PHILIPPINE HEART ASSOCIATION, INC.
PHILIPPINE COLLEGE OF CARDIOLOGY

2014 PHA CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH

CORONARY ARTERY DISEASE

Philippine Heart Association
Board of Directors

Joel M. Abanilla, MD
President

Alex T. Junia, MD
Vice-President

Romeo B. Cruz
Vice-President for Finance

Frederick M. Alegre
Vice-President for External Affairs

Raul L. Lapitan, MD
Secretary

Jorge A. Sison, MD
Treasurer

Helen Ong-Garcia, MD
Director

Nannette R. Rey, MD
Director

Aurelia G. Leus, MD
Director

Eugenio B. Reyes, MD
Immediate Past President

PHA CAD Guidelines Writing Committee

PHA Chaiman Council of CAD	Liberty O. Yaneza, MD
Chairmen of Task Forces:	
Stable Ischemic Heart Disease (SIHD)	Ma. Consolacion Dolor-Torres, MD
Non ST Elevation Acute Coronary Syndrome (NSTE ACS)	Sue Ann R. Locnen, MD
ST Elevation MI (STEMI)	Victor L. Lazaro, MD
Chairman Literature Review	Imelda Caole-Ang, MD
Chairman Technical Writing	Ivan Noel G. Olegario, MD

SIHD

Task Force Members: Maria Consolacion V. Dolor-Torres, MD (Chair), Philip U. Chua, MD, Roberto S. Cristobal, MD, Josette V. Cristobal, MD, Iris M. Garcia, MD, Kathleen F. Sabiniano, MD, Richard Nicandro R. Torres, MD, Mariel I. Barcelon-Cruz, MD, Michael B. Cabalatungan, MD

Panel of Experts: Romeo D. Saavedra, MD, Ronald E. Cuyco, MD, Edward Benjie L. Magsombol, MD

NSTE ACS

Task Force Members: Sue Ann R. Locnen, MD (Chair), Rodney M. Jimenez, MD, Clara S.Tolentino, MD, Bridget Donato-Fernandez, MD, Visvanath E. Espaldon, MD, Douglas P. Bailon, MD, Gilbert G. Florentino, MD, Lauren S. Valera, MD.

Panel of Experts: Norbert Lingling D. Uy, MD, Gregorio G. Rogelio, MD

STEMI

Task Force Members: Victor L. Lazaro (Chair), MD, Edgardo E. Ebba, MD, Regidor R. Encabo, MD, Ann Margaret P. Flores, MD, Ana Beatriz D. Medrano, MD, Christopher Oliver P. Nazal, MD, Luigi Pierre S. Segundo, MD, Maria Elizabeth V. Enriquez, MD, Philipp C. Ines, MD, Jayson M. Mutuc, MD, Jeannica Kriselle G. Lerios, MD, Hazel Stacey Michelle C. Reyes, MD

Panel of Experts: Donato R. Marañon, MD, Edwin S. Tucay, MD, Gilbert C. Vilela, MD

Approving Panel of Experts and Members of Stakeholders

PHA Board of Directors	Joel M. Abanilla, MD
	Alex T. Junia, MD
	Raul L. Lapitan, MD
	Jorge A. Sison, MD
	Helen Ong-Garcia, MD
	Nannette R. Rey, MD
	Aurelia G. Leus, MD
	Eugenio B. Reyes, MD
Philhealth	Jonathan Michael H. Ele, MD
Philippine Academy of Family Physicians	Jane Eflyn L. Lardizabal-Bunyi, MD
Philippine College of Physicians	Francisco P. Tranquilino, MD
Philippine Society of Hypertension	Dante D. Morales, MD

CONTENTS

INTRODUCTION 8

2014 Philippine Heart Association Clinical Practice Guidelines for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease 16

Initial Patient Evaluation

Statement 1 History 17
Statement 2 Physical Examination 18
Statement 3 Resting 12-lead ECG 19
Statement 4 Laboratory Tests 20
Statement 5 Chest X-ray 21
Statement 6 Echocardiography 22
Statement 7 Ambulatory ECG Monitoring 23
Statement 8 Pre-test Probability Assessment 23

Establishing Diagnosis

Statement 9 Principles of Stress Testing 25
Statement 10 Stress Imaging 26
Statement 11 Exercise ECG (Treadmill Exercise Test or TET) 29
Statement 12 Coronary Computed Tomographic Angiography 30
Statement 13 Invasive Coronary Angiography 31

Management

Statement 14 General Overview of Management 35
Statement 15 Lifestyle Modification and Treatment of Risk Factors 35
Statement 16 Pharmacologic Therapy to Improve Prognosis 39
Statement 17 Pharmacologic Therapy to Reduce Angina 42
Statement 18 Revascularization Therapy 45
Statement 19 Percutaneous Coronary Intervention 48
Statement 20 CABG Surgery 50
Statement 21 Non-conventional Treatment 51
Statement 22 Follow-up Tests 52

Special Considerations
Statement 23 Angina with Normal Coronary Arteries (Microvascular Angina or Vasospastic Angina) 53
Statement 24 Refractory Angina 55
Statement 25 Asymptomatic Patient at Risk for CAD 55
References 55

2014 Philippine Heart Association Clinical Practice Guidelines for the Diagnosis and Management of Patients with Non-ST Elevation Acute Coronary Syndrome 60

Diagnosis and Risk Assessment
Statement 1 Clinical Presentation 60
Statement 2 Electrocardiogram 62
Statement 3 Biomarkers 62
Statement 4 Non-invasive Imaging 63
Statement 5 Stress Testing 64
Statement 6 Risk Stratification 65

Hospital Care
Statement 7 General Recommendations on Initial Management 73
Statement 8 Nitrates 73
Statement 9 Beta Blockers 75
Statement 10 Calcium Channel Blockers 75
Statement 11 Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blockers 76
Statement 12 Morphine Sulfate 77
Statement 13 Aspirin 77
Statement 14 P_2Y_{12} Inhibitors 77
Statement 15 Anticoagulants 79
Statement 16 GP II_b/III_a Inhibitors 80
Statement 17 Fibrinolytic Therapy 80
Statement 18 Conservative (Medical) versus Early Invasive (Coronary Angiography and Revascularization) Strategies 80
Statement 19 Coronary Angiography 82

Statement 20 Revascularization by PCI 82
Statement 21 Revascularization by CABG Surgery 82
Statement 22 Hospital Transfer for Revascularization 82

Hospital Discharge and Long-term Management
Statement 23 Hospital Discharge and Long-term Management Advice 83
Statement 24 Drug/Medication Management 83
Statement 25 Control of Risk Factors 84
Statement 26 Cardiac Rehabilitation 84
References 84

2014 Philippine Heart Association Clinical Practice Guidelines for the Diagnosis and Management of Patients with ST Segment Elevation Myocardial Infarction 89

Early Assessment
Statement 1 Pre-hospital Recognition 89
Statement 2 Initial Evaluation at Emergency Room 90
Statement 3 ECG Evaluation 91
Statement 4 Laboratory Evaluation 91

Management
Statement 5 Initial ER Management 92
Statement 6 In-hospital Treatment 94
Statement 7 Transfer Strategy 94
Statement 8 Fibrinolysis 95
Statement 9 Primary Percutaneous Coronary Intervention 96
Statement 10 Type of Stents 96
Statement 11 Therapeutic Hypothermia 97
Statement 12 Coronary Artery Bypass Grafting 98
Statement 13 CABG Surgery after STEMI and Antiplatelet Agents 98
Statement 14 Hospital Management of STEMI 99
Statement 15 Assessment of Left Ventricular Function 100
Statement 16 Hemodynamic Assessment 100
Statement 17 Management of Arrhythmias after STEMI 101

Statement 18 Temporary Pacemaker 102
Statement 19 Permanent Pacemaker 102
Statement 20 Implantable Cardioverter Defibrillator..... 103
Statement 21 Antiplatelets and Antithrombotics 103
Statement 22 Duration of Dual Antiplatelet Therapy and Antithrombotic Combination Therapies after STEMI 103
Statement 23 Antiplatelets to Support Primary PCI with STEMI..... 104
Statement 24 Antiplatelets as Adjunctive Antithrombotic Therapy with Fibrinolysis..... 104
Statement 25 Beta Blockers 105
Statement 26 Lipid Lowering Agents 106
Statement 27 Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers 106
Statement 28 Calcium Channel Blockers 107
Statement 29 Ivabradine 108
Statement 30 Nitrates..... 108
Statement 31 Cardiac Rehabilitation 108
Statement 32 Hospital Discharge and Post-STEMI Risk Stratification: Timing of Hospital Discharge 109
Statement 33 Exercise Testing 110
References 110

Financial Disclosures.....114

Acknowledgments.....116

INTRODUCTION

In 2009, the Philippine Heart Association (PHA) Council on Coronary Artery Disease (CAD) published the Philippine Clinical Practice Guidelines (CPG) on CAD, which included guidelines on chronic stable angina pectoris (CSAP), unstable angina or non-ST elevation myocardial infarction (UA/NSTEMI), and ST-elevation myocardial infarction (STEMI).[1] The objectives of the CPGs were as follows:

General Objective:

To improve the quality of health care among Filipinos with CAD.

Specific Objectives:

1. To assist Filipino physicians in making clinical decisions in the management of coronary artery disease;
2. To define the standard of care for coronary artery disease in the local setting, and;
3. To make existing international guidelines more clinically relevant and applicable to local practice.

Since then, there have been several studies that contribute to a new knowledge base about the pathophysiology, diagnosis, treatment, and prevention of CAD. Further, the 2-year data results of ongoing PHA - Acute Coronary Syndrome Registry (PHA-ACSR) have also been useful in the formulation of these updated guidelines as the former reflects real world practice in our local setting. These present guidelines aim to update the 2009 Guidelines with this new knowledge base.

The CPG Writing Group was composed of three Task Forces, one for each clinical presentation of CAD (i.e., stable ischemic heart disease [SIHD]; non-ST elevation acute coronary syndrome [NSTE-ACS], and ST elevation myocardial infarction (STEMI). Each Task Force reviewed the 2009 Statements and updated international guidelines; and graded major published literature for CAD from 2009 until the present.

Each task forces with their own set of members and panel of recognized experts held several meetings not only among themselves but also consultative meetings with other Task Forces to discuss each one's recommendations and for consideration of any additional inputs from other task forces. Eventually, statements were presented to the current board of directors of PHA and subsequently to all stakeholders that included Philhealth, DOH, PCP, among others.

After review, the Task Forces proposed new/revised statements of recommendation, where applicable. The grading of recommendations in these guidelines was patterned after the Classes of Recommendation proposed by the

Americal College of Cardiology/American Heart Association (ACC/AHA) but stated in a simplified manner. The statements "strongly recommended"; "recommended"; "may be recommended"; or "not recommended or contraindicated" were used similar to class I, IIa, IIb, and III recommendations proposed by the ACC/AHA, respectively.

The statement "strongly recommended" means that the procedure or treatment should be performed or administered based on sufficient evidence from multiple, randomized trials or meta-analyses.

The statement "is recommended" means that the procedure or treatment is beneficial or effective based on sufficient evidence from single randomized/non-randomized trial/s, meta-analyses, or expert opinion.

The statement "may be recommended" means that the procedure or treatment is useful or effective although with some conflicting evidence from one trial to another.

The statement "not recommended or contraindicated" means that the procedure is not useful or effective, and may be harmful based on sufficient evidence from multiple/single, randomized/non-randomized trial/s or meta-analyses.

Majority rule was applied in adopting statements that would be most suitable to the local community where disagreements existed.

These CPGs are divided into three parts: one for each clinical presentation of CAD.

It must be emphasized that these guidelines should not be regarded as absolute rules, but merely as frameworks to assist clinical practitioners in the management of patients with CAD. The approach to each patient must be individualized to take into account the overall clinical picture. The healthcare provider should apply his sound clinical judgment particularly when confronted with inadequate medical facilities, limited financial resources, or when faced with unique clinical scenarios for which no set recommendations may apply.

These guidelines relied heavily on published foreign guidelines due to scarcity of large-scale local studies on CAD. Expectedly, some recommendations may not be applicable in certain communities due to limited health resources. To address this challenge, some recommendations were modified to render them suitable to local practice. Nonetheless, local data including information from the PHA ACS Registry were integrated whenever possible.[2]

The Council on CAD will also create a task force to ensure the dissemination and monitor the implementation of these CPGs. The latter will hopefully provide meaningful research questions for future studies in the Philippines and answer some questions related to health outcomes and practices.

Coronary Artery Disease: Introduction

The global and local burden of ischemic heart disease is significant. In the Philippines, cardiovascular diseases ranked among the top 10 leading causes of morbidity and was the leading cause of mortality in 2009.[3]

CAD is commonly due to obstruction of the coronary arteries, usually the epicardial arteries, by atheromatous plaque. Obstructive CAD also has many non-atherosclerotic causes, including congenital abnormalities of the coronary arteries; myocardial bridging; coronary arteritis in association with the systemic vasculitides; and radiation-induced coronary disease. Myocardial ischemia may also occur in the absence of obstructive CAD, as in the case of aortic valve disease, hypertrophic cardiomyopathy, and idiopathic dilated cardiomyopathy.

Independent risk factors include a family history of premature coronary artery disease, cigarette smoking, diabetes mellitus, hypertension, hyperlipidemia, a sedentary lifestyle, and obesity. These risk factors accelerate or modify a complex and chronic inflammatory process that ultimately manifests as fibrous atherosclerotic plaque.

On the demographics of acute coronary syndrome (ACS) locally based from the 2 year results of PHA ACS registry (November 2011-November 2013), ACS is commonly noted in males comprising 67% with mean age group of 66 years old. Hypertension was the predominant risk factor at 77% followed at an alarming rate by diabetes and smoking at 39% and 34% respectively [3].

No uniform syndrome of signs and symptoms is initially seen in patients with CAD. Chest discomfort or angina pectoris is usually the predominant symptom. Adjectives frequently used to describe this distress include “viselike,” “constricting,” “suffocating,” “crushing,” “heavy,” and “squeezing.” In other patients, the quality of the sensation is more vague and described as a mild pressure-like discomfort, an uncomfortable numb sensation, or a burning sensation. The site of the discomfort is usually retrosternal, but radiation is common and usually occurs down the ulnar surface of the left arm; the right arm and the outer surfaces of both arms may also be involved. Epigastric discomfort alone or in association with chest pressure is not uncommon. Anginal discomfort above the mandible, below the epigastrium, or confined to the ear is rare.

Anginal “equivalents” (i.e., symptoms of myocardial ischemia other than angina) are common, particularly in the elderly, and are discussed in more detail in each section of these CPGs. A history of abnormal exertional dyspnea may be an early indicator of CAD even when angina is absent or no electrocardiographic (ECG) evidence of ischemic heart disease can be found. Dyspnea at rest or with exertion may be a manifestation of severe ischemia and leads to increases in left ventricular filling pressure. Nocturnal angina should raise the suspicion of sleep apnea.

In the local setting, chest pain was the most common symptom in patients with

ACS occurring in 74% while anginal equivalents presented only in 25% [3].

CAD may present as one or more of three clinical presentations: SIHD, NSTE-ACS, and STEMI. SIHD is the stable presentation of CAD. Patients generally experience angina only upon stress conditions. The other two presentations, where patients experience active ischemic discomfort (at rest) comprise ACS, with or without ST elevation on ECG. In the absence of ST elevation (NSTE-ACS), the patient may have unstable angina (UA) or non-ST elevation myocardial infarction (NSTEMI), and are differentiated by the level of cardiac enzymes. ST elevation in ECG indicate STEMI.

While these guidelines are being prepared for publication, the 2014 ACC/AHA Recommendations for the management of NSTE ACS was published. To the best of our knowledge, the recommendations set forth here do not depart significantly from the said guidelines.

REFERENCES

Philippine Heart Association. 2008 PHA Clinical Practice Guidelines for the Management of Coronary Artery Disease. Quezon City: Philippine Heart Association, 2009.

Yaneza LO, Abanilla JM, Abola MTB, Caole-Ang IV, Fernandez MBD, Lopez EA, Punzalan FER, Reyes EB; Steering Committee Members for the Philippine Heart Association-Acute Coronary Syndrome (PHA-ACS) Registry. Philippine Heart Association-Acute Coronary Syndrome Registry: 2 year Results. Phil J Cardiol 2013;2 (in press).

Leading Causes of Mortality. Manila: Department of Health, Republic of the Philippines; 2009. Available at: http://www.doh.gov.ph/node/198.html. Accessed on July 26, 2014.

Abbreviations and Acronyms

2D echo	two-dimensional echocardiogram
ACC	American College of Cardiology
ACCOMPLISH	Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension
ACEI	angiotensin-converting enzyme inhibitor
ACS	Acute Coronary Syndrome
ADP	adenosine diphosphate
AF	atrial fibrillation
AHA	American Heart Association
AMI	acute myocardial infarction
ARB	angiotensin receptor blocker

ARR	absolute risk reduction
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
AV	atrioventricular
BBB	bundle branch block
BEAUTIFUL	Morbidity-Mortality Evaluation of the If Inhibitor Ivabradine in Patients with Coronary Disease and Left Ventricular Dysfunction Trial
BMI	body mass index
BMS	bare metal stent
CABG	coronary artery bypass graft
CAD	coronary artery disease
CASS	Coronary Artery Surgery Study
CBC	complete blood count
CCB	calcium channel blocker
CCS	Canadian Cardiovascular Society
CCTA	coronary computerized tomography angiography
CCU	coronary care unit
cGMP	cyclic guanosine monophosphate
CHF	congestive heart failure
CK	creatine kinase
CKD	chronic kidney disease
CKMB	creatine kinase MB isotype
CLARITY-TIMI28	Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction 28
CMR	cardiovascular magnetic resonance
COMMIT	Clopidogrel and Metoprolol in Myocardial Infarction Trial
COMMIT-CCS	Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study
CONSENSUS	Cooperative New Scandinavian Enalapril Survival Study
COPD	chronic obstructive pulmonary disease
CRUSADE	Can Rapid Risk Stratification of Unstable Angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guideline
CSM	carotid sinus massage
CTA	computed tomographic angiography

CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events
CURRENT-OASIS7	Clopidogrel and Aspirin Optimal Usage to Reduce Recurrent Events–Seventh Organization to Assess Strategies in Ischemic Syndromes
CV	cardiovascular
CVD	cardiovascular disease
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
DHP	dihydropyridine
ECG	electrocardiogram
ECSS	European Cardiac Society Study
EDTA	ethylene di-amine tetra acetic acid
ER	emergency room
ESC	European Society of Cardiology
EUROPA	European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease
FAME-2	Fractional Flow Reserve vs. Angiography for Multi-vessel Evaluation
FFR	fractional flow
FRISC II	Fragmin and Fast Revascularization during Instability in Coronary Artery Disease trial
FUTURA/OASIS8	Fondaparinux with Unfractionated Heparin During Revascularization in Acute Coronary Syndromes
GDMT	guideline-directed medical treatment
GFR	glomerular filtration rate
GISSI	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico
GP	glycoprotein
GRACE	Global Registry of Acute Coronary Events
HbA1c	glycated hemoglobin
HDL	high density lipoprotein
HF	heart failure
HOPE	Heart Outcome Protection Evaluation
ICA	invasive coronary angiography
ICD	implantable cardioverter defibrillator

IHD	ischemic heart disease
IMA	internal mammary artery
IONA	Impact of Nicorandil on Angina
ISIS	International Study of Infarct Survival
IV	intravenous
IVUS	intravascular ultrasound
JNC 8	Eighth Joint National Committee
LAD	left anterior descending artery
LBBB	left bundle branch block
LDL	low density lipoprotein
LM	left main artery
LV	left ventricular
LVEF	left ventricular ejection fraction
LVH	left ventricular hypertrophy
MACE	major adverse cardiac event
METOCARD-CNIC	Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction Trial
MI	myocardial infarction
MIAMI	Metoprolol in Acute Myocardial Infarction trial
MIRACL	Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering
MPI	myocardial perfusion imaging
MR	mitral regurgitation
NNT	number needed to treat
NPV	negative predictive value
NSTE-ACS	non-ST elevation acute coronary syndrome
NSTEMI	non-ST elevation myocardial infarction
NTG	nitroglycerine
OASIS-5	Organization to Assess Strategies for Ischaemic Syndromes
OCT	optical coherence
OGTT	oral glucose tolerance test
OPCAB	off-pump coronary artery bypass
PCI	percutaneous coronary intervention
PDE5	phosphodiesterase 5
PET	positron emission tomography
PHA	Philippine Heart Association
PLATO	Study of Platelet Inhibition and Patient Outcomes

PRISM	Platelet Receptor inhibition for Ischemic Syndrome Management
PRISM-PLUS	Platelet Receptor inhibition for Ischemic Syndrome Management in Patients Limited to very Unstable Signs and Symptoms
PTP	pre-test probability
RAAS	renin-angiotensin-aldosterone system
REACH	Reduction of Atherothrombosis for Continued Health
ROSC	return of spontaneous circulation
RRR	relative risk reduction
SIHD	stable ischemic heart disease
SPECT	single photon emission computed tomography
STEMI	ST elevation myocardial infarction
SVT	supraventricular tachycardia
SYNTAX	Synergy between PCI with Taxus and Cardiac Surgery
TACT	Trial to Assess Chelation Therapy
TACTICS-TIMI18	Treat Angina With Aggrastat and Determine the Cost of Therapy With an Invasive or Conservative Strategy—Thrombolysis in Myocardial Infarction 18
TET	treadmill exercise
TIA	transient ischemic attack
TIMI	Thrombolysis in Myocardial infarction
TRITON-TIMI 38	Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction
UA	unstable angina
UFH	unfractionated heparin
VA	Veterans Affairs
VALIANT	Valsartan, Captopril, or Both in Myocardial Infarction Complicated by Heart Failure, Left Ventricular Dysfunction, or Both
VIVIFY	Evaluation of the Intravenous If Inhibitor Ivabradine after ST-segment Elevation Myocardial Infarction
VT	ventricular tachycardia

2014 Philippine Heart Association Clinical Practice Guidelines for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease

Introduction

Stable ischemic heart disease (SIHD), the stable component of the entire spectrum of ischemic heart diseases (IHD), is multifaceted. Hence, the Task Force Members involved in the development of these guidelines had expertise in general cardiology, echocardiography, non-invasive imaging, invasive coronary angiography and coronary intervention, critical care cardiology and thoracic cardiovascular (CV) surgery.

The Task Force undertook a comprehensive review of the 2009 Philippine Heart Association (PHA) Guidelines on Coronary Artery Disease (CAD);[1] contemporary guidelines such as those of the European Society of Cardiology (ESC) (2013) and the American College of Cardiology/American Heart Association (ACC/AHA) (2012);[2-3] and published evidence for the diagnosis and management of SIHD during the period of December 2013 to February 2014. The level of evidence for a particular diagnostic and therapeutic strategy, as well as the risk-benefit ratio of each strategy, was extensively discussed in order to arrive at quality recommendations for these guidelines. In addition, considerable effort was given in making the statements suitable to local practice.

As a summary, Statements 1 to 22 consider patients who have a first manifestation of angina with suspected SIHD and assessed to be in a chronic stable condition. Similar to the 2009 version of the PHA Guidelines, the recommendations are mainly based on the traditional pathophysiologic mechanism of SIHD as that of a disease causing exercise or stress-related angina due to atherosclerotic narrowing of at least 50% in the left main coronary artery, and at least 70% in one or more coronary arteries. Statements 21 and 22 consider patients with normal coronaries but have angina due to microvascular dysfunction and coronary vasospasm.

The present guidelines emphasize the Pre-Test Probability (PTP) of disease as strongly influencing the diagnostic testing strategy; the importance of non-invasive imaging in the diagnosis and risk stratification of patients; the increasing evidence that physiological assessment of CAD can be done during an invasive coronary angiography; the responsibility of health professionals to give guideline-directed medical treatment (GDMT) in all patients with SIHD; and to consider revascularization with an expected benefit to the patient's prognosis and symptoms.

In order to have an impact on real-life daily practice, the Task Force envisions that the revised guidelines be applied to clinical practice in the Philippines.

INITIAL PATIENT EVALUATION

Statement 1: History

The history is STRONGLY RECOMMENDED as the most essential part of the initial evaluation and includes a detailed description of the symptom of chest pain, classification of the severity of chest pain, and determination of the presence of risk factors and co-morbid conditions.

A careful history remains the cornerstone of the diagnosis of stable angina, and it has been repeatedly stated that it is possible to make a confident diagnosis in the majority of patients based on the history alone.

The characteristics of chest pain related to myocardial ischemia include five components: quality or character; location; duration; factors that precipitate the pain; and relieving factors. The chest pain caused by myocardial ischemia is usually described as a sense of pressure or heaviness (other adjectives used are constricting, squeezing, suffocating and viselike); substernal in location or near the sternum (may be felt anywhere from the epigastrium to the lower jaw); brief in duration (no more than 10 minutes or even less but unlikely to last for seconds); precipitated by exertion, emotional stress, after a heavy meal, or cold weather; and relieved or disappears with rest or sublingual nitrates.

Definitions of typical angina are summarized in Table 1. Typical angina has been described as meeting all three of the following characteristics: substernal chest discomfort of characteristic quality and duration; provoked by exertion or emotional stress; and relieved by rest and/or nitrates within minutes. Atypical angina meets two of these characteristics and is most frequently typical angina in location and character, relieved by nitrates but has no precipitating factors. Non-anginal pain has none or meets only one of the characteristics.

It is likewise useful to classify the severity of angina using a grading

Table 1. Traditional clinical classification of chest pain

Typical angina (definite)	Meets all three characteristics: • Substernal chest discomfort of characteristic quality and duration; • Provoked by exertion or emotional stress • Relieved by rest and/or nitrates within minutes
Atypical angina (probable)	Meets two characteristics
Non-anginal chest pain	Meets none or only one of the characteristics

Table 2. Classification of angina severity according to the Canadian Cardiovascular Society

Class I	Ordinary activity such as walking or climbing stairs does not cause angina. Angina with strenuous or rapid or prolonged exertion at work or recreation.
Class II	Slight limitation of ordinary activity. Angina on walking or climbing stairs rapidly; walking or stair climbing after meals; in cold or wind; under emotional stress; or during the first few hours after awakening. Walking more than two blocks on the level or climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.
Class III	Marked limitation of ordinary physical activity. Angina on walking one to two blocks on the level, or one flight of stairs in normal conditions and at a normal pace.
Class IV	Inability to carry on any physical activity without discomfort – angina syndrome may be present at rest.

system such as that of the Canadian Cardiovascular Society Classification (CCS) as shown in Table 2.[4] This may be used to quantify the threshold at which angina occurs in relation to physical activities and to determine the functional impairment of patients. It is important to remember that the CCS class assigned is the maximum limitation and is not fixed: the patient may do better on other days or may improve with therapy. A limitation of this grading system, however, is its dependence on accurate patient observation and patients' varying tolerance for symptoms. Functional studies have also shown a weak correlation with objective measures of exercise performance.

After obtaining a detailed description of chest pain, the presence of risk factors and co-morbid conditions should be determined. Hence, the clinician should identify conventional risk factors for the development of CAD such as the presence of hypertension, dyslipidemia, cigarette smoking, diabetes or impaired glucose tolerance, obesity and sedentary lifestyle. It is also important to reliably identify co-morbid conditions such as chronic heart failure (HF), cerebrovascular disease, peripheral vascular disease, or chronic kidney disease, as these conditions may have an adverse influence on prognosis, presumably through their effect on the progression of atherosclerosis.

Statement 2: Physical Examination

A focused physical examination is STRONGLY RECOMMENDED during initial evaluation to exclude other conditions associated with

angina, search for evidence of non-coronary vascular disease and identify signs of co-morbid conditions; it is also recommended to obtain measurements of the body mass index (BMI) and waist circumference to assist in evaluation of Metabolic Syndrome.

The physical examination is often normal in patients with SIHD and is generally not useful for confirming the diagnosis. Nonetheless, a focused physical examination is important during the initial evaluation of patients. A focused physical examination may exclude other conditions associated with angina such as anemia, hypertension, valvular heart disease, hypertrophic obstructive cardiomyopathy or arrhythmias. One should search for evidence of non-coronary vascular disease such as auscultation for carotid or femoral bruit; palpation of an abdominal aneurysm; and detection of diminished peripheral pulses. Signs of co-morbid conditions such as thyroid disease, renal disease, hypertension or diabetes should be identified. The association between these findings and high-risk patients are well documented and portend an adverse CV prognosis. Other key physical examination findings are: lipid deposits such as xanthelasma and xanthomas; earlobe crease; corneal arcus senilis; and retinal arteriolar exudates; which signify the presence of risk factors for atherosclerosis (e.g., dyslipidemia, hypertension and diabetes).

A cardiac examination during or immediately after an episode of myocardial ischemia may reveal a displaced ventricular impulse; third or fourth heart sounds; and a transient apical systolic murmur of mitral insufficiency due to reversible papillary muscle dysfunction. These findings are more prevalent in patients with extensive CAD and severe left ventricular (LV) systolic dysfunction and may likewise indicate an adverse prognosis. However, these findings are not specific for SIHD.

Lastly, it is also recommended to obtain BMI, waist circumference and waist-to-hip ratio to assist in evaluation of Metabolic Syndrome and weight management for lifestyle modification.

Statement 3: Resting 12-lead ECG

A resting 12-lead electrocardiogram (ECG) IS RECOMMENDED during initial evaluation, and during or immediately after an episode of chest pain suspected to indicate clinical instability.

A resting 12-lead ECG is recommended and should be recorded during initial evaluation of all patients suspected to have SIHD. This baseline ECG will be useful for comparison in future situations.

A normal resting ECG is seen in approximately half of patients with SIHD, even in patients with severe angina, and does not exclude the diagnosis of

ischemia. In addition, a normal ECG suggests the presence of normal resting LV function and a more favorable long-term prognosis.

The most common ECG abnormalities in SIHD are nonspecific ST-T wave changes with or without abnormal Q waves. The occurrence of ST-T wave abnormalities and Q waves may correlate with the severity of underlying disease in patients with known CAD and worsens prognosis. Abnormal Q waves are specific but insensitive indicators of previous myocardial infarction (MI). Other conditions that can produce ST-T wave abnormalities include LV hypertrophy (LVH) and dilation; conduction disturbances; electrolyte abnormalities; neurogenic effects; and anti-arrhythmic drugs.

The resting ECG may also show these mentioned abnormalities such as LVH; conduction disturbances such as left bundle branch block (LBBB) or left anterior fascicular block; arrhythmias such as atrial fibrillation (AF) or ventricular premature beats; and even pre-excitation. Although these abnormalities may have low sensitivity and specificity for CAD, these findings suggest a poor prognosis since they are often associated with multi-vessel disease and impairment of LV function.

A resting 12-lead ECG should also be recorded during or immediately after an episode of chest pain to allow detection of ST-segment changes in the presence of ischemia. The ECG can be diagnostic in documenting an ST-elevation MI, or may assist in clarifying the differential diagnosis of unstable angina if the ST-T wave depressions are dynamic. Such information may then lead to appropriate investigations and treatment decisions. In patients with vasospastic angina, an ECG during or immediately after an episode of chest pain can be diagnostic because the ST-segment shifts are usually reversible once coronary vasospasm is relieved with nitrates.

Statement 4: Laboratory Tests

It IS RECOMMENDED that the following initial laboratory tests be performed to establish CV risk factors, identify possible causes of ischemia and determine prognosis:

1. **Fasting lipid profile (total cholesterol, high density lipoprotein [HDL] cholesterol, low density lipoprotein [LDL] cholesterol and triglyceride levels);**
2. **Fasting glucose and/or glycated hemoglobin (HbA1c) level if available; additional oral glucose tolerance test (OGTT) if both are inconclusive;**
3. **Complete blood count (CBC);**
4. **Creatinine level with estimation of glomerular filtration rate (GFR);**
5. **Biochemical markers of myocardial injury (Troponin T or I) if**

clinical evaluation suggests an Acute Coronary Syndrome (ACS);

6. **Thyroid hormone levels if with clinical suspicion of thyroid disorder, and;**
7. **Liver function tests early after beginning statin therapy.**

Fasting lipid profile (including total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides) and fasting plasma glucose and HbA1c (an additional OGTT if both are inconclusive) should be evaluated in all patients with suspected SIHD to establish the patient's risk profile and ascertain the need for treatment. Knowledge of lipid and glucose levels is important because of the well-recognized association between elevated levels and adverse CV outcomes.

The lipid profile and glycemic status should be re-assessed periodically to detect development of dyslipidemia and diabetes, respectively, and to determine efficacy of treatment if initiated. There are no recommendations from foreign guidelines as to the frequency of repeat measurements, but expert consensus suggests annual measurement. However, patients with initial high levels of lipids or glucose should have more frequent measurements to determine efficacy of treatment.

The CBC provides information related to possible cause of ischemia (e.g., anemia) as well as prognostic information (e.g., total white cell count). Thyroid hormone levels should also be measured when there is a clinical suspicion of a thyroid disorder.

The serum creatinine and baseline renal function, with estimation of the GFR using formulas such as the Cockcroft-Gault; Modification of Diet in Renal Disease; or Chronic Kidney Disease Epidemiology Collaboration formulae, have an impact on prognosis in patients with SIHD.[5-7]

If there is a clinical suspicion of ACS, biochemical markers of myocardial injury, such as Troponin T or Troponin I, should be determined because troponins have a central role in identifying ACS. If troponin is elevated, further management should follow the part on NSTE-ACS part of these guidelines.

Routine measurement of baseline liver function tests early after beginning statin therapy is recommended as some patients develop elevations in liver enzymes with intensive statin therapy.

Statement 5: Chest X-Ray

The chest x-ray (postero-anterior and lateral views) does not provide specific information for diagnosis, but IS RECOMMENDED in patients with signs or symptoms of congestive heart failure (CHF); aortic dissection and/or aneurysm; valvular heart disease; pericardial disease; or pulmonary disease.

The usefulness of the chest x-ray as a routine test in patients with SIHD is not well established even though a chest x-ray is frequently used in the assessment of patients with chest pain. The chest x-ray does not provide specific information for diagnosis or event risk stratification. However, it should be considered in the above conditions to be able to rule out these atypical causes of chest pain.

Statement 6: Echocardiography

A transthoracic two-dimensional and Doppler echocardiography IS RECOMMENDED in the initial evaluation of all patients for exclusion of alternative causes of angina; identification of segmental or regional wall motion abnormalities suggestive of CAD; and measurement of LV ejection fraction (LVEF) and LV diastolic function for risk stratification purpose.

Echocardiography is now recommended in the initial evaluation of all patients with symptoms suggestive of SIHD. In the first version of the PHA guidelines, echocardiography is recommended only in patients with clinically detected murmurs, history and ECG changes of prior MI, and signs or symptoms of HF.[1] Furthermore, it was stated there that most patients undergoing a diagnostic evaluation for stable CAD do not need an echocardiogram.

There are several reasons why echocardiography should be performed in all patients with a first presentation of suspected SIHD. First of all, disorders such as aortic stenosis or hypertrophic obstructive cardiomyopathy can be ruled out as alternative causes of angina. Secondly, regional wall motion abnormalities may be detected, which increase the likelihood of CAD. The segmental wall motion abnormalities seen with ischemia or infarction correspond closely with the coronary artery blood supply to the myocardium. Resting two-dimensional and Doppler transthoracic echocardiography also provide information on global ventricular function, an important prognostic parameter in patients with SIHD. Estimation of LV systolic function is important in all patients for risk stratification as stated in current foreign guidelines (ESC and ACC/AHA).[2,3]

The detection of impaired diastolic filling may be the first sign of an acute ongoing ischemia indicating microvascular dysfunction. The severity of diastolic dysfunction also correlates with the prognosis in recent published studies and a restrictive filling pattern has points to adverse consequences. Tissue Doppler imaging and strain rate measurements are additional methods for detecting heart failure with preserved LV ejection fraction in patients who complain of shortness of breath as angina equivalent.

For all these reasons, echocardiography is now recommended as a

necessary examination in the initial evaluation of all patients with suspected SIHD.

Statement 7: Ambulatory ECG Monitoring

Ambulatory ECG (24-hour) monitoring IS RECOMMENDED in patients with suspected arrhythmia, and may be recommended in patients with suspected vasospastic angina.

Ambulatory ECG (Holter) monitoring has a specific role in detecting arrhythmias and suspected vasospastic angina (ST segment elevation during acute ischemia) and is recommended in these subgroups of patients. There is, however, no good evidence to support its routine use as a diagnostic or prognostic tool over that provided by the exercise ECG and a stress imaging study.

Statement 8: Pre-Test Probability (PTP) Assessment

It IS STRONGLY RECOMMENDED that clinicians estimate the PTP for SIHD after initial evaluation; such an assessment will determine whether or not to proceed with further non-invasive or invasive testing to establish the diagnosis of SIHD.

Table 3. Diamond and Forrester pre-test probability of coronary artery disease by age, sex and symptoms

Age (years)	Sex	Probability of each kind of chest pain		
		Typical/Definite Angina Pectoris	Atypical/ Probable Angina Pectoris	Non-anginal chest pain
≤ 39	Men	Intermediate	Intermediate	Low
	Women	Intermediate	Very low	Very low
40-49	Men	High	Intermediate	Intermediate
	Women	Intermediate	Low	Very low
50-59	Men	High	Intermediate	Intermediate
	Women	Intermediate	Intermediate	Low
≥ 60	Men	High	Intermediate	Intermediate
	Women	High	Intermediate	Intermediate

High: > 90% pre-test probability
Intermediate: between 10% and 90% pre-test probability
Low: between 5% and 10% pre-test probability
Very low: < 5% pre-test probability
Adapted from Diamond GA, Forrester JS. (1982). Probability of CAD.[8]

Table 4. Likelihood that signs and symptoms are secondary to coronary artery disease

Feature	High likelihood	Intermediate likelihood	Low likelihood
History	Male > 40 years or Female > 60 years presenting with symptoms of typical angina with risk factors for CAD; known CAD or MI	Atypical angina Age > 40 years Male sex Diabetes type 2	Absence of high or intermediate likelihood features
Physical examination	Stigmata of CAD; xanthomas or xanthelasmas; extracardiac vascular disease	Extracardiac vascular disease	Chest discomfort reproduced by palpation
ECG (12-lead)	ST-segment depression in two or more leads; old MI changes	ST-segment depression in two or more leads, or normal ECG	Normal ECG
Echocardiography	Segmental wall motion abnormalities; Reduced LVEF	No wall motion abnormalities; Normal LVEF	No wall motion abnormalities; Normal LVEF

CAD=coronary artery disease; MI=myocardial infarction; ECG=electrocardiogram; LVEF=left ventricular ejection fraction.

As in the ACC/AHA and ESC guidelines, this new version of guidelines strongly recommends estimating the PTP in patients with suspected SIHD.[2,3] The process begins with a clinical assessment of the probability that a particular patient has SIHD after an initial evaluation with history, physical examination, ECG, chest x-ray (if done), and echocardiography. Diamond and Forrester have observed that the simple clinical parameters of age, gender, and description of chest pain were powerful predictors of the presence of CAD (Table 3).[8] Other determinants of PTP are the prevalence of CAD in the population; the CV risk factors; and in this revised guidelines, the incorporation of the results of the ECG, chest x-ray and echocardiography (Table 4).

Because of the interdependence of PTP and the performance of diagnostic

Table 5. Recommended approach to diagnostic testing based on PTP

PTP Category	Approach to Diagnostic Testing
Low PTP	Exclude other causes of chest pain (e.g., diagnostic testing to identify gastrointestinal, pulmonary or musculoskeletal causes)
Intermediate PTP	Should undergo noninvasive testing, preferably stress imaging study, to definitively establish SIHD
High PTP	Clinician makes a presumptive diagnosis of obstructive CAD; no further non-invasive stress testing; coronary angiography, as indicated, for further risk stratification

PTP=pre-test probability.

methods (sensitivity and specificity; positive and negative predictive values [NPV]), recommendations for diagnostic testing need to take into account the PTP.

Since non-invasive stress imaging diagnostic methods have typical sensitivities and specificities of approximately 85%, hence 15 % of diagnostic test results will be false and performing no test at all will provide fewer incorrect diagnoses in patients with a PTP below 15% or a PTP above 85%. Patients with an intermediate PTP of 15% to 85% should undergo further non-invasive stress imaging for definitive diagnosis (Table 5).

Patients with chest pain who have a low probability of significant CAD (below 15%) should have other cardiac causes of chest pain excluded, and their CV risk factors modified and treated appropriately. Under such circumstances, further non-invasive stress testing is not indicated.

Patients with a clinical PTP higher than 85% should no longer undergo non-invasive stress testing and may proceed directly to invasive coronary angiography for diagnostic purposes, because it can be assumed clinically that such high-risk patients have significant obstructive CAD (Table 5). Non-invasive stress testing may, however, be indicated for prognostic information and risk stratification.

ESTABLISHING DIAGNOSIS

Statement 9: Principles of Stress Testing

Non-invasive stress testing IS STRONGLY RECOMMENDED in patients with intermediate PTP in order to establish the diagnosis and risk stratification of patients; the incremental information provided by

such testing will influence clinical decision-making on subsequent management.

This revised version of the guidelines recommends a stepwise approach for establishing diagnosis and risk stratification of patients. Once an intermediate PTP has been established in a particular patient, the next step is to proceed with non-invasive stress testing for definitive diagnosis as well as risk stratification assessment. It is recommended to employ the stress test not only for diagnostic but for prognostic purposes as well. This concept utilizes the Bayesian approach wherein the clinician's pre-estimates of disease are integrated with the results of the non-invasive stress test in order to generate post-test disease probabilities for a given patient.

The generally higher sensitivity of a stress imaging study (70% to 90%) compared to an exercise ECG or treadmill exercise test (45% to 50%) is the reason why a stress imaging study is the preferred test modality whenever resources and expertise are available. The number of false test results will become higher in patients with PTP higher than 65% when employing the less sensitive exercise ECG.

Depending on the results of the non-invasive stress test, GDMT is instituted; or early invasive coronary angiography and subsequent revascularization may be performed.

Statement 10: Stress Imaging

A stress imaging study IS RECOMMENDED as the initial diagnostic and prognostic test, if facilities, resources and local expertise permit, in patients within the higher range of PTP; patients with LVEF less than 50% without typical angina; patients with resting ECG abnormalities and especially symptomatic patients with prior revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]). Exercise testing rather than pharmacological testing is recommended whenever possible.

A stress imaging study is based on the concept that an increased cardiac workload is necessary to elicit signs of physiologic dysfunction and ischemia. Imaging during ischemia is referred to as stress imaging.

A stress imaging study is recommended as the initial diagnostic and prognostic test of choice because of the following reasons: superior diagnostic and prognostic performance over the conventional exercise ECG or treadmill exercise test due to the ability to quantify and localize areas of ischemia; the ability to provide diagnostic information in the presence of resting ECG abnormalities or inability of the patient to exercise; the ability to establish the functional significance of lesions in patients with confirmed lesions by invasive

coronary angiography; and the ability to demonstrate myocardial viability.

In general, stress echocardiography, stress myocardial perfusion imaging (MPI) by single photon emission computed tomography (SPECT) and stress CV magnetic resonance (CMR) have similar applications. These imaging techniques may be used in combination with either exercise or pharmacological stress. Exercise testing rather than pharmacological testing is recommended whenever feasible because exercise provides a more physiological environment. Ultimately, the choice of which test to perform will depend on local facilities, expertise and cost-effectiveness considerations. A summary of the various stress imaging techniques follows:

Stress echocardiography

Because echocardiographic wall motion at rest may be normal in a patient with SIHD, stress echocardiography is necessary for diagnosis. Stress echocardiography is performed with exercise (treadmill or bicycle ergometer) or with pharmacological agents. Exercise is the test of choice because it provides physiological data such as exercise time and workload, as well as information about changes in heart rate, blood pressure and ECG. On the other hand, a pharmacological test is preferred when there is need for viability assessment and/or the patient is unable to exercise adequately. The pharmacological agent of choice is dobutamine.

Most data on the diagnostic accuracy of stress echocardiography relied on inducible wall thickening abnormalities as a marker of ischemia.[2] Recent data have demonstrated the ability of echocardiography to detect ischemia beyond wall motion assessment. Myocardial contrast echocardiography utilizes micro-bubbles allowing assessment of myocardial perfusion as well as enhancing image quality for detection of wall thickening. Tissue Doppler imaging and strain rate imaging improves the diagnostic performance of stress echocardiography by detecting LV systolic and diastolic segmental and global abnormalities in ischemic segments.

Stress MPI

SPECT using either thallium 201 or technetium-99m as radiopharmaceutical tracers are employed in association with either a symptom-limited exercise test on a treadmill or bicycle ergometer or pharmacological stress testing with adenosine or dobutamine in patients who are unable to exercise adequately. Stress MPI is performed to produce images of regional tracer uptake reflecting regional myocardial blood flow. Myocardial hypoperfusion is characterized by reduced tracer uptake during stress in comparison with the uptake at rest. Transient LV dilation, reduced post-stress ejection fraction, and

increased tracer uptake in the lung fields, are important predictors of severe and extensive CAD.

MPI using positron emission tomography (PET) is superior to SPECT perfusion imaging in terms of image quality and diagnostic accuracy, and has the ability to quantify blood flow in mL/min, which allows detection of microvascular disease. However, PET is more expensive, and the imaging radiotracers used are less widely available.

Stress CMR

CMR uses a complex technology that includes magnetic and radiofrequency fields, making it considerably different from other imaging approaches. It is a safe, non-invasive technology that benefits from not using potentially harmful ionizing radiation or nephrotoxic dyes. At present, CMR has evolved into a useful method with the potential to resolve important limitations of stress echocardiography and stress MPI.

This technique, similar to stress echocardiography, can detect wall motion abnormalities induced by ischemia from a dobutamine infusion. Stress CMR is particularly useful in patients with suboptimal acoustic windows. Even with the addition of echo contrast agents, there will be some patients who will not have adequate images of diagnostic quality for stress echocardiography. In these patients with poor echocardiographic images, fast cine CMR is capable of detecting ischemia. The diagnostic performance (sensitivity and specificity) of dobutamine stress CMR is similar to that of dobutamine stress echocardiography.

Table 6. Sensitivity and specificity of non-invasive stress studies used to diagnose SIHD

Test	Sensitivity (%)	Specificity (%)
Exercise ECG	45-50	85-90
Exercise stress echocardiogram	80-85	80-88
Exercise stress MPI	73-92	63-87
Dobutamine stress echo	79-83	82-86
Dobutamine stress CMR	79-88	81-91
Vasodilator stress echo	72-79	92-95
Vasodilator stress MPI	90-91	75-84
Vasodilator stress PET	81-97	74-91

SIHD=stable ischemic heart disease; ECG=electrocardiogram; MPI=myocardial perfusion imaging; CMR=cardiovascular magnetic resonance; PET=positron emission tomography.

Table 7. Advantages and disadvantages of the stress imaging studies used to diagnose SIHD.

Test	Advantages	Disadvantages
Stress echocardiogram	Identifies affected area of myocardium by its coronary distribution; no ionizing radiation.	Image quality may be suboptimal in obese patients but can be improved with contrast
Stress MPI	Also identifies affected area of myocardium by coronary distribution; highly prognostic of outcomes and allows evaluation of viability.	Exposure to ionizing radiation; poor image quality in very obese patients.
Stress CMR	Evaluates both wall motion and myocardial perfusion; can reliably distinguish between viable and non-viable myocardium; identifies coronary anomalies.	Increased cost of study; not widely available; complex study and requires expertise in methodology in its interpretation.

SIHD=stable ischemic heart disease; MPI=myocardial perfusion imaging; CMR=cardiovascular magnetic resonance.

Perfusion CMR is another technique for detecting ischemia and has a similar diagnostic accuracy with SPECT perfusion imaging. SPECT imaging suffers from attenuation artifacts and a relatively poor resolution, whereas CMR stress and vasodilator testing have very good temporal and spatial resolution of the cardiac images. Although CMR analysis is usually visual (identification of reduced signal areas of perfusion), quantitative CMR perfusion measurements are more accurate and show good correlations with invasive fractional flow reserve (FFR) measurements.

Table 6 shows the comparative sensitivity and specificity of the various stress imaging techniques discussed. Table 7 discusses the advantages and disadvantages of each technique.

Statement 11: Exercise ECG (Treadmill Exercise Test or TET)

An exercise ECG (TET) IS RECOMMENDED as the initial diagnostic and prognostic test, if resources and local expertise for a stress imaging study are not available, in patients with intermediate PTP who have normal resting ECGs and are able to exercise.

Because of its simplicity, lower cost and widespread availability, the TET is the initial test of choice to identify inducible ischemia in the majority of patients with intermediate PTP who are able to exercise. The low sensitivity of the TET (45% to 50%) despite a high specificity (85% to 90%) is the reason why it is not recommended in patients with a PTP greater than 65%. In the latter case, a stress imaging study is more appropriate.

It is important to remember that the TET employs exercise ECG testing and, hence, is not of diagnostic value in the presence of significant ECG abnormalities such as LBBB or right bundle branch block, intraventricular conduction defects, Wolff-Parkinson-White-syndrome, paced rhythm, LVH, AF, electrolyte imbalance and the use of digitalis, in which cases the ECG changes are not interpretable.

The main diagnostic ECG abnormality consists of a horizontal or down-sloping ST segment depression greater than or equal to 1 mm, persisting for at least 0.06 to 0.08 s after the J-point, in one or more ECG leads during peak exercise. Diagnostic ECG changes may appear only during the recovery phase in about 15% of patients. The test also provides prognostic information such as heart rate and blood pressure response; exercise duration; and maximum workload achieved. The TET should be symptom-limited; should achieve 85% of the patient's maximum predicted heart rate; and should be performed without the influence of anti-ischemic drugs to improve sensitivity significantly.

The TET may also be used to evaluate the efficacy of medical treatment and/or revascularization, and assist in the prescription of exercise after control of symptoms. It is not recommended to do routine periodic exercise testing in patients whose symptoms are controlled and have no worsening of conditions.

Statement 12: Coronary Computed Tomographic Angiography (CTA)

Coronary CTA MAY BE RECOMMENDED as an alternative to a stress imaging study or TET in patients within the lower range of intermediate PTP; patients with a non-conclusive stress study or who have contraindications to a stress study; if fully diagnostic image quality can be expected. It is not recommended as a "screening" test in asymptomatic individuals or those with a low probability of obstructive coronary artery disease.

Coronary CTA has emerged as a breakthrough non-invasive modality in the past decade to diagnose coronary artery stenosis. The reported diagnostic performance of 64-slice CT were sensitivities of 95% to 99%; specificities of 64% to 83%; and negative predictive value (NPV) of 97-99%

for the identification of individuals with at least one coronary artery stenosis by invasive coronary angiography.

The high NPV of a coronary CTA excluding the presence of significant stenosis makes the test potentially useful for patients with low intermediate PTPs (below 50%), or patients with an equivocal or non-conclusive stress imaging or TET or patients with contraindications to these studies. Coronary CTA should also be considered in patients with a stress test result that contradicts clinical judgment (e.g. a false positive stress test result and clinical judgment speaks against the presence of severe stenosis). Furthermore, a coronary CTA showing no significant stenosis can reassure patients and likewise direct referring physicians to institute GDMT and not proceed with an invasive strategy.

To obtain maximal diagnostic information, adequate technology (at least 64-slice CT) and careful patient selection are mandated for a fully diagnostic image quality. According to expert consensus, patients should have adequate breath holding capabilities, a favorable calcium score (e.g. Agatston score less 400), sinus rhythm, a heart rate of 65 beats per minute or less, and not severely obese. If necessary, the use of short-acting beta blockers or other heart rate-lowering medication is recommended.

Since the prevalence of coronary artery stenosis is high in symptomatic individuals with an Agatston score greater than 400, and the specificity of coronary CTA decreases with increasing amounts of coronary calcium, it is reasonable not to proceed with coronary CTA if the calcium score exceeds 400. Also, coronary CTA is less reliable in patients with coronary stents, due to artifacts caused by metal. On the other hand, the assessment of bypass grafts in post-CABG patients is highly accurate whereas the evaluation of native coronary vessels in these patients is difficult and prone to false positive findings.

No data are available to support the use of coronary CTA as a “screening” test in asymptomatic individuals or those with a low probability of obstructive CAD and is, therefore, not recommended for this purpose.

Statement 13: Invasive Coronary Angiography (ICA)

ICA IS RECOMMENDED in patients with high PTP either as an initial test or after an initial non-invasive study with stress imaging or TET in specific clinical circumstances; ICA is not recommended in patients who refuse invasive procedures and prefer medical therapy, and those in whom revascularization is not expected to improve functional status or quality of life.

Although ICA remains the gold standard and most accurate technique for

the diagnosis of obstructive CAD, non-invasive testing in patients with SIHD can establish the likelihood of obstructive CAD with an acceptable degree of certainty. Thus, ICA is rarely necessary for the sole purpose of establishing or excluding the diagnosis of obstructive CAD in SIHD. ICA may, however, be indicated in specific clinical circumstances for definitive diagnosis of CAD and precise assessment of its anatomical severity. ICA is recommended as an initial diagnostic and prognostic test in the following clinical circumstances:

1. Patients who survived a sudden cardiac arrest or serious ventricular arrhythmia and are now in stable condition;
2. Clinically stable SIHD patients who develop signs and symptoms of HF despite medical therapy;
3. Patients with typical angina and reduced ejection fraction (less than 50%) and are unable to undergo stress imaging studies due to contraindications;
4. Patients with severe angina (CCS III-IV) and high PTP (greater than 85%) with likelihood for CV events, particularly if the symptoms inadequately respond to medical therapy, and;
5. Patients whose special professions (e.g., pilots, bus drivers) require a definitive diagnosis.

ICA is recommended after an initial non-invasive stress imaging study or TET in the following clinical circumstances:

1. Patients with clinical characteristics and high PTP (greater than 85%) of severe CAD on non-invasive stress testing regardless of angina severity;
2. Patients with angina refractory to medical therapy;
3. Patients with mild or no angina but with high event-risk profile on non-invasive stress testing for risk stratification purpose;
4. Patients with reduced LVEF (less than 50%) with moderate risk criteria on non-invasive stress testing and demonstrable ischemia (may be recommended or reasonable to consider), and;
5. Patients with inconclusive or conflicting results from multiple non-invasive tests and in whom definitive diagnosis needs to be established (may be recommended or reasonable to consider).

The severity of luminal obstruction and location of coronary disease on ICA are important prognostic indicators in patients with SIHD. The classification of disease into one-vessel, two-vessel, three-vessel, or left main (LM) CAD has been used to relate severity of disease with the risk of subsequent cardiac events. In the Coronary Artery Surgery Study (CASS) registry, the 12-year survival rate of patients with normal coronary arteries was 91%, compared with 74% for those with one-vessel disease; 59% for

those with two-vessel disease; and 50% for those with three-vessel disease.[9] The presence of severe stenosis of the LM coronary artery and proximal left anterior descending (LAD) artery also significantly reduces the survival rate, and thus, are poor prognostic indices. It should be appreciated that absolute estimates of event risk in these older studies probably overestimated the risk of future CV events since medical therapy was not at the level of current guideline recommendations during that time.

The most serious limitation to the use of ICA as a diagnostic and prognostic test in patients with SIHD is its inability to identify which coronary lesions can be considered "vulnerable" or at high risk for future events such as MI or sudden death. It has been stated that "it is not necessarily the plaque causing the most severe stenosis that subsequently ruptures" thereby leading to MI as a result of thrombotic occlusion at the site of plaque rupture. Mild obstructions can likewise rupture and thrombose, causing MI and sudden death.

Additional methods that provide more information for event risk stratification include the imaging of coronary atheroma thru intravascular ultrasonography (IVUS) or optical coherence tomography, and the assessment of the functional severity of coronary lesions through the measurement of FFR. IVUS provides a cross-sectional view of the coronary artery, enhancing the detection, quantification and characterization of "vulnerable" coronary atheroma.

FFR, on the other hand, identifies hemodynamically relevant coronary lesions when evidence for ischemia is not available from non-invasive stress testing. Revascularization of stenosis with FFR of less than 0.8 is recommended in patients with symptoms of angina or positive non-invasive stress studies. Hence, incorporation of these new intracoronary techniques in the performance of ICA has substantially improved the diagnostic and prognostic assessment of patients with SIHD.

In summary, the decision to proceed to ICA should be based on the patient's symptomatic status despite medical therapy and high-risk status derived from clinical data and non-invasive stress test results. ICA is not warranted for patients who are asymptomatic or have mild angina and good LV function in the absence of ischemia or high-risk criteria on non-invasive stress testing.

Furthermore, it should be emphasized that ICA is not recommended in patients who refuse invasive procedures and prefer medical therapy alone; those who are not candidates for revascularization with PCI or CABG; or those in whom revascularization is not expected to improve functional status or quality of life.

Table 8 summarizes the appropriateness of the various tests used in multimodality testing for the detection and risk assessment of symptomatic SIHD patients.

Table 8. Multimodality testing for the detection and risk assessment of symptomatic ischemic heart disease.

Indication Text	Exercise ECG	Stress MPI	Stress Echo	Stress CMR	Calcium Scoring	CCTA	Invasive coronary angiography
1. Low pretest probability of CAD, ECG interpretable AND able to exercise	R	R	R	R	R	R	R
2. Intermediate pretest probability of CAD, ECG interpretable AND able to exercise	A	A	A	M	R	M	R
3. Intermediate pretest probability of CAD, ECG uninterpretable OR unable to exercise	R	A	A	A	R	A	M
4. High pretest probability of CAD, ECG interpretable AND able to exercise	R	A	A	A	R	M	A
5. High pretest probability of CAD, ECG uninterpretable OR unable to exercise		A	A	A	R	M	A

A – Appropriate; M – May Be Appropriate; R – Rarely Appropriate
ECG=electrocardiogram; MPI=myocardial perfusion imaging; CMR=cardiovascular magnetic resonance; CCTA=coronary computerized tomography angiography; CAD=coronary artery disease.

MANAGEMENT

Statement 14: General Overview of Management

The overall management of patients with SIHD encompasses lifestyle modification; control and treatment of risk factors; evidence-based pharmacological therapy to improve prognosis and reduce symptoms of angina; patient education about the disease; and revascularization when indicated.

Comprehensive management of SIHD encompasses all of the above aspects with the goal of reducing symptoms and improving prognosis (e.g., prevent MI and death). Although discussed individually in these guidelines, all of these approaches must be integrated simultaneously in each patient to eradicate symptoms and prevent the occurrence of CV events. It is also noteworthy to remember that patient preference and cost-effectiveness considerations are important components of the overall management strategy, especially in the Philippine setting where healthcare is minimally subsidized by the national government.

Statement 15: Lifestyle Modification and Treatment of Risk Factors

It IS STRONGLY RECOMMENDED that lifestyle modification and treatment of risk factors be integrated into GDMT to reduce major CV events.

Clinicians tend to focus on diagnostic and therapeutic interventions that are based on recent technological advances, often overlooking important aspects of high-quality care. Among these neglected areas are the counseling about lifestyle modification and treatment of risk factors.

Recommendations on lifestyle modification and treatment of risk factors are briefly described as follows:

Healthy diet

Diet has an important impact on CAD risk, and a healthy diet reduces CAD risk. Total caloric intake should be limited to the amount of energy needed to maintain a healthy weight (e.g., BMI of less than 25 kg/m^2). If weight reduction is desired, the balance must be in lower calorie intake. No dietary supplements are necessary when following the rules for a healthy diet, and observational studies have given the following general recommendations as follows:[2,3]

1. Increase polyunsaturated fatty acid consumption, mainly from oily fish: 2 to 3 servings of oily fish per week may help prevent CV disease (CVD);

2. Saturated fatty acids must comprise less than 10% of the total energy intake; protein sources that are low in saturated fats should replace those high in these harmful fats;
3. Limit salt intake to less than 5 grams per day; added salt should be limited;
4. Consume 30 to 45 grams of fiber per day (wholegrain products, fruits and vegetables); simple carbohydrates that have a high glycemic load should be avoided in favor of carbohydrate sources that are high in fiber;
5. Consume 200 grams of vegetables per day (2 to 3 servings or 1 to 4 cups per day);
6. Eat 200 grams of fruits per day (2 to 3 servings or 1 to 2.5 cups per day), and;
7. Limit consumption of alcoholic beverages to two glasses per day (20 grams) for men, and one glass per day (10 grams) for women

Physical activity

Physical activity should be incorporated into the patient's daily activities, with evaluation of the patient's exercise capacity and exercise-associated risk. Patients should be urged to participate in regular exercise programs in conjunction with their drug therapy. Sedentary patients should be encouraged to start light-intensity exercise programs, whereas more active patients may undergo moderate-to-vigorous intensity aerobic exercise training three to four times per week, and for at least 30 minutes per session.[10] Randomized trials have consistently demonstrated improved effort tolerance and O_2 consumption; reduction in symptoms or evidence of ischemia; and significant improvement in well-being scores from regular exercise. Others have demonstrated a direct relationship between the intensity of exercise and favorable changes in obstructive lesions (on ICA) and vascular endothelial function.

Smoking

Smoking is a strong and independent risk factor for CVD, and The Surgeon General's Report in 1964 has firmly established cigarette smoking as the leading preventable cause of CVD.[11] Clinicians treating patients with SIHD can emphasize that quitting smoking is the most effective of all preventive measures, being associated with a reduction in mortality of 36% after MI. Thus, smoking status should be assessed systematically, including passive smoking; and all smokers should be advised to quit and offered smoking cessation programs. The US Preventive Services Task Force and US Public Health Service Guidelines support a combination of counseling

and pharmacological therapy, when necessary.[12,13] Pharmacotherapies that reliably increase smoking abstinence include sustained-release bupropion hydrochloride, nicotine gum or patch (available locally), nicotine inhaler or nasal spray and nicotine lozenge.

Hypertension

Epidemiological links between elevated blood pressure and CAD, HF, cerebrovascular disease and renal failure are well established. The risk of ischemic heart disease doubles for each 20 mm Hg increment in systolic blood pressure across the entire range of 115 to 185 mm Hg. Hypertension increases myocardial O_2 demand, accelerates atherosclerosis, and intensifies ischemia in patients with obstructive CAD.

Antihypertensive therapy is associated with a reduction in CAD events and mortality. Therefore, blood pressure control is an essential aspect of the management of patients with SIHD. Lowering systolic blood pressure to lower than 140 mm Hg, and diastolic blood pressure to less than 90 mm Hg is recommended.[14]

The current 2013 ESC Guidelines on Hypertension reconfirm that diuretics, calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs) and beta blockers are all suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or as combination therapy.[14] All classes of antihypertensive drugs have their specific advantages and disadvantages, including adverse drug effects. If necessary, doses or drugs should be changed in order to balance effectiveness with tolerability. Lastly, for all patients with hypertension, the benefits of a healthy diet, regular exercise and weight control cannot be overemphasized. These lifestyle modifications have the potential to improve blood pressure control and even reduce medications.

Lipid management

Patients with CAD are considered at very high risk for CV events, and effective lipid-lowering therapy with statins should be given irrespective of LDL cholesterol levels. Based on current Western recommendations, the goals of treatment are LDL-cholesterol below 1.8 mmol/L (70 mg/dL), or greater than 50% LDL-cholesterol reduction when target level cannot be reached.[15,16] The 2005 Clinical Practice Guidelines for the Management of Dyslipidemia in the Philippines recommended a 30% to 40% reduction in baseline LDL, or lower than 77 mg/dL, as treatment goals.[17] However, the Philippine guideline on Dyslipidemia is currently being reviewed in anticipation for an updated version.

In the majority of patients, treatment goals may be achieved through

high-intensity statin therapy (20 to 40 mg of rosuvastatin, or 40 to 80 mg of atorvastatin, daily). Secondary prevention trials have provided convincing evidence that statins substantially reduce mortality in patients with CAD, suggesting that atherosclerosis regression is not the sole mechanism of benefit.[15-17] Several mechanistic studies have shown that statins improve endothelium-mediated responses in the coronary arteries; reduce circulating levels of C-reactive protein; and alter the collagen and inflammatory components of arterial atheroma; which all contribute to improvement in blood flow and reduction in inducible myocardial ischemia. Other lipid-lowering therapies (e.g., fibrates, ezetimibe, nicotinic acid) may lower LDL-cholesterol but have not shown benefit in clinical outcomes in studies. In addition, elevated levels of triglycerides and low HDL cholesterol were associated with increased CVD risk, but clinical trials were insufficient in specifying treatment targets.

Diabetes mellitus

Diabetes mellitus is a strong risk factor for CVD complications and increases the risk of progression of atherosclerosis. Blood glucose control should be on an individual basis, depending on considerations such as the patient's age, duration of diabetes and presence of complications. Based on current guideline recommendations, there should be good control of HbA1c to less than 7.0%, within the range of 6.5% to 6.9%. As for other risk factors, lifestyle modification with healthy diet, regular exercise and weight management cannot be overemphasized. Attention to management of other risk factors, such as high blood pressure, is likewise recommended (with ACEIs or ARBs due to renal protective effects). LDL-cholesterol lower than 70 mg/dL (with statin treatment) should be achieved.

Weight management

Both obesity and being overweight are associated with an increased risk of mortality in patients with CAD. Weight reduction in these patients is recommended in order to achieve beneficial effects on blood pressure, LDL-cholesterol and glucose levels.[10] In addition, symptoms of sleep apnea should be assessed and managed accordingly.[18] Sleep apnea is associated with an increase in CV morbidity and mortality.

Psychosocial factors

Although evidence for a favorable effect on morbidity and mortality in CAD is inconclusive, psychotherapy for clinically significant symptoms of depression and anxiety can reduce symptoms and improve quality of life for these patients.[10] Psychosocial distress is common in these patients and

should be addressed appropriately.

A comprehensive cardiac rehabilitation program should be considered in all patients with SIHD, and systematic referral of patients to such a program is ideally recommended if cost considerations permit. Cardiac rehabilitation has been proven to be effective in reducing CV mortality and hospital admissions for CV complications.

Table 9 shows the current recommended target levels to be achieved with each risk factor of CAD, and the corresponding interventions.

Statement 16: Pharmacologic Therapy to Improve Prognosis

It IS STRONGLY RECOMMENDED that all patients, whether or not revascularization is being considered, receive the following medications to improve prognosis, thereby reducing the risk for MI and death:

1. **Aspirin low-dose (80 to 160 mg/day)**
2. **Clopidogrel in case of aspirin intolerance (75 mg/day)**
3. **Statins irrespective of LDL-cholesterol levels**
4. **Beta blockers post-MI**
5. **ACEIs or ARBs (especially in patients with concomitant HF, hypertension or diabetes)**

Pharmacologic therapy to improve prognosis (prevent MI and death) focuses primarily on reducing the incidence of acute thrombotic events and the development of ventricular dysfunction.

Antiplatelet agents (e.g., aspirin and clopidogrel) decrease platelet aggregation, thereby reducing plaque progression and preventing thrombus formation should plaque rupture or erosion occur. Due to its low cost and favorable ratio between benefit and risk, low-dose aspirin still remains the drug of choice in most cases, and clopidogrel as an alternative in case of aspirin intolerance. Aspirin acts via irreversible inhibition of platelet cyclooxygenase-1 and subsequent thromboxane production, and this is achieved with a dosage of **80 to 160 mg/day**. Gastrointestinal side effects, including bleeding, increase at higher doses.

Clopidogrel, a P_2Y_{12} inhibitor, acts as an antagonist of the platelet adenosine diphosphate receptor P_2Y_{12}, thus inhibiting platelet aggregation. Because of the CAPRIE trial, clopidogrel is proposed as an alternative treatment to aspirin-intolerant patients. Prasugrel and ticagrelor are new P_2Y_{12} antagonists that achieve greater platelet inhibition than clopidogrel. Although they are both associated with a significant reduction in CV outcomes compared with clopidogrel in ACS patients, there are no clinical studies showing their benefit in SIHD patients. Similarly, dual antiplatelet therapy (DAPT) combining aspirin and a P_2Y_{12} inhibitor is the standard of care for patients with ACS;

Table 9. Recommended target levels and intervention for coronary artery disease risk factors.

Risk factor	Target Level	Intervention
Dietary intake	Total caloric intake limited to amount of energy needed to maintain BMI <25 kg/m^2	See healthy diet prescriptions in the section on "Lifestyle modification"
Physical activity	Regular exercise, 3 to 4 times a week, 30 minutes per session	Training programs on aerobic exercise
Smoking	Quit smoking by patient and immediate family members	Programs on smoking cessation (see section on "Smoking")
Hypertension	<140/90 mm Hg for <80 y/o	Antihypertensive drugs, as monotherapy or combination therapy (according to JNC 8 or ESC 2013 Guidelines on Hypertension)
Dyslipidemia	LDL-cholesterol < 1.8 mmol/L or < 70 mg/dL; OR LDL-cholesterol > 50% reduction from baseline when target level cannot be reached	High intensity statin therapy with either rosuvastatin 20 to 40 mg OR atorvastatin 40 to 80 mg
Diabetes mellitus	HbA1c < 7.0% Preferably within the range of <6.5 – 6.9%)	Combination treatment strategy of diabetic diet, regular exercise, appropriate oral hypoglycemic agents OR insulin, if necessary
Weight	BMI < 25 kg/m^2	Combination strategy of healthy diet and regular exercise

BMI=body mass index; JNC 8=Eighth Joint National Committee; ESC=European Society of Cardiology; LDL=low-density lipoprotein; HbA1c=glycated hemoglobin.

however, there are no clinical studies showing benefit of combined antiplatelet therapy in stable CAD patients. In a post-hoc analysis though, a significant benefit was observed in patients with a prior history of MI and documented atherothrombotic disease.[19] Altogether, combined antiplatelet therapy is not recommended routinely in SIHD, but may be reasonable in selected patients at high risk of ischemic events.

Statins should be given to all patients with SIHD irrespective of the LDL-cholesterol levels. Patients with documented CAD are regarded as being at high risk for atherosclerotic CV events and secondary prevention studies have shown that the risk of these complications is reduced by at least 30% with statin therapy. Statins lower LDL-cholesterol effectively, but anti-inflammatory and anti-thrombotic effects contribute further to the CV risk reduction. The National Cholesterol Education Program Guidelines advocate lowering of LDL-cholesterol levels to below 100 mg/dL in all patients with proven CAD or extra-cardiac atherosclerosis.[20] A more aggressive lipid-lowering is recommended by the ESC/European Atherosclerosis Society Guidelines to LDL-cholesterol levels below 70 mg/dL and/or greater than 50% reduction if the target level cannot be reached.[21]

Beta blockers have been shown in many randomized trials to achieve a 30% risk reduction for CV death and MI in post-MI patients with or without HF.[22] These trials, however, were done before the implementation of other secondary prevention therapies, such as statins and ACEIs, leaving uncertainty regarding their efficacy in reducing CV events. A recent retrospective analysis of the Reduction of Atherothrombosis for Continued Health (REACH) Registry suggested that beta blockers were not associated with a lower risk of CV events in patients with either CAD risk factors only, known CAD without previous MI, or known previous MI.[23] Nevertheless, the current consensus is that beta blockers may still be protective in patients with SIHD extrapolating evidence of its prognostic benefit from previous trials in post-MI patients, or in HF. The most widely used beta blockers here in the Philippines as well as abroad are those with predominant beta1 blockade, such as metoprolol, bisoprolol, atenolol and recently nebivolol. Carvedilol, a non-selective beta-α1 blocker, is also often used. Beta blockers with intrinsic sympathomimetic activity appear to provide less CV protection.

ACEIs are recommended for specific subgroups of patients with SIHD, such as those with coexisting HF or asymptomatic LV dysfunction (LVEF lower than 40%); hypertension; or diabetes because of a reduction in the risk of future ischemic events. Potential beneficial mechanisms of ACEIs include regression in LVH and vascular hypertrophy; prevention of atherosclerosis progression; prevention of plaque rupture and thrombosis; and a favorable

influence in coronary endothelial vasomotor function.

In patients with stable CAD and hypertension, a combination therapy consisting of an ACEI and a dihydropyridine (DHP) CCB, such as perindopril/amlodipine in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) and benazepril/amlodipine in the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, is preferred.[24,25] In patients without the coexisting conditions mentioned, ACEIs may still be considered as secondary prevention treatment unless contraindicated. Two large randomized controlled trials, Heart Outcome Protection Evaluation (HOPE) and European trial on reduction of cardiac events with Perindopril in stable CAD (EUROPA), showed a relative risk reduction of 22% and 20%, respectively, in CV death, MI and stroke.[26,27] It is of interest that both ramipril and perindopril are "tissue ACEIs" that are lipophilic and have high enzyme-binding capabilities. These properties allow greater penetrance into the atherosclerotic plaque. ARBs may be an alternative to ACEIs when the latter are not tolerated. There are no studies, however, that show a clinical benefit of ARBs in patients with stable CAD.

Lastly, aldosterone blockade with spironolactone or eplerenone may be combined with ACEIs and beta blockers in post-MI patients without significant renal dysfunction or hyperkalemia and have a LVEF of lower than 40%.

Statement 17: Pharmacologic Therapy to Reduce Angina

It IS RECOMMENDED that a beta blocker and/or CCB be given as first-line treatment to reduce symptoms of angina. for second-line treatment, it is recommended to add or substitute either a long-acting nitrate, ivabradine, nicorandil, or trimetazidine (in no particular order of preference), when initial treatment with a beta blocker or CCB is unsuccessful in reducing symptoms of angina or causes unacceptable side effects.

Pharmacologic therapy to reduce angina focuses primarily on the complete or near-complete relief of angina symptoms, and the patient's return to normal activities and functional capacity of CCS class I-II. These goals should be accomplished with minimal side effects of therapy, and the prescribed drugs should be tailored to the individual needs of the patient.

For the first-line treatment of angina, it is recommended to start treatment with a beta blocker and/or CCB to control heart rate and symptoms. Beta blockers and CCBs are similar with regard to angina control. Beta blockers act directly on the heart to reduce heart rate, contractility, atrioventricular conduction, and ectopic activity. Beta blockers also increase perfusion of ischemic areas by prolonging diastole and increasing vascular resistance in

non-ischemic areas. Beta blockers are also effective in controlling exercise-induced angina, reducing both symptomatic as well as asymptomatic ischemic episodes, and improving exercise capacity.

CCBs act chiefly by vasodilation and reduction of the peripheral vascular resistance by selective inhibition of the L-channel opening in the vascular smooth muscle and myocardium. CCBs can be classified chemically into the DHPs and non-DHPs.

The non-DHPs (e.g., verapamil and diltiazem) reduce symptoms of angina through their heart-rate lowering properties. The combination of non-DHPs with beta blockers is not advised due to the risk of heart block, symptomatic bradycardia and HF.

The DHPs (e.g., amlodipine, felodipine, and nifedipine) have greater vascular selectivity and fewer serious adverse effects (e.g., headache and ankle edema). Careful combination of DHPs with beta blockers is usually feasible and desirable. Exercise-induced angina is more effectively controlled with this combination.

For second-line treatment, it is recommended to add or substitute long-acting nitrates, ivabradine, nicorandil or trimetazidine, according to comorbidities and tolerance, when initial treatment with a beta blocker and/or CCB is unsuccessful in reducing symptoms of angina or causes unacceptable side effects.

Ivabradine is a selective sinus node inhibitor (I_f pacemaker current) with chronotropic effects, both at rest and during exercise, without an effect on inotropism or blood pressure. Based from BEAUTIFUL AND SHIFT TRIAL, Ivabradine 7.5 mg twice daily reduced cardiovascular death and hospitalization for patients with coronary artery artery disease (CAD) with heart failure or reduced ejection fraction.[28-29] However, this advantage did not translate to CAD patients without heart failure as shown in the recent results of SIGNIFY trial. This last mentioned trial showed no significant difference between the ivabradine group and the placebo group in the incidence of the primary end point which were composite of death from cardiovascular causes or nonfatal myocardial infarction.(6.8% and 6.4%, respectively; hazard ratio, 1.08; 95% confidence interval, 0.96 to 1.20; P = 0.20). Hence, based from results of these available data, the SIHD group can only recommend ivabradine to patients with CAD and with heart failure.[30]

Nicorandil, a nitrate derivative of nicotinamide, dilates epicardial coronary arteries and stimulates adenosine triphosphate-sensitive potassium channels in vascular smooth muscle. In combination with either a beta blocker or CCB, it can be used for the prevention and long-term treatment of angina. The Impact Of Nicorandil On Angina (IONA) trial showed a 14% reduction in CV

events, but relief of angina symptoms was not reported.[31]

Trimetazidine (35 mg twice daily) is a metabolic agent with a different mechanism of action from the conventional anti-anginal therapy. The heart rate

Table 10. Pharmacologic treatments in SIHD

	Mechanism of action	Class of Recommend-ations / Level of Evidence	Contraindications
Drugs for event prevention			
Aspirin	Cyclooxygenase-1 inhibitor, thus decreases thromb oxane	IA	Bleeding/Peptic ulcer Hypersensitivity History of allergy
Clopidogrel	P_2Y_{12} inhibitor decreasing platelet aggregation	IB	Same as above
Statins	3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor	IA	Myopathy Rhabdomyolysis Liver disease
ACEI/ARB	RAAS blockers	IA	Hyperkalemia Renal artery stenosis
Drugs for relief of angina			
Beta blockers	Reduce heart rate, contractility, atrioventricular conduction and ectopic activity	IA	Low heart rate Conduction disorder Asthma/COPD CHF/Cardiogenic shock Vasospastic angina Severe peripheral vascular disease
CCB (heart-rate lowering) -Verapamil -Diltiazem	Vasodilator Reduction of peripheral vascular resistance plus nodal inhibition	IA	Low heart rate Conduction disorder Sick sinus syndrome CHF/ Low blood pressure Cardiogenic shock

CCB (dihydropyridines) -Amlodipine -Felodipine -Nifedipine	Vasodilator Reduction of peripheral vascular resistance	IA	Severe aortic stenosis Obstructive cardiomyopathy Cardiogenic shock
Nitrates	Coronary arteriolar/ venous vasodilator	IIaB	Hypertrophic obstructive cardiomyopathy
Ivabradine	Sinus node If channel inhibitor	IIaB	Low heart rate Heart rhythm disorder Allergy Severe hepatic disease
Nicorandil	Stimulates K+ adenosine triphosphate channels	IIaB	Cardiogenic shock CHF/Low blood pressure
Trimetazidine	3-ketoacyl-coenzyme A thiolase inhibitor,; anti-ischemic metabolic modulator	IIbB	Allergy Parkinson's disease Tremor and movement disorders

SIHD=stable ischemic heart disease; ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; RAAS=renin-angiotensin-aldosterone system; COPD=chronic obstructive pulmonary disease; CHF=chronic heart failure; CCB=calcium channel blocker.

and rate-pressure product at rest and at peak exercise remained unchanged with trimetazidine, thus indicating a non-hemodynamic anti-ischemic action. It reduces fatty acid oxidation and stimulates glucose oxidation, thus improving cardiac performance. When added to beta blockers, it significantly improved effort-induced myocardial ischemia.

In patients with vasospastic angina, CCBs and nitrates are recommended and beta blockers should be avoided.

Table 10 shows a summary of the pharmacologic therapies used in SIHD.

Statement 18: Revascularization Therapy

Revascularization with PCI or CABG surgery IS RECOMMENDED for the improvement of survival for patients with high risk of mortality; and the improvement of symptoms for patients with limiting angina. A Heart Team approach IS RECOMMENDED to assist the physician in

decision-making regarding preferred revascularization strategy, unless a preferred approach is straightforward.

The decision for revascularization therapy should be based on the presence of significant coronary artery stenosis, the amount of related ischemia, and the expected benefit to the patient's prognosis and/or symptoms. It is important to stratify patients into categories of risk based on an analysis of clinical, non-invasive and, in some patients, angiographic variables. The four major determinants of risk are the extent of ischemia, the number of vessels diseased, LV function, and to a lesser extent, the electrical substrate. Other factors that must always be considered in the decision for revascularization are the general health status and co-morbid conditions of the patients.

The major effects of revascularization are improvement of prognosis and ischemia compared with that of medical therapy. Thus, revascularization therapy has two main objectives: improvement of survival for patients with high risk of mortality; and improvement of symptoms for patients with limiting angina.

Patients considered high risk for mortality are those with high-risk coronary anatomy and those with moderate or severe LV dysfunction. High-risk coronary anatomy includes: at least 50% stenosis of the left main coronary artery and/or significant (at least 70% stenosis) 3-vessel CAD; significant proximal LAD stenosis; and a Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score of 33 or higher. Moderate or severe LV dysfunction is defined as LVEF of less than 45% and 35%, respectively. These subset of patients have a better prognosis with CABG than with medical treatment.

Apart from this high-risk population, patients with persistent or limiting angina (CCS class III-IV) despite GDMT warrant consideration for revascularization. GDMT includes all the drugs for event prevention (e.g. aspirin or clopidogrel, statins, and ACEIs), at least one drug for angina relief (preferably either a beta blocker or CCB), and lifestyle modification of risk factors with achievement of target goals. It is imperative that GDMT should be undertaken before pharmacologic therapy to control symptoms is considered a failure. It is reasonable to pursue a strategy of initial GDMT for most patients with SIHD and CCS I-II symptoms, and to consider revascularization for those with persistent or severe symptoms despite GDMT.

The selection of the method of revascularization, whether through PCI or CABG, should be based on the likelihood of success and the risk of procedural-related morbidity and mortality. The decision whether to perform PCI or CABG is based on coronary anatomy; LV function; medical co-morbidities that may affect the patient's risk for either PCI or CABG; and patient preference for a particular revascularization procedure. In general, patients with 3-vessel

Table 11. Comparison of Revascularization Strategies in Multivessel Disease.[32]

Revascularization Strategy	Advantages	Disadvantages
Percutaneous coronary intervention	• Less invasive • Short hospital stay • Lower initial cost • Easily repeated • Effective in relieving symptoms	• Restenosis • High incidence of incomplete revascularization • Relative inefficacy in patients with severe left ventricular dysfunction • Less favorable outcome in diabetics • Limited to specific anatomical subsets
Coronary artery bypass surgery	• Effective in relieving symptoms • Improved survival in certain subsets • Ability to achieve complete revascularization • Wider applicability (anatomic subsets)	• Cost • Morbidity

Adapted from by Libby P, Bonow RO, Mann DL, Zipes DP. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 8th ed. Elsevier Science Health Science Division, 2008.[32]

disease, left main involvement, and LV dysfunction undergo CABG. On the other hand, patients without these characteristics undergo PCI. Patients with single-vessel disease in whom revascularization is deemed necessary and the coronary lesion is suitable, PCI is preferred over surgery. Table 11 shows the advantages and disadvantages of PCI and CABG in multi-vessel disease.[32]

A Heart Team approach (with the attending cardiologist or physician, a cardiovascular surgeon, and an interventional cardiologist) is recommended, to assist the physician in decision-making regarding preferred revascularization strategy, unless a preferred approach is straightforward. The vast number of clinical, anatomical, and technical factors, and the risk-benefit ratio, including

early complications, of each revascularization procedure, may be discussed and anticipated by the Heart Team in every situation for a given patient. In this regard, clinical judgment with consensual rather than individual decision-making should prevail, unless the preferred approach is quite clear-cut.

Statement 19: Percutaneous Coronary Intervention (PCI)

PCI IS RECOMMENDED for relief of angina, despite GDMT, in SIHD patients without high-risk coronary anatomy and in whom procedure risks do not outweigh potential benefit.

PCI is an important therapeutic option for relief of angina but does not provide survival benefit in patients with SIHD. It also does not eliminate the need for medical therapy but it can be more effective than medical treatment in providing relief of angina in certain patients with single-vessel and multi-vessel disease as a result of improved technology and increasing operator experience.

Certain factors need to be considered in selecting a patient suitable for PCI. The likelihood of success or failure of the procedure is related to the angiographic characteristics of the lesion, such as vessel size, extent of calcification, tortuosity and relationship to side branches. Equally important are factors such as the severity of ischemia and the percentage of viable myocardium at risk; the presence or absence of LV dysfunction; and the presence of co-morbid conditions. Features associated with an increased risk for acute PCI failure include angiographic characteristics such as small-vessel diameter, long lesion length, and total occlusion; and clinical characteristics such as advanced age, female gender, CHF and impaired renal function. Diabetes mellitus and multi-vessel disease have been associated with increased peri-procedural ischemic complications and late mortality. However, continued improvement in the technical aspects of PCI as well as increasing operator experience has led to reductions in the incidence of these complications.

Regarding stenting and peri-procedural antiplatelet strategy, current ACC and ESC guidelines recommend the newer second-generation drug-eluting stents (DES) and 6 to 12 months of DAPT with aspirin and clopidogrel in SIHD patients undergoing PCI revascularization. The second-generation DES with thinner struts and biodegradable polymers are preferred over either bare metal stents or the first- generation sirolimus-eluting stents and paclitaxel-eluting stents because they deliver superior clinical outcomes for both efficacy and safety. Although the second-generation DES have been associated with lower rates of stent thrombosis, and randomized controlled trials have suggested that a shorter duration might be sufficient, the current recommendations of

both ACC and ESC is still 6 to 12 months of routine DAPT with aspirin and clopidogrel.[2,3,33-36] This is because the clinical benefit of preventing ischemic events outweighs the bleeding risk of DAPT. Shorter durations (1 to 3 months) may be reasonable in patients with high-bleeding risk; those on concomitant anticoagulant treatment; or those undergoing surgery.

There is no evidence to recommend the use of either prasugrel or ticagrelor in SIHD undergoing elective PCI. However, these newer antiplatelet agents may be considered for off-label use in specific high-risk situations such as left main stenting, those with prior history of stent thrombosis, or those with suspicion of resistance to clopidogrel. Lastly, routine platelet function testing for either aspirin or clopidogrel is not necessary before or after elective PCI.

Another important issue with PCI revascularization strategy is the intracoronary assessment of stenosis severity with either FFR or IVUS. The measurement of FFR is recommended to identify functionally significant coronary lesions that induce ischemia when non-invasive stress imaging studies are unavailable. The recent Fractional Flow Reserve vs. Angiography for Multi-vessel Evaluation (FAME-2) study confirmed that SIHD patients with coronary stenosis having a FFR of less than 0.80 benefit from revascularization in addition to GDMT because of the reduced need for urgent revascularization.[37] Patients with coronary stenosis having a FFR greater than 0.8 should not undergo revascularization because of the absence of ischemia, and these patients have good outcomes on medical therapy alone. Although the open nature of the trial is a significant limitation, FFR can guide PCI in a clinically effective way in SIHD patients with multi-vessel disease.

Unlike FFR, IVUS is an imaging diagnostic tool and does not provide assessment of the functional severity of a stenosis. However, IVUS measurements provide anatomical characterization of the coronary lesion and plaque composition in reference to the vessel size, and can guide stent deployment and strut apposition.

Recently, optical coherence tomography (OCT) has been developed as a new intracoronary imaging tool with superior resolution (less than 10 um) that offers detailed assessment of vulnerable plaques including measurements of the thickness of the fibrous cap. OCT allows optimization of stent expansion and apposition, and long-term assessment of stent healing. However, the usefulness of OCT in SIHD patients has not been well established in clinical trials.

Lastly, recent non-randomized clinical trials and observational registries have suggested that PCI may be considered as an alternative to CABG surgery in selected stable patients with significant unprotected left main (stenosis 50% or greater) disease. It is widely agreed that CABG improves

survival in patients with left main disease as a result of the CASS registry, and left main disease is a class I indication for revascularization.[9] The data now needs to be re-evaluated in the light of more recent data showing the possibility that PCI revascularization can be undertaken in selected stable patients with left main disease. We await the results of further randomized controlled trials of CABG vs PCI in these patients.

Statement 20: CABG Surgery

CABG surgery IS RECOMMENDED to improve survival in high-risk patients based on evidence of prognostic benefit. It is also recommended to improve symptoms in patients with limiting angina despite GDMT, or in whom GDMT cannot be implemented because of contraindications or adverse effects to medications.

Current clinical practice has been largely driven by three major randomized trials of CABG that enrolled patients between 1972 and 1984: the Coronary Artery Surgery Study (CASS), the Veterans Affairs (VA) Trial, and the European Cardiac Society Study (ECSS), totaling to 2,649 patients.[38-40] The three have consistently shown that CABG prolongs survival in patients with significant left main CAD irrespective of symptoms; those with single- or double-vessel disease with proximal LAD disease; those with LV systolic dysfunction (LVEF less than 50%); or those with severe symptoms with high-risk criteria on non-invasive testing.

Improvement in survival following CABG depends on successful reperfusion of viable but non-contractile or poorly contracting myocardium. The mechanisms for improved survival in these patients may be related to improvement in LV function; reductions in LV remodeling; prevention of serious arrhythmias; and possibly a reduction in fatal ischemic events.

CABG is also highly effective in providing complete relief of angina in patients who have not been successfully treated with medical therapy, even if they are not in a high-risk subset. CABG provides greater relief of angina, better exercise performance, and a lower requirement for anti-anginal medications compared with medically treated patients. Symptomatic improvement is best maintained in patients with one or more arterial grafts and those with complete revascularization.

CABG should also be considered in special subgroups of patients: patients with diabetes and multi-vessel disease with suitable anatomy and acceptable surgical risk; those with high SYNTAX scores (greater than 33) wherein complete revascularization is more feasible; and those necessitating combined surgical procedures such as correction of concomitant valvular heart disease, ventricular septal defect or atherosclerotic disease elsewhere

in the CV system.

Over the past 50 years, traditional CABG surgery involves an extracorporeal circuit (e.g., cardiopulmonary bypass) accompanied by aortic cross clamping and intermittent infusion of cold cardioplegia solution. The principal technique in the last 25 years or more has been the use of an internal mammary artery (IMA) graft to the LAD coronary artery with supplemental vein grafts as required. The superior patency of the IMA graft has translated into a survival benefit and reduced the incidence of MI, recurrent angina and the need for repeat revascularization. Bilateral IMA grafts deliver a significant survival benefit compared with single IMA grafts, especially in patients with diabetes. The radial artery has been proposed as a second arterial graft rather than another IMA graft. However, the reality remains that locally, saphenous vein grafts are still used in the vast majority of patients, with the exception of IMA to the LAD coronary artery.

Lastly, off-pump coronary artery bypass (OPCAB) has been increasingly performed in the past few decades as a minimally invasive approach with reported reductions in stroke (particularly in the elderly and patients with heavily calcified aortas); re-operation for peri-operative bleeding; and postoperative complications, renal insufficiency, and systemic thromboembolism. The amelioration of the systemic inflammatory response that occurs after CABG using CPB is viewed as an advantage that resulted in improvement of these clinical outcomes. However, OPCAB has no significant difference in mortality and in primary composite endpoints at 30 days vs on-pump CABG.

Statement 21: Non-conventional Treatment

Non-conventional treatment (e.g., chelation therapy, vitamins C and E supplementation, coenzyme Q, acupuncture, hormonal replacement in postmenopausal women, and herbal medicine) for the purpose of improving CV outcomes IS NOT RECOMMENDED due to lack of supportive evidence.

Based on reviews of the literature, the Task Force found no convincing scientific evidence that all these non-conventional treatment, taken together, can improve CV outcomes of patients with SIHD. Furthermore, patients may be deprived of receiving GDMT, especially the drugs for event prevention.

A brief discussion on chelation therapy follows, as chelation therapy has been advocated by some clinical practitioners as being beneficial in the treatment of SIHD. Chelation therapy consists of a series of intravenous (IV) infusion primarily containing ethylene di-amine tetra acetic acid (EDTA) in combination with other substances. EDTA is water-soluble and chelates metallic ions from the blood. At normal pH, EDTA binds dissolved metals,

in decreasing order of strength, namely iron, mercury, copper, aluminum, nickel, lead, cobalt, zinc, cadmium, manganese, magnesium, and calcium. Proponents of chelation therapy believe that chelation is effective against atherosclerosis as removing calcium will lead to softening of hardened coronary arteries.

A randomized 2x2 factorial, double blind, placebo controlled study was designed to evaluate the safety and efficacy of an EDTA chelation solution vs. placebo in post-MI patients. The study was known as the Trial to Assess Chelation Therapy (TACT) Trial.[41] Results showed an 18% reduction with EDTA solution vs placebo in composite endpoints. Subgroup analysis showed that diabetics and patients with prior anterior MI had the greatest reduction of composite endpoints (39% and 37%, respectively).

Despite these results, the primary investigator proposed to confirm these findings with a larger study population to help understand the pathophysiologic mechanisms for the benefits seen. Experts who reviewed the trial cited the study as unethical due to its unsound clinical hypothesis and inadequate informed consent from the study participants. Also, the trial was criticized because the results lacked validity due to the high dropout rate of 18%. Moreover, some experts believed that the benefits seen are largely attributable to lifestyle changes such as cessation of smoking, eating more fruits and vegetables, avoidance of foods high in saturated fatty acids, and regular exercise.

Statement 22: Follow-up Tests

It IS RECOMMENDED that follow-up tests should be done in patients with worsening of angina or development of co-morbid conditions despite GDMT with or without revascularization. It is not recommended to do annual or repeat tests at regular intervals in patients without worsening of angina or change in clinical status.

The following tests are recommended for patients with worsening angina or development of co-morbid conditions:

1. Chest x-ray for patients with new or worsening heart failure symptoms;
2. Echocardiography for assessment of LVEF and segmental wall motion in patients with new or worsening angina or HF symptoms;
3. Echocardiography for evidence of new or worsening valvular heart disease by clinical evaluation;
4. Stress imaging studies (stress echo/MPI/CMR) in patients with or without prior revascularization who have a worsening of angina or significant change in symptoms or clinical status;
5. TET, if stress imaging studies are not available, in patients who have

a worsening of angina or significant change in clinical status; patients should have normal resting ECGs and are able to exercise;

6. ICA in patients with intermediate to high risk results on stress imaging studies or TET; and those with limiting angina or marked limitation of physical activity despite GDMT with or without revascularization

SPECIAL CONSIDERATIONS

Statement 23: Angina with Normal Coronary Arteries (Microvascular Angina or Vasospastic Angina)

Patients with SIHD may have typical angina with normal coronary arteries, presenting either as microvascular angina or vasospastic angina, each of which is associated with a different pathophysiology and treatment.

Many patients, especially women, present with chest pain but do not have significant obstructive CAD. Diagnosis and management of these patients represent a complex challenge.

Microvascular angina

Microvascular disease should be considered in patients with typical features of angina in terms of quality, location and duration (although relationship to exercise may be inconsistent) in whom abnormalities of the ECG and stress test results are indicative of ischemia but ICA does not show fixed or dynamic obstructions in the epicardial coronary arteries.

Primary coronary microvascular disease is frequently encountered in patients with hypertension, diabetes, or a strong family history of vascular disease. The pathophysiology of microvascular disease is a reduced coronary flow reserve resulting in impaired diastolic dysfunction. Hence, non-invasive measurement of coronary flow reserve through transthoracic Doppler echocardiography of the LAD may be considered for establishing the diagnosis. Later in the course of the disease, epicardial plaques and stenoses may develop and eventually dominate the clinical picture.

Treatment of primary microvascular angina consists of secondary prevention medications such as aspirin and statins; and traditional anti-ischemic drugs such as beta blockers, CCBs or long-acting nitrates. Beta blockers are recommended as the first-line treatment because they improve symptoms particularly in patients with increased adrenergic activity (e.g., high heart rate) at rest or during exercise. The use of CCBs and long-acting nitrates is less established, but may be given as additional drugs when symptoms are insufficiently controlled with beta blockers. In patients with persistent

symptoms despite anti-ischemic treatment, ACEIs and ARBs may improve microvascular function by counteracting the effects of angiotensin II. Lastly, all patients with microvascular angina should achieve optimal control of coronary risk factors.

Vasospastic angina

Vasospastic angina (Prinzmetal's angina or variant angina) typically presents as angina at rest, occurring at night and in the early morning hours, and usually relieved by nitrates within minutes. The ECG is classically described as showing ST elevation, but occasionally is associated with ST depression. The 12-lead ECG is recommended during angina to document ST-segment shifts associated with angina symptoms.

Demonstration of spontaneous focal or diffuse spasm (lumen reductions from 75% to 99%) in normal coronary arteries at the time of rest angina and ST elevation makes the diagnosis highly likely, although spasm is usually not observed in less straightforward cases. Hence, intracoronary provocative testing with acetylcholine or ergonovine should be considered in patients with the clinical picture of vasospastic angina. Acetylcholine injections at incremental doses of up to 200 ug, infused selectively into the left coronary artery or the right coronary artery, are used commonly in most centers to provoke coronary spasm. Provocative testing with IV ergonovine may lead to fatal complications and is not recommended in patients without known coronary anatomy nor in patients with known high-grade obstructive lesions on coronary angiography due to prolonged spasm involving multiple vessels.

Treatment of vasospastic angina includes chronic preventive treatment with the use of CCBs and optimal coronary risk factor control. Non-DHP CCBs such as verapamil or diltiazem 240-360 mg/day usually prevent spasm in the majority of patients. Long-acting nitrates may be given as additional treatment to improve the efficacy of treatment. Beta blockers are not recommended and should be avoided, as they might provoke spasm due to alpha-mediated vasoconstriction unopposed by beta-mediated vasodilation. In rare cases of refractoriness to the standard treatment, the addition of anti-adrenergic drugs such as guanethidine or clonidine may be considered.

Implantation of an automatic cardioverter defibrillator or a pacemaker is indicated in patients with life-threatening tachyarrhythmias or bradyarrhythmias, respectively. Likewise, 24-hour ambulatory ECG (Holter) monitoring is indicated in these patients to confirm the presence of arrhythmias associated with ischemic episodes.

Lastly, it is not recommended to do revascularization with either PCI or CABG even in patients with coronary vasospasm.

Statement 24: Refractory Angina

The term "refractory angina" is defined as a clinically established chronic stable angina associated with CAD, which cannot be adequately controlled by a combination of medical therapy (e.g., GDMT) and revascularization therapy (e.g., PCI or CABG).

For this patient group, there is limited evidence on available treatment options, and convincing evidence regarding reduction in mortality and ischemia is still lacking. Nevertheless, pharmacological treatment will include all the drugs for event prevention and first-line with second-line treatment for angina/ischemia relief. According to co-morbidities or tolerance, it may be indicated to use second-line therapies as first-line treatment in selected patients. Non-pharmacological treatments include enhanced external counter-pulsation therapy and neuro-stimulatory techniques (e.g., transcutaneous electrical nerve stimulation and spinal cord stimulation), which may be considered to ameliorate symptoms and improve quality of life in patients with angina refractory to optimal medical and revascularization strategies. Trans-myocardial revascularization is not recommended because it is ineffective.

Statement 25: Asymptomatic Patient at Risk for CAD

In asymptomatic adults at risk for CAD, measurement of risk factors and non-invasive stress tests MAY BE RECOMMENDED as screening investigations for the purpose of risk stratification and management principles, as has been described for symptomatic patients.

Details on the measurement of risk factors, as well as non-invasive stress tests, can be found in the new European Guidelines on Prevention and the recent ACCF/AHA Guidelines for assessment of CV risk in asymptomatic adults.[10,42] The key message of these recommendations is to perform these tests as screening investigations for the purpose of lowering the high burden of coronary deaths in asymptomatic individuals at risk for CAD. Although data demonstrating improved prognosis following appropriate management are still lacking, the same management principles, as discussed for the symptomatic patients, should apply to these individuals for medico-legal reasons.

REFERENCES

1. Philippine Heart Association. 2009 PHA Clinical Practice Guidelines for the Management of Coronary Artery Disease. Quezon City: Philippine Heart Association, 2009.
2. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013 Oct;34(38):2949-3003.
3. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis

and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2012 Dec 18;60(24):e44-e164.

4. Campeau L. Grading of angina pectoris. Circulation. 1976 Sep;54(3):522-3.
5. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.
6. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Annals Int Med. 1999;130(6):461-70.
7. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Annals Int Med. 2009;150 (9):604–12.
8. Diamond GA, Forrester JS. Probability of CAD. Circulation. 1982;65(3):641-2.
9. M Emond, M B Mock, K B Davis, L D Fisher, D R Holmes, Jr, B R Chaitman, G C Kaiser, E Alderman and T Killip. Long-term survival of medically treated patients in the Coronary Artery Surgery Study. Circulation. 1994;90:2645-2657.
10. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. European Guidelines oncardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts) * Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2012;33:1635–1701.
11. Terry, Luther et al. Smoking and Health: Report of the Advisory Committee to the Surgeon General of the United States. U-23 Department of Health, Education, and Welfare. Public Health Service Publication No. 1103. 1964.
12. Fiore MC, Bailey WC, Cohen SJ, et al. A clinical practice guideline for treating tobacco use and dependence. Rockville, Maryland. U.S. Department of Health and Human Services, Public Health Service; 2000.
13. U.S. Preventive Services Task Force. Counseling to prevent tobacco use and tobacco-caused disease. Recommendation Statement. Rockville, MD: Agency for Healthcare Research and Quality; 2003.
14. 2013 ESH/ESC Practice Guidelines for the Management of Arterial Hypertension. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, et al. Blood Press. 2014 Feb;23(1):3-16.
15. ESC/EAS Guidelines for the management of dyslipidaemias. The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Catapano AL,

Reiner Z, De Backer G, Graham I, Taskinen MR, Wiklund O, et al.; European Society of Cardiology (ESC); European Atherosclerosis Society (EAS). Atherosclerosis. 2011 Jul;217(1):3-46.
16. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et. Al. J Am Coll Cardiol. 2014 Jul 1;63(25 Pt B):2889-934.
17. Philippine Heart Association. 2005 Clinical Practice Guidelines for the Management of Dyslipidemia in the Philippines. Quezon City: Philippine Heart Association, 2008.
18. Kohler M, Stradling JR. Mechanisms of vascular damage in obstructive sleep apnea. Nat Rev Cardiol. 2010;7:677–685.
19. Bhatt DL, Flather MD, Hacke W, Berger PB, Black HR, Boden WE, et. al. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. J Am Coll Cardiol. 2007;49:1982–1988.
20. National Cholesterol Education Program (U.S.), National Heart, Lung, and Blood Institute, National Institutes of Health. Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. Bethesda, MD: National Cholesterol Education Program, National Heart, Lung, and Blood Institute, National Institutes of Health; 2002. NIH Publication No. 02–5215.
21. European Association for Cardiovascular Prevention & Rehabilitation, Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Filardi PP, Riccardi G, Storey RF, Wood D; ESC Committee for Practice Guidelines (CPG) 2008-2010 and 2010-2012 Committees. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J. 2011 Jul;32(14):1769-818.
22. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. I. Treatments following myocardial infarction. JAMA 1988;260:2088–2093.
23. Bangalore S, Steg G, Deedwania P, Crowley K, Eagle KA, Goto S, et al. Investigators RR. beta-Blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. JAMA 2012;308:1340–1349.
24. Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet 2005;366:895–906.
25. Jamerson K, Weber MA, Bakris GL, Dahlof B, Pitt B, Shi V, et al. Benazepril

plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Eng J Med 2008;359:2417–2428.
26. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Eng J Med 2000;342:145–153.
27. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo controlled, multicentre trial (the EUROPA study). Lancet 2003;362:782–788.
28. Fox K, Ford I, Steg PG, Tendera M, Ferrari R. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:807–816.
29. Swedberg K, Komajda M, Bohm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomized placebo controlled study. Lancet 2010: 376; 807-816
30. Fox K, Ford I, Steg PG, et al. Ivabradine in stable coronary artery disease without clinical heart failure. N Engl J Med 2014; 371:1091-1099
31. Effect of nicorandil on coronary events in patients with stable angina: the Impact Of Nicorandil in Angina (IONA) randomised trial. Lancet 2002;359:1269–1275.
32. Libby P, Bonow RO, Mann DL, Zipes DP. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 8th ed. Elsevier Science Health Science Division, 2008.
33. Airoldi F, Colombo A, Morici N, Latib A, Cosgrave J, Buellesfeld L, et al. Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment. Circulation 2007;116:745–754.
34. Schulz S, Schuster T, Mehilli J, Byrne RA, Ellert J, Massberg S, et al. Stent thrombosis after drug-eluting stent implantation: incidence, timing, and relation to discontinuation of clopidogrel therapy over a 4-year period. Eur Heart J 2009;30:2714–2721.
35. Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, et al. Short versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. Circulation 2012;125:2015–2026.
36. GwonHC,Hahn JY, ParkKW, Song YB, Chae IH, Lim DS, et al. Six month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. Circulation 2012;125: 505–513.
37. de Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PA, Piroth Z, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Eng J Med 2012;367:991–1001.
38. Passamani E, Davis KB, Gillespie MJ, Killip T. A randomized trial of coronary

artery bypass surgery: survival of patients with a low ejection fraction. N Engl J Med. 1985; 312: 1665–1671.
39. The VA Coronary Artery Bypass Surgery Cooperative Study Group. Eighteen-year follow-up in the Veterans Affairs Cooperative Study of Coronary Artery Bypass Surgery for stable angina. Circulation. 1992; 86: 121–130.
40. Varnauskas E. Twelve-year follow-up of survival in the randomized European Coronary Surgery Study. N Engl J Med. 1988; 319: 332–337.
41. Lamas GA, Goertz C, Boineau R, Mark DB, Rozema T, Nahin RL, et al.; for the TACT Investigators. Effect of Disodium EDTA Chelation Regimen on Cardiovascular Events in Patients With Previous Myocardial Infarction: The TACT Randomized Trial. JAMA. 2013;309(12):1241-1250.
42. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, et al.; American College of Cardiology Foundation; American Heart Association. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2010 Dec 14;56(25):e50-103.

2014 Philippine Heart Association Clinical Practice Guidelines for the Diagnosis and Management of Patients with Non-ST Elevation Acute Coronary Syndrome

INTRODUCTION

Cardiovascular disease (CVD) remains to be the number one cause of mortality and a substantial contributor to morbidity in the Philippines.[1] In the recent 2-year report of the Philippine Heart Association (PHA) Acute Coronary Syndrome (ACS) registry from November 2011 to November 2013, the mortality rate for ACS was 7.8%.[2]

CVD predominantly manifests as coronary artery disease (CAD) presenting clinically as stable ischemic heart disease (SIHD) or ACS. The latter is further classified into ST elevation ACS or non-ST elevation ACS (NSTE-ACS). The elevation of cardiac enzymes further distinguishes NSTE-ACS into non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA). This section discusses the management of suspected NSTE-ACS, updating the PHA Clinical Practice Guidelines in UA/NSTEMI published in 2009.[3]

This update has 26 statements, in contrast with the 23 statements in the 2009 PHA guidelines on UA/NSTEMI. New statements focus on the introduction of new antiplatelet agents, ticagrelor and prasugrel, as well as the importance of transfer strategy in the high-risk patient. A new score model for risk stratification has been introduced as well. In addition, numbers needed to treat (NNT) to prevent outcomes were presented based on available risk-reduction data from studies and a local event rate for mortality as 8.9% for NSTEMI and 3.2% for UA, based on the results of the PHA ACS Registry.[2] The NNT was computed as the reciprocal of the product of two factors: the local event rate and the relative risk reduction based on studies.

DIAGNOSIS AND RISK ASSESSMENT

Statement 1: Clinical Presentation

It IS RECOMMENDED that patients with the following symptoms and signs undergo immediate assessment for the diagnosis of ACS:

1. **Chest pain or severe epigastric pain, non-traumatic in origin, with component typical of myocardial ischemia or myocardial infarction (MI): Central or substernal compression or crushing chest pain pressure, tightness, heaviness, cramping, burning, aching sensation;**
2. **Unexplained indigestion, belching, epigastric pain;**
3. **Radiating pain in neck, jaw, shoulders, back, or one or both arms;**

4. **Unexplained syncope;**
5. **Palpitations;**
6. **Dyspnea;**
7. **Nausea and/or vomiting, or;**
8. **Diaphoresis.**

Patients with a high likelihood of ischemia due to CAD are at a greater risk of an untoward cardiac event than patients with a lower likelihood of CAD. Therefore, an assessment of the likelihood of CAD is the starting point for the determination of prognosis in patients who present with symptoms suggestive of an ACS. There is a great need to immediately establish the diagnosis of ACS, and thereafter distinguish between ST elevation ACS and NSTE-ACS because the management of these two syndromes diverges at initial contact. The predominant symptom of ACS is chest pain but it can present atypically through various symptoms.

The character of angina in ACS may possess all the descriptive qualities of those seen in stable ischemic disease except for some characteristic features. The traditional clinical presentations of ACS include: prolonged anginal pain (more than 20 minutes) at rest; new-onset severe angina; crescendo or accelerated angina; post-MI angina; and post-revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]) angina.

Atypical symptoms are more common in certain populations such as the elderly, women, diabetics, or chronic kidney disease (CKD) patients. There are also accompanying features that may point to the diagnosis of ischemia, such as exacerbation of symptoms upon exertion and relief upon rest or intake of nitrates. The presence of diabetes, renal deficiency and atherosclerosis of non-coronary vessels may strengthen the diagnosis of ACS.[4] In patients with no known atherosclerotic disease, age is the most important factor. Males older than 55 years, and females older than 65 years, have the highest risk for coronary disease.

The physical examination findings of patients having an ACS may be varied, ranging from normal to evident signs of cardiovascular (CV) compromise such as hypotension and respiratory distress from pulmonary congestion. The primary goal of the physical examination is to exclude non-ischemic causes and non-cardiac causes of the clinical presentation. Particular attention may be given to significantly different blood pressure recordings in the extremities; muffling of heart sounds; presence of an abdominal mass; unilateral leg edema; and presence of tenderness on palpation. Such features may point to an alternative diagnosis.

Statement 2: Electrocardiogram

It IS STRONGLY RECOMMENDED that a 12-lead electrocardiogram (ECG) be obtained immediately within 10 minutes of emergency room (ER) presentation in patients with ongoing chest discomfort.

If the initial ECG is not diagnostic, but the patient remains symptomatic and there is high clinical suspicion for ACS, serial ECGs initially at 15- to 30-minute intervals should be performed to detect the potential for development of ST segment elevation or depression. The ECG is critical not only to add support to the clinical suspicion of CAD, but also to provide prognostic information based on the pattern and magnitude of the abnormalities. Importantly, transient ST-segment changes (greater than or equal to 0.05 mV) that develop during a symptomatic episode at rest and that resolve when the patient becomes asymptomatic strongly suggest acute ischemia and a very high likelihood of underlying severe CAD.

Patients who present with ST-segment depression are initially considered to have either UA or NSTEMI; the distinction between the two diagnoses is based ultimately on the detection in the blood of markers of myocardial necrosis.

ECG results provide a crucial decision point in the management of acute myocardial ischemia. The findings on ECG of acute myocardial ischemia of the NSTE type are: new horizontal or down-sloping ST depression of at least 0.5 mV in two contiguous leads; and/or T wave inversion of at least 0.1 mV in two contiguous leads with prominent R-wave or R/S ratio greater than 1. Pseudo-normalization of previously inverted T waves during symptomatic episodes may also indicate acute ischemia.[5]

ECGs may be repeated after 3 hours, 6 to 9 hours, and 24 hours after the initial event. It should also be done anytime during recurrence of symptoms and prior to discharge.[6]

Statement 3: Biomarkers

It IS RECOMMENDED that quantitative troponin be measured in all patients with chest discomfort consistent with ACS. In patients with initially negative cardiac markers, a repeat determination within 3 hours of presentation increases the sensitivity for MI diagnosis to almost 100%.

It IS NOT RECOMMENDED to request for total creatine kinase (CK) (without MB isotype), aspartate aminotransferase, beta-hydroxybutyrate dehydrogenase, and/or lactate dehydrogenase as markers for the detection of cardiac injury.

High sensitivity troponin I or T (cTNI or cTNT) are the preferred

markers of myocardial injury because they are more specific and more sensitive than the traditional cardiac enzymes such as CK or its isoenzyme MB (CKMB). Additionally, troponins are the best biomarker to predict short-term (less than 30 days) outcome with respect to MI and death.

Cardiac troponins are elevated in NSTEMI but are within normal levels in UA. The increase in NSTEMI may be associated with the presence of a coronary thrombus.[7] Troponins start to elevate within 3 hours of initial symptom presentation and may remain elevated up to 10 to 14 days. There is currently no difference between troponin I and T assays. The high sensitivity of troponin tests allows the detection of myocardial damage undetected by CKMB in up to one third of patients. The combination of the results of these tests and the measurement of CKMB or myoglobin did not increase the sensitivity of the troponin assays. The diagnostic accuracy of high sensitivity troponins is superior in patients with recent-onset angina and is higher than standard assays particularly in the early phase of myocardial infarction. This advantage allows rapid diagnosis, early risk stratification and institution of life saving interventions in patients with NSTE-ACS.[8]

The measurement of CKMB levels may still be of value in certain clinical situations such as infarct extension, since its short half life allows another rise after an initial peak.

In spite of the excellent sensitivity of troponin elevation in the diagnosis of ACS, this should only be used in the background of compatible clinical presentation. There are several non-ischemic cardiac causes and non cardiac causes of troponin increase (Table 1).[6]

Statement 4: Non-Invasive Imaging

It IS RECOMMENDED that an echocardiogram be done in all patients suspected to have ACS for evaluation of global and regional left ventricular (LV) function, for ruling in or out differential diagnoses and for prognostic information.

It MAY BE RECOMMENDED to perform coronary computerized tomography angiography (CTA) to exclude ACS in those with non diagnostic ECG and troponin, and have a low to intermediate likelihood of CAD.

The 2-dimensional echocardiogram (2D echo) provides a rapid, objective and reliable estimate of the LV function in ACS. The LV ejection fraction (LVEF) is a major determinant of prognosis in ischemic heart disease. The 2D echo may also identify alternative diagnoses such as aortic dissection or pulmonary embolism, and the presence of co-existing cardiac conditions such

Table 1. Possible non-acute coronary syndrome causes of troponin elevation

- Chronic or acute renal dysfunction
- Severe congestive heart failure – acute and chronic
- Hypertensive crisis
- Tachy- or bradyarrhythmias
- Pulmonary embolism, severe pulmonary hypertension
- Inflammatory diseases, e.g., myocarditis
- Acute neurologic disease, including stroke, or subarachnoid hemorrhage
- Aortic dissection, aortic valve disease or hypertrophic cardiomyopathy
- Cardiac contusion, ablation, pacing, cardioversion, or endomyocardial biopsy
- Hypothyroidism
- Apical ballooning syndrome (Takotsubo cardiomyopathy)
- Infiltrative diseases (amyloidosis, hemochromatosis, sarcoidosis, scleroderma)
- Drug toxicity, e.g., adriamycin, 5-fluorouracil, trastuzumab, snake venoms
- Burns if affecting > 30% of body surface area
- Rhabdomyolysis
- Critically ill patients, especially with respiratory failure or sepsis

Adapted from the ESC Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting Without Peristent ST Segment Elevation.[6]

as valvular heart disease. The appearance of transient hypokinesia during episodes of chest pain may point to ischemia as the most certain cause.[9]

A coronary CTA may be used to exclude ACS in those with non-diagnostic ECG and troponin, and have a low to intermediate likelihood of CAD. Under expert hands, it may also provide information on differential diagnoses of chest pain syndromes such as pulmonary embolism or aortic dissection.[10]

Resting myocardial perfusion imaging by Sestamibi may be useful in triaging patients at the ER when screening tests are non-diagnostic.[11] However, since it is not universally available in all hospitals and in a 24-hour basis, its use in this clinical situation is limited in the local setting.

Statement 5: Stress Testing

It IS NOT RECOMMENDED to perform stress test in patients with active chest pain.

It MAY BE RECOMMENDED to perform stress testing in those with

non-diagnostic ECG, normal cardiac biomarkers and no active chest pain for more than 12 hours (Figure 1). These tests may be done pre-discharge or on an out-patient basis.

Whether stress ECG or stress imaging (dobutamine or exercise echocardiogram, nuclear perfusion imaging, or cardiac magnetic resonance) will be appropriate depends on patient characteristics, availability of resources and expertise in a specific institution. The sensitivity and specificity of stress imaging techniques are similar to each other (see Table 6 of the Guidelines on SIHD). The choice of specific test and the direction of management thereafter follow the recommendations set forth in stable ischemic disease.

Statement 6: Risk Stratification

It IS RECOMMENDED for patients who present with chest discomfort or other ischemic symptom to undergo early risk stratification for risk of CV events (e.g., death or MI) based on an integration of the patient's history, physical examination, ECG findings and result of cardiac biomarkers.

It IS STRONGLY RECOMMENDED that all patients presenting with chest pain syndrome also undergo risk assessment for bleeding.

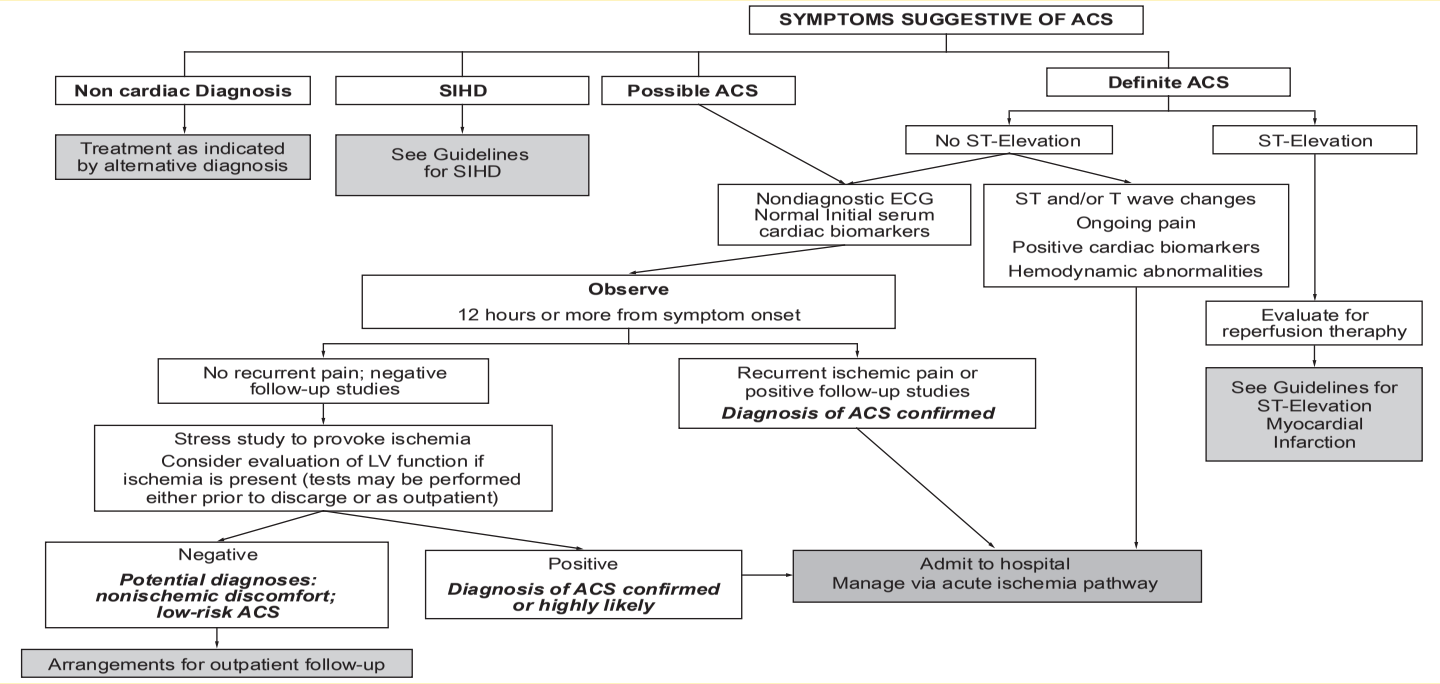
The patients presenting with NSTE-ACS have varied clinical profiles and a wide spectrum of risk. Early risk stratification is useful in the selection of the site of care (coronary care unit, monitored step-down unit, or outpatient setting); and selection of therapy, including invasive management strategy. A number of risk assessment tools have been developed in assessing risk of death and ischemic events; examples are the Thrombolysis in Myocardial infarction (TIMI) risk score (Table 2 and 3), the Global Registry of Acute Coronary Events (GRACE) risk model (Table 2 and Figure 2) and the Heart Score Model (Table 2 and 4; Figure 4).[12-14]

The predictive ability of these models to estimate risk of non-fatal CAD is moderate. Both TIMI and GRACE score systems were developed among patients already diagnosed with an NSTE-ACS, while the Heart Score Model used patients presenting with chest pain in the ER.

TIMI risk score

The TIMI risk score is determined by the sum of the presence of seven variables upon admission, with 1 point given for each present variable: age 65 years or older; at least three risk factors for CAD; prior coronary stenosis of 50% or more; ST-segment deviation on ECG presentation; at least two anginal events in the prior 24 hours; use of aspirin in the prior 7 days; and elevated serum cardiac biomarkers.

Figure 1. Algorithm for the evaluation and management of patients suspected to have ACS upon medical contact.



Adapted from the 2008 Philippine Heart Association Clinical Practice Guidelines for the Management of Coronary Artery Disease, and the 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction.[3,38]

Table 2. Variables used in risk models used in the assessment of risk of death and myocardial infarction in patients with NSTEMI and UA[14-16]

TIMI risk Score (7 variables)	GRACE risk model (8 variables)	HEART score model (5 variables)
Age 65 years or older	Older Age	History
At least 3 risk factors for CAD	Heart rate	ECG
Prior coronary stenosis of 50% or more	Systolic blood pressure	Age
ST-segment deviation on ECG presentation	ST segment depression	Risk factors
At least 2 anginal events in prior 24 hours	Killip classification	Troponin
Elevated serum cardiac biomarkers	Positive initial cardiac markers	
Use of aspirin in prior 7 days	Serum creatinine	
	Cardiac arrest at hospital arrival	

Table 3. Rate of outcome of all-cause mortality, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization using TIMI risk score.[12]

TIMI risk score	Outcome rate through 14 days after randomization (%)
0-1	4.7
2	8.3
3	13.2
4	19.9
5	25.2
6-7	40.9

TIMI risk score is determined by the sum of the presence of 7 variables at admission; 1 point is given for each of the variables.

The TIMI risk score population included patients who are classified to have UA/NSTEMI. The risk calculator is available at www.timi.org. As the TIMI risk score increases, the composite end points of all-cause mortality, new or recurrent MI, or severe recurrent ischemia prompting revascularization within 14 days increases (Table 3). An early invasive strategy may benefit a patient with a TIMI risk score of 3 and above.

GRACE risk model

In the GRACE risk model, there are 8 variables used: older age; Killip class; systolic blood pressure; ST-segment deviation; cardiac arrest during presentation; serum creatinine level; positive initial cardiac markers; and heart rate (Figure 2). The sum of scores is applied to a reference nomogram to determine the corresponding all-cause mortality from hospital discharge to 6 months. The risk score calculator is also available online (http://www.outcomes.org/grace). A patient with a GRACE score of 140 and above may benefit from an early invasive strategy.

Figure 2. GRACE score model.[13]

Background

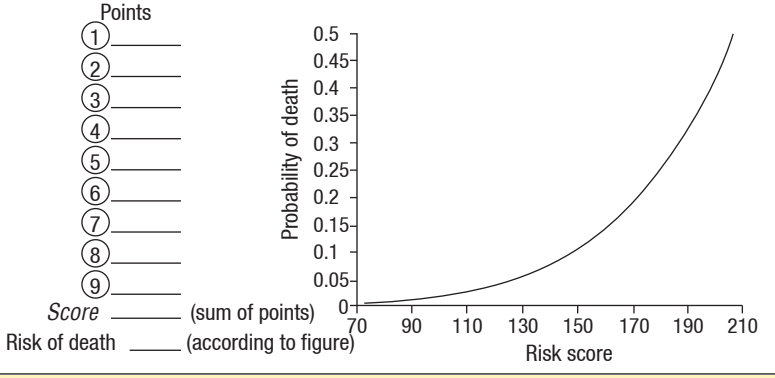
	Points
① Age, y	
≤ 29	0
30-39	0
40-49	18
50-59	36
60-69	55
70-79	73
80-89	91
≥ 90	100
② History of heart failure	24
③ History of AMI	12

Findings at time of admission

	Points
④ HR at admission, bpm	
≤ 49.9	0
50-69.9	3
70-89.9	9
90-109.9	14
110-149.9	23
150-199.9	35
≥ 200	43
⑤ SAP at admission, mmHg	
≤ 79.9	24
80-99.9	22
100-119.9	18
120-139.9	14
140-159.9	10
160-199.9	4
≥ 200	0
⑥ Depressed ST segment	11

Findings during hospital stay

	Points
⑦ Serum creatinine at admission, mg/dL	
0-0.39	1
0.4-0.79	3
0.8-1.19	5
1.2-1.59	7
1.6-1.99	9
2-3.99	15
≥ 4	20
⑧ Elevated enzymes or markers	15
⑨ No percutaneous revascularization	14



Adapted from Fox KA, et al. (2006). Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE).[13]

The GRACE risk score predicts cumulative risk of death and MI during a patient's admission, discharge and until 6 months after discharge The population included patients who are diagnosed with ACS, either STEMI or NSTE-ACS.[13] The GRACE score was better than TIMI score in predicting the risk of death or MI at 1 year after admission.[15] In a local study by Bundalian et al, the GRACE risk score was likewise able to predict more cardiac events (recurrence of MI, re-hospitalization, death and bleeding) among NSTE-ACS patients than the TIMI risk scoring system.[16]

HEART score

The HEART score model was developed among patients regardless of age, pre-hospital assumptions and previous medical treatments who consequently presented with chest pain at the ER. Patients with STEMI were excluded because these patients were directly brought to the coronary intervention unit from the ambulance. The five variables considered were: history, ECG, age, risk factors and troponin level (Table 4). Each variable is given 0, 1, and 2 points and the sum of the scores correlate with incidence of major adverse cardiac events (MACE). A total score of 0 to 3 indicates that a patient may be discharged; a score of 4 to 6 warrants further work-up and admission for observation; and a score of 7 to 10 may warrant a critical care unit admission and/or early invasive strategy.[14]

The scoring of predictors for the HEART index is as follows:

1. History - if there are no specific elements pertaining to the pattern of chest pain, onset and duration, relation with exercise, stress or cold, localization, concomitant symptoms and the reaction to sublingual nitrates, the history was classified as "nonspecific" and given 0 points. The history is "moderately suspicious" if it has both specific and non-specific elements; and "highly suspicious" if the elements are primarily specific.
2. ECG – Zero points are given to a normal ECG. If there are repolarization abnormalities without significant ST segment depression, bundle branch block (BBB), LV hypertrophy (LVH), repolarization abnormalities probably due to digoxin use, or unchanged known repolarization disturbances, a score of 1 was given. For significant ST segment depression without LVH, digoxin use or BBB, 2 points are granted.
3. Age – granted points as illustrated in Table 4.
4. Risk factors – The following were the risk factors considered: currently treated diabetes mellitus; current or recent (less than 1 month) smoker; diagnosed hypertension; diagnosed hypercholesterolemia; family history of CAD; and obesity

Table 4. HEART score model for patients with chest pain.[17]

Variable		Added score
History	Highly suspicious	2
	Moderately suspicious	1
	Slightly suspicious	0
ECG	Significant ST deviation	2
	Non-specific depolarization	1
	No	0
Age	>/= 65 years	2
	45 – 65 years	1
	< 45 years	0
Risk Factors	>/= 3 risk factors or treated atherosclerosis	2
	1 or 2 risk factors	1
	No risk factors known	0
Troponin	> 3x normal limit	2
	1-3x normal limit	1
	</= normal limit	0

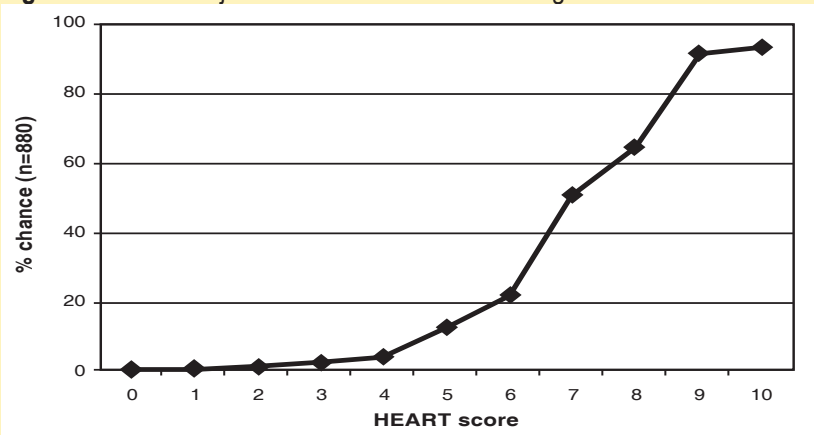
Adapted from Backus BE, et al. (2010). Chest pain in the emergency room: a multicenter validation of the HEART Score.[17]

5. Troponin – granted points as illustrated in Table 4.

The endpoints in the HEART study were acute MI; PCI; CABG; death; and a combined endpoint of acute MI, PCI, CABG and death. The HEART score model has been validated in 3 studies. In a multicenter retrospective study of patients presenting with chest pain in the emergency room, the discriminative power of HEART score is shown in Figure 3. A score of 0 to 3 has a 0.99% risk for MACE; a score of 4 to 6 has an 11.6% risk; and a score of 7 to 10 has a 65.2% risk.[17] Comparison of the HEART, TIMI and GRACE risk scores for chest pain patients at the ER yielded C-indices for 6-week MACE as follows: HEART=0.82; TIMI=0.66; and GRACE=0.70, indicating a better discriminative power for the HEART score compared with the other two.

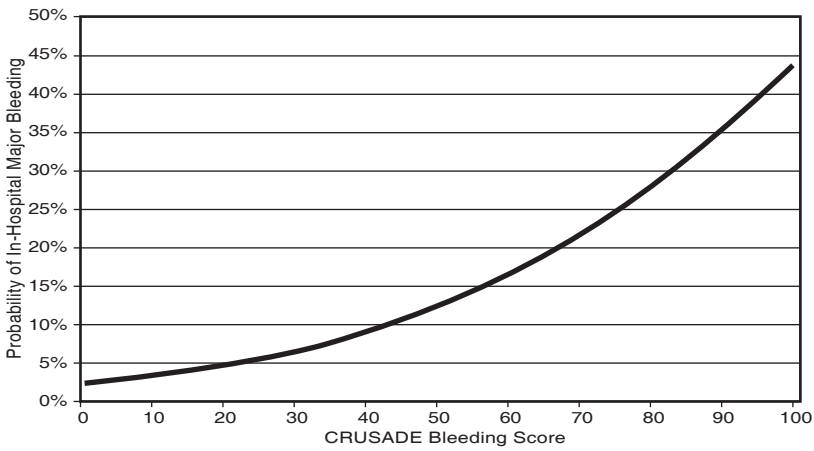
Both TIMI and GRACE score systems apply to patients who had been already classified to have an ACS, while the HEART score is used at the ER for patients presenting with chest pain, whether it is of cardiac origin or otherwise. The clinician may use any of the 3 risk scores as the situation and available data may dictate.

Figure 3. Risk of major adverse cardiac events using HEART score.[17]



Adapted from Backus BE, et al. (2010). Chest pain in the emergency room: a multicenter validation of the HEART Score.[17]

Figure 4. Predicted probability of in-hospital major bleeding across the spectrum of CRUSADE bleeding scores.[18]



Adapted from Subherwal S, et al. (2009). Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score.[18]

Bleeding risk

NSTE-ACS patients who bleed suffer a graver prognosis. The Can Rapid risk stratification of Unstable Angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guideline (CRUSADE) bleeding risk score estimates baseline risk of in-hospital major bleeding in patients with NSTEMI (Figure 4 and Table 5). It may help us consider safety issues in the

Table 5. Scoring criteria to determine the CRUSADE In-Hospital Major Bleeding[18]

Predictor	Score
Baseline hematocrit/ %	
<31	9
31-33.9	7
34-36.9	3
37-39.9	2
≥40	0
Creatinine Clearance,* mL/min	
≤15	39
>15-30	35
>30-60	28
>60-90	17
>90-120	7
>120	0
Heart rate (bpm)	
≤70	0
71-80	1
81-90	3
91-100	6
101-110	8
111-120	10
≥120	11
Sex	
Male	0
Female	8
Signs of CHF at Presentation	
No	0
Yes	7
Prior vascular disease†	
No	0
Yes	6
Diabetes mellitus	
No	0
Yes	6
Systolic blood pressure, mm Hg	
≤90	10
91-100	8
101-120	5
121-180	1
181-200	3
≥201	5

Adapted from Subherwal S, et al. (2009). Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score.[18]

management of NSTEMI. The CRUSADE score was developed and validated in over 89,000 high-risk patients with NSTEMI treated in the community. The eight variables in the final model were: female sex; history of diabetes mellitus; prior vascular disease; heart rate; systolic blood pressure; signs of congestive heart failure; hematocrit less than 36%; and creatinine clearance.[18]

The integration of both ischemic and bleeding risk scores to improve clinical decision making has not yet been achieved. At present, we know that a substantial amount of bleeding in these patients may occur because of excessive dosing of antithrombotics and antiplatelets. In relation to this, patients with high bleeding risk scores may need to have their medications adjusted accordingly.

HOSPITAL CARE

Statement 7: General Recommendations on Initial Management

It IS RECOMMENDED that the following management strategies should be instituted:

1. Patients who are admitted with the diagnosis of NTSE-ACS and are stable hemodynamically should be admitted to a unit for bed rest, with continuous ECG monitoring for ischemic and arrhythmia detection. In patients with ongoing rest pain and hemodynamic instability, admission should be to a coronary/intensive care unit where continuous ECG monitoring is provided, frequent assessment of vital and neurologic vital signs may be performed, and where the staff is adept at providing defibrillation and advanced cardiac life support if the need arises.
2. Supplemental oxygen should be administered to patients with UA/NSTEMI for patients with cyanosis or respiratory distress. Finger pulse oximetry or arterial blood gas determination should be administered to confirm adequate arterial oxygen saturation (SaO_2 greater than 90%) and continued need for supplemental oxygen in the presence of hypoxemia.

STATEMENT 8: Nitrates

It IS RECOMMENDED that nitrates (sublingual tablet or spray), followed by intravenous (IV) administration, be administered for the immediate relief of ischemic and associated symptoms. It IS NOT RECOMMENDED to administer nitroglycerine (NTG) or other nitrates within 24 hours of sildenafil use or within 48 hours of tadalafil use. The suitable time for nitrate administration after vardenafil use is not determined.

The rationale for use of nitrates in NSTE-ACS is based largely on its

mechanism of action and clinical experience. Symptom improvement may be due to its venodilator effect resulting to reduced myocardial preload, and hence, better myocardial oxygen consumption. Nitrates also dilate both normal and diseased coronary arteries, and may increase collateral blood flow.

For initial management of anginal pains, 0.4 mg sublingual NTG tablets or spray taken 5 min apart can be administered until the pain is relieved, or a maximum of 1.2 mg has been taken within 15 minutes (Table 6).

Intravenous (IV) NTG in indicated in the first 48 hours after UA/NSTEMI for treatment of persistent ischemia, HF, or hypertension. The decision to administer IV NTG and the dose used should not preclude therapy with other proven mortality-reducing interventions such as beta blockers or angiotensin-converting enzyme (ACE) inhibitors (ACEIs). If symptoms are not relieved, IV NTG may be initiated at a rate of 10 ug per minute through continuous infusion with non-absorbing tubing and increased by 10 ug per minute every 3 to 5 minutes until some symptom or blood pressure response is noted.

The following are contraindications to nitrate use: blood pressure less than 90 mm Hg or greater than or equal to 30 mm Hg below baseline; severe bradycardia (less than 50 per beats per minute); tachycardia (more than 100 beats per minute) in the absence of symptomatic HF; or right ventricular infarction.

When patients have been free of pain and other manifestations of ischemia

Table 6. Nitroglycerin and nitrates available locally

Compound	Route	Dose/Dosage	Duration of effect
Nitroglycerine	Sublingual tablets	0.3-0.6 mg up to 1.5 mg	1-7 mins
	Spray	0.4 mg as needed	similar to SL tablet
	Transdermal	0.2-0.8 mg/h every 12 h	8-12 h during intermittent therapy
	Intravenous	5-200 mg/min	tolerance in 7-8 hr
Isosorbide dinitrate	Oral	5-80 mg, 2-3 x a day	Up to 8 h
	Oral, slow release	40mg 1 or 2x daily	Up to 8 h
Isosorbide mononitrate	Oral	20 mg twice daily	12-24 hours
	Oral, slow release	60-240 mg orally daily	

for 12 to 24 hours, an attempt should be made to reduce the dose of IV NTG, and to switch to oral or topical nitrates.

Sildenafil inhibits phosphodiesterase 5 (PDE5) that degrades cyclic guanosine monophosphate (cGMP), and cGMP mediates vascular smooth muscle relaxation by nitric oxide. Thus, NTG-medicated vasodilatation is markedly exaggerated and prolonged in the presence of sildenafil. Nitrate use within 24 hours after sildenafil, or sildenafil use within 24 hours after a nitrate, has been associated with profound hypotension, MI, and even death. In case of inadvertent PDE5-nitrate combination, emergency alpha adrenergic agonist or even norepinephrine may be given.

Statement 9: Beta Blockers

It IS RECOMMENDED to initiate a beta blocker by oral route for all patients within the first 24 hours unless contraindications are present. Use of IV beta blockers should be considered with caution.

Beta blockers competitively block the effects of catecholamines on cell membrane beta-receptors. Blocking beta 1 receptors results in decrease in cardiac workload and less myocardial oxygen demand. Acute beta-blocker use seems to be associated with a 34% reduction in in-hospital mortality.[19] Beta blockers should be started early in the absence of contraindications (hemodynamic compromise including hypotension, with or without shock; active bronchospasm; severe bradycardia or heart block greater than 1st degree unless with pacemaker; myocardial infarction precipitated by cocaine use; and overt heart failure including pulmonary edema). The estimated NNT in the local setting to prevent one death is 33 and 92 for NSTEMI and UA, respectively.[2,19]

These agents should be ideally administered IV (the only locally available IV beta blocker is esmolol), followed by oral administration in high-risk patients as well as in patients with ongoing rest pain or orally for intermediate-and low-risk patients. Patients who do not receive a beta blocker during the first 24 hours because of early contraindications should be re-evaluated for beta blocker use.

Nebivolol and bisoprolol are partly secreted by the kidney, whereas carvedilol and metoprolol are metabolized by the liver and are safer in patients with renal failure.

Statement 10: Calcium Channel Blockers (CCBs)

It MAY BE RECOMMENDED to use oral long-acting calcium antagonists for recurrent ischemia in the absence of contraindication and when beta blockers and nitrates are maximally used.

CCBs are a heterogeneous group of drugs that can chemically be classified into the dihydropyridines (DHP) (e.g., amlodipine. felodipine and nifedipine) and the non-DHPs (e.g., verapamil and diltiazem), and are selective inhibitors of L-type channel openings in vascular smooth muscle and in the myocardium.

Definitive evidence for benefit with all calcium antagonists in UA is predominantly limited to symptom control. Rapid-release, short-acting dihydropyridines (e.g. nifepidine) must be avoided in the absence of adequate concurrent beta-blockade in ACS because this may increase adverse outcomes. Verapamil and diltiazem should be avoided in patients with pulmonary edema or evidence of severe LV dysfunction. Amlodipine and felodipine appear to be well tolerated by patients with chronic LV dysfunction, but have not been tested extensively in NSTE-ACS.

The administration of extended-release forms of non-DHP CCBs instead of a beta blocker, and the use of immediate-release DHP CCBs in the presence of a beta blocker, can be done but with caution. However, it is not recommended to administer immediate-release DHP CCBs in the absence of a beta blocker

Statement 11: ACEIs or Angiotensin Receptor Blockers (ARB)

It IS STRONGLY RECOMMENDED that an ACEI should be administered within 24 hours of admision to NSTE-ACS patients with pulmonary congestion, with LVEF less than 40% in the absence of hypotension and other contraindications.

The initial choice of ACEI is a low-dose, short-acting agent, which should be titrated upward towards a stable target maintenance dose at 24 to 48 hours after symptom onset. Hypotension or systolic blood pressure lower than 30 mm Hg from baseline are contraindications. Once stable maintenance is achieved, short-acting agents can be continued or converted to an equivalent-dose long-acting agent to simplify dosing . For example, captopril may be started at a dose of 6.125 mg thrice daily, then titrated towards a maximum dose of 50 mg thrice daily. Ramipril may be initiated at a dose of 1.25 mg twice daily, and titrated to a target dose of 5 mg twice daily.

ACEIs have been shown to reduce mortality rate in patients with acute MI or who recently had an MI and have LV systolic dysfunction, in diabetic patients with LV dysfunction, and in a broad spectrum of patients with high-risk chronic CAD, including patients with normal LV function.[20,21]

An ACEI is recommended for all ACS patients. The NNT using ACEIs to prevent a death is estimated at 91 for NSTEMI and 253 for UA.[2,20] ARBs should be considered in patients who are intolerant to ACEIs and/or who have HF or MI with LVEF less than 40%. The ARB valsartan was shown to be

as effective as captopril among patients with MI and systolic dysfunction in preventing CV events after MI.

It is not recommended to give an ACEI and an ARB in combination.

Statement 12: Morphine Sulfate

It is recommended that morphine sulfate be administered IV when symptoms are not immediately relieved with NTG, or when acute pulmonary congestion and/or severe agitation is present.

Morphine sulfate 1 to 5 mg IV is recommended for patients whose symptoms are not relieved after three serial sublingual NTG tablets, or whose symptoms recur despite adequate anti-ischemic therapy. Unless contraindicated by hypotension or intolerance, morphine may be administered along with intravenous NTG, with careful blood pressure monitoring, and may be repeated every 5 to 30 minutes as needed to relieve symptoms and maintain patient comfort. Naloxone (0.4 to 2.0 mg IV) may be administered for morphine overdose with respiratory and/or circulatory depression. Meperidine hydrochloride can be substituted in patients who are allergic to morphine.

Statement 13: Aspirin

It is STRONGLY RECOMMENDED that non-enteric coated aspirin be chewed by patients as soon as possible at initial presentation at an initial dose of 160 to 320 mg followed by 80 to 160 mg daily indefinitely.

Aspirin reduces the incidence of recurrent MI or death in patients with UA/NSTEMI.[22-24]

A loading dose 160 to 320 mg plain aspirin should be chewed. Daily maintenance dose is 80 to 160 mg, which is as efficacious as and safer than higher doses. The estimated NNT for aspirin is 21 and 59 for NSTEMI and UA, respectively.[2,22-24]

Statement 14: P_2Y_{12} Inhibitors

It IS STRONGLY RECOMMENDED to start a P_2Y_{12} inhibitor (ticagrelor, prasugrel or clopidogrel) in addition to aspirin for a period of 12 months unless there are contraindications such as excessive risk of bleeding.

It IS STRONGLY RECOMMENDED to discontinue ticagrelor and clopidogrel at least 5 days prior to elective CABG, and 7 days for prasugrel, unless CABG or the need for a P_2Y_{12} inhibitor outweighs the risk of bleeding.

Ticagrelor is given at a loading dose of 180 mg followed by 90 mg twice daily regardless of the initial treatment strategy (conservative or early invasive). A low aspirin maintenance dose (at most 100 mg daily) is likely to be associated

with the most favorable outcomes when using ticagrelor in patients with ACS.

Prasugrel is given at a loading dose of 60 mg followed by 10 mg daily for patients who are P_2Y_{12} naïve, less than 75 years of age, with no history of stroke or TIA, and who are undergoing early invasive strategy (PCI). Lower the maintenance dose to 5 mg in patients who weigh less than 60 kg, although the effectiveness and safety of the 5-mg dose have not been studied prospectively.

Clopidogrel is given at a loading dose of 300 mg followed by 75mg daily for patients in whom a conservative strategy is planned and who cannot receive ticagrelor. It is given at a loading dose of 600 mg in patients who are undergoing PCI when ticagrelor and prasugrel cannot be given.

There is a complete revision on the recommendations on the use of ADP-receptor antagonists with the addition of two newer P_2Y_{12} inhibitors (ticagrelor and prasugrel) and the removal of ticlopidine due to its various adverse effects such as gastrointestinal problems, neutropenia, and incidences of thrombotic thrombocytopenic purpura. Clopidogrel use was likewise revised due to the issues regarding the optimal loading dose in the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial, which failed to address it.[25] The Clopidogrel and Aspirin Optimal Usage to Reduce Recurrent Events – Seventh Organization to Assess Strategies in Ischemic Syndromes (CURRENT-OASIS 7) trial published in 2010 was designed to provide the optimal dosing guide for both clopidogrel and aspirin for those undergoing PCI and for those in whom a conservative approach is planned.[26]

The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI 38) compared prasugrel with clopidogrel among patients with UA/NSTEMI undergoing PCI.[27] Prasugrel was associated with a significant reduction in the primary efficacy endpoint but with a significant increase in the rate of bleeding, notably TIMI (Thrombolysis In Myocardial Infarction) major hemorrhage, which was observed in 2.4% of patients taking prasugrel vs 1.8% in patients taking clopidogrel, thus the restriction for its use among patients >75 years of age and with a history of stroke or TIA. Furthermore, prasugrel was used when the decision to do PCI was made based on the initial coronary angiogram. The absence of significant benefit in overall survival makes it difficult to estimate NNT for mortality with prasugrel.

The Study of Platelet Inhibition and Patient Outcomes (PLATO) was designed to determine whether ticagrelor was superior to clopidogrel in preventing vascular events and death in a broad population of patients with ACS, majority of whom were UA/NSTEMI patients, whether an initial invasive or conservative strategy was planned.[28] Compared with clopidogrel, ticagrelor was associated with a lower incidence of the primary endpoint and overall

mortality among those who underwent PCI and among those who were treated conservatively. Over clopidogrel, the estimated NNT to prevent one death with ticagrelor is 47 for NSTEMI and 142 for UA.[2,28]

The head-to-head trials of prasugrel and ticagrelor with clopidogrel have demonstrated a clear advantage and superiority of these two newer agents to clopidogrel in reducing clinical events but clinicians must weigh the risks and benefits on its use among individual patients due to their higher rates of bleeding. Furthermore, it should be emphasized that the two newer P_2Y_{12} receptor inhibitors were studied in different patient populations, and due to this reason, these agents should be used among patients with similar characteristics as those included in the study population of PLATO and TRITON-TIMI 38.

Statement 15: Anticoagulants

It IS STRONGLY RECOMMENDED to start unfractionated heparin (UFH), enoxaparin or fondaparinux in addition to antiplatelet therapy.

UFH should be given for 48 hours. A single bolus of UFH (85 IU/kg or 60 IU/kg with glycoprotein (GP) II_b/III_a inhibitors) should be added to fondaparinux at the time of PCI.

Enoxaparin or fondaparinux should be given for 5 to 8 days, or during the entire duration of hospital stay if admitted less than 5 days. Enoxaparin should be discontinued 12 to 24 hours before CABG. Fondaparinux should be discontinued 24 hours before CABG.

Discontinue anticoagulation after PCI for uncomplicated cases.

In those for invasive strategy, an increased rate of catheter-associated thrombosis was noted post-PCI in the Organization to Assess Strategies for Ischaemic Syndromes (OASIS-5) trial, but the addition of UFH eliminated such occurrences, though the dose of the UFH used was not yet fully evidence-based at that time.[29] With the publication of the Fondaparinux Trial with Unfractionated Heparin during Revascularization in Acute Coronary Syndromes (FUTURA) – OASIS 8 trial, the issue of catheter thrombosis and optimal dose of UFH was addressed with the recommendation to add a single bolus of standard-dose UFH of 85 IU/kg or 60 IU/kg with GP II_b/III_a inhibitors at the time of PCI.[30]

The NNT for UFH to prevent one death is estimated at 34 and 95 for NSTEMI and UA, respectively.[2,31] While a meta-analysis showed that enoxaparin lowered composite outcome of death or MI at 30 days, no such benefit was seen with death alone. Hence, the NNTs of enoxaparin cannot be estimated over UFH. Over enoxaparin, the respective NNTs of fondaparinux are 112 and 311.[2,29]

Statement 16: GP II_b/III_a Inhibitors

It MAY BE RECOMMENDED to give tirofiban in high-risk patients undergoing either a conservative or invasive strategy.

GP II_b/III_a Inhibitors (tirofiban, abciximab, and eptifibatide) have been proven to be beneficial among UA/NSTEMI patients managed either conservatively or invasively, particularly those with high-risk features such as elevated troponin, diabetes, and those undergoing revascularization. Locally, only tirofiban is available, hence the removal of abciximab and eptifibatide in these guidelines. The Platelet Receptor inhibition for Ischemic Syndrome Management (PRISM) and Platelet Receptor inhibition for Ischemic Syndrome Management in Patients Limited to very Unstable Signs and symptoms (PRISM-PLUS) showed that tirofiban, when given alone or in combination with heparin, reduced the likelihood of death, MI, and refractory ischemia.[32,33] These trials also suggest a more potential benefit towards the diabetic population, but this warrants further research and investigation.

The NNT to prevent one death among those with NSTEMI and UA taking aspirin are 29 and 80.[2,32]

Statement 17: Fibrinolytic Therapy

It IS NOT RECOMMENDED to use IV fibrinolytic therapy in patients with UA or in patients without acute ST-segment elevation, a true posterior MI, or a presumed new left BBB.

Statement 18: Conservative (Medical) versus Early Invasive (Coronary Angiography and Revascularization) Strategies

It IS RECOMMENDED that an early invasive strategy (as early as possible up to 72 hours) followed by revascularization (PCI or CABG) be used in patients with any of the following high-risk indicators:

1. **Recurrent angina/ischemia at rest or with low-level activities despite intensive anti-ischemic therapy;**
2. **Elevated cardiac biomarkers (Troponin T or Troponin I); or new or presumably new ST-segment depression;**
3. **Signs or symptoms of HF, or new or worsening mitral regurgitation;**
4. **High-risk findings from non-invasive testing ;**
5. **Hemodynamic instability;**
6. **Sustained ventricular tachycardia;**
7. **PCI within 6 months;**
8. **Prior CABG;**
9. **High-risk score (e.g., using GRACE), and;**
10. **Reduced LV systolic function (LVEF less than 40%).**

Patients presenting with NSTE-ACS belong to a heterogenous group in terms of risk. Those with the highest risk benefit most from early revascularization through symptom relief, shortened hospital stay and improvement of prognosis. It is therefore important to perform early risk stratification to prevent delay in revascularization. The high-risk criteria may depend upon generally accepted parameters (shown in the statement above) or upon pre-defined risk scores (e.g., GRACE scoring).

Two different treatment strategies, termed "early conservative" and "early invasive" strategies, have evolved for patients with NSTE-ACS. In the early conservative strategy, coronary angiography is reserved for patients with evidence of recurrent ischemia (angina at rest; with minimal activity or dynamic ST-T segment changes; or a strongly positive stress tests despite vigorous medical therapy). In the early invasive strategy, patients without clinically obvious contraindications to coronary revascularization are routinely recommended for coronary angiography and revascularization, if possible, within 24 to 48 after presentation to the ER.

TIMI-IIIB was the first trial to compare strategies of routine catheterization and revascularization in addition to medical therapy and selective use of aggressive treatment.[34] The Fragmin and Fast Revascularization during Instability in Coronary Artery Disease (FRISC II) trial, and the Treat Angina With Aggrastat and Determine the Cost of Therapy With an Invasive or Conservative Strategy—Thrombolysis in Myocardial Infarction 18 (TACTICS-TIMI18) trial, both support the use of catheterization and revascularization for selected patients with ACS.[35,36] The greater benefits derived from PCI in the latter two trials can be explained in part by the use of stents and GP-receptor blockers and lower peri-procedural complications.

The timing of angiography and revascularization should be based on the patient's risk profile. Patients at very high risk (refractory angina, severe HF, life-threatening ventricular arrhythmias or hemodynamic instability) should be considered for urgent angiography (within less than 2 hours). In patients with a high GRACE risk score (over 140) and one major criterion, an early invasive strategy within 24 hours is considered reasonable.[37] If the GRACE risk score is lower than 140, but one high-risk criterion is present, the invasive procedure may be delayed until 72 hours. In other lower risk patients who do not have recurrent symptoms, a non -invasive assessment for inducible ischemia is recommended prior to discharge. In the presence of reversible ischemia, coronary angiography is recommended.[6] A conservative strategy may also be instituted for patients with low risk scores or according to patient or physician preferences in the absence of high-risk features.

According to the PHA ACS Registry, patients with NSTEMI and UA received

primarily medical treatment in 66% and 75%, respectively.[2] Only 11.3% and 7.8% received PCI; 2.5% and 1.4% underwent CABG.

Statement 19: Coronary Angiography

Coronary angiography IS NOT RECOMMENDED in patients with extensive co-morbidities (e.g., liver or pulmonary failure; cancer); in whom the risks of revascularization are not likely to outweigh the benefits; in patients with acute chest pain and a low likelihood of ACS; or in patients who will not consent to revascularization regardless of the findings.

The benefits of coronary angiography should be balanced by its risks. The benefits of coronary angiography are highest among high risk patients. It is not recommended for patients whose risks may outweigh the benefits, such as in those with extensive comorbidities, or those with a low probability of ACS. In these patients, invasive evaluation can be delayed without increased risk. Non-invasive assessments of inducible ischemia may be performed before hospital discharge.

Statement 20: Revascularization by PCI

PCI IS RECOMMENDED for NSTE-ACS patients with 1- to 2-vessel CAD, with or without significant proximal left anterior descending CAD, but with a large area of viable myocardium and high-risk criteria on no-invasive testing.

If lesions are difficult to assess, fractional flow reserve measurements may be used in order to decide on the treatment strategy.

Statement 21: Revascularization by CABG Surgery

CABG IS RECOMMENDED for patients with significant left main disease, and is the preferred revascularization strategy for patients with multi-vessel coronary disease; vessels with lesions not favorable for PCI; depressed systolic function (LVEF lower than 50%); and diabetes.

The general consensus in other guidelines is that CABG is most beneficial in patients with disease of the left main coronary artery; involvement of multiple vessels; and other high-risk patients such as those with ventricular dysfunction or diabetes.[38]

Statement 22: Hospital Transfer for Revascularization

In patients initially admitted in hospitals without catheterization facilities and with at least one major high-risk feature as mentioned above, or a high GRACE risk score of over 140, transfer to a hospital

with catheterization facilities IS RECOMMENDED.

Patients at high risk (as described in these guidelines) should be considered for urgent coronary angiography, and will benefit from early invasive strategy. If evaluation using non-invasive assessment suggests inducible/reversible ischemia in these high-risk patients, invasive revascularization is beneficial.

HOSPITAL DISCHARGE AND LONG-TERM MANAGEMENT

Statement 23: Hospital Discharge and Long-term Management Advice

It IS RECOMMENDED that the following specific instructions should be given upon hospital discharge and for long-term management:

Lifestyle modification that includes smoking cessation, achievement or maintenance of optimal weight (body mass index of 18.5 to 24.9 kg/m^2), exercise, and diet;

Consider referral of patients who are smokers to smoking cessation program or clinic and/or an out-patient cardiac rehabilitation program, and;

Continued education about long term follow up, adherence to medications. Any recurrence or change in symptoms should be communicated to the healthcare team.

Secondary prevention in ACS patients cannot be overemphasized. Re-hospitalization may be as high as 20% in ACS patients. Mortality rates in those above 40 years old are as high as 18% among men and 23% among women. Upon discharge, the above recommendations should be instituted to prevent re-hospitalization and mortality. Exercise should be conducted for 30 minutes per day, for 5 days in a week.

STATEMENT 24: Drug/Medication Management

It IS STRONGLY RECOMMENDED to maintain patients who were treated medically with aspirin indefinitely, and ticagrelor 90 mg twice daily or clopidogrel 75 mg daily, for 12 months.

It IS STRONGLY RECOMMENDED to maintain patients who underwent stenting, with aspirin indefinitely, plus ticagrelor 90 mg twice daily or prasugrel 10 mg daily or clopidogrel 75 mg daily, for 12 months in patients with drug-eluting stents, and 6 months in patients with bare metal stents.

It IS STRONGLY RECOMMENDED that beta blockers be continued indefinitely for all NSTE-ACS patients unless contraindicated. In those with moderate or severe systolic dysfunction, the dosing regimen must be titrated slowly.

It IS STRONGLY RECOMMENDED to continue ACE inhibition indefinitely in all NSTE-ACS patients who have a LVEF less than 40%, hypertension, diabetes mellitus or HF. In the absence of these aggravating factors, use of ACEIs may still be RECOMMENDED. An ARB may be prescribed if an ACEI cannot be tolerated.

It IS RECOMMENDED to continue nitrates for ischemic relief.

It IS RECOMMENDED to continue CCBs as add-on therapy to beta blockers or if the latter are not tolerated for ischemic control.

STATEMENT 25: Control of Risk Factors

It IS RECOMMENDED to obtain a fasting lipid test within 24 hours of admission. Regardless of levels, it IS STRONGLY RECOMMENDED to start on statins in all NSTE-ACS patients. The goals of lipid management in secondary prevention follow those of SIHD.

It IS RECOMMENDED that hypertension be controlled to a blood pressure of less than 140/90 mm Hg.

Tight control of hyperglycemia in diabetes IS RECOMMENDED. The goal is a HbA1c of less than 7%.

STATEMENT 26: Cardiac Rehabilitation

It IS STRONGLY RECOMMENDED that patients with multiple risk factors and those who require monitoring during exercise be enrolled in a cardiac rehabilitation program if available.

According to the PHA ACS Registry, only 42% of UA patients and 44% of NSTEMI patients are referred to cardiac rehabilitation.[2] Patients who underwent invasive revascularization were more likely than those treated medically to be referred for cardiac rehabilitation (71% for CABG and 64% for PCI vs 36% in medically treated patients).

REFERENCES

1. Leading Causes of Mortality. Manila: Department of Health, Republic of the Philippines; 2009. Available at: http://www.doh.gov.ph/node/198.html. Accessed on July 26, 2014.
2. Yaneza LO, Abanilla JM, Abola MTB, Caole-Ang IV, Fernandez MBD, Lopez EA, Punzalan FER, Reyes EB; Steering Committee Members for the Philippine Heart Association-Acute Coronary Syndrome (PHA-ACS) Registry. Philippine Heart Association-Acute Coronary Syndrome Registry: 2 year Results. Phil J Cardiol 2013;2 (in press).
3. Philippine Heart Association. 2009 PHA Clinical Practice Guidelines for the Management of Coronary Artery Disease. Quezon City: Philippine Heart Association, 2009.

4. Libby P, Bonow RO, Mann DL, Zipes DP. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 8th ed. Elsevier Science Health Science Division, 2008.
5. Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction; et al. Universal definition of myocardial infarction. Circulation. 2007 Nov 27;116(22):2634-53.
6. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2011 Dec;32(23):2999-3054.
7. Okamatsu K, Takano M, Sakai S, Ishibashi F, Uemura R, Takano T, Mizuno K. Elevated troponin T levels and lesion characteristics in non-ST-elevation acute coronary syndromes. Circulation. 2004 Feb 3;109(4):465-70.
8. Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med. 2009 Aug 27;361(9):858-67.
9. ACCF/ASE/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 Appropriate Use Criteria for Echocardiography. A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance Endorsed by the American College of Chest Physicians. J Am Coll Cardiol. 2011 Mar 1;57(9):1126-66.
10. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 Appropriate Use Criteria for Cardiac Computed Tomography. A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. Circulation. 2010 Nov 23;122(21):e525-55.
11. Udelson JE, Beshansky JR, Ballin DS, Feldman JA, Griffith JL, Handler J, et al. Myocardial perfusion imaging for evaluation and triage of patients with suspected acute cardiac ischemia: a randomized controlled trial. JAMA. 2002 Dec 4;288(21):2693-700.
12. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA 2000;284:835–842.
13. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational

observational study (GRACE). BMJ 2006;333:1091.
14. Six AJ, Cullen L, Backus BE, Greenslade J, Parsonage W, Aldous S, Doevendans PA, Than M. The HEART score for the assessment of patients with chest pain in the emergency department: a multinational validation study. Crit Pathw Cardiol. 2013 Sep;12(3):121-6.
15. de Araújo Gonçalves P, Ferreira J, Aguiar C, Seabra-Gomes R. TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTE-ACS. Eur Heart J. 2005 May;26(9):865-72.
16. Bundalian IPN, Ramboyong RE. Predictive Ability of TIMI and GRACE Scoring in Outcomes of Patients with Non-ST Elevation Myocardial Infarction. Presented at: ICCAD 2011; Venice, Italy. Poster 1515.
17. Backus BE, Six AJ, Kelder JC, Mast TP, van den Akker F, Mast EG, et al. Chest pain in the emergency room: a multicenter validation of the HEART Score. Crit Pathw Cardiol. 2010 Sep;9(3):164-9.
18. Subherwal S, Bach RG, Chen AY, Gage BF, Rao SV, Newby LK, et al. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score. Circulation. 2009 Apr 14;119(14):1873-82.
19. Miller CD, Roe MT, Mulgund J, Hoekstra JW, Santos R, Pollack CV Jr., et al. Impact of acute beta-blocker therapy for patients with non-ST-segment elevation myocardial infarction. Am J Med 2007;120:685–692.
20. Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S. Angiotensin converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. Lancet 2006;368:581–588.
21. Danchin N, Cucherat M, Thuillez C, Durand E, Kadri Z, Steg PG. Angiotensin converting enzyme inhibitors in patients with coronary artery disease and absence of heart failure or left ventricular systolic dysfunction: an overview of long-term randomized controlled trials. Arch Intern Med 2006;166:787–796.
22. Theroux P, Ouimet H, McCans J, Latour JG, Joly P, Levy G, et al. Aspirin, heparin, or both to treat acute unstable angina. N Engl J Med 1988;319:1105–1111.
23. Theroux P, Waters D, Qiu S, McCans J, de Guise P, Juneau M. Aspirin versus heparin to prevent myocardial infarction during the acute phase of unstable angina. Circulation 1993;88:2045–2048.
24. Cairns JA, Gent M, Singer J, Finnie KJ, Froggatt GM, Holder DA, et al. Aspirin, sulfinpyrazone, or both in unstable angina. Results of a Canadian multicenter trial. N Engl J Med 1985;313:1369–1375.
25. Fox KA, Mehta SR, Peters R, Zhao F, Lakkis N, Gersh BJ, Yusuf S; Clopidogrel in Unstable angina to prevent Recurrent ischemic Events Trial. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) Trial. Circulation. 2004 Sep 7;110(10):1202-8.

26. Mehta SR, Tanguay J-F, Eikelboom JW, et al. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. Lancet. 2010;376:1233–43.
27. Wiviott SD, Antman EM, Gibson CM, Montalescot G, Riesmeyer J, Weerakkody G, et al.; TRITON-TIMI 38 Investigators. Evaluation of prasugrel compared with clopidogrel in patients with acute coronary syndromes: design and rationale for the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet InhibitioN with prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38). Am Heart J. 2006 Oct;152(4):627-35.
28. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al.; for the PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045–1057.
29. Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators, Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med. 2006 Apr 6;354(14):1464-76.
30. Steg PG, Mehta S, Jolly S, Xavier D, Rupprecht HJ, Lopez-Sendon JL, et al. Fondaparinux with UnfracTionated heparin dUring Revascularization in Acute coronary syndromes (FUTURA/OASIS 8): a randomized trial of intravenous unfractionated heparin during percutaneous coronary intervention in patients with non-ST-segment elevation acute coronary syndromes initially treated with fondaparinux. Am Heart J. 2010 Dec;160(6):1029-34, 1034.e1.
31. Eikelboom JW, Anand SS, Malmberg K, Weitz JI, Ginsberg JS, Yusuf S. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. Lancet 2000;355:1936–1942.
32. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. N Engl J Med. 1998; 338:1498 –505.
33. PRISM-PLUS Study Investigators. Inhibition of the platelet glycoprotein II_b/III_a receptor with tirofiban in unstable angina and non-Q wave myocardial infarction. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. N Engl J Med. 1998; 338:1488 –97.
34. Anderson HV, Cannon CP, Stone PH, Williams DO, McCabe CH, Knatterud GL, et al. One-year results of the Thrombolysis in Myocardial Infarction (TIMI) IIIB clinical trial. A randomized comparison of tissue-type plasminogen activator versus placebo and early invasive versus early conservative strategies in unstable angina and non-Q wave myocardial infarction. J Am Coll Cardiol. 1995 Dec;26(7):1643-50.
35. Lagerqvist B, Husted S, Kontny F, Ståhle E, Swahn E, Wallentin L; Fast Revascularisation during InStability in Coronary artery disease (FRISC-II) Investigators. 5-year outcomes in the FRISC-II randomised trial of an invasive

versus a non-invasive strategy in non-ST-elevation acute coronary syndrome: a follow-up study.Lancet. 2006 Sep 16;368(9540):998-1004.
36. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, et al.; TACTICS (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy)--Thrombolysis in Myocardial Infarction 18 Investigators. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein II_b/III_a inhibitor tirofiban. N Engl J Med. 2001 Jun 21;344(25):1879-87.
37. Mehta SR, Granger CB, Boden WE, Steg PG, Bassand JP, Faxon DP, et al.; TIMACS Investigators. Early versus delayed invasive intervention in acute coronary syndromes. N Engl J Med. 2009 May 21;360(21):2165-75.
38. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2012 Aug 14;60(7):645-81.

2014 Philippine Heart Association Clinical Practice Guidelines for the Diagnosis and Management of Patients with ST Segment Elevation Myocardial Infarction

INTRODUCTION

Since the last update of the Philippine Heart Association (PHA) Clinical Practice Guidelines for the Management of Coronary Artery Disease (CAD) in 2009, several updates and new approaches have already come out in the management of ST elevation myocardial infarction (STEMI), leading to the publication of guidelines updates by the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA), in 2012 and 2013 respectively.[1-3] Furthermore, the ongoing PHA Acute Coronary Syndrome (ACS) registry has released its 2-year results, which would be useful in the translation of international updates and the previous PHA CAD guidelines when formulating locally applicable and timely updates.[4]

In contrast to the 2009 PHA CAD guidelines that had 25 statements on STEMI, this update has 33 statements. Major changes include those regarding pre-hospital recognition; transfer strategies; ivabradine; therapeutic hypothermia; arrhythmias; and anti-platelets. Furthermore, emphasis is placed on risk stratification and cardiac rehabilitation. In addition, numbers needed to treat (NNT) to prevent mortality were presented based on available risk-reduction data from studies and a local event rate for mortality as 8.2% for STEMI, based on the results of the PHA ACS Registry.[2] The NNT was computed as the reciprocal of the product of two factors: the local event rate and the relative risk reduction based on studies.

EARLY ASSESSMENT

Statement 1: Pre-hospital Recognition

It IS STRONGLY RECOMMENDED that patients with possible STEMI symptoms such as chest discomfort, shortness of breath, diaphoresis, nausea, sudden weakness, or syncope should be immediately brought to the emergency room (ER) of a hospital.

Morbidity and mortality from STEMI can be reduced by early recognition of symptoms and timely medical consultation and institution of treatment. Patients and their relatives should be given information on how to recognize signs and symptoms of STEMI and should be informed of the urgency in seeking medical attention.

Statement 2: Initial Evaluation at Emergency Room

It IS STRONGLY RECOMMENDED that a targeted history taking, physical examination and a 12-lead electrocardiogram (ECG) should be taken within 10 minutes of arrival at the ER.

The objective of the initial evaluation is for the physician to rapidly and reliably diagnose STEMI, and to determine the patient's eligibility for reperfusion therapy. The patient should be placed on a cardiac monitor immediately, and emergency resuscitation equipment, including a defibrilator, should be kept nearby.

The targeted history taken in the ER should be detailed enough to establish the probability of STEMI but should be obtained rapidly so as not to delay reperfusion therapy. The history should focus on the chest discomfort and associated symptoms

The chest discomfort is often described as constricting or a sensation of something heavy on the chest. The location is usually substernal but may originate or radiate to the jaw, interscapular area, upper extremities or epigastrium. The discomfort may wax and wane, and typically lasts longer than 30 minutes. Associated symptoms of diaphoresis, nausea and vomiting, light headedness, weakness and fatigue may occur. Age- and sex-related differences in presentation should be considered. Women generally present at an older age than men. Elderly patients are less likely to complain of chest discomfort and present more often with shortness of breath, nausea or syncope.

Prior episodes of myocardial ischemia, infarction, percutaneous coronary intervention (PCI) or bypass surgery, as well as comorbid illnesses including hypertension, diabetes mellitus, possibility of aortic dissection, risk of bleeding and clinical cerebrovascular disease should be sought during the history. Severe tearing pain radiating to the back associated with dyspnea or syncope without ECG changes indicative of myocardial ischemia or infarction should raise the possibility of aortic dissection. Previous bleeding problems, history of ulcer disease, cerebrovascular accidents, and unexplained anemia should be sought since these conditions can be exacerbated with the use of fibrinolytics, anti-platelets and antithrombins in the treatment of STEMI.

A brief physical examination should be performed to aid in the diagnosis and assessment of the extent, location, and complications of STEMI. A limited neurologic examination to look for evidence of prior stroke or cognitive deficits should be performed before administration of fibrinolytic therapy.

An ECG should be taken and shown to an experienced physician within 10 minutes of arrival in the ER. If STEMI is present, a decision whether the patient will be treated with fibrinolytic therapy or PCI should be made

within 10 minutes. If the initial ECG is not diagnositc and the patient remains asymptomatic, but there is high clinical suspicion for STEMI, serial ECGs at 5- to 10-minute intervals or continuous ST segment monitoring should be done.

Statement 3: ECG Evaluation

It IS STRONGLY RECOMMENDED that patients presenting with chest discomfort and ECG finding of at least 0.1 mV ST segment elevation in two contiguous leads should receive reperfusion therapy (e.g., primary PCI or thrombolytics), if not contraindicated.

It IS RECOMMENDED to observe for ECG tracings that make the diagnosis of acute myocardial infarction (AMI) difficult, such as left bundle branch block (LBBB), ventricular paced rhythm, patients without diagnostic ST segment elevation but with persistent ischemic symptoms, isolated posterior myocardial infarction (MI) and ST segment elevation in lead aVR. In these situations, certain ECG changes are seen such as marked ST elevation and hyperacute T waves, and these require immediate reperfusion therapy.

Patients with STEMI require rapid identification and triage to initiate reperfusion therapy. An ECG should be initiated as soon as possible in all patients with suspected STEMI. If there is ST segment elevation of at least 0.1 mV in two contiguous leads, these patients will benefit from reperfusion therapy. Right precordial leads should be done in suspected right ventricular infarction. There are some ECG tracings that make the diagnosis of AMI difficult, such as LBBB, ventricular paced rhythm, persistent ischemic symptoms without diagnostic ST segment elevation, isolated posterior MI, and ST segment elevation in lead aVR. In these situations, certain ECG changes are seen, such as marked ST elevation and hyperacute T waves, and these require immediate reperfusion therapy.

Statement 4: Laboratory Evaluation

It IS RECOMMENDED that laboratory examinations should be performed as part of the management of STEMI patients but should not delay the implementation of reperfusion therapy.

Other laboratory examinations such as troponins and CK enzymes are not components in the diagnosis of STEMI. However, they are helpful in the event that STEMI is not diagnosed and other forms of MI are suspected. Other routine laboratory examinations (e.g. complete blood count, chest X rays, urinalysis, etc.) should not delay the the implementation of reperfusion therapy. Furthermore, comorbid conditions may adversely affect laboratory results (e.g., troponin in renal disease patients), and should be considered.

MANAGEMENT

Statement 5: Initial ER Management

Unless contraindicated, it IS RECOMMENDED that the following routine treatment measures be administered in STEMI patients upon arrival at the ER:

- **Aspirin 160 to 320 mg tablet (non-enteric coated, chewed);**
- **Clopidogrel 300 to 600 mg whether or not fibrinolysis will be given;**
- **Clopidgrel 600 mg or prasugrel 60 mg or ticagrelor 180 mg when a patient will undergo PCI;**
- **Nitrates, either via sublingual or intravenous(IV) routes. Nitrates are contraindicated in patients with hypotension or those who took a phosphodiesterase 5 (PDE5) inhibitor within 24 hrs (48 hrs for tadalafil);**
- **Morphine 2 to 4 mg IV for relief of chest pain, and;**
- **Supplemental oxygen MAY BE RECOMMENDED during the first 6 hours to patients with arterial oxygen saturation of less than 90%.**

Supplemental oxygen should be administered to patients suspected of STEMI particularly for those with oxygen saturation of less than 90% on pulse oximetry. The rationale for the use of oxygen is based on the observation that even with uncomplicated AMI, some patients are modestly hypoxemic initially, presumably because of ventilation perfusion mismatch and excessive lung water.

Aspirin at a dose of 160 to 320 mg should be chewed by the patient who has not yet taken aspirin before presentation with STEMI. More rapid buccal absorption occurs with non-enteric coated aspirin formulations, and should be preferred. The Second International Study of Infarct Survival (ISIS-2) have shown conclusively the efficacy of aspirin alone(absolute risk reduction [ARR] 2.4%; relative risk reduction [RRR] 23%in reducing 35-day mortality); and combined with streptokinase (ARR 5.2%; RRR 42%) in the treatment of evolving AMI.[5] Locally, aspirin use has an estimated NNT of 29 and 53, with or without streptokinase, to prevent one death.[4,5] Aspirin should not be given in those with hypersensitivity to salicylates; instead give clopidogrel.

The use of clopidogrel was demonstrated in the Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study (COMMIT/CCS-2), which randomized 45,852 patients with 24 hours of suspected AMI to 75 mg clopidogrel daily for up to 4 weeks versus placebo in addition to 162 mg of aspirin daily. The composite primary endpoint of death, reinfarction or stroke

was reduced from 10.1% in the placebo group to 9.2% in the clopidogrel group (OR 0.91 [95% CI 0.86, 0.97]).[6]

In addition, the Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction 28 (CLARITY-TIMI 28) study randomized 3,491 patients receiving fibrinolytic therapy within 12 hour of STEMI onset to either clopidogrel (300 mg oral loading dose followed by 75 mg oral daily dose) or placebo.[7] There was a reduction in the primary endpoint of an occluded infarct artery or recurrent MI before angiography from 21% in the placebo grojup to 15% in the clopidogrel group (OR 0.64 [95% CI 0.53, 0.76];p<0.001). This benefit has been thought to be primarily due to prevention of infarct-related artery occlusion. The rate of TIMI major bleeding was 1.7% in the placebo and 1.9% in the clopidogrel group (p=0.80). While clopidogrel showed a significant benefit in improving composite outcomes, the benefit on death alone was not statistically significant, making it difficult to estimate NNT.

Both the ACC and ESC recommend loading with aspirin and P_2Y_{12} inhibitor (clopidogrel, prasugrel, ticagrelor) as early as possible before angiography. After PCI, a maitenance dose of aspirin and a P_2Y_{12} inhibitor should also be given. These recommendations were based on large trials, such as the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) (prasugrel); Platelet Inhibition and Patient Outcomes (PLATO) trial (ticagrelor); and Clopidogrel in Unstable Angina to Prevent Recurrent Events (PCI-CURE), COMMIT/CCS, and CLARITY-TIMI28 (clopidogrel), which showed a reduced primary endpoint of cardiovascular (CV) death, non-fatal MI or stroke.[6-10] It should be noted that prasugrel was noted to be non-inferior to ticagrelor, while prasugrel and ticagrelor were noted to have a greater RRR of combined endpoints compared to clopidogrel, but with increased risk of bleeding. The estimated NNT for prasugrel/ticagrelor over clopidogrel in preventing one death is 49.[4,9,10] All P_2Y_{12} inhibitors should be used with caution in patients at a high risk of bleeding or with significant anemia.

Nitrates were not recommeded in the ESC guidelines, and recommendations were not included in the ACC guidelines.[2,3] However, nitrates can be used in the acute and stable phase to control anginal symptoms, or in patients with hypertension or heart failure, provided there is no hypotension, right ventricular infarction or the use of PDE5 inhibitors in the previous 48 hours.

Morphine sulfate (2 to 4 mg IV with increments of 2 to 8 mg IV repeated at 5 to 15 minute intervals) is the analgesic of choice for the management of pain associated with STEMI. Pain relief is an important element in the management of patients with STEMI and should be directed towards

acute relief of symptoms of myocardial ischemia, and relief of anxiety and apprehension. Anxiety reduction secondary to morphine reduces restlessness and adrenergic stimulation with resulting reduction in cardiac metabolic demand. Morphine is also beneficial in patients with heart failure and pulmonary edema.

Statement 6: In-hospital Treatment

Reperfusion therapy IS RECOMMENDED to all eligible patients with STEMI with symptom onset within the prior 12 hours.

Early revascularization, the goal being 12 hours, is a primary treatment goal in patients with STEMI.[2] Delayed reperfusion is associated with poorer myocardial salvage and outcomes.

Statement 7: Transfer Strategy

It IS STRONGLY RECOMMENDED that patients with STEMI who are hemodynamically and electrically stable, should immediately be transferred to the nearest hospital capable of reperfusion therapy, fibrinolysis or PCI, if expected arrival is within 12 to 24 hours of symptom onset.

In patients who are hemodynamically and electrically unstable, it IS STRONGLY RECOMMENDED to transfer the patient to a higher level hospital if the physician sees it feasible.

If unable to transfer to a reperfusion capable hospital within 12 to 24 hours of symptom onset, it IS RECOMMENDED to admit the patient in the hospital under close monitoring and start guideline directed medical therapy. Once stable the patient should be transferred for risk stratification in a tertiary hospital.

Hospitals are not standardized in the Philippines. Hospitals have different capabilities and not all are fully equipped to give the ideal care and management especially among patients with acute myocardial infarction. There are 3 Levels of hospitals in the country. These are as follows:

Level1: These are Primary Hospitals, including health centers. These hospitals are capable of giving basic medical management. However, they are not equipped to perform fibrinolysis and coronary angiography/angioplasty.

Level 2: These are Secondary Hospitals. These hospitals are capable of providing what the Level 1 hospitals can offer. In addition, they are equipped to perform fibrinolysis. They also have an Intensive Care Unit. However, they do not have the means to perform coronary angiogram/angioplasty.

Level 3. These are the Tertiary Hospitals. These hospitals are fully equipped and capable of coronary angiography/angioplasty, in addition to what level 1 and 2 hospitals can provide. These are the ideal hospitals for patients with MI, especially those with ST-elevation.

Each hospital has its own capability to treat STEMI, some better compared to the others. Because of this, transfer strategy should be created in order to treat STEMI patients adequately, with the goal of being able to initiate reperfusion therapy within the recommended time frame.

Statement 8: Fibrinolysis

It IS STRONGLY RECOMMENDED to undergo immediate thrombolysis (unless contraindicated), with a door-to-needle time of less than 60 minutes as a goal.

In the absence of contraindications and when PCI is not available, fibrinolytic therapy MAY BE RECOMMENDED for patients with STEMI if there is clinical and/or ECG evidence of ongoing chest pain within 12 to 24 hours of symptom onset and presence of multiple ST segment deviations in several leads or hemodynamic instability.

Fibrinolytic therapy IS NOT RECOMMENDED to patients with ST depression except when a true posterior (inferobasal) MI is suspected or when associated with ST elevation in lead AvR.

It IS RECOMMENDED to perform an ECG to patients treated with fibrinolysis, 60 to 90 minutes after administration to determine the presence of failed reperfusion.

Urgent transfer to a PCI-capable hospital for coronary angiography IS RECOMMENDED for patients who demonstrate evidence of failed reperfusion or reocclusion after fibrinolytic therapy.

After successful reperfusion, it MAY BE RECOMMENDED to refer the patient to a tertiary hospital for risk stratification once stable.

Fibrinolysis IS RECOMMENDED to people with acute STEMI presenting within 12 hours of onset of symptoms if primary PCI cannot be delivered within 120 minutes of the time when fibrinolysis could have been given.

In the case of failed reperfusion, offer immediate coronary angiography, with follow-on PCI if indicated. Do not repeat fibrinolytic therapy.

This management strategy was noted to be well adopted by most hospitals with cardiology training programs: as described in the 2-year report of the PHA ACS registry, median time was also noted at 60 minutes.[4]

Fibrinolysis is not recommended in patients with the following absolute contraindications: any prior intracranial hemorrhage; known structural cerebral vascular lesion; known malignant intracranial neoplasm; ischemic stroke within 3 months except acute ischemic stroke within 3 hours; suspected aortic dissection; active bleeding; or significant closed head or facial trauma.

Fibrinolysis may not be considered in patients with the following relative contraindications: history of chronic, severe, poorly controlled hypertension; history of prior ischemic stroke, dementia, or intracranial pathology; traumatic or prolonged cardiopulmonary rescucitation or major surgery; recent internal bleeding (within 2 to 4 weeks); pregnancy; active peptic ulcer disease; and current use of anticoagulants.

Statement 9: Primary Percutaneous Coronary Intervention (PCI)

Primary PCI IS RECOMMENDED in patients with STEMI and ischemic symptoms of less than 12 hours' duration.

Primary PCI IS RECOMMENDED in patients with STEMI and ischemic symptoms of less than 12 hours' duration who have contraindications to fibrinolytic therapy, irrespective of the time delay from first medical contact.

Primary PCI IS RECOMMENDED in patients with STEMI and cardiogenic shock or acute severe heart failure (HF), irrespective of time delay from MI onset.

It MAY BE RECOMMENDED in patients with STEMI if there is clinical and/or ECG evidence of ongoing ischemia between 12 and 24 hours after symptom onset.

Primary PCI is the recommended method of reperfusion when it can be performed in a timely fashion by experienced operators within 90 minutes. Based on the 2-year report of the PHA ACS registry, the median door-to-balloon time was 120 minutes, which was 30 minutes longer than what is being recommended by international guidelines.[4] Two of the primary reasons that caused delays were financial constraints and delay in securing consent. Proposals or new approaches to address these two reasons could be adopted by hospitals to ultimately improve door-to-balloon time.

Statement 10: Type of Stents

Bare metal stents (BMS) are RECOMMENDED in patients with high bleeding risk, who are unable to comply with 1 year of double anti-platelet therapy (DAPT), or who anticipate invasive or surgical procedures in the next year. Drug-eluting stents (DES) are NOT RECOMMENDED in primary PCI for patients with STEMI who are unable to tolerate or comply

with a prolonged course of DAPT because of the increased risk of stent thrombosis with premature discontinuation of one or both agents.

DES reduce the risk of repeated vessel revascularization as compared to BMS.[11] However, there is some risk of stents very late stent thrombosis and re-infarction with DES, so it is imperative for these patients to comply with long-term DAPT. The lower requirement for DAPT in BMS makes it a more recommended stent for those who cannot comply with long-term DAPT, or those who will undergo surgery within the short- to mid-term. Newer generations of DES are currently being tested against older generation DES or BMS.

Statement 11: Therapeutic Hypothermia

Therapeutic hypothermia IS RECOMMENDED as soon as possible in comatose or post-arrest patients with STEMI and out-of-hospital cardiac arrest caused by ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT), including patients who underwent primary PCI.

Several studies have shown the benefit of therapeutic hypothermia in comatose or post-arrest patients with STEMI and out-of-hospital cardiac arrest caused by VF or pulseless ventricular tachycardia, by improving survival, decreasing infarct size, and promoting neurological recovery.[12-14]

Based on the 2010 AHA Guidelines for Cardiovascular Resuscitation and Emergency Cardiovascular Care Science, studies on the timing of initiating of therapeutic hypothermia and the duration of achieving target temperature showed conflicting results.[15] Some studies showed better neurological outcomes with faster initiation of hypothermia and faster achievement of target temperature, while the others did not. The optimal duration of induced hypothermia is at least 12 hours and may be greater than 24 hours. The effect of a longer duration of cooling on outcome has not been studied in adults.

There are a number of methods to induce therapeutic hypothermia, but no one method is noted to be optimal. Different methods include endovascular catheters, surface cooling devices as well as cooling blankets and frequent application of icebags. As an adjunct, iced isotonic fluid can be infused to initiate core cooling but must be combined with a follow up method for maintenance hypothermia.

Core temperature should be monitored using an esophageal thermometer, bladder catheter in non-anuric patients, or pulmonary catheter if one is placed for other indications. Axillary and oral temperatures are inadequate for measurement of core temperature changes. It is recommended that patients with return of spontaneous circulation (ROSC) with out-of-hospital VF cardiac arrest should be cooled to 32°C to 34°C for 12 to 24 hours. Induced

hypothermia also may be considered for comatose adult patients with ROSC after in-hospital cardiac arrest of any initial rhythm or after out-of-hospital cardiac arrest with an initial rhythm of pulseless electric activity or asystole. Active rewarming should be avoided in comatose patients who spontaneously develop a mild degree of hypothermia (>32°C) after resuscitation from cardiac arrest during the first 48 hours after ROSC.

Due to the lack of ready mortality data among Filipino patients eligible for therapeutic hypothermia, an NNT could not be estimated.

Statement 12: Coronary Artery Bypass Grafting (CABG)

CABG IS RECOMMENDED in failed PCI with persistent pain or hemodynamic instability in patients with coronary anatomy suitable for surgery. It IS RECOMMENDED in persistent or recurrent ischemia refractory to medical therapy in patients who have coronary anatomy suitable for surgery, and are not candidates for PCI or fibronolytic therapy. It IS RECOMMENDED in patients with STEMI at the time of operative repair of mechanical defects.

Emergency CABG within 6 hours of symptom onset MAY BE RECOMMENDED in patients with STEMI who do not have cardiogenic shock and are not candidates for PCI or fibrinolytic therapy.

The use of mechanical circulatory support MAY BE RECOMMENDED in patients with STEMI who are hemodynamically stable and require urgent CABG.

In patients with STEMI, prompt restoration of myocardial blood flow is essential to optimize myocardial salvage and decrease mortality. This is particularly important in the first few hours of symptom onset, when the amount of myocardium salvageable by reperfusion is the greatest. Both PCI and fibrinolysis can restore blood flow in an acutely occluded coronary artery in a much shorter time than CABG, thus the two former prcedures are preferred rather than the latter. The instances when CABG is considered first before the PCI and fibrinolysis are indicated in the statement above.

Statement 13: CABG Surgery after STEMI and Antiplatelet Agents

Aspirin should not be withheld before elective or non-elective CABG after STEMI. In patients where elective CABG is planned, clopidogrel should be withheld for 5 days; ticagrelor for 3 to 5 days; and prasugrel for 7 days.

Clopidogrel or ticagrelor should be discontinued at least 24 hours before urgent CABG, if possible. Urgent CABG within 5 days of clopidogrel or ticagrelor administration or within 7 days of prasugrel

administration might be considered especially if the benefits outweigh the risks of bleeding.

It is reasonable to restart dual antiplatelet therapy as soon as considered safe in relation to the bleeding risk.

The risk of bleeding related to surgery must be balanced against the risk of recurrent ischemic events related to the discontinuation of therapy, bearing in mind the nature of the surgery; the ischemic risk and extent of CAD; the time since the acute episode; the time since PCI; and the risk of stent thrombosis.

Clopidogrel is associated with an increased risk of bleeding if discontinued less than 5 days before surgery. Prasugrel is also associated with a marked increase in bleeding risk. With respect to ticagrelor, data from the PLATO trial suggest that ticagrelor discontinued 3 to 5 days before CABG surgery yielded similar CABG-related major bleeding and transfusions as clopidogrel and ticagrelor.[10] Although non-fatal MI and stroke rates in the two groups were not significantly different in this cohort, there was half the mortality in the ticagrelor group.

Whether adenosine diphosphate (ADP) receptor antagonists should be restarted after CABG surgery has not been addressed in any specific trial, and the optimal timing of restarting remains uncertain. However, given the reduction of the primary endpoint and mortality with ticagrelor in the PLATO trial, and the continued risk for ischemic events in patients post-CABG, it is reasonable to restart DAPT as soon as considered safe in relation to bleeding risk.[10] In the event of bleeding associated with DAPT, follow the standard protocol for treatment of bleeding due to the respective medication used.

Statement 14: Hospital Management of STEMI

General recommendations for a patient with STEMI in the Coronary Care Unit (CCU): It IS RECOMMENDED that STEMI patients should be immediately admitted to a quiet and comfortable environment with qualified personnel; placed on continuous ECG monitoring and pulse oximetry; and have ready access to facilities for hemodynamic monitoring and defibrillation. Administer aspirin and beta-blockers in adequate dose to control heart rate, and assess the need for intravenous nitroglycerin for control of angina, hypertension and heart failure.

When stable for 6 hours, the patient should be reassessed for oxygen need (i.e., saturation of less than 90%) and discontinuation of supplemental oxygen should be considered.

Nursing care should be provided by individuals knowledgeable in critical care.

Risk stratification of STEMI: It IS RECOMMENDED that STEMI

patients should be stratified as high risk or low risk.

STEMI patients should be admitted to a coronary care unit or similar unit suitable for intensive patient monitoring and management. Staff should be familiar with the management of ACS, arrhythmias, HF, mechanical circulatory support, and invasive/and non-invasive hemodynamic monitoring, and respiratory monitoring, among other similarly intensive procedures.

ECG monitoring for arrhythmias and ST-segment deviations should be continuous.

Control of heart rate, pain, hypertension, and HF should be performed through appropriate pharmacotherapy as described.

Statement 15: Assessment of Left Ventricular (LV) Function

It IS RECOMMENDED to measure LV ejection fraction (LVEF) in all patients with STEMI.

It IS STRONGLY RECOMMENDED that a bedside echocardiogram should be done when complications of STEMI are considered, including but not limited to acute mitral regurgitation (MR), ventricular septal perforation, free wall rupture or tamponade, right ventricular involvement, HF or thrombus.

An echocardiogram should be done to stratify patients as high risk or low risk. High-risk patients are those with recurrent ischemia, reinfarction, life-threatening arrhythmias or clinical evidence of pump dysfunction; those with mechanical complications of infarction (cardiogenic shock, ventricular septal defect, acute mitral regurgitation, and free wall rupture). Low-risk patients are those with absence of recurrent ischemia, heart failure, or hemodynamically compromising arrhythmias. Low-risk patients who have undergone successful PCI should be admitted directly to telemetry or a regular room under close supervision for post-PCI care rather than in the CCU. Furthermore, low-risk STEMI patients who demonstrate 12 to 24 hours of clinical stability should be transferred out of the CCU.

Statement 16: Hemodynamic Assessment

It IS RECOMMENDED that high-risk patients with mechanical complications of STEMI and/or progressive hypotension should have a pulmonary catheter and intra-arterial pressure monitoring. Intra-aortic balloon pump (IABP) counterpulsation and early revascularization should be considered.

Invasive hemodynamic assessment through pulmonary catheterization and intra-arterial pressure monitoring allows for a more precise assessment for patients with complications of STEMI, such as HF or hypotension.

In selected patients (e.g., those who are not responding adequately to conservative measures; those with ongoing ischemia, persistent ST elevation or new LBBB, early revascularization should be considered).

IABP counterpulsation is a popular method to mechanically treat cardiogenic shock. The aortic diastolic inflation and systolic deflation of IABP improves myocardial and peripheral perfusion, and reduces afterload and myocardial oxygen consumption. The evidence supporting the use of IABP is conflicting, especially with improved outcomes from recent developments in pharmacotherapy and reperfusion strategies. The Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS) trial suggest that adding IABP to thrombolysis lowered 6-month mortality in patients with severe hemodynamic impairment.[16] The mortality data for this specific subset of patients is unavailable from the PHA ACS registry, preventing NNT estimation.

Statement 17: Management of Arrhythmias after STEMI

It IS RECOMMENDED to immediately terminate VF or pulseless VT with 200 J (biphasic) or 360 J (monophasic) defibrillation.

It IS RECOMMENDED to immediately terminate any hemodynamically significant VT, or VT associated with angina or pulmonary edema with 100 J synchronized cardioversion, and increasing energies if initially unsuccessful.

It IS RECOMMENDED to terminate sustained VT which is hemodynamically stable and not associated with angina nor pulmonary edema with amiodarone boluses of 150 mg over 10 min, repeated over 15 minutes as needed. Amiodarone infusion can be given at 1mg/kg body weight/min for 6 hours, then 1mg/kg body weight/min for 18 hours, not exceeding 2.2 g in 24 hours.

It IS RECOMMENDED to immediately terminate atrial fibrillation or flutter with hemodynamic compromise and/or ischemia with 50 to 100 J (atrial flutter) or 120 to 200 J (atrial fibrillation) synchronized cardioversion, and increasing energies if initially unsuccessful.If unresponsive or recurrent, amiodarone infusion or digoxin may be used for rate-control.

It IS RECOMMENDED to immediately terminate paroxysmal supraventricular tachycardia (SVT) with carotid sinus massage (CSM); if unsuccessful, with intravenous adenosine; or if still unsuccessful and blood pressure permits, verapamil.

It IS RECOMMENDED to terminate paroxysmal SVTs with 50 J cardioversion if unsuccessful with CSM or medications. Increase

energies if initially unsuccessful.

It IS NOT RECOMMENDED to treat isolated premature ventricular contractions and non-sustained VTs.

Arrhythmias and conduction impairments are common complications of STEMI. The most common arrhythmias are new-onset atrial fibrillation, VT, sinus bradycardia, and VF. Early VF or VT may predict an increased risk for 30-day mortality.

Arrhythmias may also be manifestations of serious underlying condition, such as continuing ischemia, pump failure, altered autonomic tone, hypoxia, and electrolyte- and acid-base disturbances. When identified, these conditions must be corrected appropriately.

The management of ventricular and supraventricular arrhythmias are outlined in the above statements. Most antiarrhythmic drugs are ineffective as first-line management of life-threatening ventricular arrhythmias and should not be used in the prevention of sudden death.

Statement 18: Temporary Pacemaker

It IS RECOMMENDED to use temporary pacing for symptomatic bradyarrhythmias unresponsive to medical treatment.

Sinus bradycardia is common in the first hours of STEMI, especially in inferior infarction. In some cases, this is caused by opioids and may require no treatment. Symptomatic bradycardia and those leading to hypotension should be treated medically (e.g., IV atropine). However, when medical treatment fails, temporary pacing is recommended.

Statement 19: Permanent Pacemaker

It IS RECOMMENDED to do permanent pacing with an appropriately chosen device for the following:

a. **Persistent 2^{o} atrioventricular (AV) block with bilateral bundle branch block**
b. **Transient high-degree AV block**
c. **Persistent and symptomatic 3^{o} AV block**

It IS RECOMMENDED to immediately transfer a STEMI patient with persistent 2^{o} AV block with bilateral bundle branch block, transient high-degree AV block, or persistent and symptomatic 3^{o} AV block to a hospital capable on implanting a permanent pacemaker.

The indications for the use of permanent pacing are described above. However, the ACC/AHA Guidelines for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices recommends to consider on the type of conduction disturbance, location of the infarction, and relation of the electrical

disturbance to infarct time when deciding to implant a permanent pacemaker for AV blocks.[17]

Statement 20: Implantable Cardioverter Defibrillator (ICD)

After reperfusion therapy (PCI or fibrinolysis) in patients with STEMI who present with VF or sustained VT after 48 hours, it IS RECOMMENDED to implant an ICD.

In patients with VF or sustained VT, ICD therapy is associated with significant mortality reduction vs antiarrhythmic drug therapy, mainly amiodarone.[18] Patients who are indicated to benefit from ICD placement should undergo specialized electrophysiological evaluation, preferably before discharge, for placement of an ICD.

Statement 21: Antiplatelets and Antithrombotics

It IS RECOMMENDED that aspirin should be used indefinitely in all patients with STEMI with a dosage of 80 to 100 mg/day.

It IS RECOMMENDED that clopidogrel 75 mg per day orally should be added to aspirin in patients with STEMI and maintained for at least 14 days.

It IS RECOMMENDED that patients who are truly intolerant to aspirin can instead receive clopidogrel 75 mg per day as long-term secondary prevention.

Antiplatelets can interfere with a number of platelet functions, including aggregation and platelet-mediated vascular constriction, thus giving benefit to patients with ACS. Aspirin block the enzyme cyclooxygenase that mediates the first step in the biosynthesis of prostaglandins and thromboxanes from arachidonic acid, which are potent stimulators of platelet aggregation. The platelet P_2Y_{12} receptor blockers (clopidogrel, ticagrelor, prasugrel) block the binding of ADP to a specific platelet P_2Y_{12}, thereby inhibiting activation of the glycoprotein II_b/III_a complex and platelet aggregation.

Statement 22: Duration of Dual Antiplatelet Therapy and Antithrombotic Combination Therapies after STEMI

DAPT by combining aspirin and an ADP-receptor blocker (clopidogrel, prasugrel or ticagrelor) IS RECOMMENDED in patients with STEMI who are undergoing primary PCI (for up to 12 months) or (clopidogrel) fibrinolysis (for up to 12 months, although the data available pertain only to one month of DAPT), and in those who have not undergone reperfusion therapy (for at least 1 month and up to 12 months).

DAPT treatment for 12 months after stenting and following STEMI has

traditionally been recommended by consensus in Western guidelines.[2,3] It is important to inform patients and their primary physicians about the need to avoid premature discontinuation of DAPT.

Statement 23: Antiplatelets to Support Primary PCI with STEMI

Aspirin 160 to 320 mg IS RECOMMENDED before primary PCI. After PCI, aspirin should be continued indefinitely. P_2Y_{12} inhibitor therapy IS RECOMMENDED as a loading dose and maintained for 1 year to patients with STEMI who receive a stent (bare-metal or drug-eluting) during primary PCI using the following doses:

- **Clopidogrel 600 mg loading dose then 75mg daily; or**
- **Prasugrel 60 mg loading dose then 10 mg daily; or**
- **Ticagrelor 180 mg loading dose then 90 twice a day.**

It MAY BE RECOMMENDED to use 80 mg of aspirin per day in preference to higher maintenance doses after primary PCI.

Prasugrel IS NOT RECOMMENDED to patients with a history of prior stroke or transient ischemic attack (TIA), and is generally not recommended in patients 75 years of age and older, or in patients with lower body weight, as it was not associated with net clinical benefit.

Continuation of a P_2Y_{12} inhibitor beyond 1 year may be recommended in patients undergoing DES placement.

See the discussion in Statement 5: Initial management in the emergency room with regards to anti-platelets.

Prasugrel is contraindicated in patients with prior stroke/TIA. Its use is generally not recommended in patients aged 75 years old or older, or in patients with lower body weight, as it was not associated with net clinical benefit in the subset group of TRITON TIMI-38.[9]

Statement 24: Antiplatelets as Adjunctive Antithrombotic Therapy with Fibrinolysis

Aspirin (160- to 320-mg loading dose) and clopidogrel (300-mg loading dose for ≤75 years of age, 75-mg dose for patients older than 75 years of age) IS RECOMMENDED to patients with STEMI who receive fibrinolytic therapy.

Aspirin should be continued indefinitely and clopidogrel (75 mg daily) should be continued for at least 14 days and up to 1 year in patients with STEMI who receive fibrinolytic therapy.

It MAY BE RECOMMENDED to use aspirin 80 mg per day in preference to higher maintenance doses after fibrinolytic therapy.

See the discussion in Statement 5: Initial managemet in the emergency

room with regard to antiplatelets.

Statement 25: Beta Blockers

It IS RECOMMENDED that oral beta blockers should be started within the first 24 hours in the absence of any contraindication, regardless of the intervention used. Ideal target heart rate is set at 55 to 60 beats per minute. Judicious use of beta-blocker therapy after PCI MAY BE RECOMMENDED.

Beta-adrenergic receptor blocking agents (beta blockers) are drugs with multiple actions on the heart. Blockade of beta-1 receptors results in the slowing of heart rate, reduction in myocardial contractility, and lowering of systemic blood pressure. In the context of AMI, which represents a state of reduced oxygen supply to the affected portion of the heart, these effects may be beneficial as they result in reduced myocardial workload and oxygen demand. Furthermore, beta blockers may reduce the risk of ventricular arrhythmias, which are an important cause of death following AMI.

Several studies have assessed the value of beta blockers in patients with STEMI, although varying in terms of the other treatment provided to the enrolled patients and the type, dose, and route of administration of the beta blocker. The COMMIT Trial showed that the use of early beta-blocker therapy in AMI reduces the risks of re-infarction and VF, but increases the risk of cardiogenic shock, especially during the first day or so after admission.[6] Consequently, it might generally be prudent to start beta-blocker therapy in-hospital only when the hemodynamic condition after MI has stabilized.

The ISIS-1 study compared treatment with atenolol (IV followed by oral) with placebo in patients within 12 hours of presentation.[19] Atenolol treatment was associated with lower mortality over 7 days (RRR 15%, ARR 0.6%; p=0.05). The Metoprolol in Acute Myocardial Infarction (MIAMI) trial compared metoprolol (IV followed by oral) with placebo, and found reductions in 15-day mortality similar to those found in ISIS-1.[19,20] Both trials were performed in patients who did not receive acute reperfusion therapy, which is currently the standard of care for patients with STEMI.

In the Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction Trial (METOCARD-CNIC), STEMI patients with anterior Killip class II or lower undergoing primary PCI, early IV metoprolol before reperfusion reduced infarct size and increased LVEF with no excess of adverse events during the first 24 hours after STEMI.[21] While this study showed a 45% reduction in composite outcomes, mortality rate in both arms were low and similar. Thus, we are unable to estimate NNT for mortality.

Statement 26: Lipid Lowering Agents

High-dose statins are RECOMMENDED in all patients during the first 24 hours of admission for STEMI, irrespective of the patient's cholesterol concentration, in the absence of contraindications (allergy, active liver disease). Atorvastatin or rosuvastatin are recommended during the early phase of therapy up to at least four weeks.

It IS RECOMMENDED to give high-dose rosuvastatin (20 to 40 mg) or atorvastatin (40 to 80 mg) therapy before emergency percutaneous coronary intervention to reduce periprocedural inflammatory response, to reduce myocardial dysfunction, and to prevent contrast-induced nephropathy.

The use of statins as secondary prevention in patients who survive a MI is no longer of question. Its use in the early phase of ACS has also proven to confer some benefit as seen in the study Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL). Atorvastatin 80 mg vs placebo was started within 24 to 96 hours in patients with unstable angina and AMI in this trial. Though there was no mortality benefit in the atorvastatin arm, there is a significant reduction in the recurrent ischemic events in the first 16 weeks post-AMI.[22]

In a prospective cohort study using data from the Swedish Registry of Cardiac Intensive Care on patients admitted to the CCU of 58 Swedish hospitals, early use of statins, given before discharge for their first recorded AMI, improved 1-year mortality (RR 0.75; 95% CI 0.63, 0.89, p=0.001).[23]This translates to a local NNT of 49.[4,23]

Furthermore, high-dose statins (atorvastatin and rosuvastatin) prior to PCI may decrease peri-procedural inflammation and decrease the occurrence of post procedural acute kidney injury.

Statement 27: Angiotensin-Converting Enzyme Inhibitors (ACEI) and Angiotensin Receptor Blockers (ARB)

It IS RECOMMENDED that an ACEI be given to patients within 24 hours, unless contraindicated (hypotension, significant renal failure and known allergy). It IS RECOMMENDED that an ARB be given to patients who are intolerant of ACEIs.

Several studies have shown the benefit of ACEIs in acute STEMI within the first 24 hours of the event. In the Fourth International Study of Infarct Survival (ISIS-4) study, a 7% RRR in 5-week mortatlity of AMI patients who were given captopril vs placebo.[24] The benefit was mostly noted in those with anterior infarction. In the Third Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3) trial, administration of lisinopril to patients

with STEMI or non-ST elevation MI resulted to a decrease in mortality at 6 weeks vs active control.[25] In both studies the survival benefit was significant during the first week of the AMI, hence the emphasis on early treatment. Furthermore, the report by the Chinese Cardiac Study group, which enrolled more than 16,000 patients, also showed survival benefit in the early use of captopril in AMI patients.[26] A meta-analysis on early ACEI administration conducted in both major and smaller trials showed a 12% odds reduction in mortality.[27] However, one trial that did not show any improvement of survival is the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II), which randomized AMI patients to either IV enalapril or placebo.[28] In addition, enalapril resulted to hypotension especialy among the elderly, which led to premature discontinuation of the study due to safety issues.

In summary, there is enough evidence to support initiating ACEIs in AMI in the absence of contraindications (hypotension, bilateral renal artery stenosis, significant renal failure and known allergy). The estimated NNT to prevent one death is 102.[4,27] Patient should be started on low doses initially and titrated to the recommended levels in the absence of adverse reactions. The subsets of patients who benefit most from ACEIs are those with HF, anterior infarction and low LVEF. The data is equivocal among low-risk patients, although no harm has been documented.

In the study Valsartan, Captopril, or Both in Myocardial Infarction Complicated by Heart Failure, Left Ventricular Dysfunction, or Both (VALIANT), valsartan was as effective as captopril in patients who are at high risk for CV events after MI.[29] Combining valsartan with captopril increased the rate of adverse events without improving survival. Other studies show that the administration of valsartan instead of ACEIs in patients with medium-risk STEMI attenuates pathological LV remodeling and improves LV systolic function.[30] However, as these results were obtained within the first 6 months after infarction, these results can not be generalized to the later period after STEMI.

Statement 28: Calcium Channel Blockers

It IS NOT RECOMMENDED to give calcium channel antagonists early in the course of STEMI as it has been shown to cause harm.

A meta-analysis showed that the use of calcium antagonists early in the course of a STEMI may lead to harm.[31] The role of calcium antagonists is in the chronic phase to prevent reinfarction and death. Patients with contraindications to beta blockers may benefit from verapamil, especially if without heart failure. It may be used with caution in patients with impaired LV function. Routine use of dihydropyridines do not show benefit after STEMI

and should only be used for clear indications such as hypertension or angina.[2]

Statement 29: Ivabradine

Ivabradine MAY BE RECOMMENDED among patients with contraindications to beta blockers, to slow the heart rate to target values in STEMI.

In the Evaluation of the Intravenous If Inhibitor Ivabradine after ST-segment Elevation Myocardial Infarction (VIVIFY) study, intravenous ivabradine was shown to safely slow down the heart rate in STEMI.[32] Further studies are needed to characterize its effect on infarct size, LV function and clinical outcomes in this population. A smaller study suggested that ivabradine may be administered early (12 hours after PCI) to patients who successfully underwent PCI for anterior STEMI and with impaired LV function, elevated heart rate, and sinus rhythm.[33]

In addition, ivabradine may be used to control heart rate in patients with heart rate uncontrolled by beta blockers.

Statement 30: Nitrates

Nitrates, given intravenously, MAY BE RECOMMENDED, during the acute phase in patients with hypertension or HF. Its use is contraindicated among patients with hypotension, right ventricular infarction, or the use of PDE 5 inhibitors in the previous 48 hours.

Oral nitrate use IS RECOMMENDED in the acute and stable phase for the control of anginal symptoms.

See the discussion of statement 5: Initial management in the emergency room with regards to nitrates.

Statement 31: Cardiac Rehabilitation

It IS RECOMMENDED that all patients with ST segment elevation undergo cardiac rehabilitation. If no cardiac rehabilitation personnel and facilities are available, it IS RECOMMENDED to refer the STEMI patient to a hospital with adequate facilities and personnel once stable.

Cardiac rehabilitation is a comprehensive, long-term program involving medical evaluation, prescription of exercise program, cardiac risk factor modification, education, and counselling. Cardiac rehabilitation should start as early as possible. A substantial proportion of coronary heart disease deaths occur in people already known to have the disease. Measures to influence the course in already recognized coronary heart disease might help significantly to reduce the total attribute mortality. Much emphasis for referral to cardiac rehabilitation should be done by hospitals to ensure that it is part

of treatment strategy for STEMI patients. Based from 2 year data results of PHA ACS Registry, the referral to cardiac rehabilitation was dismal at 42%. Rehabilitation goals include all secondary prevention goals. This is defined as an effort towards risk factor reduction designed to lessen the chance of subsequent cardiac events, and to slow and perhaps stop progression of the disease process.

Rest, Exercise and Exercise Training

Rest

Physical rest or bed rest is necessary in patients with HF. Passive mobilization exercises are carried out to prevent untoward effects resulting from prolonged bed rest and to decrease the risk of venous thrombosis.

Exercise

In order to prevent muscle de-conditioning, a stable patient should be advised on how to carry out daily physical activities that do not induce symptoms. Strenuous or isometric exercises, as well as competitive and tiring sports should be discouraged. If the patient is employed, their work tasks must be assessed and advised on whether they can be continued.

Exercise Training

Exercise training programs are encouraged in stable patients. Some randomized trials have shown that regular exercise can safely increase physical capacity by 15% to 25%, and improve symptoms and perception of quality of life in patients with stable class II and III HF.[34]

Statement 32: Hospital Discharge and Post-STEMI Risk Stratification: Timing of Hospital Discharge

If the patient has undergone reperfusion therapy with no significant arrhythmias, recurrent ischemia or congestive HF, patient can be safely discharged in less than 5 days.

It IS RECOMMENDED that patients with STEMI who have not undergone PCI and do not have any high-risk clinical profile be subjected to non-invasive testing before discharge to assess the presence of inducible ischemia.

It MAY BE RECOMMENDED that non-invasive testing might be considered to guide the post-discharge exercise prescription.

A patient's length of stay in the CCU and hospital should be determined on an individual basis, considering the patient's medical and social conditions, including premorbid health and hospital course. Low-risk patients after successful primary PCI could be discharged from the hospital after 3 days. Since this time frame may not be enough to properly educate the patient

and up-titrate preventive medications, post-discharge consultations should be conducted.

After reperfusion, risk assessment should be done. Low-risk patients may be assessed using non-invasive tests prior to discharge to assess inducible ischemia and assist in the prescription of exercise upon discharge.

Statement 33: Exercise Testing

Exercise testing IS RECOMMENDED either before discharge (submaximal), early after discharge (within 2 to 3 weeks) or late after discharge (within 3 to 6 weeks) for prognostic, activity prescription, evaluation of medical therapy.

Submaximal protocol requires that the patient exercises until symptoms of angina appear, ECG changes of ischemia are seen, or 5 metabolic equivalents are reached. Exercise testing is not indicated in patients with severe co-morbidity likely to limit the expectancy and/or candidacy for revascularization; and those in HF, cardiac arrhythmia or non-cardiac condition that limit their ability to exercise.

REFERENCES

1. Philippine Heart Association. 2009 PHA Clinical Practice Guidelines for the Management of Coronary Artery Disease. Quezon City: Philippine Heart Association, 2009.
2. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, Borger MA, et al. Eur Heart J. 2012 Oct;33(20):2569-619.
3. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2013 Jan 29;127(4):e362-425.
4. Yaneza LO, Abanilla JM, Abola MTB, Caole-Ang IV, Fernandez MBD, Lopez EA, Punzalan FER, Reyes EB; Steering Committee Members for the Philippine Heart Association-Acute Coronary Syndrome (PHA-ACS) Registry. Philippine Heart Association-Acute Coronary Syndrome Registry: 2 year Results. Phil J Cardiol 2013;2 (in press).
5. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised Trial of Intravenous Streptokinase, Oral Aspirin, Both, or Neither Among 17 187 Cases of Suspected Acute Myocardial Infarction: ISIS-2. Lancet 1988;332(8607):349–360.
6. Chen ZM, Jiang LX, Chen YP, Xie JX, Pan HC, Peto R, et al.; COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative

group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet. 2005 Nov 5;366(9497):1607-21.
7. Sabatine MS, Cannon CP, Gibson CM, López-Sendón JL, Montalescot G, Theroux P, et al.; CLARITY-TIMI 28 Investigators. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med. 2005 Mar 24;352(12):1179-89.
8. Mehta SR, Yusuf S; Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) Study Investigators. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial programme; rationale, design and baseline characteristics including a meta-analysis of the effects of thienopyridines in vascular disease. Eur Heart J. 2000 Dec;21(24):2033-41.
9. Wiviott SD, Antman EM, Gibson CM, Montalescot G, Riesmeyer J, Weerakkody G, et al.; TRITON-TIMI 38 Investigators. Evaluation of prasugrel compared with clopidogrel in patients with acute coronary syndromes: design and rationale for the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet InhibitioN with prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38). Am Heart J. 2006 Oct;152(4):627-35.
10. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al.; for the PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045–1057.
11. Kastrati A, Dibra A, Spaulding C, Laarman GJ, Menichelli M, Valgimigli M, et al. Meta-analysis of randomized trials on drug-eluting stents vs. bare metal stents in patients with acute myocardial infarction. Eur Heart J 2007;28: 2706–2713.
12. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346:557–563.
13. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346:549–556.
14. Belliard G, Catez E, Charron C, Caille V, Aegerter P, Dubourg O, et al. Efficacy of therapeutic hypothermia after out-of-hospital cardiac arrest due to ventricular fibrillation. Resuscitation 2007;75:252–259.
15. Peberdy MA, Callaway CW, Neumar RW, Geocadin RG, Zimmerman JL, Donnino M, et al.; American Heart Association. Part 9: post-cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular CareCirculation. 2010 Nov 2;122(18 Suppl 3):S768-86.
16. Ohman EM, Nanas J, Stomel RJ, Leesar MA, Nielsen DW, O'Dea D, et al. Thrombolysis and counterpulsation to improve survival in myocardial infarction complicated by hypotension and suspected cardiogenic shock or heart failure: results of the TACTICS Trial. J Thromb Thrombolysis 2005;19:33–39.
17. American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Pacemaker Implantation). ACC/AHA Guidelines for Implantation of Cardiac Pacemakers and Antiarrhythmia

Devices: Executive Summary. Circulation.1998; 97: 1325-1335.
18. Lee DS, Green LD, Liu PP, Dorian P, Newman DM, Grant FC, Tu JV, Alter DA. Effectiveness of implantable defibrillators for preventing arrhythmic events and death: a meta-analysis. J Am Coll Cardiol 2003;41:1573–1582.
19. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. First International Study of Infarct Survival Collaborative Group. Lancet. 1986 Jul 12;2(8498):57-66.
20. Metoprolol in acute myocardial infarction. Narcotic analgesics and other antianginal drugs. The MIAMI Trial Research Group. Am J Cardiol. 1985 Nov 22;56(14):30G-34G.
21. Pizarro G, Fernández-Friera L, Fuster V, Fernández-Jiménez R, García-Ruiz JM, García-Álvarez A, et al. Long-Term Benefit of Early Pre-Reperfusion Metoprolol Administration in Patients With Acute Myocardial Infarction: Results From the METOCARD-CNIC Trial (Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction). J Am Coll Cardiol. 2014 Jun 10;63(22):2356-62.
22. Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, et al.; Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. JAMA. 2001 Jan 24-31;285(4):430-6.
23. Stenestrand U, Wallentin L; Swedish Register of Cardiac Intensive Care (RIKS-HIA). Early statin treatment following acute myocardial infarction and 1-year survival. JAMA. 2001 Apr 4;285(13):1711-8.
24. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction", The Lancet 1995;345 (8951):669–682.
25. GISSI-3 Group. Effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. The Lancet. 1994. 343(8906):1115-22.
26. Oral captopril versus placebo among 14,962 patients with suspected acute myocardial infarction: a multicenter, randomized, double-blind, placebo controlled clinical trial. Chinese Cardiac Study (CCS-1) Collaborative Group. Chin Med J (Engl). 1997 Nov;110(11):834-8.
27. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al.; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005 Oct 8;366(9493):1267-78.
28. Swedberg K, Held P, Kjekshus J, Rasmussen K, Rydén L, Wedel H. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction. Results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). N Engl J Med. 1992 Sep 3;327(10):678-84.

29. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Køber L, Maggioni AP, et al.; Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med. 2003 Nov 13;349(20):1893-906.
30. Ovricenco E, Sinescu C, Dinescu S. Effect of angiotensin II type 1 receptor antagonist valsartan on cardiac remodeling and left ventricular function in patients with acute ST-elevation myocardial infarction. J Med Life. 2008 Jul-Sep;1(3):323-33.
31. Yusuf S, Held P, Furberg C. Update of effects of calcium antagonists in myocardial infarction or angina in light of the second Danish Verapamil Infarction Trial (DAVIT-II) and other recent studies. Am J Cardiol 1991;67:1295–1297.
32. Steg P, Lopez-de-Sà E, Schiele F, Hamon M, Meinertz T, Goicolea J, et al.; VIVIFY (eValuation of the IntraVenous If inhibitor ivabradine after STsegment elevation mYocardial infarction) investigators. Safety of intravenous ivabradine in acute ST-segment elevation myocardial infarction patients treated with primary percutaneous coronary intervention: a randomized, placebo-controlled, double-blind, pilot study. Eur Heart J Acute Cardiovasc Care. 2013 Sep;2(3):270-9.
33. Fasullo S, Cannizzaro S, Maringhini G, Ganci F, Giambanco F, Vitale G, et al. Comparison of ivabradine versus metoprolol in early phases of reperfused anterior myocardial infarction with impaired left ventricular function: preliminary findings. J Card Fail. 2009 Dec;15(10):856-63.
34. Lawler PR, Filion KB, Eisenberg MJ. Efficacy of exercise-based cardiac rehabilitation post-myocardial infarction: a systematic review and meta-analysis of randomized controlled trials. Am Heart J 2011;162(4):571–584 e572.

Financial Disclosure of the PHA CAD Council Panel of Experts and Members

Disclosure of financial relationships with the pharmaceutical companies within 12 months of the date of final resolution of this PHA Clinical Practice Guidelines.

Consultant or Advisory Board *
Employment †
Honorarium ‡
Ownership §
Partnership ||
Receipt of Equipment or Supplies ¶
Research Grants or Support #
Speaker's Bureaus **
Stock/Bond Holdings (excluding Mutual Funds) ††
Other Personal or Professional Relationship (please list) ‡‡
Other Financial Support §§

Technical Writing Committee

Liberty O. Yaneza, MD, FPCP, FPCC (Chair)	none
Imelda Caole-Ang, MD, FPCP, FPCC	none
Ivan Noel G. Olegario, MD	†

Task Force on the Diagnosis and Management of Stable Ischemic Heart Disease (SIHD)

Task Force Members:

Maria Consolacion V. Dolor-Torres, MD, FPCP (*Chairperson*)	none
Philip U. Chua, MD, FPCP, FPCC	none
Roberto S. Cristobal, MD, FPCS, FPATACSI	none
Josette V. Cristobal, MD, FPCP, FPCC	none
Iris M. Garcia, MD, FPCP, FPCC	none
Kathleen F. Sabiniano, MD, FPCP, FPCC	none
Richard Nicandro R. Torres, MD, FPCP, FPCC	**
Mariel I. Barcelon-Cruz, MD, FPCP	none
Michael B. Cabalatungan, MD, FPCP	none

Panel of Experts:

Romeo D. Saavedra, MD, FPCP, FPCC	*
Ronald E. Cuyco, MD, FPCP, FPCC	**
Edward Benjie L. Magsombol, MD, FPCP, FPCC	‡, **

Task Force on the Management of Patients with Non ST Elevation Acute Coronary Syndrome (NSTE-ACS)

Task Force Members:

Sue Ann R. Locnen, MD, FPCP, FPCC (Chair)	**
Rodney M. Jimenez, MD, FPCP, FPCC	none
Clara S.Tolentino, MD, FPCP, FPCC	none
Bridget Donato-Fernandez, MD, FPCP, FPCC	none
Visvanath E. Espaldon, MD, FPCP, FPCC	none
Douglas P. Bailon, MD, FPCP	none
Gilbert G. Florentino, MD, FPCP	none
Lauren S. Valera, MD, FPCP	none

Panel of Experts:

Norbert Lingling D. Uy, MD, FPCP, FPCC	*, **, ††
Gregorio G. Rogelio, MD, FPCP, FPCC	none

Task Force on Management of ST Segment Elevation Myocardial Infarction (STEMI)

Task Force Members:

Victor L. Lazaro (Chair), MD, FPCP, FPCC	**
Edgardo E. Ebba, MD, FPCP, FPCC	**
Regidor R. Encabo, MD, FPCP, FPCC	none
Ann Margaret P. Flores, MD, FPCP, FPCC	none
Ana Beatriz D. Medrano, MD, FPCP, FPCC	none
Christopher Oliver P. Nazal, MD, FPCP, FPCC	‡, **
Luigi Pierre S. Segundo, MD, FPCP, FPCC	‡
Maria Elizabeth V. Enriquez, MD, FPCP	none
Philipp C. Ines, MD, FPCP	none
Jayson M. Mutuc, MD, FPCP	none
Jeannica Kriselle G. Lerios, MD, DPCP	none
Hazel Stacey Michelle C. Reyes, MD, DPCP	none

Panel of Experts:

Donato R. Marañon, MD, FPCP, FPCC	none
Edwin S. Tucay, MD, FPCP, FPCC	none
Gilbert C. Vilela, MD, FPCP, FPCC	*, †, ‡, **

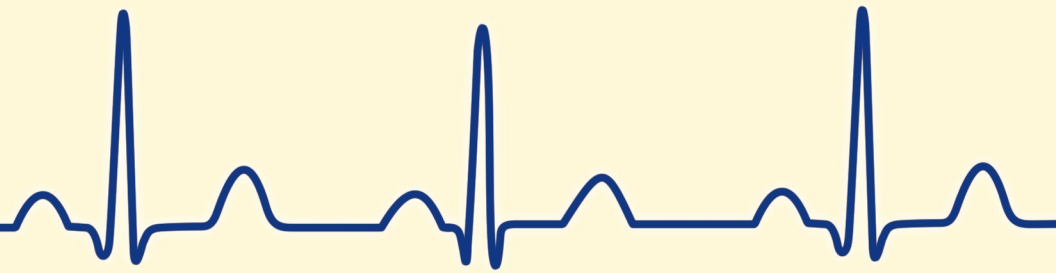
ACKNOWLEDGMENTS:

The writing committee of this guideline is expressing their heartfelt gratitude to the following:

- Panel of experts, PHA directors, members of stakeholders and all members of each taskforces who have unselfishly rendered their precious time and expertise
- PHA secretariat represented by Myrna de la Cruz and Gene Banawa
- AstraZeneca Pharmaceuticals (Phils.), Inc. for providing the grant in the printing of this guidelines

NOTES:

2014 PHA CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH CORONARY ARTERY DISEASE



Date of Publication: November 2014