

Title: Quantitative “Learning” Analysis Supports Effectiveness of Heparin for STEMI

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Objectives:

The purpose of our analysis was to investigate the effectiveness of a heparin regimen for ST-Segment Elevation Myocardial Infarction (STEMI). Whether Unfractionated Heparin (UFH) is efficacious in treating STEMI is equivocal mainly due to lack of controlled clinical studies. Recent meta-analysis of the randomized clinical trials indicated that intravenous UFH has not been shown to prevent reinfarction or death [1]. However, although not approved by FDA, heparin is recommended to treat STEMI by American College of Cardiology (ACC) guidelines based only on class C evidentiary support (expert opinion) [2]. Following current ACC guidelines, heparin should be administered intravenously for continuous 48 hours after a patient has been diagnosed as STEMI.

Methods:

Our analyses were based on a recent clinical study, in which heparin was used as the only control in a ~10,000 patient mortality/morbidity study with no placebo group. The primary endpoint was all-cause mortality or recurrent MI. Heparin was administered as I.V. bolus of 60 U/kg with the maximum dose of 4000U; and then it was given as continuous i.v. infusion at 12 U/kg/hr, with the maximum dose of 1000 U/hr. Patients in the trial received heparin for 2-175 hours, with the median heparin treatment duration of 48 hours.

To answer a question about effectiveness, two groups are typically compared (*e.g.* heparin versus placebo). Because there is no placebo group in the trial, our analyses were limited to the cohort of patients randomized to UFH. We employed a time-dependent Cox Proportional Hazard analysis which assigns heparin treatment as a dichotomous variable for each subject. Thus, the treatment variable is assigned “1” for as long as a subject remains on heparin and then “0” for later times. The primary effectiveness variable was the time to all-cause mortality or recurrent MI. The risk for the same subject to have events while “off-treatment” was then compared to that while “on-treatment”.

Results:

The event-free survival curve was presented in Figure 1. Kaplan-Meier curve shifted after 48 hours. Cox model indicated that heparin treatment significantly reduces hazard of major events of interest ($P < 0.0001$). Risk of death or recurrent MI immediately “off” heparin treatment was 31-fold higher than “on” treatment.

A sensitivity analysis was conducted using subsets of data with different heparin duration times to explore the benefit of heparin treatment with different duration time. Subsets of data with heparin duration times less than or equal to 82.7, 48.08, and 16.8 hours (corresponding to 90th, 50th, and 10th percentile of the heparin duration time in the TIMI-25 trial) respectively were employed in the Cox Proportional Hazard analysis using heparin treatment as time-dependant variable. Statistically significant ($P < 0.0001$) heparin treatment effect can be demonstrated for the time to major events for all the subsets. Although, subjects with short heparin treatment duration time of ≤ 16.8 hours were usually high-risk patients and tended to have early events, the hazard of events for an average subject increased about 3-fold when the heparin treatment was discontinued.

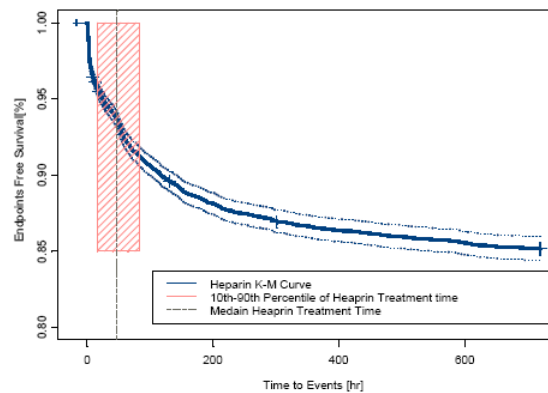
In order to further address the question whether the treatment effect demonstrated in the Cox Proportional Hazard Model was a coincident time effect from the disease progression, a permutation test was conducted. The results indicated that the false-positive rate is acceptable at 4%. The hazard ratio from the observed data and the permuted data was presented in Figure 2. The hazard ratio values, for the permuted data sets, are close to 1 and the observed hazard ratio from the Cox Proportional Hazard analysis is 31, which is

far above any values seen in the permuted datasets. The results indicate that the observed heparin treatment effect and the hazard ratio are not purely by chance or entirely driven by natural disease progression.

Conclusions:

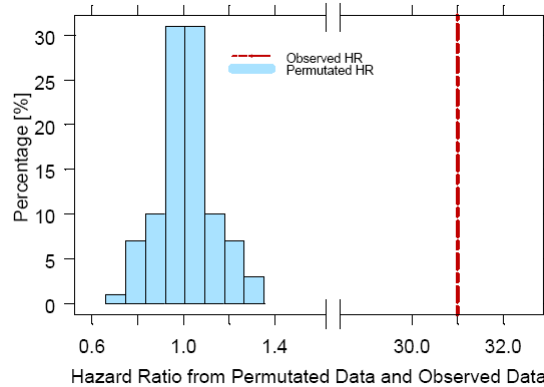
This heparin withdrawal study confirms that heparin is effective in treating STEMI, but the current recommended treatment duration (48 hours) is too short.

Figure 1 Kaplan-Meier Plot for Time to Major Events



*: Kaplan-Meier curve shifted after 48 hr (median heparin duration time).

Figure 2 Hazard Ratio from Observed and Permuted Datasets



References:

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 [2] T.J. Ryan, E.M. Antman, N.H.Brooks, R.M.Califf, L.D. Hilis, L.F. Hiratzka, E.R. Barbara Riegel, R.O. Russell, E.E. Smith, III, W.D. Weaver, R.J. Gibbons, J.S. Alpert, K.A. Eagle, T.J. Gardner, A.Garson, J.G. Gregoratos, R.O. Russell, T.J. Ryan and S.C. Smith, Jr. *Circulation*, 1999; 100; 1016-1030.