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RACP Foundation Research Awards

FINAL REPORT

Project / Program Title		Optimising application of high-sensitivity troponin in clinical practice
Name		Dr Ming-yu (Anthony) Chuang
Award Received		2019 RACP Fellows Research Entry Scholarship
Report Date		15 April 2020
Chief Investigator / Supervisor		Professor Derek P Chew
Administering Institution		Flinders University
Funding Period	Start Date:	1 February 2019
	Finish Date:	1 February 2020

PROJECT SUMMARY

Cardiac troponin is a biomarker that has been universally accepted as the test of choice to diagnose myocardial infarction (also known as 'heart attack'). In 2009, a new generation of troponin test was developed that is more precise and sensitive. For this new test to be fully integrated into clinical practice, we need to find the best way to apply it in clinical decision pathways in order to ensure best patient outcome and cost-effectiveness. The goal of my PhD is to optimise the application of this new generation troponin test in clinical practice.

PROJECT AIMS / OBJECTIVES

Cardiac troponin testing forms the cornerstone for myocardial infarction (MI) diagnosis. In 2009, a newer generation of troponin assay, high-sensitivity troponin, was introduced into clinical practice enabling the detection of troponin at a much lower level and with greater precision. Compared to older assays, high-sensitivity troponin could theoretically reduce previous levels of uncertainty and further refine risk stratification in two previously challenging areas:

1. **Low-risk population:** Rapid and accurate risk assessment of a heterogeneous group of patients with predominantly very low risk/pre-test probability, i.e. patient presenting to the emergency department (ED) with suspected acute coronary syndrome (ACS).
2. **High-risk population:** Invasive management has been shown to be beneficial in patients with troponin elevation in the setting ACS. However, whether invasive management could modify risk in patients with elevated troponin not due ACS remains undetermined. With the greater precision of high-sensitivity troponin, I aim to risk stratify patients with nonspecific troponin elevation with the goal to identify patients whose risk may be modified by coronary-specific investigation and treatment with greater specificity.

Whilst diagnostic accuracy is an important measure, for any new 'diagnostic test' to be fully integrated into clinical practice, there are at least **three additional** aspects that needs to be evaluated – **1) place in a clinical decision pathway**, **2) effect on patient outcomes**, and **3) cost effectiveness**. Although there is robust evidence for its technical accuracy, little evidence exists for the remainder three aspects in these two challenging areas.

The goal of my PhD is to comprehensively evaluate the clinical utility of troponin in the two aforementioned challenging areas using data derived from randomised trials and large-scale electronic health data. The planned studies and their methodology are detailed below.

SIGNIFICANCE AND OUTCOMES

Low-risk population

Health services are replete with innovations promising improvements in care and outcome. Realizing these benefits requires parallel evolution of clinical decision making, supported by objective, and validated evidence. Improvements in troponin test performance are one such innovation (i.e. high-sensitivity troponin), with the potential to disposition of emergency department (ED) patients presenting with suspected acute coronary syndromes (ACS) by facilitating earlier recognition of myocardial infarction, thereby reducing treatment delay, and through ruling out ACS allowing for earlier discharge. To date, large published studies using accelerated troponin protocols (less than the current standard of 6 hours) have been **observational**. These studies have not evaluated prospective patients clinically managed according to the troponin protocols and did not include a randomized control. To address this, we have performed a **Bayesian analysis (published)** and a **pragmatic randomized trial that will comprehensively evaluate the safety, clinical effectiveness, and resource implications of a 1-hour protocol using high-sensitivity troponin-T in the care of patients with suspected ACS**.

This randomised trial has recently completed recruitment (over 3000 patients) and we aim to present the 30-day outcome as a 'late breaking trial' at the 2019 European Society of Cardiology Conference in August 2019. A number of secondary analyses have been planned a priori, including cost-effective analysis, interaction with other clinical risk scores, and utility of further testing in the rule-out arm.

My research will likely change the current standard-of-care on how we assess patients presenting to the ED with suspected ACS by optimizing the use of high-sensitivity troponin. Specifically, it will likely (i) shorten the length of stay, (ii) decrease the degree of uncertainty and (iii) decrease healthcare delivery costs. Given the significant healthcare burden of suspected ACS presentations (accounting for up to 15% of all emergency department presentations), I believe my research will have a positive health and value impact on the patient outcome and the Australian healthcare system.

High risk population

The improved analytical sensitivity of the new high-sensitivity troponin assay facilitates early diagnosis of myocardial infarction. However, these assays come with new challenges including increased identification of troponin elevations above the conventional reference threshold (>99th percentile upper reference limit) in patients without objective evidence of myocardial ischemia (e.g. on echocardiography or ECG). The recently published Fourth Universal Definition of Myocardial Infarction is the first guideline to formally define this syndrome as **'myocardial injury'** (troponin elevation without cardiac ischaemia) and distinguish it from myocardial infarction (troponin elevation with cardiac ischaemia). **While there is abundant evidence to guide the management of myocardial infarction, there is no evidence to guide the management of patients with myocardial injury**. Given that these patients often represent a major diagnostic

and management challenge and make up of **at least 20% of all patients undergoing troponin testing**, this research will likely significantly influence on how this condition is managed.

The studies I have published during my PhD have demonstrated that troponin elevation (both the magnitude and rate) is associated with worse outcome regardless of its etiology. Furthermore, in another study, I highlighted that fact that invasive management (in the form of coronary angiography) is highly interactive with non-cardiac comorbidities.

Most recently, I performed a state-wide, population-level study assessing the short- and long-term temporal consequences associated different patterns of troponin elevation, which have been submitted for peer-review to ***Circulation***.

We have two studies which are ongoing:

1. A randomised controlled trial assessing the safety and effectiveness of anatomical investigation (i.e. coronary angiography) in patients with troponin elevation without evidence of myocardial infarction. Currently, there is no evidence of guide management of this group of patients, which accounts for up to 50% of patients with troponin elevation. This trial would be of great value to guide management of this complex patient population. The design of this trial has been published and has commenced recruitment in December 2018 (ACTRN12618000378224p).
2. 2. An observation study examining the predictive value of troponin on coronary angiography findings.

PUBLICATIONS / PRESENTATIONS

As a recipient of the 2019 RACP Fellows Research Entry Scholarship, I would like to express my sincere gratitude for the opportunities and privileges that the scholarship has created and allowed me to begin the academically and clinically rewarding journey. These include publication of **five research articles in high-impact journals and a textbook chapter**, two **publication awards from Flinders University**, delivery of **three national and international conference presentations** with **two competitive international presentation awards**, as well as two ongoing research projects with a planned late-breaking trial presentation.

The details of the publications are listed below:

Published papers since receiving scholarship

Original research article (accepted manuscript)

Chew DP, Lambrakis K, Blyth A, Seshadri A, Edmonds MJR, Briffa T, et al. A Randomized Trial of a 1-Hour Troponin T Protocol in Suspected Acute Coronary Syndromes: The Rapid Assessment of Possible Acute Coronary Syndrome in the Emergency Department With High-Sensitivity Troponin T Study (RAPID-TnT). Circulation. 2019;140(19):1543-56.

Original research article (accepted manuscript)

Jones D, Chew P, Horsfall M, **Chuang A**, Sinhal A et al. Multidisciplinary Transcatheter Aortic Valve Replacement Heart Team Program Improves Mortality in Aortic Stenosis. BMJ Open Heart 2019.

Original research article

Chuang A, Hancock D, Halabi A, Horsfall et al. Invasive management of acute coronary syndrome: Interaction with competing risks. International journal of cardiology, 2018. DOI: 10.1016/j.ijcard.2018.07.078

Original research article

Chapple A, **Chuang A**, Clark R, Horsfall M et al. Clinician assessment of acute coronary syndrome in the emergency department: an observational sub-analysis of nurse and doctor risk assessment and the impact on patient outcomes. British journal of cardiac nursing, 2018.

Original research article (methods paper, grant ID: APP1146512)

Lambrakis K, French JK ..., **Chuang A** et al. The appropriateness of coronary investigation in myocardial injury and type 2 myocardial infarction (ACT-2): A randomized trial design. Am Heart J 2018;208:11-20.

Published chapter since receiving scholarship

Chuang A, Brogan R, and Chew D. Chapter 33 - Catheter-based reperfusion in acute myocardial infarction. Interventional Cardiology and Cardiac Catheterisation: The Essential Guide, Second Edition

Submitted manuscript/abstract

Circulation

Troponin elevation pattern and subsequent cardiac and non-cardiac outcomes: Implementing the Fourth Universal Definition of Myocardial Infarction at a population level (CIRCULATIONAHA/2019/041548)

Awards from publications

- 2018 PhD Postdoctoral Publication Award. College of Medicine and Public Health, Flinders University (Adelaide, Australia)
- 2018 Higher Degree by Research Publication Award. College of Medicine and Public Health, Flinders University (Adelaide, Australia)

Conference presentations since scholarship

- March 2019 - American College of Cardiology Annual Scientific Session (Chicago, USA)
- December 2018 - Royal Australasian College of Physicians South Australia Scientific Meeting (Adelaide, Australia)
- November 2018 - American Heart Association Scientific Session (New Orleans, USA)

Awards from conference presentations

- 2019 Finalist for the American College of Cardiology Young Investigator Competition. American College of Cardiology (New Orleans, USA)
- 2018 American Heart Association Council on Basic Cardiovascular Sciences (BCVS) International Travel Grant. American Heart Association (Chicago, USA)

ACKNOWLEDGEMENTS

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