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Small Grant Proposal

Clinical roles of soluble ST2 for the outcomes of cardiac valve operations

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Executive summary

Soluble ST2 is a novel cardiac biomarker that reflects cardiac injury and the response to treatment. Previous studies showed that ST2 has less confounding and more specific than NT-proBNP. ACCF/AHA has proposed 2013 Guidelines for the Management of Heart Failure that includes ST2 in the recommendations. In the research proposal, we will assess the clinical role of serum ST2 level in cardiac non-coronary valve surgical patients.

We will recruit 70 patients who undergo cardiac non-coronary valve operations. Serum levels of ST2 and NT-proBNP and troponin-T will be measured at preoperative baseline, postoperative 24 hours, and postoperative 5 to 10 days in the routine blood sampling. The endpoints include hospital mortality, all-cause mortality, unexpected ICU return, MACE, time to extubation, and total length of stay. We will also collect various preoperative, operative, and postoperative variables, such as EuroScore-II. Their relationships will be analyzed.

We expect to demonstrate the superior role of ST2 to NT-proBNP and other variables in risk stratification and outcome prediction and assessment in our cohort.

Keywords

ST2, NT-proBNP, heart failure, troponin-T, biomarker

List of investigator groups

Cardiovascular Surgery, Cardiology, and Clinical Research, Taipei Tzuchi Hospital, New Taipei City, Taiwan;

Surgery, Tzuchi University College of Medicine, Hualian, Taiwan.

Third parties involved in the project

Health One Network Co., Ltd. New Taipei City Taiwan, (telephone: 886-2-22993688--x13; cellphone: 886-930142606); Critical Diagnostics.

Backgrounds

Soluble ST2 (sST2) is a novel biomarker (Dieplinger et al. 2009) of fibrosis (Moore and Januzzi 2010) that reflects cardiac dysfunction such as remodeling or post-injury scaring (Sanada et al. 2007, Weir et al. 2010, Willems et al. 2013, Díez 2008). According to previous research, its trending has superior signal-to-noise and clinical relevance for cardiac prognosis to conventional biomarkers for heart failure such as NT-proBNP (Weinberg et al. 2002, Pascual-Figal et al. 2011a, Santhanakrishnan et al. 2012). For valvular heart disease patients and their outcomes, we would like to investigate the association and predictive value of ST2 in cardiac surgical non-coronary valve patients.

Conventional biomarkers for assessing heart failure are BNP / NT-proBNP. But they have various confounders like age, BMI, and renal disease (Mueller and Dieplinger 2013). When heart perceives stress, their serum levels begin to rise and their random variations are high. Thus their role of monitoring heart failure prognosis may be unsatisfactory for physicians who need timely responses (Willems et al. 2013, Bayes-Genis et al. 2011, Rehman et al. 2008).

Soluble ST2 can reflect the process of cardiac remodeling and myocardial post-injury fibrosis in heart failure (Rehman et al. 2008, Schmitz et al. 2005, Moore and Januzzi 2010), and so it has much less confounding than conventional BNP/NT-proBNP (Mueller and Dieplinger 2013). When ST2 serum levels climb, it means there is considerable myocardial damage (Broch et al. 2012, Lupón et al. 2013). After treatment we can check if ST2 begins to drop to assess whether the treatment works (Pascual-Figal et al. 2011a, Chen et al. 2013). Even in the asymptomatic patients (Wang et al. 2013), if the ST2 serum levels are higher than the cutoff 35 ng/ml, it means there is significant cardiac damage (Mueller and

Dieplinger 2013, Januzzi 2013). We can monitor ST2 serum level to predict disease occurrence (Chen et al. 2013) and make treatment plans as early as possible (Boisot et al. 2008, Manzano-Fernández et al. 2012). In addition ACCF/AHA has proposed the 2013 Guideline for the Management of Heart Failure that includes ST2 in the recommendations (Yancy et al. 2013). ST2 and NT-proBNP can work together for better sensitivity and specificity (Pascual-Figal et al. 2011a, Bayes-Genis et al. 2011, Sabatine et al. 2008).

As above, there are also various prior research studies that demonstrated the association of sST2 with acute and chronic heart failure (Mueller et al. 2008, Shah et al. 2009, Wojtczak-Soska et al. 2013, Daniels et al. 2010, Bhardwaj and Januzzi 2010, Henry-Okafor et al. 2012, Manzano-Fernández et al. 2011, Shah and Januzzi 2010, Weinberg 2003).

Aims

1. To stratify the operation risk of valvular heart patients by preop sST2 and other known preop variables;
2. To correlate the operation outcomes of valvular heart patients by postop sST and other known postop variables;
3. To compare sST2 and other known predictive variables.

Impact

Currently we can implement ST2 in the following scenarios:

1. Health checkup and outpatient screening (Wang et al. 2013);
2. Acute inpatients and routine assessments (Díez 2008, Aldous et al. 2012, Pascual-Figal et al. 2009);
3. Post-treatment and prognosis for the recovery evaluation, maybe as long as three to six months (Bayes-Genis et al. 2011, Lupón et al. 2013, Pascual-Figal et al. 2011b, Ky et al. 2011).

Methods

We will collect ST2, and other cardiac biomarkers at different time points of cardiac valve surgical patients and investigate their relationships with different outcome measures and also may compare the performance of these biomarkers on predicting various outcomes (Gaggin et al. 2014).

Design

Prospective observational longitudinal clinical study

Data collection overview

(1) Serum biomarker levels of ST2, NTproBNP, and troponin-T from blood sample drawing at the same time of clinical routine blood drawing: preop, postop 24-hour, postop 5-10 days; three time points.

(2) ST2 will be done by special kits sponsored by the vendor. NTproBNP and troponin-T will be measure in hospital central lab.

(3) Preop, op, postop, and outcome variables will be collected as the following details.

Expected Difficulties and Troubleshooting

Since the study does not alter routine clinical practice, little resistance from patients and family is anticipated. Thorough explanation of the informed consent will be helpful for recruiting participating patients.

Inadequate sample size or insufficient power to detect difference may be encountered. Since we have many dependent variables or outcome variables, we may select the some to present.

Procedures

Ethical Considerations

The research protocol will be evaluated by the institutional review board.

All participating patients will have thorough understanding of the study regarding the aims and potential risks as explained by the research staff members. They also sign the informed consensus personally or by a qualified proxy.

We have a conflict of interest to declare: the laboratory kits are partially sponsored by the local distributor, Health One Network Co., Ltd. New Taipei City Taiwan, (telephone: 886-2-22993688--x13; cellphone: 886-930142606).

Cohort definition

We will prospectively recruiting the valvular heart patients who are admitted for elective corrective operations in Far Eastern Memorial Hospital.

The recruited patients must meet all of the inclusion criteria: adult with age over 20 years, pure valvular operations, elective setting, single or multiple valves, conventional or minimally-invasive approach, either without or with previous cardiac or major aorta operations.

The exclusion criteria are: pregnant, combined concurrent major cardiac procedures such as coronary or aorta operations, non-elective settings such as urgent or emergency, refusal of participation by the patient or family due to any reason.

If the inclusion or exclusion of a case is in doubt, the decision is made by the consensus or majority of principal investigators (PI and co-PI).

Data collection

Each patient will have three serum samples collected before operation, 24 hours after operation, and around one week (from five to ten days) after operation. The blood drawing will be made concurrently with other laboratory tests as needed clinically. There is no extra blood drawing purely just for the study. For cardiac biomarkers, we will measure sST2, NT-proBNP, and troponin-T.

Our routine cardiac surgery database will also collect preop, op, and postop variables for all the patients, such as EuroScore-II. The outcome-related variables will include: time to extubation (TOE), intensive care unit (ICU) time, total length of stay (LOS), and hospital mortality.

The variables for each patients are listed but not limited as below:

Biomarkers (preop, postop 24 hour, postop 5-10 days): sST2, NT-proBNP, troponin-T (Table 1).

Table 1.

Biomarker sampling schedule

Biomarkers	Preop	Postop 24 hour	Postop 5~10 days
sST2			
NT-proBNP			
Troponin-T			

Preop: Birthday, date of operation, op diagnosis, last preop LVEF, last preop RVSP (SPAP), creatinine, dialysis or not, diabetes, hypertension, COPD;

Op: operation procedure, op time, ischemia time, pump time

Postop: time to extubation, ICU time, total LOS, unexpected ICU return, hospital mortality (also date), major adverse cardiac event (MACE) (also date), first postop LVEF, and first postop RVSP (SPAP).

Laboratory bench work

To measure sST2 serum levels, we will use the kits and protocols as advised by the vendor (Mueller and Dieplinger 2013). To measure NT-proBNP and troponin-T serum levels, we will send the samples to hospital central lab for result reporting since they have been our clinical routines.

Data Analysis

We plan to recruit 70 patients and measure three serum samples per case. There will be 210 laboratory tests. Due to budget limitation, we set the sample size to be 7, since we can only afford 210 laboratory tests. We set the alpha-level to be 0.05.

The outcome variables (dependent variables) will be the following and we will select more appropriate variables to present according to the interim analysis results. The primary endpoints include: hospital mortality, all-cause mortality, unexpected ICU return, and MACE. The secondary endpoints include: time to extubation, ICU time, and total LOS.

We will transform several variables to facilitate analysis. Renal function will be graded by GFR (glomerular filtration rate) as estimated by creatine-related formulae. Comorbidity such as diabetes or hypertension will be determined by clinical judgment. For biomarker analysis (sST2, NT-proBNP, troponin-T), in addition to absolute values, we will use relate values for better demonstrate the change from baseline and the trends. Relative serum level (RSL) is a dimensionless value defined as the ratio of serum level to the baseline (level divided by baseline).

For comparing scale or ordinal (quasi-scale) variables, we will use Mann-Whitney U test for two groups and Kruskall-Wallis test for three or more groups. For comparing nominal variables, we will use Fisher's exact test. For comparing time-event variables, we will use log-rank test. For modeling predictions, we will choose appropriate statistical regression methods based upon dependent variables. For scale dependent variable, we will use linear or log-linear regression models depending the likelihood of normality violation. For binary dependent variables, we will use logistic regression model. For time-event variables, we will use Cox regression model. For evaluating biomarker performance on accuracy of classification, we will receiver operating characteristic (ROC) analysis. The truth variables will be one of the outcome variables and the classifier variables will be ordinal-ranged biomarker absolute level or RSL. The tentative optimal cutoff values for each biomarker may be proposed depending on the outcome variables or clinical scenarios.

The backbone for the results presentation will be: cohort background statistics, time trends of biomarkers, biomarker and predictors for the outcomes, and comparisons of biomarkers.

The statistical software we used will be Stata/MP 13.1 for Mac (64-bit Intel).

Timetable

(1) ST2 and other cardiac biomarker lab assay;

(2) Statistical analysis of the study;

(3) Interpretation and implement of the study results.

(Table 2)

Table 2.
Research working timetable

Time (month)	1-2	3-4	5-6	7-8	9-10	11-12
Data collection	@	@	@	@		
Statistical analysis		@	@	@	@	
Result interpretation			@	@	@	
Report writing				@	@	@

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Funding program

Pending; maybe yearly university hospital research grant.

Project

University and hospital cardiovascular research project.

Call

Cardiovascular research call.

Hosting institution

Taipei Tzuchi Hospital, Tzuchi University College of Medicine, Buddhist Tzuchi Medical Foundation.

Ethics and security

Consenting, safety, and data policy all comply to ICH (International Conference on Harmonisation) Good Clinical Practice (GCP). University and hospital institutional review board (IRB) will evaluate the approval.

Conflicts of interest

The research is partially sponsored by the local distributor who donates some of the laboratory kits, Health One Network Co., Ltd. New Taipei City Taiwan, (telephone: 886-2-22993688--x13; cellphone: 886-930142606).

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