

Anticoagulants: ¿Which, What for, When, Why and How?

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Disclosure

- **Nothing to declare**

Session

Arrhythmias and Clinical EP

Ablation & Anticoagulation in Atrial Fibrillation

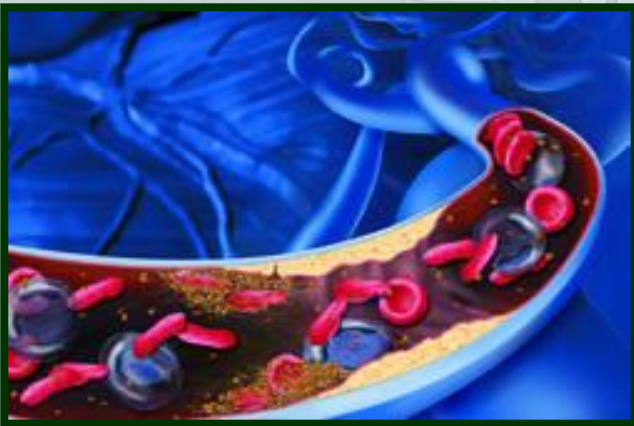
Anticoagulants:

¿Which, What for, When, Why and How?

- AC patient and Atrial Fibrillation (new diagnosis)
- Valvular Atrial Fibrillation
- Non valvular Atrial Fibrillation... 5 W's

1. ¿Which?

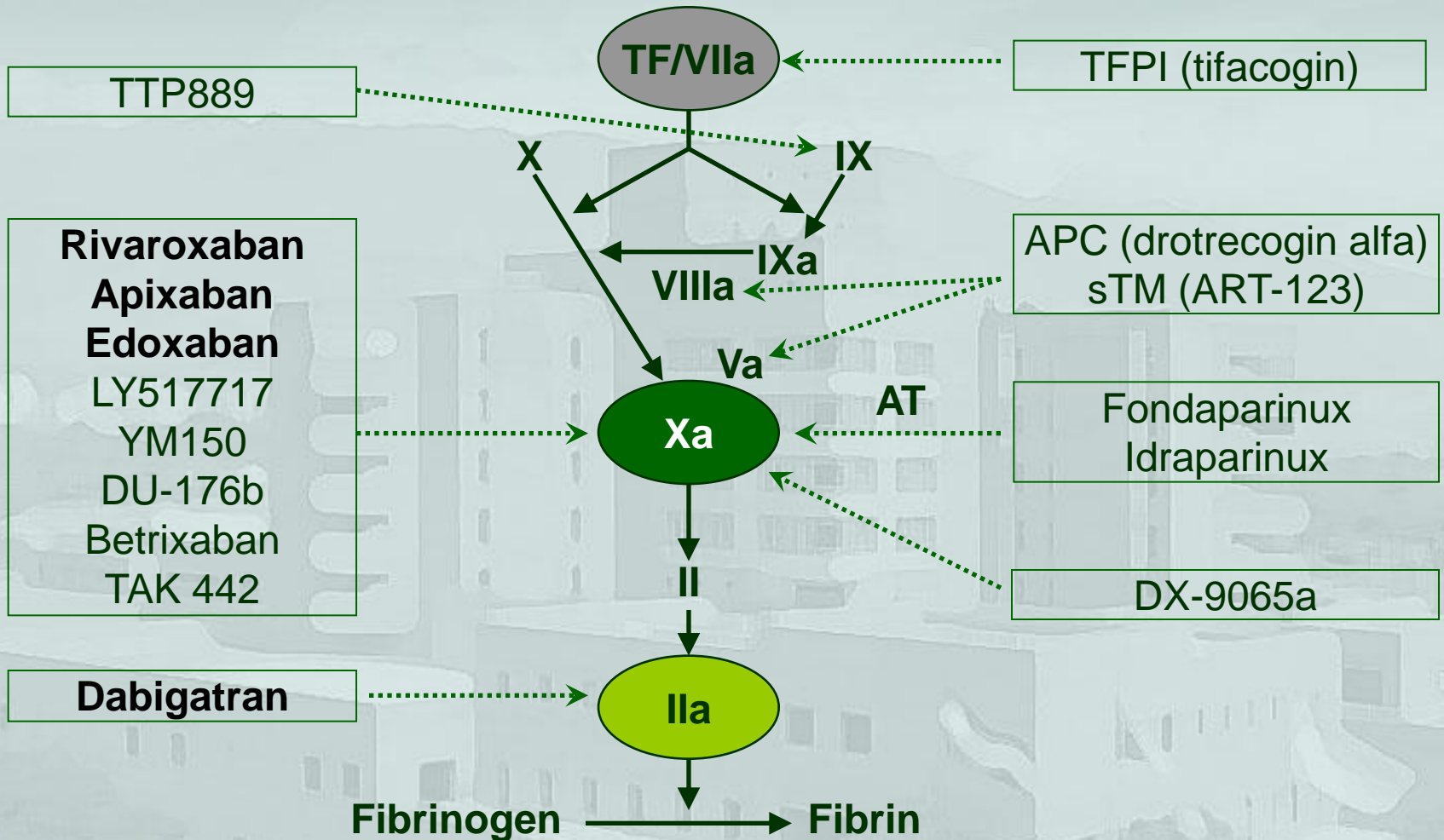
- Warfarin
- Dabigatran
- Rivaroxaban
- Apixaban
- Edoxaban
- Betrixaban
- Tercarafin
- DU-176b
- YM150
- AZ D0837
- TTP889: FIXa partial inhibitor



1. ¿Which?

ORAL

PARENTERAL



2. ¿What for?

- AF is the most common cardiac arrhythmia, affecting approximately 2.4 million Americans
- The prevalence of AF in the United States is 1% and increases with age, such that approximately 70 % of cases of AF are in patients between 65 and 85 years of age
- The number of patients with AF is expected to increase 150% by 2050, with more than 50 % of patients being over the age of 80

Lin HJ, et al. Stroke 1996;27:1760-1764

Hart RG, et al. J Am Coll Cardiol 2000;35:183-187

Marini C, et al. Stroke 2005;36:1115-1119

Rosamond W, et al. Circulation 2008;117:e25-146

Watson T, et al. Lancet 2009;373:155-166

Camm AJ, et al. Eur Heart J. 2010;31:2369-429

2. ¿What for?

- Patients with atrial fibrillation are at increased risk for stroke
- Atrial fibrillation increases the risks of stroke and death
- Atrial fibrillation is associated with an increase in the risk of ischemic stroke by a factor of four to five and accounts for up to 15% of strokes in persons of all ages and 30% in persons over the age of 80 years

ARISTOTLE. *NEJM*. 2011; 365 (11): 981 – 992
RELY. *NEJM*. 2009; 361 (12): 1139 – 1151
ROCKET - AF. *NEJM*. 2011; 365 (10): 883 – 891

Call - Colombia

2. ¿What for?

- Stroke related with atrial fibrillation is related with more disability and mortality
- Every hour, approximately 8 Americans suffer from an ischemic stroke arising from AF
- Oral systemic anticoagulation provides significant clinical benefit by reducing stroke or systemic embolism in patients with AF at moderate or high risk

Conolly SJ. et al. NEJM. 2009; 361 (12): 1139 – 51

Wallentin L. et al. NEJM. 2011; 365 (11): 981 – 92

Califf R. et al. NEJM. 2011; 365 (10): 883 – 91

Giugliano RP et al. NEJM. 2013; 369 (22): 2093 - 104

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3. ¿When?

CHAD2S 2 VASc	Pts (7,329)	Stroke Rate (%/y)
0	1	0
1	422	1,3
2	1,230	2,2
3	1,730	3,2
4	1,718	4,0
5	1,519	6,7
6	679	9,8
7	294	9,6
8	82	6,7
9	14	15,2

HAS BLED	Major Bleed Rate (%)
<u>H</u> ypertension	0 points= 1.13
<u>A</u> bnormal Liver/Renal function	1 points= 1.02
<u>S</u> troke	2 points= 1.88
<u>B</u> leeding	3 points= 3.74
<u>L</u> abile NR	4 points= 8.70
<u>E</u> lderly > 65 yo	>5 points= 12.5
<u>D</u> rugs or alcohol	

CHADS2	Pts (1.733)	Stroke Rate (%/y)
0	120	1,9 (1,2 – 3,0)
1	463	2,8 (2-3,8)
2	523	4,0 (3,1-5,1)
3	337	5,9 (4,6-7,3)
4	220	8,5 (6,3-11,1)
5	65	12,5 (8,2-17,5)
6	5	18,2 (10,5-27,4)

3. ¿When? Exclusion criteria in trials

¿¿¿Go for Warfarin???

Cardiac-Related Conditions

- Hemodynamically significant mitral valve stenosis
- Prosthetic heart valve (annuloplasty with or without prosthetic ring, commissurotomy and/or valvuloplasty are permitted)
- Transient atrial fibrillation caused by a reversible disorder (e.g., thyrotoxicosis, PE, recent surgery, MI)
- Known presence of atrial myxoma or left ventricular thrombus
- Active endocarditis

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3. ¿When? Exclusion criteria in trials

¿¿¿Go for Warfarin???

Hemorrhage Risk-Related Criteria

- Active internal bleeding
- History of or condition associated with increased bleeding risk including, but not limited to:
 - Major surgical procedure or trauma within 30 days before the randomization visit
 - Clinically significant gastrointestinal bleeding within 6 months before the randomization visit
 - History of intracranial, intraocular, spinal, or atraumatic intra-articular bleeding
 - Chronic hemorrhagic disorder
 - Known intracranial neoplasm, arteriovenous malformation, or aneurysm
- Platelet count < 90.000-100.000/uL
- Sustained uncontrolled hypertension: $\geq 180/100$ mmHg

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Wallentin L. et al. NEJM. 2011; 365 (11): 981 – 92

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3. ¿When? Exclusion criteria in trials

¿¿¿Go for Warfarin???

Concomitant Conditions and Therapies

- Severe, disabling stroke (modified Rankin score of 4 to 5) within 3 months or any stroke within 14 days before the randomization visit
- Transient ischemic attack within 3 days before the randomization visit
- Anemia (hemoglobin < 10 g/dL)
- Pregnancy or breast-feeding
- Known significant liver disease (acute clinical hepatitis, chronic active hepatitis, cirrhosis), or ALT >3 x the ULN

Conolly SJ. et al. NEJM. 2009; 361 (12): 1139 – 51

Wallentin L. et al. NEJM. 2011; 365 (11): 981 – 92

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4. ¿Why? Chronology

Warfarin vs placebo
2.900 pts

NOACs vs Warfarin
71.683 pts

6 Trials
Warfarin vs placebo

ROCKET AF
Rivaroxaban

ENGAGE AF-TIMI 48
Edoxaban

1989 - 1993

2009

2010

2011

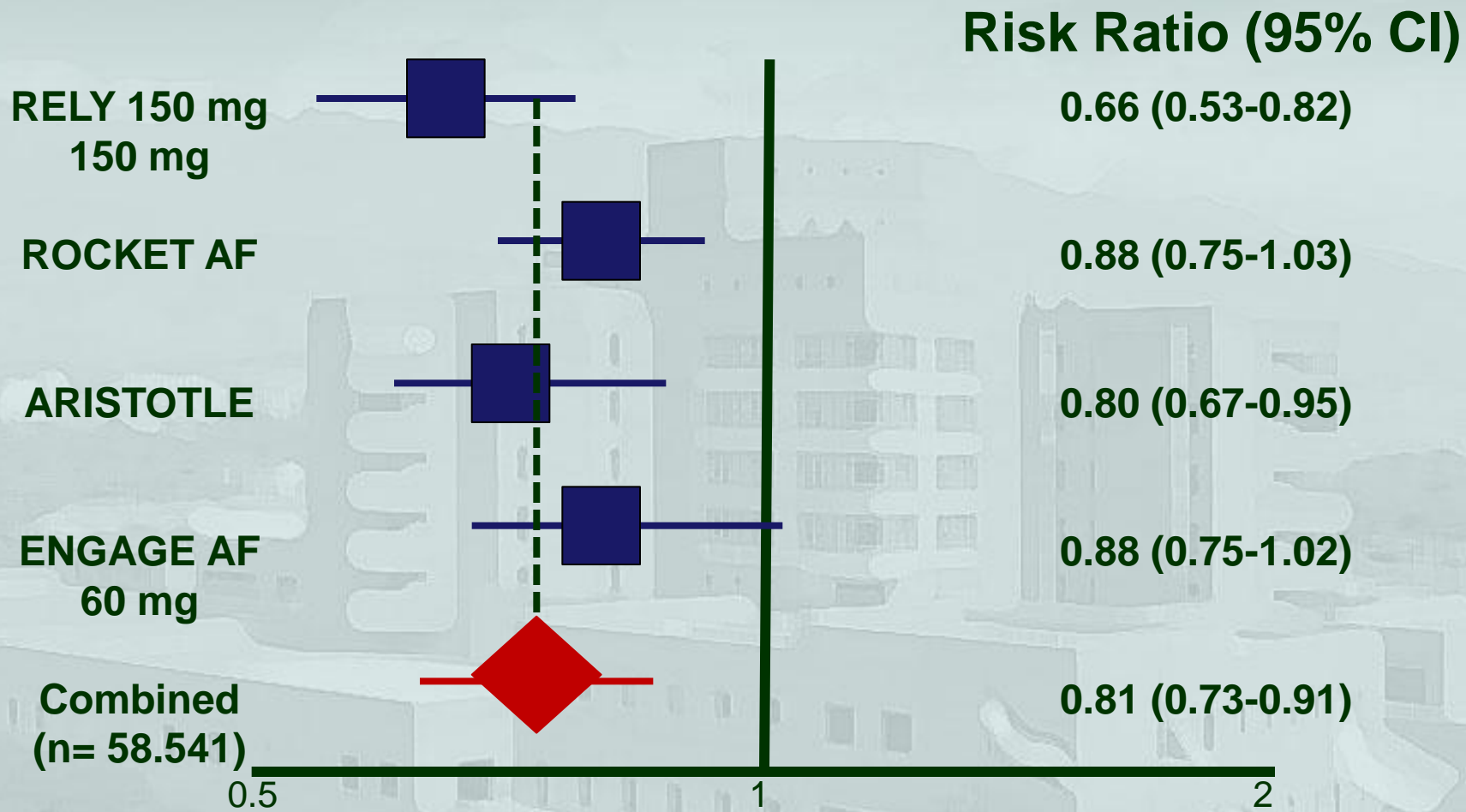
2013

RE-LY
Dabigatran

ARISTOTLE
Apixaban

4. ¿Why?

NOAC Meta-analysis Stroke - SE



Favours NOAC

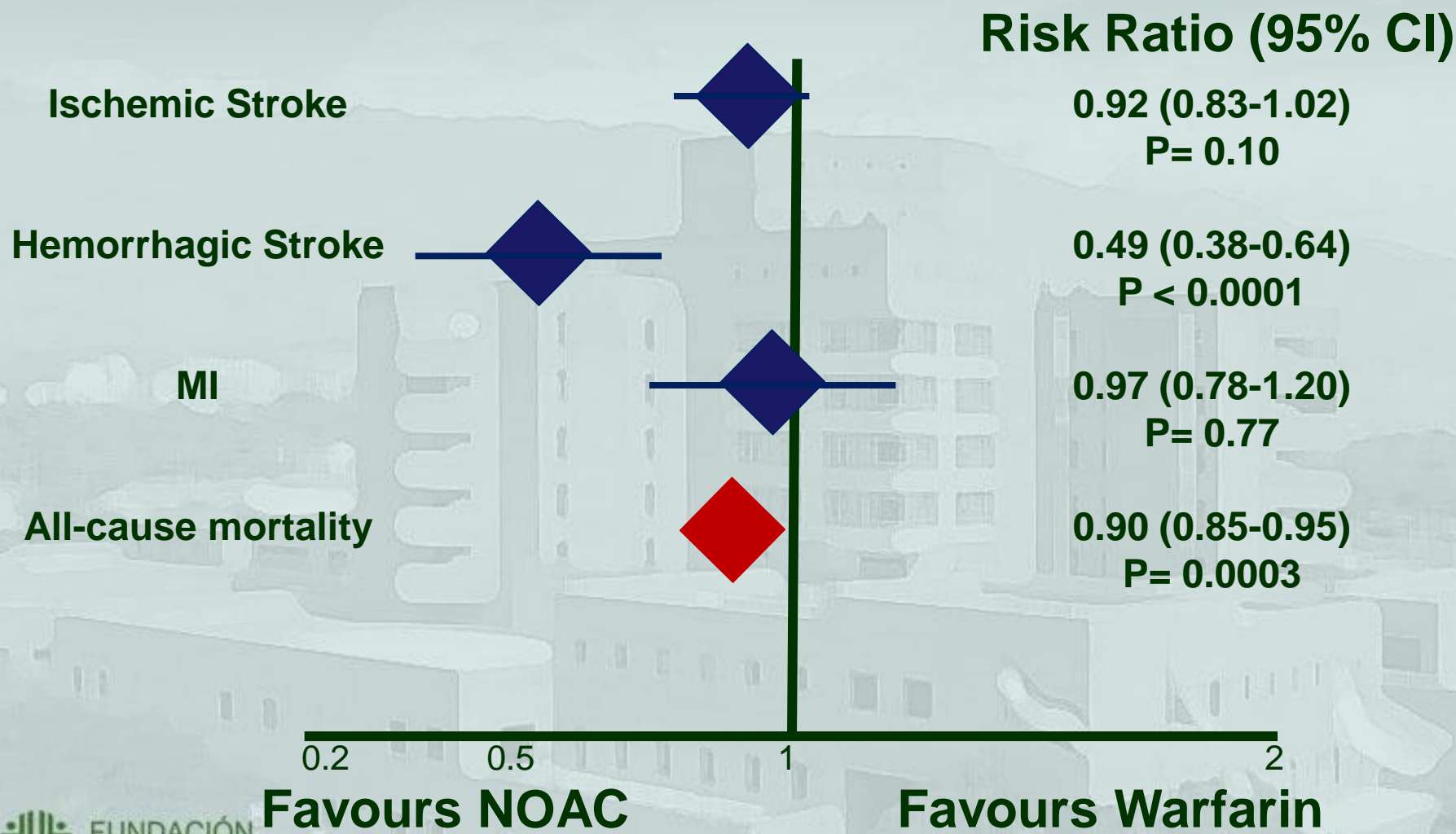
Favours Warfarin

Ruff CT et al. Lancet. 2014; 383: 955 - 962

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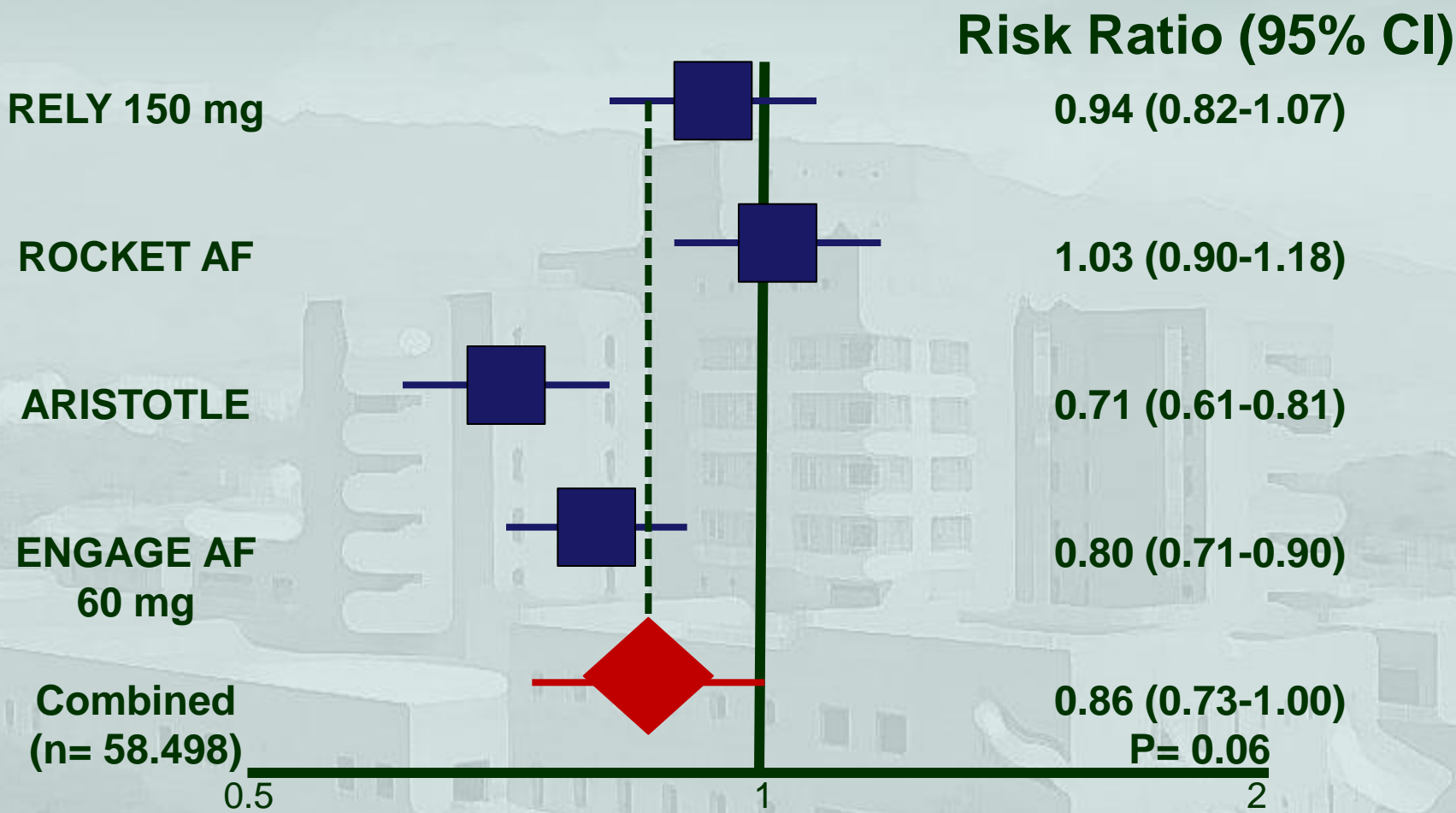
4. ¿Why? NOAC Meta-analysis

Secondary Efficacy Outcomes



4. ¿Why?

NOAC Meta-analysis Major Bleeding



Favours NOAC

Favours Warfarin

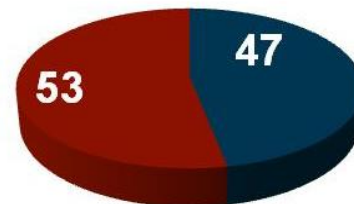
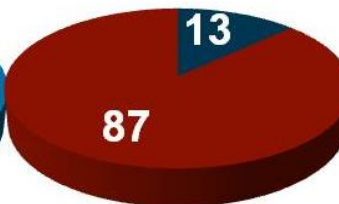
5. ¿How?

- **Which?** Different options
 - *VKA, NOACs, none*
- **What for?** Different indications
 - *AC, Valvular & non valvular Atrial Fibrillation*
- **When?** Different comorbidities
 - *Prosthetic valve, CKD, Thrombus, etc.*
 - *CHADS2 / CHA2DS VASc / HASBLED*
- **Why?** Different trials, results, options
 - *Rocket-AF, Rely, Aristotle, Engage...*

5. ¿How? Trials

	RELY	ROCKET-AF	ARISTOTLE	ENGAGE
N	18.113	14.266	18.201	21.105
Age, years	72 ± 9	73 (65-78)	70 (63-76)	72 (64-78)
Female, %	37	40	35	38
Dose	110 / 150 BID	20 QD	5 BID	30 / 60 QD
Design	Noninferiority	Noninferiority	Noninferiority	
CHADS2 Score	> 1	> 2	> 1	> 2
Primary Outcome	Stroke - SE	Stroke - SE	Stroke – SE	Stroke – SE
Safety Outcome	Major bleeding	Major bleeding	Major bleeding	Major bleeding
Paroxysmal AF, %	32	18	15	25
VKA Naive, %	50	38	43	41
TTR, mean %	64	55	62	68.4

CHADS₂



5. ¿How? Pharmacology

Characteristic	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	<i>II, VII, IX, X</i>	<i>Thrombin</i>	<i>Xa</i>	<i>Xa</i>	<i>Xa</i>
Renal Clearance, %	<i>Liver</i>	<i>80</i>	<i>33</i>	<i>25</i>	<i>50</i>
CYP Metabolism,%	<i>High</i>	<i>None</i>	<i>32</i>	<i>< 32</i>	<i>< 4</i>
Bioavailability, %	<i>98</i>	<i>3-7</i>	<i>60-80</i>	<i>60</i>	<i>62</i>
Half-life, hrs	<i>40</i>	<i>12 – 17</i>	<i>5 – 11</i>	<i>8 - 15</i>	<i>8 - 10</i>
Protein binding, %	<i>99</i>	<i>35</i>	<i>93</i>	<i>87</i>	<i>50</i>
Dosing	<i>QD</i>	<i>BID</i>	<i>QD</i>	<i>BID</i>	<i>QD</i>
Absorption with food	<i>Affect</i>	<i>Not affect</i>	<i>↑ 39%</i>	<i>Not affect</i>	<i>↑ 6-22%</i>
Intake with food	<i>Variable</i>	<i>No</i>	<i>Mandatory</i>	<i>No</i>	<i>?</i>
GI Tolerance	<i>Dyspepsia</i>	<i>Dyspepsia</i>	<i>No</i>	<i>No</i>	<i>No</i>

5. ¿How? Non-Valvular Afib...

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Stroke / Embolism	↑	↑ ↑?	↑?	↑ ↑?	↑ ↑?
ICH	↓	↑	↑	↑	↑
Major GI Bleed	↑	↓	↓	↑	↓
Major Bleed	↑	↑	↑	↑↑	↑↑
Manage Bleed	↑	↓	↓?	↓?	↓?
MI	↑	↓?	- ?	- ?	- ?
DC Rate / Dyspepsia	-	↓ / ↑	-	↑	-
Low renal fx / Cr Cl	↑↑	CI < 30	CI < 30	CI < 15	CI < 30
Cost (40\$ - 110\$/mo)	↑↑	↓	↓	↓	↓
Half life pros / cons	Dosing frequency, impact of missed dose, bleed management				
Monitoring	Need for/ability to monitor INR has pros & cons				
↑↑ Best	↑ Good	- Variable	↓ Problem		

¿Which, What for, When, Why and How?



Thanks...

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