

# AVERROES

## *Apixaban Versus ASA To Reduce the Risk Of Stroke*

Coordinated by Population Health Research institute  
Hamilton, Ontario, Canada

Sponsors: Bristol-Myers Squibb Co. & Pfizer, Inc.

S. Connolly Disclosure: Received research grants,  
lecture and consulting fees from sponsors

# Apixaban

- Oral, selective, direct Factor Xa inhibitor
- 12 hour half-life, multiple excretion pathways (25% renal)
- No routine coagulation monitoring
- ADVANCE 1-3 trials showed that apixaban is effective and safe for VTE prevention in orthopaedic surgery

# AF Patients Unsuitable for VKA

- There is a high risk of stroke in AF patients
- Vitamin K antagonist (VKA) therapy is effective against stroke, but it is considered unsuitable for up to 50% of patients
  - Difficult to control INR
  - Bleeding on VKA
- There is a need for an effective, safe and easy-to-use antithrombotic therapy for AF patients, unsuitable for VKA

# AVERROES Design

36 countries, 522 centres

AF and  $\geq 1$  risk factor, and demonstrated or expected unsuitable for VKA

Apixaban 5 mg BID

2.5 mg BID in selected patients

R

5,600 patients

Double-Blind

ASA (81-324 mg/d)

Primary Outcome: Stroke or Systemic Embolic Event (SEE)

# Study Design and Execution

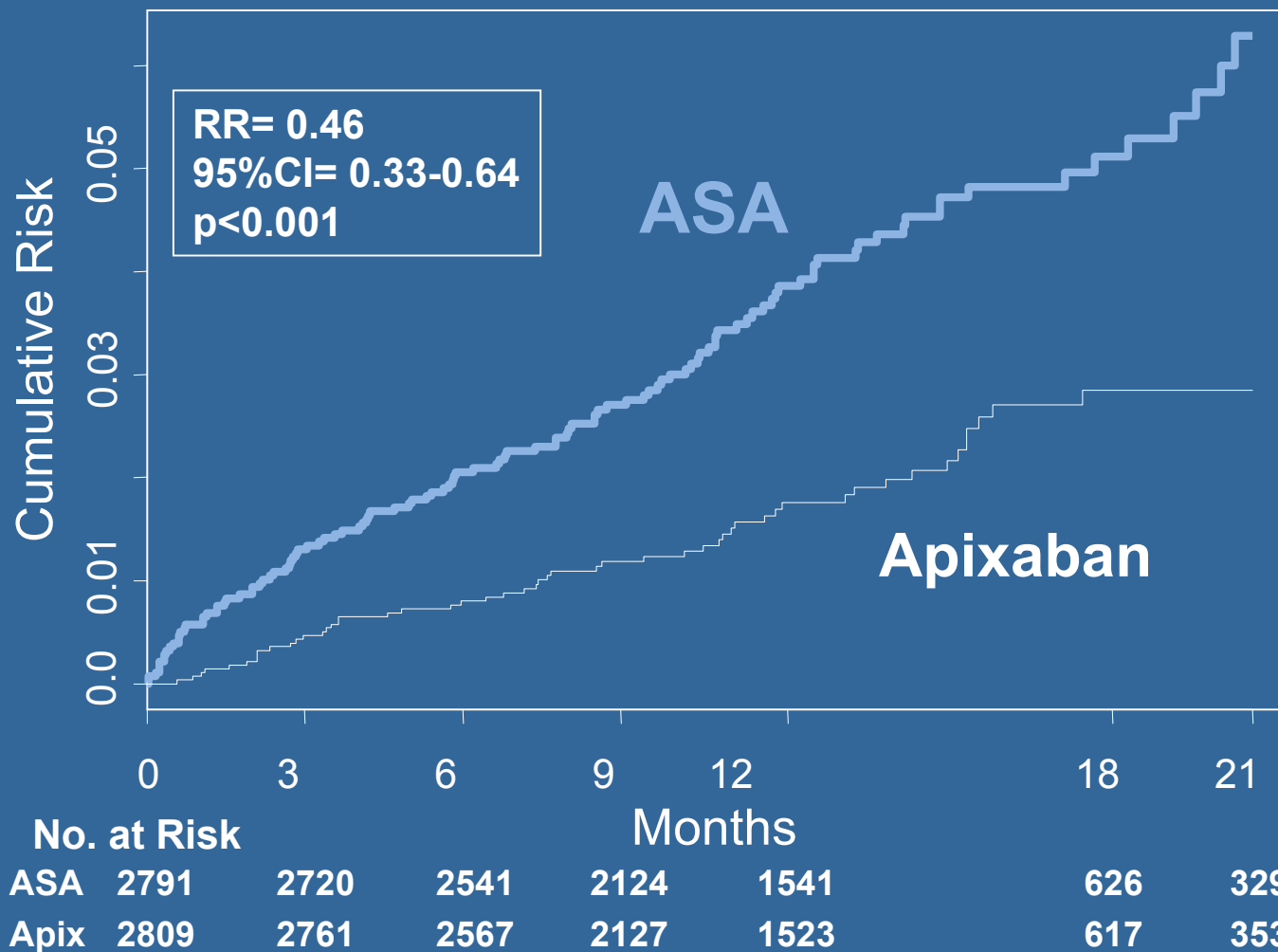
- DMC recommended early study termination at 1<sup>st</sup> analysis of efficacy – May 28, 2010
  - 4 SD x 2 in favour of apixaban
  - Long Term open label apixaban follow up
  - Preliminary analysis for ESC presentation performed by unblinded DMC statistician
- 94% patients received Apixaban 5 mg BID
- 91% patients received ASA  $\leq$ 162 mg daily
- Median Follow up 1.0 years

# Preliminary Results

# Baseline Characteristics

Characteristic	Apixaban	ASA
Randomized	2809	2791
Age (mean and SD)	70 ±10 yrs	70 ±10 yrs
Male	59%	58%
CHADS2 score (mean and SD)	2.1 ± 1.1	2.1± 1.1
0-1	36%	37%
2	37%	34%
3+	27%	29%
Prior stroke/TIA	14%	13%
Diabetes	19%	20%
Hypertension	86%	87%
CHF	40%	38%
Baseline ASA	76%	74%
Unsuitable for VKA		
VKA used and discontinued	39%	40%
VKA expected unsuitable	61%	60%

# Stroke or Systemic Embolic Event



preliminary Results

# Primary Outcome Events

Outcome	Apixaban		ASA		Apixaban vs. ASA		
	events	Annual rate	events	Annual rate	RR	95% CI	P
<b>Stroke or SEE</b>	<b>52</b>	<b>1.6</b>	<b>112</b>	<b>3.6</b>	<b>0.46</b>	<b>0.33-0.64</b>	<b>&lt;0.001</b>
<b>Stroke</b>	<b>50</b>	<b>1.5</b>	<b>103</b>	<b>3.3</b>	<b>0.48</b>	<b>0.34-0.68</b>	<b>&lt;0.001</b>
<b>Ischemic</b>	<b>35</b>	<b>1.1</b>	<b>92</b>	<b>2.9</b>	<b>0.38</b>	<b>0.26-0.56</b>	<b>&lt;0.001</b>
<b>Hemorrhagic</b>	<b>8</b>	<b>0.2</b>	<b>8</b>	<b>0.2</b>	<b>1.01</b>	<b>0.38-2.68</b>	<b>0.99</b>
<b>Type not determined</b>	<b>8</b>	<b>0.2</b>	<b>4</b>	<b>0.1</b>	<b>1.99</b>	<b>0.60-6.62</b>	<b>0.26</b>
<b>SEE</b>	<b>2</b>	<b>&lt;0.1</b>	<b>13</b>	<b>0.4</b>	<b>0.15</b>	<b>0.03-0.69</b>	<b>0.01</b>

# Stroke Severity

Outcome	Apixaban		ASA		Apixaban vs. ASA		
	events	Annual rate	events	Annual rate	RR	95% CI	P
<b>Modified Rankin Score</b>							
<b>0-2</b>	<b>20</b>	<b>0.6</b>	<b>36</b>	<b>1.1</b>	<b>0.56</b>	<b>0.32-0.96</b>	<b>0.04</b>
<b>3-6</b>	<b>30</b>	<b>0.9</b>	<b>67</b>	<b>2.1</b>	<b>0.45</b>	<b>0.29-0.69</b>	<b>&lt;0.001</b>
<b>Fatal (≤7 days)</b>	<b>18</b>	<b>0.5</b>	<b>27</b>	<b>0.8</b>	<b>0.67</b>	<b>0.37-1.21</b>	<b>0.18</b>

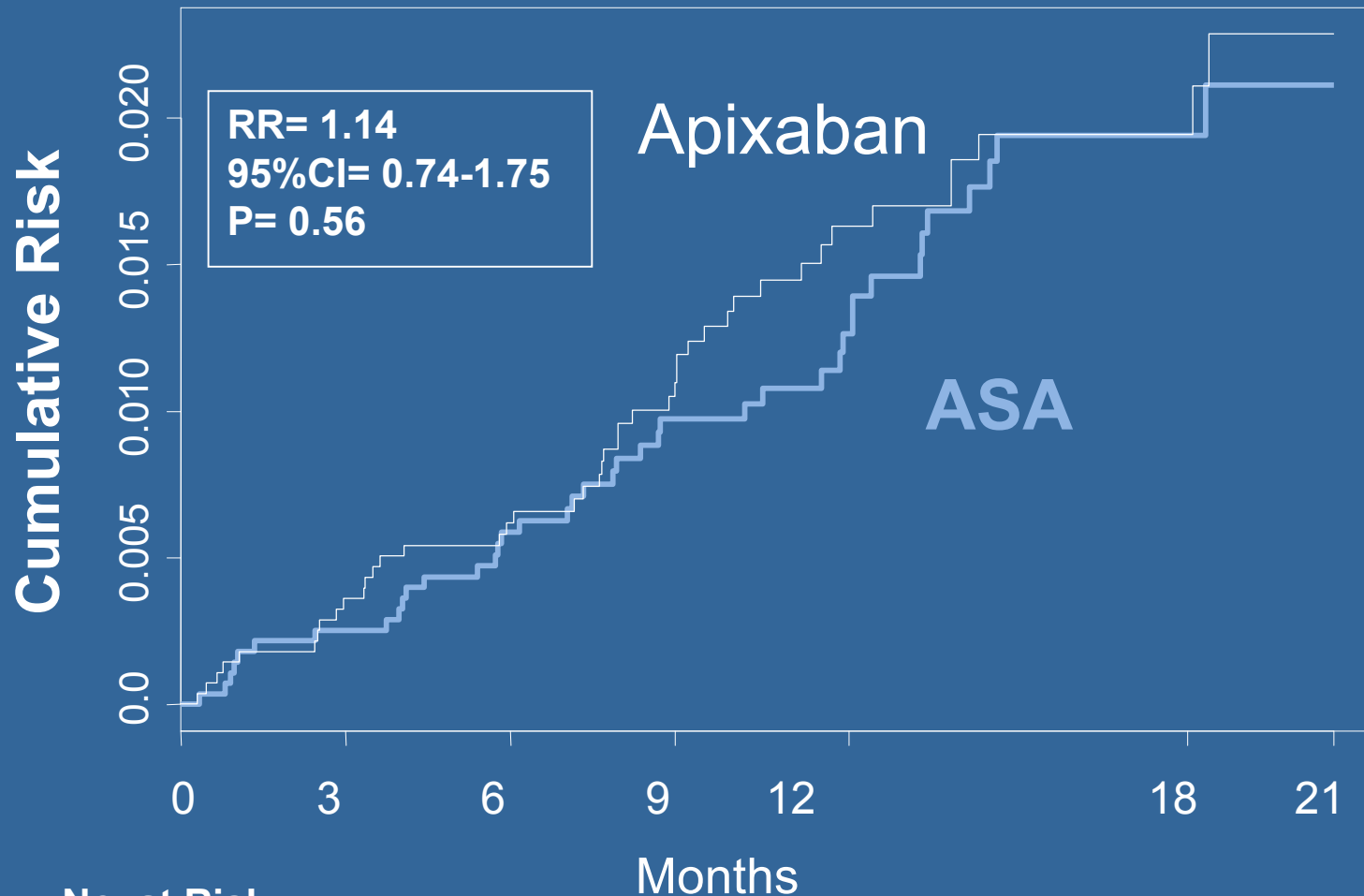
Modified Rankin Score: 0-2=non-disabling, 3-5=disabling, 6=fatal

preliminary Results

# Secondary and Other Efficacy Outcomes

Outcome	Apixaban		ASA		Apixaban vs. ASA		
	events	Annual rate	events	Annual rate	RR	95% CI	P
<b>Stroke, SEE,MI, or Vasc Death</b>	<b>129</b>	<b>4.1</b>	<b>193</b>	<b>6.2</b>	<b>0.66</b>	<b>0.53-0.83</b>	<b>&lt;0.001</b>
<b>MI</b>	<b>22</b>	<b>0.7</b>	<b>26</b>	<b>0.8</b>	<b>0.85</b>	<b>0.48-1.50</b>	<b>0.57</b>
<b>Vasc Death</b>	<b>81</b>	<b>2.5</b>	<b>94</b>	<b>2.9</b>	<b>0.86</b>	<b>0.64-1.16</b>	<b>0.33</b>
<b>CV Hospitaliz.</b>	<b>346</b>	<b>11.8</b>	<b>432</b>	<b>14.9</b>	<b>0.79</b>	<b>0.68-0.91</b>	<b>&lt;0.001</b>
<b>Total Death</b>	<b>110</b>	<b>3.4</b>	<b>139</b>	<b>4.4</b>	<b>0.79</b>	<b>0.62-1.02</b>	<b>0.07</b>

# Major Bleeding



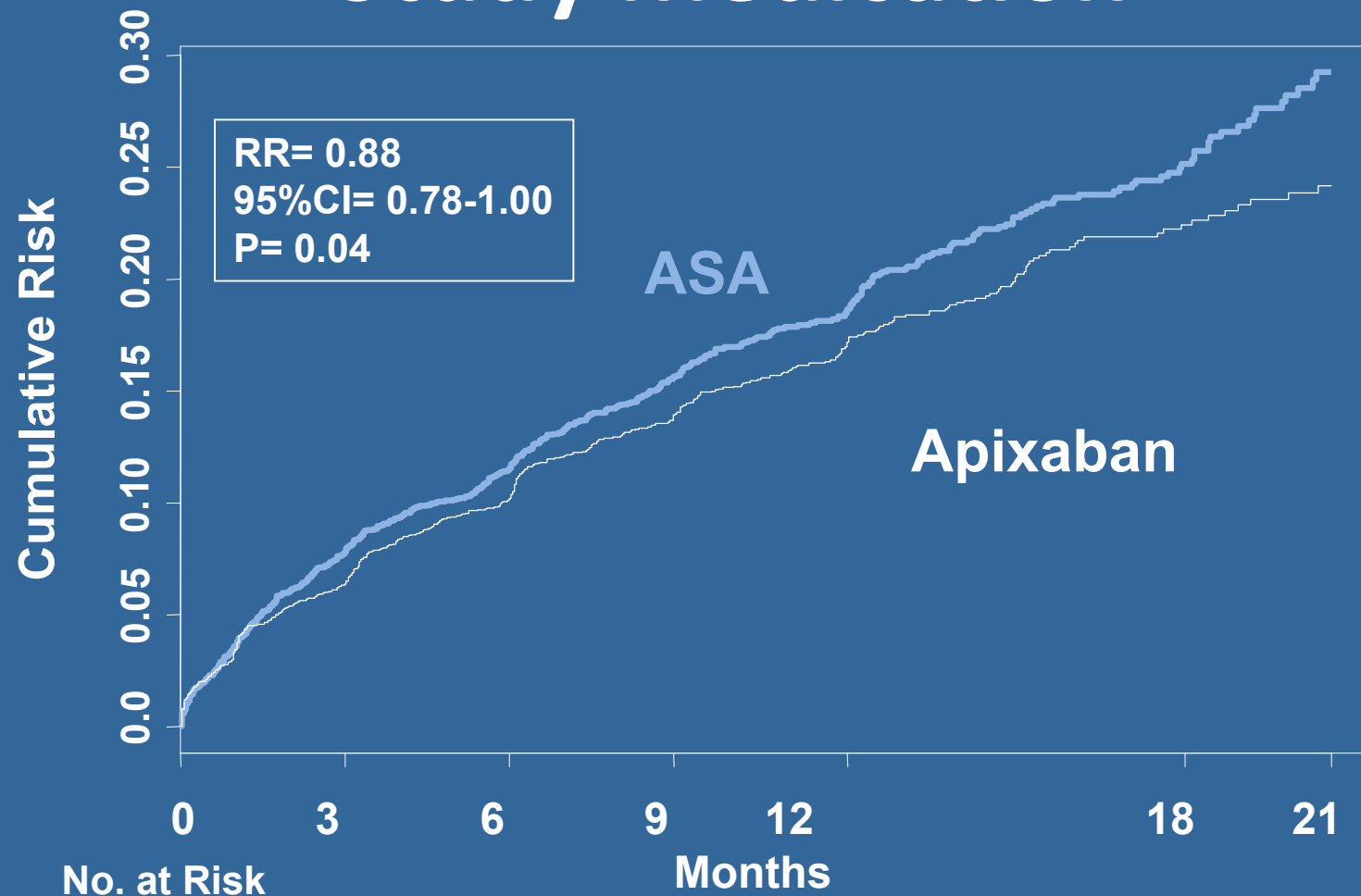
No. at Risk		Months					
	0	3	6	9	12	18	21
ASA	2791	2744	2572	2152	1570	642	340
Apix	2809	2763	2567	2123	1521	622	357

preliminary Results

# Bleeding

Outcome	Apixaban		ASA		Apixaban vs. ASA		
	events	Annual rate	events	Annual rate	RR	95% CI	P
<b>Major</b>	<b>44</b>	<b>1.4</b>	<b>39</b>	<b>1.2</b>	<b>1.14</b>	<b>0.74-1.75</b>	<b>0.56</b>
<b>Clinically Rel. Non-major</b>	<b>95</b>	<b>3.0</b>	<b>81</b>	<b>2.6</b>	<b>1.18</b>	<b>0.88-1.58</b>	<b>0.28</b>
<b>Minor</b>	<b>159</b>	<b>5.2</b>	<b>126</b>	<b>4.1</b>	<b>1.27</b>	<b>1.01-1.61</b>	<b>0.04</b>
<b>Fatal</b>	<b>5</b>	<b>0.1</b>	<b>6</b>	<b>0.1</b>	<b>0.84</b>	<b>0.26-2.75</b>	<b>0.77</b>
<b>Intra-cranial</b>	<b>13</b>	<b>0.4</b>	<b>12</b>	<b>0.3</b>	<b>1.09</b>	<b>0.50-2.39</b>	<b>0.83</b>

# Permanent Discontinuation of Study Medication



	No. at Risk						
ASA	2791	2567	2325	1906	1365	534	266
Apix	2809	2624	2356	1909	1328	521	299

preliminary Results

# Serious Adverse Events >2% on either treatment

System Organ Class	Apixaban	ASA	P
Total SAE Events	1040	1230	
Patients with at least one SAE Event	21.7%	26.6%	<0.001
Cardiac disorders	11.0%	11.6%	
Cardiac arrhythmias	4.2%	4.3%	
Coronary artery disorders	2.1%	2.3%	
Heart failure	4.3%	4.5%	
Gastrointestinal disorders	2.3%	2.7%	
General disorders/administration site	2.7%	2.8%	
Infections and infestations	4.2%	5.2%	
Nervous system disorders	3.0%	6.3%	<0.001
Injury, poisoning, procedural complications	2.1%	2.1%	
Respiratory, thoracic and mediastinal	2.4%	2.5%	

# Liver Function Test Monitoring

	Apixaban		ASA		P-value
	N	%	N	%	
AST or ALT $\geq$ 3 x ULN	21	0.7	32	1.1	0.12
AST or ALT $\geq$ 5 x ULN	8	0.3	9	0.3	0.57
AST or ALT $\geq$ 10 x ULN	1	<0.1	3	0.1	0.31
AST or ALT $\geq$ 3 x ULN and total bilirubin $\geq$ 2 x ULN	2	0.1	2	0.1	1.0

# 1000 Patients Treated with Apixaban for one year, instead of ASA

- Expect to Prevent
  - 18 strokes, mostly larger
  - 10 deaths\*
  - 31 cardiovascular hospitalizations
  
- At a cost of
  - 2 major bleeds\*

\* Statistically Non-significant

# Conclusions

- In patients unsuitable for VKA, apixaban reduces stroke by >50% compared to ASA, without a significant increase in major bleeding,
- Apixaban is well tolerated compared to ASA, without evidence of liver toxicity
- For AF patients unsuitable for VKA, apixaban has a favourable risk benefit profile

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# BACKUP Slides

# Comparison of Antithrombotic Treatments versus ASA in AF

Stroke Reduction

Increase in Intracranial Bleeding

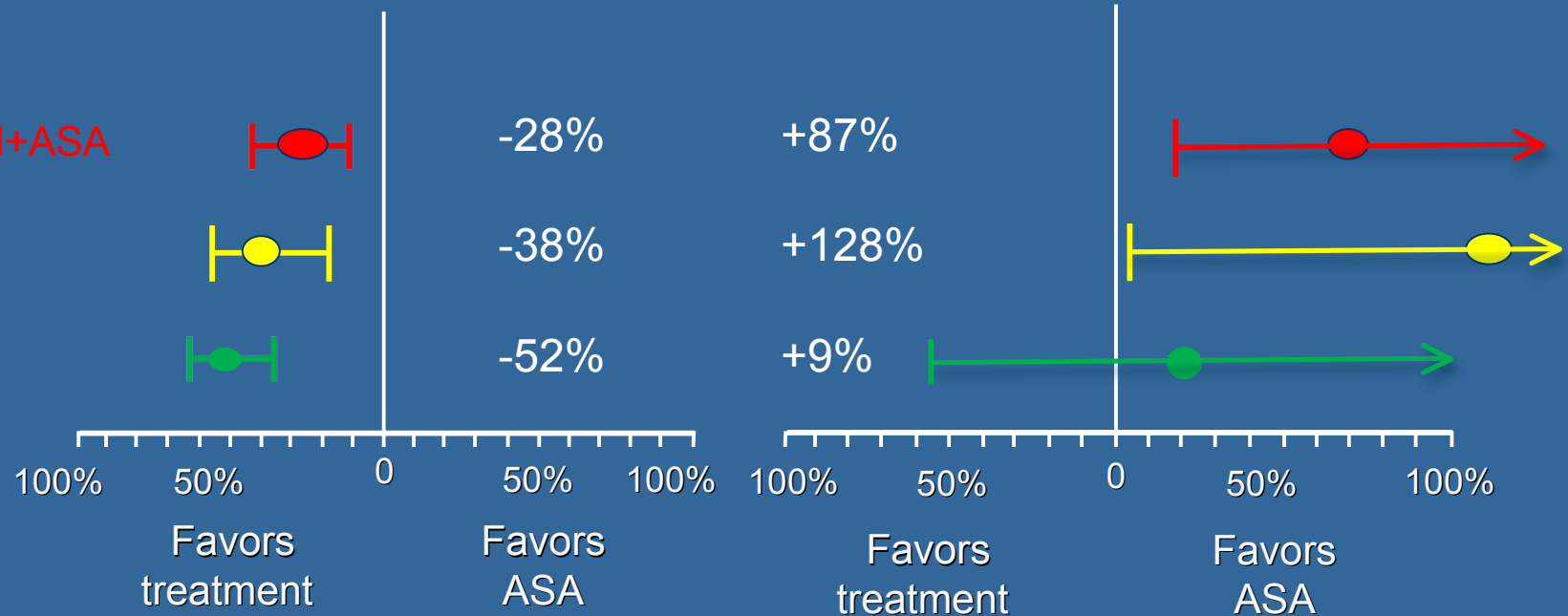
Relative risk reduction (95% CI)

Relative risk increase (95% CI)

\* Clopidogrel+ASA

\*\* VKA

\*\*\* Apixaban



\* ACTIVE A, N Engl J Med 2009; 360: 1-13

\*\* Hart RG, et al. *Ann Intern Med.* 2007;146:857-867

\*\*\* AVERROES; ESC Hotline 2010

# Apixaban Trials in AF

	Unsuitable for VKA	Suitable for VKA
Current Treatment	ASA	Vitamin K Antagonist
Limitations of Therapy	Less effective	Higher bleeding risk and Hard to control
Apixaban Trial	AVERROES	ARISTOTLE
Design	Apixaban vs. ASA	Apixaban vs. warfarin