

Meta Analysis for All-cause Death for Apixaban vs. Placebo Or Control in SPAF Trials

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BACKGROUND

- Apixaban was superior to warfarin for reduction of all-cause death in ARISTOTLE SPAF trial¹
- Apixaban reduced the incidence of all-cause death comparing to aspirin (ASA) although it was not statistically significant in AVERROES SPAF trial²
- It is of great interest to identify the effect of apixaban vs. placebo or control (other than warfarin and ASA) in terms of reducing all-cause death in SPAF trials

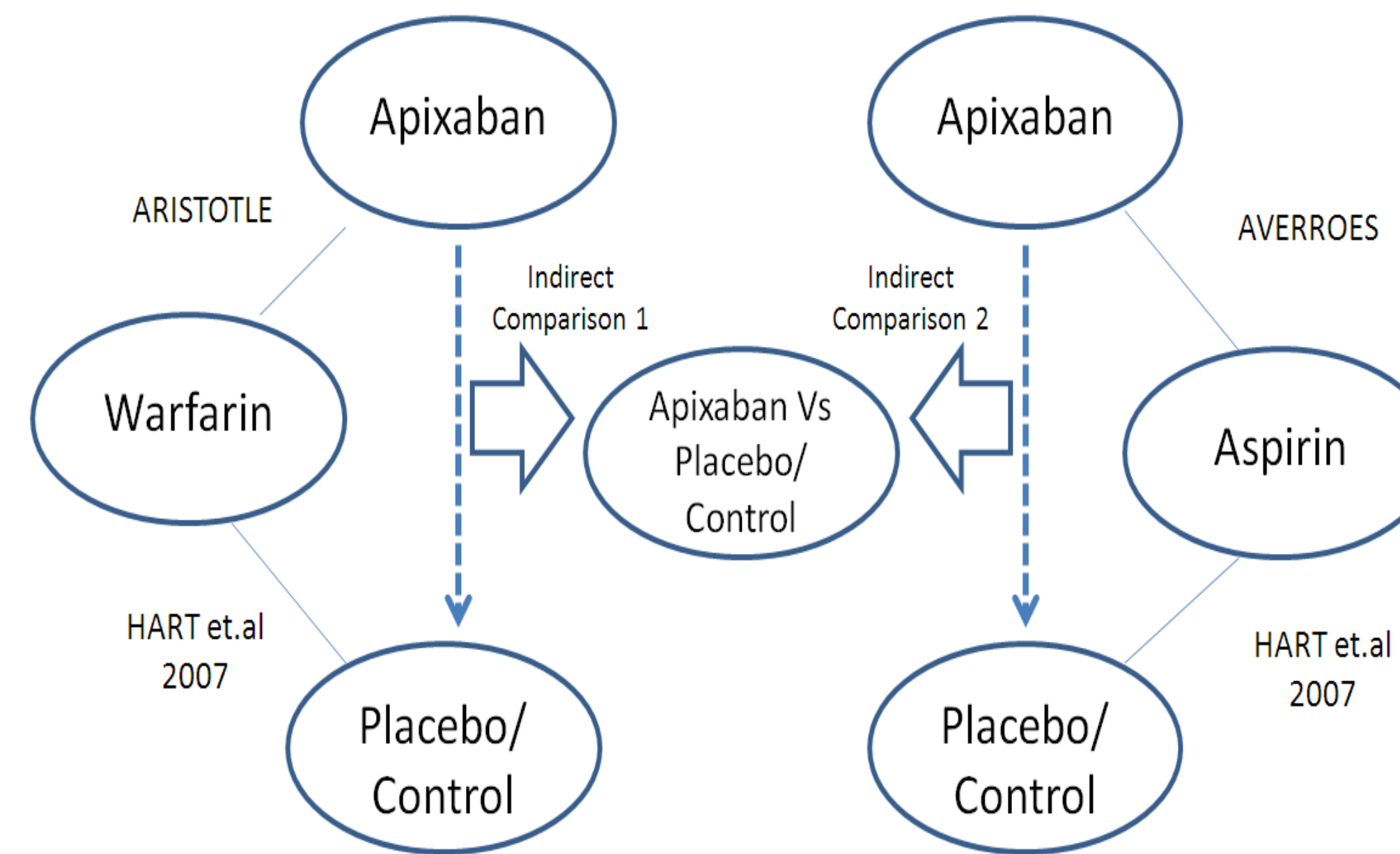
DATA AVAILABILITY

- Apixaban vs. warfarin¹
- Apixaban vs. ASA²
- Warfarin vs. placebo or control³
- ASA vs. placebo or control³

METHODOLOGY

- Indirect Comparison:
 - When head to head direct comparison data is not available, indirect comparison is a very useful tool to make inferences
 - Naïve indirect comparison should be avoided⁴
 - Adjusted indirect comparison usually gives consistent results with direct comparison⁵
- Meta Analysis:
 - When there are more than one trial with the same comparators, Meta-analysis is often used to combine findings from these independent trials to provide a more precise estimate of the treatment effect, weighted by the size of the studies
 - Heterogeneity between trials should be explored

PROPOSED ANALYSIS DIAGRAM



STATISTICAL ANALYSIS DETAILS

- Indirect Comparison for Odds Ratio:

$$\ln(OR_{Ind}) = \ln(OR_{AB}) - \ln(OR_{CB})$$

$$\text{Var}(\ln OR_{Ind}) = \text{Var}(\ln OR_{AB}) + \text{Var}(\ln OR_{CB})$$

- Meta analysis with random effect model:

$$\hat{\theta}_i = \theta + v_i + \varepsilon_i. \quad \hat{\theta}_i \sim N(\theta, \xi_i^2 + \tau^2)$$

- DerSimonian and Laird (1986): to estimate random variance m_w and standard error of m_w on natural log of OR:

$$m_W = \frac{\sum_i w_i y_i}{\sum_i w_i}, \quad w_i = 1/(t^2 + s_i^2)$$

$$\text{s.e.}(m_W) = 1/\left(\sum_i w_i\right)^{1/2}$$

STATISTICAL ANALYSIS DETAILS (cont.)

$$I^2(\text{DL}) = \max\left\{0, \frac{\left[\sum_i w_i(y_i - y_w(0))^2\right] - (k-1)}{\left[\sum_i w_i - \sum_i w_i^2 / \sum_i w_i\right]}\right\},$$

$$y_w(0) = \frac{\sum_i w_i y_i}{\sum_i w_i}, \text{ and } w_i = 1/s_i^2$$

RESULTS

	Treatments Compared	Odds Ratio	Odds Ratio 95% CI	Nominal P-value
ARISTOTLE	A vs. W	0.89	(0.79, 1.00)	0.0458
Hart et.al 2007	W vs. P	0.74	(0.57, 0.97)	
Indirect Comparison 1	A vs. P	0.66	(0.50, 0.88)	0.004
	Treatments Compared	Odds Ratio	Odds Ratio 95% CI	Nominal P-value
AVERROES	A vs. ASA	0.78	(0.60, 1.01)	0.0555
Hart et.al 2007	ASA vs. P	0.86	(0.69, 1.07)	
Indirect Comparison 2	A vs. P	0.67	(0.48, 0.94)	0.02
	Treatments Compared	Odds Ratio	Odds Ratio 95% CI	Nominal P-value
Meta Analysis Combining Two Indirect Comparisons	A vs. P	0.66	(0.53, 0.82)	0.0002

$I^2(\text{DL}) = 0$ and the p-value for heterogeneity is 0.94 which is not significant

CONCLUSION AND DISCUSSION

- In this meta analysis, apixaban reduced all-cause death comparing to placebo or control
 - Each indirect comparison shows that apixaban reduced all-cause death by at least 33% when compared to placebo or control with a 95% CI with upper bound < 1
 - Apixaban effect is highly consistent in two indirect comparisons
 - This meta analysis combining two indirect comparisons shows that apixaban reduced all-cause death by 34% when compared to placebo/control with a 95% CI with upper bound < 1
- Caveat:
 - The result depends on the assumption of similarity of treatment effect in indirect comparison, which is not testable
 - Only two trials were used to assess between study variation in this meta analysis

- Future Research:

- Bayesian network with more complex models

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