Acute Coronary Syndrome:

Bridging the Gap

Li, Ruijie

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Publications

Full papers

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1. Rui-Jie Li, Mang Zhang, Qian-Huan Zhang, Ming Dong, Bryan Yan, Qing Zhang, Gabriel Wai-Kwok Yip, Ding Ding, Cheuk-Man Yu. Impact of Percutaneous Coronary Intervention on Quality of Life in Elderly. Circulation 2010; 122; e44
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LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ACEI	Angiotensin Converting Enzyme Inhibitor
ACS	Acute Coronary Syndrome
AHA	American Heart Association
ALT	Alanine Transaminase
APQLQ	Angina Pectoris Quality of Life Questionnaire
ARB	Angiotensin Receptor Blockers
AUC	Area Under The Curve
AV	Atrial-Ventricular
BNP	Brain Natriuretic Peptide
CABG	Coronary Artery Bypass Surgery
CCS	Canadian Cardiovascular Society
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CI	Confidence Interval
CK	Creatine Phosphokinase
CK-MB	Creatinine Kinase – MB
CRP	C - Reactive Protein
EF	Ejection Fraction
EQ-5D	European Quality of Life - 5 Dimension Health Classification
EQ-VAS	European Quality of Life - Visual Analogue Scale

ESC	European Society of Cardiology
GP	Glycoprotein
GRACE	Global Registry of Acute Coronary Events
IABP	Intra-Aortic Balloon Pump
IQR	Inter-Quartile Ranges
MCS	Mental Component Summary
MI	Myocardial Infarction
NHP	Nottingham Health Profile
NSTEMI	Non ST Segment Elevation Myocardial Infarction
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
PCS	Physical Component Summary
QLMI	Quality of Life After Myocardial Infarction
ROC	Receiver Operating Characteristic
SAQ	Seattle Angina Questionnaire
SF-36 / MOS SF-36	Short Form-36 / Medical Outcome Survey Short Form 36
STEMI	ST Segment Elevation Myocardial Infarction
UA	Unstable Angina

ABSTRACT

Acute coronary syndrome (ACS), a term used to cover a group of clinical symptoms compatible with acute myocardial ischemia, represents a high-risk group of patients with coronary heart disease (CHD). To improve quality of care, international guidelines for the management of ACS have been established and are updated regularly. In the era of evidence based medicine, adherence to therapeutic guidelines is essential for optimal care of ACS patients. However, most data on ACS epidemiology, treatment and outcomes are derived from western population. There are limited data in Chinese population in terms of prevalence, presentation, response to treatment and clinical outcome.

The Hong Kong ACS registry was designed to investigate epidemiology, treatment and outcome of ACS patients under current medical care system, it was conducted in a university affiliated teaching hospital from February 2006 to December 2009. Clinical characteristics and treatment data were collected at baseline, 30 days and 6 months after onset in a standard defined case report form. SF-36 questionnaire was completed after admission and at 6 months. Outcomes were evaluated mortality and morbidity in clinical aspect and quality of life in aspect of health status.

The Main findings were as followed:

Totally 1001 patients admitted with ACS were recruited. Among all patients enrolled, 31.7% were diagnosed with ST-segment elevation myocardial infarction, 42.7% with non-ST-segment myocardial infarction and 21.6% with unstable angina. The

median age was 72 (interquartile range 61-79) years; 77.2% were >60 years old, and 31.5% were women.

Women presented more often with NSTE-ACS than men (77.3% of women vs. 63.2% of men, $p<0.001$). Despite having greater comorbidities including hypertension, diabetes, hypercholesterolemia, renal impairment and history of heart failure etc., women were observed to have higher GRACE (global registry of acute coronary events) score than men (128±32 vs. 118±37, $p<0.01$). Women were less likely to be assigned invasive procedures (43.3% vs. 62.9%, $p<0.001$) as well as pharmacotherapies such as clopidogrel (41.1% vs. 58.8%, $p<0.001$), glycoprotein (GP) IIb/IIIa antagonists (5.3% vs. 11.6%, $p=0.001$) and statins (64.1% vs. 77.2%, $p<0.01$) et al. than men. For in-hospital mortality, the adjusted odds ratio for men compared to women was similar (odds ratio [OR]: 1.32, 95% CI: 0.62-2.83, $p=0.47$). The higher 6 month mortality and major cardiac events rate in women were not significant after adjusting for differences in clinical characteristics and percutaneous coronary intervention (PCI) (OR=1.02; 95% CI 0.62 to 1.68; $p=0.95$). In summary, there were differences in baseline characteristics and in the management of women and men admitted for ACS. Advanced age and high comorbidities prevalence could explain most of the difference between genders suggesting that decision making bias in clinical practice is anti-age but not anti-female. Overall, in-hospital and 6 months mortality was similar for women and men after adjustments.

Patients with ACS were divided into low- and high-predicted risk of mortality at 6 months using the GRACE risk score (≥142.5 was defined as high-risk). We evaluated the use of in-hospital angiography, revascularization, anti-platelet, angiotensin

converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), β-blockers and statins therapy between high and low-risk patients. There were 259 patients in the high- and 742 in the low-risk groups. Paradoxically, high-risk compared to low-risk patients were less likely to underwent coronary angiography and/or revascularization during the index hospitalization (33% vs. 64% and 25% vs. 50%, both $p<0.01$). Hospital initiated pharmacotherapies are also lower in high-risk patients (24% vs. 55% for clopidogrel, 49% vs. 58% for ACEI/ARBs, 54% vs. 69% for β-blockers and 56% vs. 77% for statins; all $p<0.01$). After adjustment, high-risk patients remained less likely to undergo revascularization (adjusted odds ratio [OR], 0.47; 95% CI, 0.33-0.73, $p<0.001$) than low-risk patients. Advanced age, increased creatinine level and higher GRACE score were independent predictors for failure to administer evidence-based therapies. Thus, patients with ACS at high risk of mortality were paradoxically less likely to undergo revascularization or receive medications according to guidelines. Better adherence to evidence-based therapies in high-risk patients may improve clinical outcome and quality of health care.

Among 624 patients finished Short Form (SF)-36 questionnaires, health related quality of life (HRQoL) were compared between patients underwent PCI versus those treated conservatively across 3 age groups (<60, 60-79 and ≥80 years). PCI was performed in 73.6%, 55.7% and 21.3% in patients aged <60, 60-79 and older than 80 years, respectively ($p<0.01$). Elderly patients were more likely to be female (16.9 vs. 35.4 vs. 54.6%, $p<0.01$) and had more co-morbidities ($p<0.01$). Older patients were less likely to undergo angiography (84.8 vs. 65.2 vs. 24.8%, $p<0.01$). Baseline HRQoL decreased with advancing age ($p<0.01$). However, elderly patients who underwent PCI

experienced the most improvement in physical health than younger age groups. PCI was an independent predictor (OR, 1.79, 95% CI: 1.10-2.92) of better physical health status at 6 months. In conclusion, elderly ACS patients who underwent PCI experienced the most improvement in physical health compared to younger patients. Our findings suggest that age *per se* should not deter against revascularization because of potential benefits in HRQOL.

In summary, this is the first registry which described patients' characteristics, treatment and management practices, and hospital outcomes over the whole spectrum of ACS in Hong Kong. The study identified gaps between guideline and clinical practice as well as the reasons of these gaps, and measured the impact of such gaps on the outcomes of patients with ACS. Compared with internationally reported data, Hong Kong patients are different in terms of age and risk factors distribution. Treatment gaps exist between international therapeutic guideline recommendations and clinical practice, especially among the high risk population, the elderly and female patients. Better understanding and narrowing these gaps between guideline and practice will lead to improvement in quality of care and clinical outcomes. Increase use of risk stratification models and health status assessments may improve decision making in the management of ACS.

摘要

急性冠脈綜合征，其定義涵蓋一組由於急性心肌缺血所引發的臨床症狀，是冠心病的高危亞組。冠心病在世界各國均有較高的發病率，在發達地區已成為致死病因的第一位。對於冠心病的研究已深入到流行病學、症狀、治療及預後等各個方面，在這些研究的基礎上，急性冠脈綜合征治療指南應運而生並跟據研究進展每定期更新。因此在循證醫學時代，是否遵循指南對提高醫療品質有非常重要的意義。另一方面，雖然冠心病的研究已有充分資料，但幾乎完全基於西方人種。關於冠心病在中國人種的發病率、臨床表現、治療反應及預後的資料非常有限。

香港急性冠脈綜合征註冊研究以探索流行病學和現行醫療體制下急性冠脈綜合征患者的治療與預後為目的，于香港中文大學附屬教學醫院展開，並設計有標準化表格收集患者的臨床特徵及入院、出院時、30 天和 6 個月治療情況。SF-36 問卷用於評估患者入院時及 6 個月後的生命品質。死亡率及心臟事件用於評估臨床轉歸，生命品質用於評估健康狀態。

主要研究結果如下：

2006 年 2 月至 2009 年 12 月期間，本研究共納入 1001 名急性冠脈綜合征患者。其中 31.7%表現為 ST 段抬高型心肌梗死，42.7%為非 ST 段抬高型心肌梗死，21.6%為不穩定心絞痛。中位年齡為 72 (61-79)歲，77.2%患者在 60 歲以上，且 31.5%為女性患者。

女性較之男性更多表現為非 ST 段抬高型 ACS。與男性患者相比，女性患者更易合併高血壓、糖尿病、高血脂、腎功能不全及心衰等症。于女性患者中我們觀察到較高的 GRACE 評分 (128±32 vs. 118±37, p<0.01) 。女性較少接受介入操作(43.3% vs. 62.9%, p<0.001) 及氯吡格雷(41.1% vs. 58.8%, p<0.001)、糖蛋白 IIb/IIIa 阻滯劑(5.3% vs. 11.6%, p=0.001)及他汀(64.1% vs. 77.2%, p<0.01)等藥物治療。院內死亡率在女性患者中較高，但校正後男性 與女性風險無差別(odds ratio [OR]: 1.32, 95% CI: 0.62-2.83, p=0.47)。6 個月死亡率及主要心臟事件率亦呈現相似趨勢：在女性患者中較高，校正後無性別差異(OR=1.02; 95% CI 0.62 to 1.68; p=0.95)。總而言之，ACS 患者在臨床特徵、及治療方面存在的性別差異，基本可由年齡差別解釋。此結果提示臨床決策中存在年齡偏倚而非性別偏倚。校正後的院內及 6 個月死亡率無性別差異。

我們以 GRACE 評分將 ACS 患者分為高危及低危組，並比較兩個組之間冠脈造影、再血管化及藥物治療情況。在 259 名高危及 742 名低危患者中，高危患者接受冠脈造影和/或再血管化治療率 (33% vs. 64% and 25% vs. 50%, 均為 p<0.01)，院內藥物治療率均低於低危患者。校正後，高危患者較之低危患者，仍較少接受介入操作(校正 OR, 0.47; 95% CI, 0.33-0.73, p<0.001)、ACEI/ARBs (OR, 0.57; 95% CI, 0.4-0.81, p<0.01), β 受體阻滯劑 (OR: 0.59, 95% CI: 0.41-0.84, p<0.01) 及他汀類 (OR: 0.47, 95% CI: 0.32-0.68, p<0.01)藥物治療。高齡、高肌酐水準及高 GRACE 評分是未接受循證治療的獨立預測因素。綜上，高危 ACS 患者反常地較少接受指南推薦治療，在這類患者中更加嚴格遵詢循證治療可改善預後及提高醫療品質。

我們分析了 624 位完成 SF-36 問卷患者的健康相關生命品質，在三個年齡組(<60, 60-79 及 ≥80 歲)內比較了接受介入治療及保守治療患者的資料。由 60-80 歲，三個年齡組內接受 PCI 患者比例分別為 73.6%，55.7%及 21.3% (p<0.01)。與 60-79 歲及<60 組相比，80 歲以上患者多為女性(16.9 vs. 35.4 vs. 54.6%, p<0.01)，有較多合併症(p<0.01)，並較少接受冠脈造影(84.8 vs. 65.2 vs. 24.8%, p<0.01)。基礎生命品質與年齡呈負相關(p<0.01)，但年長患者接受 PCI 後身體健康狀態與較年輕患者相比提升最多。PCI 治療是 6 月後機體健康改善的獨立預測因素(OR, 1.79, 95% CI: 1.10-2.92)。我們的研究結果表明：考慮到生命品質因素，患者高齡不應作為 PCI 的反指征。

綜上，本研究為香港第一個描述急性冠脈綜合征患者特徵、治療及預後的註冊研究。本研究發現現有醫療服務與治療指南的差距，探索差距原因及該差距對 ACS 患者轉歸的影響。與國際已發表資料相比，香港 ACS 患者年齡與危險因素分佈均有不同。ACS 患者接受再血管化及循證藥物治療率較國際發表資料為低，此現象在年長、高危及女性患者中更加突出。瞭解臨床實踐與指南的差距及其原因有助於提高醫療服務品質。嚴格遵詢指南、結合臨床危險及健康狀態評估的臨床實踐模式有利於改善 ACS 患者預後轉歸。

CHAPTER ONE

INTRODUCTION

CHAPTER 1. INTRODUCTION

The term acute coronary syndrome (ACS) refers to a range of acute myocardial ischaemic states. It encompasses unstable angina (UA), non ST segment elevation myocardial infarction (NSTEMI) to ST segment elevation myocardial infarction (STEMI). Acute coronary syndrome is often the first presentation of coronary artery disease and is the leading cause of mortality and morbidity in the developed world. Over the last decade, the understanding of ACS pathophysiology, diagnosis and treatment has improved remarkably. Clinical data informing the management of ACS are plentiful and includes rigorous multi-center randomized controlled trials. The American Heart Association (AHA)/American College of Cardiology (ACC)/European Society of Cardiology (ESC) have published regularly updated guidelines for the management of ACS based on the latest clinical evidence. Adherence to current management guidelines has become an important benchmark in improving health care and outcomes of ACS patients. A local ACS registry database will be developed to prospectively collect standardized data on baseline characteristics, short- and long-term outcomes of consecutive patients presenting with ACS to the Prince of Wales Hospital. Data collected will enable monitoring of institutional and professional performance, identify needs gaps in ACS management, guide quality improvement initiatives and inform resource allocation.

1.1 Acute coronary syndrome: the epidemiology

1.1.1 Size of the problem

Coronary heart disease (CAD) is a worldwide health epidemic. In the United States, it is reported that 17.6 million Americans have CAD by the end of 2006, including more than 8.5 million patients who already have had myocardial infarction. CAD caused 1 in every 6 deaths in the USA in 2006.[1] The estimated prevalence of CAD and acute myocardial infarction in China was 63 million (4.6% of total population) and 2 million, respectively, in 2003. The annual incidence of CAD in 2006 was estimated at 5.7 million, and >60% of deaths due to heart disease was secondary to CAD.[2, 3]

In Hong Kong, CAD is the commonest cause of cardiovascular deaths, accounting for 42.9% of cardiovascular deaths in men and 35.4% in women. Furthermore, nearly half of all deaths from cardiovascular disease were due to CAD.[4, 5]

Health improvements have increased life expectancy globally by an average of 20 years –from 46 years in 1950 to 66 years in 1998[6].

Although death rate from CAD have been falling since the 1950-70's in western countries such as UK[7] and USA[1], it has continued to rise in Hong Kong till the end of 1990's and the end of 20th century in China[8, 9]. This rate has fallen 59% from 1950-1999 and 36.4% from 1996-2006 in USA, whilst the death rate of coronary heart disease has dropped by 36-37% in Hong Kong[8], by 24-46% in UK, by 48% in Australia and by 54% in Norway from 1990-2000. However, during this period, many countries including China and some other regions such as countries in Eastern Europe have experienced

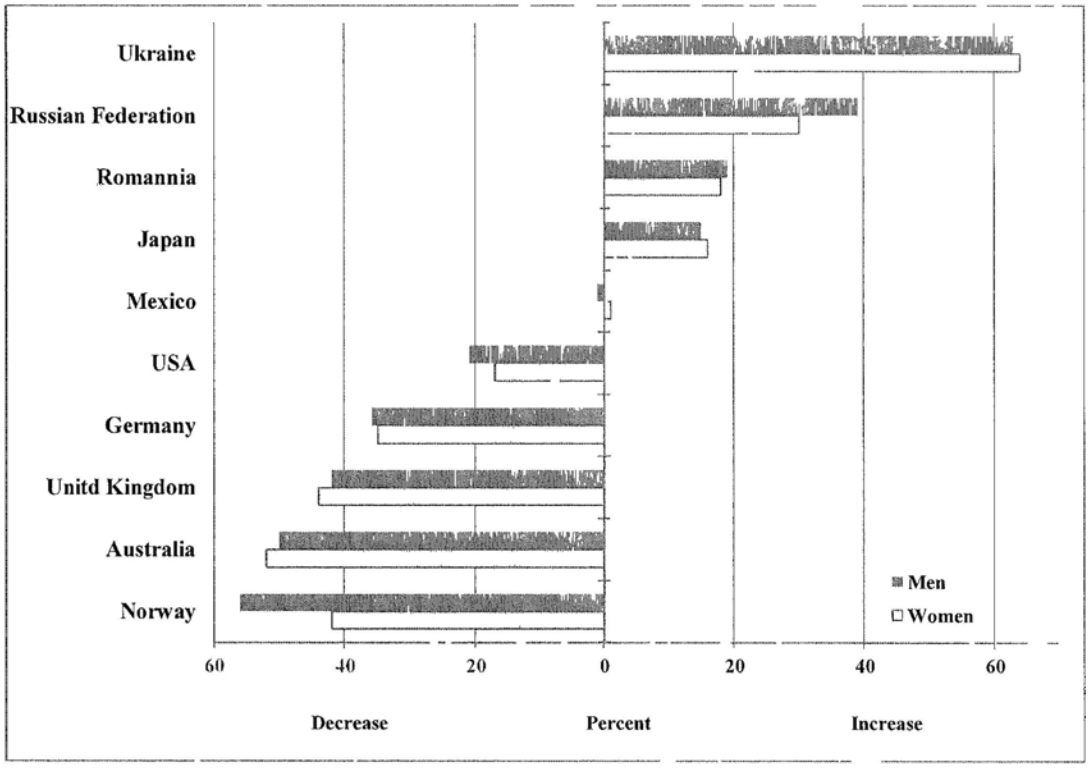
increased mortality from CAD: in China there has been an increase in coronary mortality by 41% from 1986-1999, and over 60% in Ukraine. (Figure1.1.1)

Although age-specific events related to CAD have fallen dramatically in the last few decades in developed world, the overall prevalence has risen as population ages and survival from heart attacks improves. Furthermore, growing epidemics of diabetes and obesity as a consequence of lifestyle changes in developing countries is likely to increase the incidence of CAD. The Center for Disease Control and Prevention in the United States estimated that life expectancy might be increased by 7 years if CAD and its complications were eradicated.[10]

Acute coronary syndrome is the most common presentation of cardiac disease admitted to an acute care hospital. It is estimated that 1.4 million patients with ACS were admitted annually in the United States. In Hong Kong, about 5,000 patients annually had a hospital discharge diagnosis of acute myocardial infarction (AMI). However, this number is likely to underestimate the true incidence of ACS as patients admitted with UA were excluded.

Accompanied with the increasing prevalence of CAD, the cost of CAD is also on the rise. In the United States, the estimated direct and indirect cost of CAD increased from 129.9 billion US dollars in 2003 to 177.1 billion in 2010. In-hospital costs for a patient with a discharge diagnosis of AMI increased from US$10,428 in 2000 to US$14,009 in 2006.[11-15] In Hong Kong, the average cost was US$12,344 for patients with discharge diagnosis of AMI in 2000 and this cost has kept on increasing in the following years. [16]

Figure 1.1.1 Change of CAD Mortality from 1986-1999 in different regions and countries (Coronary Heart Disease Statistics. 2007 British Heart Foundation)



1.1.2 Risk Variables

The mortality rate of patients with CAD increases with age. There is a 15-fold increase in mortality rate in men and an approximately 30–fold increase in women from 35-44 years to 55-64 years. This may be due to the accumulation of co-morbidities and risk factors associated with increasing age. The median age of patients presenting with ACS varies from region to region and is in parallel with life expectancy of that region. For example, the median age of ACS patients is 52 years for men and 62 years for women in mid-east area[17]; 57.5 years in India[18]; 63 years in men and 73 years in women in [19]Switzerland[19]; 66 years in Canada[20], and 65 years in the global registry of acute coronary events (GRACE) registry which is a global registry of ACS with patients from 7 countries in Europe, North America and Australia. In Hong Kong, a city with the second longest life expectancy in the world[21], the median age of ACS patients is 68 years in men and 76.5 years in women.

The rate of CAD among men aged 35 to 44 years is 4 to 6 times higher than that of their same-age female counterparts[15]. This disparity appears to lessen with increasing age, but the onset of CAD in women is about ten years later than men. Since women are older, they tend to have more co-morbidities and thus poorer outcomes than men.

Ethnicity is a recognized un-modifiable factor associated with CAD. In the United States, the prevalence of CAD among African Americans males is 9.6%, which is the highest; 9% in African American females; 8.8% in white males, 6.6% in white females; and the lowest is 4.3%[14] in Asian Americans. This racial difference may be due to the variation of risk factors for CAD among different races. Given the association of a

risk factor with CAD is similar across ethnicities, the prevalence of this factor might vary, resulting in different population attributable risks . For example, serum cholesterol level may be lower in Chinese population and thus dyslipidemia is less a risk factor for CAD in south Asians[22], [23]. Whereas hypertension, which is more prevalent may be more important among Chinese [23]population[23];[23].

In addition to non-modifiable risk factors such as age, gender and race, there are many modifiable risk factors associated with CAD, including smoking, abdominal obesity, hypertension, diabetes mellitus, dyslipidemia, psychosocial factors, consumption of fruits and vegetables, exercise, alcohol consumption, etc.[24] A global case-control study of 52 countries—the INTERHEART study explored 9 potentially modifiable risk factors associated with acute myocardial infarction (MI)[25]. In this study, abnormal lipids, smoking, history of hypertension or diabetes, abdominal obesity, dietary pattern, lack of physical activity, excess alcohol consumption and psychosocial factors were identified as key risk factors and accounted for more than 90% of the risks for acute MI. The impact of these risk factors was consistent in men and women across different geographic regions and ethnicities. Furthermore, according to the INTERHEART study, the strength of association of diabetes with acute MI was higher for the Chinese than for other countries, while the strength of association of waist-to-hip ratio and acute MI was lower in Chinese than in western countries.

1.1.3 Outcomes

Patients presenting with ACS continue to have a poor outcome despite advances in modern therapies. Thirty-six percent of those admitted with presumed ACS will ultimately be diagnosed with MI during their index admission[26]. Thirty-day and 6-month mortality for patients with ACS is particularly high in those with elevated cardiac troponin concentrations. The presence of ST segment deviation is an even stronger predictor of adverse outcome than elevations in troponin concentrations. [27, 28]

The GRACE is the largest multinational cohort study of patients covering the full spectrum of ACS. It includes in hospital outcome and 6-month follow-up on about 100,000 patients from 245 hospitals in 30 countries. Each center reported on the findings and outcomes of the first 10-20 patients with ACS who present per month. Analysis shows that 34% of presenting patents had STEMI, 30% had NSTEMI, and 29% had UA. In-hospital mortality rates were 8%, 4% and 3% among STEMI, NSTEMI and UA, respectively. Mortality risk was found to increase with age where 10.7% of patients >75 years with ACS compared with 5.6% of patients aged between 65 and 75 years died during index hospitalization. Even for patients who were considered to be at low-risk (i.e. without troponin release or dynamic ECG changes) their clinical outcomes are not benign: at 6 months 23% required readmission, 12% underwent revascularization procedure, and 3% died. Fox and his colleagues reported 9 independent predictors of death and the combined end point of death or MI in the period from admission to 6 months after discharge, included age, development or history of heart failure, peripheral vascular disease, systolic blood pressure, Killip class, initial serum creatinine

concentration, elevated initial cardiac markers, cardiac arrest on admission, and ST segment deviation[29].

1.1.4 Risk Assessment Tools

Early risk stratification and the tailoring of therapeutic strategy according to risk stratum play an important role in the management of ACS because benefits of aggressive therapy is proportional to the level of stratified risk [30-32]. Several clinical risk scores have been developed to stratify patients with ACS. They include TIMI [33](The thrombolysis in Myocardial Infarction) and PURSUIT[34](platelet glycoprotein IIb/IIIa in unstable angina: Receptor Suppression Using integrilin) which are specific for NSTE-ACS; CADILLAC[35](The Controlled Abciximab and Device Investigation to Lower Late Angioplasty complications) and PAMI[36] (Primary Angioplasty in Myocardial Infarction) scores and TIMI for STEMI[37] which are specific for STEMI. The GRACE score was validated for the entire spectrum of ACS. These risk scores are calculated using initial clinical history, ECG, and laboratory tests, thus enable early risk stratification on admission. Table 1.1.1 summarized items and points for each element used in these risk score systems.

Table 1.1.1-a. Risk Stratification Scores for STEMI

	Risk Factors	Points
TIMI for STEMI	Age 65-74/≥75 yrs.	2/3
(0-14)	Systolic blood pressure <100 mm Hg	3
	Heart rate >100 beats/min	2
	Killip's classification 2–4	2
	Anterior STEMI or left branch bundle block	3
	Diabetes mellitus, hypertension, or angina	1
	Weight <67 kg	1
	Time to treatment >4 h	1
CADILLAC	Baseline left ventricle ejection fraction <40%	4
(0–18)	Renal insufficiency	3
	Killip's classification II–IV	3
	Final TIMI flow 0–2	2
	Age >65 yrs	2
	Anemialow asterisk	2
	3-Vessel disease	2
PAMI	Age >75 yrs.	7
(0–15)	Age 65-75 yrs.	3
	Killip's classification >I	2
	Heart rate >100 beats/min	2
	Diabetes mellitus	2
	Anterior STEMI or left branch bundle block	2
GUSTO	Age	
(93-115)	30	1
	40	1
	50	2
	60	3
	70	5
	80	6
	90	8
	ECG heart rate	
	40	0
	60	1
	80	2

Risk Factors	Points
100	3
≥120	4
Ejection fraction,%	
10	99
20	98
30	97
40	96
50	95
60	94
70	93
80	92
Previous Infarction	2
In-hospital CHF/PE	2

Table 1.1.1–b. Risk Stratification Scores for NSTE-ACS

	Risk Factors	Points
PURSUIT	Age, Decade [UA (MI)]	
(0–18)	50	18 (11)
	60	19 (12)
	70	11 (13)
	80	12 (14)
	Sex	
	Male	1
	Female	0
	Worst CCS-class in previous 6 weeks	
	No angina or CCS I/II	0
	CCS III/IV	2
	Signs of heart failure	2
	ST-depression on presenting ECG	1
TIMI	Age ≥65 years	1
(0–7)	≥3 risk factors for CAD	1
	Use of ASA (last 7 days)	1
	Known CAD (stenosis ≥50%)	1
	>1 episode rest angina in <24h	1
	ST-segment deviation	1
	Elevated cardiac markers	1

Table 1.1.1-c Variables used to construct the GRACE score

	Risk Factors	Points
GRACE (0-258)	Age(Years)	
	<40	0
	40-49	18
	50-59	36
	60-69	55
	70-79	73
	≥80	91
	Heart rate(bpm)	
	<70	0
	70-89	7
	90-109	13
	110-149	23
	150-199	36
	≥200	46
	Systolic BP(mmHg)	
	<80	63
	80-99	58
	100-119	47
	120-139	3
	140-159	26
	160-199	11
	>200	0
	Creatinine(mg/dL)	
	0-0.39	2
	0.4-0.49	5
	0.8-1.19	8
	1.2-1.59	11
	1.6-1.99	14
	2-3.99	23
	>4	31
	Killip class	
	Class I	0
	Class II	21
	Class III	43
	Class IV	64
	Cardiac arrest at admission	43
	Elevated cardiac markers	15
	ST-segment deviation	30

1.1.4.1 Non-ST segment elevation ACS risk models

The TIMI risk score is well validated to assess risk in ACS patients.[37] This model was developed from the TIMI 11B and ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparine in Unstable Angina and Non-Q-Wave MI) trials and is therefore applicable to patients with UA and NSTEMI. The TIMI risk score is calculated using 7 variables to predict a composite risk of death, MI or urgent revascularization at 14 days. The score is easy to use and has been validated in diverse clinical settings. Increased risk scores are associated with similarly increased incidence of individual outcomes.[33] Higher TIMI scores also predicted improved response to early invasive therapy compared to medical management in ACS patients[30]. However, the TIMI model does not incorporate heart or renal failure into the scoring system, which is known to be associated with poor prognosis.

The PURSUIT risk score was constructed based on a study of 9,461patients with NSTE-ACS, to predict death or MI at 30 days[34]. This score included heart failure as an important predictor of prognosis.

1.1.4.2 STEMI risk models

The GUSTO score was one of the earliest models for risk stratification in the era of thrombolytic therapy for STEMI derived from the GUSTO-1(Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) trial[38,39]. The 5-variable model was able to predict 90% of mortality at 30 days. In this

model, age was the strongest predictor of mortality. The mortality rate among patients younger than 45 was 1.1% compared to 20.5% for patients older than 75 years of age. Hemodynamic instability was another strong predictor of mortality and adverse events.

The CADILLAC and PAMI risk scores were derived from randomized trials of AMI patients who underwent primary percutaneous coronary intervention (PCI). The 2 risk scores were validated using external data sets from other primary PCI trials[35, 36].

The TIMI risk score for STEMI was derived from a different data set compared to the original TIMI score — the Intravenous recombinant tissue-type plasminogen activator (rt-PA) for Treatment of Infarcting Myocardium II trial (InTIME II) and validated using an external data set from the TIMI 9 trial[37]. The score predicts 30-day mortality using 8 variables. Age and heart failure were the strongest predictors in this model[40].

1.1.4.3 GRACE risk score

The GRACE score was derived from a large global registry which enrolled the entire spectrum of ACS. The investigators developed 6 well validated models to predict mortality as well as combined rates of death and MI during the index hospitalization and 6 months post discharge[27-29]. A GRACE score calculator is available online (Figure 1.1.2).

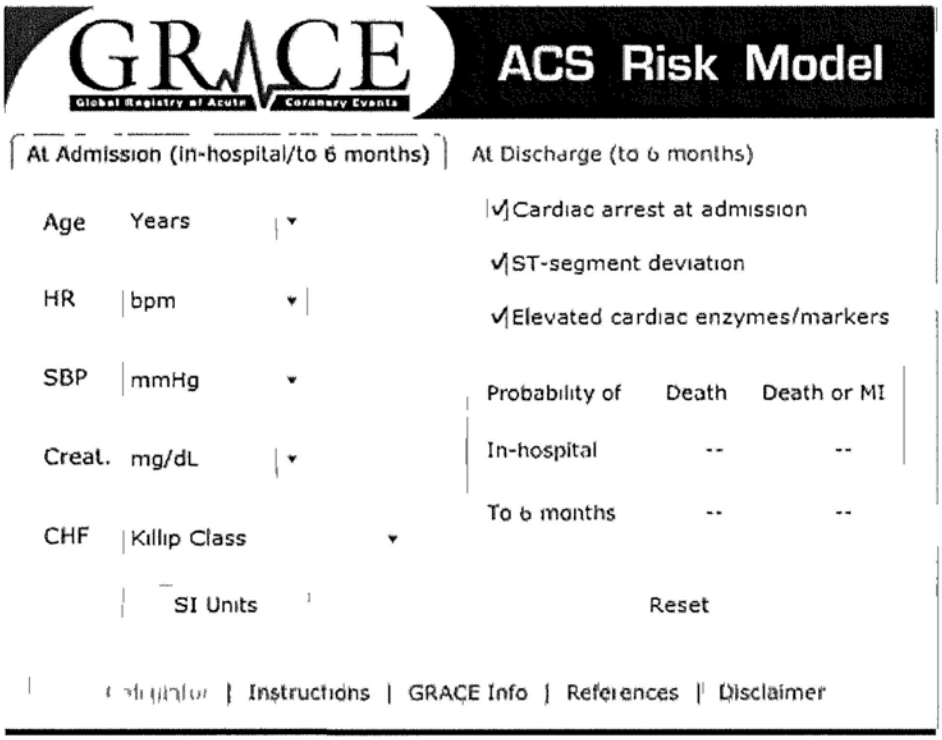


Figure 1.1.2 GRACE risk calculator for mortality and the combined rates of death and myocardial infarction from admission to hospital to 6 months after discharge with simplified model (www.outcomes.org/grace)

Accuracy of these models has been compared to find the best model for clinical use. The GRACE score appeared to have better predictive accuracy (area under the curve [AUC], 0.715) for death or MI at 6 month and 1 years post discharge compared to TIMI (AUC, 0.585) and PURSUIT (AUC, 0.630) scores for NSTE-ACS patients[41]. Yan et al.[42] compared the discriminatory performance of TIMI, PURSUIT and GRACE risk scores for in-hospital and 1 year mortality in NSTEACS patients and found GRACE and PURSUIT scores both allowed better discrimination than TIMI score for in-hospital and 1 year mortality. However, for STEMI patients, the GRACE score did not perform as well as for patients with NSTEACS. Lev and colleagues[43] compare the performance of the TIMI, CADILLAC, PAMI and GRACE scores to predict 30 days and 1 year in STEMI patients. The authors found that the CADILLAC, TIMI, and PAMI risk scores all had relatively high predictive accuracy for 30-day and 1-year mortality (AUC range 0.72 to 0.82) as well as reinfarction at 30 days (AUC 0.6 to 0.7). The GRACE score did not perform as well and had low predictive accuracy for mortality (AUC= 0.47).

1.2 Gender Difference in Acute Coronary Syndrome

For decades, CAD was considered a predominantly male disease because the majority of MI patients were male and majority of observational and epidemiological studies, randomized trials, and clinical guidelines have focused mainly on males. Gender differences in cardiac diagnosis and treatment was first reported by Ayanian[44] in the early 1990's, and has been extensively studied over the past 2 decades. Although CAD

is now recognized as a leading cause of death in women, gender differences in terms of presenting symptoms, diagnosis and treatment of ACS persists.

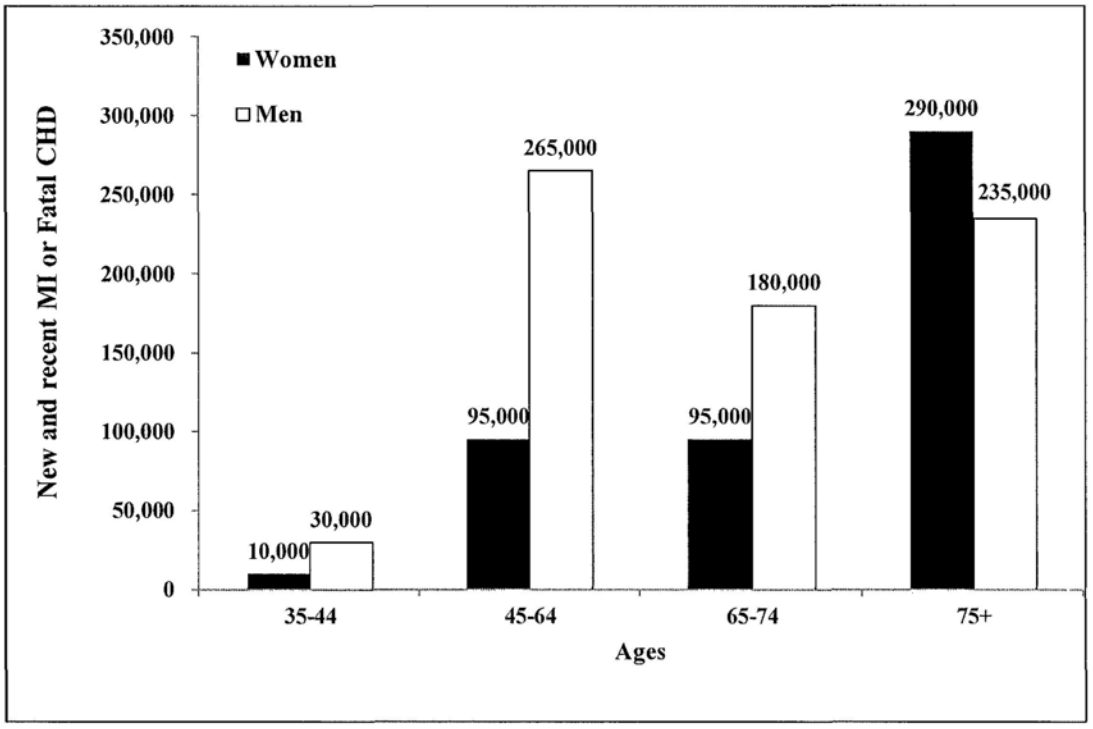
1.2.1 Gender disparity in epidemiology

On average, women are almost a decade older than men at time of their initial MI.[45-47] Mean ages of women with ACS were 6-8 years older than men[47-49]. Incidence of MI in women increases sharply with advancing age. (Figure 1.2.1)

Studies have shown that women with ACS were more likely to have comorbid conditions such as diabetes mellitus, hypertension and heart failure than men. And this disparity is independent of age. [45-47]

Women were more likely to present with UA and less likely to present with MI than men.[50-51] Moreover, NSTEMI was more common than STEMI in women.

Figure 1.2.1 Annual number of adult newly diagnosed as MI or fatal CHD. (Source from NHLBI, USA.[14])



1.2.2 Symptoms and presentation of ACS in women

Several studies have shown gender differences in terms of symptom and presentation of ACS. [46, 52-55] Women were more likely to present with "atypical" and less likely to present with "classical" symptoms compared to men. Overall, women with ACS were less likely to complain of chest pain or discomfort. Compared to men, women were more likely to describe their chest pain or discomfort as less severe; not prolonged; not related to exertion; unlike prior cardiac symptoms; not in typical location or quality.[55]

Epidemiological studies have found about 1/4 to 1/3 ACS patients presented without chest pain or discomfort[46, 52-54], and the absence of chest pain or discomfort was noted more commonly in women than in men. Canto et al. review 69 studies and reported the cumulative rates of ACS without chest pain or discomfort in women and men were 37% vs. 27%, respectively[46].

The frequency of other associated symptoms with ACS also differed between women and men. Generally, women are were more likely to experience middle or upper back pain[52, 54, 56-58], neck pain[56], jaw pain[56], shortness of breath[54, 57], paroxysmal nocturnal dyspnea[58], nausea or vomiting[56], indigestion[57], loss of appetite[54,58], weakness or fatigue[54], cough, dizziness, and palpitations[57] compared with men. Differences in the frequency of diaphoresis have been inconsistent between men and women.[52, 56] Women appear to have experienced more associated non-chest pain symptoms accompany with their ACS presentation compared with men (average of 2.6 symptoms in women vs. 1.8 in men). [57]

Besides symptoms, non-specific ECG changes were more common in women which render resting ECG as the first-line diagnostic tool in ACS is also a less reliable diagnostic tool in females presenting to emergency rooms with ACS. There are less frequent ST elevations and higher rates of ST depressions and T-wave inversions, as well as nonspecific alterations.[59]

Furthermore, gender differences in cardiac-specific biomarkers have recently been raised. Wiviott et al[60] reported among 1865 patients with NSTE-ACS from the TACTICS-TIMI 18 study that women presented less often with elevated creatinine kinase – MB (CK-MB) or troponins and more often with elevated high-sensitivity C – reactive protein (CRP) or brain natriuretic peptide (BNP). Three possible explanations for this difference were proposed: First, female patients with chest pain are a lower-risk population compared to men; Second, small cardiac enzyme leakage is more readily detectable in men because of larger cardiac muscle mass in men; Third, ACS or coronary thrombus formation in women is more likely to be caused by plaque erosions than plaque rupture which causes larger thrombus formation and hence infarction and enzyme rise [61].

Women ACS patients who underwent coronary angiography were more likely to have normal coronary angiographic findings than men.[62] The culprit coronary lesion were often less complex on angiography in women than in men .[63]

1.2.3 Treatments of ACS in women

Women, especially those older than 65 years, are more likely present or seek medical care later than men. This in turn may lead to delayed treatment and worse prognosis. [64] In the emergency rooms, women presenting with chest pain are also more likely to receive psychological than cardiac diagnoses. Women seem to be evaluated less intensively; cardiac-specific examinations including non-invasive and invasive examinations are performed less for women patients with chest pain than men. Furthermore, among patients with confirmed STEMI, reperfusion therapy is provided less to women than men. These gender differences could not be totally explained by difference in age or co-morbidities.

Despite presenting with higher risk characteristics and having higher in-hospital risk, women are treated less aggressively than men during hospitalization: they are less likely to be referred for coronary angiography, which results in less revascularization procedures.[19, 47, 65] Acute therapies such as heparin, glycoprotein IIb/IIIa antagonists, Angiotensin converting enzyme inhibitor (ACEI) and β-blockers were less used in women even after adjusting for age, medical history and presenting characteristics (e.g. ST change in ECG and signs of CHF).[47, 63]

Women with ACS are also less often prescribed secondary preventive drugs compared to their male counterparts.[19,47,66-19, 67] The prescriptions of aspirin, clopidogrel, β-blockers and lipid-lowering drugs are lower in women compared to men, while women are more likely to be prescribed calcium channel blockers and diuretics[19, 68].

However, the gender disparity diminishes after adjustment of age and comorbidities which may have precluded the use of certain drugs.[19]

1.2.4 Outcomes of women patients with ACS

Studies comparing clinical outcomes of men and women with ACS have provided conflicting results and unanswered questions. Unadjusted comparisons of mortality after AMI have generally indicated that women have a poorer outcome than men,[69, 70] less favorable near-term outcomes after revascularization procedures[69] and increased risk for adverse outcomes.[71-73] Radovanovic et al. analyzed more than 20,290 patients with ACS in a Swiss cohort and found women had higher in-hospital mortality than men only in subgroups under 60 years, and differences between genders diminished with increasing age.[19]

Gender differences in treatment as a cause of worse prognosis in women remained controversial. In FRISC II and in RITA 3, the benefits of early invasive treatment were seen only in men.[74] While the TACTICS TIMI-18 trial showed a clear benefit of an early invasive approach in NSTE-ACS regardless of gender.[75] More recently, it has been suggested that the difference in outcome between women and men treated with PCI had decreased and that the outcome in women had improved.[76-78] Authors from the CADILLAC trial suggested that the higher mortality seen in women compared with men after interventional treatment for AMI might be explained by differences in body size and clinical risk factors.[79] However, smaller target vessel size was associated with an increased risk of restenosis, but did not appear to be a predictor

of mortality.[73] Nevertheless, basic biological differences in response to AMI between men and women have been advocated[72, 80] in addition to anatomical differences.[50] It has also been suggested that there may be different pathophysiology of ACS in younger, but not in older women.[81]

Women on the whole received less optimal treatment than men (delayed therapy and less intense medical and invasive therapies), which might contribute to poorer prognosis. However, these differences appeared to have lessened in recent studies.[82] The ACC-National cardiovascular data registry (NCDR) reported similar in-hospital mortality and complication rates between women and men patients with ACS who underwent PCI.[63]

Studies on elderly patients with ACS have shown less aggressive treatment and higher mortality than in younger patients.[81] However, gender differences in mortality were not obvious,[69, 83] and a recent analysis of the National Registry of Myocardial Infarction found that the excess risk of mortality for women was accentuated at an earlier age and tended to disappear in older patients.[69, 70, 84] A higher 1-year mortality was seen in women with AMI in the French USIC Registry, owing to a higher risk of death in women aged 30–67 years during the initial hospitalization.[85] However, another study showed worse early outcome in elderly women with STE-ACS compared with men after adjustment for comorbidities, whereas similar outcomes were noted among patients with NSTE-ACS.[86]

1.3 Current treatment patterns of ACS—The Guideline Adherence

The field of ACS management experienced a remarkable evolution since the decade of the 1990s.This change was primarily due to a large number of randomized clinical trials exploring all aspects of the diagnosis and treatment of ACS, including, but not limited to, the development of cardiac biomarker assays, early use of antithrombotic and antiplatelet drugs, β-blockers, ACEIs and early invasive treatment strategies. In recognition of the importance of these data, the ACC together with the AHA issued clinical practice guidelines addressing the standard for the diagnosis and management of patients with ACS and constructed a framework for clinical decision making.[78, 87-91] However, despite the publication and wide distribution of these guidelines, their routine clinical application has been slow, incomplete, and often ineffective.[87, 88, 91] Gaps in patient management between guidelines and actual patterns of care are discussed, and areas for improvement are suggested.

1.3.1 Overview of guideline Recommendations

The latest ACC/AHA guideline for STEMI was released in 2004 and updated in 2009, for NSTEACS in 2007 and for the secondary prevention of vascular events in 2006[90, 92-94]. Aimed to cover the entire ACS continuum of care, these guidelines detailed the evidence and expert opinions regarding initial evaluation and stabilization, coronary revascularization, hospital discharge, and outpatient management.

1.3.1.1 Acute management

The ACC/AHA guidelines recommend acute medical therapies and invasive procedures for patients with STEMI and NSTE-ACS with high-risk features (i.e. ischemic electrocardiographic changes, positive cardiac markers, age>75 years, signs of CHF, and/or hemodynamic instability. For patients with STEMI, acute reperfusion should be applied to every patient without contraindications, primary PCI is recommended within 90 minutes of hospital arrival or thrombolytic therapy within 30 minutes in a hospital without cardiac catheterization laboratory.

1.3.1.2 Secondary prevention

Patients with ACS carry significant increased risk of MI, stroke and vascular-related death.[15] Secondary prevention strategies include both lifestyle modifications and comprehensive medical therapy targeting the multiple pathways of atherothrombosis. The ACC/AHA guidelines recommend long-term use of four major categories of drugs for secondary prevention: antiplatelet agents, β-blockers, ACEI, and statins. Table 1.3.1 summarizes the ACC/AHA recommendations for secondary prevention of cardiovascular events following ACS.

Table 1.3.1 American College of Cardiology/American Heart Association (ACC/AHA) recommendations for secondary prevention following unstable angina (UA), non ST-segment myocardial infarction (NSTEMI), and ST-segment myocardial infarction (STEMI)

Therapy	ACC/AHA 2002 Guidelines for UA/NSTEMI (Class of Indication/Level of Evidence)	ACC/AHA 2004 Guidelines for STEMI (Class of Indication/Level of Evidence)	ACC/AHA 2006 Guidelines for Secondary Prevention of Vascular Disease (Class of Indication/Level of Evidence)
Aspirin	Aspirin 75–325 mg daily (I/A)	Aspirin 75–162 mg daily (I/A)	Aspirin 75–162 mg/day (I/A)
Clopidogrel	Clopidogrel 75 mg daily when aspirin is not tolerated (I/A) Combination therapy with clopidogrel and aspirin for 9 months (I/B)	Clopidogrel 75 mg daily when aspirin is not tolerated (I/C) Clopidogrel 75 mg/day plus aspirin 325 mg/day for 1 month after bare-metal stent implantation, 3 months after sirolimus DES implantation, and 6 months after paclitaxel DES implantation. Ideally, patients with stent implants should continue the clopidogrel 75 mg/day plus aspirin 325 mg/day for up to 12 months if they are not at high risk for bleeding	Combination therapy with clopidogrel 75 mg/day and aspirin for up to 12 months after ACS or PCI (I/B)
β-blockers	β-blockers in the absence of contraindications (I/B)	β-blockers in high-risk patients (I/A) β-blockers in low-risk patients with normal ventricular function, successful reperfusion, and no significant ventricular arrhythmias (IIa/A)	β-blockers in high-risk patients, unless contraindicated (I/A)
RAAS inhibitors	ACEI for patients with CHF, LV dysfunction (EF<40%), hypertension, or diabetes (I/A)	ACEI for all patients without contraindications (I/A) ARBs in patients intolerant of ACEI and with heart failure or LVEF≤40% (I/B) Consider combination ACE inhibitor +	ACEI in patients with LVEF ≤40%, hypertension, diabetes or chronic kidney disease (I/A) Consider ACEI for all other patients (I/B) ARBs in patients intolerant of ACEI and with

		ARB in patients with persistent symptomatic heart failure and LVEF<40% (IIb/B) Aldosterone antagonists in combination with ACE inhibitor in patients with LVEF ≤40% and diabetes or heart failure (I/A)	heart failure or MI with LVEF ≤40% (I/A) Consider ARBs in other patients who are ACE inhibitor tolerant (I/B) Aldosterone antagonists in combination with ACE inhibitor and β-blockers in patients with LVEF ≤40% and diabetes or heart failure (I/A)
Statins*	Lipid-lowering agents in patients with LDL-C>130 mg/dl (I/A) Lipid-lowering agents in patients with LDL-C>100 mg/dl (I/B)	Lipid-lowering therapy, with preference given to statins, for patients with LDL-C>100 mg/dl (I/A) Lipid-lowering therapy, with preference given to statins, for patients with LDL-C<100 mg/dl or unknown LDL-C (I/B)	Lipid-lowering therapy for patients with LDL-C >100 mg/dl (I/A) Lipid-lowering therapy to achieve LDL-C<100 mg/dl (I/A) and reasonable to achieve <70 mg/dl (II/A)

*NEC ATP III guidelines recommend lipid-lowering therapy, with preference given to statins, to achieve an LDL-C<70 mg/dl in high-risk populations, including patients following ACS[95]
Class of indication: Class I—conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective. Class IIa—conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness/efficacy of a procedure or treatment, with the weight of evidence/opinion in favor of usefulness/efficacy. Level of evidence: A—randomized controlled trial or meta-analysis. B—other evidence (e.g., a well-designed, nonrandomized clinical trial or nonquantitative systemic review). C—consensus viewpoint or expert opinion.

1.3.2 Guideline Adherence

Although guidelines providing standard and evidence-based therapies for management of patients with ACS have been released for over 10 years, studies of practice patterns have consistently demonstrated underutilization of these effective therapies.[49, 81, 96]

1.3.2.1 Acute STEMI management

Early recognition of STEMI on ECG and rapid administration of reperfusion is critical to save myocardium. However, in clinical practice, the time for initiation of thrombolytic therapy or revascularization in STEMI varies greatly, and that some patients who seem to be eligible for reperfusion strategies do not receive them.[49, 81, 88, 96, 97] For example, the National Registry of Myocardial Infarction reported that, of more than 300,000 patients enrolled in the registry between 1990 and 1994, only one-third received reperfusion therapy, even though half to two-thirds of these patients were probably eligible for the treatment.[97] Similar findings were reported in a 1994–1998 study of 772 531 patients, a quarter of those eligible did not receive any form of reperfusion therapy.[88]

In more recent registries performed to explore modern treatment pattern of ACS in a broader range of patients, the rate of primary reperfusion remained similar to the early studies. The Euro Heart Survey conducted in 25 countries in Europe and the Mediterranean basin in 2000-2001, enrolled 9,798 patients with ACS. The primary reperfusion rate among 4,431 patients with STEMI was 55.8%, one third of patients

underwent primary reperfusion were treated with primary PCI.[98] The GRACE registry recruited patients with ACS from 13 countries, in an analytic cohort of 9,251 patients enrolled in 1999, 70% patients within 12 hours of symptom onset received reperfusion.[99] More recent data from the GRACE registry[49], on the trend of treatment pattern among 31,982 patients from 2001-2007 in 25 countries showed the use of reperfusion therapy for STEMI was 68% overall and was similar over the course of time from 2001-2007.

1.3.2.2 Secondary prevention

Risk factor modification and long-term medical therapies are important aspects of secondary prevention as ACS patients continue to experience significant risk of cardiovascular events after the index event. The European Action on Secondary Prevention through Intervention to Reduce Events II survey analyzed 8,181 patients from 15 countries admitted for ACS between 1999 and 2000[100]. After a median of 17 months post-discharge, target blood pressure and cholesterol levels were achieved in 50% and 42% of patients, respectively. Drug therapies for patients at discharge and on subsequent follow-up included: antiplatelet therapy 90% and 86%, β-blockers 66% and 63%, ACEI 38% and 38%, and lipid-lowering drugs 43% and 61%, respectively. The Canadian Acute Coronary Syndromes Registry examined 4,627 patients hospitalized with ACS between 1999 and 2001[20]. The use of aspirin, β-blockers, ACEI, and lipid-lowering therapy at discharge was observed in 88%, 76%, 56%, and 55% of patients. The American College of Cardiology Evaluation of Preventive Therapeutics (ACCEPT) study demonstrated similar findings in approximately 5,000 patients admitted for UA,

MI, first coronary artery bypass surgery (CABG), or first PCI. The more recent expanded GRACE registry analyzed the trend of changing in rates of guideline recommendations from 2001-2007 among 31,982 patients in 25 countries.[49] The use of secondary prevention medications increased gradually from 2001-2007 with modest increase in prescription rates of aspirin, β-blockers, ACEI/ARBs, and statins. The use of clopidogrel and statins increased the most during this period, e.g. prescription rates for patients with STEMI at discharge increased from 22% to 80% for clopidogrel, and 55-80% for statins respectively.[49]

1.3.2.3 Efforts to close the guideline-treatment gap

Adherence to guideline recommended therapies is associated with improved clinical outcomes in ACS. The association between key performance indexes and clinical outcomes was confirmed in an analysis of hospital care in 350 centers involved in the CRUSADE initiative. When overall composite guideline adherence was evaluated as a continuous function, every 10% increase in adherence was associated with a corresponding 10% decrease in the risk of mortality at that institution.[96]

During the past decade, numerous efforts have been made to improve adherence to treatment guidelines. [49, 101, 102] For example, in-hospital initiation of secondary preventive therapies is an effective strategy to improve guideline adherence and patient compliance with recommended therapy. A retrospective analysis of 2126 CAD patients who underwent PCI demonstrated that 77% of those started lipid-lowering therapy during their hospitalization continued taking cholesterol medication at 6 months

following discharge compared to 25% of those discharged without these drugs.[103] A retrospective analysis of 55,315 patients who had a first acute MI between 1995 and 2002 showed that those patients who were not prescribed β-blockers and ACEI within the first 30 days and statin within the first 180 days after the event were unlikely to receive prescriptions at a later time.[104] The importance of in-hospital initiation is underscored by the fact that hospital physicians are more likely than general practitioners to prescribe β-blockers (84.4% vs. 15.1%) and ACEI (77.9% vs. 21.5%) in the first 30 days and statins (72.1% vs. 27.2%) in the first 180 days.[104]

In addition to observational studies, intervention trials designed to increase in-hospital initiation of secondary prevention measures have demonstrated improved treatment rates, long-term compliance, and clinical outcomes. The Cardiac Hospitalization Atherosclerosis Management Program (CHAMP) at the University of California, Los Angeles was a comprehensive hospital-based system targeting patients with CAD.[48] CHAMP incorporated educational materials for patients and health care professionals, preprinted admission orders, patient tracking forms, and discharge checklists to improve adherence to guidelines. Using a simplified treatment algorithm guided by national clinical recommendations, CHAMP significantly increased both immediate use of aspirin, statins, β-blockers, and ACEI at hospital discharge and long-term compliance at one year following discharge.[89] Moreover, enhanced utilization of appropriate secondary prevention therapies was associated with improved clinical outcomes, including significant reductions in recurrent MI, hospitalization and mortality during the first year after discharge. The ACC Guidelines Applied in Practice (GAP) initiative employs seven components to facilitate adherence: acute MI order sets, clinical

pathways, pocket guides, patient information forms, patient discharge forms, chart stickers, and hospital performance charts[105]. Initial results from the program showed significant improvements in the usage of aspirin at discharge and smoking cessation counseling, and favorable trends towards increased adherence to other treatment goals. Even among elderly patients, a population particularly susceptible to undertreatment, appropriate therapies were implemented more frequently following the institution of the GAP initiative. More recently, these improvements in guideline adherence have been proven to benefit patient outcomes. In a sample of Medicare beneficiaries in Michigan, implementation of the GAP initiative was associated with significant reductions in 30-day (−26%) and one-year (−22%) mortality, even after adjustment for clinical findings, tests and treatments.[106] The CRUSADE study, a program led by the Duke Clinical Research Institute focused on UA and NSTEMI, used streamlined forms and targeted educational interventions demonstrated improved adherence to guidelines regarding appropriate discharge therapy.[107]

1.3.3 Risk-treatment paradox

Recommended therapies for ACS remain underutilized in high-risk patients despite clear clinical benefit in reducing cardiovascular morbidity and mortality. Older individuals, women, and patients with multiple comorbidities are less likely to be prescribed evidence-based therapies for their CAD than younger and/or healthier individuals.[108-111] This *treatment-risk paradox* in cardiovascular pharmacotherapy has been observed in recent years where by low-risk patients were more likely to receive treatment than high-

risk patients who are expected to derive the greatest benefit from treatment.[109, 112-114] Prescription of pharmacotherapy, reperfusion therapies and revascularization procedures were all lower in patients at high-risk than those at low-risk of death.

Analyses of 1,763 patients presented with STEMI within 12 hours of symptom onset from GRACE cohort[99] showed the trend that elderly patients ≥75 years, those presenting without chest pain, with diabetes, congestive heart failure, myocardial infarction, or coronary bypass surgery were less likely to receive reperfusion therapy. Similarly, Roe et al analyzed treatment patterns of 77,760 patients with NSTE ACS from CRUSADE study cohort between 2001 and 2003, who were stratified as low-, moderate and high-risk for in hospital mortality according to the PURSUIT risk score.[112] The use of guideline-recommended acute medications, invasive cardiac procedures and discharge medication and interventions was significantly lower in patients with high-risk features (i.e. with diabetes mellitus, renal insufficiency, signs of congestive heart failure on presentation, and age ≥75 years). The rate of PCI within 48 hours was 39% for patients at low-risk compared to 17% for patients at high-risk. Similar trends were observed in the use of aspirin, heparin, GP IIb/IIIa antagonists and secondary prevention medicines at discharge.

Some studies attempted to explore the potential reasons of this treatment-risk paradox.[115, 116] McAlister and colleagues analyzed more than 200 characteristics of 2,436 patients with CAD from APPROACH study,[115] and suggested that treatment-risk paradox could be attenuated by adjusting for exceptional capacity and depressive symptoms. They concluded the treatment-risk paradox reported in administrative database analyses is attributable to clinical factors not typically captured in these

databases, and that patients with reduced functional capacity, depression, or both are at higher risk for underuse of these beneficial therapies. In another analyses performed using data from a ACS registry in Australia,[116] Joynt et al stratified 2,599 patients with ACS by numbers of acute risk factors (e.g., heart rate, ECG change, cardiac biomarker et al.) and chronic risk factors (e.g., age, chronic obstructive pulmonary disease, malignancy et al.) and found patients with higher numbers of acute risk factors were more likely to receive evidence based therapies while those with higher numbers of chronic risk factors were less likely to receive such therapies.

The mismatch between treatment and risk stratification, in the words of one editorialist, it is "the premise of matching risk to level of care that physicians fail to accept, heed, or understand".[117] However, clinicians should recognize that prescription pattern and patient adherence are multifactorial and may be influenced by factors other than those coded in databases which are constructed predominantly for billing claims.

1.4 Health related quality of life in ACS

Health related quality of life (HRQoL) measures the impact of a disease state on patient's function and well-being as reported by the patient. The measurement of HRQoL is increasingly recognized as an important outcome measure in the management of CAD and should be employed more often in clinical practice. Many clinical trials now incorporate measurements of HRQoL as a clinical outcome.

1.4.1 Health related quality of life: definition

Health-related quality of life has been defined as "the discrepancy between actual and desired function" in a given patient with chronic disease.[118] HRQoL is a proxy for health status, and an outcome variable of epidemiological, clinical, and health systems research studies; it is also an independent predictor for the analysis of the use and cost of health services.[119] Tracking HRQoL in different populations can identify subgroups with poor physical or mental health and can help guide policies or interventions to improve their health.

1.4.2 Main instruments of HRQoL measures in patients with CAD

Many instrument of measures of HRQoL have been developed and validated over the last several decades.[120] Measurement of HRQoL generally includes variables concerning the impact of disease, effects of treatment and other aspects affecting patients' lives. HRQoL instruments can be divided into generic surveys, such as the Short-Form 36 (SF-36) which measured overall physical and mental health status without disease-specific question;[121] and disease-specific surveys like the SAQ[122, 123] which was specifically developed for use in patients with CAD and measure angina frequency, angina stability, physical limitation, quality of life, and treatment satisfaction related to angina. Generic measures focus on general issues of health, while disease-specific instruments which comprise content specific to the disease are more clinically sensitive and potentially more responsive in detecting changes. Both generic and disease-specific

measures have their advantages and weaknesses, and current studies usually use both types of measures.[124-126]

1.4.2.1 Generic instruments

Some generic instruments are commonly used in clinical evaluation and research of patients with CAD. The most commonly used instruments include the SF-36, Euro QoL, and the Nottingham Health Profile.

Medical outcomes Study 36-item short form health survey (SF-36)

The SF-36 is perhaps the most well-known and widely used generic HRQOL instrument. It consists of 36 items grouped into eight dimensions: physical functioning (10 items), physical role functioning (4 items), emotional role functioning (3 items), social functioning (2 items), bodily pain (2 items), mental health (5 items), vitality (4 items), general health perceptions (5 items), and another single item which solicits a self-assessment of health change over the past year. [127] Each dimension is scaled on a continuum and ranges from 0 (worst imaginable health state) to 100 (best imaginable health state). It would cost about 15 minutes to complete the self-administered questionnaire. The abbreviated forms, SF-12 and more recently the SF-8 are also available and widely used, which take even less time to complete.[128]

The SF-36 has been translated to more than 20 languages including traditional and simplified Chinese, and validated in patients with CAD and in the general

population of Hong Kong.[129] Moreover, this instrument has been used in research on angina, MI and patients underwent PCI/CABG. In patients with recent MI, SF-36 has been shown to be a sensitive tool for detecting improvement in HRQoL after intervention.[124, 130]

EuroQOL

The EuroQOL is a preference-based, generic, self-reported questionnaire composed two parts: the EQ-5 dimension (EQ-5D) health classification and the EQ-visual analogue scale (EQ-VAS).[131] The EuroQOL questionnaire has been previously validated in various settings.[132-134]

The EQ-VAS is a 20-cm visual analogue scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state) on which patients are asked to grade their current state of health. An advantage of the EQ-VAS is its relative ease of use and interpretation, although this advantage is offset by the lack of specificity concerning the particular aspect of HRQOL being measured.

The EQ-5D is the approach most commonly used in the European community; it assesses five dimensions of HRQOL: mobility, self-care, usual activities, pain or discomfort, and anxiety/depression. Each dimension is measured on a 3-point ordinal scale where a higher score represents a worse health state (no limitation, some limitation, and greatest limitation in HRQOL). A strength of the EQ-5D is that through their response, patients can effectively locate themselves into one of 245 possible health states

for which a global value (i.e., a "utility score") is assigned. The utility score has been previously determined based on the preferences of a sample of 3,395 members of the United Kingdom general population.[135] A utility score of 1 corresponds to the highest degree of HRQOL, and score of 0 is compatible with a level of HRQOL equivalent to death. A negative score indicates a state of HRQOL that is worse than death.

Nottingham Health Profile

The NHP was developed to measure lay perceptions of health status.[136] It has been proved as a useful survey tool to assess patients with or without severe health problems. There are 2 parts of the NHP. Part 1 includes 38 yes or no statements, which are grouped into six scales: mobility, pain, energy, sleep, emotional reactions, and social isolation. Part 2 of the NHP mainly collects information on the effects of health on seven areas of daily life: work, looking after the home, social life, home life, sex life, interests and hobbies, and holidays. The NHP is short and can be completed in a few minutes because of the limited response choices. However, due to the ceiling effects and poor responsiveness, NHP is thought to be not suitable for clinical use but may be used to track large changes in health status such as pre- to post-cardiac surgery.

1.4.2.2 Disease-specific instruments

There are more than 10 disease specific instruments available for heart disease. The most common used instruments include the quality of life after myocardial infarction

(QLMI),[137] the Seattle angina questionnaire (SAQ)[123] and the angina pectoris quality of life questionnaire (APQLQ)[138] etc.

Seattle Angina Questionnaire (SAQ)

The SAQ is a 19-item, disease-specific questionnaire designed to quantify physical limitations due to angina. There are 5 dimensions in SAQ: exertional capacity, angina stability, angina frequency, treatment satisfaction, and disease perception.[123] Each component score ranges from 0 (worst possible health state) to 100 (best possible health state). An advantage of the SAQ is the high sensitivity of angina stability scale in identifying changes in clinical conditions thus this domain may be able to identify minor changes in a patient.[139] Furthermore, the SAQ has been previously validated and applied in patients with CAD and ACS.[122, 123, 140, 141]

Quality of life after Myocardial infarction (QLMI) questionnaire

The QLMI is a 26-item self-administered questionnaire designed to evaluate the effectiveness of a comprehensive cardiac rehabilitation program. [142] It evaluated 5 aspects of quality of life: symptoms, restriction, confidence, self-esteem and emotion. The QLMI was proved to be less sensitive to clinical changes than SAQ and not able to discriminate between patients in Canadian Cardiovascular society (CCS) classes I-III as SAQ did in a study conducted among patients with angina.[143]

Angina Pectoris Quality of Life Questionnaire (APQLQ)

The APQLQ has 22 items evaluating 4 domains of HRQoL in patients with angina: physical activities, somatic symptoms, emotional distress, and life satisfaction. It has good psychometric properties for discriminative purposes. However, the length of the index and its lack of "ease to use" make it difficult to apply in clinical practice.

Other disease specific instruments designed for CAD include the Myocardial Infarction dimensional Assessment Scale (MIDAS)[144] which comprises 35 items covering 7 areas (physical activity, insecurity, emotional reaction, dependency, diet, concerns over medications and side effects), the Cardiovascular Limitations and Symptoms Profile (CLASP)[145] which was designed to evaluate 5 functional limitations (mobility, social life and leisure activities, activities within the home, concerns and worries and gender) and 4 symptoms scales (angina, short of breath, ankle swelling and tiredness).

1.4.3 Usefulness of HRQoL in ACS

In clinical research of CAD and ACS, HRQoL is usually used as an independent predictor of prognosis in risk stratification or for the analysis of the use and cost of health services.

Patients' evaluation of their health status often is not consistent with that of physicians. It is common that clinicians fail to identify functional disabilities reported by patients.[146]

Poor HRQoL was a risk factor for long-term mortality in patients with CAD[140, 147]. Curtis and colleagues analyzed 1,778 patients who underwent CABG and demonstrated physical health status derived from SF-36 post CABG was an independent predictor of in-hospital mortality and prolonged length of stay; every 10 points decrease in the physical component summary increased the odds of in-hospital mortality by 61% independent of established clinical risk factors[148]. Similarly, Mayer et al assessed the self-reported functional status using SF-36 pre- and 1.5 years post CABG. The analysis showed that functional status was a significant predictor of CABG outcome which was more reliable than age.[149] Quality of life in patients with established CAD assessed by SAQ was demonstrated to be independently associated with 1 year mortality and ACS by Spertus et al in a cohort of 5,558 patients[140]. The author then suggested that quality of life should be added as a factors used for risk stratification in clinical practice. Lenzen et al. evaluated quality of life in 5,619 patients with CAD undergoing angiographic procedures using EQ-5D and found patients who reported no problem on all five dimensions had significantly lower mortality at 1 year than those patients who reported problems. The authors also found that lower rating on health status was the most powerful independent predictors of mortality[150]. Based on these findings, quality of life has been recognized as a major component of health status and established as a performance measure of high-quality care by the AHA/ACC [151]. However, 5 years later, there is little evidence that quality of life measurements have been part of standard assessment in clinical practice.

Measurement of HRQoL is also useful in the assessment of therapies and decision making between therapies with the equivalent efficiency and safety. For example,

whether to select PCI or medical therapy for patients with stable coronary artery disease remains controversial. Many researchers choose HRQoL as primary outcome to compare these 2 therapies [124, 130, 152, 153]. Pfisterer et al compared HRQoL in 282 elderly patients with chronic CAD randomized to PCI or optimized medical therapy (the trial of Invasive versus Medical therapy in Elderly patients, TIME[152]); patients invasively treated had similar quality of life, symptoms and mortality with those treated conservatively at 6 and 12 months. In a larger randomized trial comparing PCI and optimized medical therapies (the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation, COURAGE)[153], Weintraub et al. assessed quality of life in 2,287 patients with stable coronary disease using SAQ and RAND-36, and the results showed patients in both arms experienced remarkable improvements in HRQoL during 36 months' follow-up. Similar results have been shown by Beltrame et al. in a smaller single-centered registry cohort.[124] In the Fragmin and/or Early Revascularization During instability in Coronary Artery Disease (FRISC II) trial, 2,457 patients with unstable CAD were randomized to invasive or noninvasive therapy[125]. In this study, the invasive group not only experienced a significant reduction in mortality but also substantial improvement in HRQoL compared to those treated non-invasively. The third Randomized Intervention Trial of unstable Angina (RITA-3)[126] evaluated early invasive strategy versus conservative strategy in 1,810 patients with NSTE ACS, using SF-36, SAQ and EuroQoL questionnaires to evaluate QoL at baseline, 4 and 12 months after admission. Both generic and disease-specific surveys showed a trend of better quality of life in patients treated with early invasive strategy. These findings added evidence to early invasive therapy in patients with NSTEACS.

1.5 Summary

Acute coronary syndrome is one of the most common presentations of CAD and is a leading cause of mortality and morbidity in the developed world. Current management guidelines of ACS are based on high level of evidence accumulated over the years. Evidence based management of ACS has led to significant improvement in mortality rates and clinical outcomes of patients with ACS. However, there are still gaps in our knowledge and between evidence and practice. For example, there are gaps in the applicability of current guidelines on the Chinese population based on data obtained mainly from western population; there are gaps in evidence of therapy for specific groups such as female and the elderly; there are gaps in the use of HRQoL measure in clinical practice and there are gaps in adherence to guideline recommendations in clinical practice. Bridging these gaps may help to improve prognosis of ACS patients.

CHAPTER TWO

METHODOLOGY

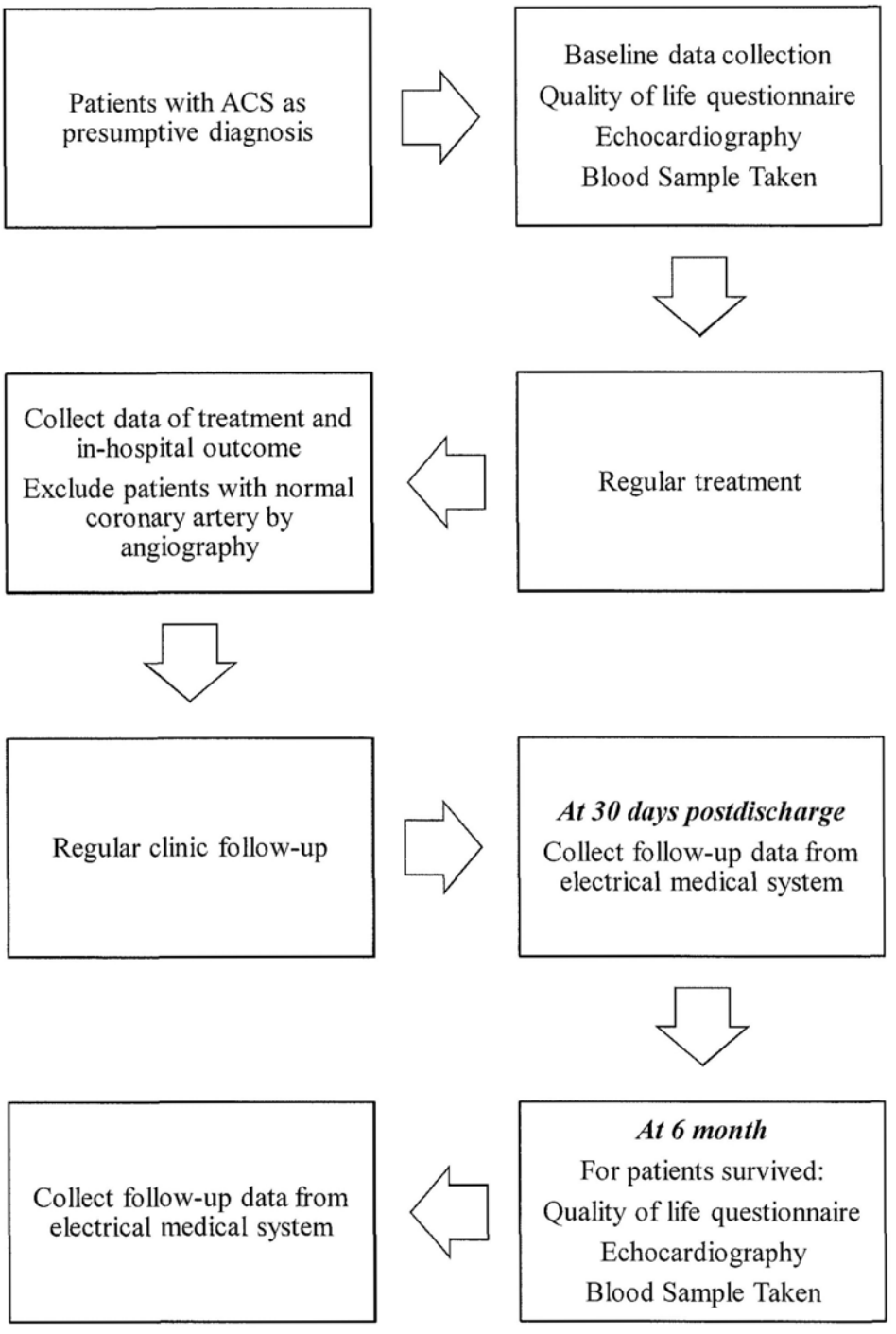
CHAPTER 2. METHODOLOGY

2.1 Study design and protocol

This is a single center, prospective, observational cohort study. The purpose of this study is to explore the local demographics and current treatment pattern of ACS. Consecutive patients admitted to the Prince of Wales Hospital, Hong Kong with ACS as the admission diagnosis were eligible for inclusion into the study.

Figure 2.1 showed the flow of our study: Patient meeting all enrollment criteria for this study would be recruited within 1-2 days of the index hospitalization. Patient consent was obtained prior to HRQoL assessment, echocardiography and blood tests. Follow-up was performed at 30 days and 6 months after hospital discharge. Clinical events including death, MI, hospital readmission, revascularization procedures and medications at 30 days and 6 months were recorded. Quality of life questionnaire, echocardiography and blood tests were repeated at 6 months after review by a cardiologist.

Figure 2.1. Flow chart of recruitment and follow-up.



2.2 Research Questions

Epidemiology

Research question 1: Do demographic characteristics, treatment pattern and outcome of acute coronary syndrome patients in Hong Kong differ with published data?

Research question 2: Do demographic characteristics, treatment pattern and outcome of acute coronary syndrome patients in Hong Kong differ between genders?

Research question 3: How did demographic characteristics, treatment pattern and outcome differ between genders?

Guideline Adherence

Research question 4: Were there any gaps between current treatment pattern of ACS patients and guideline?

Research question 5: Was the guideline adherence similar between ACS patients with different presentation?

Research question 6: Are high risk patients treated more aggressively?

Research question 7: Are there predictors of undertreatment of ACS?

Quality of life

Research question 7: What are the changes of quality of life in patients after ACS?

Research question 8: What is the impact of invasive therapy on quality of life in young and elderly patients with ACS?

Research question 9: How did management strategies influence quality of life in ACS patients across whole spectrum of age?

2.3 Data elements

Data elements for the clinical description of ACS and its management have been proposed by the American College of Cardiology (ACC) and American Heart Association (AHA), the definitions have been internationally endorsed by the European Society of Cardiology (ESC)[75]. The design of our case report form was based on guidelines and included the following domains:

2.3.1 Baseline

a. Baseline characteristics data including demographic characteristic and medical history were collected. Data elements including gender, date of birth, level of education, profession, income and race for demographic characteristics and previous myocardial infarction, prior congestive heart failure, previous PCI and/or CABG,

history of stroke, peripheral arterial disease, diabetes, hypertension, smoking, dyslipidemia, renal impairment, family history of coronary artery disease (CAD) and chronic lung disease (i.e., chronic obstructive pulmonary disease) for medical history were collected in a manner of check box of yes/no and a free text for note if necessary.

b. Clinical presentation: including date and time of the onset of symptoms that prompted the patient to seek medical care, date and time the patient first presented to the hospital, Killip class of the patient at the time of hospital admission, heart rate, systolic and diastolic blood pressure at the time of presentation, height, weight, location of chest pain and other accompany symptoms (e.g., nausea, vomit, syncope etc.).

c. Electrocardiographic findings: date and time of first12-lead ECG, rhythm, bundle-branch block and type, location of ECG changes and type of ECG changes which including ST-segment elevation, ST- segment depression, T-wave inversion and Q waves.

d. Laboratory tests: the initial and peak value of cardiac biomarkers (i.e., troponin T and creatinine kinase), initial and peak value of serum creatinine, first lipid profile (i.e., total serum cholesterol, low density lipoprotein, high density lipoprotein and total triglyceride), complete blood count, liver function text, random and fasting glucose, and hemoglobin A1c.

e. Cardiac procedures: the first ejection fraction obtained during the hospitalization if echocardiography was performed, date and results (i.e., maximum stenosis by

vessels) of diagnostic cardiac catheterization/angiography performed during the hospital stay, date and time of PCI if the procedure was performed, PCI status as elective or primary, type of PCI (angioplasty only or stenting), type of stent used (bare metal stent / drug eluting stent), date of CABG if the procedure performed, Intra-aortic balloon pump (IABP) used during this admission and temporary or permanent pacemaker placed during this admission.

f. Medication: Use of cardiovascular medications were recorded in 3 time points: before/at admission (i.e., chronic therapy), during hospitalization (not including medications given pre-hospital) and at hospital discharge. Medications including: fibrinolytic agents, Beta-blockers, Calcium channel blockers, aspirin, antithromin agents, warfarin, ACEI, Angiotensin II receptor blockers, diuretics, digitalis, and lipid-lowering agents. Medication information collected included class, brand and dosage.

g. Hospital-associated outcomes: date of death if patient died during this hospitalization, date of the patient was discharged, arrhythmia was recorded in case of: a new episode of atrial fibrillation/flutter, supraventricular tachycardia requiring treatment, ventricular tachycardia or ventricular fibrillation requiring cardioversion and/or intravenous antiarrhythmic and any level of AV-block including first degree to third-degree AV block.

h. Quality of life assessment (SF-36): date of the questionnaire completed.

2.3.2 Follow-up Measures

a. Death: the patient died since the previous visit, including all deaths regardless of cause of death. Date of the death should be recorded as well as the reason of death, which might be divided into 2 categories: cardiovascular death indicates cause of death from sudden cardiac death, MI, unstable angina or other CAD related events; vascular death (e.g., stroke, arterial embolism, pulmonary embolism, rupture of aneurysm, or dissection); congestive heart failure; or cardiac arrhythmia; while non-cardiovascular death includes death from respiratory cause, infection, cancer, trauma, suicide, or any other already defined cause (e.g., liver disease or renal failure)

b. Adverse events: patients with documented evidence of myocardial infarction, or any type of stroke which was not fatal. Date should be recorded.

c. Cardiac catheterization and revascularization: indicates cardiac catheterization procedures and/or PCI and/or CABG performed since the previous visit, date should be recorded.

d. Cardiac readmission: readmission to a hospital for cardiac reasons that included MI, unstable angina, angina, PCI, CABG, CHF, arrhythmia or conduction disturbance, other cardiovascular problem without MI.

e. Medication use: type and dosage of antiplatelet (i.e., aspirin, clopidogrel, cilostazol, others), ACEI, ARBs, beta-blockers, calcium channel blockers, regular nitrates and lipid lowering drugs and other cardiac medications would be collected.

f. Quality of life assessment (SF-36) would be repeated at 6 months.

2.4 Study Patients

From year 2006 to 2009, 1001 consecutive patients admitted with diagnosis of ACS in Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong were prospectively recruited.

2.5 Inclusion/Exclusion Criteria

2.5.1 Inclusion criteria

Patients must meet the following criteria to be recruited in this study:

a. Patient has one of the ACS as a presumptive diagnosis

b. Patient is ≥ 18 years old.

c. Patient is alive at the time of hospital presentation.

d. The criteria for ACS as defined below must be met, with one exception: Patients hospitalized for < 1 day that die and do not meet the criteria may be enrolled provided that the cause of death is confirmed to be due to ACS.

e. Patients who meet eligibility criteria and who die shortly after admission e.g. in the emergency room should also be included.

2.5.2 Exclusion Criteria:

a. The qualifying acute coronary syndrome has been precipitated or accompanied by a significant co-morbidity such as a motor vehicle accident, trauma, severe gastrointestinal bleeding, operation or procedure.

b. Patient who develops ACS symptoms while hospitalized for any reason.

2.6 Diagnosis of Acute Coronary Syndrome

Acute Coronary Syndromes, an umbrella term including a spectrum of acute myocardial ischemia from unstable angina, non-ST elevated myocardial infarction to ST elevated myocardial infarction).

Eligible patients should have symptoms considered as consistent with acute cardiac ischemia within 24 hours of hospital presentation, plus at least one of the following:

- ECG Changes

    a. Transient ST segment elevations of ≥ 1 mm∗

    b. ST segment depressions of ≥ 1mm

    c. New T wave inversions of ≥ 1mm∗

    d. Pseudo-normalization of previously inverted T waves∗

    e. New Q-waves (1/3 the height of the R wave or ≥ 0.04 seconds)∗

f. New R wave > S wave in lead V1 (posterior MI)

g. New left bundle branch block

* Changes should be seen in two or more contiguous leads.

- Documentation of Coronary Artery Disease

a. History of MI, angina, CHF felt to be due to ischemia or resuscitated sudden cardiac death

b. History of, or new positive stress test, with or without imaging

c. Prior, or new, cardiac catheterization documenting coronary artery disease

d. Prior, or new, PCI or CABG

- Increase in Cardiac Enzymes

a. Positive troponin T, defined as >0.1 ng/ml.

b. Total creatine phosphokinase (CK) > 2x upper limit of the hospital's normal range.

2.7 Risk stratification

GRACE score was used for risk stratification. This is a risk evaluation model derived from data of more than 70000 patients in a prospective multi-center registry of acute coronary events[27, 28]and was validated in western population[41, 42, 154].

Total 6 models were developed for predicting mortality, rates of death and myocardial infarction during index hospitalization, during 6 months since coronary events onset and 6 months post discharge. The model predicting in-hospital mortality was widely used in publications[41, 42, 154], while a calculator released at the site of the GRACE project could be used to calculate each patient's risk of death and myocardial infarction at different period of acute coronary events.

Six months mortality predicting model was used in this study, scores were calculated from eight individual variables: the age of the patient, admission systolic blood pressure, heart rate, Killip score, baseline creatinine level, cardiac arrest on admission, ST segment deviation on initial ECG and elevation of cardiac biomarkers. Estimated risk of death at 6 months was derived using GRACE calculator. (The calculator is available at http://www.outcomes-umassmed.org/GRACE/).

The receiver operating characteristic (ROC) curves was used to relate the predicted mortality at 6 months calculated by GRACE model to the rate of death at 6 months. The cut-off points identified with the ROC curves was used to separate the studied population in low- and high-risk patients.

2.8 Health related quality of life evaluation

2.8.1 SF-36 questionnaire

Health status assessment was performed at baseline and follow-up using the Medical Outcome Survey Short Form 36 (MOS SF-36, traditional Chinese version), a 36-item questionnaire that measures eight health scales including physical functioning, role-limitation due to physical problems, role limitation due to emotional problems, vitality, emotional well-being, social functioning, bodily pain, and general health. Each scale is composed of 2 to 10 items, and each item consists of a 2 to 6 point scale (Table 2.1). The scale score is calculated by sum scores of items belonging to the same scale. Score for each scale ranges from 0-100, with higher score reflecting better health status. The SF-36 has been previously validated in patients with ischemic disease and local general population [129].

2.8.2 Calculation of physical and mental component summary

The Physical component summary (PCS) and Mental component summary (MCS) scores, which reflect overall physical and mental health status, are derived from the eight original scales of SF-36(Figure 2.2). The PCS and SC scores are easier to interpret and analyze statistically in clinical trials and longitudinal studies. Because correlation between each of the SF-36 scales and the two summary scales are different, the two component summary scales are weighted by the appropriate physical or mental factor coefficient before aggregation to form the final scores.

Table 2.1. The SF36 quality of life (QoL) scoring system and its scales and dimensions.

Items	Scales	Dimensions
3 Vigorious activities 4 Moderate activities 5 Lift, carry groceries 6 Climb several flights 7 Climb one flight 8 Bend, kneel 9 Walk mile 10 Walk several blocks 11 Walk one block 12 Bath, dress	Physical Functioning	Physical Health
13 Cut down time 14 Accomplished less 15 Limited in kind 16 Had difficulty	Role-physical	Physical Health
21 Pain-magnitude 22 Pain-interfere	Bodily Pain	Physical Health
1 General health rating 33 Sick easier 34 As healthy as anyone 35 Health worse 36 Excellent	General Health	Physical Health *
23 Pep/Life 27 Energy 29 Worn out 31 Tired	Vitality	Physical Health * Mental Health
20 Social-time 32 Social-extent	Social Functioning	Mental Health
17 Cut down time 18 Accomplished less 19 Not careful	Role-emotional	Mental Health
24 Nervous 25 Down in dumps 26 Peaceful 28 Blue/Sad 30 Happy	Mental Health	Mental Health
2 Change in reported health		

* Significant correlation with other summary measure

Note that *Vitality and General Health* scales are overlapping components of both *Physical Health* and *Mental Health* dimensions Question #2, self-evaluation of change in health during the past year (Reported Health), does not belong to any score, dimension or the total SF36 score

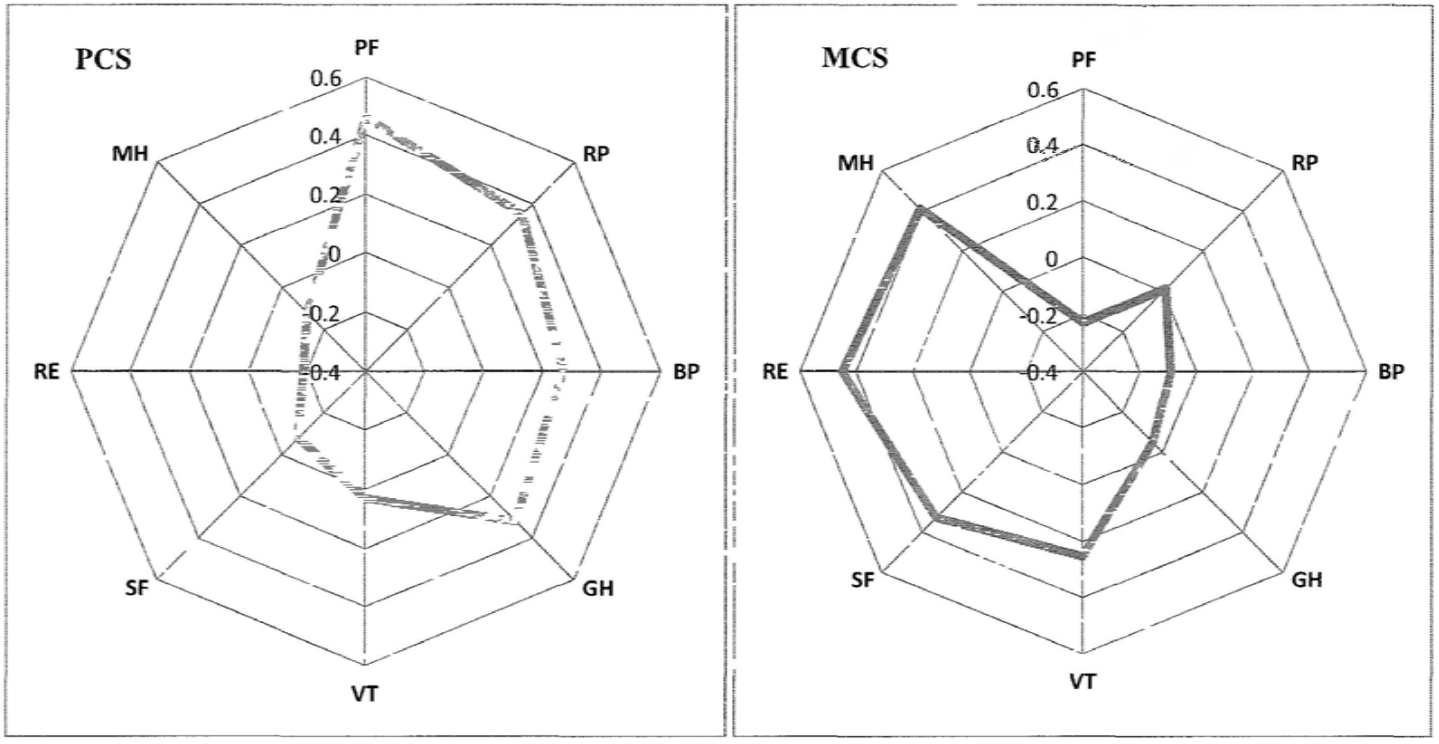


Figure 2.2 Correlations between the SF-36 scales and two principal components in Hong Kong general population: correlation strength was different in different SF-36 scales between PCS and MCS. PCS: physical component scales; MCS: mental component scales; PF: physical functioning; RP: role-physical; BP: bodily pain; GH: general health; VT: vitality; SF: social functioning; RE: role-emotional; MH: mental health.

The calculation of PCS and MCS included 2 steps:

a. z-score transformation:

   Sums of each scales should be transformed into z-score before they were used to calculate the PCS and MCS. Transformation was performed follow the equation below:

$$z\ score = \frac{observed\ score - population\ means}{population\ standared\ deviation}$$

b. Component summary scales calculation:

   For easier interpretation, standardized population means and SD of 50 and 10 were recommended for the norm-based scoring:

$$PCS = \sum(\text{z score of each scale} \times \text{respective physical factor coefficient}) \times 10 + 50$$

$$MCS = \sum(\text{z score of each scale} \times \text{respective mental factor coefficient}) \times 10 + 50$$

For interest to allow population-specific interpretation, we used the population means and SDs of Hong Kong population and factor coefficients derived from the local general population published to calculate the Hong Kong specific component summary scales[129]. The algorithm is summarized below:

z-score of Hong Kong specific SF-36 scales

$$PF_z = \frac{\text{PF} - 91.82573}{12.88527} \qquad RP_z = \frac{\text{RP} - 82.42739}{30.97154}$$

$$BP_z = \frac{\text{BP} - 83.97801}{21.89251} \qquad GH_z = \frac{\text{GH} - 55.97759}{20.17986}$$

$$VT_z = \frac{\text{VT} - 60.27178}{18.64714} \qquad SF_z = \frac{\text{SF} - 91.19295}{16.56710}$$

$$RE_z = \frac{\text{RE} - 71.65975}{38.36354} \qquad MH_z = \frac{\text{MH} - 72.78506}{16.56739}$$

Hong Kong specific SF-36 PCS and MCS

$$\begin{aligned} PCS = (&PF_z \times 0.46095 + RP_z \times 0.27474 + BP_z \times 0.35475 + GH_z \times 0.32470 \\ &+ VT_z \times 0.03257 + SF_z \times -0.07846 + RE_z \times -0.19399 \\ &+ MH_z \times -0.12198) \times 10 + 50 \end{aligned}$$

$$\begin{aligned} MCS = (&PF_z \times -0.22743 + RP_z \times 0.01327 + BP_z \times -0.09483 + GH_z \\ &\times -0.05122 + VT_z \times 0.25123 + SF_z \times 0.33064 + RE_z \\ &\times 0.44834 + MH_z \times 0.41167) \times 10 + 50 \end{aligned}$$

2.9 Data analyses

2.9.1 Data collection

A standardized data abstraction form has been developed for study use. Standardized definitions for patient-related variables and clinical diagnoses are used. The case report forms were filled after discharge according to medical record in ward and the electronic medical record system. Death postdischarge and reason of death was acquired from electronic record system, as well as adverse events and current medications. Questionnaires were performed 1-2 days after admission and repeated at 6 months' interview. In case the patients refused follow-up, questionnaires would be performed by phone calls.

2.9.2 Statistical Methods

Data transformation, recoding, aggregating and statistical analyses were performed using SPSS version 17.0 for Windows (SPSS Inc., Chicago, Illinois). All calculated p values were two-sided and p value <0.05 were considered statistically significant.

2.9.2.1 Statistical tests used for the research questions

Categorical data were expressed as percentages, and continuous variables expressed as mean±SD and/or median with inter-quartile ranges (IQR). Continuous variables were compared using Student's *t*-tests. For comparison of parametric variables across 3 or

more groups, one way analysis of variance with the Scheffé correction was used for significance. Linear regression analysis was performed to investigate the correlation between parametric variables. Categorical variables were compared using Fisher exact or Pearson chi-square tests as appropriate. Multivariate regression was performed to adjust for potential bias of covariates such as age and gender et al.

2.9.2.2 Propensity Score

A propensity score of probability in undergoing PCI was used to adjust for potential bias in treatment selection. This was accomplished by performing a multivariable logistic regression analysis using PCI as the dependent outcome variable and entering all demographics, physical examination findings, clinical presentation and medications that were likely to affect the probability of PCI. Stepwise backward elimination was employed and the resultant independent predictors of undergoing PCI were then used to calculate the probability of undergoing PCI (propensity score). The propensity score was forced into the multivariate regression model of outcomes to balance the potential bias due to treatment selection.

2.9.2.3 Multiple Imputation

Multiple imputation of missing data typically involves generating 3-5 data series with complete data, analyzing each separately, and then combining the results such that the parameter estimates and standard errors of the models reflect the uncertainty of multiple

imputation.

First, missing SF-36 baseline values were imputed using demographic and baseline clinical variables. We generated 5 such data series. Then we randomly selected one of these and imputed missing 6 month values using demographic and clinical variables, and the baseline value, whether observed or imputed, again generating 5 such data series. Observed scores of SF-36 domains were used to impute missing values of other SF-36 domains concurrent with the follow-up time of the missing value.

Multiple imputation algorithms implemented in the missing value analysis module in the SPSS was used to impute missing data.

SECTION THREE

CHAPTER 3.CLINCAL FEATURES AND OUTCOMES OF PATIENTS WITH ACUTE CORONARY SYNDROME

3.1 Background

Guidelines for the management of ACS are well established by the ACC/AHA/ESC [47, 78, 92, 93, 155]. The real challenge lies in effective application of evidence based medicine to clinical practice. The disparity between outcomes in clinical trials and clinical practice demands further attention.[96]

This treatment gap between evidence and practice is not surprising, given the heterogeneity of different clinical environments.[156] Registries are invaluable for quality assurance measures and in validating the effectiveness of costly interventions and therapies.[157]

There are 3 important clinical questions for physicians and cardiologists caring for patients with ACS: 1) what are the rates of death and recurrent myocardial infarction among local patients and the comparison between international and local outcomes; 2) whether ACS patients received evidence based treatment and, if not, why not; 3) what is the optimal therapy for certain patient subgroups, such as the elderly, where evidence is lacking. To address these questions, many individuals and institutions have recognized the need to acquire local data among patients presenting with ACS. Local data with standardized definitions may allow for effective comparisons with international clinical trials and registries, and encourage collaboration between institutions with similar

interests and research. Therefore, we performed this registry to explore epidemiology, current treatment pattern and outcomes of ACS patients in Hong Kong.

3.2 Methods

Details of the study have been listed in Chapter II of methodology and are outlined briefly as follow. Patients admitted to our institute with acute coronary syndrome as possible diagnosis were recruited from February, 2006 to December, 2009. To ensure the representatives of the data, patients were recruited prospectively and consecutively. Patients were defined as unstable angina, NSTEMI and STEMI according to the ECG change and level of cardiac enzymes including troponin T and creatine phosphokinase. Demographics, clinical and procedural data were collected using a predesigned case report form after the consents were obtained from patients. Statistical comparisons of baseline characteristics, investigations and procedures during hospitalization, medications and outcomes across different presentation of ACS were performed using the χ^2 test or the Fisher's exact test for categorical variables, and the two-tailed Student's ***t***-test for continuous variables with SPSS version 17.0(SPSS Inc., Illinois, Chicago, IL, USA).

3.3 Results

3.3.1 Clinical Features

Patients in ACS registry were enrolled prospectively from Feb 2006. By the end of December 31, 2009, the present study has enrolled a total of 1,001. Patients were divided into groups labeled with STEMI (31.7%), NSTEMI (42.7%) and unstable angina (21.6%), using the diagnostic criteria described in method. The patients' baseline characteristics and risk factors were listed in Table 3.1.

Only 26% of patients with STEMI were female while women composed 41% of those with UA. Furthermore, the presentation of ACS changed with age: among patients younger than 40, only 11.1% were female; while among patients older than 80, more than a half of those were women (Figure 3.1). Most patients had a history of smoking, and 21.7% of these were smokers at the time of admission and these patients were more likely to present with STEMI. More than half the patients with ACS had a history of hypertension. Approximately three fourth of the patients were >60 years old. Patients presented with STEMI were significantly younger than those presented with NSTEMI and UA. Similarly, the clinical presentation of the patients varied with age: although the frequency of unstable angina was consistent over the various age groups, there was a trend toward increasing frequency of NSTEMI and decreasing frequency of the presentation as STEMI with advanced age (Figure 3.2).There were significant differences in the rates of previous myocardial infarction, which was more often in patients admitted for unstable angina than for myocardial infarction (25 vs. 15 vs. 10% in UA, NSTEMI and STEMI, respectively, $p<0.001$). A history of myocardial infarction,

cerebral vascular attack, or previous coronary artery revascularization was more frequent among patients with unstable angina than among those with myocardial infarction, and among the MI patients, was most frequently found among patients with NSTEMI (Table 3.1). Sixteen percent of the patients with STEMI and up to 64% of the patients with unstable angina were on aspirin therapy before the qualifying episode of ACS.

Table 3.1. Baseline Characteristics at Admission of Patients enrolled.

	STEMI (n=317)	NSTEMI (n=428)	UA (n=256)	p
Age, years ± SD	67.0±13.5	70.8±11.8	71.0±11.9	<0.001
Female (%)	81(26%)	171(40%)	106(41%)	<0.001
Medical History (%)				
Previous Ischaemic Heart Disease	47(15%)	154(36%)	156(61%)	<0.001
Previous myocardial infarction	28(10%)	58(15%)	60(25%)	<0.001
Previous revascularization	22(7%)	65(15%)	85(33%)	<0.001
History of CHF	7(2%)	53(12%)	40(16%)	<0.001
Hypertension	171(54%)	280(65%)	155(61%)	0.007
Hypercholesterolemia	106(33%)	164(38%)	92(36%)	0.39
LDL Level				<0.001
> 4.1 mmol/L	11.3%	12.6%	7.2%	
<4.1 and >2.6 mmol/L	49.3%	45.9%	31.4%	
Diabetes mellitus	101(32%)	170(40%)	104(41%)	0.04
History of stroke	23(7%)	46(11%)	43(17%)	0.001
Renal Impairement*	18(6%)	55(13%)	27(11%)	0.005
Smoker	174(69%)	168(62%)	105(68%)	<0.001
Current Smoker	106(34%)	75(18%)	36(15%)	<0.001
Ex-smoker	68(35%)	93(44%)	69(53%)	0.004
BMI	24.1±4.2	24.5±4.8	24.5±3.7	0.57
Killip Classification				
I	229(72%)	271(63%)	189(74%)	<0.001
II	54(17%)	108(25%)	58(23%)	
III	16(5%)	37(9%)	8(3%)	
IV	18(6%)	12(3%)	1(0%)	
GRACE Score†	128.6±36.3	122.2±35.1	107.7±30.6	<0.001

*Renal impairement defined as creatinine≤2.5mg/dl for men and ≤2.0mg/dl for women.

† Model predicting 6 months mortality. UA: Unstable angina.

Figure 3.1. Frequency of gender according to age group

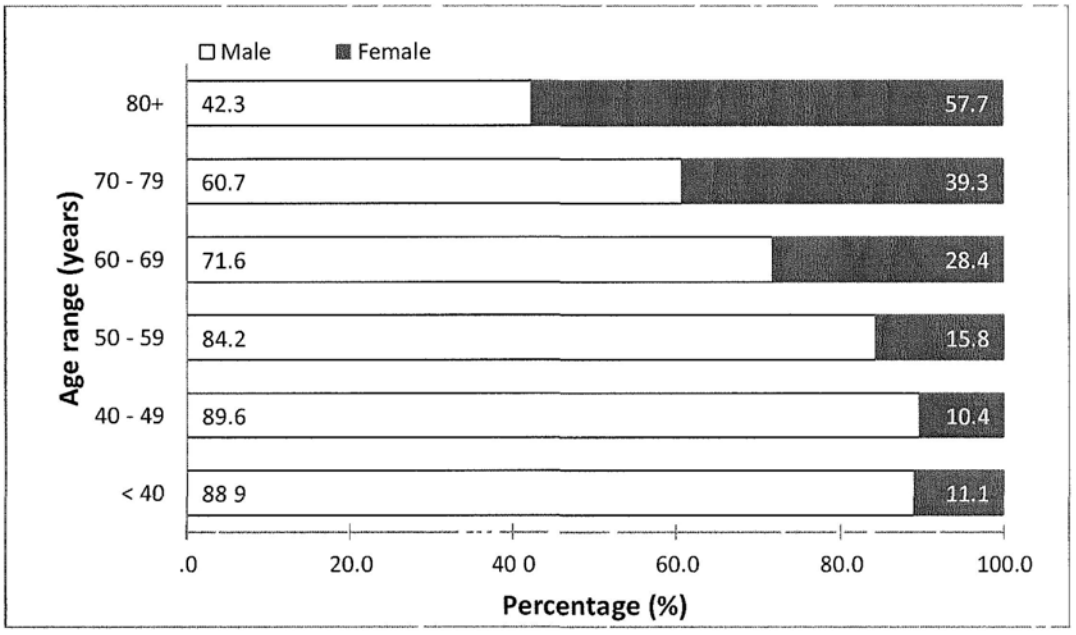
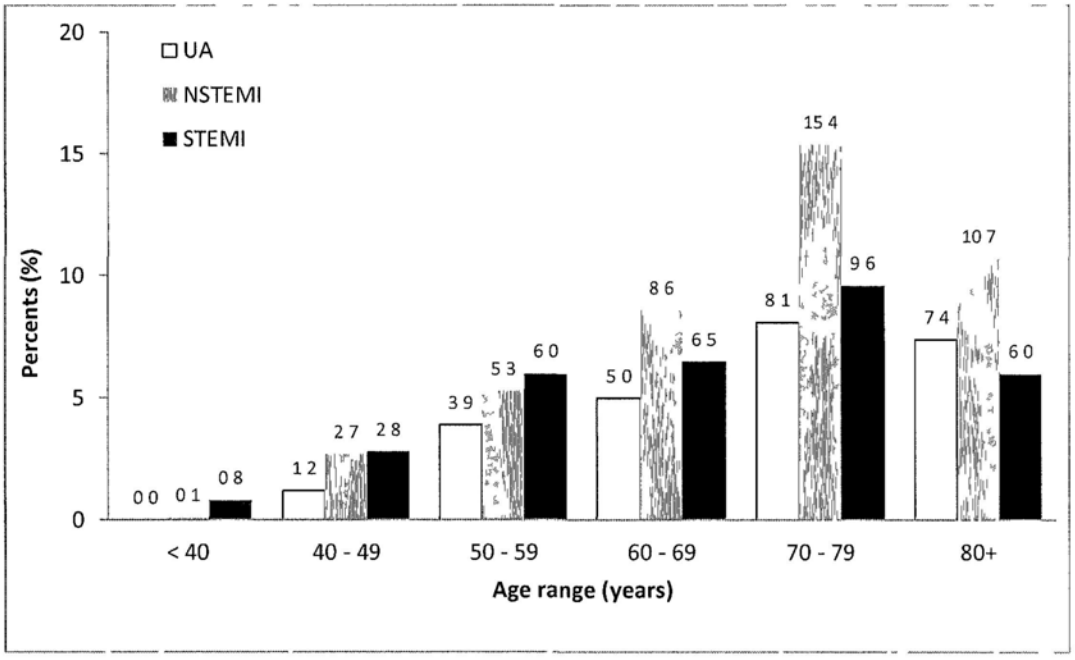


Figure 3.2. Prevalence of presentation as STEMI, NSTEMI, or unstable angina according to age group.



3.3.2 Management Practice

The pharmacologic treatments of patients with ACS were listed in Table 3.2. Aspirin was almost unanimously prescribed during the index hospitalization. Low-molecular-weight heparins were used in approximately 50% to 80% of patients. Thrombolytic agents were used in nearly 40% of the patients with STEMI. The agents used for thrombolytic therapy of STEMI were streptokinase in 41.5% of patients, tissue plasminogen activator in 58.5%. Of the patients with STEMI who had a PCI, 48 (26%) underwent primary PCI. Overall, reperfusion therapy (thrombolytic therapy or primary PCI) was used in 54% of these patients with STEMI.

Coronary angiography was performed more frequently during the index hospital stay in patients admitted for STEMI (70%) and NSTEMI (55%) than in patients with unstable angina (39%; $p<0.001$). There was also more frequent use of PCI in patients with STEMI (58 vs. 39 vs. 24% in STEMI, NSTEMI, and unstable angina, respectively; $p<0.001$). Stents were planted in 95%, 98%, and 94% of interventions performed in patients with STEMI, NSTEMI, and unstable angina, respectively. Altogether, 42% of all patients underwent PCI during the index admission and 96% of these patients were implanted with ≥ 1 stent. When patients who underwent primary intervention for STEMI during the first 12 hours of symptom onset were excluded, PCI was performed in 51% of those with STEMI. In patients who underwent PCI, approximately 24% with MI and 5% with unstable angina were treated with intravenous glycoprotein IIb/IIIa antagonists. Coronary artery bypass grafting was performed in 2% of patients with STEMI, 3% of those with NSTEMI, and 2% of those with unstable angina ($p=0.5$). Seventy-eight percent patients with STEMI underwent echocardiography, the rates of

echocardiography in patients with NSTEMI and UA were 64% and 62% respectively ($p<0.001$).

3.3.3 Hospital Outcomes

Hospital mortality rates were higher for patients with STEMI and NSTEMI compared with patients with unstable angina (6 vs. 4 vs. 2 for STEMI, NSTEMI and UA, respectively, $p=0.05$). The median length of hospital stay was 8 days (range 6 to 11) for patients with STEMI, 7 days (range 5 to 10) for patients with NSTEMI, and 6 days (range 5 to 8) for those with unstable angina ($p<0.001$). At discharge, approximately 92% of patients were prescribed aspirin and 54% of the patients were prescribed a statin. Other prescriptions at discharge were listed in Table 3.2.

Table 3.2 Pharmacologic treatments during hospital stay and at discharge

	STEMI (n=317)	NSTEMI (n=428)	UA (n=256)	p
In hospital				
Aspirin	239 (75%)	376 (88%)	222 (87%)	<0.001
Clopidogrel	215 (68%)	214 (50%)	95 (37%)	<0.001
With Angiography	167 (91%)	144 (85%)	55 (89%)	0.27
Without Angiography	48 (36%)	70 (27%)	40 (21%)	0.01
Thrombolysis	123 (39%)	0 (0%)	1 (0%)	<0.001
LMWH	155 (49%)	353 (82%)	172 (67%)	<0.001
Glycoprotein IIb/IIIa antagnists	69 (22%)	21 (5%)	3 (1%)	<0.001
During PCI	66 (36%)	20 (12%)	3 (5%)	<0.001
Without PCI	3 (2%)	1 (0%)	0 (0%)	0.04
Statins	200 (63%)	243 (58%)	154 (62%)	0.25
At discharge*				
Aspirin	291 (98%)	394 (96%)	234 (94%)	0.04
Clopidogrel	195 (66%)	178 (44%)	82 (34%)	<0.001
With PCI	58 (94%)	153 (91%)	175 (96%)	0.20
Without PCI	24 (13%)	25 (11%)	20 (18%)	0.15
Warfarin	11 (5%)	6 (2%)	7 (3%)	0.07
ACEI/ARB	15 (5%)	130 (32%)	129 (51%)	<0.001
Statin	178 (60%)	234 (57%)	125 (50%)	0.06
Beta-blocker	182 (61%)	275 (67%)	175 (70%)	0.09
Calcium antagonists	13 (4%)	72 (18%)	52 (21%)	<0.001
Nitrates	1 (79%)	1 (71%)	1 (73%)	0.06

* Analysis only included patients who survived hospitalization.

3.4 Discussion

This study is the first registry to collect data on the full spectrum of patients with ACS in Hong Kong. Besides providing epidemiological data in Hong Kong where the population has the second longest expectation life in the world[21], the registry also provided consecutive, longitudinal data that enable health care providers the opportunity to identify potential treatment gaps between guideline and practice in real-world.

Regional and racial differences in the management and outcomes of ACS were well recognized and reported.[2-18] Even in large randomized study of the treatment of ACS, outcomes can vary considerably among different regions: In the HERO-2 trial, mortality rates varied among regions were: 6.7% in Western countries, 10.2% in Eastern Europe, and 13.2% in Russia, despite similar baseline characteristics and treatments.[158, 159] Similarly, TIME-II trial, reported the lowest mortality rates in North America (5.7%) and the highest mortality rates in Latin America (10.1%).[160] More recently, Kramer et al.[161] looked at interregional variation in outcome in the two SYMPHONY trials. Ninety-day mortality was found to be significantly different across regions. Patients were more likely to die in Asia (3.3%) and Latin America (3.2%) than in Canada (1.4%) or the United States and Europe (1.6%) within 90 days after onset of ACS. Moreover, regional differences existed in almost every aspect of treatment and outcomes in patients with ACS, including seeking early care[162], reperfusion strategies[163, 164], guideline adherences[165-167], in hospital stay[168] and adverse events[161] as well. Furthermore, not only regional but also racial differences in ACS were reported: coronary disease mortality was higher in blacks than in whites[169-171] and native Americans were more likely to underwent revascularization with lower in-hospital mortality.[172] In the INTERHEART

study[173], the strength of association between diabetes and AMI was found to be higher for the Chinese than for other countries, while and the strength of association of waist to hip ratio and AMI was lower in Chinese than in western countries.

However, the majority of ACS registry data to date, including the GRACE registry, were performed in regions where majority of population are Caucasians. [174] As a result, there is limited data on the Chinese population, especially in Hong Kong where the health care is much different with mainland China. Thus, our study could fill the blank in data of local epidemiology, treatment pattern and outcome in patients with ACS in Hong Kong under current health care system.

Chinese was reported to have lower cardiovascular risk factors compared to patient in the western world. Teo et al[173] reported better risk factor profiles in Chinese participants than other countries, such as lower prevalence of hypertension, diabetes and lower levels of lipids in AMI patients from the INTERHEART study which compared modifiable risk factors of AMI patients between different regions. They also found relatively stronger relationship between diabetes and AMI in Chinese population, while Chinese were protected from high waist to hip ration compared to western countries. In this study, we found the similar prevalence of risk factors among analytic cohort as that reported in INTERHEART. Moreover, prevalence of hyperlipidemia was even lower in ACS patients: 36.2% vs. 45.6% in GRACE cohort and 64.2% in a New Zealand cohort and similar with expanded GRACE-China data of 29.2%[68, 174], while lower LDL level were also found among our patients, as 2.7 ±1.6 compared to 3.2 in Chinese AMI patients and 3.6 in western countries reported in INTERHEART[173]. Furthermore, our patients were nearly 5-8 years older than other published data, with median age of 72

(range 61-79) compared to 65 years of age reported by GRACE[174], 66 in Canada[175] and AMIS[19] registry from Switzerland. One of the explanations for these differences might be healthier food with more vegetables and fruits which may lead to less hyperlipidemia. Moreover, lower prevalence of hyperlipidemia might be one of the reasons why patients suffered ACS later than other regions. However, delayed onset ACS also might bring insufficient treatment due to advanced age.[176]

The results of our study can also be used to evaluate the incorporation of evidence-based therapies into practice and adherence to guidelines.[78, 93, 155, 177] It is striking that, despite the evidence of the benefit of glycoprotein IIb/IIIa antagonists in ACS,[78, 93, 155, 177] they are used in a minority of patients. Even in patients who underwent PCI for STEMI, the rate of use of glycoprotein IIb/IIIa antagonists was as low as 36%. In patients with ACS who did not undergo percutaneous intervention, the rate were even lower, as only 2% of patients with STEMI and 1 out of more than 400 NSTEMI patients received glycoprotein IIb/IIIa antagonists whose benefits have been clearly established in these patients. Furthermore, in patients who had a primary PCI, the delay from admission to PCI was on average nearly 3 hours, a time far exceeding the length of time shown to be either desirable[178] or recommended in guidelines. Likewise, despite the considerable attention given to the use of primary angioplasty in STEMI, it is noteworthy that it remains a relatively rare modality of management of STEMI. Lytic therapy was used in more than 70% of patients who received reperfusion therapy, and, in this registry, streptokinase was the most frequently used lytic agent. However, only 54% of patients with STEMI received any form of reperfusion therapy. These findings suggest that there remains important room for improvement in the care of patients with

STEMI. A more consistent and early provision of reperfusion therapy may ultimately have more impact than the choice between reperfusion modalities or lytic agents.[179] Unfortunately, when compare current treatment pattern in our institute with previous studies, the rates of guideline recommended therapies were lower than those recently published data,[49, 165] but similar with those published more than 5 years ago such as GRACE registry[174] which implicated the guideline-practice gap and significant room for improving treatment and outcomes of patients with ACS.

There were some limitations of this study. First, this is a single center observational study. Regional selection bias and small sample size should be concerned. However, this study took place in a university-affiliated hospital which is one of the largest public hospitals in Hong Kong and may represent current epidemiology and treatment pattern of ACS in this region. Patients were recruited prospectively and consecutively during the analysis period, this would help to minimize the selection bias. Secondly, the study started in 2006 when the latest ACC/AHA guideline for STEMI published in 2004 and for NSTEMI/UA published in 2002, these two guidelines were later revised in 2007. However, our analysis period (Feb 2006 to June 2009) spanned the 2 versions of guidelines. The changing indications for guideline recommendations may have influenced treatment patterns presented in this analysis.

In summary, we described patients' characteristics, treatment and management practices, and hospital outcomes in a Hong Kong population. Our study has provided data for health care providers the opportunity to identify care gaps, potentially

implement changes to the diagnostic and management approach to suspected ACS patients, and measure the impact of such changes on the quality of patient care.

CHAPTER 4.GENDER DIFFERENCES OF MANAGEMENT AND OUTCOME IN ACUTE CORONARY SYNDROME

4.1 Background

Women composed one third of ACS patients, and CAD is the leading killer of women in the developed world.[10] Although CAD related mortality among men has decreased with the development of diagnosis and treatment of ACS during last decade, the death rate among women has continued to rise. Alarmingly, more women than men have died of cardiovascular disease in every year since 1980's.[1] Furthermore, women have higher rates of recurrent MI and age-adjusted mortality after their first MI.[45]

Gender disparity in diagnosis and treatment has been well studied since the phenomenon was first described in 1991 which reported that women were less likely than men to undergo diagnostic coronary angiography and revascularization.[44] Some recent studies have also reported similar gender bias, while some contradicted. Thus, the debate is ongoing.

Some of the gender differences in management of ACS has been attributed to differences in age and comorbidity,[180] while some studies suggested that differences in coronary artery involved could account for some of the difference in selected populations.[47, 181] However, a possible interpretation of the difference in management between men and women might be the controversy of whether women benefited the same from revascularization as men.[30, 74, 182] Furthermore, the fact that women were

more likely to present with high risk features than men may contribute to gender difference in management and outcomes because of under-treatment in high-risk patients.

The AHA/ACC have recently published the updated guidelines for management of STEMI and NSTE-ACS.[78, 92] The recommendations contained in the guidelines are "gender-neutral". Whether the gender differences still exist despite widely disseminated guidelines for the treatment of ACS patients and whether less treatment in women lead to worse outcome, we aimed to investigate these problems in this analysis.

4.2 Methods

Details of methodology were listed in Section II of this thesis, and would be introduced briefly in the following.

4.2.1 Patient Population

Consecutive patients presenting with ACS were prospectively enrolled into the Acute Coronary Syndrome registry from February, 2006 to December, 2009 at a university affiliated hospital.

Acute coronary syndrome encompasses unstable angina, non-ST elevation and ST-elevation myocardial infarction (UA, NSTEMI and STEMI, respectively). The definition and diagnosis criteria were detailed in the Chapter II of methodology.

Demographic, clinical and procedural characteristics were prospectively recorded on case report forms using standardized definitions for all fields. The use of cardiovascular medications, including antithrombotic agents, statins, angiotensin-converting enzyme inhibitors (ACEI) /angiotensin-receptor blockers (ARB), and β-blockers before admission, in hospital, at discharge, at 30 days and 6 months were also recorded.

4.2.2 Statistical analysis

The objective of this analysis was to explore the relations between gender and the use of guideline-recommended therapy, in-hospital as well as 6 months clinical outcomes. All 1001 patients were included in the analyses of patient characteristics, management patterns, and in-hospital outcomes. In determining the frequency of use of each secondary prevention medication, only patients survived hospitalization were included in the analyses of discharge medication (622 men and 338 women).

We reported frequencies for categorical variables and mean ± SD and/or median with IQR when necessary for continuous variables. Continuous variables were compared using Student's t-tests and categorical variables using Fisher's exact or chi-square tests as appropriate. These variables included baseline patient clinical risk factors, including age, family history of coronary artery disease, hypertension, diabetes, smoking status, hypercholesterolemia, previous MI, previous PCI, previous coronary artery bypass grafting, previous congestive heart failure, previous stroke, renal insufficiency, ST-segment depression, transient ST-segment elevation, positive cardiac markers, signs

of congestive heart failure, heart rate, as well as blood pressure at admission. Logistic regression was performed to adjust for differences in patient characteristics.

For all the tests, differences were considered significant at $p<0.05$. All analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA).

4.3 Results

4.3.1 Baseline Characteristics

Among 1001 patients recruited to the cohort, 35.7% was women. Women were older and had more cardiovascular comorbidities including hypertension, smoking, diabetes mellitus, hypercholesterolemia, renal impairment and history of heart failure (Table 4.1). The same proportion of women and men presented without chest pain or discomfort (16% vs. 14%, $p=0.20$). More female patients presented with palpitation (8.7% vs. 4.8%, $p=0.02$) and in Killip classes II/III (37.4% vs. 22.9%, $p<0.001$) compared to men. Furthermore, more women presented with NSTE-ACS, higher GRACE score.

4.3.2 Angiographic Characteristics and Revascularization

The rates of coronary angiography during index admission were significantly lower in women than men (43.3% vs. 62.9%, $p<0.001$). Of those who underwent angiography, the distribution and extent of number of diseased vessel involved were similar between and men. (Table 4.2)

In addition to a lower rate of coronary angiography, women were less likely to undergo subsequent revascularization. Of women presenting with STEMI and NSTE-ACS, 46.9% and 26.4% underwent PCI during hospitalization, respectively. By contrast, 62.7% ($p=0.01$) of men patients with STEMI and 38.7% ($p<0.001$) of men with NSTE-ACS underwent PCI during hospitalization. This trend was still apparent at 6 months after admission (Figure 4.1) and was seen in the group with confirmed MI. However, female gender was no longer an independent factor for not undergoing PCI after adjusting for age and comorbidities.

Table 4.1 Baseline Characteristics

	Male	Female	p value
Number (%)	643	358	
Age	66.6±12.6	75.1±10.2	<0.001
Current smoker	32.4%	4.9%	<0.001
Hypertension	53.3%	73.5%	<0.001
Diabetes mellitus	32.7%	46.1%	<0.001
Hypercholesteremia	33.1%	41.6%	0.007
Previous MI	16.3%	14.8%	0.55
History of Revascularization	18.2%	15.4%	0.26
AF	5.4%	10.1%	0.006
Documented CHF	7.0%	15.4%	<0.001
Renal Impairment	7.2%	15.1%	<0.001
History of CVA	9.5%	14.3%	0.02
Presentation			
UA	23.5%	29.6%	<0.001
NSTEMI	40.0%	48.2%	
STEMI	36.8%	22.7%	
Killip class at admission			
I	73.6%	60.3%	<0.001
II	17.9%	29.3%	
III	5.0%	8.1%	
IV	3.6%	2.2%	
Disease severity			
Creatinine	132±127	133±146	0.87
SBP at admission	141±30	154±33	<0.01
HR at admission	82±21	83±21	0.55
GRACE score	118±37	128±32	<0.01

Table 4.2 Angiographic Characteristics of Patients Underwent Angiography

	Male	Female	p value
Number (%)	412	155	
Non-obstructive disease	3.2%	7.7%	0.63
Coronary arteries involved			0.37
Single vessel	40.5%	36.1%	
Two vessels	27.9%	25.2%	
Three vessels	28.4%	31.0%	
LMS involved	8.0%	9.4%	0.63

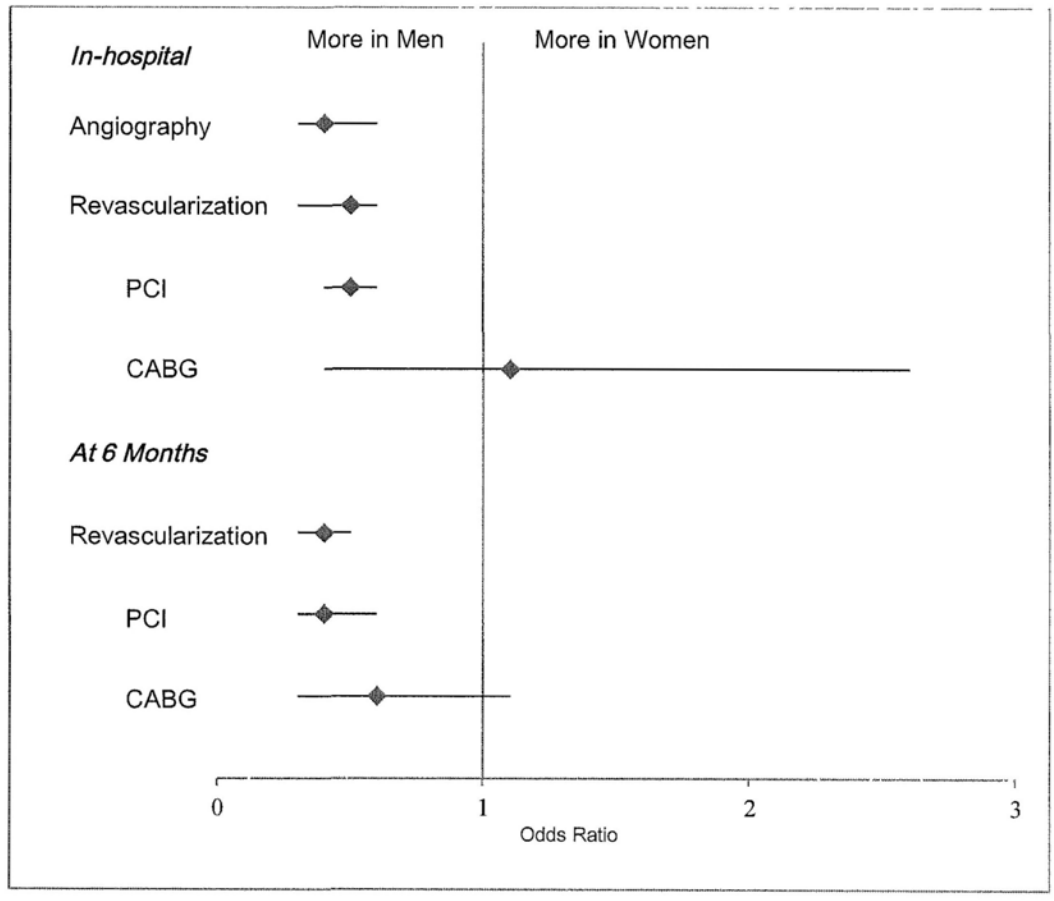


Figure 4.1. Invasive procedures of patients with ACS by gender.

4.3.3 Pharmacological therapy

Treatment disparities were present for women with both acute and discharge medications (Table 4.3). Women were less likely to receive glycoprotein (GP) IIb/IIIa antagonists regardless of troponin results. In addition, women were less likely to initiate statins in hospital than men (69.3% vs. 77.1%, $p<0.01$). Similar treatment patterns existed for discharge medication use where fewer women than men were prescribed clopidogrel and statins. (Table 4.3) Furthermore, the disparity in treatment pattern extended to 6 months after admission. However, after adjustment for age and comorbidities, treatment patterns were similar between women and men.

We further explored the relationship between gender and treatment in stratifications of each 10 years of age, most of differences in treatment between genders were no longer significant in same age stratum (Table 4.3).

In subgroup analysis, treatment patterns were compared between men and women presented as STEMI, NSTE-ACS at high- and low-risk (Table 4.4). Women patients with STEMI or low-risk NSTE-ACS were less often referred for angiography (55.6% vs. 75%, $p<0.001$ for STEMI, 31.5% vs. 43.6%, $p=0.005$ for low-risk NSTE-ACS respectively). Similarly, these differences could be adjusted by age and co-morbidities.

Table 4.3 Procedures and Treatments according to Age groups

	All Patients			<60			60-69			70-79			≥80		
	Male	**Female**	**p**	**Male**	**Female**	**p**	**Male**	**Female**	**p**	**Male**	**Female**	**p**	**Male**	**Female**	**p**
Number (%)	643	358		196	32		144	57		201	130		102	139	
LMWH	63.9%	75.1%	<0.001	60.2%	75.0%	0.11	58.3%	71.9%	0.07	66.7%	73.8%	0.17	73.5%	77.7%	0.45
GP IIb/IIIa	11.6%	5.3%	0.001	15.4%	9.4%	0.37	16.0%	7.0%	0.09	9.0%	6.9%	0.50	3.0%	2.2%	0.69
Aspirin	80.6%	89.1%	<0.001	82.1%	87.5%	0.46	81.9%	91.2%	0.10	79.1%	89.2%	0.02	78.4%	88.5%	0.03
Clopidogrel	58.8%	41.1%	<0.001	77.0%	71.9%	0.52	74.1%	77.2%	0.65	51.5%	40.8%	0.06	16.7%	19.4%	0.58
Statins	60.9%	59.8%	0.73	65.5%	70.0%	0.63	66.9%	75.4%	0.24	58.4%	62.5%	0.46	48.5%	48.6%	1.00
Angiography	62.8%	43.3%	<0.001	81.1%	81.3%	0.98	77.8%	82.5%	0.46	57.7%	46.9%	0.06	16.7%	15.1%	0.74
Revascularization in index admission															
PCI	47.4%	31.3%	<0.001	62.8%	59.4%	0.71	61.1%	63.2%	0.79	40.3%	33.8%	0.24	12.7%	9.4%	0.40
CABG	2.2%	2.2%	0.95	3.6%	3.1%	0.90	2.1%	1.8%	0.88	1.5%	3.1%	0.33	1.0%	1.4%	0.75
Revascularization within 6 months															
PCI	51.8%	32.7%	<0.001	67.9%	59.4%	0.35	69.4%	66.7%	0.70	42.3%	36.2%	0.27	14.7%	9.4%	0.20
CABG	7.3%	4.7%	0.11	9.7%	9.4%	0.95	11.1%	10.5%	0.90	5.0%	4.6%	0.88	2.0%	1.4%	0.75
Discharge Medication															
Aspirin	96.6%	94.7%	0.14	96.4%	96.9%	0.89	97.9%	96.5%	0.57	95.4%	94.4%	0.67	97.8%	93.5%	0.15
Clopidogrel	55.6%	35.0%	<0.001	71.6%	62.5%	0.30	71.5%	58.9%	0.09	46.6%	33.9%	0.02	15.9%	18.0%	0.69
ACEI/ARB	57.1%	53.8%	0.34	52.8%	46.9%	0.53	59.2%	61.4%	0.77	62.8%	55.6%	0.21	50.6%	50.4%	0.98
β-blockers	65.6%	66.3%	0.83	68.2%	75.0%	0.44	69.0%	71.9%	0.69	64.8%	68.5%	0.49	56.2%	59.2%	0.66
CCB	10.6%	21.0%	<0.001	6.7%	12.5%	0.25	11.3%	19.3%	0.13	10.7%	24.2%	0.00	18.0%	20.8%	0.61
Statins	77.1%	69.3%	0.009	80.0%	83.9%	0.61	87.0%	78.9%	0.16	73.8%	75.6%	0.72	62.1%	54.5%	0.28

Table 4.4 Procedures and Treatments according to Presentation of ACS

	All Patients			STEMI			NSTE-ACS High risk			NSTE-ACS Low risk		
	Male	**Female**	**p**	**Male**	**Female**	**p**	**Male**	**Female**	**p**	**Male**	**Female**	**p**
Number (%)	643	358		236	81		77	74		330	203	
LMWH	63.9%	75.1%	<0.001	45.3%	59.3%	0.03	67.5%	77.0%	0.19	76.4%	80.8%	0.23
GP IIb/IIIa	11.6%	5.3%	0.001	24.2%	14.8%	0.08	4.0%	1.4%	0.32	4.3%	3.0%	0.44
Aspirin	80.6%	89.1%	<0.001	72.9%	82.7%	0.08	79.2%	87.8%	0.15	86.4%	92.1%	0.04
Clopidogrel	58.8%	41.1%	<0.001	71.5%	58.0%	0.03	23.4%	12.2%	0.07	58.1%	44.8%	0.003
Statins	60.9%	59.8%	0.73	63.8%	62.5%	0.83	37.3%	41.9%	0.57	64.2%	65.3%	0.79
Angiography	62.8%	43.3%	<0.001	75.0%	55.6%	0.001	31.2%	18.9%	0.08	61.5%	47.3%	0.001
Revascularization in index admission												
PCI	47.4%	31.3%	<0.001	62.7%	46.9%	0.01	16.9%	13.5%	0.56	43.6%	31.5%	0.005
CABG	2.2%	2.2%	0.95	1.7%	1.2%	0.770	0%	4.1%	0.07	3.0%	2.0%	0.46
Revascularization within 6 months												
PCI	51.8%	32.7%	<0.001	66.5%	48.1%	0.003	20.8%	13.5%	0.24	48.5%	33.5%	0.001
CABG	7.3%	4.7%	0.11	5.9%	1.2%	0.09	1.3%	4.1%	0.29	9.7%	6.4%	0.18
Discharge Medication												
Aspirin	96.6%	94.7%	0.14	97.8%	98.6%	0.67	93.9%	88.1%	0.24	96.4%	95.5%	0.62
Clopidogrel	55.6%	35.0%	<0.001	69.3%	54.9%	0.03	18.5%	18.2%	0.97	53.5%	33.5%	<0.001
ACEI/ARB	57.1%	53.8%	0.34	60.6%	56.9%	0.58	53.0%	40.3%	0.14	55.5%	57.3%	0.68
β-blockers	65.6%	66.3%	0.83	59.3%	66.7%	0.26	56.1%	58.2%	0.80	71.8%	68.8%	0.47
CCB	10.6%	21.0%	<0.001	3.1%	8.3%	0.06	18.2%	23.9%	0.42	14.2%	24.6%	0.003
Statins	77.1%	69.3%	0.009	80.3%	75.7%	0.41	57.1%	47.0%	0.25	78.8%	74.5%	0.26

4.3.4 Clinical outcomes

In-hospital mortality rates were 5.6% for women and 3.3% for men (p=0.08). Unadjusted in-hospital mortality was higher in women with NSTE-ACS than in men patients (4.0% vs. 2.7%, p=0.36), while 11.1% in women and 4.2% in men with STEMI (p=0.03). Mortality among patients who underwent PCI were comparable between women and men (0.9% vs. 0.7%, p=0.8) (Figure4.2). However, after adjustments for all differences between women and men by multivariable analysis, female gender was no longer significantly associated with greater in-hospital mortality (OR: 1.32, 95% CI: 0.62-2.83, p=0.47).

At 6 months, all-cause death rates were still higher in women compared to men (Figure 4.2). Major adverse cardiac events (reinfarction, stroke and death) occurred in 18.2% of women patients and in 13.5% of men (p=0.05). Reinfarction occurred in 5.3% of women and 5.0% of men (p=0.82) and stroke in 1.0% women and 0.8% men (p=0.71). The differences in mid-term mortality and the occurrence of major cardiac events in women were not significant once adjusted for differences in clinical characteristics and PCI (OR=1.02; 95% CI 0.62 to 1.68; p=0.95). Table 4.5 listed the predictors of 6 months upon admission, female gender was not associated with worse outcome after multivariate adjustment.

Figure 4.2. In-hospital and 6 months outcome of patients with acute coronary syndrome by gender.

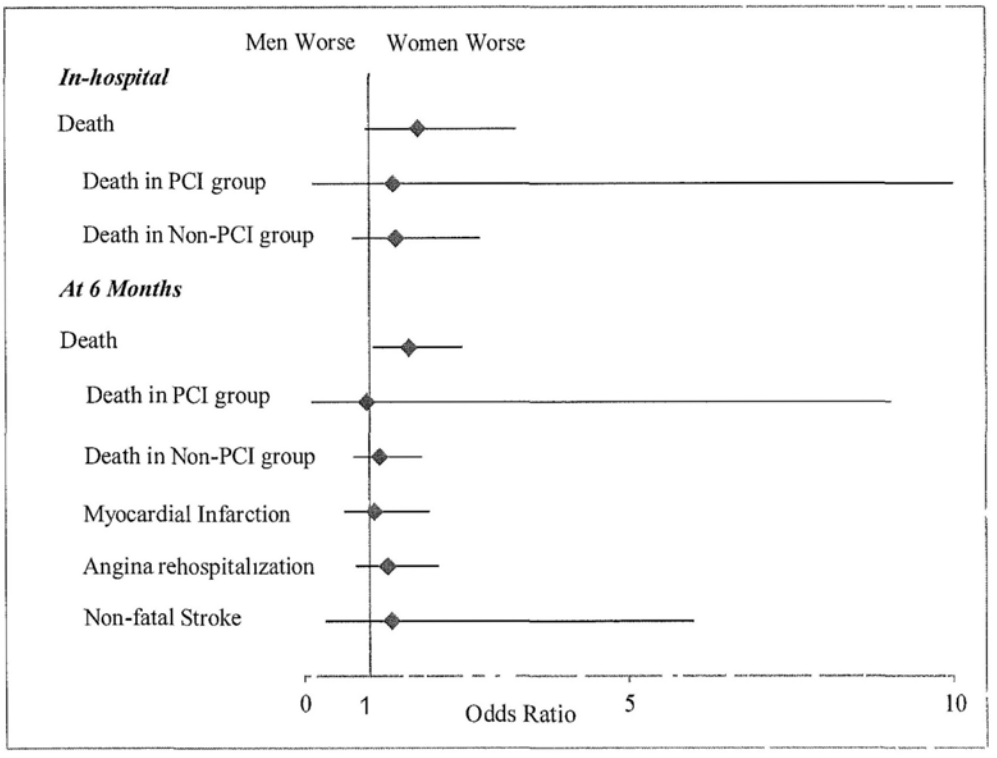


Table 4.4 Predictor of in-hospital mortality upon admission by multivariable analysis

Predictor	Odds ratio (95% CI)	p Value
Age (for each additional year)	1.07(1.02-1.12)	<0.001
Systolic Blood Pressure (per 10mmHg increasing)	0.87(0.77-0.98)	0.03
Killip III/IV	1.83(1.30-2.58)	0.001
ST Elevation	2.44(1.13-5.28)	0.02
PCI in hospital	0.23(0.06-0.88)	0.03
Statin in hospital	0.43(0.20-0.93)	0.03
Female	1.32(0.62-2.83)	0.47

Table 4.5 Predictors of 6 months mortality upon admission by multivariable analysis.

Predictor	Odds ratio (95% CI)	p Value
Age (for each additional year)	1.05(1.02-1.08)	<0.001
Renal Impairment	1.88(1.03-3.41)	0.04
Sign of CHF	1.79(1.09-2.98)	0.02
PCI	0.10(0.04-0.30)	<0.001
Female	1.02(0.62-1.68)	0.95

4.4 Discussion

Our finding suggested that there were not only differences in baseline characteristics between men and women admitted for ACS in Hong Kong between 2006-2009 but also in their management, from acute management such as reperfusion therapy to PCI and secondary prevention prescriptions. Our data also showed that, PCI has become the preferred treatment in both STEMI and NSTE-ACS patients in women as well as in men. Although performed less often than in men, women benefited similarly from PCI and it was associated with lower in-hospital mortality in the whole spectrum of ACS. Indeed, the unadjusted in-hospital mortality of women with STEMI was 11.1% and of women with NSTE-ACS 4.0%, which was lower than the in-hospital mortality for both genders in the National registry of Myocardial Infarction 4[183] (14.3% for STE-ACS and 12.5% in NSTE-ACS).

Our results confirm previous studies, which showed that women with ACS are treated less aggressively than men,[184] despite women with AMI may have similar or even better outcomes after PCI.[185, 186] Hvelplund et al reported that despite presenting with higher risk characteristics and having a higher in-hospital risk, women with ACS were less invasively examined and treated than men.[65] Heer et al observed similar results in Europe for AMI that women were less referred to angiography and revascularization as well as received secondary prevention medications such as aspirin, β-blockers and statins.[187, 188] Data from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse outcomes With early Implementation of the American college of Cardiology/American Heart Association Guidelines (CRUSADE) registry had shown similar findings in NSTE-ACS patients.[47, 110]

The reason why female patients were undertreated remained unclear. Some studies reported the gender disparity in treatment could be adjusted by age and co-morbidities which were not balanced between genders;[180] women patients were usually older and with more comorbidities than men, thus the difference of treatment between genders was actually the difference between elderly and younger patients or high- and low-risk patients. In the ACS registry from Denmark which found the gender disparity in invasive treatment could not be adjusted by age and co-morbidities,[65] the author tried to explain the difference with possible different in data not collected in that study, such as different symptom presentation in women and a high proportion of ST-elevation MI in men. Moreover, other study explained the gender difference in treatment as due to physician bias: Anand et al. performed a post-hoc analysis of gender differences in the management and outcomes of patients with ACS from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial and found that the probability of a woman being referred for angiography was unrelated to her TIMI score,[66] that is, high-risk women were not more likely to be referred to angiography than low-risk women. The authors concluded that the disparity in treatment of women with ACS derived not from differences in the disease itself but rather from physician decisions unrelated to risk assessment. In our study, differences between genders were diminished after adjusting for age and comorbidities. Possible interpretations of these results might be twofold. Firstly, after 2 decades of study on gender disparity in management and outcome in ACS, increasing awareness of impact of gender on decision making may have led to the narrowing of the gap between genders. Secondly, increasing use of risk score models in clinical decision making in ACS management may negate physician bias against the female gender.

Studies comparing outcomes of men and women with ACS have provided conflicting results and unconvincing explanations. Unadjusted mortality after ACS reported in some studies was higher in women than men,[69, 70, 189] women have less favorable short-term outcomes after revascularization procedures[69] and are at increased risk of adverse outcomes.[19, 71-73] In some studies, long-term but not short-term mortality was higher for women patients who underwent primary angioplasry[190], while in other studies female gender was a risk factor for in-hospital mortality after PCI, mainly because of a higher rate of non-cardiac death.[191] The TACTICS TIMI-18 trial showed a clear benefit of an early invasive approach in NSTE-ACS regardless of gender,[30] whereas in FRISC II and in RITA 3, the benefits of such an approach were seen only in men.[74, 182] More recently, it has been suggested that the difference in outcome between women and men treated with PCI had decreased and that the outcome in women had improved.[76-78] Authors from the CADILLAC trial suggested that the higher mortality seen in women compared with men after interventional treatment for AMI might be explained by differences in body size and clinical risk factors.[79] However, smaller target vessel size in women is associated with an increased risk of restenosis, but does not appear to be a predictor for mortality.[73] Nevertheless, basic biological differences in response to AMI between men and women have also been advocated[72, 80] in addition to anatomical differences.[50] Overall, our study showed similar outcomes in-hospital and at 6 months for men and women after adjusting for age and clinical characteristics, treatments such as reperfusion and PCI were included in the model.

Our study has some limitations common to registry studies. First, this is a single-center observational study, the design may limit the generalization of our data. Second, in the logistic regression analyses, the burden of comorbidity was limited to

cardiovascular related diseases such as history of coronary artery disease, hypertension, dyslipidaemia, diabetes, renal impairment and stroke. Although there were no significant gender differences in the proportion of COPD (3.6% in female vs. 5.4% in male, $p>0.05$) in the whole dataset, other factors such as neoplasm which might have impact on the outcomes were not available in the dataset. Moreover, no summary variable reflecting comorbidities was available for all patients in the dataset. Finally, our study concentrated on in-hospital and mid-term mortality; there are no long-term follow-up data available for further comparison of outcomes.

In summary, this study showed that there were differences in baseline characteristics and in the management of women and men admitted for ACS. In particular, PCI was performed less often in women than in men. Advanced age could explain most of the difference between genders suggesting that decision making bias in clinical practice is anti-age but not anti-female. Overall, in-hospital and 6 months mortality was similar for women and men after adjustments.

CHAPTER 5.RISK-TREATMENT PARADOX IN ACUTE CORONARY SYNDROME

5.1 Introduction

Acute coronary syndrome (ACS) remains a major cause of morbidity and mortality despite tremendous advancement in therapy over the last 3 decades. Current therapeutic guidelines recommend prompt reperfusion therapy for ST elevation myocardial infarction (STEMI) and the treatment strategy for non-ST elevation (NSTE) ACS consists of risk stratification and decision between early conservative medical management with antiplatelet and anticoagulation therapy versus early invasive revascularization therapy. Angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), β-blockers and statin therapy should be initiated for most patients during index hospital admission in the absence of contraindications.[78, 93, 155, 177] Given the proven mortality benefits of these therapies, it is important to ensure that all ACS patients, especially those at high-risk of death, receive evidence-based therapies.[89, 96, 192]

Recent reports have shown a paradoxical relationship where patients at the highest risk of mortality were least likely to receive evidence-based therapies.[112, 193] However, there is paucity of data investigating the reasons underlying this paradox and how individual risk factors might contribute to decision-making for the use of the guideline recommended therapies.

The aim of this study was to assess adherence to guideline recommended therapies according to risk stratification in the management of ACS and to explore factors associated with the use of guideline recommendations.

5.2 Method

The study population, inclusion/exclusion criteria and other details of method were introduced in the section of Methodology. The following described specific methods associated with analysis in this chapter.

5.2.1 Risk evaluation

The GRACE score, a risk-evaluation tool developed on data from more than 70,000 patients in a prospective, multi-center registry of acute coronary events, was calculated from the initial clinical history, electrocardiogram and laboratory values collected on admission according to the model predicting mortality at 6 months.[27, 28] A calculator of the score released at the website of the GRACE project was used to calculate each patient's score. (The calculator is available at http://www.outcomes-umassmed.org/GRACE/).

5.2.2 Statistical analysis

Continuous variables with a normal distribution were expressed as mean value and standard deviation, otherwise expressed as median and inter-quartile range.

Normality was tested using the Shapiro-Wilks test. Discrete variables were expressed as frequencies and percentage values.

ROC curve was used to relate the predicted mortality at 6 months calculated by GRACE model to the actual rate of death at 6 months. The C-statistic, or area under the curve (AUC), was used as a measurement of the predictive accuracy of the GRACE risk score. The cut-off point identified with the ROC curve was used to separate the studied population into low- and high-risk patients.

Statistical comparisons of baseline characteristics, investigations and procedures during hospitalization, medications and outcomes according to predicted baseline risk of death were performed using the χ^2 test or the Fisher's exact test for categorical variables, and the two-tailed Student's ***t***-test for continuous variables. Logistic regression models were built to investigate factors associated with use of treatment

Further analysis was performed between STEMI and NSTE-ACS patients because of differences in therapeutic decision making between the two groups. We also performed subgroup analysis between patients ≥75 vs. <75 because age is a well established predictor for less aggressive therapy.[194-196] Treatment patterns were examined according to risk for patients with STEMI vs. NSTE-ACS and ≥75 vs. <75 years of age as well. Acute reperfusion therapies including thrombolysis and primary percutaneous coronary intervention (PCI) (defined as PCI within 12 hours of symptom onset of acute myocardial infarction) were only examined in patients presented with STEMI.

Sensitivity analyses were performed to further explore the risk-treatment association in selected patients eligible for prescription of anti-platelets, ACEI/ARBs,

β-blockers and statins. For example, we expected that increased serum creatinine level (≥176.8 μmol/L [2.0 mg/dL]) might influence prescription of ACEI/ARBs; therefore, treatment rates were re-examined in patients with peak creatinine during hospitalization <176.8 μmol/L (<2.0 mg/dL). Similarly, of the use of β-blockers were examined in patients without bradycardia (heart rate >60/min), any degree of atrio-ventricular block during hospital stay and without chronic obstructive pulmonary disease or asthma. For statins, we examined those patients without chronic or acute liver disease and alanine transaminase (ALT) <40 IU/L during the hospital stay.

For all comparisons, two-tailed tests of significance were reported and p value <0.05 was considered statistically significant. Statistical analysis was performed with SPSS version 17.0 (SPSS Inc., Illinois, Chicago, IL, USA).

5.3 Results

5.3.1 Patients

A total of 1,001 patients were recruited in the ACS Registry from February 2006 to June 2009. Among patients enrolled, 317 (31.7%) presented with STEMI, 428 (42.8%), NSTEMI and 256 (25.6%) unstable angina. The mean age was 69.7±12.5 years, 412 (41.2%) patients were ≥75 years, and 358 (35.8%) were women. Overall, 960 patients (95.9%) survived at discharge and 13 (1.3%) died within 30 days after discharge, thus 960 and 947 patients were eligible for the analyses of prescription rates of guideline recommended drugs at discharge and 30 days, respectively.

5.3.2 GRACE Risk-Score

The mean GRACE risk-score for the entire ACS population was 120.5±35.3. The discriminatory accuracy of the GRACE risk-score to predict death at 6-months in the analytic cohort was good (AUC=0.80; 95% confidence interval [CI]: 0.75-0.84; p<0.001). Patients were divided into high-risk and low-risk groups according to the cut-off point of GRACE risk-score at 142.5 points identified on the ROC curve.

Patients with high GRACE risk-score were more likely to be older, male, had lower hemoglobin level and higher rates of cardiovascular comorbidities such as hypercholesterolemia, history of stroke and heart failure (Table 5.1).

5.3.3 Management

Overall, 55.8% of patients underwent angiography and 43.8% underwent PCI or CABG during hospitalization. Rates of angiography and revascularization were paradoxically lower for patients with a high GRACE risk-score (33% vs. 64% and 23% vs. 48%, respectively, both p<0.001) compared to low-risk group. Similarly, the likelihood of a patient to be prescribed guideline recommended pharmacotherapy such as clopidogrel and statins during index hospitalization was inversely related to the patient's risk score. (Figure 5.1A)

Among patients who survived hospitalization, the trend of low prescription rates of guideline recommended therapies in high-risk patients remained at discharge (Figure 1B) and 30 days follow-up (Figure 1C). Moreover, prescription rates of

statins in high-risk patients were consistently lower during index hospitalization (47% vs. 65%, p<0.001), at discharge (56% vs. 77%, p<0.001) and 30-days post-discharge (57% vs. 76%, p<0.001), compared to low-risk patients. However, there was no longer differences at 6-months follow-up (81% vs. 85%, p=0.20).

In sensitivity analysis, prescription rates of ACEI/ARBs, β-blockers and statins at hospital discharge and 30 days after discharge were examined for patients eligible for these drugs and without contraindications according to current guidelines. A risk-treatment paradox was present in a broad range of ACEI/ARBs, β-blockers and statins. Inclusion of patients died in hospital (and their treatments at the time of death) in the analysis also yielded the similar results.

5.3.4 Clinical Outcomes

The rate of in-hospital death the whole cohort was consistent with the predicted mortality derived from GRACE risk model (12.9% observed vs. 9.4% predicted death rate). Figure 5.1D shows the relationship between patients' baseline risk status and the observed rates of death at discharge, 6-month mortality and rates of MI and non-fatal stroke at 6 months.

Absence of PCI was related to worse clincal outcome. Mortality in patients underwent PCI was significantly lower than those treated conservatively in all patinets expect those at lowest risk with GRACE score <100 (Figure 5.2).

5.3.5 Subgroup Analysis

5.3.5.1 STEMI vs. NSTE-ACS

Among patients recruited, 34% of them presented with STEMI, and 22% with NSTE-ACS (Table 5.2). High-risk STEMI patients were less likely to undergo thrombolysis or primary PCI, and were less likely to receive coronary angiography and elective PCI during hospitalization compared to low-risk patients (Table 5.4). Prescription rates of aspirin ACEI/ARBs, β-blockers and statins were also lower in high-risk STEMI patients.

5.3.5.2 Advanced age

Patients aged ≥75 years had higher rates of death during hospitalization and at 6-month compared with patients <75 years of age. In both older and younger age groups, patients with high-risk of mortality had more comorbidities such as renal dysfunction and anemia (Table 5.5).

Guideline recommended medications (except for aspirin) were used less commonly in high-risk patients compared with low-risk patients in both age groups. In group ≥75 years, high-risk patients were less likely to undergo invasive cardiac procedures than lower-risk patients in same age group. Whereas in patients <75 years of age, the rates of angiography and revascularization was not related to risk status (Table 5.4).

5.3.6 Independent Predictors of Guideline Recommended Therapies by Multivariable Analysis

Age was not associated with prescription rates of aspirin (p=0.41) and ACEI/ARBs (p=0.93) at discharge. While increasing age has decreased the likelihood of receiving β-blockers (odds ratio [OR], 0.88; 95% CI, 0.78-0.98; p=0.02, per decade of age) and statins (OR: 0.67; 95% CI, 0.59-0.77; p<0.001, per decade of age) at discharge. Female patients were less often prescribed statin therapy (OR: 0.67; 95% CI, 0.50-0.91; p<0.01).

Adjusting for patient age, sex, and presentation of ACS (STEMI/NSTE-ACS), OR for PCI was 0.47 (95% CI, 0.33-0.73; p<0.01) in high-risk groups compared to low-risk patients. ACEI/ARBs, β-blockers and statins were less likely to be prescribed at discharge in high-risk patients, with adjusted ORs of 0.57 (95% CI, 0.40-0.81; p<0.01), 0.59 (95% CI, 0.41-0.84; p<0.01) and 0.47 (95% CI, 0.32-0.68; p<0.01) respectively, relative to the high-risk group.

STEMI (OR, 2.24 ; 95% CI, 1.61-3.12; p<0.01) was an independent predictor of PCI whereas advanced age (OR, 0.52 ; 95% CI, 0.46-0.60, per decade of age; p<0.001), history of stroke (OR, 0.48 ; 95% CI, 0.28-0.82; p<0.01) and higher initial creatinine level (OR, 0.87 ; 95% CI, 0.76-0.99, per 100 μmol/L [1.13mg/dl]; p=0.04) were factors against PCI. STEMI, higher systolic blood pressure on admission, history of diabetes and increasing peak creatinine during hospitalization were independent predictors of ACEI/ARBs prescription (Table 5.6). Predictors against use of β-blockers included lower heart rate, lower systolic blood pressure, signs of heart failure at presentation and history of hypertension; while advanced age, higher

ALT level, absence of documented hypercholesterolemia and conservative management during hospitalization predicted against use of statins.

Table 5.1. Baseline Characteristics According to GRACE Score Prediction of 6 month mortality.

Characteristics	High-Risk (n=259)	Low-Risk (n=742)	p value
Age (years)	79±8	66±12	<0.001
Female	231 (33%)	116 (46%)	<0.001
Presentation variables			
Systolic Blood Pressure (mmHg)	131±33	151±29	<0.001
Heart Rate (beats/min)	92±48	79±19	<0.001
Creatinine (μmol/L)	177±174	115±108	<0.001
Hemoglobin (g/L)	12±2	13±2	<0.001
Co-morbid conditions			
History of Revascularization	136 (20%)	24 (10%)	<0.001
Previous Myocardial Infarction	95 (14%)	47 (19%)	0.07
Diabetes Mellitus	259 (37%)	100 (40%)	0.49
Hypertension	414 (59%)	164 (65%)	0.12
Hypercholesterolemia*	274 (39%)	67 (26%)	<0.001
Prior history of stroke	68 (10%)	39 (15%)	0.014
Documented CHF	53 (8%)	43 (17%)	<0.001
GRACE score for 6 month mortality	165±21	105±24	<0.001

GRACE: Global registry of acute coronary events; CHF: congestive heart failure.

Table 5.2. Baseline Characteristics According to Risk Status and Presentation of Acute Coronary Syndrome.

	STEMI			NSTEACS		
	High-Risk (n=109)	**Low-Risk (n=208)**	**p value**	**High-Risk (n=151)**	**Low-Risk (n=533)**	**p value**
Age (years)	78.3±7.9	61.1±12.0	<0.001	80.2±7.9	68.3±11.4	<0.001
Female	44(40%)	37(18%)	<0.001	74(49%)	203(38%)	0.02
Presentation variables						
Systolic BP (mmHg)	123.9±31.8	139.8±25.9	<0.001	136.2±33.5	154.6±30.0	<0.001
Heart Rate (beats/min)	83.6±24.6	77.9±19.6	<0.001	98.1±58.1	80.4±19.2	<0.001
Creatinine (μmol/L)	133.1±70.7	106.5±109.6	0.04	207.2±212.9	123.2±130.2	<0.001
Hemoglobin (g/L)	12.7±1.9	14.2±1.7	0.01	11.4±2.3	13.1±2.0	<0.001
Killip class	-	-	<0.001	-	-	<0.001
I	45(41%)	184(88%)		36(24%)	424(80%)	
II	37(34%)	17(8%)		71(47%)	95(18%)	
III	12(11%)	4(2%)		33(22%)	12(2%)	
IV	15(14%)	3(1%)		11(7%)	2(0%)	
Positive Troponin at initial	83(81%)	105(56%)	<0.001	105(71%)	193(37%)	<0.001
Comorbid conditions						
Smoke	-	-	<0.001	-	-	0.03
Never	65(60%)	74(36%)		98(65%)	310(58%)	
Former	21(19%)	51(25%)		39(26%)	126(24%)	
Current	23(21%)	83(40%)		14(9%)	97(18%)	
History of Revascularization	6(6%)	16(8%)	0.47	20(13%)	130(24%)	0.003
CABG	0	1		3	30	
PCI	6	14		17	97	
Previous Myocardial Infarction	13(13%)	15(8%)	0.16	35(23%)	83(17%)	0.08
Diabetes Mellitus	39(36%)	62(30%)	0.28	64(42%)	210(39%)	0.51
Hypertension	67(61%)	104(50%)	0.05	104(69%)	331(62%)	0.13
Hypercholesteremia*	65(60%)	151(73%)	0.02	63(42%)	344(65%)	<0.001
Prior history of CVA	12(11%)	11(5%)	0.06	28(19%)	61(11%)	0.02
Documented CHF	4(4%)	3(1%)	0.20	40(26%)	53(10%)	<0.001
GRACE score for 6M mortality	168.1±23.0	107.9±22.2	<0.001	163.2±19.4	103.6±24.6	<0.001

Table 5.3. Baseline Characteristics According to Risk Status and Age Group.

	≥75			<75		
	High-Risk (n=195)	**Low-Risk (n=217)**	**p value**	**High-Risk (n=65)**	**Low-Risk (n=524)**	**p value**
Female	98(50%)	118(54%)	0 40	20(31%)	122(23%)	0 183
Presentation variables						
Systolic BP (mmHg)	133 9±32 7	159 8±27 6	<0 001	122 4±34 0	146 5±29 6	<0 001
Heart Rate (beats/min)	91 6±52 3	79 7±19 0	<0 001	93 3±29 2	79 7±19 4	<0 001
Creatinine (μmol/L)	166 7±149 2	118 4±61 7	0 003	204 4±227 2	118 6±143 2	<0 001
Hemoglobin (g/L)	11 7±2 2	12 4±1 8	<0 001	12 7±2 2	13 8±1 9	0 004
Killip class	-	-	<0 001	-	-	<0 001
I	64(33%)	163(75%)		17(26%)	445(85%)	
II	85(44%)	48(22%)		23(35%)	64(12%)	
III	32(16%)	6(3%)		13(20%)	10(2%)	
IV	14(7%)	0(0%)		12(18%)	5(1%)	
Positive Troponin at initial	142(74%)	72(34%)	<0 001	46(77%)	226(45%)	<0 001
Presentation of ACS	-	-	<0 001	-	-	0 001
Unstable Angina	31(16%)	87(40%)		4(6%)	134(26%)	
NSTEMI	88(45%)	99(46%)		28(43%)	213(41%)	
STEMI	76(39%)	31(14%)		33(51%)	177(34%)	
Comorbid conditions						
Smoker	-	-	0 64	-	-	0 12
Never	125(64%)	147(68%)		38(58%)	237(45%)	
Former	46(24%)	43(20%)		14(22%)	134(26%)	
Current	24(12%)	27(12%)		13(20%)	153(29%)	
Prior Revascularization	16(8%)	48(22%)	<0 001	10(15%)	98(19%)	0 51
CABG	3	12		0	19	
PCI	13	33		10	78	
Previous MI	33(18%)	38(18%)	0 89	15(24%)	60(13%)	0 02
Diabetes Mellitus	73(37%)	88(41%)	0 52	30(46%)	184(35%)	0 08
Hypertension	134(69%)	156(72%)	0 48	37(57%)	279(53%)	0 57
Hypercholesteremia	43(22%)	75(35%)	0 005	26(40%)	218(42%)	0 81
Prior history of CVA	85(44%)	125(58%)	0 004	43(66%)	370(71%)	0 46
Documented CHF	33(17%)	40(18%)	0 71	7(11%)	32(6%)	0 15
GRACE score for 6 months mortality	37(19%)	35(16%)	0 45	7(11%)	21(4%)	0 02

Table 5.4. In-hospital and discharge management of patients with STEMI and NSTE-ACS according to risk status.

	STEMI			NSTE-ACS		
	High-Risk	**Low-Risk**	**p value**	**High-Risk**	**Low-Risk**	**p value**
No. of patients (n)	109	208		150	534	
Acute Reperfusion (%)						
Thrombolysis	22 (20%)	101 (49%)	<0.001	-	-	
Primary PCI	8 (7%)	40 (19%)	0.01	-	-	
Investigations and procedures during hospitalization (%)						
Angiography	48 (44%)	174 (84%)	<0.001	38 (25%)	299 (56%)	<0.001
PCI	36 (33%)	149 (72%)	<0.001	23 (15%)	208 (39%)	<0.001
CABG	1 (1%)	4 (2%)	0.49	3 (2%)	14 (3%)	0.67
Acute Therapy (%)						
Aspirin	83 (76%)	156 (75%)	0.82	126 (83%)	472 (89%)	0.09
Clopidogrel	47 (43%)	168 (81%)	<0.001	27 (18%)	282 (53%)	<0.001
LMWH	71 (65%)	80 (38%)	<0.001	108 (72%)	412 (77%)	0.14
GPIIb/IIIa	16 (15%)	53 (25%)	0.03	4 (3%)	20 (4%)	0.53
Statin	61 (56%)	139 (67%)	0.06	59 (40%)	338 (65%)	<0.001
Medication at discharge (%)						
Aspirin	91 (99%)	200 (98%)	0.44	120 (91%)	508 (96%)	0.02
ACEI/ARB	50 (54%)	128 (62%)	0.16	61 (46%)	298 (56%)	0.04
β-blockers	46 (49%)	136 (66%)	<0.01	76 (58%)	374 (71%)	<0.01
Statins	60 (67%)	172 (85%)	<0.001	67 (52%)	394 (77%)	<0.001
Observed Mortality at 6 Month (%)	24 (23%)	7 (4%)	<0.001	40 (28%)	21 (4%)	<0.001

Table 5.5. In-hospital management of patients ≥75 and <75 years of age according to risk status.

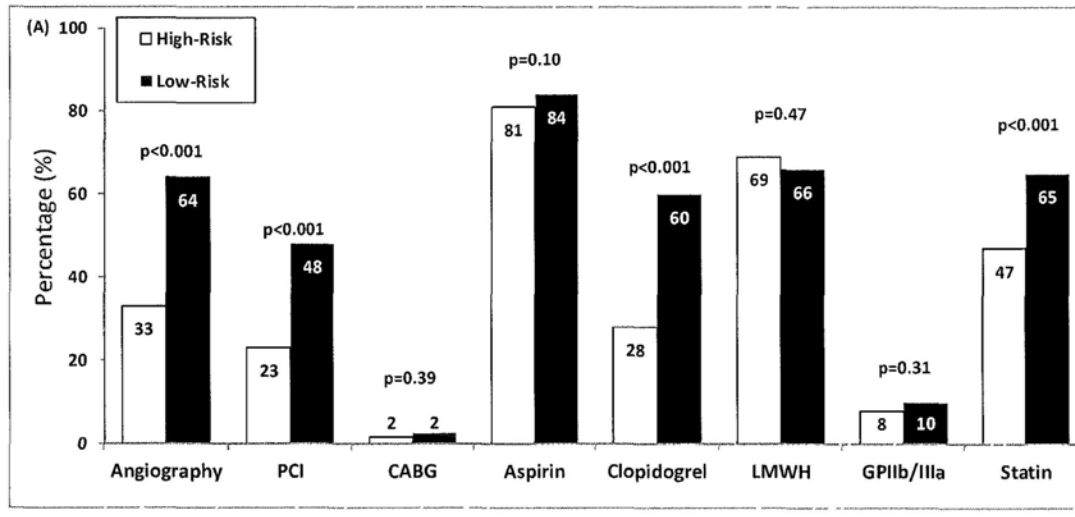
	≥75			<75		
	High-Risk	**Low-Risk**	**p value**	**High-Risk**	**Low-Risk**	**p value**
No. of patients (n)	194	218		65	524	
Investigations and procedures during hospitalization (%)						
Angiography	39 (20%)	79 (36%)	<0.001	47 (72%)	394 (75%)	0.61
PCI	26 (13%)	55 (25%)	0.002	33 (51%)	302 (58%)	0.29
CABG	3 (2%)	3 (1%)	0.89	1 (2%)	15 (3%)	0.54
Acute Therapy (%)						
Aspirin	158 (81%)	189 (87%)	0.09	51 (78%)	439 (84%)	0.28
Clopidogrel	36 (18%)	74 (34%)	<0.001	38 (58%)	376 (72%)	0.03
LMWH	140 (72%)	157 (72%)	0.90	39 (60%)	335 (64%)	0.54
GPIIb/IIIa	12 (6%)	12 (6%)	0.78	8 (13%)	61 (12%)	0.85
Statin	85 (44%)	129 (60%)	0.001	35 (56%)	348 (68%)	0.06
Medication at discharge (%)						
Aspirin	153 (94%)	202 (95%)	0.69	59 (95%)	505 (97%)	0.40
ACEI/ARB	77 (47%)	128 (60%)	0.01	35 (56%)	297 (57%)	0.93
β-blockers	88 (54%)	141 (66%)	0.01	34 (55%)	369 (71%)	0.01
Statins	87 (55%)	146 (71%)	0.002	40 (66%)	421 (83%)	0.001
Observed Mortality at 6 Month (%)	57 (31%)	14 (7%)	<0.001	7 (11%)	14 (3%)	0.001

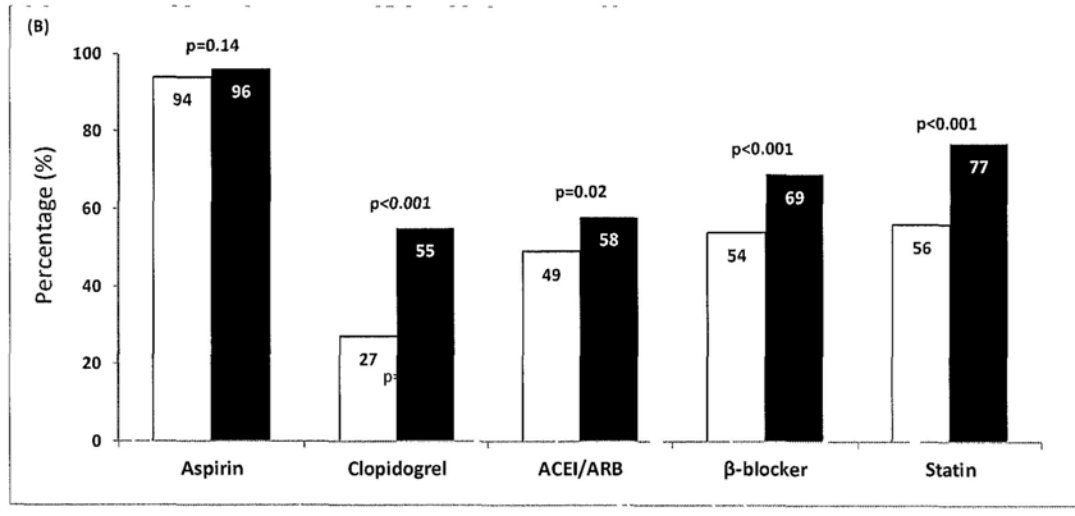
Table 5.6. Independent Predictors of Guideline Recommended Therapies.

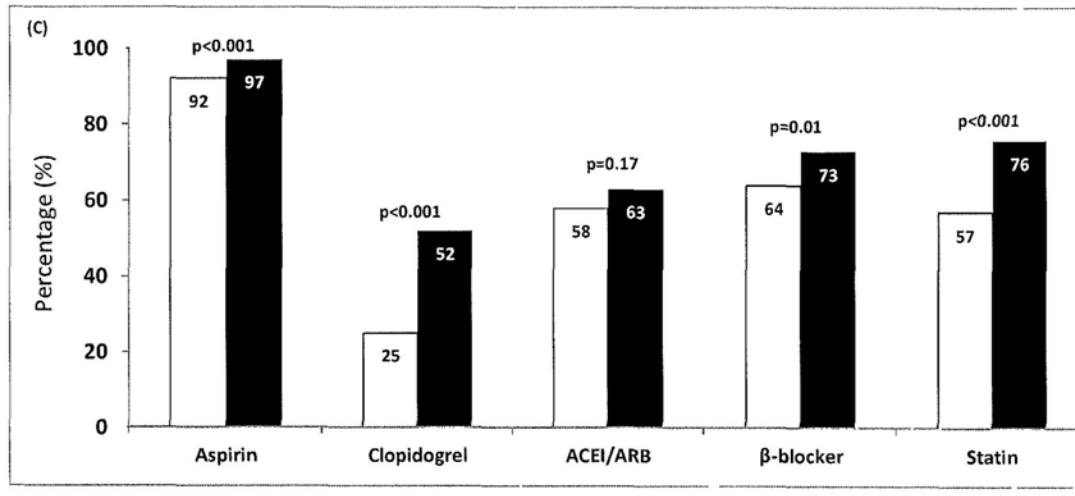
	OR	95% CI	p value
ACEI/ARBs			
STEMI	1.38	1.01-1.90	0.05
Systolic Blood Pressure (per 10 mmHg)	1.07	1.03-1.13	<0.001
Diabetes Mellitus	1.42	1.05-1.92	0.02
Peak Creatinine during Hospitalization	0.73	0.83-0.99	0.04
ß-blockers			
History of Hypertension	1.78	1.29-2.45	<0.001
Heart Rate (per 10 beats/min)	1.08	1.02-1.19	0.01
Systolic Blood Pressure (per 10 mmHg)	1.05	1.01-1.12	0.02
Heart Failure on Admission	0.65	0.45-0.92	0.02
Statins			
Age (per decade of age)	0.82	0.66-0.91	<0.001
ALT (per 100 IU/L)	0.76	0.61-0.97	0.03
Hypercholesterolemia (LDL>2.6mmol/L)	3.45	2.47-4.82	<0.001
Revascularization in Hospital	1.46	1.01-2.11	0.05
Peak Creatinine during Hospitalization	0.93	0.82-1.00	0.05

Analysis performed using multivariable logistic regression, variables in the model including baseline characteristics in table 5.1, laboratory results and investigation during index admission.

Figure 5.1.


(A)
High-Risk
Low-Risk
Percentage (%)
p<0.001
64
33
p<0.001
48
23
p=0.39
2
2
p=0.10
84
81
p<0.001
60
28
p=0.47
69
66
p=0.31
10
8
p<0.001
65
47
Angiography
PCI
CABG
Aspirin
Clopidogrel
LMWH
GPIIb/IIIa
Statin


(B)
Percentage (%)
p=0.14
96
94
p<0.001
55
27
p=0.02
58
49
p<0.001
69
54
p<0.001
77
56
Aspirin
Clopidogrel
ACEI/ARB
β-blocker
Statin


(C)
Percentage (%)
p<0.001
97
92
p<0.001
52
25
p=0.17
63
58
p=0.01
73
64
p<0.001
76
57
Aspirin
Clopidogrel
ACEI/ARB
β-blocker
Statin

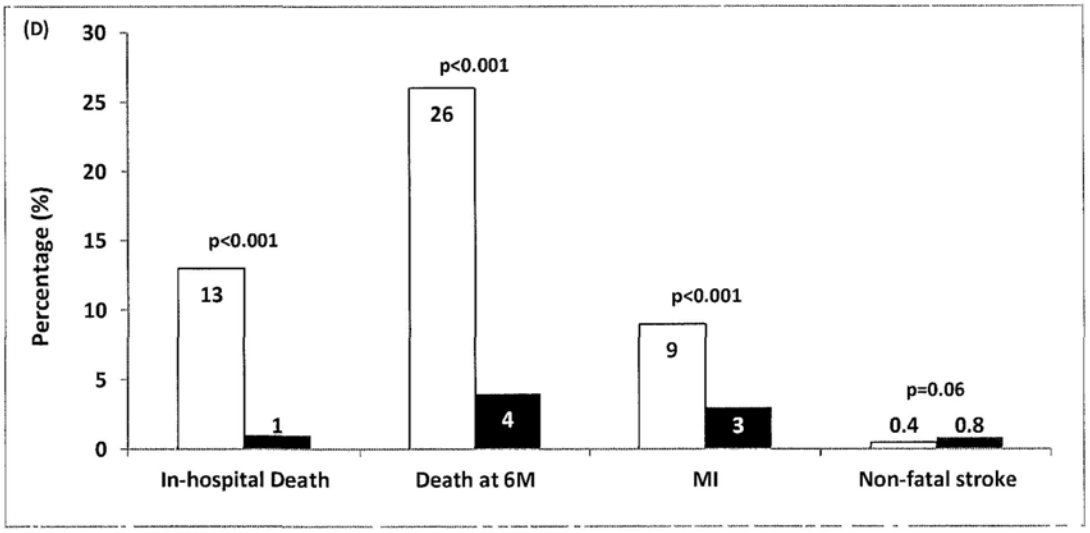
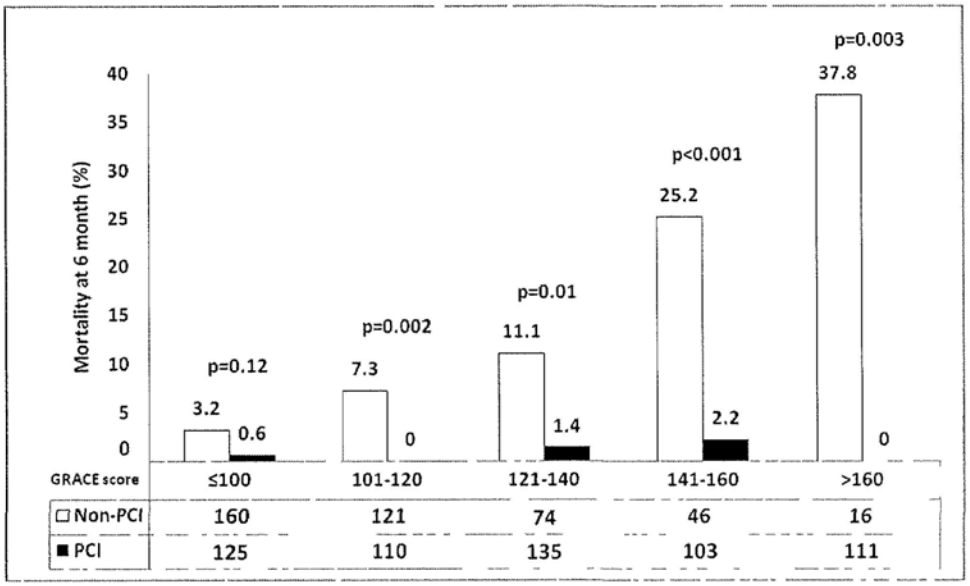


Figure 5.1. (A) Rates of in-hospital investigations, procedures and drugs used by risk status. (B) Prescription rates of guideline recommended drugs at discharge in high- and low-risk patients. (C) Prescription rates of guideline recommended drugs at 30 days after discharge in high- and low-risk patients. (D) In-hospital death rate and rates of death, myocardial infarction and non-fatal stroke at 6-month by risk status.

Figure 5.2 Mortality at 6 months of patients with or without PCI in strata by GRACE score.



5.4 Discussion

Although the benefits of revascularization and pharmacotherapy including antiplatelet, ACEI/ARBs, β-blockers and statins in patients with ACS are well established [78, 93], their use in high-risk ACS patients remain suboptimal in clinical practice. In our study, an inverse association was found between predicted 6-month mortality and rates of guideline-recommended therapies. The paradoxical relationship remained after adjustment for presentation of ACS (STEMI vs. NSTE-ACS), age and perceived contraindications which could potentially affect the risk-treatment relationship. These findings highlighted the treatment gap between guideline and practice in the "real world" and the potential space for improving quality of health care and prognosis of ACS patients, especially those at high risk of death.

Other studies have also described similar risk-treatment paradox in ACS. Ko et al. reported that prescription of statins diminished as baseline cardiovascular risk increased among high-risk ACS patients.[113] In the CRUSADE registry, Roe ***et al*** demonstrated that NSTE-ACS patients with advanced age, diabetes, heart failure and/or those with renal insufficiency had lower rates of all treatments.[112] Fox ***et al*** also reported an inverse relationship between rates of PCI and patient risk status in the GRACE registry in both STEMI and NSTE-ACS.[193] Our findings added to current knowledge regarding risk-treatment patterns by demonstrating that paradox between rates of treatments and mortality risk existed across the entire spectrum of patients with ACS independent of advanced age even when the patient cohort was limited to those without contraindications to therapies.

A potential explanation for this inverse relationship between risk and treatment could be an overestimation of the risk-benefit ratio for invasive management. In our analytic cohort, among high risk patients, those older than 75 years of age, with renal impairment and/or signs of heart failure at admission were less often assigned angiography and concomitant revascularization. High risk clinical characteristics were usually interrelated and clustered together, and these patients were usually excluded from large clinical trials. Thus, clinicians might be reluctant to broaden the clinical trial results to patients with advanced age and cluster of risk factors on the grounds that such patients may experience fewer benefits and greater harm from the adverse effects of therapy. For example, high-risk elderly patients were associated with increased risk of bleeding complications post PCI. Furthermore, patients who underwent early catheterization were more likely to receive all guideline-recommended medications.[110, 111, 197] Thus, patients who were evaluated as high-risk not only lose their opportunity of undergoing invasive procedures and also the subsequent guideline recommended medications. Overemphasis on harm combined with underestimation of benefits may favor a more conservative hands-off approach to treatment in high-risk patients. [198, 199]

There are a number of limitations of this study. First, this is a single-center observational study and this may limit generalization of the results. Second, although we accounted for several important contraindications to guideline recommendations, other undocumented relative contraindications (e.g. cough), which were not detailed in medical records but might lead to withholding of certain drugs, were not assessed. Finally, the study started in 2006, while the guidelines for STEMI and NSTEMI/UA were revised by ACC/AHA in 2007. Changes in indications for guideline recommendations might affect treatment patterns presented in this analysis.

5.5 Conclusion

In summary, invasive management and drugs recommended in guidelines were underused in patients with ACS. Patients considered at high-risk of death were less likely to receive guideline recommended treatment. The clinical use of risk scores may be helpful to identify such high-risk patients who should be treated more aggressively. Stricter adherence to evidence-based therapies in high-risk patients may improve clinical outcome and quality of health care.

CHAPTER 6.QUALITY OF LIFE AFTER PERCUTANEOUS CORONARY INTERVENTION IN THE ELDERLY WITH ACUTE CORONARY SYNDROME

6.1 Background

The prevalence of elderly patients presenting with acute coronary syndrome (ACS) is on the rise with an ageing population and their management remains a major therapeutic challenge. Advanced age is an important determinant of outcomes for patients with ACS. However, community practice reveals a disproportionately lower use of cardiovascular medications and invasive treatment among elderly patients with ACS who would stand to benefit. Reasons include limited trial data to guide the care of the elderly and uncertainty about benefits and risks of newer medications and invasive treatments. This population is often referred late for revascularization and is at the highest risk of procedural complications owing to the high prevalence of associated co-morbidities[200]. However, the elderly have the potential to gain the most clinical benefit from an early invasive approach (compared with conservative management) because of their higher baseline risk[199].

A disease orientated approach to ACS management focusing on the reduction of mortality, morbidity and the risk of subsequent events has led to neglect of health-related quality of life (HRQoL) as an important outcome measure in ACS management. HRQoL is increasingly more relevant in the management of ACS patients as survival increases and the population ages. Studies have shown that health status in terms of extent of angina symptoms strongly predicts long-term clinical outcomes in patients with coronary artery disease (CAD).[126, 140, 201] In one

study, physical limitation was a significant and independent predictor of 1-year mortality while angina frequency was a predictor of 1-year ACS readmission.[140] In another study, early PCI provided greater gains in HRQoL compared with conservative therapy, mainly due to improvements in angina symptoms.[126] As a result, HRQoL is increasingly used as an endpoint in clinical trials and in cost-effectiveness analysis.

Furthermore, racial differences on HRQoL have been shown in a study by Spertus et al where African Americans had more angina, worse HRQoL and worse physical function one year after an ACS than do whites.[202] The majority of studies on HRQoL and CAD were performed in Caucasians and there is a paucity of data on HRQoL after ACS in an Asian population. The aim of this study is to evaluate the impact of PCI on HRQoL in patients of different age groups presenting with ACS.

6.2 Methods

6.2.1 Patient Population

Consecutive patients presenting with ACS were prospectively enrolled into a Registry from February 2006 to May 2008 at a university affiliated teaching hospital. Patients who underwent PCI within 30 days of index ACS presentation (PCI group) were compared to patients who received conservative therapy (non-PCI group).

ACS encompasses UA, NSTEMI and STEMI, respectively and was defined as having symptoms considered as consistent with acute cardiac ischemia plus one of the followings: 1) ECG changes, including transient ST segment elevations or new T wave inversions of $\geq$1mm or pseudo-normalization of previously inverted T waves

or new Q-wave in two or more contiguous leads, ST segment depressions of ≥1mm and new left bundle branch block; 2) increase in cardiac enzymes (Creatinine phosphokinase >twice upper limit of the hospital's normal range or troponin T >0.1mg/dl) and 3) documented coronary artery disease on coronary angiography.[78,93]

Demographic, clinical and procedural characteristics were prospectively recorded on case report forms using standardized definitions for all fields. The study protocol was approved by the ethics committee of the institution and written informed consent was obtained in all patients.

6.2.2 Health Related Quality of Life Assessment

Health status assessment was performed at baseline and follow-up using the Medical Outcome Survey Short Form 36 (MOS SF-36, traditional Chinese version), a 36-item questionnaire that measures eight health constructs including physical functioning, role-limitation due to physical problems, role limitation due to emotional problems, vitality, emotional well-being, social functioning, bodily pain, and general health[121, 126, 203]. Score for each domain range from 0-100, with higher scores reflecting better health status. The SF-36 has been previously validated in patients with ischemic disease[204-206] and our general population.[129]

The Physical component summary (PCS) and Mental component summary (MCS) scores, which reflect overall physical and mental health status, are derived from the eight original scales of SF-36. Both summary scores were standardized to the local general population of interest[121] to allow population-specific interpretation.

6.2.3 Follow-up

In-hospital complications were recorded at the time of discharge. Six month follow-up was conducted by interview or telephone to assess HRQoL. Cardiac events were retrieved from review of patient medical records though the dedicated electronic system which recorded patient events, hospitalizations and details of clinic follow up. Death included all-cause mortality and cause of death outside hospital was confirmed with the patient's primary care physician.

6.2.4 Statistical analysis

Categorical data were expressed as percentages, and continuous variables expressed as mean±SD and/or median with IQR. Continuous variables were compared using Student's *t*-tests. Categorical variables were compared using Fisher exact or Pearson chi-square tests as appropriate.

Primary analyses were conducted with the PCS and MCS derived from SF-36 as outcome variables. Secondary analyses were conducted using the scores from the 8 domains of SF-36 as outcome variables. Mean SF-36 domain scores, PCS and MCS between groups at baseline and follow-up were compared with unpaired t-tests.

A propensity score of probability in undergoing PCI was used to adjust for potential bias in treatment selection. This was accomplished by performing a multivariable logistic regression analysis using PCI as the dependent outcome variable and entering all demographics, physical examination findings, clinical presentation and medications that were likely to affect the probability of PCI. Stepwise backward elimination was employed and the resultant independent

predictors of undergoing PCI were then used to calculate the probability of undergoing PCI (propensity score). By introducing the propensity score into regression adjustment, the effect of PCI is estimated by adjustment for the impact of background covariates. The bias in the background covariates between PCI and non-PCI groups could be removed by adjustments made with the propensity score.

Multivariate analysis was then performed to determine independent predictors of changes in PCS and MCS. Adjustment was made with regression 7 developed in backward selection mode using variables in Table 1 ($p<0.1$ to remain in model), and then adding the management strategy (i.e. PCI or non-PCI) to the selected models. Further analyses were performed including all variables in Table 1 as covariates in the models to maximize control of confounding. The propensity score was forced into all the models as covariate to balance the potential bias due to treatment selection. The results of selected and overall models were similar. Therefore, results from the backward selected models were presented in this study.

Missing follow-up health status assessments can potentially produce selection bias from survey non-responders. Multiple imputation strategy was employed to account for missing scores. The rates of missing in each of the 36 items of SF-36 were listed in Table 6.1. The results of sensitivity analysis using imputed data were similar to analytic cohort and were not presented in this paper. We also compared baseline characteristics between respondents and non-respondents of HRQoL assessment.

Statistical analyses were performed using SPSS version 17.0 for Windows (SPSS Inc., Chicago, Illinois). All calculated p values were two-sided and p value <0.05 were considered statistically significant.

6.3 Results

6.3.1 Patient Population

A total of 624 consecutive patients admitted with ACS to our institution were enrolled and completed baseline HRQoL assessment. Of these, 287 patients (45.9%) underwent PCI (PCI group), 39 (6.3%) underwent coronary artery bypass surgery and 298 (47.8%) were treated conservatively (non-PCI Group) (Figure 6.1). Thirty-three patients died before 6-month interview. At 6-month follow-up, there were 233 (81.5%) respondents in the PCI group and 218 (81.9%) in the non-PCI group after exclusion of deaths.

6.3.2 Survey respondents versus non-respondents

There were no significant differences between non-respondents and respondents in terms of age, gender and most baseline characteristics except that non-respondents were more likely to have previous documented CAD (40.8% vs. 29.3%, p=0.007), heart failure (12.2% vs. 6.7%, p=0.04) and impaired renal function (17% vs. 5.1%,p<0.001). Patients who underwent PCI were more likely to be respondents (80.4% vs. 69.2%, p=0.001). There were no differences in baseline SF-36 score for HRQoL and adverse clinical events between respondents and non-respondents.

6.3.3 Baseline Characteristics

Baseline characteristics of PCI and non-PCI groups were stratified by age groups (<60yrs, 60-79 yrs, and ≥80yrs old) as shown in Table 6.2. Patients who underwent

PCI were younger, more likely to be male and had lower prevalence of co-morbidities such as heart failure and impaired renal function. Majority of patients presented with STEMI were treated with PCI. These differences between PCI and non-PCI groups were maintained within each age group. As expected, older patients were more likely to be females and had more co-morbidities, including hypertension, prior heart failure and history of myocardial infarction than younger patients. With regards to treatment strategy, older patients were less likely to undergo diagnostic angiography (84.8 vs.65.2 vs.24.8%, $p<0.001$) and PCI (73.6 vs. 55.7 vs. 21.3%, $p<0.001$) than younger patients.

6.3.4 Health Related Quality of Life

Table 6.3 showed the unadjusted SF-36 scores at baseline and 6 month by age and treatment strategy. Older patients had lower HRQoL at baseline. Within each age group, unadjusted baseline HRQoL between PCI and non-PCI groups was comparable. At 6-month follow-up, HRQoL scores were significantly higher than baseline in all 8 domains, with improvements ranging from 4.5 points for mental health to 12.8 points for role emotional and 28.9 points for physical functioning in the overall cohort. Patients treated with PCI had higher scores at 6 months in all 8 domains than those treated conservatively, 4 were significant (Table 2). In particular, patients who underwent PCI had better physical health status than those treated conservatively as reflected by higher mean PCS in all age groups.

After risk adjustment, there were no longer differences in HRQoL between PCI and non-PCI in patients <60 years except in role physical domain. For patients aged 60-79 years and those over the age of 80 years, their physical health status

including physical functioning, bodily pain and the physical component summary were significantly better with PCI than medical therapy (Table 6.4). Patients aged ≥80 experienced the most improvement in score of most domains (Figure 6.2) and PCS (Figure 6.3) after PCI. After adjustment, improvements in mental domains and MCS remained significant between the 2 treatment strategies only in the younger age group but not in elder groups.

In multivariable analyses (Table 6.5), independent predictors of better 6-month physical health status (i.e. PCS) for the total study population were PCI (Odds Ratio [OR]=1.79, 95% Confidence Interval [CI]: 1.10-2.92), without previous revascularization (OR=2.04, 95% CI: 1.01-4.15) and age (per ten years increase, OR=1.27, 95% CI: 1.02-1.57).

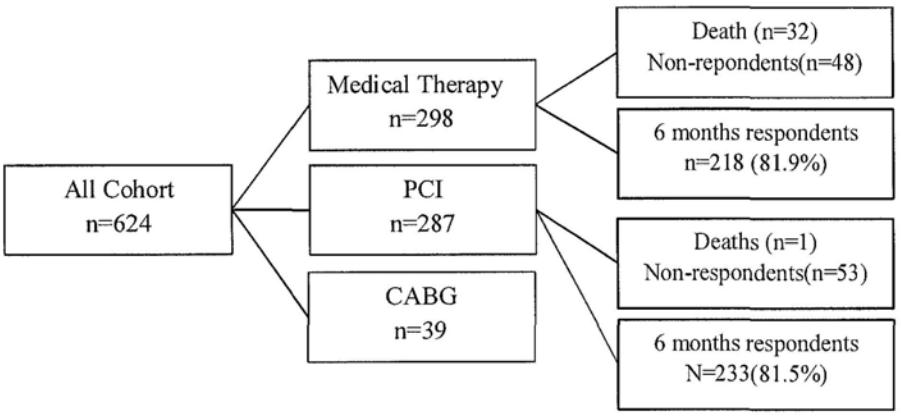


Figure 6.1 Flowchart illustrating the final cohort of patients at 6 month.

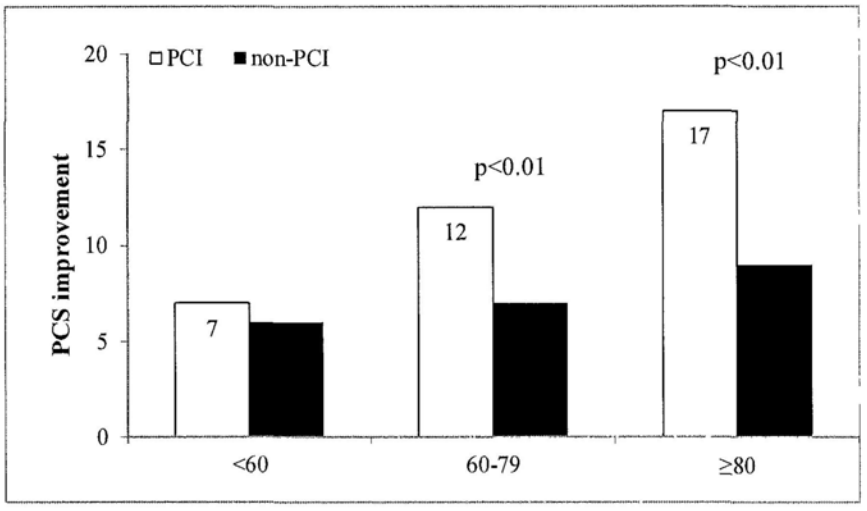


Figure 6.3 Risk-adjusted improvements in physical component summary (PCS) at 6 month by age group and treatment.

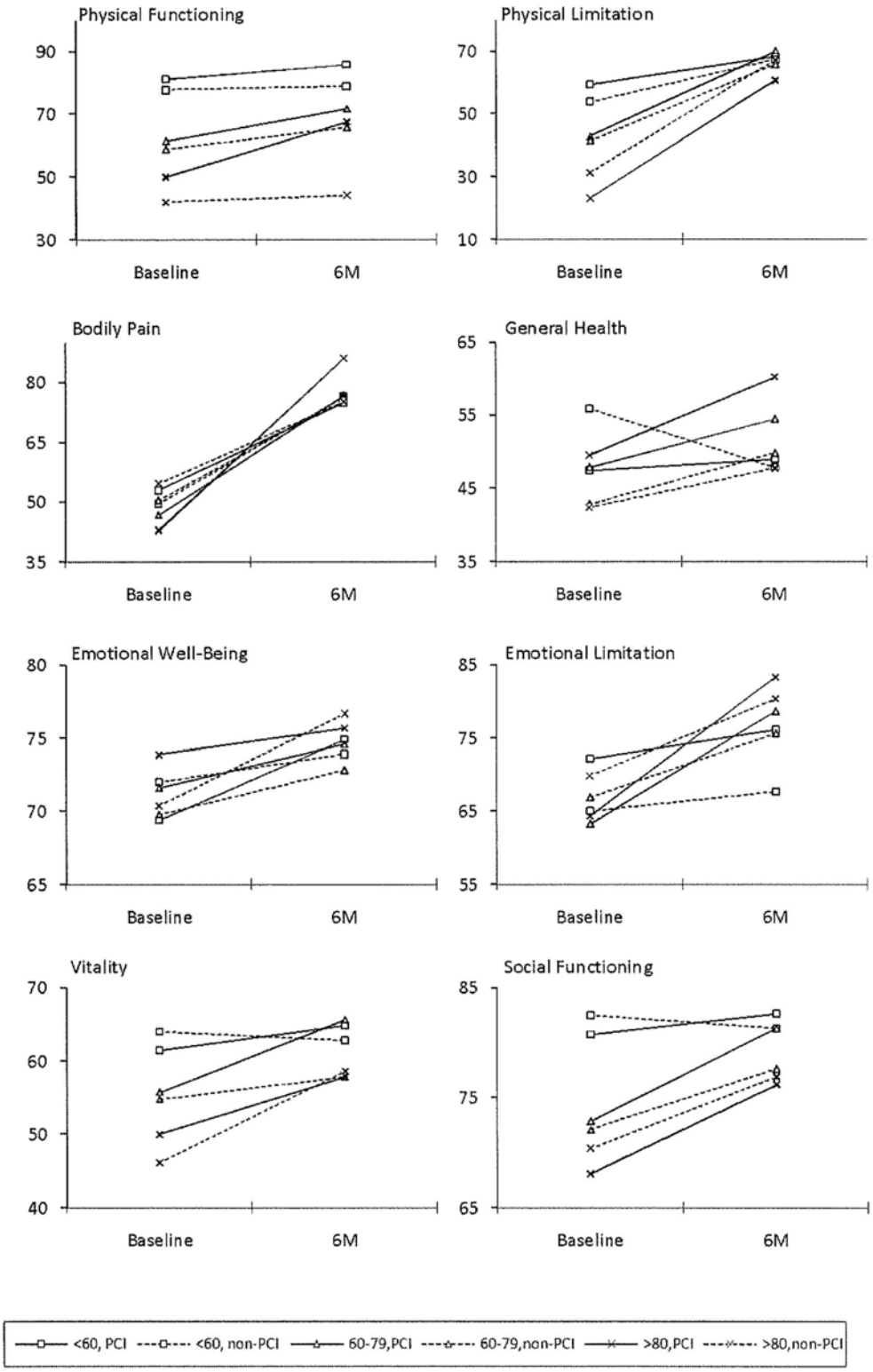

Physical Functioning
90
70
50
30
Baseline
6M
Physical Limitation
70
50
30
10
Baseline
6M
Bodily Pain
80
65
50
35
Baseline
6M
General Health
65
55
45
35
Baseline
6M
Emotional Well-Being
80
75
70
65
Baseline
6M
Emotional Limitation
85
75
65
55
Baseline
6M
Vitality
70
60
50
40
Baseline
6M
Social Functioning
85
75
65
Baseline
6M
<60, PCI
<60, non-PCI
60-79,PCI
60-79,non-PCI
>80,PCI
>80,non-PCI

Figure 6.2 Risk Adjusted Changes in Health-Related Quality of Life according to Treatment and Age Groups. The quality of life scores in 8 domains derived from SF-36 questionnaire, slopes of the lines represent change in 8 domains. The larger the slope, the more improvement patients gained in quality of life.

Table 6.1 Missing rates of 36 items in SF-36 among respondents.

Baseline		6 Months	
Item	**Missing Rate(%)**	**Item**	**Missing Rate(%)**
1	0	**1**	0
2	0	**2**	0.8
3	0	**3**	0.9
4	0	**4**	0.9
5	0.3	**5**	0.9
6	0	**6**	0.8
7	0	**7**	0.8
8	0.2	**8**	1.1
9	0.2	**9**	0.8
10	0.2	**10**	0.8
11	0.2	**11**	0.8
12	0.2	**12**	0.9
13	0.2	**13**	1.5
14	0.3	**14**	1.7
15	0.3	**15**	1.7
16	0.3	**16**	1.7
17	0.2	**17**	1.5
18	0.3	**18**	1.7
19	0.2	**19**	1.7
20	0.5	**20**	1.3
21	0.5	**21**	1.1
22	2.4	**22**	1.3
23	0	**23**	0.9
24	0	**24**	0.9
25	0	**25**	1.1
26	0.3	**26**	1.1
27	0.2	**27**	0.9
28	0.5	**28**	1.3
29	0.3	**29**	1.1
30	0.8	**30**	1.1
31	0.2	**31**	0.9
32	1.9	**32**	1.7
33	0.5	**33**	1.3
34	0.8	**34**	1.3
35	0.5	**35**	1.3
36	0.5	**36**	1.1

Table 6.2 Baseline characteristics.

	All Patients			<60 years			60-79 years			≥80 years		
	PCI N=233	Non-PCI N=218	p	PCI N=78	Non-PCI N=28	p	PCI N=132	Non-PCI N=105	p	PCI N=23	Non-PCI N=85	p
Demographics												
Age	64±11	73±11	<0 01									
Female	61(26%)	96(44%)	<0 01	13(17%)	5(19%)	0 74	36(27%)	48(46%)	<0 01	14(63%)	45(53%)	0 50
Current smoker	72(31%)	44(20%)	<0 01	33(42%)	8(28%)	0 15	36(27%)	21(20%)	0 21	3(14%)	12(14%)	0 97
Hypertension	135(58%)	135(62%)	0 35	29(37%)	8(30%)	0 46	90(68%)	67(64%)	0 52	17(75%)	63(74%)	0 94
Prior MI	26(11%)	35(16%)	0 16	9(11%)	4(16%)	0 47	12(9%)	15(14%)	0 25	7(31%)	17(20%)	0 30
Prior Revascularization	35(15%)	33(15%)	0 95	12(15%)	4(16%)	0 89	21(16%)	18(17%)	0 81	3(13%)	10(12%)	0 93
Prior heart failure	7(3%)	24(11%)	<0 01	1(1%)	1(3%)	0 58	5(3%)	8(8%)	0 05	1(6%)	15(18%)	0 24
Diabetes	70(30%)	81(37%)	0 09	19(24%)	8(30%)	0 52	44(33%)	44(42%)	0 16	6(25%)	28(33%)	0 56
Dyslipidemia	58(25%)	55(25%)	0 90	20(25%)	7(25%)	0 99	30(23%)	32(30%)	0 25	10(44%)	14(16%)	0 01
Prior impaired renal dysfunction	7(3%)	18(7%)	0 03	3(4%)	0(0%)	0 23	4(3%)	7(7%)	0 12	0(0%)	10(12%)	0 15
Presenting syndrome												
STEMI	98(42%)	44(20%)	<0 01	37(47%)	8(30%)	0 08	53(40%)	17(16%)	<0 01	7(31%)	19(22%)	0 51
NSTEMI	95(41%)	100(46%)	0 33	26(34%)	11(38%)	0 70	57(43%)	52(50%)	0 27	13(56%)	36(43%)	0 28
UA	40(17%)	74(34%)	<0 01	15(19%)	9(32%)	0 11	22(17%)	36(34%)	<0 01	3(13%)	30(35%)	0 08
Disease severity												
Systolic blood pressure	139±27	142±24	0 53	139±26	146±25	0 16	145±31	152±35	0 11	162±28	149±35	0 18
Heart rate on admission	79±16	80±13	0 70	78±16	79±14	0 84	79±21	84±24	0 07	76±13	82±23	0 34
Most recent ejection fraction	53±13	56±12	0 24	51±7	52±6	0 64	54±14	57±14	0 23	51±13	54±18	0 66

Table 6.3. Unadjusted Scores of Health-related Quality of life.

QoL	All patients			<60 years			60-79 years			≥80 years		
	PCI N=233	Non-PCI N=218	p	PCI N=78	Non-PCI N=28	p	PCI N=132	Non-PCI N=105	p	PCI N=23	Non-PCI N=85	p
Baseline												
PCS	32±15	29±15	0.03	39±13	37±14	0.70	29±15	30±15	0.80	22±9	23±12	0.69
Physical functioning	68±26	59±28	<0.01	78±22	74±26	0.39	64±27	64±25	0.98	51±24	42±28	0.23
Bodily Pain	46±31	49±30	0.39	51±32	46±34	0.46	45±31	49±31	0.28	37±24	50±25	0.06
Role physical	49±44	46±43	0.42	58±43	48±46	0.25	44±45	44±43	0.97	43±44	46±42	0.74
General Health	48±24	46±26	0.40	47±24	52±30	0.31	48±24	44±25	0.17	46±19	45±25	0.91
MCS	51±12	53±14	0.24	50±12	50±16	0.97	52±12	52±13	0.87	51±12	55±13	0.19
Role emotional	68±41	64±42	0.36	73±40	62±43	0.18	66±42	66±43	0.98	63±42	63±40	0.97
Social functioning	73±24	70±25	0.21	77±22	75±27	0.61	72±24	71±25	0.78	63±27	67±26	0.62
Mental Health	70±22	70±22	0.96	69±23	71±20	0.67	70±21	69±22	0.96	75±21	69±22	0.38
Vitality	58±26	53±26	0.07	60±26	59±29	0.80	57±26	55±25	0.46	49±23	48±25	0.90
6 Month												
PCS	42±13	35±15	<0.01	46±11	41±15	0.04	41±14	36±15	0.01	40±11	30±15	0.02
Physical functioning	77±23	60±30	<0.01	86±16	78±22	0.02	73±24	63±29	<0.01	65±21	45±27	0.01
Bodily Pain	76±26	75±26	0.53	75±26	73±27	0.78	76±26	75±26	0.73	84±18	75±27	0.20
Role physical	72±39	67±42	0.21	72±39	62±45	0.22	72±39	68±41	0.43	66±42	67±42	0.88
General Health	54±23	49±26	0.02	52±20	48±30	0.40	55±24	49±27	0.06	63±21	49±23	0.03
MCS	53±10	54±11	0.29	51±10	51±12	0.98	54±10	54±11	0.69	55±13	57±11	0.45
Role emotional	79±36	76±39	0.39	75±39	71±41	0.59	80±35	76±38	0.40	85±30	78±39	0.45
Social functioning	82±22	77±25	0.04	83±22	77±24	0.26	81±22	78±26	0.20	79±25	76±26	0.69
Mental Health	76±18	75±19	0.68	75±17	75±18	0.96	75±19	73±20	0.32	78±19	78±18	0.97
Vitality	66±24	60±25	0.01	66±25	63±27	0.64	66±24	59±26	0.03	60±27	59±23	0.88

Table 6.4. Adjusted Changes in Health-Related Quality of Life according to Treatment

Quality of Life	All patients			<60 years			60-79 years			≥80 years		
	PCI	Non-PCI	p	PCI	Non-PCI	p	PCI	Non-PCI	p	PCI	Non-PCI	p
	N=233	N=218		N=78	N=28		N=132	N=105		N=23	N=85	
PCS	11±10	8±8	<0.01	7±9	6±8	0.67	12±10	7±9	<0.01	17±9	9±8	<0.01
Physical Functioning	11±17	1±13	<0.01	6±15	-4±13	0.57	13±16	-2±12	<0.01	21±22	6±14	<0.01
Role Physical	24±37	24±32	0.97	15±39	22±31	0.02	27±35	24±32	0.42	31±35	25±32	0.46
Bodily Pain	28±27	25±25	0.14	23±27	35±25	0.41	31±27	23±26	0.04	37±25	22±24	0.02
General Health	6±12	3±15	0.04	7±13	2±18	0.25	6±12	3±15	0.16	6±13	4±14	0.71
MCS	2±6	4±12	0.04	3±6	8±13	0.01	2±6	4±12	0.13	2±7	4±12	0.65
Mental Health	5±14	7±16	0.15	7±15	8±14	0.88	4±14	6±16	0.35	3±12	8±17	0.28
Role Emotional	13±33	15±33	0.71	10±33	18±31	0.05	14±33	11±33	0.45	21±30	18±34	0.72
Social Functioning	8±19	6±20	0.34	5±19	5±20	0.13	9±19	3±19	0.02	11±24	10±21	0.79
Vitality	9±16	9±22	0.87	7±16	6±25	0.90	10±16	7±21	0.41	17±16	12±21	0.35

Table 6.5. Multivariate analysis: Predictors of Improved PCS at 6M (n=451)

Variables	Adjusted OR (95% CI)	p value
Age, per 10 years increase	1.27(1.02-1.57)	0.03
Female	0.67(0.39-1.15)	0.15
Current Smoker	0.86(0.50-1.48)	0.59
Hypertension	0.97(0.59-1.61)	0.91
Prior MI	1.02(0.44-2.35)	0.97
Prior Revascularization	0.49(0.24-0.98)	0.04
Prior heart failure	1.69(0.58-4.89)	0.33
Diabetes	1.00(0.61-1.66)	0.99
Dyslipidemia	1.12(0.65-1.90)	0.69
Impaired Renal Dysfunction	0.61(0.22-1.66)	0.33
PCI in 30 days	1.79(1.10-2.92)	0.02
Propensity Score	0.30(0.06-1.48)	0.14

6.4 Discussion

We compared HRQoL outcomes between 3 age groups of ACS patients undergoing PCI and medical therapy. The main findings of our study include: (i) PCI was associated with significant improvement in physical health status at 6 months across all age groups; (ii) elderly patients, especially those ≥80 years of age, experienced the greatest benefit in terms of improvement in physical functioning; (iii) PCI had less impact on mental health than physical health and (iv) PCI and incremental age were independent predictors of improvement in physical component of HRQoL.

A number of studies have demonstrated improved quality of life in patients with coronary artery disease after revascularization procedures including PCI and CABG.[126, 201, 207-210] Fewer studies compared improvement in quality of life in CAD patients undergoing revascularization procedures versus medical therapy over time.[125, 153, 201, 211] In a recent sub-study of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial which randomized 2,287 patients with chronic CAD to either PCI plus optimal medical therapy or optimal medical therapy alone, Weintraub et al[153] evaluated HRQoL using the Seattle Angina Questionnaire (SAQ) and RAND-36. They reported PCI had small but significant incremental benefits in health status compared to optimal medical therapy. For patient with ACS, two previous studies assessed HRQoL using SF-36.[125, 126] In the study of the third Randomized intervention Trial of unstable Angina (RITA-3)[126], Kim et al. assessed 1,810 ACS patients randomized to early invasive therapy or conservative therapy and demonstrated that early invasive strategy provided greater gains in HRQoL in patients with ACS compared to conservative strategy at 4 and 12 months follow-up, mainly due

to improvements in angina grade. Another study compared differences in HRQoL outcomes among 2,457 patients with unstable angina randomized to invasive and conservative strategy[125], with HRQoL assessment at baseline, 3, 6, and 12 months follow-up. Patients in the invasive group showed higher HRQoL scores in 7 of the 8 scales and mainly PCS (2.8 points) after 1 year follow-up. Similar to findings in our study, there was no significant difference in MCS. Overall, our findings are consistent with these previous studies with predominantly PCS improvement (4 points) in invasively treated patients. Furthermore, we recruited whole spectrum of ACS including STEMI, NSTEMI and UA and with more elderly patients comparing to previous studies.

High prevalence of CAD in the elderly combined with reports of poorer outcomes after PCI have led to some uncertainty as to whether PCI should be offered to elderly patients routinely[208]. A large observation study of patients undergoing PCI reported that octogenarians were more likely to present with ACS and had significantly increased short- and long-term mortality and major adverse cardiac event rates[200]. Although some trials demonstrated significant improvement of symptoms relief and quality of life after revascularization in elderly patients[152], PCI remained a risky procedure with high peri-procedural complications in the elderly than in younger patients[212]. In addition to survival benefits, gains in quality of life should be considered an important outcome in the elderly whose life expectancy may be limited and their physical health status and independence in activities of daily living becomes increasingly important. The ability to live independently within the community will likely reduce direct health-care costs such as hospitalization or nursing care as well as indirect costs to the patient's family. Our finding that the oldest group of patients benefited the most from PCI in terms of

physical health status compared to younger patients suggested that age *per se* should not deter against revascularization given the combined survival and quality of life benefits.

Previous population-based studies using the SF-36 summary scales have found that a change of >3.8 on the physical function scale was associated with substantial improvement in physical health[203]. Thus, the adjusted changes in scores for physical health in both invasive and conservative treatment groups (11 vs. 7 points, respectively) in our study were considered clinically significant. There was no significant difference in mental health status at baseline or follow-up between treatment groups, this was similar with studies assessing PCI vs. medical therapy in chronic coronary artery disease[153]. The main explanation for better physical health in patients treated invasively is likely to be better control of angina symptom after revascularization. More than 13.2% patients in the medical therapy group were readmitted for refractory angina during follow-up compared to 6.5% of patients in the PCI group ($p<0.01$). Patients treated invasively also improved more in the bodily pain scale which could reflect severity of angina indirectly. This finding is consistent with studies which reported incremental benefit from PCI in terms of angina frequency and angina stability using a disease-specific instrument such as Seattle Angina Questionnaire (SAQ) to evaluate HRQoL of patients after PCI compared to medical therapy.[126, 153]

One of the advantages of using a generic HRQoL instrument such as the SF-36, is ease of use[139]. As the mostly used instruments to evaluate quality of life in cardiovascular disease[147], SF-36 also provides information on a patient's global state of well-being and allows comparability of relative health states across different disease[213]. Although SF-36 may lack the range, sensitivity & flexibility for particular illness

compared to disease-specific instrument as SAQ, use of a generic measure appeared to be as good a predictor of physical health status as a disease-specific measure in CAD[147]. However, as an evaluative tool in the field of ischemic heart disease, the mental health and general health scales do not appear to be responsive to change, and the role emotional and role physical scales are prone to ceiling effects[139].

Our study has several limitations. The study size is small and being a single-center study, generalizability of these results is limited. Further research should examine impact of PCI on quality-of-life improvement in ACS patients in larger, multicenter studies. Only 80% of patients completed 6-month follow-up. However, non-respondent rates are high in studies of HRQoL because of length of questionnaire and patient refusal to answer personally directed questions. Although non-respondents in this study were more like to have co morbid medical conditions such as heart failure and renal impairment, they had similar scores of HRQoL with respondents at baseline. Treatment and adverse event rates were also similar between respondents and non-respondents. Despite adjustment for selection bias using propensity score, other factors such as general health status, socioeconomic factors and patient preference which may affect decision making were not accounted for in our study. Such selection bias might lead to more pronounced benefits of the elderly patients as compared to younger patients. Whether elderly patients are better selected for intervention by a more restrictive approach towards invasive treatment is unclear. Further studies are warranted to assess optimal selection criteria for invasive therapy in the elderly population. Sensitivity analyses were performed and did not identify significant bias to account for missing data

due to non-response. Finally, longer follow-up would be a invaluable to assess the durability of HRQoL benefits of PCI.

6.5 Conclusion

We have observed significant improvements in HRQoL in ACS patients treated invasively which is largely attributable to improvements in physical functioning. In particular, elderly patients experienced the greatest enhancement in physical functioning than younger patients. Further studies are required to identify elderly ACS patient most likely to derive HRQoL benefits from PCI. As the population ages and survival increases in patients with ischemic heart disease, HRQoL is an important clinical outcome to consider in addition to traditional hard clinical end-points and should become routine clinical practice.

SECTION FOUR

SUMMARY

CHAPTER 7. SUMMARY

Acute coronary syndrome (ACS), a term used to cover a group of clinical symptoms compatible with acute myocardial ischemia, represents a high-risk group of patients with coronary heart disease (CHD). To improve quality of care, international guidelines for the management of ACS have been established and are updated regularly. In the era of evidence based medicine, adherence to therapeutic guidelines is essential for optimal care of ACS patients. However, most data on ACS epidemiology, treatment and outcomes are derived from western population. There are limited data in Chinese population in terms of prevalence, presentation, response to treatment and clinical outcome.

Our study was designed to investigate epidemiology, treatment and outcome of ACS patients under current medical care system in Hong Kong. The study was conducted from February 2006 to September 2009 in a university affiliated teaching hospital and consecutive patients admitted with ACS were prospectively recruited. Clinical characteristics and treatment data were collected at baseline, 30 days and 6 months after onset. Quality of life assessment using SF-36 questionnaire was performed on admission and at 6 months. Outcomes were evaluated using mortality and morbidity in clinical aspect and quality of life in aspect of health status.

We firstly described patients' characteristics, treatment and management practices, and hospital outcomes of ACS in Hong Kong. Using standardized definition of dataset, we compared our results with data reported internationally. Our study identified gaps

between guidelines and clinical practice, potential reasons for these gaps, and measured the impact of such gaps on the outcomes of patients with ACS.

Female composed one third of ACS patients, while coronary artery disease is among the leading causes of death in most developed countries. Women ACS patients have be receiving increasing attention since studies have reported gender disparities existed in many aspects of ACS. We explored gender differences in management and outcomes of ACS patients. In brief, women patients were older and more likely to have comorbidities such as hypertension, hypercholesterolemia, diabetes, renal impairment and history of heart failure compared to men. Rates of revascularization and evidence-based therapies were lower and 6 months mortality and adverse event rates were higher among female patients. Outcomes were similar between different genders. However, advanced age and high comorbidities prevalence could explain most difference between male and female in terms of management. Therefore, advanced age might be a more dominant factor associated with less treatment than female gender. Increasing awareness of gender disparity as well as better adherence to guidelines may also have helped in narrowing the gap.

The managements of ACS have been summarized as guidelines by ACC/AHA/ESC. It is important to ensure adherence to therapeutic guidelines in patients at higher risk of death given the effectiveness of treatments in reducing mortality. However, some studies have reported a risk-treatment mismatch suggesting that those patients at higher risk were less likely to receive proven treatments. We performed the analysis investigating guideline adherence according to risk stratification in contemporary clinical practice and found patients with ACS were undertreated in

current clinical practice, especially those at high risk of death. The rates of coronary angiography and revascularization were lower in high-risk patients during index admission, and prescription rates of guideline recommended drugs were also lower in high risk STEMI and NSTE-ACS patients. Furthermore, the paradoxical trend extended to 6 months after onset. However, the clinical use of risk scores may be helpful to identify such high-risk patients who should be treated more aggressively. Stricter adherence to evidence-based therapies in high-risk patients may improve clinical outcome and quality of health care.

Quality of life has been accepted as an important predictor of outcomes and mortality in ACS patients. We compared quality of life evaluated by SF-36 between patients who underwent PCI versus those treated conservatively across 3 age groups (<60, 60-79 and ≥80 years). Elderly ACS patients have lower revascularization rates and quality of life at baseline and follow-up. However, elderly patients who underwent PCI experienced the most improvement in physical health compared to younger patients. PCI was an independent predictor of improvement of 6-month physical health status.

This study is the first registry in Hong Kong focused on the epidemiology, current treatment patterns and outcomes over the whole spectrum of ACS patients. Compared with internationally reported data, Hong Kong ACS patients are different in terms of age and risk factors distribution. Treatment gaps exist between international therapeutic guideline recommendations and clinical practice, especially among the high risk populations, the elderly and female patients. Better understanding and narrowing these gaps between guideline and practice will lead to improvement quality of care and

clinical outcomes of ACS patients. Increase use of risk stratification models and health status assessments may improve decision making in the management of ACS.

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