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# LANDMARK TRIALS OF 2017/2018 THAT WILL IMPACT PRACTICE

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November 17, 2019

# CONFLICT OF INTEREST

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- ▶ I have no real or potential conflict of interest to report

# LEARNING OBJECTIVES

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**AT THE END OF THIS PRESENTATION, THE ATTENDEE SHOULD BE FAMILIAR WITH AND/OR BE BETTER ABLE TO:**

1. Select clinical trials examining topics relevant to a practicing hospital pharmacist
2. Provide an interpretation of the validity and/or applicability of these trial results to our patients in hospital practice
3. Understand how the results of these trials may impact clinical practice
4. Apply findings to patient-specific cases in our day-to-day practice

## CASE 1

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- ▶ **P.E. (57M)**, is admitted to Neurosurgery following a **generalized tonic-clonic seizure**. He was given IV Lorazepam 2mg and a loading dose of **Phenytoin 1.5g**, after which he was **continued on Phenytoin 200mg po q12hr**.
- ▶ **CT and MRI**: left fronto-temporal lesion; surgically debulked.
- ▶ **Pathology**: Glioblastoma multiforme.
- ▶ The plan from Medical Oncology is for P.E. to eventually receive chemo with **Temozolomide**.
- ▶ **On day 8** of admission he complains of swelling and difficulty moving his left leg.
- ▶ An ultrasound Doppler revealed a **DVT of the left popliteal vein**. He had received prophylaxis with Enoxaparin 40mg sc daily since post-op day 1.

## CASE 1: NOTABLE FINDINGS

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- ▶ Weight: 80kg; Height: 183 cm,
- ▶ SCr/GFR (Cockcroft-Gault) – 70  $\mu\text{mol/L}$  / 110 mL/min
- ▶ Platelet count - 150
  
- ▶ PMHx: CAD, Dyslipidemia, Hypertension
  
- ▶ Allergies: ASA (swelling)
  
- ▶ Medications:
  - ▶ - Clopidogrel 75mg po daily
  - ▶ - Rosuvastatin 10mg po daily
  - ▶ - Ramipril 10mg po daily

## CASE 1

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- ▶ Thrombosis has written for Edoxaban 60 mg orally once daily. What is your assessment?

# EDOXABAN

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- ▶ Factor Xa inhibitor
- ▶ Approved Indications:
  - Treatment of DVT and PE (post 5-10 days of treatment with LMWH)
  - Nonvalvular atrial fibrillation (to prevent stroke and systemic embolism)
- ▶ Dose: 60 mg oral once daily
  - 30 mg oral once daily for:
    - Weight less than or equal to 60 kg
    - Concurrent therapy with select P-gp inhibitors
    - CrCl 30-50 ml/min

# HOKUSAI VTE CANCER TRAIL

*The NEW ENGLAND JOURNAL of MEDICINE*

ORIGINAL ARTICLE

## Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

Gary E. Raskob, Ph.D., Nick van Es, M.D., Peter Verhamme, M.D.,  
Marc Carrier, M.D., Marcello Di Nisio, M.D., David Garcia, M.D.,  
Michael A. Grosso, M.D., Ajay K. Kakkar, M.B., B.S., Michael J. Kovacs, M.D.,  
Michele F. Mercuri, M.D., Guy Meyer, M.D., Annelise Segers, M.D.,  
Minggao Shi, Ph.D., Tzu-Fei Wang, M.D., Erik Yeo, M.D., George Zhang, Ph.D.,  
Jeffrey I. Zwicker, M.D., Jeffrey I. Weitz, M.D., and Harry R. Büller, M.D.,  
for the Hokusai VTE Cancer Investigators\*

N ENGL J MED 378;7  
Thromb Haemost 2015;114:1268-1276



## CLINICAL QUESTION

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- ▶ Following an initial course of five days of LMWH for the **treatment of cancer-associated venous thromboembolism**, is **edoxaban as safe and effective as dalteparin** for the **prevention of recurrent VTE** and **occurrence of major bleed**?

# METHODOLOGY

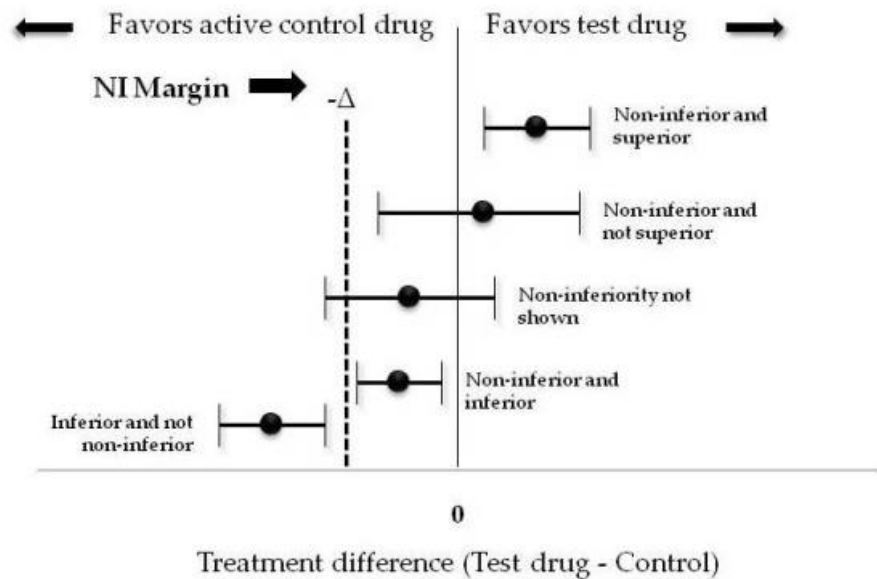
Population	<p>N= 1050 (525 edoxaban, 525 dalteparin) adult patients with active cancer and an acute symptomatic or incidental VTE</p> <p>Notable baseline characteristics: 98% active cancer, 53% metastatic disease, 72% with tx w/in 4 weeks of enrollment, mean age 64, 47% female, avg weight 79 kg, 7% CrCl 30-50 ml/min, 6% plts 50-100K, 23% meeting criteria for low dose edoxaban</p> <p><b>Notable exclusions:</b>(refer to supplemental appendix) increased risk of hemorrhage due to:</p> <ul style="list-style-type: none"><li>• Increased edoxaban plasma level</li><li>• Pharmacodynamic interactions</li><li>• Diseases/procedures with increased hemorrhagic risks</li></ul>
Intervention N=525	<p>LMWH for 5 days followed by oral edoxaban 60 mg daily</p> <ul style="list-style-type: none"><li>• 30 mg daily: CrCl 30-50 ml/min, weight &lt;60kg, concurrent P-glycoprotein inhibitor, or risk factors for bleeding</li></ul>
Comparator N=525	<p>SC dalteparin 200 IU/Kg daily for one month (max 18, 000 IU), then 150 IU/Kg SC daily thereafter</p>
Outcome	<p>Primary composite of recurrent VTE or major bleeding for at least 6 months and up to 12 months</p>

# METHODOLOGY

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- Multinational, prospective, randomized, open-label, blinded endpoint (PROBE), non-inferiority study
  - 114 centers in 13 countries
  - Enrollment: 2015-2016
- Sample size calculation:
  - MCID of 1.5 and a two-sided alpha of 0.05
  - N~1000 for a HR of 1.0 to expect 200 primary events (20%) at 12 months
  - 80% power to confirm non-inferiority of edoxaban
- Primary analysis: Modified intention-to-treat
- Secondary analysis: Per-protocol

# SIDEBAR: MCID/NON-INFERIORITY MARGINS



# RESULTS: PRIMARY OUTCOME MODIFIED ITT ANALYSIS

Table 2. Clinical Outcomes during the Overall Trial Period.\*

Outcome	Edoxaban (N=522)	Dalteparin (N=524)	Hazard Ratio (95% CI)	P Value
Primary outcome				
Recurrent venous thromboembolism or major bleeding — no. (%)	67 (12.8)	71 (13.5)	0.97 (0.70–1.36)	0.006 for noninferiority; 0.87 for superiority

→ (CI 0.70-1.36) P<0.006%  
✓ Non-inferiority established

# RESULTS: SECONDARY OUTCOMES MODIFIED ITT

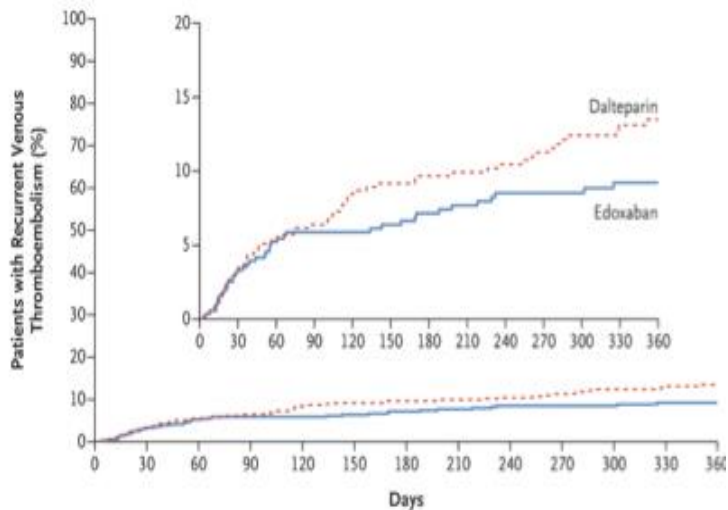
	Edoxaban N=522)	Dalteparin N=524)	Hazard ratio (95% CI)	P Value
<b>Secondary outcomes</b>				
Recurrent venous thromboembolism — no. (%)	41 (7.9)	59 (11.3)	0.71 (0.48–1.06)	0.09
Recurrent deep-vein thrombosis — no. (%)	19 (3.6)	35 (6.7)	0.56 (0.32–0.97)	
Recurrent pulmonary embolism — no. (%) <sup>†</sup>	27 (5.2)	28 (5.3)	1.00 (0.59–1.69)	
Major bleeding — no. (%)	36 (6.9)	21 (4.0)	1.77 (1.03–3.04)	0.04
Severity of major bleeding among those with major bleeding — no./total no. (%) <sup>‡</sup>				
Category 1	0	0		
Category 2	24/36 (66.7)	8/21 (38.1)		
Category 3	12/36 (33.3)	12/21 (57.1)		
Category 4	0	1/21 (4.8)		
Clinically relevant nonmajor bleeding — no. (%) <sup>§</sup>	76 (14.6)	58 (11.1)	1.38 (0.98–1.94)	
Major or clinically relevant nonmajor bleeding — no. (%) <sup>§¶</sup>	97 (18.6)	73 (13.9)	1.40 (1.03–1.89)	

**ARI = 2.9%**  
**NNH= 35 patients**

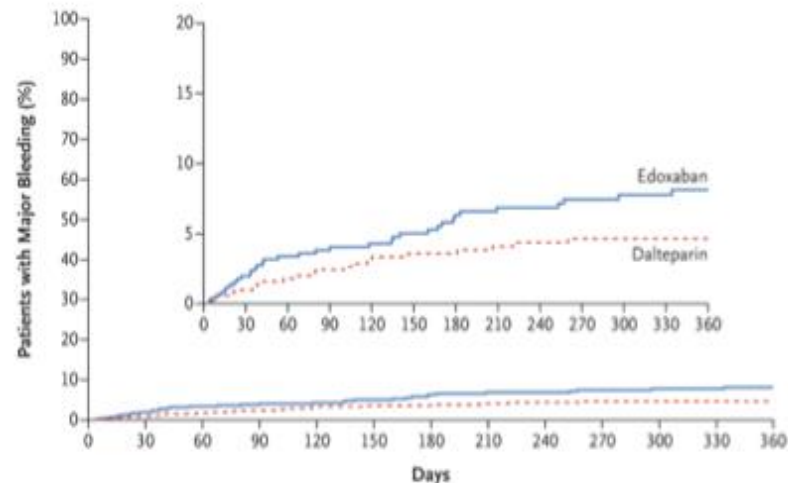
**NNT = 33 (for every 33 patients treated with edoxaban, one recurrent DVT is prevented)**

**NNH=35 (If you treat 35 patients with edoxaban, one will experience a major bleeding event)**

# RESULTS: KAPLAN-MEIER CUMULATIVE EVENT RATES FOR SECONDARY OUTCOMES



No. at Risk	0	30	60	90	120	150	180	210	240	270	300	330	360
Edoxaban	522	480	437	415	395	370	356	340	320	307	281	245	161
Dalteparin	524	488	452	423	389	370	358	348	333	321	282	246	174



No. at Risk	0	30	60	90	120	150	180	210	240	270	300	330	360
Edoxaban	522	484	447	426	404	375	358	343	323	308	282	248	168
Dalteparin	524	497	466	436	409	390	378	356	346	335	298	262	183

N ENGL J MED 378;7

# RESULTS: PER-PROTOCOL POPULATION

Clinical outcomes	Edoxaban (N=490)	Dalteparin (N=508)	HR with Edoxaban (95% CI)
Primary outcome: 1 <sup>st</sup> recurrent VTE or major bleed – no. (%)	51 (10.4)	53 (10.4)	<b>0.99 (0.68-1.46)</b> <b>P=0.0177</b> <b>(non-inferiority established)</b> <b>P=0.9685 (superiority)</b>
<b>Safety outcomes</b>			
Major bleeding	29 (5.9)	16 (3.1)	1.83 (0.99-3.39) P=0.0535
Clinically relevant non-major bleeding	64 (13.1)	18 (9.4)	1.35 (0.93-1.97)
Major or clinically relevant non-major bleeding	82 (16.7)	59 (11.6)	1.42 (1.01-1.98)



# INTERNAL VALIDITY: RISK OF BIAS

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▶ Are the results reliable?

- Low risk selection bias
- Unclear information bias
  - PROBE design = high risk of performance bias
  - VTE and bleed were measured in a standard, valid and reliable way = low risk detection bias
- Follow up well defined and complete = low risk attrition bias
- Clinically important outcomes considered and reported
- Heavy involvement of industry sponsor concerning



# INTERNAL VALIDITY: METHODOLOGY

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Strengths:

- ▶ Non-inferiority margin defined on basis of statistical reasoning and clinical judgment\*
- ▶ Adequately powered\*
- ▶ LMWH (dalteparin) as a comparator is standard of care
- ▶ Criteria for non-inferiority met in all sensitivity analyses
- ▶ Subgroup analyses pre-defined

# INTERNAL VALIDITY: METHODOLOGY

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Limitations:

- ▶ Composite primary outcome of safety and efficacy
- ▶ Wide non-inferiority margin of 1.5
- ▶ Small sample size
- ▶ Cannot be certain that the confidence interval exclude a clinically important difference
- ▶ Number of primary outcome events lower than anticipated
- ▶ Median duration of assigned treatment shorter in dalteparin group = influence efficacy of the assigned treatments?
- ▶ Lack of transparency

# AUTHORS' CONCLUSIONS

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- Following a five day lead-in with LMWH, once daily edoxaban for up to 12 months is non-inferior to subcutaneous dalteparin with respect to the composite outcome of recurrent venous thromboembolism or major bleeding.

## EXTERNAL VALIDITY

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- ▶ Statistically significant as per the study design
- ▶ Questionable clinical safety and efficacy
- ▶ Not widely applicable at this time
  - Cost and lack of ODB funding
  - Complex dosing conditions (e.g., drug interactions, labile renal function, hepatic function)
- ▶ Many questions remain unanswered.

**Additional prospective data required**

# WHAT THE EXPERTS ARE SAYING: GUIDELINE RECOMMENDATIONS

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- ▶ For *initial tx* of established cancer-associated VTE:
  - LMWH for 5-10 days in patients with CrCl>30 mL/min (NCCN Category 2A for 5-7 days; ITAC-CME Grade 1B for 10 days; ASCO Evidence-based, Strong recommendation, Strong-quality evidence)
    - Unfractionated heparin (UFH) or fondaparinux (NCCN Category 2A; ITAC-CME Grade 2D) if contraindication to LMWH

DynaMed Plus [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. 921773, treatment of cancer-associated thrombosis; [updated 2017 Dec 22, cited **2018/03/15**, ]; [about 33 screens]. Available from <http://www.dynamed.com/login.aspx?direct=true&site=DynaMed&id=921773>.

# WHAT THE EXPERTS ARE SAYING: GUIDELINE RECOMMENDATIONS

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- ▶ For *long-term* management of cancer-associated VTE
  - LMWH monotherapy for first 6 months (Strong recommendation)
  - LMWH or switch to VKA for long-term therapy after 6 months (strong recommendation)
  - DOACs (weak recommendation)
    - In patients with stable cancer not receiving chemo
    - In patients where VKA not available, or in patients who refuse

DynaMed Plus [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. 921773, Treatment of cancer-associated thrombosis; [updated 2017 Dec 22, cited **2018/03/15**, ]; [about 33 screens]. Available from <http://www.dynamed.com/login.aspx?direct=true&site=DynaMed&id=921773>.

# WHAT THE EXPERTS ARE SAYING: GUIDELINE UPDATES

## VTE-E, 2 of 5

Internal request:

### Combination Therapy Options

Consider whether the recommendation for LMWH followed by edoxaban, as listed with dosing details under "Combinations with Edoxaban", is supported by high-level evidence as an option for therapeutic anticoagulation for venous thromboembolism.

Uniform panel consensus supported revising the recommendation for LMWH followed by edoxaban to a category 1 treatment option.

### Supporting References:

- Prescribing information: Dalteparin sodium injection, for subcutaneous use; 2017. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/020287s069lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020287s069lbl.pdf).
- Prescribing information: Enoxaparin sodium injection for subcutaneous and intravenous use; 2013. Available at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/020164s102lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020164s102lbl.pdf)
- Prescribing Information: Edoxaban tablets, for oral use; 2017. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/206316s012lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/206316s012lbl.pdf).
- Raskob GE, Es Nv, Verhamme P, et al. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. *New England Journal of Medicine* 2018;378:615-624.



# THROMBOSIS INSIGHTS

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- ▶ Considerable practice variation seen between thrombosis physicians
- ▶ LMWH or edoxaban are reasonable for cancer associated VTE in the *right* patient
  - Meaningful discussion:
    - Will it interact with my chemotherapy?
    - Is it safe and effective?
    - Is it convenient (tablet vs needles)?
- ▶ Oral agents have been used for some time with good results
  - Decreased cost, increased compliance and convenience
- ▶ The next few months anticipated to be chaotic, however standardization expected this year with further prospective data and guideline updates

# THROMBOSIS INSIGHTS

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- ▶ When LMWH may be a better option:
  - GI/GU malignancy
  - Patients at increased risk of bleed
    - Eg: DAPT, acute leukemia, profound thrombocytopenia
  - Extremes of weight
  - Drug interactions with known or potential clinical implications
    - (ex: gliomas requiring antiepileptics)
  - Fulminant hepatic failure

Dr. Marc Carrier, telephone communication, March 20, 2018

## BACK TO OUR PATIENT...

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- ▶ Phenytoin - **PGP Inducer** = decreased efficacy of DOACs.
- ▶ Clopidogrel - Risk versus benefit of combining Edoxaban with antiplatelet. (Of note, patient has an ASA allergy and cannot be changed over)
- ▶ Patient has excellent renal function (contraindication for use in Afib)
  - Query clinical implication for cancer-associated VTE treatment
- ▶ Temozolomide: grade 3/4 thrombocytopenia in up to 9% of patients.

**LMWH preferred anticoagulant in our patient**

## FUTURE RESEARCH

<b>Title</b>	<b>Rivaroxaban in the Treatment of Venous Thromboembolism (VTE) in Cancer Patients</b>
Intervention	Rivaroxaban 15 mg BID for 21 days, followed by 20 mg once daily over 3 months
Comparator	LMWH according to individuals study center
Primary Outcome	Patient-reported treatment satisfaction with Rivaroxaban in treatment of acute VTE in cancer patients compared to standard LMWH treatment

<b>Title</b>	<b>Apixaban for the Treatment of Venous Thromboembolism in Patients with Cancer (CARAVAGGIO)</b>
Intervention	Apixaban 10 mg BID for 7 days, followed by 5 mg BID (total treatment period: 6 months)
Comparator	Dalteparin 200 IU/kg sc x 1 month, then 150 IU/kg sc for 5 months
Primary Outcome	Recurrent venous thromboembolism

## BOTTOM LINE

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- ▶ Non-inferiority does not mean equivalent
  - important *relevant* difference may exist
- ▶ Edoxaban may be a reasonable convenient oral alternative to LMWH for the treatment of cancer related VTE *in select patients*
- ▶ Ongoing, larger trials required to define the role of DOACs for treatment of cancer associated VTE

## CASE #2

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- ▶ AS is a 65 year old female admitted to the orthopedic surgery unit, POD 0 for a total hip arthroplasty
- ▶ PMHx:
  - NSTEMI January 2018
    - PCI w/ DES prox LAD on DAPT with ASA 81 mg and clopidogrel 75 mg oral daily
    - Metoprolol 25 mg oral bid
    - Atorvastatin 80 mg oral daily
  - Dyslipidemia
  - HTN (perindopril 4 mg po qam)
  - T2DM (metformin 1g po BID, Gliclazide MR 30 mg po brk)
  - Osteoporosis (alendronate 70 mg po Sunday, acetaminophen prn),

## CASE #2

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- ▶ Post-operatively, the orthopedic resident has written for home medications to continue and to start:
  - Celebrex 100 mg po q12h x 7 days
  - Rivaroxaban 10 mg once daily for 35 days

**What is your assessment?**

## EPCAT-II TRIAL

*The* NEW ENGLAND  
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

FEBRUARY 22, 2018

VOL. 378 NO. 8

### Aspirin or Rivaroxaban for VTE Prophylaxis after Hip or Knee Arthroplasty

D.R. Anderson, M. Dunbar, J. Murnaghan, S.R. Kahn, P. Gross, M. Forsythe, S. Pelet, W. Fisher, E. Belzile, S. Dolan, M. Crowther, E. Bohm, S.J. MacDonald, W. Gofton, P. Kim, D. Zukor, S. Pleasance, P. Andreou, S. Doucette, C. Theriault, A. Abianui, M. Carrier, M.J. Kovacs, M.A. Rodger, D. Coyle, P.S. Wells, and P.-A. Vendittoli  
N ENGL J MED 378;8



## CLINICAL QUESTION

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- ▶ Following an initial course of **rivaroxaban for five days post-operatively**, is an additional **9 day course of thromboprophylaxis with aspirin for total knee arthroplasty or 30 day course for total hip arthroplasty**, as safe and effective for the prevention of symptomatic VTE and bleeding complications **compared to** extended prophylaxis for the identical periods with **rivaroxaban**?

# STUDY DESCRIPTION

Population	<p>N= 3424 adult patients undergoing elective unilateral primary or revision hip or total knee arthroplasty (mean age 62.8, 47.8% men, avg hospital stay 3.5 days, ~25% on long term ASA)</p> <p><b>Notable exclusions:</b> (refer to supplemental appendix)</p> <ul style="list-style-type: none"><li>• Hip or lower limb fracture in previous 3 months</li><li>• metastatic cancer</li><li>• hx major bleed, active PUD/gastritis</li><li>• CrCl &lt;30 ml/min</li><li>• plts &lt;100 x 10<sup>9</sup> /L</li><li>• chronic daily aspirin &gt;100 mg a day</li><li>• concomitant inducers/inhibitors of both P-gp and CYP3A4</li></ul> <p>*Discouraged but did not prohibit use of other non-steroidal anti-inflammatory agents.</p>
Intervention N=1707	<p>In hospital prophylaxis with oral rivaroxaban 10 mg once daily up to and including POD5. POD 6: ASA 81 mg oral daily for thrombophylaxis for an additional nine (TKA) or 30 days (THA)</p>
Comparator N=1717	<p>In hospital prophylaxis with oral rivaroxaban 10 mg once daily up to and including POD5 and continued for an additional nine (TKA) or 30 days (THA)</p>
Outcome	<p>Primary efficacy: symptomatic VTE within the 90 days Primary safety: major or clinically relevant non-major bleeding</p>

# METHODOLOGY

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- ▶ Multicenter, double-blind, randomized controlled trial involving 15 university-affiliated Canadian health centers
- ▶ Non-inferiority design
- ▶ Sample size calculation
  - N= 3,392 (1696 subjects per group) assuming MCID 1.0%
    - Increased to N=3426 to account for loss to follow-up/withdrawal of consent
  - 90% power at a 5% significance level
- ▶ Primary analysis: intention-to-treat

# RESULTS

**Table 2. Primary Effectiveness and Safety Outcomes.**

Outcome	Rivaroxaban (N=1717)	Aspirin (N=1707)	P Value
	<i>no. of patients (%)</i>		
Venous thromboembolism	12 (0.70)	11 (0.64)	0.84*
Pulmonary embolism	6 (0.35)	5 (0.29)	
Proximal deep-vein thrombosis	4 (0.23)	4 (0.23)	
Pulmonary embolism and proximal deep-vein thrombosis	2 (0.12)	2 (0.12)	
Major bleeding	5 (0.29)	8 (0.47)	0.42
Any bleeding†	17 (0.99)	22 (1.29)	0.43

→ (CI -0.55 to 0.66) P<0.001%  
✓ Non-inferiority established

} Not statistically significantly different

\* P<0.001 for noninferiority, as defined by the upper boundary of the 95% confidence interval for the absolute between-group difference.

† This category includes major bleeding and clinically relevant nonmajor bleeding.

# RESULTS: SUBGROUP ANALYSIS

**Table 3. Primary Effectiveness and Safety Outcomes, According to Surgical Procedure.**

Outcome	Total Hip Arthroplasty			Total Knee Arthroplasty		
	Rivaroxaban (N=902) no. (%)	Aspirin (N=902) no. (%)	P Value	Rivaroxaban (N=902) no. (%)	Aspirin (N=902) no. (%)	P Value
Venous thromboembolism	5 (0.55)	7 (0.78)*	0.001†	7 (0.86)	7 (0.87)	1.00‡
Pulmonary embolism	2 (0.22)	3 (0.33)	0.001†	4 (0.49)	3 (0.37)	0.29
Proximal deep-vein thrombosis	3 (0.33)	1 (0.11)	0.001†	3 (0.37)	3 (0.37)	1.00
Pulmonary embolism and proximal deep-vein thrombosis	0	1 (0.11)	0.001†	0	1 (0.12)	0.001†
Major bleed	3 (0.33)	3 (0.33)	1.00	2 (0.25)	5 (0.62)	0.29
All bleeding‡	7 (0.78)	11 (1.22)	0.48	10 (1.23)	11 (1.37)	0.83

\* P=0.001 for noninferiority.

† P=0.03 for noninferiority.

‡ This category includes major bleeding and clinically relevant nonmajor bleeding.

**No statistically significant difference**

# RESULTS-SUBGROUP ANALYSIS

**Table 4.** Subgroup Analysis of Primary Outcomes, According to Use of Long-Term Aspirin Therapy.

Outcome	Long-Term Aspirin Therapy			No Long-Term Aspirin Therapy		P Value
	Rivaroxaban (N=429)	Aspirin (N=426)	Relative Risk (95% CI)	Aspirin (N=1281)	Relative Risk (95% CI)	
Venous thromboembolism	9 (2.1)	9 (2.1)	1.00	8 (0.62)	1.00*	
Major bleeding	4 (0.94)	4 (0.94)	0.22	4 (0.31)	1.00	
All bleeding†	5 (1.17)	8 (1.88)	0.42	14 (1.09)	0.70	

\* P<0.001 for noninferiority.

† This category includes major and clinically relevant nonmajor bleeding.

No statistically significant difference

# RESULTS-SECONDARY OUTCOMES

## ▶ Death

- 1 ASA vs. 0 Rivaroxaban (P not provided)

## ▶ Wound infection

- 2.6% ASA vs. 3.4% Rivaroxaban

## ▶ MI

- 0.1% in each group (P=NS)

## ▶ Stroke/TIA

- 0 in each group (P=NS)

*No statistically significant difference*

# INTERNAL VALIDITY: STRENGTHS

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- ▶ **Methodologically sound**
  - MCID defined on basis of statistical reasoning and clinical judgment
  - Strict non-inferiority margin
  - Adequately powered
  - Rivaroxaban as a comparator is standard of care
  - Subgroup analyses pre-defined
  - Non-inferiority established in ITT and PP analyses



# INTERNAL VALIDITY: STRENGTHS

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- ▶ **Low risk of bias = reliable results**
  - Selection bias
    - Adequate sequence generation
    - Appropriate allocation concealment
  - Performance bias and detection bias
    - Patients, physicians, study coordinators, outcome adjudicators blinded
    - Pharmacy had access to randomization lists in case of emergency requiring unblinding
    - Evaluation of suspected DVT and PE standardized
  - Attrition bias unlikely
  - Clinically important outcomes considered and reported
  - Not industry sponsored

# INTERNAL VALIDITY

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- ▶ Limitations:
  - Bio-creep?

## AUTHORS CONCLUSION

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- ▶ Aspirin is non-inferior to rivaroxaban for the prevention of symptomatic VTE after total hip or total knee arthroplasty following an initial 5 day post-operative course of rivaroxaban.

# EXTERNAL VALIDITY: CAN WE APPLY THE RESULTS TO OUR PATIENT?

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- ▶ Pro's:
  - Statistically significant and clinically meaningful outcome
  - ASA is convenient, inexpensive, widely available, few drug interactions

# EXTERNAL VALIDITY: CAN WE APPLY THE RESULTS TO OUR PATIENT?

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▶ Limitations:

- Feasibility of trial regimen for day surgery patients
  - Average length of hospital stay post-op slightly under 2 days at TOH
- ASA 81mg not ODB funded vs Rivaroxaban covered
- Subgroup analysis **suggests** similar outcome rates if previously on ASA or receiving concurrent NSAIDS
- Role of trial regimen in patients receiving DAPT unclear
- Role of trial regimen in patients with impaired renal function unclear
- Should we be approaching our obese patients differently?

# WHAT THE EXPERTS ARE SAYING

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- ▶ Surgeon consensus:
  - Lack of guideline consensus to direct management
  - Results of the EPCAT-II trial trailing behind current medical practice
    - Avg length of hospital stay now 2 days
  - Standard of practice for **most** elective hip and knee arthroplasties at TOH
    - Exception to the regimen of rivaroxaban into ASA
      - Patients receiving concurrent CYP inducers, CYP inhibitors
      - Severe renal impairment
      - DAPT
  - Reduced bleeding rates (reported)
  - Reduced infection rated (observed)

J Gauthier, RPh, e-mail communication, March 12, 2018  
M Marien, MD, e-mail communication October 25, 2018  
W Gofton, MD, verbal communication, November 13, 2018

# WHAT THE EXPERTS ARE SAYING

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## How to handle the rejects?

### ▶ DAPT:

- *Pre-op:*

- **High risk patients** (i.e. early post-stenting) should be assessed by **thrombosis**
- D/C clopidogrel, continue ASA

- *Post-op:*

- **Day 0:** Lovenox 40 mg SC q24h x2 days, continue ASA, resume clopidogrel

### ▶ Renal impairment:

- No clear consensus; ideally UFH for a minimum of 10-14 days, then ASA

# WHAT THE EXPERTS ARE SAYING

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## How to handle the rejects

### ▶ Obesity:

- Disclosure: not well managed, not well studied
- Increased venous stasis, pro-inflammatory
- Previously, dose adjusted LMWH (e.g. Enoxaparin 40 mg SC BID)
- Unclear guidance with rivaroxaban, ASA...Anti-Xa?
- Demographic needs attention with our expanding population



# FUTURE DIRECTIONS

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- ▶ EPCAT-III (site recruitment in progress)
  - Direct head-to-head comparison ASA vs rivaroxaban

## FOOD FOR THOUGHT

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To what extent do we think aggressive, early mobilization of uncomplicated, stable patients post-op has dramatically reduced the incidence of VTE in patients who undergo elective TH/TKA?

## BACK TO OUR PATIENT...

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- ▶ Upon discussion with the orthopedic surgery resident:
  - D/C celebrex
  
- ▶ No evidence to support:
  - Option 1: Start Enoxaparin 40 mg SC qhs x 2days, continue ASA 81 mg oral daily and clopidogrel 75 mg oral daily
  - Option 2: Continue ASA 81 mg daily, start rivaroxaban 10 mg po daily x5 days. Resume clopidogrel POD 6

## BOTTOM LINE

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Among patients with total hip or total knee arthroplasty:

- ▶ Aspirin 81 mg daily, following a 5 day regimen of rivaroxaban 10 mg daily post-op, appears *no worse* than established therapy with rivaroxaban when taken for the specified duration
- ▶ Aspirin is a safe, effective and attractive agent for VTE prophylaxis in *most patients*
  - Convenient, inexpensive, well tolerated, few drug interactions, less adverse events, generic
  - *Consider avoiding study regimen in patients with severe renal impairment, concurrent CYP 3A4 inducers/inhibitors*

# BOTTOM LINE

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## Where should we focus our interventions?

- ▶ Prioritize the *outliers*
  - Impaired renal function
  - High cardiovascular risk on DAPT
  - The obese demographic
  - The “unstable” patient with post-op complications
  - Concurrent CYP inducers/inhibitors

## CASE #3

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- ▶ AH (65 M) presented to the ED 7 days prior with **hemiplegia** of the lower half of the contralateral face, upper and lower extremities, **aphasia**, **hemispatial neglect**, and a **gaze deviation**; preference towards the right consistent with a **right MCA stroke**.
- ▶ Investigations:
  - CT head: **Right MCA stroke**
  - Carotid doppler: <50% luminal stenosis
  - ECHO: negative for intracardiac thrombus
  - Bubble study: negative for PFO
  - ECG: HR 68, sinus rhythm
- ▶ Labs: cbc, plts, pTT, INR within normal limits

## CASE #3

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- Notable findings

- ▶ Weight: 80kg; Height: 183 cm,
- ▶ SCr/GFR (Cockcroft-Gault) – 70  $\mu\text{mol/L}$  / 110 mL/min
  
- ▶ NKDA
  
- ▶ PMHx: T2DM, HTN, TIA (2008), dyslipidemia
  
- ▶ Meds PTA:
  - Metformin 500 mg po bid
  - Perindopril 8 mg daily
  - ASA 81 mg po daily
  - Rosuvastatin 10 mg po qhs

## CASE 3

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- ▶ The neurology team has diagnosed the patient with an **embolic stroke of undetermined source** and prescribed **rivaroxaban 15 mg oral daily** for the **secondary prevention of stroke**.

**What is your assessment?**



# NAVIGATE ESUS TRIAL

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

N ENGL J MED 378;23

## CLINICAL QUESTION

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- ▶ In patients with recent **embolic stroke of undetermined source (ESUS)**, is anticoagulant therapy with **rivaroxaban** 15 mg once daily superior to antiplatelet therapy with **aspirin** 100 mg once daily, for reducing the risk of **recurrent ischemic or hemorrhagic stroke** and **systemic embolism**?

# STUDY DESCRIPTION

<p>Population</p> <p>(See trial for full list of inclusion and exclusion criteria)</p>	<p>N= 7123 patients ≥ 50 yo with non-lacunar ischemic stroke, without extracranial/intracranial atherosclerosis causing &gt;50% luminal stenosis in arteries supplying ischemic area and without risk factor for cardiac source of embolism, between 7 days and 6 months before screening were eligible for inclusion. (72% Caucasian, mean age 67, 62% men, 77% HTN, 25% DM, 18% prior stroke/TIA, 17% ASA use before qualifying stroke)</p> <p><b>Notable exclusions:</b> (see trial for full details)</p> <ul style="list-style-type: none"><li>• Severe disabling stroke (modified Rankin score of ≥4)</li><li>• Indication for chronic anticoagulation or antiplatelet therapy</li><li>• History of major bleed w/in 6 month, non-traumatic ICH, high risk for bleed</li><li>• Estimated GFR &lt;30 ml/min/1.73m<sup>2</sup></li><li>• Use of strong inhibitors of CYP 3A4 and P-glycoprotein</li><li>• Chronic or regular use of NSAIDs</li><li>• DAPT</li></ul>
<p>Intervention</p> <p>N=3609</p>	<p>Rivaroxaban 15 mg oral once daily + matching placebo</p>
<p>Comparator</p> <p>N=3604</p>	<p>Aspirin 100 mg oral once daily + matching placebo</p>
<p>Outcome</p>	<p><b>Primary efficacy:</b> time to recurrent stroke (ischemic, hemorrhagic, undefined, TIA) or systemic embolism</p> <p><b>Primary safety:</b> ISTH major bleeding</p> <p><b>Secondary efficacy:</b> composite death from any cause; death from CV cause, recurrent stroke, systemic embolism and MI; disabling stroke; fatal stroke</p> <p><b>Secondary safety:</b> life-threatening or fatal bleed; clinically relevant non-major bleed; ICH</p>

# METHODOLOGY

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- ▶ International, prospective, randomized, double-blinded, active comparator, event driven, phase III trial
- ▶ Superiority design
- ▶ Sample size calculation
  - N=7000 to detect a 30% reduction in primary efficacy outcome events in rivaroxaban assigned group
    - estimated rate of 3.8% per year among aspirin-assigned patients
  - 90% power and a two sided alpha of 0.05
- ▶ Primary analysis: intention-to-treat

# RESULTS: EFFICACY OUTCOMES

**Table 2. Efficacy Outcomes.\***

Outcome	Rivaroxaban Group (N=3609)	Aspirin Group (N=3604)	Hazard Ratio (95% CI)†
<i>no. of patients (annualized rate)</i>			
Primary efficacy outcome: any recurrent stroke or systemic embolism	172 (5.1)	160 (4.8)	
Secondary efficacy outcomes			
Any recurrent stroke‡	171 (5.1)	160 (4.7)	1.08 (0.87–1.34)
Ischemic stroke‡	157 (4.4)	146 (4.1)	1.01 (0.81–1.26)
Hemorrhagic stroke§	1 (0.0)	2 (0.1)	6.50 (1.47–28.8)
Systemic embolism	1 (<0.1)	2 (0.1)	0.50 (0.05–5.51)
Any recurrent stroke, death from any cause, or death from cardiovascular causes, or death from unknown causes¶	207 (6.2)	195 (5.8)	1.06 (0.87–1.29)
Stroke	41 (1.2)	29 (0.8)	1.42 (0.88–2.28)
Myocardial infarction	17 (0.5)	23 (0.7)	0.74 (0.39–1.38)
Death from any cause	65 (1.9)	52 (1.5)	1.26 (0.87–1.81)
Death from cardiovascular causes¶	34 (1.0)	23 (0.7)	1.48 (0.87–2.52)

*No statistically significant difference*

- ▶ Trial was terminated on October 5, 2017 at the second, pre-planned interim analysis, after 74% of the anticipated 450 efficacy events occurred.
- ▶ Rationale:
  - Excess risk of bleeding among rivaroxaban assigned patients
  - Absence of an offsetting benefit in reducing the risk of stroke
  - Little estimate of benefit being found if trial proceeded to completion

# RESULTS: SAFETY OUTCOME

**Table 3. Safety Outcomes.\***

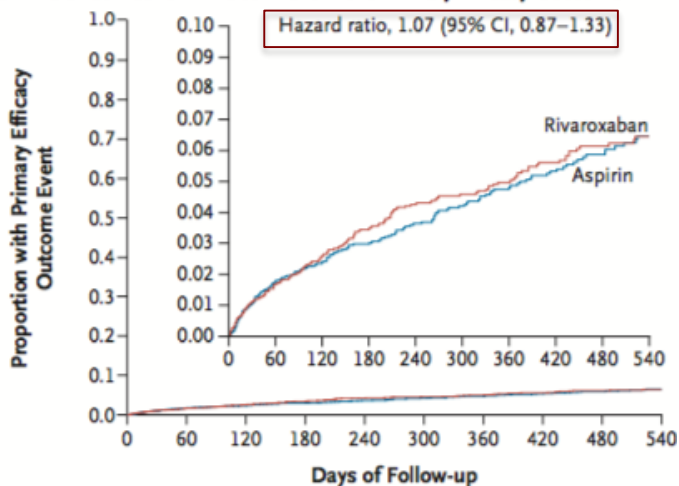
Outcome	Rivaroxaban Group (N=3609)	Aspirin Group (N=3604)	Hazard Ratio (95% CI) <sup>†</sup>	P Value
	<i>no. of patients (annualized rate)</i>			
Primary safety outcome: ISTH major bleeding <sup>‡</sup>	62 (1.8)	23 (0.7)	2.72 (1.68–4.39)	<0.001
Secondary safety outcomes				
Life-threatening or fatal bleeding	35 (1.0)	15 (0.4)	2.34 (1.28–4.29)	0.004
Clinically relevant nonmajor bleeding	118 (3.5)	79 (2.3)	1.51 (1.13–2.00)	0.004
Symptomatic intracranial hemorrhage <sup>§</sup>	20 (0.6)	5 (0.1)	4.02 (1.51–10.7)	0.003
Intracerebral hemorrhage	12 (0.3)	3 (0.1)	4.01 (1.13–14.2)	0.02
Subarachnoid hemorrhage <sup>¶</sup>	5 (0.1)	1 (0.0)	5.03 (0.59–43.0)	0.10
Subdural or epidural hematoma <sup>¶</sup>	3 (0.1)	2 (0.1)	1.51 (0.25–9.02)	0.65

**NNH = 91 people treated for 1 year will result in one more occurrence of the primary safety outcome; median duration of treatment was 11 months**

ARI = 1.1% NNH 91

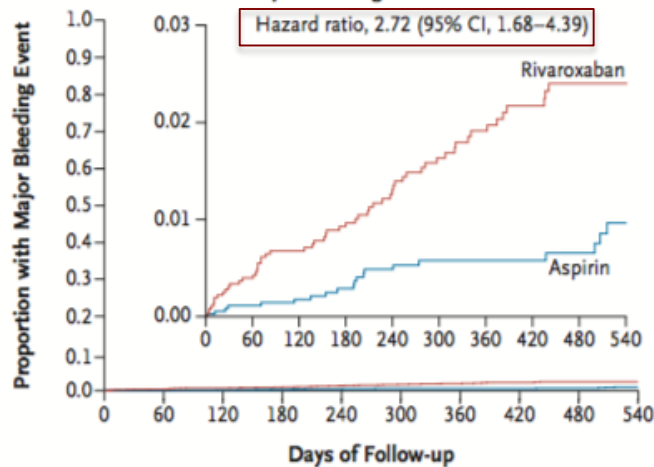
# CUMULATIVE INCIDENCE OF THE PRIMARY EFFICACY OUTCOME AND THE PRIMARY SAFETY OUTCOME, ACCORDING TO TREATMENT ASSIGNMENT

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



No. at Risk	0	60	120	180	240	300	360	420	480	540
Rivaroxaban	3609	3211	2854	2525	2156	1874	1584	1306	1046	786
Aspirin	3604	3205	2858	2531	2166	1880	1579	1319	1036	779

3 Kaplan–Meier Curves for Time to Major Bleeding Event



No. at Risk	0	60	120	180	240	300	360	420	480	540
Rivaroxaban	3609	3249	2906	2582	2206	1911	1615	1342	1071	807
Aspirin	3604	3254	2918	2597	2231	1939	1637	1371	1083	822

Mean follow up: 11 months

# NAVIGATE-ESUS MAIN RESULTS

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- ▶ No reduction in recurrent stroke by rivaroxaban 15 mg daily vs aspirin, and major bleeding was increased
- ▶ Trial terminated early with 74% of planned primary events, but adequate power to exclude benefit by rivaroxaban
- ▶ High rate of recurrent stroke at ~5% per year with either treatment



# INTERNAL VALIDITY: RISK OF BIAS

- Selection bias
  - Adequate sequence generation
  - Appropriate allocation concealment
  - Baseline characteristics between groups well balanced
- Performance bias and detection bias
  - Investigators, patients and adjudication committee were unaware of treatment assignments
  - Evaluation of primary safety and efficacy outcomes standardized
  - Central adjudication committee verified outcome events
- Attrition bias unlikely
- Clinically important outcomes considered and reported
- Free of selective outcome reporting
- Low industry involvement



**Low risk of bias = reliable results**

# INTERNAL VALIDITY: METHODOLOGY

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- ▶ Strengths
  - Pragmatic design, methodologically sound, statistically robust
  - ASA as a comparator is standard of care
  - Clinically appropriate, relevant and rigorous inclusion/exclusion criteria
  - Secondary/subgroup analyses pre-defined
    - Investigators acknowledge that number of events did not provide adequate power to determine significance
  - Consistent findings between ITT and PP analyses
  - Interim analyses pre-specified
  - Underpowered, but results spark considerable clinical interest
  - Precise results; can be certain the confidence intervals excluded clinically meaningful differences, despite trial being terminated early

# INTERNAL VALIDITY: METHODOLOGY

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- ▶ Limitations:
  - Did the investigators enroll the correct patients?
  - Was the dose of rivaroxaban appropriate at 15 mg daily rather than 20mg?\*
  - Should a dual agent have been considered?
  - Trial underpowered due to early termination
    - Too soon to detect a meaningful difference?

## AUTHORS CONCLUSION

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- ▶ **Rivaroxaban is *not superior* to aspirin** with regard to the **prevention of recurrent stroke** after an initial embolic stroke of undetermined source and is associated with a **higher risk of bleeding**

# EXTERNAL VALIDITY: CAN WE APPLY THE RESULTS TO OUR PATIENT?

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▶ Pro's:

- Study population reflective of patients seen in general practice
- Clinically meaningful outcomes reported and readily measurable
- Interventions evaluated standard of practice



✓Generalizable results

# EXTERNAL VALIDITY: QUESTIONS THAT REMAIN UNANSWERED

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- ▶ Unclear:
  - Relative effects of rivaroxaban vs aspirin on different embolic sources?
  - Potential role of rivaroxaban in patients with higher NIHSS and modified Rankin Scores?
  - Role of DOAC in patients previously on DAPT?
  - Patients with atherosclerotic lesions (i.e. high-grade intracranial stenosis, or carotid-artery stenosis of <50% etc) may have benefited from antiplatelet therapy. Altered results?
  - Geographic differences in treatment effects?

## WHAT THE EXPERTS ARE SAYING: GUIDELINE RECOMMENDATIONS

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- ▶ In patients with a history of non-cardioembolic stroke, oral anticoagulation for secondary prevention of stroke is associated with higher all-cause mortality and major bleeding events
- ▶ Patients with ischemic stroke or transient ischemic attack should be prescribed antiplatelet therapy for secondary prevention of recurrent stroke [Evidence level A]
  - aspirin 81-325 mg/day
  - combination aspirin 25 mg/day plus extended-release dipyridamole 200 mg/day
  - clopidogrel 75 mg/day

Stroke. 2014;45(7):2160. Epub 2014 May 1

Chest. 2012;141(2 Suppl):e601S

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CSN 2017, Oct

## **BACK TO THE CASE...**

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## FUTURE DIRECTIONS

<b>Title</b>	<b>Randomized, double-blind, Evaluation in secondary Stroke Prevention comparing the EfficaCy and safety of the oral Thrombin inhibitor dabigatran etexilate vs. acetylsalicylic acid in patients with Embolic Stroke of Undetermined Source (RE-SPECT ESUS).</b>
Intervention	Dabigatran 100 mg or 150 mg oral twice daily
Comparator	ASA 100 mg oral daily
Primary Outcome	Time to first recurrent stroke (ischemic, hemorrhagic, or unspecified)

<b>Title</b>	<b>Apixaban for the treatment of embolic stroke of undetermined source (ATTICUS randomized trial)</b>
Intervention	Apixaban 5 mg oral bid (2.5 mg oral bid in patients with a CrCl of 15-30 ml/min or with at least two of the following three factors: age $\geq$ 80, body weight $\leq$ 60 kg or SCr $\geq$ 133 $\mu$ mol/L)
Comparator	ASA 100 mg oral daily
Primary Outcome	Occurrence of at least one new ischemic lesion detected by FLAIR/DWI MRI after 12 months compared with baseline MRI

## BOTTOM LINE

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- ▶ The choice of antithrombotic therapy for secondary prevention of stroke in ESUS patients is challenging, as a clear treatment target has not been identified
- ▶ Rivaroxaban confers no added benefit compared to aspirin for the prevention of stroke in patients with ESUS
- ▶ Oral anticoagulant therapy may be associated with higher all cause mortality and major bleeding
- ▶ Long-term antiplatelet therapy with either aspirin, clopidogrel, or the combination of aspirin with extended-release dipyridamole should be considered for secondary prevention of stroke in ESUS patients

# QUESTIONS?

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