FORECASTING RISK IN ACUTE MYOCARDIAL INFARCTION

By

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Research conducted in association with:

NHMRC Clinical Trials Centre, University of Sydney.

Dedicated to Faye and David O’Connell

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SUMMARY

Coronary heart disease is the most common cause of death worldwide with an estimated 7 million deaths per year. The majority of these deaths are due to acute myocardial infarction (AMI) so the burden of illness and mortality from AMI worldwide is immense. Existing short-term risk assessment strategies in AMI are limited to Western patient populations. In this thesis we have proposed risk models for prediction of mortality after AMI based on the geographically diverse Hirulog and Early Reperfusion or Occlusion (HERO-2) trial. The HERO-2 trial randomised 17 073 patients to either unfractionated heparin or bivalirudin in conjunction with fibrinolytic therapy with streptokinase, for the treatment of ST-segment Elevation MI. Patients were recruited from 46 countries from Europe, North and Latin America and Asia, including Australia, New Zealand and Russia. We have developed a comprehensive risk model to identify significant predictors of 30-day mortality. This model was subsequently simplified to a basic risk index and predictive accuracy was compared. We have also proposed two new methods for directly comparing the calibration and ranking performance of two risk strategies.

The geographical diversity of the HERO-2 trial also provided a unique opportunity to examine international differences in clinical outcomes following AMI. We have undertaken a comprehensive comparison of patient characteristics, treatment and outcomes across 5 pre-specified regions: Western countries, Latin America, Eastern Europe, Russia and Asia. We found that mortality rates were lower in Western countries and that these differences could not be attributed to patient case-mix, treatments or national health and economic statistics.

An important issue in applying findings from randomised clinical trials is the procedure to estimate risk among members of other patient populations. Using the HERO-2 trial we compared methods for updating risk models for AMI. A variety of re-calibration and model revision strategies were compared with a global modeling strategy having a built-in region effect. The relative performance of these methods in the different geographical regions, which vary in sample size, was of primary interest. Model revision was found to only provide a slight improvement in predictive performance over the global model. We concluded that a global model with regional re-calibration is adequate.

We also studied data from 5 additional multinational trials: GUSTO-1, GUSTO-2b, GUSTO-3, ASSENT-2 and ASSENT-3. We further explored the adequacy of applying simple re-calibration to update a model for the context of applying a previously developed model to a new trial. We found that new models do not need to be developed for risk assessment in new trials; prior models with re-calibration will suffice.

STATEMENT OF CANDIDATE

I certify that the work in this thesis entitled "**Forecasting risk in acute myocardial infarction**" has not previously been submitted for a degree nor has it been submitted as part of the requirements for a degree to any other university or institution other than Macquarie University.

I also certify that the thesis is an original piece of research and it has been written by me. Any help and assistance that I have received in my research work and the preparation of the thesis itself have been appropriately acknowledged.

In addition, I certify that all information sources and literature used are indicated in this thesis.

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I would also like to thank Professor Ian Marschner who was involved in this project during the early days and came on board again as my principal supervisor after Malcolm retired. Thanks for allowing me the opportunity all those years ago to carry out the analysis to derive the HERO-2 risk model and teaching me the fundamental skills to develop risk models. More recently thanks for your ideas, feedback and assistance which has been very helpful in finishing off this thesis.

I would also like to thank the NHMRC Clinical Trials Centre, University of Sydney for allowing me the opportunity to undertake this PhD. I am indebted to Professor John Simes who has set up a world class clinical trials research unit. The standard of intellectual contribution and creative thinking among my colleagues is exceptional. This environment has fostered a culture of learning and personal development and has cultivated the research and statistical skills that I am proud to have today. Thanks John for your ideas with the analysis and help with identifying the key messages.

I would also like to acknowledge Professors Hudson, Marschner and Simes for their collaboration in publishing parts of this work as described in full on page viii.

Special thanks to Professor Val Gebski, Adrienne Kirby and Professor Tony Keech for giving me adequate time to devote to this project.

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Lastly I would like to thank my family for their enduring support, love and encouragement. It has been a long, arduous road which has taken much perseverance. I could not have achieved this without you.

PUBLICATIONS

The following publications have resulted from work contained in this thesis:

1. O'Connell RL and Hudson HM. Risk of mortality after acute myocardial infarction: Performance of model updating methods for application in different geographical regions. Computational Statistics & Data Analysis 2009; 53(3): 834-46.

2. Simes RJ, O'Connell RL, Aylward PE, Varshavsky S, Diaz R, Wilcox RG, Armstrong PW, Granger CB, French JK, Van de Werf F, Marschner IC, Califf R, White HD; for the HERO-2 Investigators. Unexplained international differences in clinical outcomes after acute myocardial infarction and fibrinolytic therapy: lessons from the Hirulog and Early Reperfusion or Occlusion (HERO)-2 trial. American Heart Journal 2010; 159(6): 988-97.

In both publications I took the lead on all analyses. I also took the lead in writing paper 1 and contributed to the writing of paper 2. For inclusion in this thesis paper 2 has been expanded with the inclusion of additional analyses and rewritten to focus on the statistical aspects of the work.

Other related publications on which I am a coauthor:

3. The Hirulog and Early Reperfusion or Occlusion (HERO)-2 Trial Investigators. Thrombin-specific anticoagulation with bivalirudin versus heparin in patients receiving fibrinolytic therapy for acute myocardial infarction: the HERO-2 randomised trial. Lancet 2001; 358: 1855-63.

4. Edmond JJ, French JK, Stewart RAH, Aylward PA, De Pasquale CG, Williams BF, O'Connell RL, Simes RJ, and White HD, for the HERO-2 Investigators. Frequency of recurrent ST elevation myocardial infarction after fibrinolytic therapy in a different territory as a manifestation of multiple unstable coronary arterial plaques. American Journal of Cardiology 2006; 97(7): 947-51.

5. Edmond JJ, French JK, Aylward PE, Wong CK, Stewart RA, Williams BF, De Pasquale CG, O'Connell RL, Van den Berg K, Van de Werf FJ, Simes RJ, and White HD, for the HERO-2 Investigators. Variations in the use of emergency PCI for the treatment of re-infarction following intravenous fibrinolytic therapy: impact on outcomes in HERO-2. European Heart Journal 2007; 28(12):1418-24.

ACRONYMS

ACS	Acute Coronary Syndrome
AMI	Acute Myocardial Infarction
ANN	Artificial Neural Network
ASSENT-2	Assessment of the Safety and Efficacy of a New Thrombolytic
ASSENT-3	Assessment of the Safety and Efficacy of a New Thrombolytic Regimen
AUC	Area under the curve
BNP	Brain Natriuretic Peptide
CABG	Coronary Artery Bypass Graft
CART	Classification and Regression Trees
CHD	Coronary Heart Disease
CI	Confidence Interval
CT	Computed Tomography
CV	Cross-validation
DALE	Disability Adjusted Life Expectancy
ECG	Electrocardiographic
EPV	Events per variable
GDF-15	Growth Differentiation Factor-15
GISSI	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico
GNI	Gross National Income
GRACE	Global Registry of Acute Coronary Events
GUSTO-I	Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries
GUSTO-IIb	Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes
GUSTO-III	Global Use of Strategies to Open Occluded Coronary Arteries
HERO-2	Hirulog and Early Reperfusion or Occlusion
HF	Heart Failure
HGR	HERO-2 Global Risk
HPI	HERO-2 Prognostic Index
IDI	Integrated Discrimination Improvement
InTIME-II	Intravenous NPA for the Treatment of Infarcting Myocardium Early
IP	Integral of “one minus specificity”
IQR	Interquartile range
IS	Integrated Sensitivity
IV	Intraveneous
LP	Linear Predictor
MAGIC	Magnesium In Coronaries trial
MRI	Magnetic Resonance Imaging
NGRP	Net Gain in Reclassification Proportion
NRI	Net Reclassification Improvement
NSTEMI	Non-ST-segment Elevation MI
NT-ProBNP	N-terminal Pro β-type Natriuretic Peptide
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
PREDICT	Predicting Risk of Death In Cardiac Disease Tool
PURSUIT	Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin (eptifibatide) Therapy
RCT	Randomised Clinical Trial
ROC	Receiver Operating Characteristic
SE	Standard Error
SYSBP	Systolic Blood Pressure
TIMI	Thrombolysis in Myocardial Infarction
t-PA	Tissue Plasminogen Activator
UA	Unstable Angina
VIGOUR	Virtual Coordinating Centre for Global Collaborative Cardiovascular Research