



## RACP Foundation Research Awards

### PROGRESS REPORT

<b>Project / Program Title</b>	Stress hyperglycaemia and mortality in critical illness: Defining the association and underlying mechanisms	
<b>Name</b>	Dr Tien Foong Lee	
<b>Award Received</b>	2015 RACP NHMRC Kincaid-Smith Scholarship	
<b>Report Date</b>	3 July 2017	
<b>Chief Investigator / Supervisor</b>	A/Prof Morton Burt	
<b>Administering Institution</b>	Flinders University	
<b>Funding Period</b>	Start Date:	1 June 2015
	Finish Date:	1 June 2018

#### PROJECT SUMMARY

There are 76,000 acute admissions to Intensive Care Units (ICU) in Australia per annum. Hyperglycaemia is common in these patients; up to 46% recording a blood glucose  $>10$  mmol/L. There is a strong association between hyperglycaemia and mortality in critically ill patients. Early studies reported that maintaining glucose between 4.4-6.1 mmol/L reduced mortality in critically ill patients. However, these findings were not replicated in a larger, international, multi-centre trial, which conversely reported increased mortality with tight glycaemic control. As such, the relationship between hyperglycaemia and mortality in critically ill patients with diabetes and the benefits of glycaemic control in ICU remain an area of controversy.

This PhD thesis will be based around two studies. First, I will evaluate whether relative hyperglycaemia is more strongly associated with in-hospital mortality in critically ill patients than absolute hyperglycaemia. Secondly, I will investigate mechanisms by which acute hyperglycaemia could increase mortality. These studies may form a basis for appropriate selection of patients for tight glycaemic control in ICU based on relative, rather than absolute, hyperglycaemia.

In the first study, 1,400 consecutive non-pregnant adult patients that were acutely admitted to the ICU at Flinders Medical Centre for reasons other than hyperglycaemia and who did not have a blood transfusion within 24 hours of ICU admission were studied. To date, we have preliminary data on 1,193 patients including mortality data from the ICU registry. From this preliminary data, we found that relative hyperglycaemia, as defined by SHR, predicts mortality in ICU patients across the glycaemic spectrum independent of other prognostic clinical variables, while absolute glucose does not. This is the first prospective observational study and adds to other published research by demonstrating the prognostic utility of quantifying relative hyperglycaemia. This should provide a basis to pursue studies on the mechanisms by which stress hyperglycaemia increases mortality, and also for interventional prospective studies using calculated individualized

therapeutic targets for glucose-lowering therapy based on relative, rather than absolute, glycemic thresholds.

The second study is an investigation of whether an acute glucose elevation induces changes in vascular function that could underlie an association between stress hyperglycaemia and adverse outcomes in patients without and with diabetes. This study will be conducted on volunteers with and without diabetes.

### **PROJECT AIMS / OBJECTIVES**

Part I: To determine if relative hyperglycaemia is more strongly associated with all-cause mortality in critically ill patients than absolute hyperglycaemia.

Part II: To define mechanisms that could explain a relationship between relative hyperglycaemia and mortality in patients across the glycaemic spectrum. Specifically, we will investigate if relative hyperglycaemia adversely affects well-validated markers of cardiovascular risk; and if the relationship between relative hyperglycaemia and mortality/ vascular function is similar in patients with and without background hyperglycaemia.

### **SIGNIFICANCE AND OUTCOMES**

To date, we have preliminary data on 1,193 patients including mortality data from the ICU registry. From this preliminary data, we found that relative hyperglycaemia, as defined by SHR, predicts mortality in ICU patients across the glycaemic spectrum independent of other prognostic clinical variables, while absolute glucose does not. This is the first prospective observational study, and adds to other published research by confirming the prognostic utility of quantifying relative hyperglycemia. This should provide a basis to pursue studies on the mechanisms by which stress hyperglycaemia increases mortality, and also for interventional prospective studies using calculated individualized therapeutic targets for glucose-lowering therapy based on relative, rather than absolute, glycemic thresholds.

### **PUBLICATIONS / PRESENTATIONS**

Abstract submitted for Endocrine Society of Australia Annual Scientific Symposium 2017, and for the Bryan Hudson Young Investigator Award.