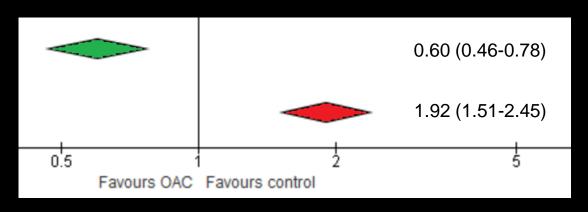
- Is there a role for OAC?

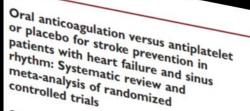
Heart failure with sinus rhythm: a prothrombotic condition



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

Green: stroke reduction hemorrhage risk Red:





and present of Street

© 2019 Morriel Stroke Disparation Article rescue quidelines: collection than being the beautiful to the second DOI: 18.1179/JANASSISSITEM \$SAGE

George Ntaios | 6, Konstantinos Vemmos | and Gregory

Abstract
Background: Previous meta-analyses of randomized controlled trish of oral anticoagulation in patients with heart failure
and store absolute analyses of randomized controlled trish of oral anticoagulation in patients with heart failure
to decrease and store and store and store and the st Background: Previous meta-analyses of randomized controlled trials of oral anocoagulation in patients with heart talure and sinus rhythm reported reduced stroke risk and increased bleeding risk compared to antiplatelets or placebo. However, the effect estimates may be subject to innorecision, as all included trials were prematurely terminated, stroke was not the 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, at all included trials were prematurely terminated; stroke was not be a stroke trial. Recently, the property of t

the effect estimates may be subject to imprecision, as all included trials were prematurely terminated; stroke was not to 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 Aim: To provide more accurate estimates of the effect of oral anticoagulation on stroke risk in heart failure patients with an expension of stroke risk in heart failure patients with an expension of stroke risk in cluding recently published.

Methods: We searched PubMed and Scopus for full-text articles of randomized controlled trials of oral anticoagulation according to all the pubments of the same fallows assisted with allowed between inversely and 28 August Methods: We searched PubMed and Scopus for full-text articles of randomized controlled trials of oral anticoagulation and R. The outcomes accessed source and streets, ensure bleasture. And death, Results: In five trials (9490 patients; 21,067 patient-years), oral anticoagulation-treated patients had lower stroke risk running (CB) 0.40 9000 0.44.0 78 absolute make reductions: 1.30 months and descriptions of 130 months and the contract of 130 months and 130 months

Results: In five traits (9490 patients; 21.067 patient-years), oral anticoagulation-treated patients had lower stroke risk (948, 0.66, 95%CE 0.46-0.78; absolute-risk-reduction: 1.3%; number-needed-to-treat: 77), higher major and on simulfactures of the control Codds ratio (OR) 0.60, 95%Ct: 0.46–0.78, absolute-risk-reduction: 1.3%, humber-needed-to-treat: 77), higher major and death ratio of the non-section of the no-section of the non-section of the non-section of the non-sectio Conclusions: In the largest meta-analysis to date, oral anticoagulation is associated with a considerable reduction of structure in the control of the contr 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 anti-parameter date anticoagulation rather date anticoagulation rather date anticoagulation rather date anticoagulation is associated with a considerable reduction of anticoagulation rather date anticoagulation is associated with a considerable reduction of anticoagulation rather date and anticoagulation is associated with a considerable reduction of anticoagulation rather date and anticoagulation is associated with a considerable reduction of anticoagulation and anticoagulation is associated with a considerable reduction of anticoagulation rather date and anticoagulation is associated with a considerable reduction of anticoagulation rather date and rather date stroke risk, which is offset by a significant increase in major bleeding risk. For every 1000 patients treated with oral additional major hemorrhages occur, without significant difference in death rates.

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

Introduction

The well-established association between heart failure the wearestacountary association between occur same (HF) and ischemic stroke is mainly mediated by thromtriry and nearence strong a manny measurem by marine by degrees which is pathophysiologically explained by nogenesis minco in patan-payaonganany capanana vy Virchow's triad. The low cardiac output, the dilated yarmawa tinar. The now carease output one outside chambers, and the poor contractility result in "abnormal" channers, and me poor contracting term in aconomic flow, which is coupled with structural heart abnormalnors, which is couped who seructural reast absorbina-ities "vessel wall absormalities" and thirdly, "absormnics vesses was autoremattees and unevery, standardishies of blood flow," i.e. hemostasis and platelets and

Department of Internal Medicine, Faculty of Medicine, Sobool of Mexico. General University or Themap, Larena, Greece
Science, University of Berningham, Bresngham, United Kangdon

Benneyton, United Kirpton
Limposi Catera to Cardonacular Sonnes, University of Literpool Services where the Committee Services and Committee or Services and United Services the Unippos Heart & Unit Hoppos, Unippos, United Angelon
Ashborg Thromboss Research, Unit, Department of Chical Medicine,
Ashary Lineaus, Ashara, Passasa,

Corresponding author:
George Nazos, Department of Internal Medicine, Faculty of Medicine,
Google Nazos, Communication of Internal Medicine,
Google School of Health Sciences, University of Thessay, Larins, Gresce,

International Journal of Stroke, O(0)

Ntaios, et al. Int J 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?
- Carotid filter for stroke prevention?

Heart failure with sinus rhythm

- Is there a role for OAC?

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, myo- cardial 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, J.W. Eixeldoom, S.J. Connolly, J. Dosch, G.R. Dagenars, R.G. Trais,
O. Shestakovska, R. Diaz, M. Alings, E.M. Lonn, S.S. Anand, P. Widimsky, U. Snestakovska, R. Diaz, M. Alings, E.M. Lonn, S.S. Anano, P. Wiolmsky, M. Hori, A. Avezum, L.S. Piegas, K.R.H. Branch, J. Probstfield, D.L. Bhatt, J. Zhu, V. Lang, A.D. Manning, D. Long, Languille, at Pythonoglia, Voltage V.A.A. Eco. Y. Liang A.P. Maggioni, P. Lopez-Jaramillo, M. O'Donnell, A. Kakkar, K.A.A. Fox. Y, Liang, A.P., Maggioni, P., Lopez-Jaramillo, M. O'Donnett, A., Kakkar, K.A.A., FOR, A.N., Parkhomenko, G., Ertl, S., Stork, M., Keltai, L. Ryden, N., Pogosova, A.L. Dans, Company, A.L. Dans, Company, C., Carle, C. R., Vanhamman, C., Carle, C. R., Vanhamman, C., Carle, C. R., Vanhamman, C., Carle, C. R., Car 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. Fela, K. Yusoff, P.G. Steg. K.P., Metsarinne, N. Cook Bruns, F. Misselwitz, E. Chen, D. Leong, and S. Yusuf,

BACKGROUND

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

In this double-blind trial, we randomly assigned 27,395 participants with stable assignment vaccination vaccination of the process of the pro In this double-brind trial, we randomly assigned 27,395 participants with stable atherosclerotic vascular disease to receive fivarousban (2.5 mg twice daily) plus Brainy Research Bidg. Humbon General Respiral 232 Batton St. E. Humbon General ameroscierous vascular disease to receive rivaroxaban [2.5 mg twice daily) plus Brainy Research Bidg. Hamfloon General aspirin (100 mg once daily), rivaroxaban (5 mg twice daily), or aspirin (100 mg once Heapina, 237 Barton St. T. Hambloon General Association of Control of C care to the primary outcome was a composite or carmovascular ucita, subset, or myo-cardial infarction. The study was stopped for superiority of the rivaroxaban-plus-

The primary outcome occurred in fewer patients in the rivaroxaban-plus-aspirin The primary outcome occurred in newer patients in the rivaroxanan-pais-aspiring group than in the aspirin-alone group (379 patients [4, %] by, 496 patients [5,4%]). group tran in the aspiring arone group (3/7 parions 14/18) vs. 470 parions (3/7 parions 16/18) vs. 470 hazaro istan, w.o.; y.o.; contrastive interval; it.i., w.o. to u.o.; recumul; z=-4.120).

but major bleeding events occurred in more patients in the rivarcaban-plus-app.

sin common (1949 residuate 17 84.1 or 170 residuate 18 08.1. Language and 1.3 70. corp., 17 but major toccume creates occurred in more patients in the rotational patients in group (288 patients [3, Fk] vs. 170 patients [1,9%]; hazard ratio, 1.70; 95% Cl. 1.40 to 2.05; Pc0.001). There was no significant difference in intractanial or fatal Low to 2405; reconcept, latter was no significant unitatives in instantance or take bleeding between these two groups. There were 313 deaths (3.4%) in the rivators about the configuration of the con bleeding between these two groups. There were 313 deaths (3.4%) in the rivarous aban-plus-aspirin group as compared with 378 (4.5%) in the aspirin-along group as compared with 378 (4.5%) in the aspirin-along group of the state anar-pus-aspura group as compared with 376 (4.7%) in the aspuratione group (hazard ratio, 0.82; 95% CL, 0.71 to 0.96; P=0.01; threshold P value for significance occurs and occurs of the pushing of the (nazard ratio, 0.8.2; 95% Cd, 0.71 to 0.56; P=0.01; threshold P value for significancy from primary outcome did not occur in significantly free patients in the sension should be sension be sension by sension Mandrians. tance, 0.00423), the primary outcome out not occur in agenticanny rever parents in the fivaronaban-alone group than in the aspirin-alone group, but major bleeding

Among patients with stable atherosclerotic vascular disease, those assigned to riva-ronanan (2.5 mg twice daily) pius aspirm nad better cardiovascular outcomes anu more major bleeding events than those assigned to aspirin alone. Rivaronaban i musico Action along and action and the second in house confluenced to retrogram above assigned. more major occume corns man more assigned to aspun asone. Kvationaran to invite daily) alone did not result in better cardiovascular outcomes than aspirer twice daily) alone did not result in Detter Cardiovascular outcomes than aspiring abone and resulted in more major bleeding events. (Funded by Eayer; COMPASS)

ON LEL 2X2, Canada, or at elsebj®

M complete list of the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) Investigaors is provided in the Supple Appendix, available at NEJM org.

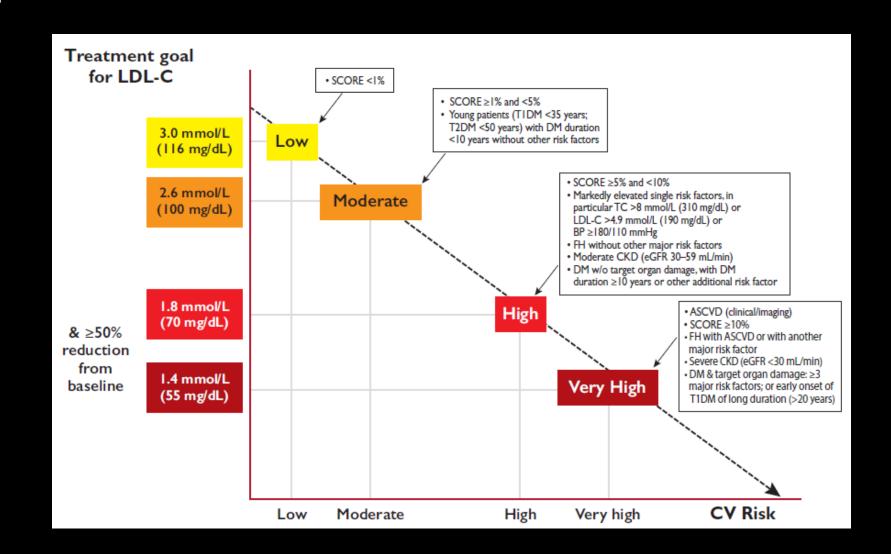
This article was published on August 27, 2017, at NEJM.org.

DOI: 10.1056/NEJMoa1709118 Copyright © 2017 Mattachand to Medical Society

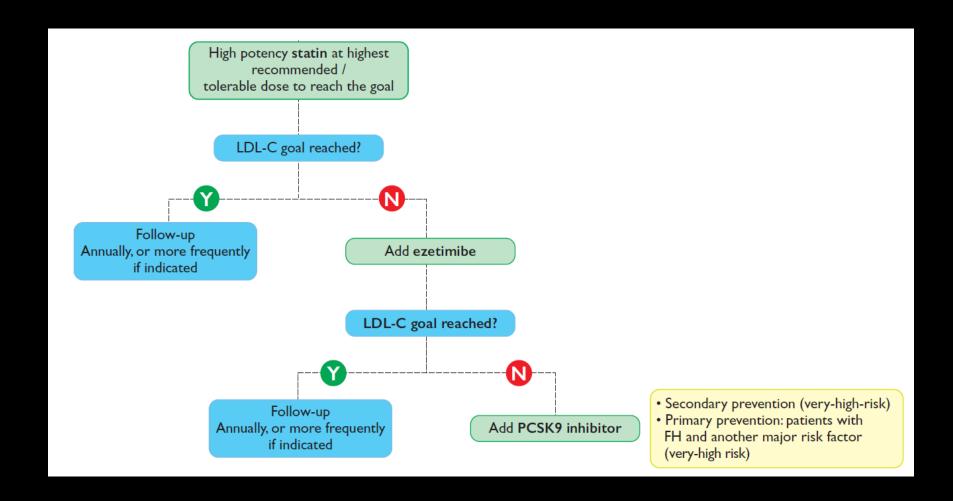
Chaicaltrials.gov number, NCIV1776424.)

Among panents with several plants as a plant based by Enject; COMPAN and Texture and results the action and results in peter cardiovascular to come of the plants of the p

Atherosclerotic strokes: LDL targets



Algorithm for LDL management



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?

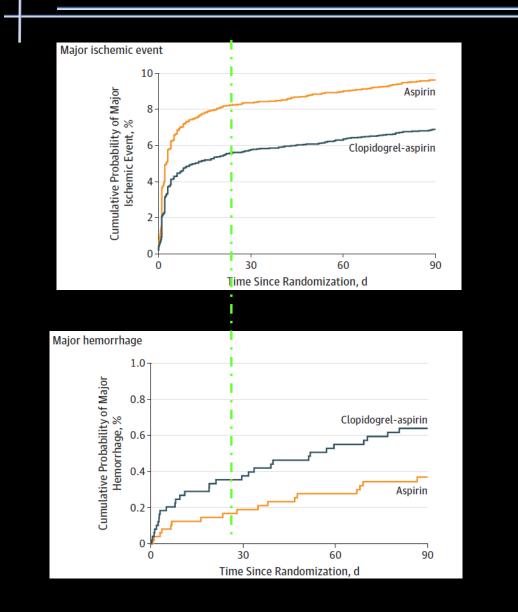
Atherosclerotic stroke

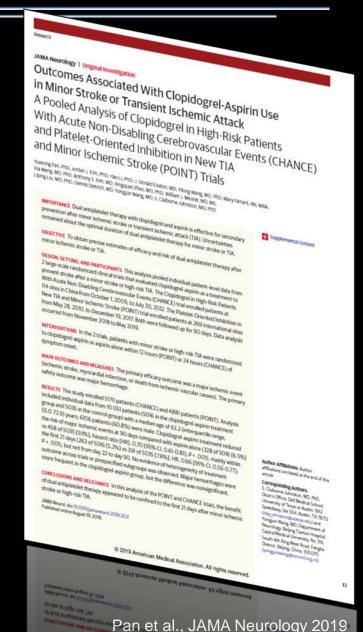
- low-dose rivaroxaban & aspirin
- LDL targets

Minor strokes

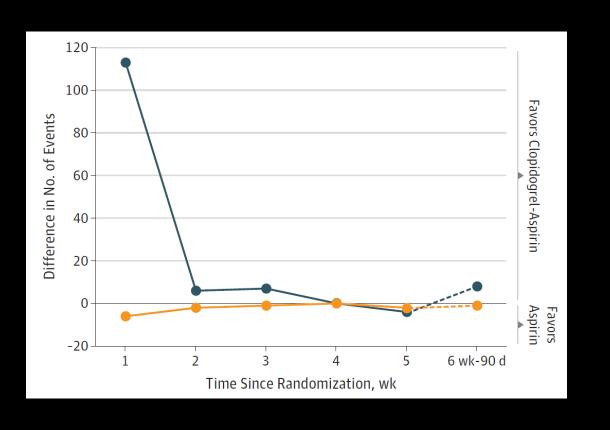
Dual antiplatelet treatment: for how long?

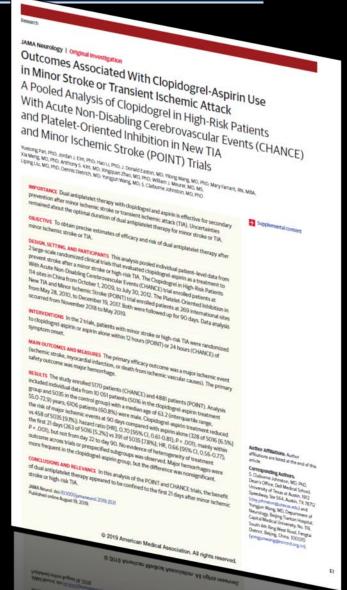
Dual antiplatelet in the early phase of minor stroke





Dual antiplatelet in the early phase of minor stroke





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

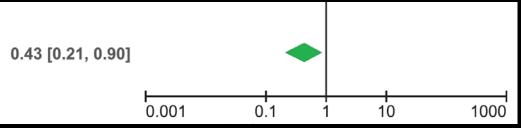
Dual antiplatelet treatment: for how long?

PFO

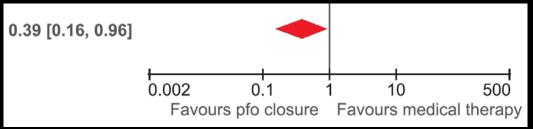
- Closure or medical treatment?
- OAC or aspirin in non-closed PFOs?

PFO closure

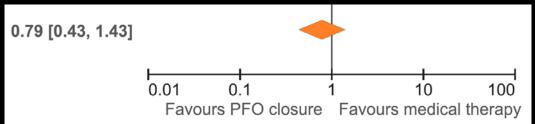
Green: stroke reduction all patients



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 Vemmos, MD; Thorsten Steiner, MD; Patrik Michel, MD Background and Purpose—Previous systematic reviews and meta-analyses compared the efficacy and safety of patent foreamous conductive fo lackground and Purpose—Previous systematic reviews and meta-analyses compared the efficacy and safety of patent foramen ovable (PFO) closure versus medical treatment in patients with cryptogenic stroke or transient schemic attack. (TIA). Recently, new evidence from randomized trials became available.

Methods—We searched PubMed until September 24, 2017, for trials comparing PFO closure with medical treatment in a strong control of the control of trials comparing processing available and resource of the control of trials comparing processing available and resource of trials and resource of tr Jethods.—We searched PubMed until September 24, 2017, for trials comparing PFO closure with medical treatment in patients with cryptogenic stroke/TTA using the items: stroke or cerebrovascular accident or TTA and patent foramen ovale

or paradoxical embolism and trial or study.

Results—Among 851 identified articles, 5 were eligible. In 3627 patients with 3.7-year mean follow-up, there was significant or the following attacks recovering to the following country of \$3,000 to the following cou Finally—Among 851 identified articles, 5 were eligible. In 3627 patients with 3.7-year mean follow-up, there was significant confidence in ischemic stroke recurrence (0.53 versus 1.1 per 100 patient-years, respectively; odds ratio [OR], 0.43; 95% absolute fisk reduction, 2.11%; and number needed to difference in ischemic stroke recurrence (0.53 versus 1.1 per 100 patient, years, respectively; odds ratio [OR], 0.43; 95% confidence intervals (CI), 0.21–0.90; relative risk reduction, 5.0.5%; absolute risk reduction, 2.11%; and number need to a received 1 moset 46.5 for 3.7 versus 1.7 there was no alomificant differences in TLAX(IC) 78 versus 0.08 new 100 inflorms, versus 0.00 for the resulting to the resulting of the resulting to the resulting to the resulting of the resulting to the resulting to the resulting of the resulting to the resulting to the resulting of the resulting to the resulti confidence intervals (CI), 0.21–0.90; relative risk reduction, 50.5%; absolute risk reduction, 2.11%; and number needed to treat to prevent 1 event, 46.5 for 3.7 years). There was no significant difference in TLAs (0.78 versus 0.98 per 100 patient-versus preventionly CIR to see the contractive of the versus 0.98 per 100 patient-versus per patient versus pe treat to prevent I event, 46.5 for 3.7 years). There was no significant difference in TLAs (0.78 versus 0.98 per 100 patient-years, respectively; OR, 0.80; 95%; CI, 0.53, -1.19) and all cause mortality (0.18 versus 0.23 per 100 patient-years, respectively, or 1.7 v. 0.60; CI (1.74, 1.74). Moreovers stead flivitlation occurrence freezuments in the ptt? cleaners are (1.74 versus 0.75 Over 1.74). respectively; OR, 0.80; 95% CI, 0.53–1.19) and all-cause mortality (0.18 versus 0.23 per 100 pulsent-years, respectively; OR, 0.75; 95% CI, 0.34–1.56). New-onset atrial fibrillation occurred more frequently in the PFO closure arm (1.3 versus 0.25 per 100 pulsent-years, respectively; OR, 5.15; 95% CI, 2.18–12.15) and resolved in 72% of cases within 4.5 days, whenever place.

0.73; 95% CT, 0.34–1.56). New-onset atrial fibrillation occurred more frequently in the PFO closure arm (1.3 versus 0.25 per 100 patient-years, respectively; OR, 5.15; 95% CT, 2.18–12.15) and resolved in 72% of cases within 45 days, whereas rate of new 100 patient-years restoration (1.1) versus 0.10 per 100 patient-years restoration (1.2) versus 0.10 per 100 patient-years restoration (1.2) versus 0.10 per 100 patient-years restoration (1.2) versus 0.25 per 100 per 100 patient-years restoration (1.2) versus 0.25 per 100 per 100 patient-years restoration (1.2) versus 0.25 per 100 per 100 patient-years restoration (1.2) versus 0.25 per 100 p 100 patient-years, respectively; OR, 5.15; 95% CI, 2.18–12.15) and resolved in 72% of cases within 45 days, whereas fales of thousand output (7.3 versus 0.00) per 100 patient-years, respectively; OR, 1.22; 95% CI, 0.25–5,01) and any serious adverse overst (7.3 versus 7.3 ver 100 rationt-years, respectively; OR, 1.07; OKG, CT, 0.02–1.25; versus similar. adverse events (7.3 versus 7.3 per 100 patient-years, respectively; OR, 1.07; 95% CI, 0.92–1.25) were similar.

Conclusions—In patients with cryptogenic stroke/TIA and PFO who have their PFO closed, techenic stroke recurrence is less from a compared with national sensitiving moderal treatment. Arrival about the formula best records from the control of the control onchristons—In patients with cryptogenic stroke/HA and PFO who have their PFO closed, ischemic stroke recurrence is less frequent compared with patients receiving medical treatment. Afrial fibrillation is more frequent but mostly transfer.

There is no difference in TLA all-cause mountainty of mycocardial information. (Stroke 2018; 40:113.41), 170.11. 10.11.51.11. less frequent compared with patients receiving medical treatment. Atrial fibrillation is more frequent but mostly transient. There is no difference in TLA, all-cause mortality, or myocardial infarction. (Stroke, 2018;49:412-418, DOI: 10.1161/

Key Words: embolism, paradoxical ■ foramen ovale, patent ■ ischemic attack, transient ■ meta-analysis ■ review

nameu us a suprancana proposition or patiento with user-emic stroke and terms like cryptogenic or embolic stroke of one stoke and sering has exproperate of enhance stoke of undetermined source are continuely used to describe these angermanea source are commonly used to ocscine toose cases. Patent foramen ovale (PFO), a frequent finding in the general population is considered a possible underly. ng mechanism in a proportion of embolic stroke of undeterg mechanism in a proposition or emotive servac or unserest aned source patients, and its closure has been suggested as an efficacious intervention on top of medical treatment. Until eccently, only 3 randomized controlled trials had tested this hypothesis yielding inconclusive results.

In a previous systematic review and meta-analysis, we did in a previous symematic review and meta-analysis, we did not find evidence to support PFO closure in patients with cryptogenic stroke or transient ischemic attack (TIA) with ctypugenic store or transfer intering attack (11A) with undelected devices. However, in subgroup analysis, selected to the control of the con unselected oevices. However, in sungroup analysis, scienced closure devices seemed to be superior to medical treatment in the superior to the superior to medical treatment in the superior to medical treatment in the superior to the supe consuc ocvices scenera to oc superior to memora usuamena, and an individual putent data meta-analysis revealed a

Recently, new evidence from randomized trials became Recently, new evidence from randomized trians occame available 0.14 The aim of this work is to update the results of available, The aim of this work is so uptane the results of the Previous systematic reviews and meta-analyses with the

Received November 6, 2017; stail revision received December 13, 2017; accepted December 15, 2017.

Because of Modeline, University of Thesapy, Larvas, General Governor, 15, 2017.

Because (15), Popularism of Modeline, University of Thesapy, Larvas, General Governor, 15, 2017.

Because (15), Popularism of Modeline, University of Leach, Universi Germany (T.S.), and Stocke Center, Lamanus University Hospital, Switzerland (PM.)

The online-only Data Supplement is available with this article at http://direks.ahajournals.org/lookup/suppledci.th.11618/TROKE-AHA

Constitution of Cores Maries ATV 140-164.7

Constitution of Cores Mari DCT.

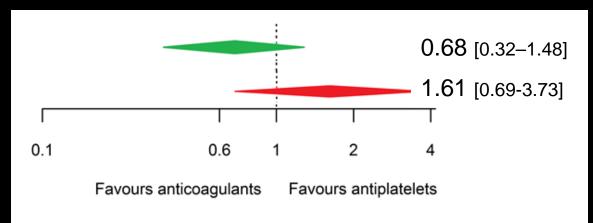
Jense to George Nisios, MD, MSc, PhD, Department of Medicine, University of Thouady, Biopolis 41110, Larinza, Greece, E-mail gustaios 69

DOI: 10.1161/STROKEAHA.117.020630

Ntaios, Michel et al. Stroke 2018

OAC vs aspirin for non-closed PFO

Green: stroke reduction hemorrhage risk Red:



Original Contribution

Antithrombotic Treatment in Cryptogenic Stroke Patients Systematic Review and Meta-Analysis

Dimitrios Sagris, MD; Georgios Georgiopoulos, MD; Kalliopi Perlepe, MD; Constantinos Patoras Mco. Elani Krosomovski, MD; Kalliopi Perlepe, MD; Konstantinos Makaritsis M

Dimitrios Sagris, MD; Georgios Georgiopoulos, MD; Kalliopi Perlepe, MD;
Konstantinos Pateras, MSc; Eleni Korompoki, MD; Konstantinos Makaritsis, MD;

Kranspantinose Vicanopue MTD: Handlandon: MILLONG MARATISIS, MD;

onstantinos Pateras, MSc; Eleni Korompoki, MD; Konstantinos Makaritsis, MD Konstantinos Vemmos, MD; Haralampos Milionis, MD; George Ntaios, MD

Background and Purpose—It is unclear whether treatment with anticoagulants or antiplatelets is the optimal strategy in oasients with stroke or transient ischemic attack of undetermined cause and patent foramen ovale that is not percutaneously ackground and Purpose—It is unclear whether treatment with anticoagulants or antiplatelets is the optimal strategy in patients with stroke or transient ischemic attack of undetermined cause and patent foramen ovale that is not percutaneously account to proceed the process of randomized controlled trials in companies. patients with stroke or transient ischemic attack of undetermined cause and patent foramen ovale that is not percutaneously and meta-analysis of randomized controlled trials to compare

anticoagulant or antiplatelet treatment in this population.

Methods—We searched PubMed until July 16, 2019 for trials comparing anticoagulants and antiplatelet treatment in patients with stroke/transient ischemic attack and medically treated oatent foramen ovale using the terms: "cryptogenic or embolic GROODS—We searched PubMed until July 16, 2019 for trials comparing anticoagulants and antiplatelet treatment in patients with stroke/transient ischemic attack and medically treated patent for amen ovale using the terms: "cryptogenic or embolic actions of transient in the patients of the product of the pro with stroke/transient ischemic attack and medically treated patent foramen ovale using the terms: "cryptogenic or embodic stroke of undetermined source" and "stroke or cerebrovascular accident or transient ischemic attack." and "patent foramen ovale or rearestivated ambidien" and "stroke or dataly," and "antityraphodic or antityraphodic or antityraphod stroke of undetermined source" and "stroke or cerebrovascular accident or transient ischemic attack" and "patent foramen ovale or paradoxical embolism" and "trial or study" and "antithrombotic or anticoagulant or anticoagulant of a study of the contraction of ovale or patent foramen ovale or paradoxical embolism" and "trial or study" and "antithrombotic or anticoaguiant or antiplatelet." The outcomes assessed were stroke recurrence, major bleeding, and the composite end point of stroke resurrance or major bleeding. We need 3 random-effects models: (1) a reference model based on the inverse variance

antiplatelet. The outcomes assessed were stroke recurrence, major bleeding, and the composite end point of stroke fecurrence or major bleeding. We used 3 random-effects models: (1) a reference model based on the inverse variance major bleeding and trackman hotoeropopolity estimator: (2) a strict model incommentation the Hartung and Knanon recurrence or major bleeding. We used 3 random-effects models: (1) a reference model based on the inverse variance method with the Sidik and Jonkman heterogeneity estimator; (2) a strict model, implementing the Hartung and Knapp that assessment models are the large heatened with a portion that assessment models to large heatened and Knapp and Knapp that the large heatened with a portion that assessment models are the large heatened with a portion of the large heatened with a portion of the large heatened with a portion of the large heatened with the la method with the Sidik and Jonkman heterogeneity estimator; (2) a strict model, implementing the Hartung and Knapp method; and (3) a commonly used Bayesian model with a prior that assumes moderate to large between-study variance.

**The Common of method; and (3) a commonly used Bayesian model with a prior that assumes moderate to large between-study variance.

Results—Among 112 articles identified in the literature search, 5 randomized controlled trials were included in the metaanalysis (1720 natients, mean follow-up 2.3±0.5 years). Stroke recurrence occurred afficiate of 1.73 per 100 natients, years. esults—Among 112 articles identified in the literature search, 5 randomized controlled trials were included in the meta-analysis (1720 patients, mean follow-up 2.3±0.5 years). Stroke recurrence occurred at a take of 1.73 per 100 patient, years in anticoagulant-assigned patients (hazard ratio, 0.68; 95% CI, 0.32–1.48 for the analysis (1720 patients, mean follow-up 2.3±0.5 years). Stroke recurrence occurred at a rate of 1.73 per 100 patient-years in anticoagulant-assigned patients and 2.39 in antiplatelet-assigned patients (hazard radio 0.68; 95% CL 0.32–1.48 for the in anticoagulant-assigned patients and 2.39 in antiplatelet-assigned patients (hazard mito, 0.68; 95% Cl, 0.32–1.48 for the Sidik and Jonkman estimator). Major bleeding occurred at a rate of 1.16 per 100 patient-years in anticoagulant assigned nations, and 0.68 in antionagulant-assigned nations, 1.61: 05% Cl, 0.72–3.50 for the Sidik and Jonkman Sidik and Jonkman estimator). Major bleeding occurred at a rate of 1.16 per 100 patient-years in anticoagulant-assigned patients and 0.68 in an antipolated-assigned patients (hazard ratio, 1.61; 95%, Cl. 0.72-3.59 for the Sidik and Jonkman estimator). The commonite outcome occurred in \$42. antipolated and \$4. antipolated account of the sidik and Jonkman and \$4. antipolated account of the sidik and Jonkman and \$4. antipolated account of the sidik and Jonkman and \$4. antipolated account of the sidik and Jonkman and \$4. antipolated account of the sidik and Jonkman account of the sidik account of the sidik and Jonkman account of the sidik patients and 0.68 in antiprarelet-assigned patients (hazard ratio, 1.61; 95% Ct. 0.72-3.59 for the Sidik and Jonkman eatimator). The composite outcome occurred in \$2 antipolated assigned and \$4 antiplatelet-assigned patients (odds

estimator). The composite outcome occurred in 52 antigoaguiant assigned and 54 antiplatelet assigned patients (odds ratio, 1.05; 95% CT, 0.65, 76) for the sink and Jonkman estimator).

Conclusions—We cannot exclude a large reduction of stroke recurrence, in anticoaguiant-assigned patients compared with antiplatelet-assigned, suffour against all differences in major fileeding. An adequately powered randomized anclusions—We cannot exclude a large reduction of stroke recurrence in anticoagulant-assigned patients compared with antiplatelet-assigned, without separational differences in major fleeding. An adequately powered randomized controlled treat of a page strategy of the stroke and account of the stroke account of the stroke and account of the stroke and account of the stroke account of the st with antiplatelet-assigned, without significant differences in major bleeding. An adequately powered randomized controlled Ital of a non-witamin K antagonist versus aspirin is warranted. (Stroke, 2019;20:00-00, DOI: 10.1161/

Key Words: aspirin ■ anticoagulant ■ embolism ■ meta-analysis ■ paradoxical embolism ■ patent foramen ovale

 $n\approx 17\%$ of all patients with ischemic stroke, the underlying n # 11% or an panents with personal stroke, the usacriying cause remains undetermined, despite proper diagnostic in A cause remains undetermined, despite proper magnorate in-vestigation, ¹² Patent foramen ovale (PPO) is a potential cause vestigation. Fragent iteration ovaic (FFA) is a positional cause of stroke, and randomized controlled trials have confirmed the or nations, and tanasomated constituted using have constituted use efficacy of its closure in patients with stroke of undetermined

are any age cass years.

It is unclear whether treatment with anticoagulants or antiplatelets is the optimal preventive strategy in patients with

stroke of undetermined cause and PFO who are not treated stroke of undetermined cause and FPU who are not reason with percutaneous PFO closure. A previous meta-analysis win percutaneous PTO closure. A previous meus-anatysis from observational studies and randomized trials of patients from observational studies and randomized thats of patients with cryptogenic stroke and PFO, assigned to vitamis K with cf progenic area and first, assegned to vicanium a anagonists or antipatelet, did not show a significant difference

Received May 31, 2019, fand acvision received July 18, 2019, accepted August 7, 2019

From the Department of Information Engineering August 7, 2019

Kerney School of Homestical Engineering Advances, Except of Medicine, School of Health Sciences, University of Thousaly, Larius, Groce (D.S., K. Perlege, Information, Info Jedeine, University of Ionnius, Geoce (HM.)

The endine-only Data Supplement is available with this article at https://www.ahajournals.org/doi/suppl/10.1164/STROKEAHA.119.00612.

pages of Internal Medicine, University of Thomas, Biopolis 41110, Larina, Greece, Env.

DOI: 10.1161/STROKEAHA.119.026512

Sagris, Ntaios et al. Stroke 201

DOL: BAHALSTROKEARA.119

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?

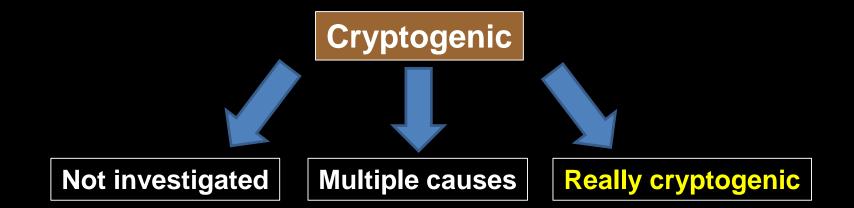
PFO

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

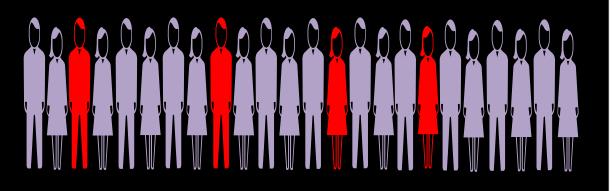
ESUS

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

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 schemic strokes, in whom embolism is the likely stroke mechanism. It has been hyrothestized that anticoxeulation is more ackground 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 applications than anticoagulation as more constitution of the property of the prope 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 a studies involving 2015 ESUS rations, the mean are was 65 years and 42% were women: the mean

enuln.—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 180 studies are studies orser (4 studies 1772 ESUS outbooks). Most (86%) ESUS outbooks word freamed with 17%. From 8 studies involving 2045 ESUS patients, the mean age was 65 years and 42% were women; the mean age was 65 years and 42% were women; the mean an applications of the stroke onset (4 studies, 1772 ESUS patients). Most (86%) ESUS patients were treated with the annualized occurrent stroke rate averaging 4.5% ner year during a mean NIH stroke score was 5 at stroke onset (4 studies, 1772 ESUS patients). Most (86%) ESUS patients were treated with antiplated 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 analysed volume compared usin other to-homic stroke in 6, Patients with ischemic stroke meeting criteria for ESUS were under volume compared usin other to-homic stroke undergoes and had on aureance minor strokes, consistent with small .onchusions — 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 emboil. Retrospective methods of available studies limit confidence in stroke recurrence rates but surpoor a subtrainful.

relatively young compared with other ischemic stroke subtypes and had, on average, minor strokes, consistent with small emboir. Retrospective methods of available studies limit confidence in stroke recurrence rates but support a substantial confidence in stroke recurrence during (negative anisolated they are. There is an important need to define 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) antiphatelet therapy. There is an important need to define the activity occurring subtype of ischemic stroke. (Stroke. 2017:48:06-00. (>4% per year) rate of stroke recurrence during (mostly) antiphatelet therapy. There is an important need to define DOI: 10.1161/STROKEAHA.116.016414.1

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

a 2014, the clinical construct of "embolic stroke of undeteca 2014, the chancal construct of "empolic strokers underection under mined source" (ESUS) was introduced to adontify patients A mineral source (ESUS) was introduced an atomaty patients with non-lacunar cryptogenic ischemic atrokes in when embowith nonlicular cryptogenic ischemic strucerin warm emo-ism was the likely stroke mechanism thewas hypothesized that anticospulant might be more effections than antiplate for secondary study according to the control of the that anticospusings migas be more emeastors man antipose-let agents for secondary stroke prevention in ESUS patients. er agents for secondary strong prevention in East's passents.

At the time of the original publication, little information was

Ever to secondary strong the control of the At the time of the original publication, time information was available to estimate the frequency of ESUS, patient features, available to estimate the frequency of EAU's, patient reatures, or prognosis, Interest in ESUS has been fueled, in part, by 3 or prognosas, interest in 1531/3 has need roctor, in part, vy 2 onegoing randomized trials comparing nonvitamin K antagoongoing randomized unan comparing normations is amago-nist direct-acting oral anticoagulants with aspirin for second-oral conductions and the second-oral conductions are second-oral conductions.

Here, we report the results of a systematic review of pub-Here, we report the results of a systematic review of pub-lished studies about ESUS and summarize additional recent

A PRISMA-paided systematic PubMed search strategy was instruct to basely the system of instead (the last Garchel on A PRISMA-pushed systematic PubMed search strategy was ini-tiated to identify the studies of interest (the last searched on Proceedings 6, 2016; Essent) We also sectorated as a sector of the control of traced to identify the studies of interest (the last searched on December 6, 2016; Figure). We also performed a hand searching

of, bibliographies and estations of included studies. For the online scatch strates; the larms tembolic arche of unknown source OR ESIS sections and with tembolic arche of unknown source OR professions, and with tembolic arche of the or properse stroke OR configuration and the Children of the Configuration of the Children of the Chi graphies and entitions of included studies. For the online 2014. Two collishos TRC II H. and I. (;) independently reviewed arti-cises that energied from the searches for potential inclusion in review. Smaller prelimber in shurar only were not included. Discrepancies to the review was marked to research to the contract of the Singlest published in sibilizar only were not included. Discrepancies between the reviewers were resolved by Constense, Publication of the Constant of the Con between the reviewers were resolved by consensus. Publications in any language were included if reporting new information based on the letter of the reviewers for the recommendation of the reviewers. Strategies of the recommendation of the reviewers of the resolution of the resolut in my language were included if reporting new information based on the ESUS criteria; proposed by the Cryptogenic Micholesus of Language Comp. (Table 1). One study sporting a highly excluded Comp. (Comp. (Comp. Comp. Comp. Comp. Comp. Comp. Comp. Comp. (Comp. Comp. Comp International Working Group (Table 1). One study reporting a highly selected ESUS, cobort was not included; a new ways 5 published case account of the backet studies wave selectively even selectively even selectively even selectively. selected ESUS cohort was not included; nor were 5 published case reports in Investigators of included studies were selectively con-

ched seeking additional data."

Because accertainment has between different studies could poten-izably be more outlooken dust read-on error tributed to corrects strate Because accordanged has perween different studies could poten-tially be more misleading than fundom error related to sample to the residue son recognised book as weaked than semiporary tusty be more musicading than random error related to sample sizes, the pooled results as: Presented both as weighted (by numbers of patients) and unweighted (nveraging values for each study) manus.

Beceived December 21, 2016, final existon received January 13, 2017, accepted January 20, 2017

But the Department of Medicine (Neurology) (RG EH. L. C. K. S.P.), Population Health Research Institute and Department of Medicine (Carlicology) (Research Larius University Hospital, University of Demand, Groce (G.N.)

Larius, Groce (G.N.) Overall, the quality of the included studies was only fair.

adius, Greco (G.N.)

Grespondence D Robert G. Hart, MD. Population Health Research Institute, DBCVSRI C4-105, 237 Barton St. E. Hamilton, Ontario LEL XXX.

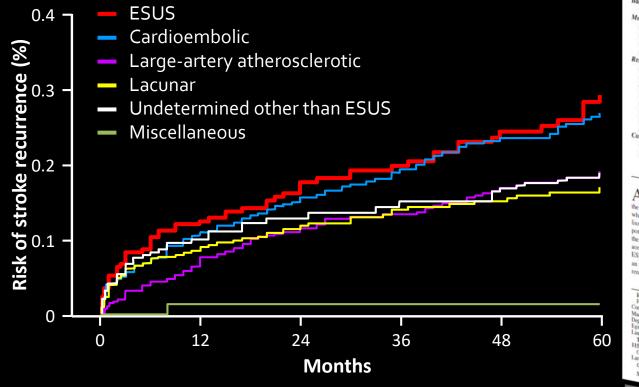
DOI: 10.1161/STROKEAHA.116.016414

Strain is straighte at http://decolorabs/permats.org

DOI: BAHGASTROKEARIN

Hart, Ntaios, et al. Stroke 2015

ESUS: high recurrence rate



Embolic Strokes of Undetermined Source in the Athens An Outcome Analysis

George Niaios, MD; Vasileios Papavasileiou, MD; Haralampos Milionis, MD; George Nunos, MD; vasueios rapavasneiou, MD; Haranampos Milionis, MD; Konstantinos Makaritsis, MD; Anastasia Vemmou, MD; Eleni Koroboki, MD;

Konstantinos Makaritsis, MD: Anastasia Vemmou, MD: Eleni Koroboki, MD: Eleni Koroboki, 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 envokes a detailed analysis of outcomes of a large ESUS reconlation 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 principal End scaled waves mountains stocks according to the Cryptogenic Stroke/ Acthods—Data set was derived from the Athens Stroke Registry, ESUS was defined according to the Cryptogenic Stroker
ESUS International Working Group criteria, End points were mortality, stroke recurrence, functional outcome, as
a commonistic cardiovascular end noist comprising recurrent stroke, invocardial infarction, acritic aneurosum nuntume.

ESUS International Working Group criteria. End points were mortality, stroke recurrence, functional outcome, and a composite cardiovascular end point comprising recurrent stroke, myocardial infarction, acrite aneurysm inputer, according to such a cardiac death. We nevfermed Kardan, Masier analyses to estimate cumulative probabilistics. a composite cardiovascular end point comprising recurrent stroke, myocardial infarction, aortic aneuryan rupture, strokentone de strokentone and Cox promotion to trouvelloste substitute strokentone be strokentone and Cox promotion to trouvelloste substitute strokentone providence. systemic embolism, or sudden cardiac death, we performed Kaptan-Meier analyses to estimate cumulative of outcomes by stroke type and Cox-regression to investigate whether stroke type was outcome predictor.

Results.__2731 outlents successful for a mean of \$1.5 \(\alpha \). 24 tensorbs. There were, 73 176 \(\alpha \). (A death of outcomes by stroke type and Cox-repression to investigate whether stroke type was outcome predictor.

Results—2731 patients were followed up for a mean of 30.5224.1 months. There were 73 (26.5%) deaths 60 (21.8%)

recurrences: and 78 (24.26) connection coordinates relatives to the 275 feet remainst. The communities conduction of the content of th Jesuits—2731 patients were followed-up for a mean of 30.5±24.1mooths. 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 ESTIC was 65 60. (OSG. rossidoscos intervals ECTI 50 002..77 702.) simulative probability intervals ECTI 50 002..77 702.)

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 cardioembodic stroke (38.8%, 95% CI, 34.9%—42.7%). The cumulative probability of stroke recurrence in ESUS was 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 150.00 and 150.00 an 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 accounts of conservation of cardioembolic strokes (26.8%, 95% CI, 22.1%-31.5%), but significantly higher the conservation of cardioembolic strokes (26.8%, 95% CI, 22.1%-31.5%), but significantly higher the cardioembolic strokes (26.8%, 95% CI, 22.1%-31.5%), but significantly higher the cardioembolic strokes (26.8%, 95% CI, 22.1%-31.5%), but significantly higher the cardioembolic strokes (26.8%, 95% CI, 22.1%-31.5%), but significantly higher the cardioembolic strokes (26.8%, 95% CI, 22.1%-31.5%), but significantly higher the cardioembolic strokes (26.8%, 95% CI, 22.1%-31.5%), but significantly higher the cardioembolic strokes (26.8%, 95% CI, 22.1%-31.5%), but significantly higher the cardioembolic strokes (26.8%, 95% CI, 22.1%-31.5%), but significantly higher the cardioembolic strokes (26.8%, 95% CI, 22.1%-31.5%), but significantly higher the cardioembolic strokes (26.8%, 95% CI, 22.1%-31.5%), but significantly higher the cardioembolic strokes (26.8%, 95% CI, 22.1%-31.5%), but significantly higher the cardioembolic strokes (26.8%, 95% CI, 22.1%-31.5%), but significantly higher the cardioembolic strokes (26.8%, 95% CI, 22.1%-31.5%), but significantly higher the cardioembolic strokes (26.8%, 95% CI, 22.1%-31.5%), but significantly higher the cardioembolic strokes (26.8%, 95% CI, 22.1%-31.5%), but significantly higher the cardioembolic strokes (26.8%, 95% CI, 22.1%-31.5%), but significantly higher the cardioembolic strokes (26.8%, 95% CI, 22.1%-31.5%), but significantly higher the cardioembolic strokes (26.8%, 95% CI, 22.1%-31.5%), but significantly higher the cardioembolic strokes (26.8%, 95% CI, 22.1%-31.5%), but significantly higher the cardioembolic strokes (26.8%, 95% CI, 22.1%-31.5%), but significantly higher the cardioembolic strokes (26.8%, 95% CI, 22.1%-31.5%), but significantly hig 29.0% (95% CL 22.3%—35.7%), similar to cardioembolic strokes (26.8%, 95% CL 22.1%—31.5%), but significantly higher compared with all types of noncardioembolic stroke. One hundred seventy-two (62.5%) ESUS patients had favorable and 303.160 (96.3 in larve-areas subconclosus, ESUS 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 atherosciencie. ESUS patients had favorable estables types with the exposure of a solid stable stroke types. 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 lactnar cardiovascular end of 70 (40.2.0 Q41).

strokes, which had significantly lower risk (adjusted hazard ratio, 0.70 [05% CI, 0.52-0.04]).

Conclusions—Long-term mortality risk in ESUS is lower compared with cardioembolic strokes, despite similar rates of recurrence and conversitie cardiovascular and eccint Recurrence stroke risk is bloby in EGLIC than in econventionability. Jonchusions—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. 2015;46:3687.3993. DOI: 10.1141/STD/SKE/AHA.116.009334.

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 A Undetermined Source (ESUS) was recently introduced by the Cryptogenic Stroke/ESUS International Working Group, as capping and a patients for whom the source of embosuch received despite recommended investigation name valuation unmarked and accordance and accordance include the mitral and accordance valves. personance vinance accuracy manager was named and accuracy accuracy the left cardiac chambers, the proximal cerebral arteries of the acrtic arch, and the venous system via paradoxical embolism. actur, and the venous system via parasocuear emousism.

ESUS has been proposed as a potential therapeutic entity with an indication for anticoagulation, a hypothesis which is cur-

Recently, we presented a descriptive analysis of an ESUS

neverny, we presented a occupance manyas of an tasto population originating from the Athens Stroke Registry.⁴ Among the overall stroke population, 10% of patients were Among the overall stroke population, 10% of patients were classified as ESUS These strokes were of mild-moderate as ESUS These strokes were the established the es cantereo as EAU/3. Tiene MINNES WEE of Into-inconsisted as severity, and covert atrial fibrillation (AF) was identified as the underlying etiopathogenetic mechanism in +40% of ESUS

In routine clinical practice, and based on randomized na rounne canneas praesuce, and onaces on randomized stadies, is the vant majority of ESUS patients are treated with

Received March 4, 2015, fluid servition received lane 6, 2015. Accepted lane 9, 2015.

From the Dipuriment of Madiscine, Latinus University Hospital, School of Madiscine, University of Thematy, Latinus, General Gardenburghan, School of Madiscine, University of Thematy, Latinus, General Gardenburghan, School of Madiscine, University of Thematy, Latinus, General Gardenburghan, Comparison of Canada Theoryotics, Madiscine, Insurance of Canada Gardenburghan, School of Madiscine, University of Gardenburghan, Canada Gardenburghan

Language, Statement of Maj.

The colline-only Data Supplement is available with this article at http://stroke.aha/journals.org/look/mp/supplidsc/10.1164/STROKEAHA.

Consecrations to George Nation MT/MC/CEST Const. 14. 115.0093.W.OV.T.

Correspondence to George Statos, MD, MSc (ESO Stroke Medicine), PhD, FESO, Amintant Professor of Internal Medicine, Department of Medicine, Co2015 American Heart Association, Inc.

O 2015 American Heart Association, Inc.

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

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 al¹6‡	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 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 schemic strokes, in whom embolism is the likely stroke mechanism. It has been hyrothestized that anticoxeulation is more ackground and Purpose—Embolic stroke of undetermined source (ESUS) designates patients with nonlacunar cryptogenic lschemic strokes in whom embolism is the likely stroke mechanism. It has been hypothesized that anticoagulation is more accountable theorems for executary circles represented in ESUS relief with relief sources. 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 research unrestricted by Incompany.

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 ratients, the mean age was 65 years and 42% were women; the mean enuln.—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 180 studies are studies orser (4 studies 1772 ESUS outbooks). Most (86%) ESUS outbooks word freamed with 17%. From 8 studies involving 2045 ESUS patients, the mean age was 65 years and 42% were women; the mean ageing a stroke onset (4 studies, 1772 ESUS patients). Most (86%) ESUS patients were treated with the annualized occurrent stroke rate averaging 4.5% ner year during a mean NIH stroke score was 5 at stroke onset (4 studies, 1772 ESUS patients). Most (86%) ESUS patients were treated with antiplated 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 analysed volume compared usin other technolic stroke in 6, Patients with ischemic stroke meeting criteria for ESUS were under volume compared usin other technolic stroke in 6, Patients with ischemic stroke meeting criteria for ESUS were .onchusions — 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 emboil. Retrospective methods of available studies limit confidence in stroke recurrence rates but surpoor a subtrainful.

relatively young compared with other ischemic stroke subtypes and had, on average, minor strokes, consistent with small emboir. Retrospective methods of available studies limit confidence in stroke recurrence rates but support a substantial confidence in stroke recurrence during (negative anisolated they are. There is an important need to define 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) antiphatelet therapy. There is an important need to define the activity occurring subtype of ischemic stroke. (Stroke. 2017:48:06-00. (>4% per year) rate of stroke recurrence during (mostly) antiplatelet therapy. There is an important need to define DOI: 10.1161/STROKEARIA.116.016414.)

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

a 2014, the clinical construct of "embolic stroke of undeteca 2014, the clinical construct of "empire stroke or undered mined source" (ESUS) was introduced to adontify patients A mineral source (ESUS) was introduced an attenuty patients with non-lacunar cryptogenic inchemic atrokes in when embowith nonlicunar cryptogenic mehemic parokeoin whom empo-jism was the likely stroke mechanism. Hawas hypothesited that anticospulanta might be more efficacious than antiplate

that anticospusans maga be more ethicacious than ampaiar-let agents for secondary stroke prevention in ESUS putients. er agents for secondary strong prevention in East's passents.

At the time of the original publication, little information was

the re-At use time of the original punication, time information was available to estimate the frequency of ESUS, patient features, available to estimate the frequency of EAUA, patient reatures, or prognosis, Interest in ESUS has been fueled, in part, by 3 or progness, interest in 1531/3 has need tucket, in part, vy 2 on organig randomized trials comparing nonvitamin K antagoone control resources the comparing normation is an agro-nist direct-acting oral anticoagulants with aspirin for accond-

Here, we report the results of a systematic review of pub-Here, we report the results of a systematic review of published studies about ESUS and summarize additional recent

A PRISMA-prided systematic PubMed search strategy was instruct on the other man strategy of interest (the but Sourched on A PRISMA-pended systematic PubMed search strategy was im-processing to identify the studies of interest (the last searched on the constant of the last searched on the constant of the consta trace to latently the strates of interest time has searched on December 6, 2016; Figure). We also performed a hand searching

ac, belongraphes and existions of included studies. For the online scales fitness, the same tembolic studies of unknown source Oig Exists embolisms, and such sembolisms of these Oig Propersis stroke Oig Confirms, and such sembolisms of the organization of the propersis stroke Oig Confirms of the ATT of t traphies and estations of included studies. For the online 2014. TWO COMBON THE LH. and L.C.) independently reviewed arti-ciscs that energed from the searches for potential inclusion in review. Smaller principles in abstract only were not included. Discrepancies to the review were residual to reconstant phase consequences. Singlest published in sibilizar only were not included. Discrepancies between the reviewers were resolved by Constense, Publication of the Constant of the Con between the reviewers were resolved by consensus. Publications in any language were included if reporting new information based on the letter of the reviewers for the recommendation of the reviewers. Strategies of the recommendation of the reviewers of the resolution of the resolut in any anguage were included if reporting new information nation on the ESUS criteria; proposed by the Cryptogenic Stroke-ESUS continuation of the Computing Group (Table 1). One study reporting a slightly continuate of the Computing Computing a slightly continued for the Computing Computing a slightly continued for the Computing Computing a slightly continued for the Computing Conditions of International Working Group (Table 1). One study reporting a highly selected ESUS, others was not included; and were 5 published case consequences of stocked studies was not published case. special range experience quelle que la constant par la proposition de la constant que la constant de la constan

edos sociatos adamenta una...

Becanic sociatos accestismente basa between different studies could potensiente, ha monte sentimonios desas renderos actual telescotos de sentimonios de Because accurant areast has newconditioned studies could poten-tally by more misteading than fandom error related to sample to the occuled routh and accurated both a waveled from numbers of nary or more managang than random error related to sample tizes.

The probled results are presented both as weighted (by furnishers of emission) and unway-there of proposess values for such sample towards. the posted remain are presented both as weighted thy numbers of patients) and unweighted (averaging values for each study) means.

Becoved December 21, 2016, final exvision received January 13, 2017, accepted January 20, 2017.

January 11, 2016, final exvision received January 13, 2017, accepted January 20, 2017.

January 11, 2016, final exvision received January 13, 2017, accepted January 20, 2017.

January 11, 2017, Advanter University, Hamilton Health Science, Cluster, Canada, Department of Medicine, Larisan University Hospital, University of Themaly, and Company 11, 2017, accepted January 20, 2017. Overall, the quality of the included studies was only fair.

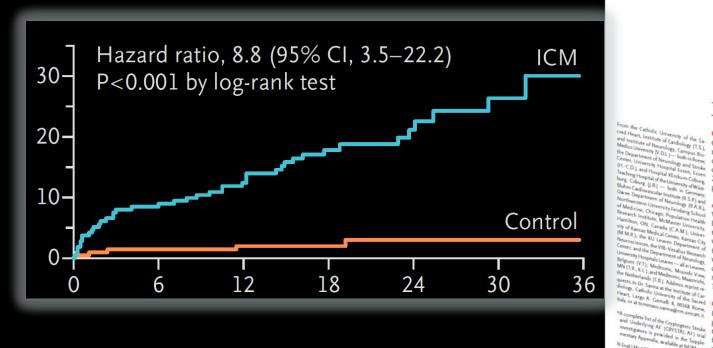
arinas, Grecce (C.N.)
Cresspondence do Bobert G. Hart, MD. Populaison Health Research Institute, DBCVSRI C4-105, 237 Baricus St. E. Hamilton, Ontario LEL 2022.

DOI: 10.1161/STROKEAHA.116.016414

Strake is residable at http://droke.abayer

DOI: 10.1161/STROKEARA. 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. Tommaso Sanna, M.D., Harry-Unristoph Uneries, M.D., Ph.D., Rod S. Passman, M.D., M.S.C.E. Vincenzo Di Lazzaro, M.D., NOG 3. FESSIMAN, M.D., M.S.L.E., VINUENZO LITERZEATO, M.D., Richard A. Bernstein, M.D., Ph.D., Carlos A. Morillo, M.D. Mariyn Mollman Rymer, M.D., Vincent Thijs, M.D., Ph.D. Tyson Rogers, M.S., Frank Beckers, Ph.D., Kate Lindborg, Ph.D. 19-оп коgers, м.э., этапк вескез, эт.ы., кале ыпивогд, эт.ы., and Johannes Brachmann, М.D., for the CRYSTAL AF Investigators*

BACKGROUND

Current guide ines recommend at least 24 hours of electrocardiographic (ECG) Current gamesines recommend at 1628-24 hours of electrocardiographic (EULI) monitoring after an ischemic stroke to rule out atria! fibrillation. However, the most affine three durations durations and type of monitoring laws not how norshillshard and the course monitoring after an isonemic stroke to ruje out after Horization. However, the most effective duration and type of monitoring have not been established, and the cause of isothernic stroke remains increasing duestion a complete discussive weaknessive accurately. of ischemic stroke remains uncertain despite a complete diagnostic evaluation in or ascience stroke temains uncertain uesque a complete diagnosoi: evaluation in 20 to 40% of cases (cryptogenic stroke). Detection of atrial fibrillation after cryptogenic stroke has therapsutic implications.

We conducted a randomized, controlled study of 441 patients to assess whether transfers manipulation with an interpretable cardiac manipulation (ICM) is more adjacable. we consucted a randomized, controlled study of 441 patients to assess whether long-term monitoring with an insertable cardiac monitor (ICM) is more effective jong-term monitoring with an insertance cartiac monitor (a.m.) is more effective than conventional follow-up (control) for detecting atrial fibrillation in patients of the control of the man convenional renowap (curror) for occurring arrial from about in patients with cryptogenic stroke, Patients 40 years of age or o'der with no evidence of arrial when cryptogenic strong, rathern su years or age or other with no evalence or attraction during at least 24 hours of EGG monitoring underwent randomization within 90 days after the index event. The primary end point was the time to first within 90 days after the index event. The primary end point was the time to IIIst detection of artial fibrillation (lasting >30 seconds) within 6 months. Among the covereday out rosing was the time to first detection of artial fibrillation within secondary end points was the time to first detection of attial fibrillation within secondary end points was the time to this occurran or arrial raterial occurrance.

12 months, Data were analyzed according to the intention-to-treat principle.

By 6 months, atrial fibrillation had been detected in 8.9% of patients in the ICM by o months, attait internation nau octs octeture in 0.7% or patients in the a.or.
group (19 patients) versus 1.4% of patients in the control group (3 patients) hazard group (19 patients) versus 1.4% or patients in the control group (3 patients) mazard ratio, 6.4; 95% confidence interval [CI], 1.9 to 21.7; Pc(0.001), by 12 months, arrial ratio, 6.4; 92% constituence interval (6.1), 1.29 to £1.7; FCOMM13- by 1.2 months, attituence of feet and the feet of the feet of the feet of patients in the ICM group (29 patients) of notional in the results o Fibrillation had been detected in 12.4% or patients in the RAM group (29 patients) versus 2.0% of patients in the control group (4 patients) (hazard ratio, 7.3; 95% CL.

ECG monitoring with an ICM was superior to conventional follow-up for detections associated association associated association associated by Machananic CEVETAL AF EAS MODIFICITIES WITH AN ILLY WAS SUPERIOR TO CONVENTIONAL DELOW-UP FOR DETECTION OF THE CRYPTOGENIC STOKE. (Funded by Meditonic, CRYSTAL AF

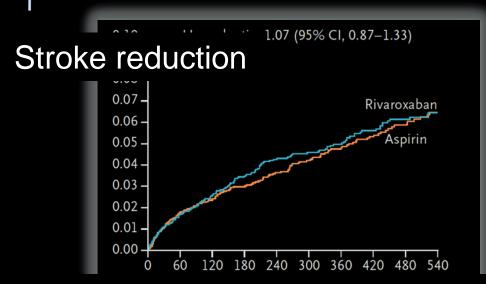
2478

mentary Appendix, available at NEJM.org

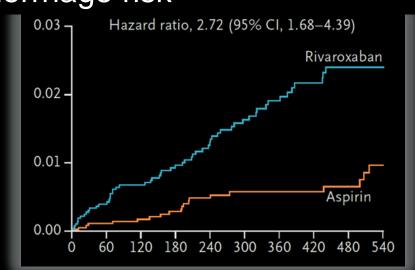
N Engl J Med 2014;370:2478-86. DOI: 10.1056/NEJMoul 51.1600 Copyright C 2014 Management Medical Society

ECG monitoring with 34 proposedis strone, (runder ing striat fibrilliators after expressed strone). (fillifealfithats, gov mimber, InCT00924638.)

NAVIGATE ESUS



Hemorrhage risk



TER NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source

R.G., Hart, M., Sharma, H., Mundi, S.E. Kasner, S.I. Bangdiwala, S.D. Berkowitz, B. Swaminathan, p. Lavados, Y. Wang, Y. Wang, A. Davalos, N. Shamalov, a structured at the contract of the con

B. Swaminathan, P. Lavados, Y. Wang, Y. Wang, A. Davalos, N. Shamalov, R. Mikulik, L. Cunha, A. Lindgren, A. Arauz, W. Lang, A. Członkowska, J. Eckstein, o r. Canbardi, B. Ansarano, C. E. Amarien, Y. Tatliermal, D. Validaron, C. Lander, R. Callonkowska, J. Eckstein, and C. Lander, R. Callonkowska, J. Eckstein, C. C. Lander, R. Callonkowska, C. C. Lander R.J. Gagliardi, P. Amarenco, S.F. Ameriso, T. Tatlisumak R. Veltkamp. G.J. Hankey, D. Toni, D. Bereczki, S. Uchlyana, G. Ntalos, B.-W. Youn, R. Brouns, as Crotrac V.W. Maid, M. Rometein, C. Obtiof, M. L. O'Donnall, neer, D. Duni, D. Bereczki, S. Ochiyama, G. Pitalox, B.-W. 1001, K.
M. Endres, K.W. Muir, N. Bornstein, S. Ochurk, M.J. O'Donnell, M. Engres, K.W. Munr, P. Bornstein, S. Octurk, M.J. O Donner, 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 MAVIGATE ESUS Investigators

ABSTRACT

BACKGROUND

Embolic strokes of undetermined source represent 20% of ischemic strokes and are associated with a kitch rate of recurrence. Anticoagontana treasment with rivate. The author, full names, academic green, and afficiations are listed in Embolic strokes of undetermined source represent 20% of ischemic strokes and are associated with a high rate of recurrence. Anticoagulant treatment with rivate green and affactor Xa inhibitor may recurly in a logour rick of programme strokes.

The authory full names, academic degrees and affactors are listed in the Appendix Address reprint requests to Dr.

We compared the efficacy and safety of rivaroxaban (at a daily dose of 15 mg) with a state state of the most for the repeatables of recurrent stretch in nonlinear We compared the efficacy and safety of rivaroxaban (at a daily dose of 15 mg) with a daily dose of 100 mg) for the prevention of recurrent stroke in patients with recent is chemic stroke that was resourced to be from cerebral embed is most linear ligators is provided in the Supple without afterial stenosis, facune, or an identified cardioembolic source. The primary efficacy outcome was the first recultence of ischemic or hemorrhagic stroke. The article was published on May 16, 2018,

at RGM org.

A total of 7213 participants were enrolled at 459 sites; 3609 patients were ran-A total of 7.412 participants were enroised at 439 Mics; 3009 patients were ran-domly assigned to receive rivaroxaban and 3604 to receive aspirin. Patients had how, 6et send for a median of 11 mounts when the refut were terminated only domy assigned to tweeve invariances and soos to tweeve aspects, rathern state been fellowed for a median of 11 months when the trial was terminated early account of a task of baseline of Maedian of because of a tack of benefit with regard to stroke risk and because of bleeding view physics of the primary officient stroke risk and because of bleeding the primary of th because of a tack of benefit with regard to stroke risk and because of occurring associated with rivaroxaban. The primary efficacy outcome occurred in 172 parameters are according to the state of the associated who regulation, are primary criticacy outcome occurred in 1/2 pa-tients in the rivaronaban group (annualized rate, 5.1%) and in 160 in the aspirin orrano (annualized rate, 4.8%) (based rate, 1.07, 95%, confidence inserval term thems in the routenation group temmutatized late, 5.7%) and in 100 in the aspiring group (annualized rate, 4.8%) (hazard ratio, 1.07; 95% confidence interval [CI]. group sammanized into moral (nazatu ranu, LM); you commune manya, tob.

0.87 to 1.33; P=0.52). Recurrent ischemic stroke occurred in 158 patients in the

stroke occurred in 158 patients in the stroke occurred in 158 patients in the

stroke occurred in 158 patients in the stroke occurred in 158 patients in the stroke occurrence in the stroke occ U.M. to 1.33; F=0.24; Accurrent incremic allune occurred in 13e patients in the fivareathin group (annualized rate, 4.7%) and in 156 in the aspirin group famulation of the spring from famulation of the spring for the spring for the five reservation. rearriagum group (annualized rate, 4.7%) and in 130 in the appring group time nualized rate, 4.7%). Major bleeding occurred in 62 patients in the featurable arrange (securities of the 1.9%) and in 52 in the appring commendated rate of the featurable of rate of the feature of manazeu tate, 4,7%, major oneuing occurreu in oc paracus in the manazanian group famualized rate, 1,8%) and in 23 in the aspirin group famualized rate, 1,8% and in 23 in the aspirin group famualized rate, 1,8% of 2 on 1,000 per 1,000 pe

CONCLUSIONS

Rivarozaban was not superior to aspirin with regard to the prevention of recurrent An annualism was not superior to aspirat with regard to the prevention of recurrent stroke after an initial embodic stroke of undetermined source and was associated stroke after an initial employs stroke or undetermined source and was associated with a higher risk of bleeding. (Funded by Bayer and Janssen Research and Levelwith a nigater rask or needing. [Funded by payer and panasen Aeseatch opment; NAVIGATE ESUS ClinicalTrials.gov number, HCT02313909.]

NENGLIMED NOM.ORC

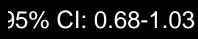
DOI: 10.1056/NEJMo41802686 Species C XXII Metachones Medical Joseph

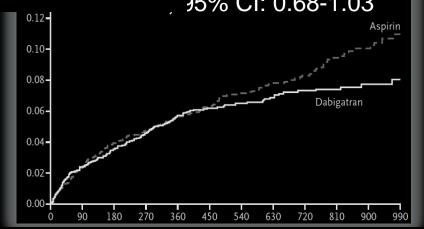
Hart, et al. NEJM 2018

OPHIGHE NAVIGATE ESJN CIRCUITATA-gov number, NCT02313909.3 Ryarozakia wai molai embolic stroke of unascen a stroke aner an initial embolic grunded by Bayer and Junsten a with a bigker trisk of bleeding, (Funded by Bayer and Fundamental and Bayer and Bayer

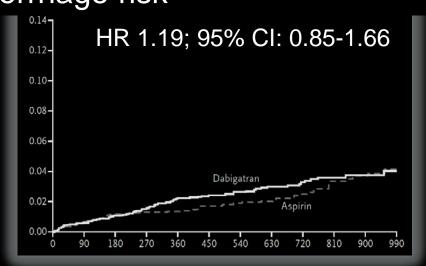
RE-SPECT ESUS

Stroke reduction





Hemorrhage risk



THE NEW ENGLAND TOURNAL 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,

1. Consola, D. Cotton, C. Granger, M. Reusedmann, M. Chernyatina J. Kreuzer, L. Cronin, D. Cotton, C. Grauer, M. Brueckmann, M. Chernyatna, G. Donnan, J.M. Ferro, M. Grond, B. Kallmürzer, J. Krupinski, B. C. Lee. G. Donnan, J.M. Perro, M. Grond, B. Kallmurzer, J. Krupinski, B.-L. Lee, R. Lemmens, J. Masjuan, M. Odinak, J.L. Saver, P.D. Schellinger, D. Toni, M. Lemmens, J. Masjuan, M. Oumak, J.L. Saver, P.D. Scheininger, U. 10m, and K. Toyoda, for the RE-SPECT ESUS Steering Committee and Investigators

BACKGROUND ABSTRACT

grees, and affiliations are listed in the Appends. Address reprint requests to Dr. Dener at the Faculty of Medicine, University Duisburg Esten and University Hos pital Essen, Hufelandatz, 55, 45147, Essen, rmany, or at hans dieser@uk essende. *A complete list of the RE-SPECT ESUS

die, available at NEJM.org.

N Engl J Med 2019; 380:1906-17.

DOI: 10.1054/NE]MoalE11959

genic strokes are considered to be embolic and of undetermined source. An eargenic stokes are consucred to be emoure and or undetermined source. An eariler randomized trial showed that rivaroxaban is no more effective than aspirin in

suppose trials after a resourced supposition as inclusives. per randomized trial showed that invaluation is no more effective than aspirin in preenting recurrent stroke after a presumed embodic stroke from an undetermined of the control of the co preventing recurrent answer after a presented entitled across from an university mined source. Whether dabigatran would be effective in preventing recurrent

committees and principal investigators is provided in the Supplementary Appen meany Appen-Chiefle O 30 1 Materians (1991) posts

We conducted a multicenter, randomized, double-blind trial of dabigatran at a dose of 150 mg or 110 mg wice daily as compared with aspirin at a dose of 100 mg one had had an embolic eresks of undersembned tourse. The or 130 mg or 130 mg owice Gary as compared with aspirin at a close or 100 mg once daily in patients who had had an embolic stroke of undetermined source. The daily in patients who had had an embotic stroke of undetermined source. The primary outcome was recutrent stroke. The primary safety outcome was major

A total of 5390 patients were enrolled at 564 sites and were randomly assigned to A total of 5350 patients were enrolled at 504 sites and were randomly assigned to receive dabigatran (2695 patients) or aspirin (2695 patients). During a median distribution of 10 processes, successed as processes of the proces receive datigatran (2695) patients) or aspirin (2695) patients). Luring a median follow-up of 19 months, recurrent strokes occurred in 177 patients (6.6%) in the aspiring or support and in 207 residents (770c) in the aspiring or near the content of the section totion-up of 19 months, recurrent strokes occurred in 177 patients (6.0%) in the dabigatran group (4.1%, per year) and in 207 patients (7.7%) in the aspirin group, 44 sec. now many the part of sec. one of the part of the p uanigatian group (8.1% 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; 10.6 to 1.06 (4.8% per year) (hazard ratio, 0.85; 99% confidence interval (C.H. 0.69 to 1.03; P=0.10). Ischemic strokes occurred in 172 patients (4.0% per year) and 203 parameters (4.0% per year) and 203 Fe-9,10). Ischemic strokes occurred in 1/2 patients (4.0% per year) and 203 pa-tients (4.7% per year), respectively (hazard ratio, 0.84; 95% CL 0.6% to 1.03). Major Macdino recurred in 77 rational (1.7%, now ways) in the Ashkimson aroun, and in tionts (4.7% per year), respectively (hazard ratio, 0.84; 95% Cl, 0.66 to 1.03). Major bleeding occurred in 77 patients (1.7% per year) in the dabigairan group and in 4.6 per tions of a section or and the average ratio 1.10. ogs. Cl 0.85 theoring occurred in // patients (L/% per year) in the canogarian group and in 64 patients (L#k per year) in the aspirin group (hazard ratio, 1.19; 99% CI, 0.85 ct. of 1.66). Pitalically, reduces to reconstitute Monetten procurred in 70 maximum 15 CC. see 64 patients (1.4% per year) in the aspurin group (nazaro ratio, 1.19; 95% CL, U.E.) to 1.66). Clinically relevant nonmajor bleeding occurred in 70 patients (1.6% per wear) and 41 miliones (0.0%, nor wear) poerweigned.

CONCLUSIONS

In patients with a recent history of embolic stroke of undetermined source, dableconstruction and account of application appropriate exercise. The incidence of in patients with a revent analogy or emboure stroke of undertermined source, data-gatian was not superior to aspirin in preventing recurrent stroke. The incidence of analogs Manufacture uses uses reasons to a short-ability are stroken at an in the sension occurs. garran was not supernor to aspura in prevenuing recurrent stroke. The incidence of major bleeding was not greater in the dabigatian group than in the aspirin group.

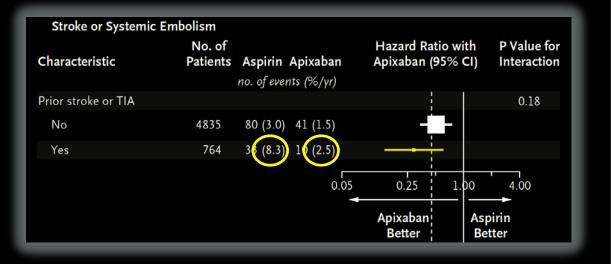
Less those those those clinically relevant manufactor bleeding evenus in the dabigation. major recoung was not greater in the unaugutan group than in the aspirin group but there were more clinically relevant nonmajor bleeding events in the dalagrand and the dalag can taket were more camarany receasis nonmany necessing everas in the unorganism group. (Funded by Eochtinger Ingesheim; RE-SPECT ESUS ClinicalTrials.gov number.

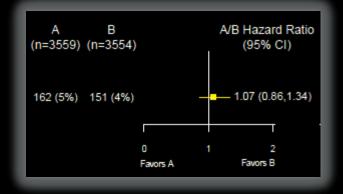
Downloaded from nejm. org by DIMITRIOS 5AGRIS on May 15, 2019. For personal use only. No other uses without permission.

Conversely C 2018 Massachusent Made 15 Section. All rights reserved. Downleaded from nepa org by DDMITEADS SACRES on May 11.

Diener, et al. NEJM 2018

AVERROES





THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apixaban in Patients with Atrial Fibrillation Stuart J. Connolly, M.D. John Eikelboom, M.B., B.S. Campbell Joyner, M.D. Stuart J. Connoily, M.D., John Eixelboom, M.D., v.S., Campbell Joyner, M.D., Harts Christoph Diener, M.D., Ph.D., Robert Hart, M.D., Sergey Golitsyn, M.D., Ph.D., Robert Hart, M.D., Sergey Golitsyn, M.D., Ph.D., Ph.D., Robert Hart, M.D., Sergey Golitsyn, M.D., Ph.D., Ph.D., Robert Hart, M.D., Sergey Golitsyn, M.D., Ph.D., Robert ans-Christoph Diener, M.D., Ph.D., Kobert Hart, M.D., Sergey Gottsyn, M.D., Ph.D., Stefan H. Hohnloser, M.D., Greg Flaker, M.D., Anvaro Avezum, M.D., Ph.D., Stetan Fr. Fronnioser, M.D., Rafael Diaz, M.D., Mario Talajic, M.D., Jun Zhu, M.D., Prem Pais, M.B., B.S., M.D. Andrei Budai, M.D., Mano Haape, M.D., Jun Citu, M.D., Frem Yata, M.D., D.S., M.D., Andrei Budai, M.D., Ph.D., Alexander Parkhomenko, M.D., Ph.D., Petr Jansky, M.D. Andrzej Budaj, M.D., Pri.D., Arciander Parknomersko, M.D., Pri.D., Petr Jamsy, M.D., Patrick Commerford, M.B., Ch.B., Ru San Tan, M.B., B.S., Kui-Hian Sim, M.B., B.S., Wei-Hian Sim, M.B., B.S., Valley, M.B., Walley, M.B., Wall Basil S. Lewis, M.D., Walter Van Mieghem, M.D., Gregory Y.H. Lip, M.D., S. LOWIS, M.D., Waiter van Miegnern, M.D., Gregory Y.H. Up, Jae Hyung Kim, M.D., Ph.D., Fernando Lanas-Zanetti, M.D., Jac rryung xim, M.U., Ph.U., Pernanoo Lanas-Canetti, M.U.,
Antonio Gonzalez-Hermosillo, M.D., Antonio L. Dans, M.D., Antonio Gonzalez-Hermosino, M.D., Antonio L. Dans, M.D., Muhammad Munawar, M.D., Ph.D., Martin O'Donnell, M.B., Ph.D., John Lawrence, M.D., Gayle Lewis, Rizwan Afzal, M.Sc. and Salim Tusur, M.D., D.S., U.P. no., Or the AVERROES Steering Committee and Investigators and Salim Yusuf, M.B., B.S., D.Phil.

ABSTRACT

SACKGROUND

Vitamin K antagonists have been shown to prevent stroke in patients with atrial

Vitamin K antagonists have been shown to prevent stroke in patients with atrial

Or receive vitamin K antagonist therapy, and these patients have a high risk of stroke,

Adixahan, a novel factor Xa inhibitor, may be an alternative treatment for such patients.

The affiliations of the adhers are instead of the adhe

in a double-blind study, we randomly assigned 5599 patients with atrial fibrillation who in a double-trind study, we randomly assigned 2004 patients with after institution who were at increased risk for stroke and for whom vitamin K antagonist therapy was were at increased risk for stroke and for whom visiting a antagonial inersity was unsuitable to receive apixaban (at a dose of 5 mg (wice da7y) or asprin & 1 to 324 mg unsuratore to receive aptication (see a casee or 3 ting twice easily) or asparing to the original per day), to determine whether apticaban was superior. The mean follow up period was per casy), to occermine waterner apixanon was superior. The mean rottow up period was 1.1 years. The primary outcome was the occurrence of stroke or systemic embelism.

Before enrollment, 40% of the patients had used a vitamin K antagoniss. The data neouse envolument, we're or the patients and used a vitation. A antagonist, the data and safety monitoring board recommended early termination of the study because of and sarry monoring touro recommended early termination or the study occasise or a clear benefit in favor of apixaban. There were 51 primary outcome events (1.6% per a ciest benera in tavor of apixaban. There were 51 primary outcome events [LIANs per year) among patients assigned to apixaban and 113 (3.7%, per year) among those year) among panents assigned to apraban and 115 (3.7% per year) among those assigned to aspirin (hazard ratio with apraban, 0.45; 95% confidence interval [CI]. assigned to aspirin (hazard ratio with apraidin, 0.45; 95% continuous interval 0.42, 0.62; Pc0.001). The rates of death were 3.5% per year in the aphaban group and on the second death were 3.5% per year in the aphaban group and 0.5% of 0.00 pc. 0 0.3.2 to 0.3.4; FCUAMI). The rates or ocan were 3.7% per year in the apexanan group and 4.4%, per year in the aspirin group (hazard ratio, 0.7%, 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 on the second of the incre were 44 cases or major decening (1.4% per year) in the apixadan group and 39 (1.2% per year) in the aspirin group (hazard ratio with apixadan, 1.13; 95% CI. 39 (1.2% per year) in the aspirin group (hazard ratio with apizaoan, 1.13; 95% U., 0.74 to 1.75; Pc.0.57); there were 11 cases of intracranial bleeding with apixaban 0.74 to 1.75; P=0.57E there were 11 cases or intracrantal necessing with aspiran and 13 with aspirin. The risk of a first hospitalization for cardiovascular causes was and 13 with aspirin. The risk of a first nospitalization for cardiovascular causes was reduced with apixaban as compared with aspirin (12.6k per years, 15.9% per year, recused with apitaban as compated with aspatin (12.0% per year vs. 13.7% per jc. 0001). The treatment effects were consistent among important subgroups.

CONCLUSIONS

In patients with atrial fibrillation for whom vitamin K antagonist therapy was unin patients with arrai internation for whom vitamin is antagonise therapy was un-suitable, apixaban reduced the risk of stroke or systemic embelsion without signifisurance, aparaman reduced the tisk of major bleeding or intractantal hemorrhage. (Funded by cantry increasing the risk of image recogning or intracranian nemormage, trumo Bristel-Myers Squibb and Pfizer; CinicalTriat's gov number, NCT00496709.)

Downloaded from neigh org on February 10, 2011. For personal list only. No other uses without permission.

Some state of the control of the c raisoned from neum org on February 10, 2011. For personal use only. No other uses without permissis-From the NEIM Archive, Copyright (c) 2010 Massachusett Medical Society, All rights reserved.

The New Emphine Security of Medicine and The New Emphine Security of other uses a walkeded door seem on a security of the New York of the New York Australia (C. 2010 Manachaneni Medicine Security All on From the NEIM Anchors. Copyright (C. 2010 Manachaneni Medicine Security All on From the NEIM Anchors. Copyright (C. 2010 Manachaneni Medicine Security All on From the NEIM Anchors. Copyright (C. 2010 Manachaneni Medicine Security All on From the Neimann Security All on Secur Connolly, et al. NEJM 2011

with the spinish in the read of spinish of spinish

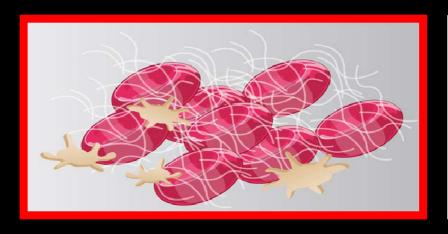
E., Hamilton, ON LBL 2X2, Canada, or at *A complete list of the AVERROES IA pix

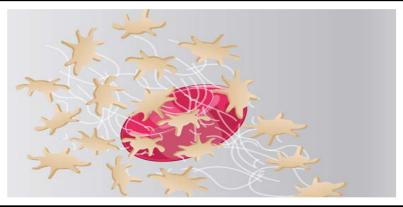
aban Versus Acetylsalcylic Acid [ASA] to Powers Stroke in Atrial Fabrilation Pa-Provent Stroke in Africa Figuration Fa-tents Who Have Failed or Are United able for Vitamin K Antagonist Treatme Steering Committee members and site investigators is available in the Sur entary Appendix, available at NEJM org.

This article (10.1056/NEJMoa1007432) war published on February 10, 2011, at NEJM

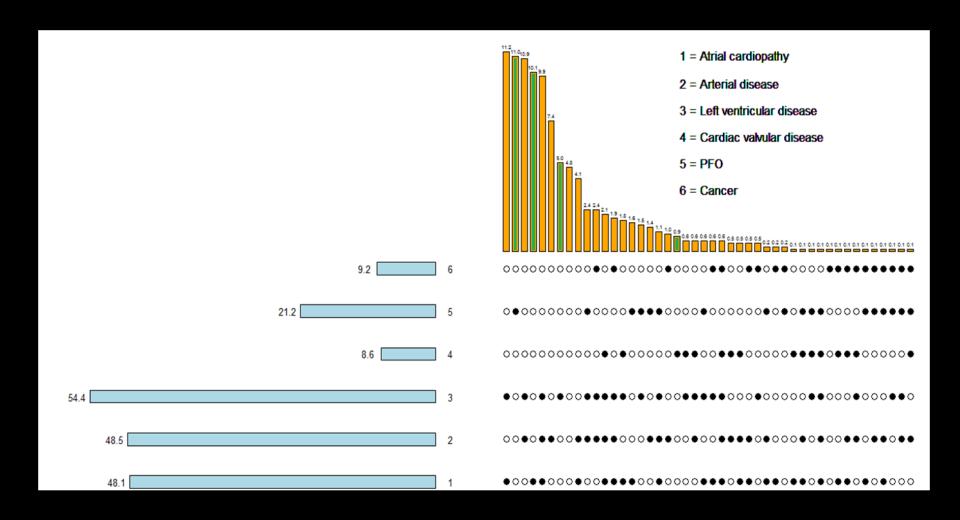
N Engl J Med 2011 Colorida G 102 Waterprops Megral Johns

ESUS: red & white thrombi

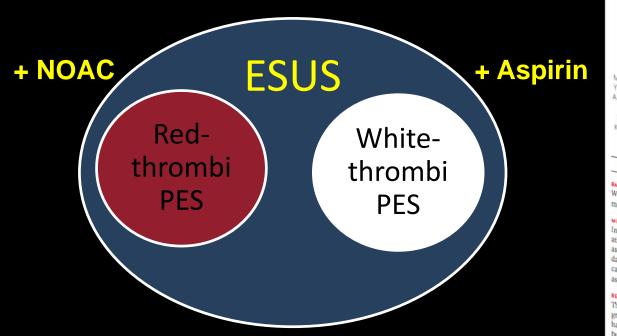




ESUS: Overlap of potential embolic sources



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, myo- cardial 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, J.W. Eixelboom, S.J. Connolly, J. Bosch, G.R. Dagenars, R.G. Trans, O. Shestakovska, R. Diaz, M. Alings, E.M. Lonn, S.S. Anand, P. Widimsky, O. Shestakovska, K. Diaz, M. Anngs, E.M. Long, S.S. Anano, P. Wiomnsky, M. Hoff, A. Avezum, L.S. Piegas, K.R.H. Branch, J. Probstfield, D.L. Bhatt, J. Zhu, Long, A. B. Manning, D. Long, Languilla, M. Cychannall, A. Kaldar, M.A. & Country, M. Fron, A. Avezum, L.S. Fregas, R.K.Fr. branch, J. Proostneio, U.L. bhatt, J. Chu, Y. Liang, A.P. Maggioni, P. Lopez-Jaramillo, M. O'Donnell, A. Kaklar, K.A.A. Fox.

Y. Liang, A.P. Maggioni, P. Lopez-Jaramillo, M. O'Donnell, A. Kaikkal, K.A.A. Fox, A.N. Parkhomenko, G. Ertl, S. Stork, M. Keltal, L. Ryden, N. Pogosova, A.L. Dans, C. Tano, Daddaran, T.L. Cinil, D.B. Vanhamman, A.L. Dans, C. Tano, Daddaran, T.L. Cinil, D.B. Vanhamman, C. Tano, Daddaran, T. Cinil, D.B. Vanhamman, C. Tano, Daddaran, C. Tano, Dadda 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. Fela, K. Yusoff, P.G. Steg. K.P. Metsarinne, N. Cook Bruns, F. Misselwitz, E. Chen, D. Leong, and S. Yusuf,

BACKGROUND

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

In this double-blind trial, we randomly assigned 27,395 participants with stable asharrentary vacces to recoive rhappened in the property of the stable place. In this double-blind trial, we randomly assigned 27,395 participants with static atherosclerotic vascular disease to receive rivatoraban (2.5 mg twice daily) plus atheroscierous vascular disease to receive rivatoxatum (2.5 mg twice daily), fivatoxatum (5 mg twice daily), or aspirim (100 mg once daily), or aspirim (100 mg once daily), or aspirim (100 mg once daily). aspiring two ring carce daily), irrationalistic to the twice daily), the primary outcome was a composite of cardiorascular death, stroke, or more castled in Greenland, space which were commonly as a remarkable of this discussion, when when the common two carcinolastics of this discussion, when the carcinolastic of the discussion of the discussion of the common terms. usays an epimary viscome was a composite or various state usate, states, or myo-cardial infarction. The study was stopped for superiority of the rivaroxaban-plus-

The primary outcome occurred in fewer patients in the rivaroxaban-plus-aspirin The primary outcome occurred in newer patients in the rivaroxanan-pais-aspiring group than in the aspirin-alone group (379 patients [4, %] by, 496 patients [5,4%]). group train in the aspiring arone group (3/4) particular (2.174) va. 770 particular (2.174) hazard ratio, 0.76; 95% confidence interval [CI], 0.66 to 0.86; Pc0.001; z=-4.126). hazaru mini, w/o; yyz connance miniva; [c.i.], woo to u.oo; recumul; z=-a,120). but major bleeding events occurred in more patients in the rivarcaban-plus-app. sin pages (300 patients); y.i. a. 130 maintain is occ. Language and a 30. occ. sin but major toccume creates occurred in more patients in the rotationatum-patients in group (288 patients [3, Fk] vs. 170 patients [1,9%]; hazard ratio, 1.70; 95% Cl. in group too paucits 15.5 kg vs. 170 paucits 14.7 m; meatu ratio, 140; 205; Pc0.001). There was no significant difference in intractanial or fatal bleeding between these two groups. There were 313 deaths (3.4%) in the rivarosaban-plus-aspirin group as compared with 378 (4.74) in the aspirin-alone group anni-puis-aspirin group as compared wan 576 (5-184) in the asparananne group (hazard ratio, 0.82; 95% CL, 0.71 to 0.96; P=0.01; threshold P value for signifi-(mazard ratio, 0.8.2; 97% CL, 0.71 to 0.90; V=0.01; threshold V value for agmits care, 0.0025). The primary outcome did not occur in significantly fiver patients in the accretional constraint of the care of the tance, 0.00423), the pathody outcome out not occur in against and personal in the rivaroxabar-alone group than in the aspirin-alone group, but major bleeding

Among patients with stable atherosclerotic vascular disease, those assigned to rivastronge paterna with states attachmenture vasculat uncess; those assigned to tree togathan (2.5 mg twice daily) plus aspirin had better cardiovascular outcomes and account above account toomous (e.) mg (w.e.c unity) pun aspura mas uciter varunvascular unitumes and more major bleeding events than those assigned to aspirin alone. Rivaronaban [5 mg acceptance of the control of the contro more major occume events than more assigned to aspure above. Avaitabase to ing twice daily) alone did not result in better cardiovascular outcomes than aspure advantage of the control of twace ususy) atome und not its until the control of the control of

The authors' full names, academic degrees, and affiliations are listed in the Appendis. Address reprint requests to Dr. Ekelboom at the population Health Retearch institute, McMaster Universit and Hamilton Health Sciences, David Braley Research Bldg. Hamilton General Hospital, 237 Barton St. E., Hamilton ON LEL 2X2, Canada, or at elkebj@

M complete list of the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) Investigaors is provided in the Supple Appendix, available at NEJM org.

This article was published on August 27, 2017, at NEJM.org.

DOI: 10.1056/NEJMoal709118 Colorida © XIII. Macorporers weeked 2006A

Tinkalinals gov number, NCI01776424.)

The state of the s

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 \rightarrow <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