Anti Coagulation for Stroke Prevention in Atrial Fibrillation The Case for Coumadin vs. NOACS

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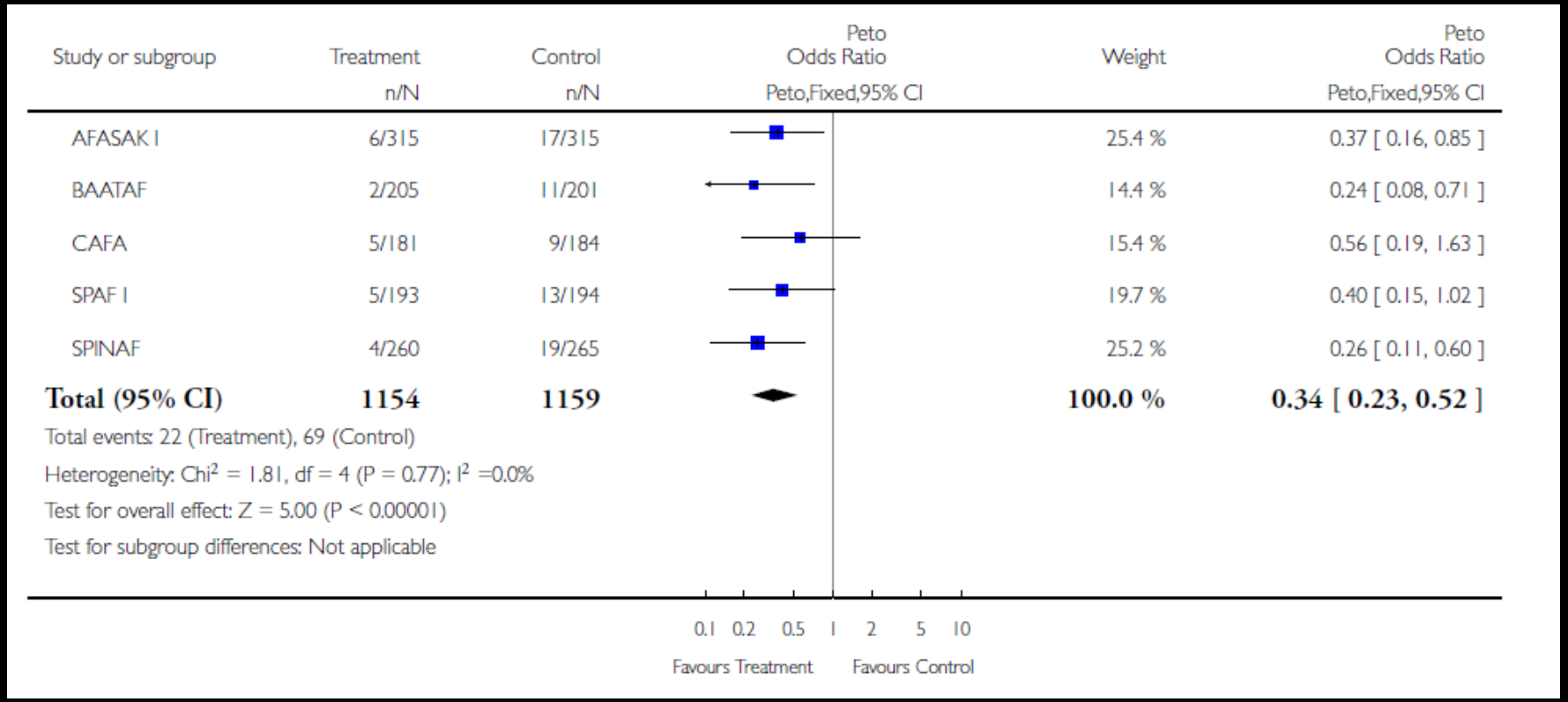
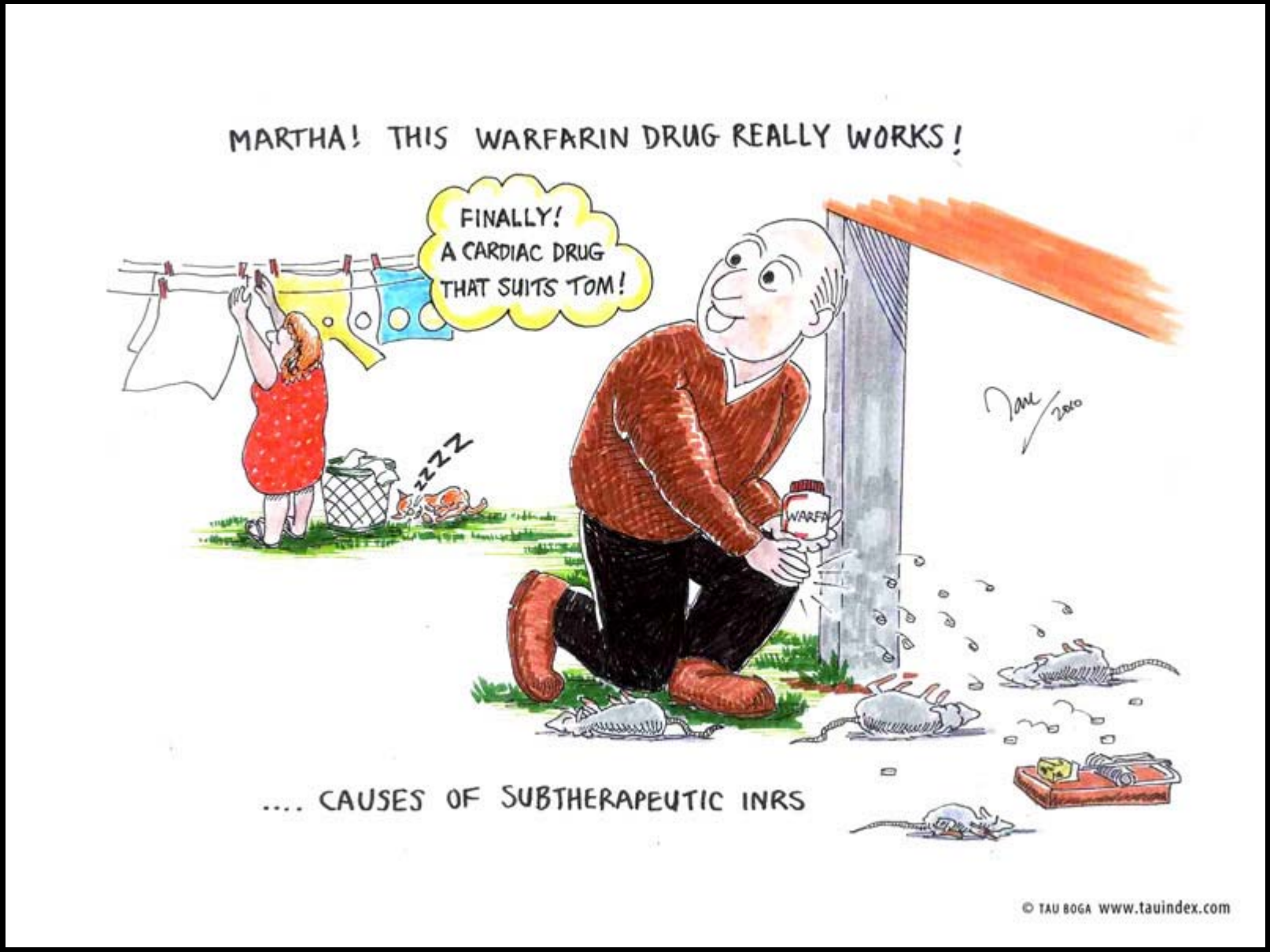
מודיעין על היריב

- ד"ר לילך דולב – אחראית מערך אישורי תרופות בחטיבת הקהילה של הכללית
- היא חשובה
- היא יכולה לא לאשר לי תרופות
- מה עושים?
- בתחבולות תעשה לך מלחמה (משלי כ"ד, ו)
- להיות בצד שלה - , לתת לה להגן על עמדתי כדי שתשכנע

למה קומדין עדיין מאד רלבנטית ושימושית
למניעת שבץ מוחי בפרפור פרוזדורים


Study or subgroup
Treatment n/N
Control n/N
Peto Odds Ratio Peto,Fixed,95% CI
Weight
Peto Odds Ratio Peto,Fixed,95% CI
AFASAK I 6/315 17/315 25.4 % 0.37 [0.16, 0.85]
BAATAF 2/205 11/201 14.4 % 0.24 [0.08, 0.71]
CAFA 5/181 9/184 15.4 % 0.56 [0.19, 1.63]
SPAF I 5/193 13/194 19.7 % 0.40 [0.15, 1.02]
SPINAF 4/260 19/265 25.2 % 0.26 [0.11, 0.60]
Total (95% CI) 1154 1159 100.0 % 0.34 [0.23, 0.52]
Total events: 22 (Treatment), 69 (Control)
Heterogeneity: Chi² = 1.81, df = 4 (P = 0.77); I² =0.0%
Test for overall effect: Z = 5.00 (P < 0.00001)
Test for subgroup differences: Not applicable
0.1 0.2 0.5 1 2 5 10
Favours Treatment
Favours Control


MARTHA! THIS WARFARIN DRUG REALLY WORKS!
FINALLY! A CARDIAC DRUG THAT SUITS TOM!
ZZZZ
WARF
.... CAUSES OF SUBTHERAPEUTIC INRS
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What they will tell you

- Indicated for all
- Fixed dose
- No need for monitoring
- Easy to use
- More effective than Coumadin
- Safer than Coumadin

Limitations of current treatment options for stroke prevention in AF

- Many patients with AF do not receive effective thromboprophylaxis due to limitations of currently available agents
- Aspirin is convenient to use but provides insufficient protection for stroke prevention in high-risk patients[1]
- Vitamin K antagonists have greater efficacy but a range of limitations make them challenging agents to use:[2,3]
  - Narrow therapeutic window
  - Variable and unpredictable pharmacokinetics and pharmacodynamics
  - Wide variety of drug–drug and drug–food interactions
  - Need for regular anticoagulation monitoring and dose adjustments
  - Slow onset and offset of action

1. ACC/AHA/ESC guidelines: Fuster V et al. Circulation 2006;114:e257–354 & Eur Heart J 2006;27:1979–2030; **2.** Turpie AG. Eur Heart J 2008;29:155–65; **3.** Khoo CW et al. Int J Clin Pract 2009;63:630–41

VKAs require regular anticoagulation monitoring

- Careful monitoring of patients being treated with VKAs is critical due to the:
  - Narrow therapeutic window
  - Unpredictable relationship between VKA dose and the anticoagulant response
  - Influence of the quantity of vitamin K in the diet that can change over time

INR = international normalized ratio; VKAs = vitamin K antagonists

1. Heneghan C et al. Lancet 2006;367:404–11; **2.** Levi M. Expert Rev Cardiovasc Ther 2008;6:979–85; **3.** Braun S et al. Anal Bioanal Chem 2009;393:1463–71; **4.** Connock M et al. Health Technol Assess 2007;11:iii–66

Requirements of new antithrombotic agents

- **At least as effective as warfarin**
- **Predictable response**
- **Wide therapeutic window**
- **Low incidence and severity of adverse effects**
- **Oral fixed dose**
- **No need for routine anticoagulation monitoring**
- **Low potential for food or drug interactions**
- **Fast onset and offset of action**

Adapted from Lip GY et al. EHJ Suppl 2005;7:E21–5

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Exclusion Criteria in Major NOAC Studies

	Pradaxa	Apixa	Rivaroxa
Valve Disease	Haemodynamically Relevant Valve Disease	Mod-severe MS	Hemodynamically significant mitral valve stenosis
Prosthetic Valves	+	+	+
Intracranial Bleeding	+	+	+
Hx of GI Bleeding	+ (1 YR)		+ (6 months)
BP >180/100	+	+	+
Renal Failure	GFR < 30	GFR <25 or Cr> 2.5	GFR < 30
ASA	-	+ >165 mg/d	>100 mg/d
Simultaneous ASA+thienopyridines	-	+	+
Planned Cardioversion			+

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Phase III AF Trials vs. Warfarin- Design

	Dabigatran RE-LY	Apixaban ARISTOTLE	Rivaroxaban ROCKET-AF
Dosing	150 mg x2 110 mg x2	5 mg x2 2.5 mg x2 (age ≥ 80 years, body weight ≤ 60 kg, serum cr ≥ 1.5 mg/dL)	20 mg once daily 15 mg once daily for CrCl 30–49 ml/min

Dose Adjustments

- Dabi:
  - >80 yr – 110 mg bid
  - >75 – treat with caution
  - GFR < 50– 110 mg bid
- Apixa:
- two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dl- 2.5 mg bid

- Rivaroxa: Cr Cl 30-50 – 15 mg /d

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- Antidotes

- No Tests yet to monitor therapeutic Effect
- Inability to test
- With Coumadin – home monitoring allows self titration and easy control of INR.
- Treatment by dedicated clinic allows monitoring of Coumadin every 6-8 weeks

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Ease of Use

- One daily dose
- Switching to other anticoagulants
- Perioperative management

Perioperative Managemant

- Coumadin- Easy. Can stop 4-5 days prior to procedure and monitor effect and restarting also easy

Perioperative Management

Table 2 summarizes discontinuation rules before invasive or surgical procedures.

Renal function (CrCL in ml/min)	Estimated half-life (hours)	Stop dabigatran before elective surgery	
		High risk of bleeding or major surgery	Standard risk
≥ 80	~ 13	2 days before	24 hours before
≥ 50 – < 80	~ 15	2-3 days before	1-2 days before
≥ 30 – < 50	~ 18	4 days before	2-3 days before (>48 hours)

Apixa

- ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of bleeding. This includes interventions for which the probability of clinically significant bleeding cannot be excluded or for which the risk of bleeding would be unacceptable.
- Eliquis should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding. This includes interventions for which any bleeding that occurs is expected to be minimal, non-critical in its location or easily controlled

Dabi

- Adjust the starting time of the VKA based on CrCL as follows:
- • CrCL ≥ 50 ml/min, start VKA 3 days before discontinuing dabigatran etexilate
- • CrCL ≥ 30-< 50 ml/min, start VKA 2 days before discontinuing dabigatran etexilate
- VKA to

Apixa

- When converting patients from Eliquis to VKA therapy, continue administration of Eliquis for at least 2 days after beginning VKA therapy. After 2 days of coadministration of Eliquis with VKA therapy, obtain an INR prior to the next scheduled dose of Eliquis. Continue coadministration of Eliquis and VKA therapy until the INR is ≥ 2.0.

Riva

- In patients converting from Xarelto to VKA, VKA should be given concurrently until the INR is ≥ 2.0. For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing guided by INR testing. While patients are on both Xarelto and VKA the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of Xarelto. Once Xarelto is discontinued INR testing may be done reliably at least 24 hours after the
- last dose

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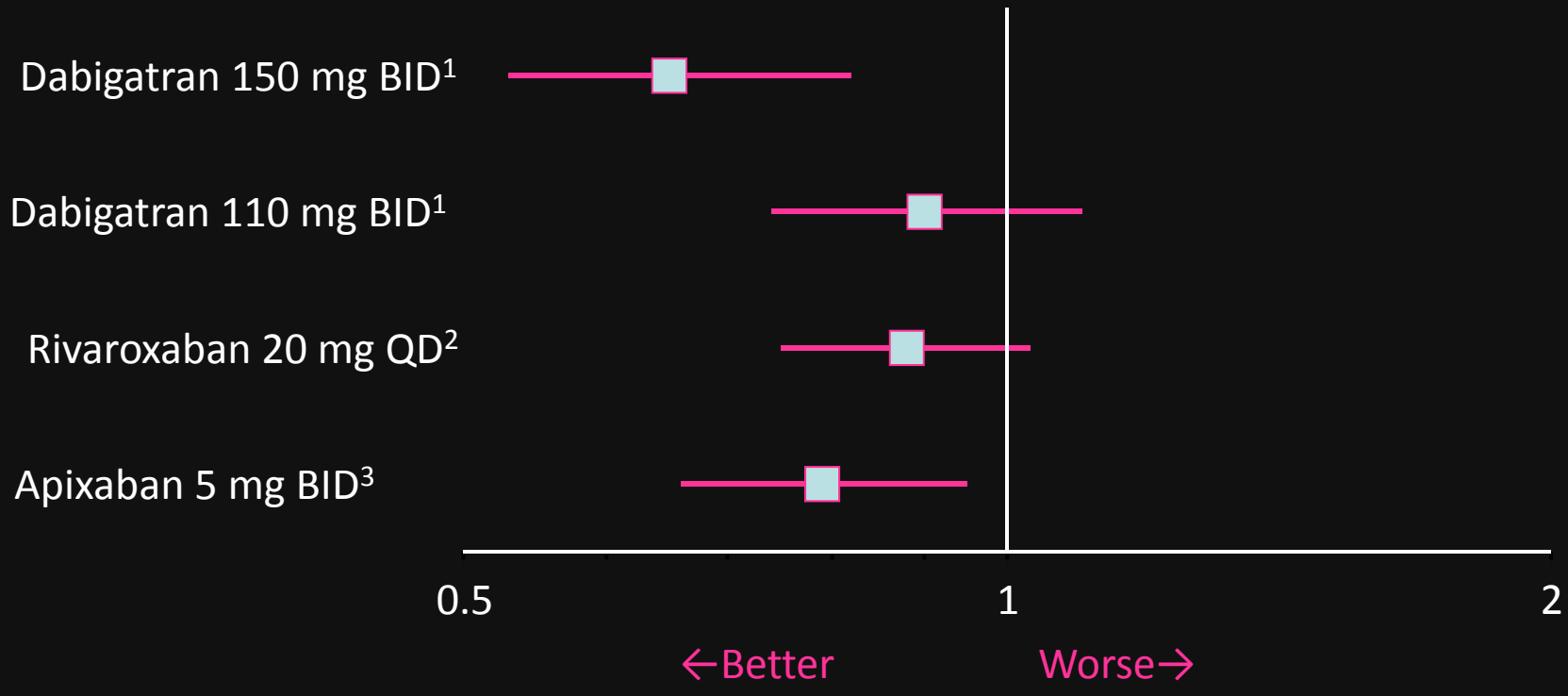
New Anticoagulant Therapies Vs. Warfarin:

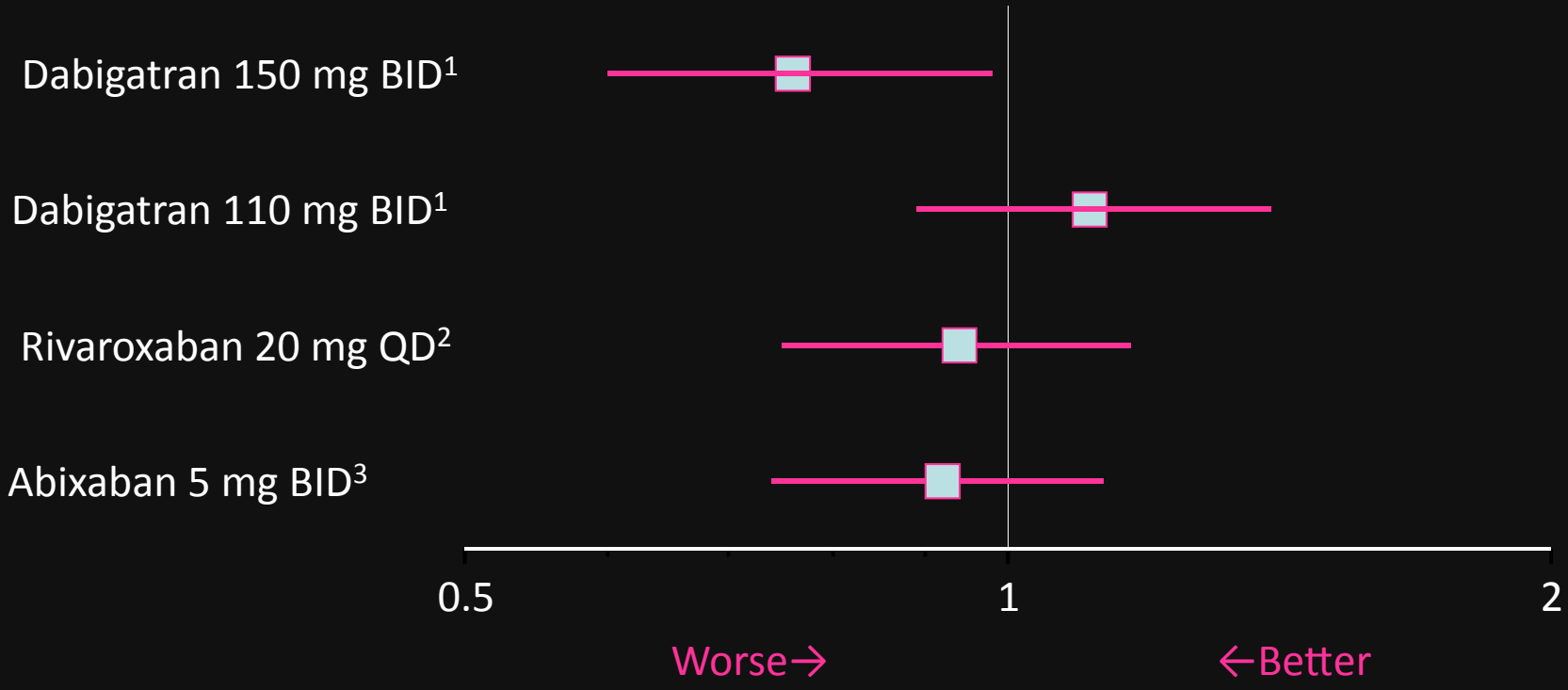
Stroke or Systemic Embolism



Connolly SJ et al. *N Engl J Med*. 2009;361:1139-1151. .1
Patel M et al. *N Engl J Med*. 2011; 365:883-891. .2
Granger CB et al. *N Engl J Med*. 2011;365:981-992. .3

New Anticoagulant Therapies Vs. Warfarin:

Stroke of Ischemic or Unknown Type



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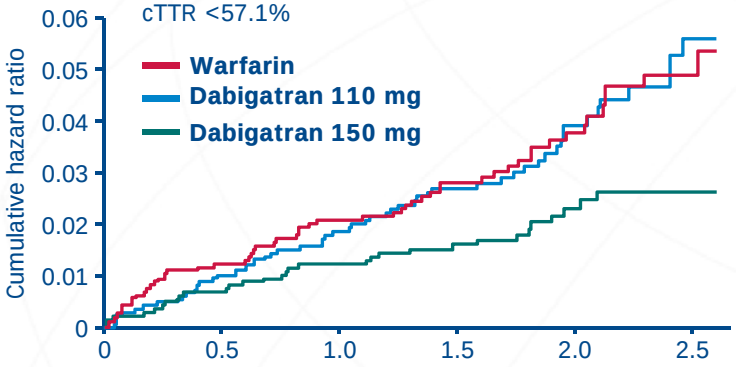
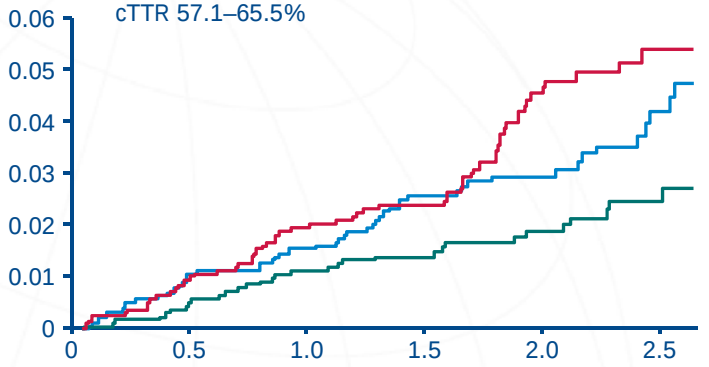
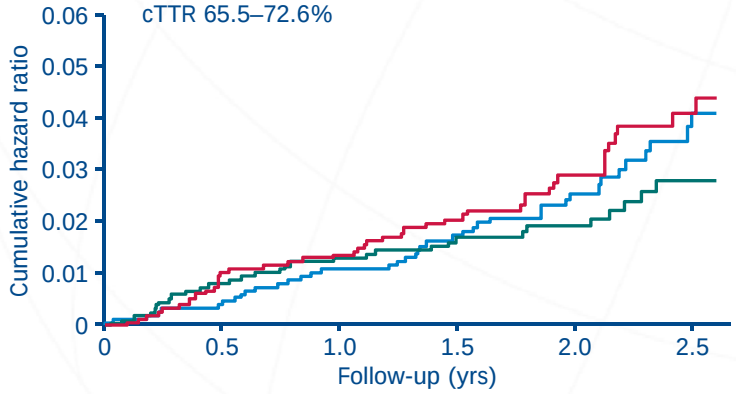
TTR subgroup analysis: time to primary outcome

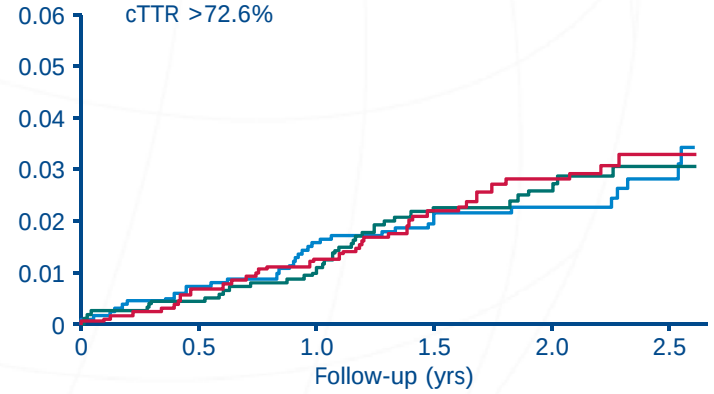




Number at risk						
Dabigatran 110 mg	1497	1450	1411	1144	649	274
Dabigatran 150 mg	1509	1469	1427	1164	699	283
Warfarin	1504	1445	1395	1094	640	242

	1524	1477	1440	1169	783	379
	1526	1493	1453	1192	801	394
	1514	1476	1438	1175	752	351





Number at risk						
Dabigatran 110 mg	1474	1456	1420	1142	760	370
Dabigatran 150 mg	1484	1445	1419	1153	761	369
Warfarin	1487	1458	1436	1150	755	359

	1482	1444	1405	1108	730	347
	1514	1487	1437	1135	750	367
	1509	1476	1440	1166	737	366

cTTR = centre mean TTR; TTR = time in therapeutic range

Wallentin L et al. Lancet 2010;376:975–83

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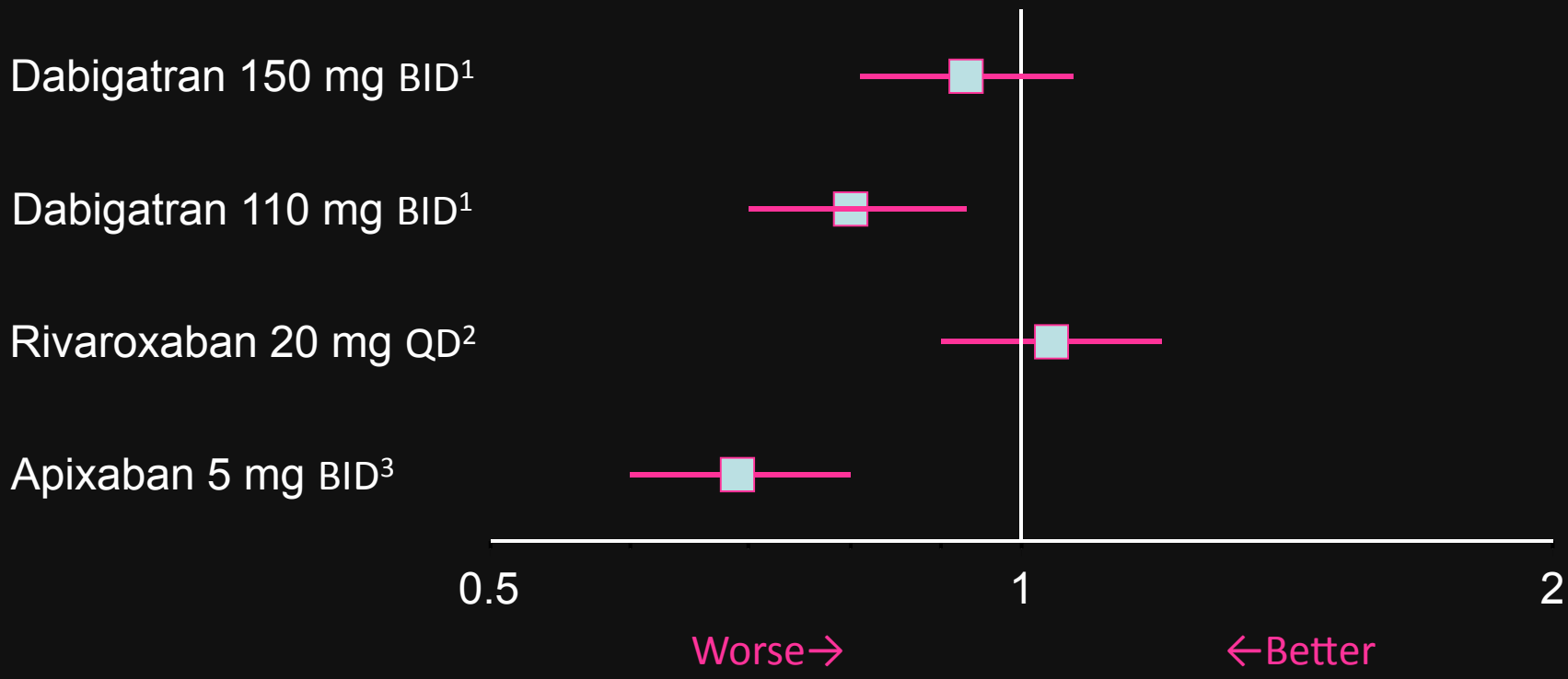
New Anticoagulant Therapies Vs. Warfarin:

Major Bleeding



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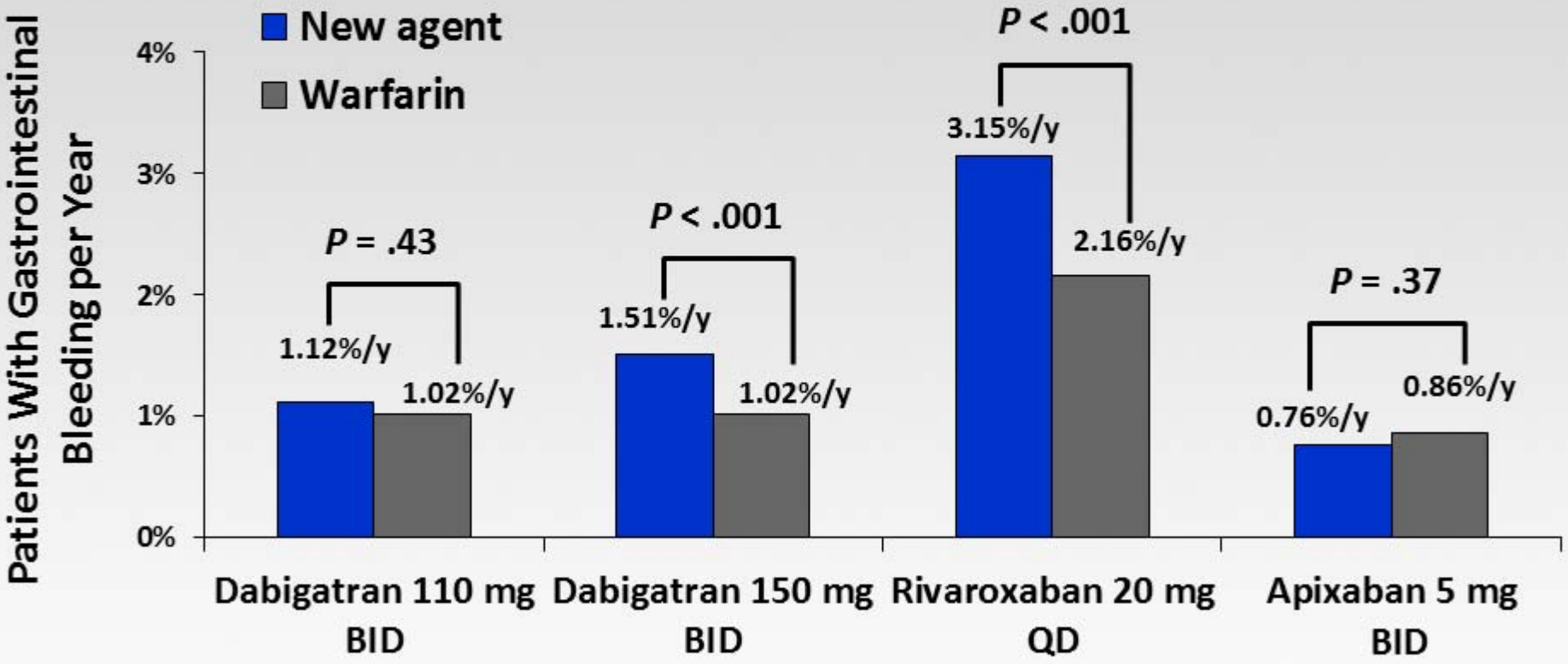
Recent Oral Anticoagulation Trials:
Gastrointestinal Bleeding



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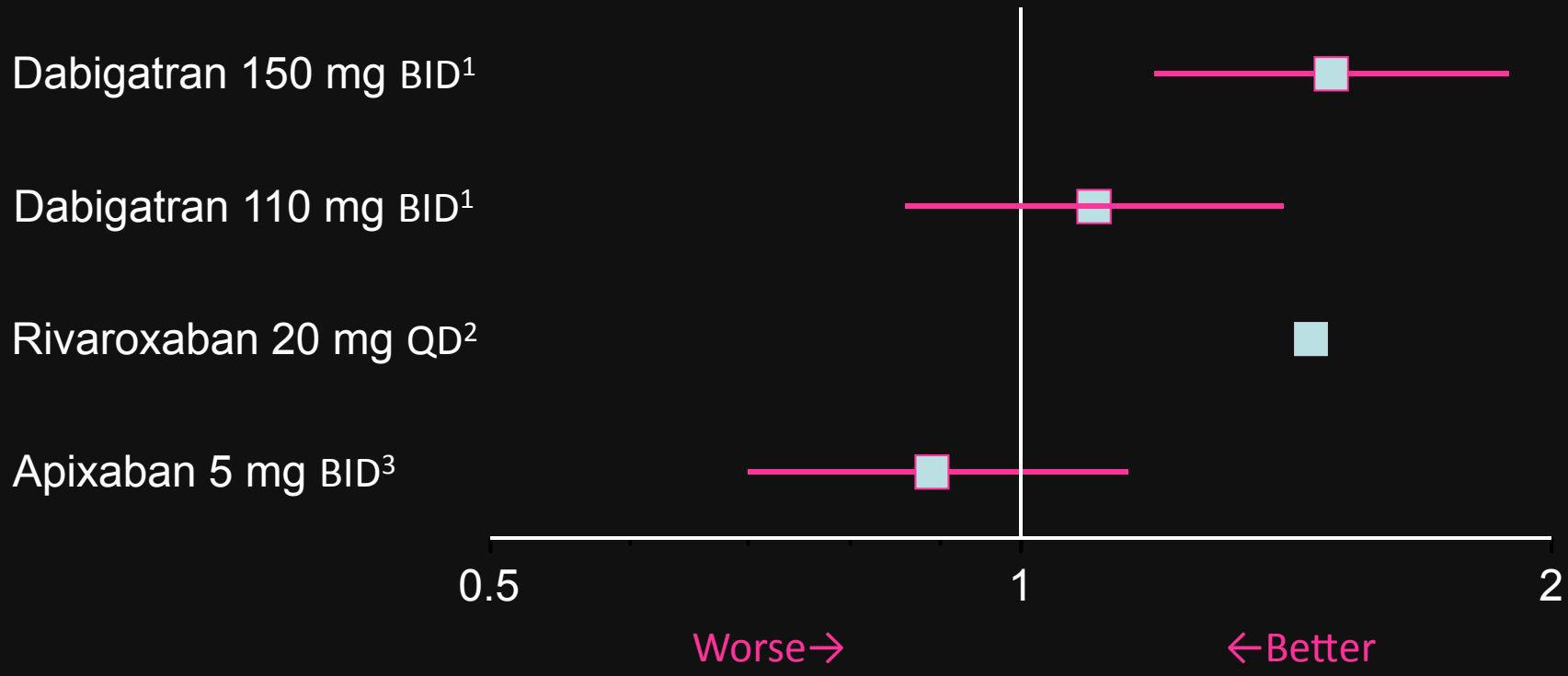
New Anticoagulant Therapies Vs. Warfarin:

Gastrointestinal Bleeding



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- Drug Interactions

Drug Interactions

	Dabigatran	Apixaban	Rivaroxaban
<u>P-gp Inhibitors</u> amiodarone, verapamil, quinidine, ketoconazole clarithromycin Itraconazole, tacrolimus and cyclosporine	↑ ↑ ↑reduce to 110 bid ↑ ↑ Contra- indicated ↑ Contra- indicated Contra- indicated Contra- indicated	↑ Contra- indicated ↑ Contra- indicated	↑ Contra- indicated ↑ Contra- indicated
Protease Inhibitors	Not Recommended	↑ Contra- indicated	↑ Contra- indicated
Dronedarone	Not Recommended		SHOULD BE AVOIDED
Dual antiplatelets	↑ bleeding	↑ bleeding	↑ bleeding
ASA/NSAIDS	↑ bleeding	↑ bleeding	↑ bleeding

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Antidotes

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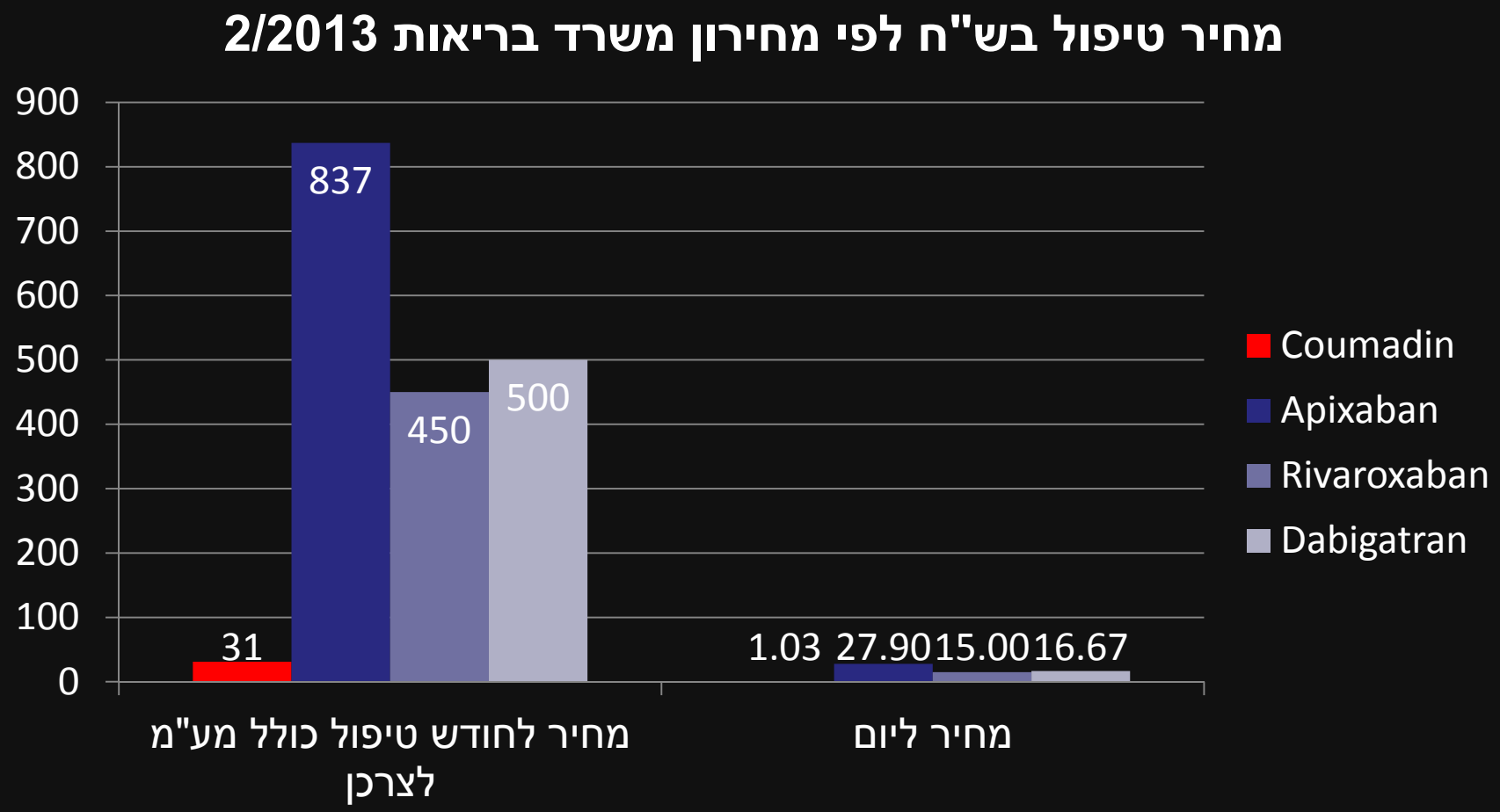
Cost



http://www.old.health.gov.il/pages/default.asp?maincat=1&catid=111&pageid=5089

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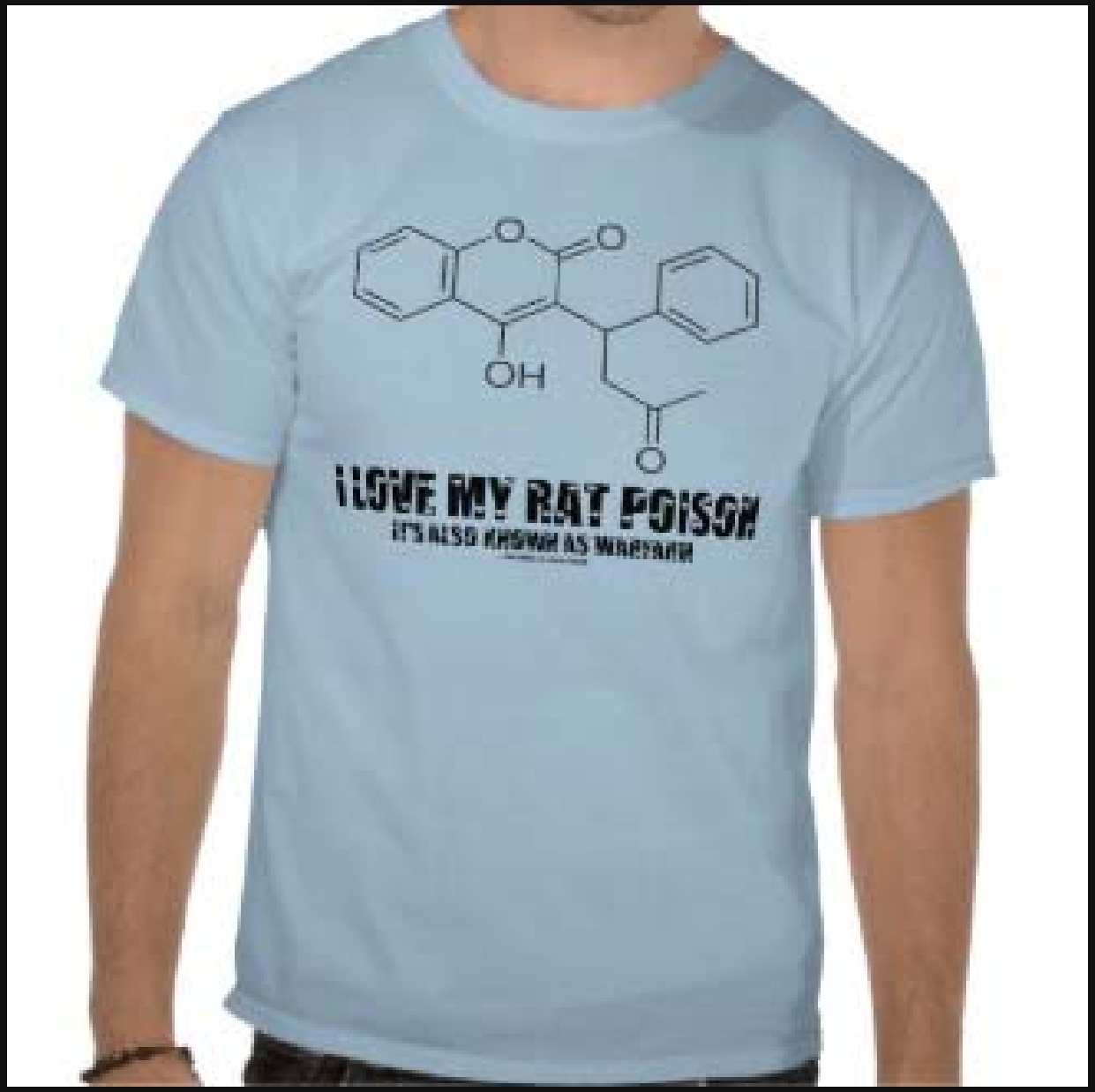
Conclusion

- NOACS are good alternatives
- They have their pluses and minuses
- They are not good for all
- Monitoring is not available
- Specific antidotes are not there yet
- Coumadin is still a good medication that is effective for stroke prevention in AF (valvular and NVAF)


OH
I LOVE MY RAT POISON
IT'S ALSO KNOWN AS WARFARIN

Thank You

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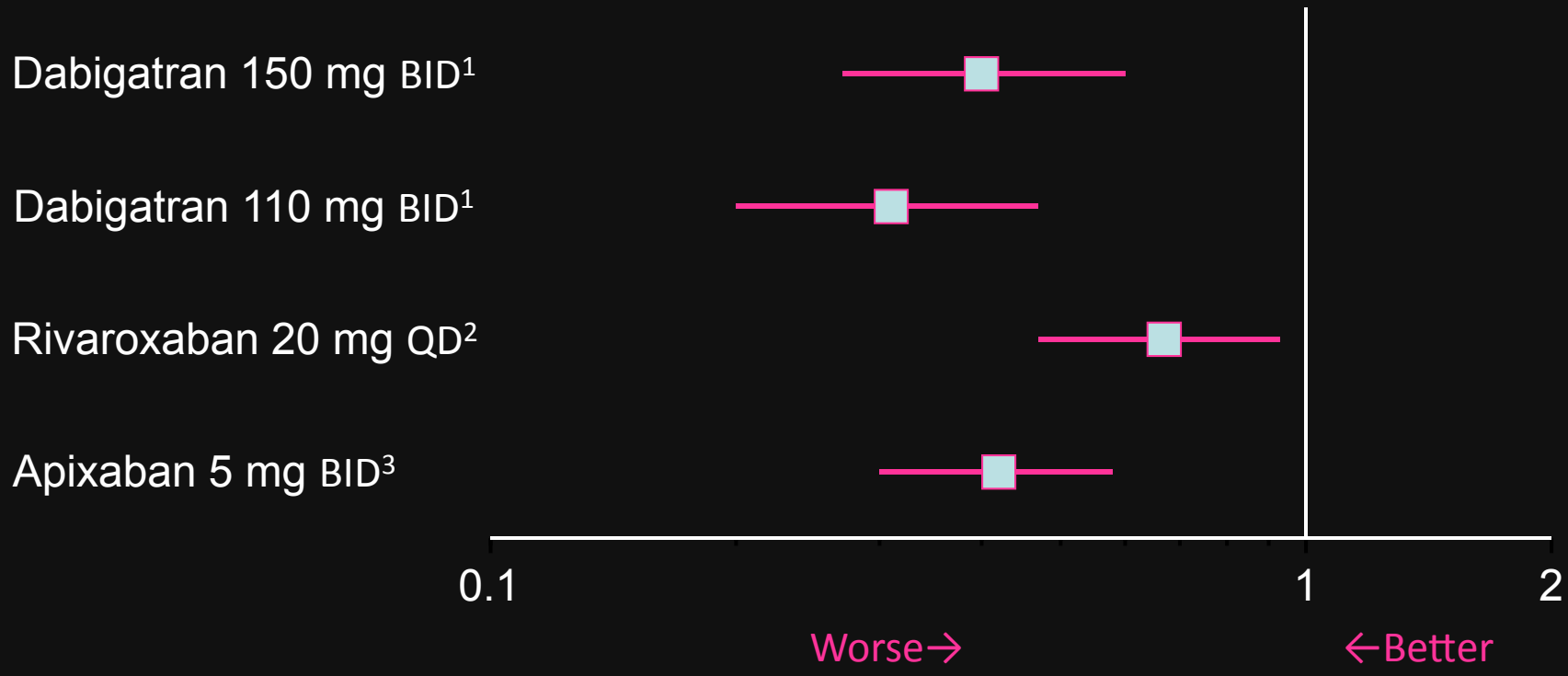
New Anticoagulant Therapies Vs. Warfarin:

Intracranial Hemorrhage



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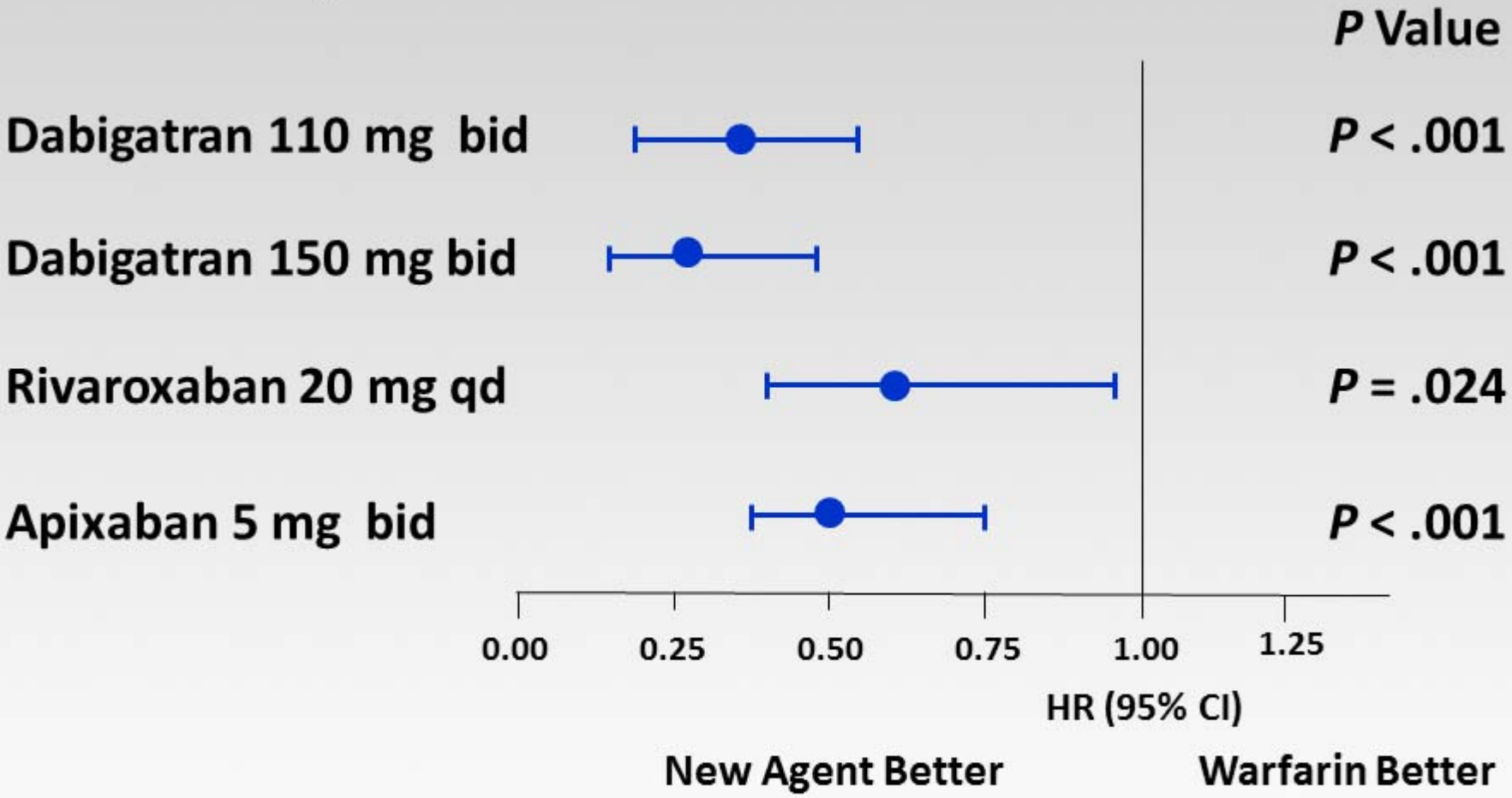
Recent Oral Anticoagulation Trials:
Hemorrhagic Stroke



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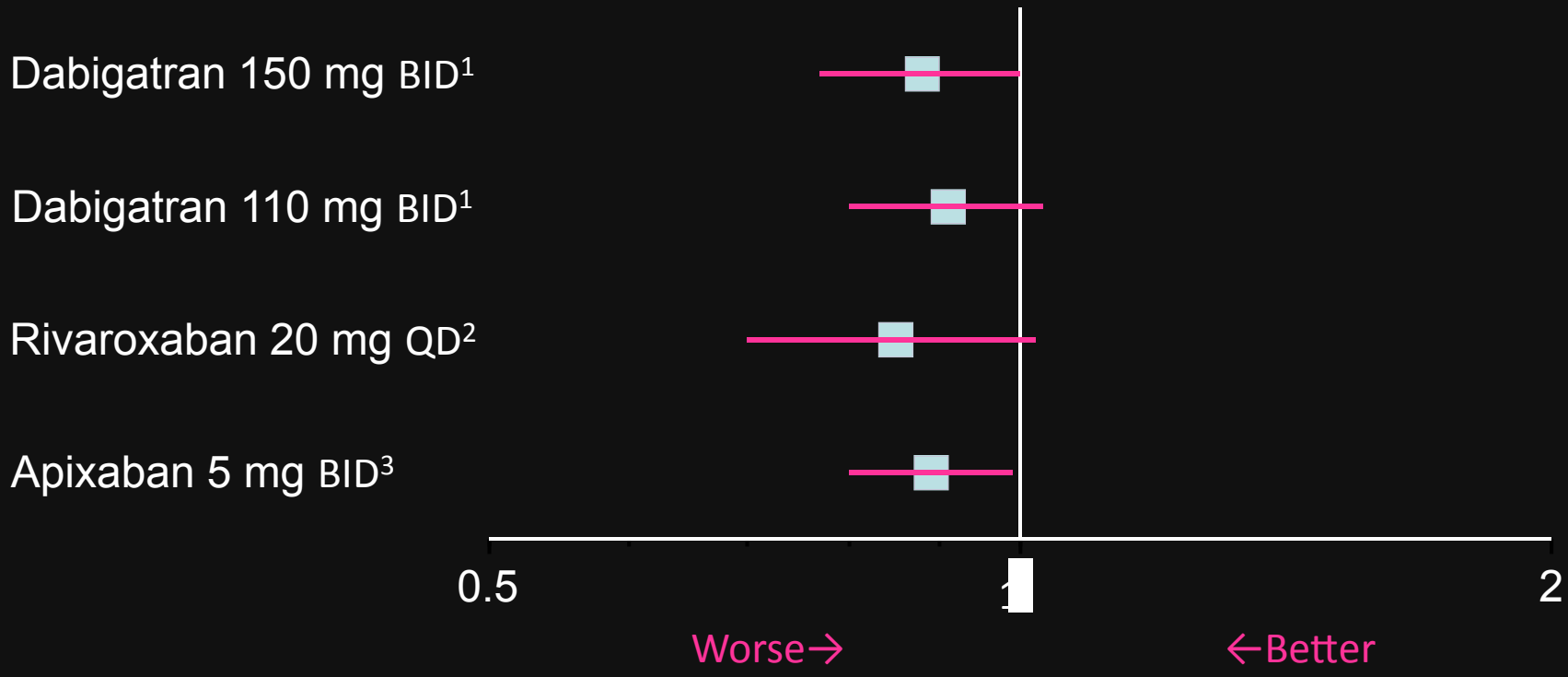
New Anticoagulant Therapies Vs. Warfarin:

All-cause Mortality



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