Preserving Specificity of Trial Endpoints and Cause of Death Attribution in Cardiovascular Trials; Insights from the MARINER trial

Shea E. Hogan, Mario Enrico Canonico, Robert W. King, Cecilia C. Low Wang, Mark R. Nehler, Jessica Parr, R. Kevin Rogers, Wentao Lu, John Albanese, Elliot S. Barnathan, Alex C. Spyropoulos, James D. Douketis, Marc P. Bonaca, Warren H. Capell

Denver Health, Denver, CO, USA
CPC Clinical Research, Aurora, CO, USA
University of Colorado, Aurora, CO, USA
Janssen Research and Development, Ambler, PA
Donald and Barbara Zucker School of Medicine at Hofstra/Northwell and Institute of Health Systems Science, Hempstead, NY, USA
St. Joseph's Healthcare Hamilton and McMaster University, Hamilton, Ontario, Canada

BACKGROUND

- The MARINER trial examined rivaroxaban to prevent short-term venous thromboembolism (VTE) after hospital discharge in a diverse, medically ill population deemed high risk for VTE.
- The trial did not meet its primary endpoint due to a lesser effect of rivaroxaban on 'VTE-related death' (which included uncertain events) than on non-fatal VTE events.
- We hypothesized that specific, rather than inclusive, definitions of VTE-related death would lead to fewer overall events, but with hazard ratios (HRs) more consistent with non-fatal VTE events.

METHODS

- Primary source documents for the 241 deaths in the MARINER trial were reviewed by blinded adjudicators not involved with the original trial.
- Pre-specified definitions for VTE-related death were used, and 'Death of Unknown Etiology' was allowed instead of the original inclusive endpoint 'Cannot rule out PE."
- HRs and 95% CIs for rivaroxaban vs placebo were calculated for pre-specified cardiovascular outcome composites.

RESULTS

- Re-reviewed death cases showed strong concordance with original results, except deaths originally categorized as 'Cannot rule out PE' were redistributed, largely to undetermined death (60%; Table).
- The re-reviewed MARINER primary endpoint revealed a HR 0.46 (95% CI 0.23-0.91, Figure), compared to the original trial HR 0.76 (95% CI 0.52-1.1).

Cause of death in medically ill patients enrolled in VTE trials is heterogenous. VTE endpoint definitions specific for VTE events are more likely to capture the true impact of the therapy under study.

For more information, email
Shea.Hogan@cpcmed.org

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TABLE

		CPC Determination							
		Confirmed Fatal VTE	VTE Contributing to Death	Probable VTE death	Possible VTE death	Other CV Death	Non-CV death	Unknown Etiology	Total
Original Trial Determination	Confirmed Fatal VTE	6	4	0	0	0	0	0	10
	Cannot Rule out PE	2	1	1	5	23	13	67	112
	Other CV Death	0	1	1	0	43	6	3	54
	Non-CV death	0	0	1	3	1	57	3	65
	Total	8	6	3	8	67	76	73	241

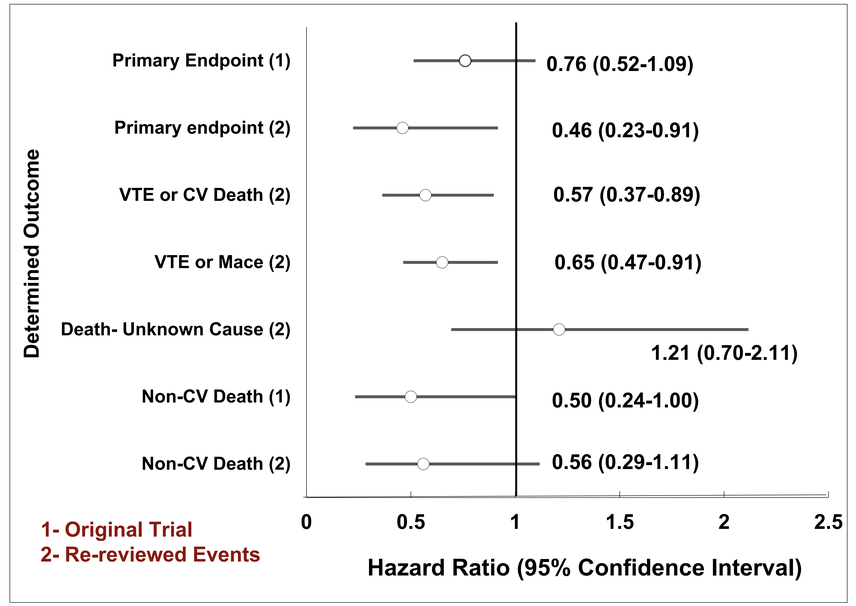
Event determinations in the original trial (Index Diagnosis) compared to re-review using more specific VTE death definitions.

DISCUSSION

Our results suggest

- Changing from an inclusive ('Cannot Rule Out') endpoint to a more specific VTE death definition can improve the ability to detect differences between study arms.
- Deaths for which a specific cause cannot be reliably determined are common in the outpatient setting.
- Further exploration of these unknown death events revealed the majority did not have additional knowable information that would have improved understanding regarding the cause of death.
- Deaths of unknown etiology must be clearly demonstrated and accounted for in trial analysis.

FIGURE



Increased death endpoint specificity improves the ability to detect a treatment effect. Results shown include only deaths that occurred within the 45-day primary endpoint window, consistent with the original MARINER trial analysis. CV, cardiovascular; MACE, major adverse cardiovascular events*; SCD, sudden cardiac death; VTE, venous thromboembolism.

*MACE includes cardiovascular death, non-fatal myocardial infarction and non-fatal ischemic stroke.

1= Original trial; 2=Re-reviewed determination using new definitions

CONCLUSION

This post-hoc exploratory analysis of endpoint design demonstrates that designing specific trial endpoints, particularly for cause-specific death, can minimize the risk of a type II error. Employing standardized endpoint definitions that maintain disease specificity, such as the International Society on Thrombosis and Haemostasis definition for VTE-related death, across trials can help achieve this goal.

DISCLOSURES

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