Updating the Probability of Success of Clinical Development Programs Over Time

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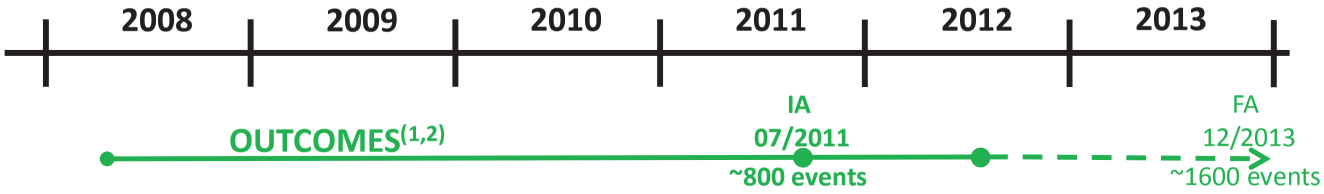
Disclaimer

This a retrospective case study after the development of dalcetrapib was terminated.

Drug Development for Cardiovascular Diseases

dalcetrapib[5] *Example*



Primary Endpoint: CV risk reduction. 15871 patients, event driven. $p < 0.001$ at IA, $p < 0.049$ at FA, powered at 90% for HR = 0.85.

VESSEL[4] 06/2010

Primary Endpoint: Blood pressure. 476 patients, **36 weeks** duration. CV events collected and adjudicated as in OUTCOMES study.

PLAQUE[3] 12/2010

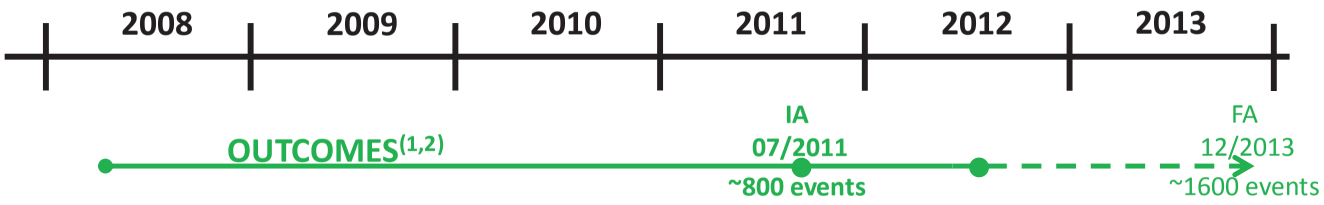
Primary Endpoint: Imaging plaque burden. 130 patients, **2 years** duration. CV events collected and adjudicated as in OUTCOMES study.

All studies: dalcetrapib versus placebo.

(1) N Engl J Med 2012; 367:2089-2099. (2) Am Heart J 2009; 158(6):896-901. (3) Lancet 2011; 378(9802):1547-59.
(4) Eur Heart J 2012; 33(7):857-6. (5) http://www.roche.com/media/media_releases/med-cor-2012-05-07.htm.

Drug Development for Cardiovascular Diseases

dalcetrapib[5] *Example*



Information obtained after IA: "Continue study as planned", i.e., observed HR between 0.792 and 1.025 (based on 814 events).

Note: Even for HR < 0.792, DSMB may have not recommended to stop trial. Not taken into account here.

VESSEL[4] 06/2010

Information obtained: Primary endpoint(s), in addition: 7 MACE events, 2 dalcetrapib, 5 placebo (HR = 0.40, [0.08, 2.04], p = 0.27).

PLAQUE[3] 12/2010

Information obtained: Primary endpoint(s), in addition: 6 MACE events, 1 dalcetrapib, 5 placebo (pooled 3/10: HR = 0.29, [0.08, 1.05], p = 0.06).

(1) N Engl J Med 2012; 367:2089-2099. (2) Am Heart J 2009; 158(6):896-901. (3) Lancet 2011; 378(9802):1547-59.
(4) Eur Heart J 2012; 33(7):857-6. (5) http://www.roche.com/media/media_releases/med-cor-2012-05-07.htm.

Decision Making and Information Milestones

- **OUTCOMES** study at core of development program, designed to lead to first marketing authorization if successful (**pivotal study**)
- Investment decisions to be made while pivotal study is still ongoing, e.g., investment in second outcomes (OUTCOMES2[6]) study

Information may become available while pivotal trial still ongoing, e.g.,

- **External** to the pivotal trial, e.g.
  - Results from smaller studies (VESSEL study, PLAQUE study)
  - Information from literature
- **Internal** to the pivotal trial, e.g.
  - Passing an interim analysis

Question: Do results becoming available carry information regarding "Probability of Success" (PoS) of the pivotal study?

Need:

1. Criteria for "success" and measure for "likelihood of success", and
2. "Best guess" regarding true drug effect based on information available to date

(6) http://www.clinicaltrials.gov/ct2/show/NCT01516541?term=NC25608&rank=1

Notation and Methodology
Probability of Success (PoS)

θ	true but unknown logged hazard ratio (drug vs. placebo)
$p(\theta)$	(prior) distribution describing belief about logged hazard ratio
$\hat{\theta}_{\text{IA}}, \hat{\theta}_{\text{FA}}$	observed hazard ratios at interim or final analysis of pivotal study
$\text{Ev}_{\text{IA}}, \text{Ev}_{\text{FA}}$	events at interim (814) or final (1600) analysis of pivotal study

"Success" in pivotal study at final analysis is here defined as reaching a statistically significant result, i.e.,

$$\text{PoS}(\theta) = P_\theta\left(\hat{\theta}_{\text{FA}} + q_{1-\alpha/2} \cdot \sqrt{4/\text{Ev}_{\text{FA}}} < 0\right), \quad \text{PoS} = \int \text{PoS}(\theta) \cdot p(\theta)\, d\theta$$

Applicable if only information **external** to pivotal trial, i.e., no "knowledge" on data from pivotal trial itself, is available.

In case information **internal** to pivotal trial , i.e., "continue as planned" after an interim analysis is (i.e., $\theta_L \le \hat{\theta}_{\text{IA}} \le \theta_U$) becomes available, use PoS as below

$$\text{PoS}(\theta) = P_\theta\left(\hat{\theta}_{\text{FA}} + q_{1-\alpha/2} \cdot \sqrt{4/\text{Ev}_{\text{FA}}} < 0 \,|\, \theta_L \le \hat{\theta}_{\text{IA}} \le \theta_U\right), \quad \text{PoS} = \int \text{PoS}(\theta) \cdot p(\theta)\, d\theta$$

(here $\theta_L = \log(0.792)$ and $\theta_U = \log(1.025)$.)

Notation and Methodology
Updating Information on Drug Effect

θ true but unknown logged hazard ratio (drug vs. placebo)

$p_0(\theta)$ initial (prior) distribution describing belief about logged hazard ratio

Given "data" update information on θ via Bayes' Formula: $p(\theta \mid \text{data}) \propto g(\text{data} \mid \theta) \cdot p(\theta)$

Assume **"data"** regarding θ become available in terms of

i. an observed HR $\hat{\theta}$ based on EV events leading to the likelihood function

$$g_1(\text{data} \mid \theta) \propto \exp\left(-\left(\hat{\theta}-\theta\right)^2 \cdot \text{EV}/8\right)$$

ii. interval information $\theta_L \le \hat{\theta}_{\text{IA}} \le \theta_U$ after an interim analysis of the pivotal study based on EV_{IA} events leading to the likelihood function

$$g_1(\text{data} \mid \theta) \propto \Phi\left((\theta_U-\theta)/\sqrt{4/\text{EV}_{\text{IA}}}\right) - \Phi\left((\theta_L-\theta)/\sqrt{4/\text{EV}_{\text{IA}}}\right)$$

Together with prior information $p_0(\theta)$, Bayes formula leads to the posterior

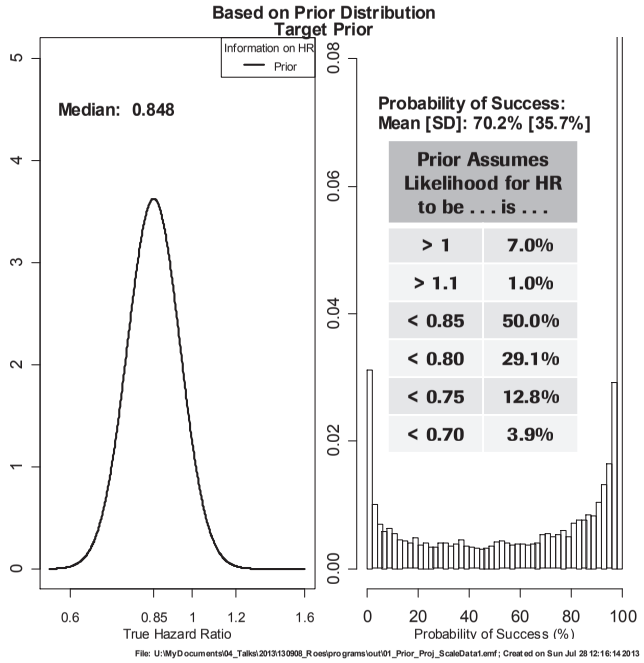
$$p_1(\theta \mid \text{data}) \propto g_1(\text{data} \mid \theta) \cdot p_0(\theta)$$

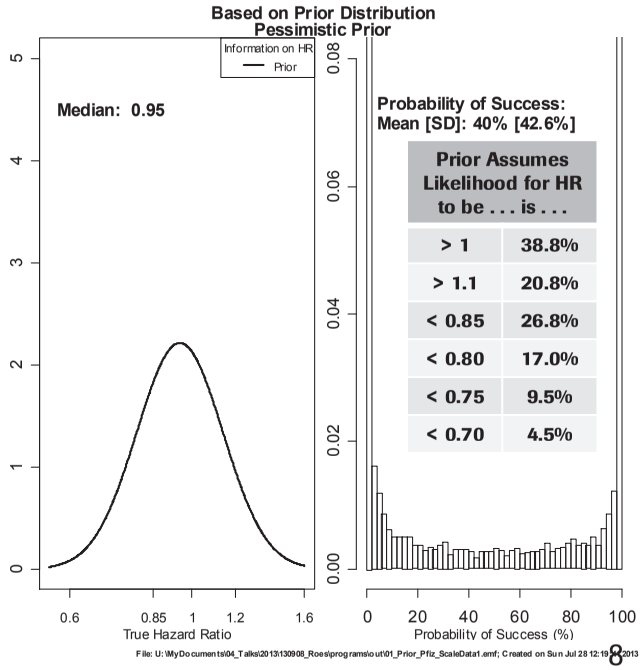
As "data" $g_2(\theta), g_3(\theta), \ldots$ become available iteratively, update information on θ via

$$p_i(\theta \mid \text{data}) \propto g_i(\text{data} \mid \theta) \cdot p_{i-1}(\theta), \quad i \ge 1$$

Prior Distribution $p_0(\theta)$

- dalcetrapib increases HDL-c by about 30%. In 2006, epidemiologic data suggested ~1.5% relative CV risk reduction per 1mg/dL increase in HDL-c [2]
- **Realistic target** assessment: reflect uncertainty in epid. data and drug effect on HDL-c
- More **pessimistic** assessment: Consider torcetrapib[7] failure in 2006

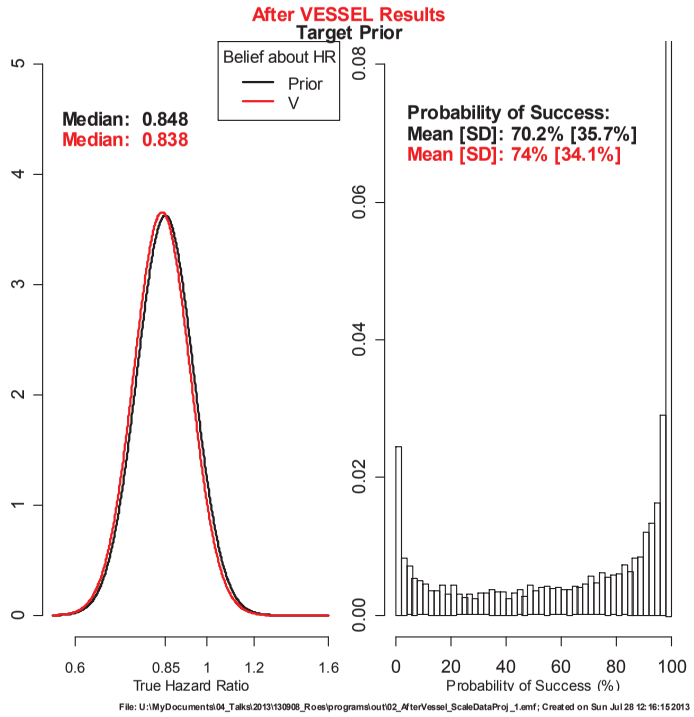


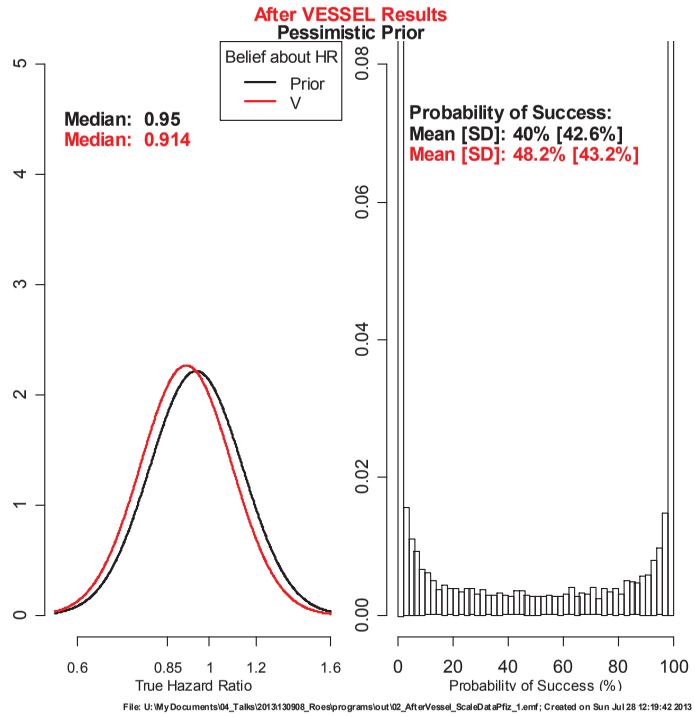


(2) Am Heart J 2009; 158(6):896-901. (7) N Engl J Med 2007; 357:2109-2122.

June 2010: VESSEL CV Events

- 2 (dalcetrapib) vs. 5 (placebo) events: $\hat{\theta} = \ln(0.4), \hat{\sigma} = 0.837$





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Less Weight to data?

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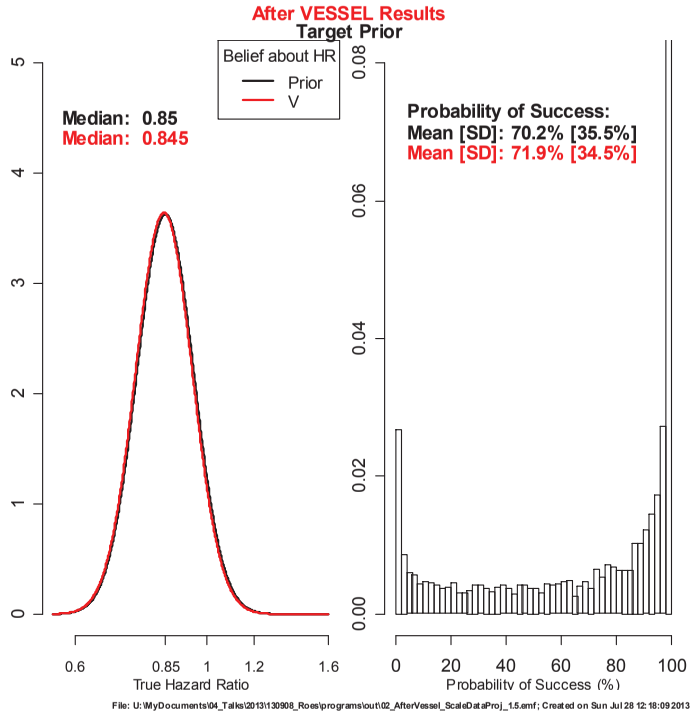
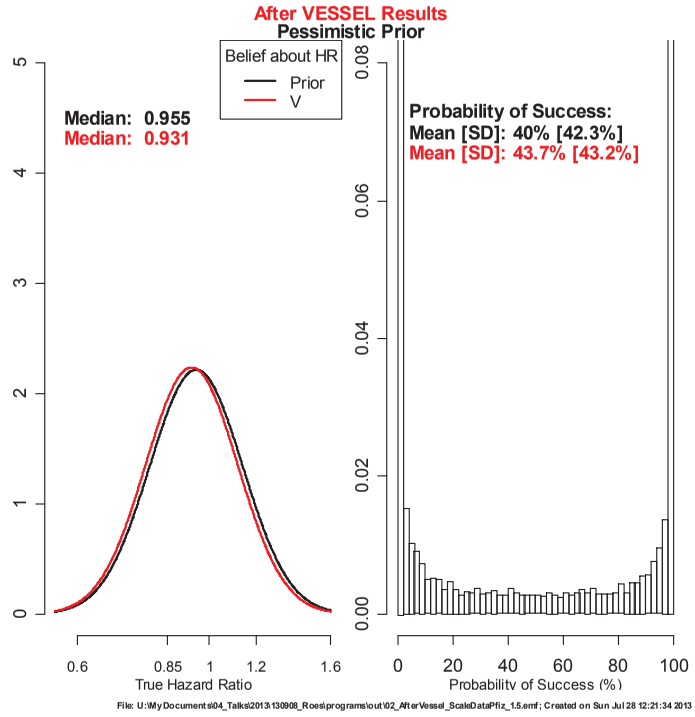
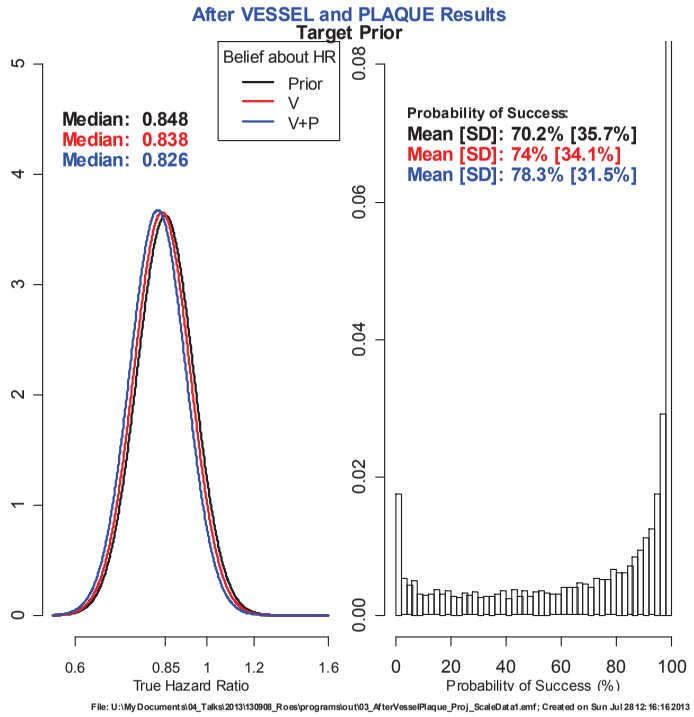
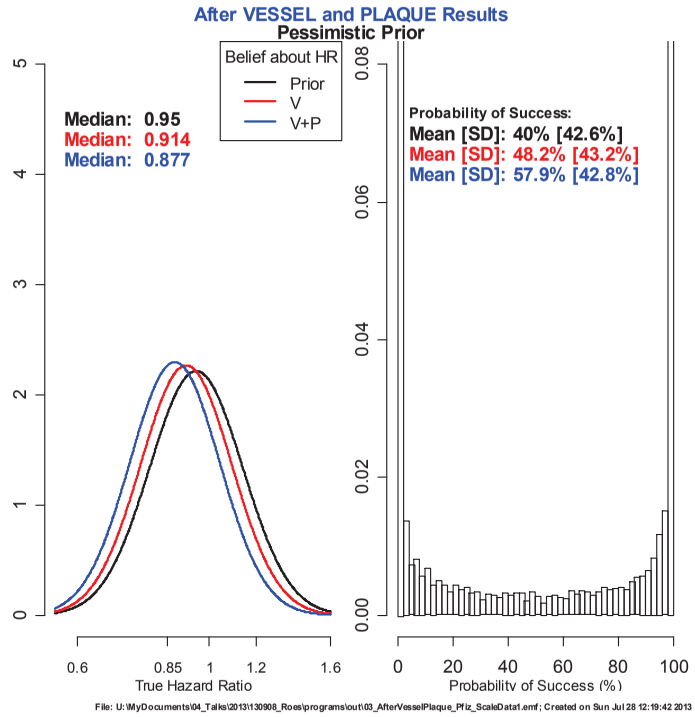




December 2010: VESSEL and PLAQUE CV Events

- 3 (dalcetrapib) vs. 10 (placebo) events: $\hat{\theta} = \ln(0.29), \hat{\sigma} = 0.658$





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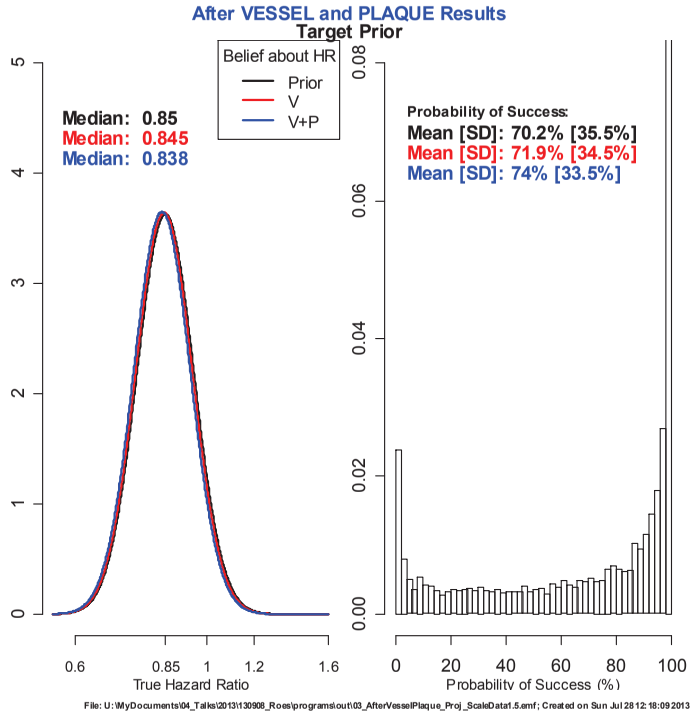
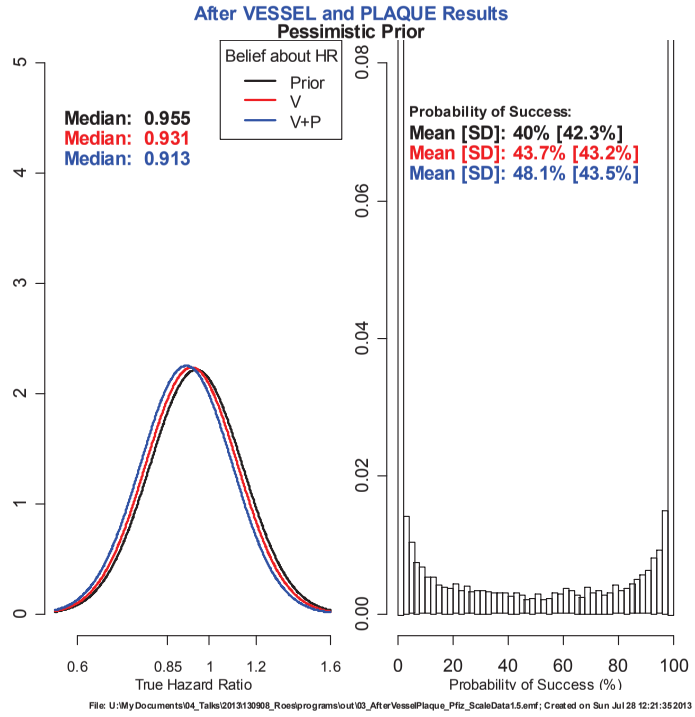




July 2011: OUTCOMES Interim Analysis Passed

Interim analysis (IA) at **814** of 1600 targeted events.

Protocol on "efficacy" aspect

. . . the DSMB may recommend stopping the trial for early proof of efficacy if a significant difference between treatments is seen with respect to the primary endpoint at $p < 0.001$.

DSMB charter on "futility" aspect

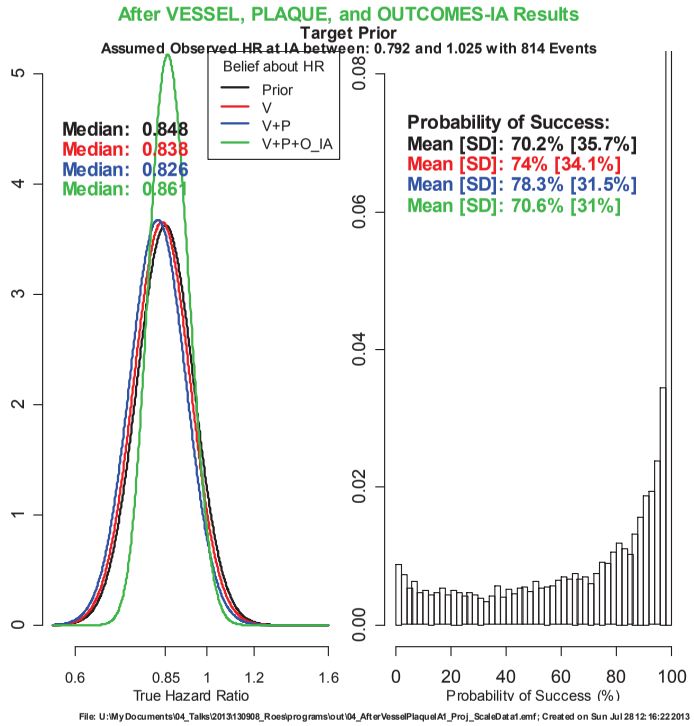
. . . after 50% of the total number of expected primary endpoint events have been adjudicated by the CEC, an interim assessment of efficacy and futility will be performed based upon the adjudicated primary endpoint events. For the futility assessment, a conditional power of less than 20% (under the original alternative hypothesis) may result in a recommendation to discontinue the trial for futility.

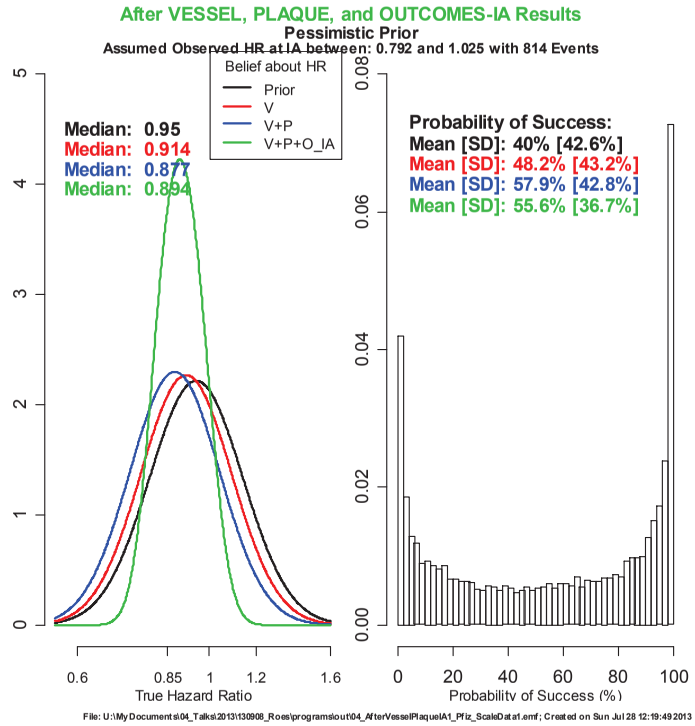
Based on these criteria, having passed the interim analysis may have lead to "knowledge" that, based on 814 events, $\theta_L \le \hat{\theta}_{\text{IA}} \le \theta_U$ with

$$\theta_L = \log(0.792) \text{ and } \theta_U = \log(1.025).$$

July 2011: OUTCOMES Study – Interim Analysis Passed

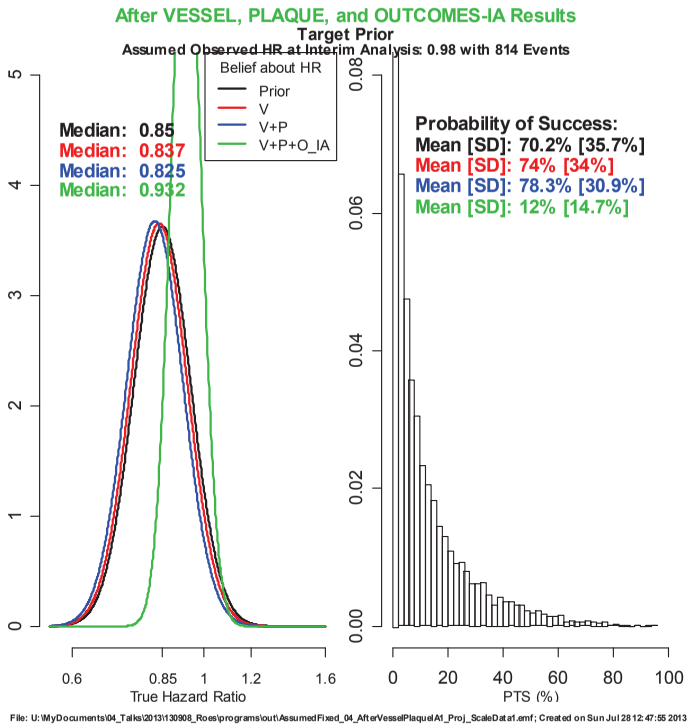
- Passing interim analysis after 814 evens: $\log(0.792) \le \hat{\theta}_{\text{IA}} \le \log(1.025)$

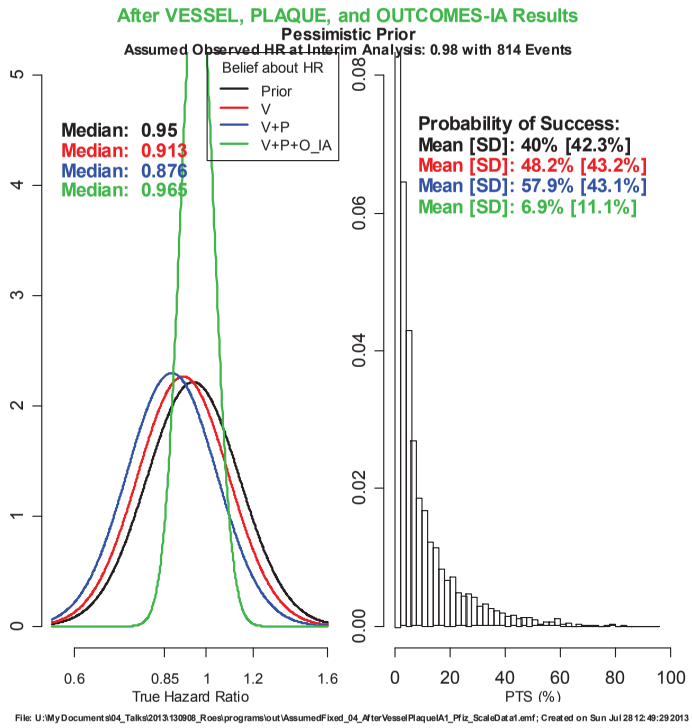




July 2011: OUTCOMES Study Interim Analysis Passed

Had the Results been Known: HR = 0.98 [0.85, 1.12]





Practical Considerations

- Prospective discussions with teams needed
  - Choice of prior distribution
  - Change in PoS to match clinical assessment
- Update based on "futility" only, i.e., use $\theta_L = -\infty$?
  - Formulas and technical implementation ok, but . . .
  - Too optimistic: Consider what drug may really be able to do!
- PoS is subject to uncertainty
  - Averaging across distribution of θ provides mean, but . . .
  - Decision making should also consider variability