Predictors of In-Hospital Mortality in Acute Decompensated Heart Failure (Thai ADHERE)

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Background: *Heart failure had emerged as a major public health problem and became the leading cause of hospitalization. The Acute Decompensated Heart Failure National Registry (ADHERE) of US patients hospitalized with a primary diagnosis of acute decompensated heart Failure (ADHF) had been reported worldwide for the risk stratification and predicting In-hospital mortality.*

Objective: *Identify clinical risk factors or treatment procedures that could predict In-hospital mortality in Thai patients with ADHF.*

Material and Method: *Thai ADHERE is a multicenter, observational, prospective study. The data were collected via web-based electronic data capture and analyzed. Two thousand forty one hospitalization episodes involving 1,671 patients in the 18 participating hospitals between March 2006 and September 2007 were analyzed. All clinical factors associated with In-hospital mortality identified by univariated analysis were further analyzed by Logistic regression model.*

Results: *One hundred thirteen patients died during the hospitalization period with overall mortality rate of 5.5%. Systolic blood pressure <90 mmHg, creatinine >2.0 mg/dL, history of stroke/TIA, and NYHA class IV were independent risk factors for In-hospital mortality with adjusted OR (95% CI) = 3.45 (1.77-6.79), 1.99 (1.30-3.05), 1.85 (1.11-3.08) and 1.69 (1.08-2.64) respectively. Hypertensive cause of CHF, prior use of lipid lowering drug, and hemoglobin level were associated with lower risk, adjusted OR (95% CI) = 0.35 (0.15-0.81), 0.51 (0.34-0.78) and 0.90 (0.82-0.98) respectively.*

Conclusion: *The clinical predictors for In-hospital mortality of Thai ADHERE that associated with worse outcome were systolic blood pressure <90 mmHg, creatinine >2.0 mg/dL, history of stroke/TIA, and NYHA class IV. Hypertensive cause of CHF, prior use of lipid lowering drug, and hemoglobin were associated favorable outcome.*

Keywords: *Predictors, In-hospital mortality, Thai-ADHERE*

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Heart failure is one of the major consequences of cardiovascular diseases and a leading cause of hospitalization worldwide including Thailand. This condition is associated with an enormous burden to medical care due to inpatient management and substantial risk of readmission. Decompensated heart failure occurred in patients with new-onset heart failure as well as exacerbation of chronic heart failure. This complex clinical syndrome due to an underlying events such as acute myocardial infarction, myocarditis, hypertension or valvular heart disease, lead to a high incidence of in-hospital mortality, ranging from 2 to 20%[1-6] and approximately 20% per year in spite of optimal advanced therapy[7]. Regarding to variability of clinical course of patients with heart failure was observed. Understanding factors related to subsequent mortality may help to identify which patients needed more intense monitoring and therapy. Many previous

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studies demonstrated a number of variables that were associated with increased mortality such as etiology, age, initial clinical assessment at the time of hospitalization, Left ventricular function (LVEF), serum sodium, serum hemoglobin (anemia), cardiac troponins, serum creatinine, serum natriuretic peptide, obesity, wide QRS complex and others[8-18]. The US Acute Decompensated Heart Failure National Registry (US ADHERE) was a large, observational, multicenter study done in USA. Patient characteristics, pattern of care and outcomes of hospitalized with acute decompensated heart failure (ADHF) were assessed with the purpose of improving care for patients[19]. This large database was collected from acute care hospitals across the United States and had been reported in many aspects. The present study analyzes the pool data of the THAI ADHERE registry in Thailand. The aim of the present study was to explore which clinical parameters, etiologies or management can predict the in-hospital mortality of patients with ADHF in order to improve the quality of care for Thai patients.

Material and Method

Registry design

Thai ADHERE registry is a multicenter, observational, prospective study endorsed by the Heart Association of Thailand under the Royal Patronage. Data were collected from post-discharge medical records of patients hospitalized with the diagnosis of heart failure using web-based electronic data capture (EDC). The registry will not collect unique patient identifying information in order to preserve patient anonymity.

Patients eligibility and identification

All adult patients with age equal or greater than 18 years at the time of admission to hospital with the diagnosis of HF are eligible. ADHF were defined as new onset HF with decompensation or chronic HF with Decompensation. The authors excluded the HF that presented as a co-morbid condition and not a principle focus of diagnosis or treatment during this hospitalization episode. Informed consent of the individual patients is required for the registry.

Data capture

Data capture from medical records included demographics information, medical history, baseline clinical characteristics, initial evaluation, hospitalization, and any specific types of treatment or procedure and outcomes. All causes in-hospital mortality was the principle outcomes of the present study. Registry entries reflect events of hospitalization (patients' episodes) not individual patients thus multiple hospitalizations of the same patient may be entered into this registry as separate records. Longitudinal outcomes for each patient are not available. The investigator coordinator must sign documentation indicating that all eCRFs have been completed and reviewed accurately.

Statistical analysis

All demographic characteristics, clinical presentation, all treatment procedures, and medicines were categorized as variables and reported as numbers and percentages between the dead group and the survived group. The association between these factors and mortality were univariate analysis using Pearson chi square test. Unadjusted odds ratio and 95% confidential interval (CI) of each variables were presented. Continuous data were expressed as median with interquartile range (IQR) and difference comparison between groups were analyzed by Mann-Whitney U- test. All variables identified previously as significant factors that could affect mortality ($p<0.05$) were put into logistic regression model for determining independent predictors of in-hospital mortality. All statistic calculations were performed using SPSS 9 package. For all tests, $p<0.05$ (two-sided) was considered as statistically significant.

Results

Two thousand forty one hospitalization episodes involving 1,612 patients from 18 participating hospitals (13 government hospitals, 5 private hospitals) between March 2006 and September 2007 were analyzed. One hundred thirteen patients died during the hospitalization period with an overall mortality rate of 5.5%.

As in Table 1, patients who died were older ($p = 0.02$) with higher proportion of age more than 75 years ($p = 0.03$). There were no significant difference among body weight, gender, or history of previous heart failure including LVEF <40%. Regarding other risk factors, previous stroke/TIA ($p = 0.01$) and chronic renal insufficiency patients ($p = 0.02$) were the only two parameters that associated with mortality [unadjusted OR 1.84 (1.13-2.99) and 1.70 (1.11-2.60) respectively]. Coronary artery disease, myocardial infarction, hypertension, diabetes, smoking and dyslipidemia were major risk factors in the present

Table 1. Demographic characteristics and medical history

Characteristics	Total n = 2,041 (%)	Survive n = 1,928 (%)	Dead n = 113 (%)	Unadjusted OR (95% CI)	p-value
Demographic					
Age (yrs, meadian, IQR)	67 (57:75)	67 (57:75)	70 (58:80)	-	0.02
Age >75	484 (23.4)	448 (23.2)	36 (31.9)	1.55 (1.03-2.33)	0.03
Weight (kg, median, IQR)	60 (50:70)	60 (50:70)	54 (47:64)	-	0.05
Male	1,012 (49.6)	957 (49.6)	55 (48.7)	1.04 (0.71-1.52)	NS
Medical history					
Prior heart failure	1,357 (66.5)	1,283 (66.5)	74 (65.5)	0.95 (0.64-1.42)	NS
History LVEF <40%	485 (39.8)	458 (39.5)	27 (44.3)	1.22 (0.72-2.04)	NS
Coronary artery disease	951 (46.6)	899 (39.5)	52 (46.0)	0.98 (0.67-1.43)	NS
Myocardial infarction	544 (26.7)	511 (26.5)	33 (29.2)	1.14 (0.75-1.74)	NS
Hypertension	1,322 (64.8)	1,249 (64.8)	73 (64.6)	0.99 (0.67-1.48)	NS
Dyslipidemia	1,030 (50.5)	981 (50.9)	49 (43.3)	0.74 (0.50-1.28)	NS
Stroke/TIA	246 (12.1)	224 (11.6)	22 (19.5)	1.84 (1.13-2.99)	0.01
Atrial fibrillation	491 (24.1)	468 (24.3)	23 (20.4)	0.80 (0.50-1.28)	NS
Pacemaker or ICD	62 (3.0)	57 (3.0)	5 (4.4)	1.52 (0.60-3.87)	NS
Peripheral vascular disease	67 (3.3)	62 (3.2)	5 (4.4)	1.39 (0.55-3.54)	NS
Chronic renal insufficiency	396 (19.4)	364 (18.9)	32 (28.3)	1.70 (1.11-2.6)	0.02
Diabetes	966 (47.3)	912 (47.3)	54 (47.8)	1.02 (0.70-1.49)	NS
COPD or asthma	161 (7.9)	150 (7.8)	11 (9.7)	1.28 (0.67-2.43)	NS
Smoking	768 (42.8)	731 (43.1)	37 (38.1)	0.81 (0.54-1.24)	NS

study. However, they did not impact mortality rate between the death and the survived group.

Concerning clinical presentation and initial evaluation, patients with NYHA class IV had a higher risk of death [unadjusted OR 1.68 (1.10-2.57)] as show in Table 2. There was a greater risk of death with decreased in systolic blood pressure. Systolic BP<90 mmHg had unadjusted OR 3.57 (1.87-6.84), (p<0.001), when compared to patients with higher blood pressure. No significantly different clinical presentations with fatigue, Rales, edema, pulmonary congestion, respiratory rate, and heart rate were observed. In addition, the prevalence of atrial fibrillation and wide ORS complex (>120 ms) were similar in both groups. For initial blood chemistry measurement, serum BUN, creatinine in the dead group were higher than those of the survived group (p<0.001). Conversely, hemoglobin level and serum albumin were lower in the dead group (p = 0.02, p<0.001 respectively). Median LVEF was lower in the dead group compared with those of the survived group, 35% vs. 42%. Unadjusted OR for LVEF <40% vs. >40% were 1.70 (1.05-2.76) (p = 0.03).

According to the previous use of medications as in Table 3, aspirin and lipid lowering drugs were associated with lower in-hospital mortality with unadjusted OR 0.68 (0.46-1.0) and 0.59 (0.39-0.88) respectively. Nitroglycerin, dopamine, and dobutamine, which were used in seriously ill patients, were associated with higher mortality (data not shown). The data were too small for the other intravenous cardiovascular drugs such as mirinone, levomesimendan, and nitroprusside, to analyze their influence on mortality in the present registry.

Table 4 demonstrates the association between etiologies of heart failure and mortality. The most common cause of heart failure in this registry was coronary heart disease 46.2% and more than half of the dead group had coronary artery disease. However, CAD showed no significant effect on mortality OR 1.45 (0.98-2.14). Hypertensive heart disease and Cardiomyopathy/myocarditis recorded as the etiology of each episodes were the only two parameters associated with lower mortality, unadjusted OR 0.39 (0.17-0.90) and 0.39 (0.18-0.84) respectively, while others were not.

Logistic regression model are shown in Table 5. SPB <90 mmHg was the highest predictor of mortality with 3.45 folds risk of death [adjusted OR 3.45 (1.77-6.79)]. History of stroke/TIA was almost two folds increase risk of mortality as well as any patients who had NYHA class IV adjusted OR 1.85 (1.11-3.05) and 1.69 (1.08-2.64) respectively. Renal insufficiency (creatinine >2 mg/dl) was also the risk in the present study adjusted OR 1.99 (1.30-3.05). Higher serum hemoglobin was the preventive factor

Table 2. Clinical presentation and initial evaluation

Clinical presentation	Total n = 2,041 (%)	Survive n = 1,928 (%)	Dead n = 113 (%)	Unadjusted OR (95% CI)	p-value
NYHA class IV	1,283 (62.9)	1,200 (62.2)	83 (73.5)	1.68 (1.10-2.57)	0.02
Fatique	735 (36.0)	685 (35.5)	50 (44.2)	1.44 (0.98-2.11)	NS
Rales	1,726 (84.6)	1,628 (84.4)	98 (86.7)	1.20 (0.69-2.10)	NS
Edema	1,215 (59.5)	1,145 (59.4)	70 (61.9)	1.11 (0.75-1.65)	NS
Systolic BP mmHg (median, IQR)	130 (111:155)	130 (112:155)	120 (100:149)	-	<0.001
Diastolic BP mmHg (median, IQR)	77 (65:90)	78 (66:90)	70 (60:80)	-	<0.001
Systolic BP <90 mmHg	74 (3.6)	62 (3.2)	12 (10.6)	3.57 (1.87-6.84)	<0.001
Heart rate (median, IQR)	91 (78:106)	91 (78:106)	90 (79:106)	-	NS
Respiratory rate (median, IQR)	24 (20:28)	24 (20:28)	24 (20:28)	-	NS
Pulmonary congestion	1,790 (93.7)	1,692 (93.6)	98 (95.1)	1.33 (0.53-3.34)	NS
LVEF <40%	523 (43.9)	483 (43.1)	40 (56.3)	1.70 (1.05-2.76)	0.03
EKG					
AF	451 (22.1)	431 (22.4)	20 (17.7)	0.75 (0.45-1.22)	NS
QRS complex >120 ms	299 (15.7)	282 (15.6)	17 (15.7)	1.01 (0.59-1.72)	NS
Sodium <130 mg/dL	198 (9.9)	186 (9.8)	12 (10.8)	1.11 (0.60-2.06)	NS
Creatinine >2.0 mg/dL	474 (23.7)	432 (22.8)	42 (37.8)	2.06 (1.38-3.06)	<0.001
BUN mg/dL (median, IQR)	23 (16.0:34.4)	22 (16.0:34.4)	30 (21.0:54.0)	-	<0.001
Hemoglobin gm/dL (median, IQR)	11.7 (10.2:13.3)	11.7 (10.2:13.4)	10.9 (9.8:12.5)	-	0.02
Albumin gm/L (median, IQR)	3.6 (3.2:4.0)	3.6 (3.2:4.0)	3.3 (2.8:3.8)	-	<0.001
Uric acid mg/dL (median, IQR)	8.8 (6.8:11.1)	8.8 (6.8:11.0)	9.7 (7.2:12.7)	-	NS

Table 3. Chronic use of medication prior to hospitalization

Drugs	Total n = 2,041 (%)	Survive n = 1,928 (%)	Dead n = 113 (%)	Unadjusted OR (95% CI)	p-value
Loop diuretic	1,167 (57.2)	1,107 (57.4)	60 (53.1)	0.84 (0.57-1.23)	NS
Spironodactone	256 (12.5)	244 (12.7)	12 (10.6)	0.82 (0.44-1.51)	NS
ACE-I	525 (25.7)	499 (25.9)	26 (23.0)	0.86 (0.55-1.34)	NS
ARB	240 (11.8)	232 (12.0)	8 (7.1)	0.56 (0.27-1.16)	NS
Nitrate	765 (37.5)	732 (38.0)	33 (29.2)	0.67 (0.44-1.02)	NS
B-blocker	533 (26.1)	503 (26.1)	30 (26.5)	1.02 (0.67-1.57)	NS
Digoxin	439 (21.5)	418 (21.7)	21 (18.6)	0.82 (0.51-1.34)	NS
Warfarin	273 (13.4)	261 (13.5)	12 (10.6)	0.76 (0.41-1.40)	NS
Clopidogrel	892 (43.7)	288 (14.9)	17 (15.0)	1.01 (0.59-1.71)	NS
Aspirin	977 (47.9)	933 (48.4)	44 (38.9)	0.68 (0.46-1.00)	NS
Lipid lowering	892 (43.7)	856 (44.4)	36 (31.9)	0.59 (0.39-0.88)	NS
Erythropoetin	52 (2.5)	46 (2.4)	6 (5.3)	2.29 (0.96-5.49)	NS
Others	331 (16.2)	310 (16.1)	21 (18.6)	1.19 (0.73-1.94)	NS

that had OR 0.90 (0.82-0.98). Lipid lowering drug was the only prior medicine use that associated with lower mortality while aspirin was not. Furthermore, hypertensive heart disease was also the only etiology of heart failure that could affect lower mortality when compare to others.

Table 4. Association between etiology of heart failure and in-hospital mortality

Etiology	Total n = 2,041 (%)	Survive n = 1,928 (%)	Dead n = 113 (%)	Unadjusted OR (95% CI)	p-value
Coronary artery disease	913 (46.2)	853 (45.7)	60 (55.0)	1.45 (0.98-2.14)	NS
Valvular heart disease	382 (18.7)	358 (18.6)	24 (21.2)	1.18 (0.74-1.88)	NS
Hypertension	249 (12.2)	243 (12.6)	6 (5.3)	0.39 (0.17-0.90)	0.02
Cardiomyopathy/myocarditis	283 (14.1)	276 (14.6)	7 (6.2)	0.39 (0.18-0.84)	0.01
Others	214 (10.5)	198 (10.3)	16 (14.2)	1.44 (0.83-2.50)	NS

Table 5. Logistic regression for predictors of in-hospital mortality

Predictors (n = 1,958)	Adjusted OR (95%CI)	p-value
SBP <90 mmHg	3.45 (1.77-6.79)	<0.0001
Creatinine >2.0 mg/dL	1.99 (1.30-3.05)	0.002
History of stroke/TIA	1.85 (1.11-3.08)	0.02
NYHA class IV	1.69 (1.08-2.64)	0.02
Etiology of heart failure; hypertension	0.35 (0.15-0.81)	0.01
Prior use of lipid lowering drug	0.51 (0.34-0.78)	0.002
Hemoglobin gm/dL	0.90 (0.82-0.98)	0.02

Discussion

The mortality rate in from Thai ADHERE registry was 5.5%, which was slightly higher than those of the US ADHERE[19] and OPTIMIZE-HF registry[10] that has US population (4% and 3.8% respectively). Regarding the demographic data (Table 1), Thai ADHERE showed that older age, low body weight, prior history of stoke/TIA, and history of chronic renal insufficiency were associated with increased mortality by univariate analysis. Body weight could not be the final model as a predictor although obesity is a well-recognized cardiovascular risk factor as reported from Fonarow et al[17]. They reported that higher BMI was associated with lower in-hospital mortality. The authors' data also showed that patients with higher body weight had lower mortality rate. However, this phenomenon might be true around the world. There was no evidence of increased risk in patients who had prior heart failure, LVEF <40%, and COPD in the present study while the OPTIMIZE-HF registry had mentioned to be the predictors.

NYHA class IV, low systolic blood pressure, in-hospital LVEF <40%, serum Cr >2 mg/dL, high serum BUN, low hemoglobin level, and low serum albumin were initially evaluated as the higher risk of death. Other clinical parameters that had shown from several studies as important risk factors such as heart rate, respiratory rate, wide QRS complex, serum sodium, and serum uric acid could not demonstrated as predictors in the present study. Due to limited numbers of test on B-type natriuretic peptide and cardiac troponin, no data was shown and analyzed in the present study.

Surprisingly, lipid-lowering drug was the chronic medicine that was associated with lower risk of death. This result was markedly different from data of Clinical Quality Improvement Network Investigators[5], which demonstrated the benefit of prior use of ACE inhibitors, warfarin, aspirin, beta-blockers, and calcium channel blocker. Ischemic heart disease was reported by Pocock et al[9] as a predictor for mortality while it could not in the present study. In addition, hypertension was the protective factor in our final model. Abraham et al reported on the preventive effects of nitroglycerin or nesiritide when compared to dobutamine or mirinone in US ADHERE registry[20]. In the present study, there were limited data regarding the use of intravenous medication such as nitroglycerin, mirinone, levosimendan, and nesiritide to identify the effects of this medicine.

The present study identified seven final independent predictors, SBP <90 mmHg, serum Cr >2 mg/dL, history of stoke/TIA, NYHA class IV, hypertensive etiology, prior use of lipid lowering agent, and hemoglobin level. Some of variables such as LVEF and serum albumin level were detected as

extreme risks initially but not in the logistic regression due to insufficient numbers of episodes. According to highly correlation with serum Cr >2 mg/dL, history of chronic renal insufficiency, and serum BUN were excluded from the model. The ADHERE of the US hospitals was used to develop the regression tree analysis that three variables were identified as a providing the greatest amount of prognostic information regarding in-hospital mortality risk. They were BUN level >43 mg/dL, Crlevel >2.75 mg/dL, and SBP <115 mmHg[1]. The subsequent analysis of >100,000 hospitalizations from the ADHERE, CART analysis identified high serum BUN, lower SBP, low serum sodium, older age, serum Cr, presence of dyspnea at rest, and absence of chronic beta-blocker use as mortality risk factors[8]. As mentioned above, most predictors from the ADHERE in Thai patients were quite similar to those of the US. The benefit is to explore which patients judged to be high-risk and need higher-level monitoring in an intensive or coronary care unit and earlier, more intensive treatment for patients with ADHF.

Conclusion

The clinical predictors for In-hospital mortality of Thai ADHERE were similar to those previously reported. This information will provide valuable information for further improvement of care in patients with ADHF.

Study Limitation

This is an observational registry. Therefore, complete data could not be obtained. Some of the missing data were interpreted as negative value. Furthermore, the multiple readmission of the same patients and other confounding circumstances will diminish the accuracy testing of the present model. Furthermore, some important predictive variables could not be included in the model because there were an insufficient numbers to be statistically significant. Nevertheless, the clinical predictors of the present study were similar to those from many studies.

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Potential conflicts of interest

None.

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การพยากรณ์การเสียชีวิตในโรงพยาบาล ของโรคหัวใจล้มเหลวแบบเฉียบพลัน

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ภูมิหลัง: *ภาวะหัวใจล้มเหลวเป็นภาวะที่เป็นปัญหาสำคัญต่อระบบสาธารณสุขเป็นอย่างมากอันเนื่องจากมีอัตราการนอนโรงพยาบาลและมีอัตราการตายที่สูง อันเป็นที่มาของการศึกษาผู้ป่วยหัวใจล้มเหลวเฉียบพลันที่ต้องได้รับการรักษาในโรงพยาบาล*

วัตถุประสงค์: *ต้องการหาปัจจัยที่เป็นตัวพยากรณ์การเสียชีวิตในโรงพยาบาลของผู้ป่วยที่ป่วยด้วยโรคหัวใจล้มเหลวแบบเฉียบพลัน*

วัสดุและวิธีการ: *เป็นการศึกษาผู้ป่วยแบบสหสถาบันจาก 18 โรงพยาบาลในประเทศไทย ที่ทำการลงทะเบียนในประเทศไทยตั้งแต่มีนาคม พ.ศ. 2549 ถึง กันยายน พ.ศ. 2550 โดยมีการเก็บข้อมูลแบบอิเล็กทรอนิกส์ผ่านทางระบบอินเตอร์เน็ต*

ผลการศึกษา: *ข้อมูลจากผู้ป่วย 1,671 ราย ที่มีการนอนโรงพยาบาลจำนวน 2,041 ครั้ง พบว่ามีผู้ป่วยจำนวน 113 ราย เสียชีวิตคิดเป็นอัตราตาย เท่ากับ 5.5% การวิเคราะห์ปัจจัยต่าง ๆ ที่มีผลต่อการเสียชีวิตในช่วงแรก วิเคราะห์จาก univariate analysis และนำปัจจัยที่มีผลต่อการเสียชีวิตเหล่านั้นที่มีผลมากวิเคราะห์ต่อด้วย logistic regression analysis พบว่าปัจจัยเสี่ยงที่มีผลต่อการเสียชีวิตของการศึกษานี้คือ ความดันโลหิตซิสโตลิค <90 มิลลิเมตรปรอท ระดับครีแอทินิน >2 มิลลิกรัมต่อเดซิลิตร ประวัติของโรคหลอดเลือดสมอง และ NYHA class IV โดยมี adjusted OR เท่ากับ 3.45 (1.77-6.79), 1.99 (1.30-3.05), 1.85 (1.11-3.08) และ 1.69 (1.08-2.64) ตามลำดับ ส่วนปัจจัยที่มีความสัมพันธ์กับความเสี่ยงต่อการเสียชีวิตที่น้อยกว่าคือ ความดันโลหิตสูงที่เป็นสาเหตุของโรคหัวใจล้มเหลว ประวัติการใช้ยาลดไขมันและระดับฮีโมโกลบินในเลือดโดยมี adjusted OR เท่ากับ 0.35 (0.15-0.81) 0.51 (0.34-0.78) และ 0.90 (0.82-0.98) ตามลำดับ*

สรุป: *การศึกษาตัวพยากรณ์โรคที่ได้นี้ ไม่แตกต่างจากผลการการศึกษาในอดีตของต่างประเทศ ซึ่งข้อมูลที่ได้หวังว่าจะเป็นประโยชน์ต่อการดูแลผู้ป่วยหัวใจล้มเหลวต่อไป*