Echocardiographic assessment and B-type natriuretic peptide for risk evaluation in acute coronary syndromes

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I livets lopp finns det inget målsnöre. De snören vi passerar är starten till ett nytt lopp.

Okänd

To Jonathan and Daniel

Abstract

Acute coronary syndromes (ACS) is one of the most common causes of emergency medical care and the single most common cause of death in Sweden in both men and women. Despite a significant improvement in survival in the acute phase, the frequency of rehospitalization and death in subsequent years is unacceptably high. An estimation of future risk should therefore be a central part of the care of patients with ACS. Echocardiography for the evaluation of left ventricular (LV) function has become an important component in risk assessment. Further, the usefulness of various biochemical variables has been recognized and B-type natriuretic peptide (BNP) has been proven to be an important prognostic marker among patients with heart failure (CHF) and recently also in ACS.

The aim of this thesis was to assess whether the incorporation of BNP and Doppler echocardiographic variables in risk stratification strategies in patients with ACS can improve the prediction of mortality and rehospitalization for CHF during long-term follow-up.

The study included consecutive patients with ACS who received coronary care at Sahlgrenska University Hospital from September 1995 to March 2001. Clinical variables were collected during hospitalization, blood for the determination of BNP was sampled in the acute phase and a Doppler echocardiographic examination was performed. The echocardiographic 4-chamber view and Doppler curves were saved digitally or digitized and a range of systolic and diastolic variables, which reflect cardiac structure and function, were calculated. Patients were followed prospectively for a maximum of 110 months with regard to death and rehospitalization due to CHF.

We found that BNP was significantly higher in deceased patients than in those who survived. BNP provided prognostic information, even when adjusting for Killip class >1, age and LV ejection fraction (LVEF), and also among patients without clinical evidence of CHF (Killip class 1). The presence of significant mitral regurgitation, low LVEF and increased levels of BNP were all independently associated with death, while rehospitalization for CHF was predicted by mitral regurgitation and LVEF. In a multivariate analysis, the LV volume index in systole (LVVIs) and the ratio of maximum systolic and diastolic pulmonary venous flow velocities (PV-s/d) were associated with all-cause mortality, cardiovascular mortality

and rehospitalization due to CHF. Patients with a restrictive LV filling pattern had a poorer prognosis than those with normal filling and this diastolic abnormality remained a significant predictor of outcome even after adjustment for BNP and clinical risk factors, as assessed by the GRACE risk score. Further, additional prognostic information was provided by the LV outflow tract velocity integral (LVOT-VTI), LVEF and PV-s/d ratio.

In conclusion, our results indicate that BNP, as well as a restrictive filling pattern, mitral regurgitation and other Doppler echocardiographic variables, such as LVOT-VTI, LVVIs, LVEF and PV-s/d ratio, provide prognostic information on long-term survival and rehospitalization due to CHF in patients with ACS, over and above clinical risk factors. For this reason, both information from a single echocardiographic view and BNP levels appear to be useful tools in the identification of high-risk ACS patients. Further studies are needed to clarify exactly how these risk markers should be used in the clinical routine.

Key words: acute coronary syndromes, BNP, NT-proBNP, mitral regurgitation, Doppler echocardiography, mortality, congestive heart failure, restrictive filling pattern

Svensk sammanfattning

Akut kranskärlssjukdom eller akut koronart syndrom (på engelska acute coronary syndromes, ACS), innefattande hjärtinfarkt och instabil kärlkramp, är en av de vanligaste orsakerna till akut sjukhusvård och den enskilt vanligaste dödsorsaken i Sverige hos både kvinnor och män. En hjärtinfarkt uppkommer när blodförsörjningen till ett område av hjärtat plötsligt täpps till eller kraftigt försämras. Hjärtmuskeln får då inte den mängd syre den behöver och detta leder till att en skada uppstår på hjärtat, en hjärtinfarkt. Orsaken till att blodflödet plötsligt försämras är vanligtvis en blodpropp, som bildats i anslutning till åderförkalkningsförändring i något av hjärtat blodkärl. Hur stor hjärtinfarkten blir och hur mycket hjärtats funktion försämras av infarkten beror på om blodproppen sitter i ett stort eller litet kärl och på storleken på det område som får sin blodförsörjning av kärlet i fråga. Infarktens storlek spelar roll för patientens fortsatta prognos. Med instabil kärlkramp menar man den bröstsmärta som uppkommer pga en övergående syrebrist i hjärtmuskeln. Orsaken kan vara en blodpropp som aldrig täpper till blodflödet helt, och som därför inte leder till någon bestående skada på hjärtmuskeln, men som hotar att göra det. Trots att behandlingsmetoderna avsevärt förbättrats på senare år, återinsjuknar en betydande andel av de patienter som inkommer till sjukhus pga ACS och en inte oväsentlig andel dör i sviterna av sitt koronarsyndrom. Det är därför av stor vikt att bland patienter med ACS kunna identifiera dem som löper störst risk att dö en för tidig död eller att återinsjukna.

Ekokardiografisk undersökning (hjärtultraljud) för värdering av hjärtfunktionen är en viktig metod vid riskbedömning av patient med ACS. Ekokardiografi tillsammans med Dopplerteknik (registrering av blodflöden i hjärtat) ger möjlighet att mäta en rad olika variabler som beskriver hjärtats funktion och struktur. Den skada på hjärtat som en hjärtinfarkt innebär, bland annat en förstoring av hjärtats vänstra kammare i avslappat (diastole) eller sammandraget (systole) läge, och en nedsättning av dess pumpförmåga, kan beskrivas med hjälp av dessa variabler. Diastolisk fas kan också kallas vilofas eller fyllnadsfas, eftersom kammaren under denna fas fylls med syresatt blod från lungorna. Systole är hjärtats arbetsfas, då blod pumpas ut i kroppen. En annan faktor som kan ses som ett uttryck för hjärtats försämrade funktion i samband med ACS är en ökad frisättning från hjärtat av ett litet äggviteämne som kallas B-typ av natriuretisk peptid (BNP). Hög blodkoncentration av BNP har visat sig innebära en ökad risk för komplikationer och för att dö i förtid.

Målsättningen med avhandlingen var att undersöka om Doppler ekokardiografiska variabler, uppmätta i en enda standardiserad 4-kammarprojektion, var och en för sig och i kombination med BNP och kliniska riskfaktorer, såsom ålder, tidigare hjärtsvikt, EKG, njurfunktion mm, skulle kunna bidra till en förbättrad riskbedömning av patienter med ACS. I de fyra arbeten som ingår i avhandlingen studerade vi detta på litet olika sätt bland en stor grupp patienter med ACS, som under perioden september 1995 till mars 2001 vårdades på hjärtinfarktavdelning på Sahlgrenska sjukhuset. Vi följde patienterna i närmare 10 år med avseende på död och återinläggning på sjukhus pga sviktande hjärtfunktion.

Vi fann att förhöjda nivåer av BNP i blodet, förutom nedsatt pumpförmåga (ejektionsfraktion, vilket innebär skillnaden mellan diastolisk och systolisk volym, dvs slagvolym, dividerad med diastolisk volym) hos hjärtat, var associerade med risk att efter ACS återinsjukna i hjärtsvikt eller att avlida i förtid. Ett anmärkningsvärt fynd var att även hos patienter utan tecken på att hjärtat sviktat i samband med infarkten sågs en relation mellan BNP förhöjning och framtida risk. Läckage i en av hjärtats klaffar, en så kallad mitralisinsufficens, bedömd med doppler ekokardiografi, visade sig kunna förutsäga såväl ökad dödlighet som ökat insjuknande i hjärtsvikt. Vid jämförelse mellan många olika ekokardiografiska mått på hjärtats funktion fann vi att ökad systolisk volym hos vänster kammare och nedsatt systolisk fas i lungvensflöde, som tecken på ökat tryck under hjärtats fyllnadsfas, var förenade med sämre prognos. Likaså visade det sig att tecken på att vänster kammare under fyllnadsfasen var styvare än normalt (restriktiv fyllnad) innebar en ökad risk för komplikationer. De ekokardiografiska variablerna och BNP hade betydelse för prognosen oberoende av varandra och även när man tagit hänsyn till kliniska riskfaktorer.

Sammanfattningsvis visar avhandlingen att ekokardiografiska variabler och BNP, enskilt och i kombination, är användbara instrument vid risk stratifiering av den stora gruppen patienter med akut kranskärlssjukdom.

List of papers

I. Omland T, Persson A, Ng L, O´Brien R, Karlsson T, Herlitz J, Hartford M, Caidahl K. N-terminal pro-B-type natriuretic peptide and long-term mortality in acute coronary syndromes. Circulation 2002;106:2913-8

II. Persson A, Hartford M, Herlitz J, Karlsson T, Omland T, Caidahl K. Long-term prognostic value of mitral regurgitation in acute coronary syndromes. Heart 2010;96:1803-8

III. Persson A, Hartford M, Herlitz J, Caidahl E, Karlsson T, Caidahl K. The long-term prognostic value of a single echocardiographic view in acute coronary syndromes. Submitted

IV. Persson A, Hartford M, Caidahl E, Herlitz J, Karlsson T, Omland T, Caidahl K. Restrictive left ventricular filling and B-type natriuretic peptide as prognostic indicators in acute coronary syndromes. Submitted

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Abbrevations

ACS	Acute coronary syndromes
ANP	Atrial natriuretic peptide
BNP	B-type natriuretic peptide
BSA	Body surface area
CABG	Coronary artery bypass grafting
CCU	Coronary care unit
CHF	Congestive heart failure
CI	Confidence interval
CK-MB	Creatine kinase MB
CV	Cardiovascular
ECG	Electrocardiogram
EDTA	Ethylene diamine tetraacetic acid
GRACE	Global Registry of Acute Coronary Events
HR	Hazard ratio
IRT	Isovolumic relaxation time
IVS	Interventricular septum
LAVI	Left atrial volume index
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVET	Left ventricular ejection time
LVOT-VTI	Left ventricular outflow tract – velocity time integral
LVVIs	Left ventricular volume index, systole
MI	Myocardial infarction
MPI	Myocardial performance index
NSTEMI	Non-ST-elevation myocardial infarction
NT-proBNP (=N-BNP)	N-terminal pro B-type natriuretic peptide
PCI	Percutaneous coronary intervention
PEP	Pre-ejection period
PRACSIS	Prognosis and Risk of Acute Coronary Syndromes in Sweden

PV-s/d	Pulmonary venous flow systole / diastole
RAVI	Right atrial volume index
STEMI	ST-elevation myocardial infarction
UAP	Unstable angina pectoris

Introduction

Mortality in cardiovascular (CV) disease has decreased considerably over the past few decades.[1-3] Despite this decline, acute coronary syndromes (ACS), and especially acute myocardial infarction (MI), which imposes a great burden on society and the individual patients, is still one of the major causes of death in Sweden.[4] ACS represents a spectrum of clinical conditions ranging from unstable angina (UAP) without myocardial necrosis to ST-segment-elevation MI (STEMI) with clear evidence of myocardial damage.[5, 6] The underlying cause of ACS is atherosclerosis, an inflammatory disease that starts early in life as fatty streaks in the coronary arteries and may progress to atherosclerotic plaques, which, if ruptured, may lead to thrombus formation and the impairment of coronary flow.[7,8]

Definitions

Despite sharing a common pathophysiological mechanism, the clinical presentation differs between patients with ACS, and based on established management strategies the syndrome has been divided into two distinct categories:[9, 10]

1) STEMI, with typical ECG changes, indicating the total occlusion of a coronary artery without collateral flow protecting the jeopardized zone, and
2) Unstable coronary artery disease or non-ST-elevation acute coronary syndrome, including both UAP and non-STEMI (NSTEMI), with a subtotal or intermittent coronary occlusion, embolization, or a total occlusion with transmural ischemia prevented by collateral circulation.

The diagnosis is based upon symptoms of ischemia, ECG changes and biochemical markers of myocardial necrosis and damage. UAP is characterized by an aggravated effort angina, i.e. the sudden worsening of previously stable angina or new-onset severe angina, with or without ischemic changes on the ECG but without signs of myocardial necrosis as estimated by biomarkers. [9] While STEMI[10]by definition is associated with ST-segment elevation on the ECG, NSTEMI[9] may or may not have ischemic ECG changes other than ST elevation. Both STEMI and NSTEMI have increased levels of cardiac markers of necrosis. The diagnostic techniques for the detection of myocardial necrosis have been successively refined over the years, as more specific biochemical markers have become available, and today the troponins are the central markers for infarct detection. The

advantage of the troponins over creatine kinase MB (CK-MB) was first stressed by the Joint European Society of Cardiology (ESC) and American College of Cardiology (ACC) Committee for the redefinition of MI in 2000 and reinforced by the committee in 2007 when the first document was updated.[11, 12]

Although biomarkers and ECG are the keystones in the definition of an acute MI, non-invasive imaging techniques, such as echocardiography, may in some unclear cases be useful in the establishment of the diagnosis. [13, 14]

Definitions of ACS	
ACS	A spectrum of clinical conditions encompassing unstable coronary syndrome and ST-elevation MI.
STEMI	MI with ST-segment elevation on the presenting ECG and a rise in cardiac biomarkers reflecting myocardial necrosis.
NSTEMI	MI without ST-segment elevation on the presenting ECG but with a rise in cardiac biomarkers reflecting myocardial necrosis.
UAP	Ischemic chest pain, more frequent, more severe or extended than the patient's usual angina, occurring at rest or on minimal effort, or new-onset severe angina; no rise in cardiac biomarkers reflecting myocardial necrosis.

Etiology

The atherosclerotic process is an inflammatory disorder which starts early in life with the infiltration of lipoproteins in the intima of large and medium-sized arteries.[7, 8] A dysfunctional endothelium that generates a proatherogenic environment is essential in the process.[15] The retention of lipoproteins, their oxidation with a subsequent maladaptive inflammatory reaction, followed by the recruitment of blood-borne cells, the development of lipid-laden macrophages, the proliferation of smooth muscle cells and extracellular matrix deposition are just some of the complicated processes leading to the formation of an atherosclerotic plaque.[16, 17] At an early stage, the atherosclerotic plaque constitutes an asymmetrical thickening of the arterial intima but does not cause any impairment of the coronary artery. As the plaque gradually grows, it leads to the successive narrowing of the coronary artery. Whether a plaque can be responsible for the initiation of an acute coronary event has little to do with the degree of obstruction that it causes.[18] In victims of sudden coronary death, non-critical stenosis

was present in around 40%.[19] Coronary plaque rupture, and subsequent thrombus formation when the thrombogenic lipid core is exposed to blood in the arterial lumen, precipitates the majority of events.[20] Underlying plaque rupture was the etiology of sudden death in 55-60%, while plaque erosion, i.e. endothelial denudation with the exposure of subendothelial connective tissue, was the mechanism in around 30% and thrombi attributed to a calcified nodulus in 2% to 7%.[21] The vulnerable, rupture-prone plaque typically has a lipid core, which is an extracellular mass of lipid-containing cholesterol and its ester that is covered by a thin cap of fibrotic issue.[18, 21, 22] Non-symptomatic plaque ruptures contribute to the non-linear progression of coronary obstructions, as can be observed in repeated angiographic studies in patients.[23]

The etiology of atherosclerosis is still not fully understood, but there are several factors that contribute to its progression. The four major risk factors for atherosclerotic disease and death are probably hypertension, smoking, dyslipidemia, and diabetes, but obesity, stress, genetics and a host of other factors are also involved, perhaps via a primary action on the endothelium, making it susceptible to lipid retention.[15, 24] In the recent INTERHEART study, nine factors were identified that accounted for > 90% of the risk of MI: smoking, history of hypertension or diabetes, waist/hip ratio, dietary patterns, physical activity, consumption of alcohol, blood apolipoproteins (Apo) and psychosocial factors.[25]

Men develope atherosclerosis and suffer their first MI at an earlier age, than women.[26] As to the underlying mechanisms in the development of an acute event, women have been reported to have erosions more frequently than men.[21] After the menopause, women have almost the same frequency of plaque rupture as men and, compared with younger women with plaque, they have more calcifications and a larger necrotic core.[27]

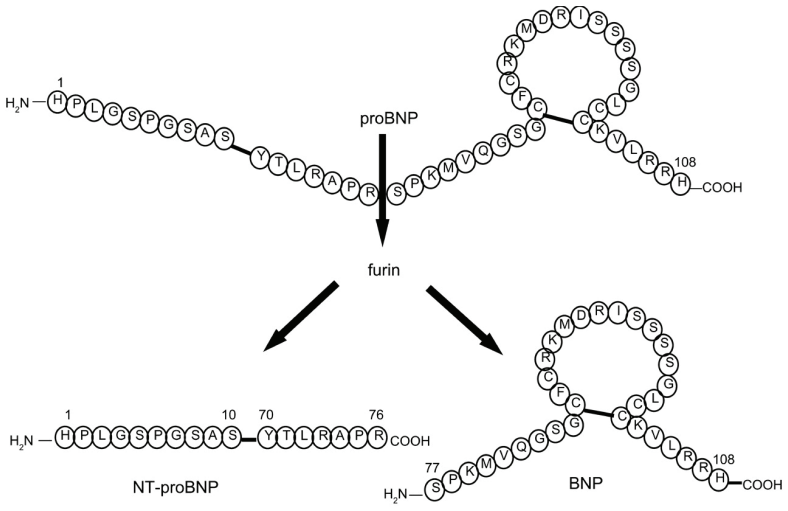
Brain natriuretic peptides

In 1981, de Bold and coworkers observed that the heart has an endocrine function, which resulted in the detection of the atrial natriuretic peptid (ANP).[28] It has since become apparent that there is a family of natriuretic peptides that play an important role in the control of CV homeostasis and also myocardial and vascular structure and function.[29-32] Three natriuretic peptides have so far been identified and well characterized in humans; in addition to ANP, they also include the B-type natriuretic peptide (BNP) and the C-type natriuretic peptide (CNP). [33, 34] While ANP and BNP both have the heart as their major source of origin, the CNP is predominantly released from the

endothelium. CNP lacks the strong natriuretic and diuretic effects that are characteristic of ANP and BNP.[35] Although ANP and BNP have similar physiological effects, BNP has emerged as the biomarker of choice in CV diseases.

BNP is released as a preproBNP peptide of 134 aminoacids from the cardiomyocytes, in response to the excessive stretching of the left ventricular (LV) wall, and cleaved into proBNP (108 amino acids) and a signal peptide with 26 amino acids. ProBNP is subsequently cleaved into BNP (32 amino acids) and the inactive N-terminal proBNP (Figure 1).[34]

Schematic drawing of proBNP showing enzymatic cleavage into biologically active BNP and NT-proBNP.



Adapted by permission from BMJ Publishing Group Limited.
Essential biochemistry and physiology of (NT-pro)BNP
Hall C Eur J Heart Fail 2004;6:257-260

Figure 1. A model for natriuretic peptide secretion

In addition to increased wall stress, neurohormonal activation and hypoxia/ischemia stimulate BNP secretion.[31, 36] There are probably also as yet unknown factors that contribute to its release. The prevailing view has been that BNP and NT-proBNP are released in a 1:1 proportion, but this assumption has lately been refuted.[37, 38] The elimination of BNP is dependent on receptors and enzymatic degradation, while the mechanisms for NT-proBNP clearance are less well understood.[38] It has been suggested that NT-proBNP is more dependent on renal function for its clearance than BNP, but this concept has been challenged.[39] NT-proBNP is a larger molecule than BNP and its

half-life is longer (120 vs. 20 minutes), which explains the higher circulating levels of NT-proBNP compared with BNP. NT-proBNP has been proven to be more stable than BNP during sampling and management, as well as during freezing and long-term storage.[40, 41] Various measures have been tested in order to offset the degradation of BNP that occurs after sampling. They have involved the use of plastic tubes, the addition of EDTA and also the addition of protease inhibitors.[40]

A number of commercial immunoassays are available for the measurement of BNP and NT-proBNP, some of which are applied at the bedside, while others are designed for use in automated laboratory systems.[42, 43] There is a lack of standardization and the normal ranges for both peptides differ between the various methods. The publication of quality specifications for each assay in peer-reviewed journals has therefore been recommended.[44] The presence of alternate circulating pro-BNP and BNP forms with which commercial BNP assays may cross-react has been suggested and this may be one explanation of why marked variations in BNP levels can be found in seemingly homogeneous populations.[37] It is also noteworthy that the release of BNP has been shown to be influenced by a number of physiological factors. The secretion increases with age and is higher in women in comparison with men.[45] Obesity appears to reduce the levels, as does treatment with some drugs (angiotensin converting enzyme inhibitors, angiotensin receptor antagonists, β-adrenoceptor antagonists, and diuretics).[30, 46] All these variables contribute to the variation in BNP/NT-proBNP levels and may confound the interpretation of elevated values. Another confounding factor is a substantial within-subject biological variability.[47] Although BNP was first recognized as a diuretic and vasodilator hormone, a number of additional important physiological paracrine and autocrine effects have been identified since its discovery.

The most important are as follows:

- The suppression of the sympathetic nervous system, peripherally and centrally
- The suppression of the renin-angiotensin-aldosterone system
- The inhibition of the growth of vascular smooth muscle and possibly an antifibrotic effect on the heart muscle
- The reduction of peripheral vascular resistance
- An increase in endothelial permeability

Over the years, both BNP and NT-proBNP have emerged as promising biomarkers in CV disease and there are data to support the use of B-natriuretic peptides in a number of clinical situations, such

as the diagnosis and ruling out of CHF, the detection of asymptomatic LV systolic or diastolic dysfunction, monitoring the response to therapy in CHF, as a marker of prognosis not only in CHF but also in the general population, in MI patients and in patients with ACS.[48-58] Studies have indicated that B-natriuretic peptides might predict the risk of mortality and CHF, in both the short and long term, even in ACS patients without evidence of myocardial necrosis or CHF.[50, 59-61] In several recent reports, BNP/NT-proBNP has been included in multimarker approaches in order to improve the prediction of outcome in ACS patients, and also other populations, and it has been shown to provide independent information, in addition to variables such as LVEF, C-reactive protein and measures of renal function, on both the short- and long-term prognosis.[62-65]

In addition to various situations with a left heart condition, increased levels of BNP and NT-proBNP have been registered in patients with hypoxia and right ventricular disorders, such as acute or chronic pulmonary disease and pulmonary embolism.[66, 67] There are also a number of non-cardiac conditions in connection with which elevated levels have been observed, e.g. renal dysfunction, diabetes mellitus, anemia, thyrotoxicosis and liver cirrhosis.[68]

Although an enormous amount of experience has been acquired in recent years, there are still a number of unanswered questions related to the role of B-natriuretic peptides in clinical medicine. As to the relative merit of one type of peptide in favor of another, current data appear to agree that the performance of BNP and NT-proBNP is similar in most populations.[48, 69] Measurements of B-natriuretic peptides are included in the international guidelines for the treatment of CHF, including the establishment of diastolic LV dysfunction,[70, 71] but so far there are no universally accepted recommendations for the routine assessment of B-natriuretic peptides in ACS. In this patient population, one important question is still the optimal time point for assessment and whether serial analyses provide more information than a single measurement. At present, the prevailing opinion appears to be that B-natriuretic peptides should not be routinely analyzed in all patients with ACS, as, in most patients, this would not lead to any change in therapy, or any other action that would influence mortality or morbidity to any significant extent.[34, 72]

Doppler echocardiography

Echocardiography, the ultrasound technique for cardiac examinations, was introduced by the Swedish cardiologist Inge Edler and engineer Helmuth Herz in 1953.[73, 74] In the beginning, only registrations along one transecting beam, initially in terms of amplitude mode (A-mode) or

brightness mode (B-mode) and subsequently so-called motion mode (M-mode) with time on the horizontal axis, were possible.[75, 76] Some 20 years later, in the 1970s, two-dimensional recordings became possible, initially with mechanical so-called sector scanners, while digital transducers (phased array) were subsequently introduced.[77, 78] It has also been possible for several years to construct three-dimensional (3D) images, but clinically useful techniques have only been available in the last few years, initially depending on several beats but now even allowing real time 3D imaging.[78, 79] The Doppler effect was initially described by Christian Doppler in the 1820s and this principle is now applied in a technique for estimating blood flow velocities.[80] Echocardiography is based on the registration of the time it takes for an emitted sound signal to return to the sender (transducer), which is a piezoelectric crystal capable of also acting as a receiver. Doppler, on the other hand, is based on registrations of the so-called Doppler shift, or the change in frequency between an emitted sound and the reflected sound.[81] This Doppler shift can identify both the direction and the speed of a moving object (such as red blood cells). By using Doppler, it is possible to measure a maximum velocity along the beam by continuous-wave Doppler, or the velocity at a specific point using pulsed-wave Doppler.[81] This is possible since the window from which sound is received can be determined in depth, as the velocity in tissue is known, thereby also making it possible to determine the time it will take to reach and return from a certain point in the tissue. The result of combining pulsed-wave Doppler information from an area instead of only one specific point can be displayed in color mode, where the color indicates the direction and velocity of moving objects at various points. Both pulsed- and continuous-wave Doppler, as well as the color Doppler technique, are used for the evaluation of valvular leakage and valvular stenosis.[77, 82] Pulsed-wave Doppler from blood flow and from tissue (so-called tissue Doppler) in particular is very useful for determining cardiac function.[83, 84] The combination of echocardiography and Doppler techniques, particularly color Doppler, is called the duplex technique. Nowadays, the non-invasive evaluation of cardiac function by echocardiography and Doppler has more or less replaced invasive techniques for the assessment of cardiac defects, even preoperatively. Doppler echocardiography is not only non-invasive, it is also comparatively inexpensive, mobile, can be used at the bedside and moreover, involves no X-ray radiation.

Doppler echocardiography enables the investigation of global and regional function in coronary artery disease, as well as in other conditions. After a coronary event, locally impaired myocardial function with subsequent dilation and hypertrophy can be evaluated and followed as an effect of the myocardial damage.[85] The systolic function, especially the LV ejection fraction (LVEF),

has been shown in several studies to be an important predictor of outcome after an MI,[86] and LVEF as the only predischarge test may identify a large low risk group after a first MI.[87]

However, a reduced LVEF, and in particular locally reduced myocardial function, can result from irreversible myocardial damage, but it can also be caused by a reversibly reduced functional impairment. An early assessment of LVEF after MI can be misleading due to an acute myocardial stunning effect. [88] After an MI, the myocardial damage and increased wall stress can lead to LV remodeling with ventricular dilation during the initial weeks. This kind of remodeling may be prevented by angiotensin converting enzyme inhibitors.[89, 90] Ventricular dilation, especially an increase in systolic volume, may be more indicative of serious LV impairment than LVEF, since a systolic dilation may indicate both poor contractile performance and ventricular enlargement. White et al. were the first to state that LV volumes may contain more prognostic information than LVEF.[91]Not only LV dilation and LVEF, but also regional function has an impact on symptoms, even in the general population,[92] may be used to determine anti-remodeling therapy,[93] and could possibly carry prognostic information beyond that of LVEF.[94] In addition to LVEF, right ventricular (RV) function e.g. the fractional area change has predictive value.[95] Important drawbacks regarding both evaluation of wall motion and RV function, however, are the subjectivity in visual interpretation of regional function, and the complex geometry of the right ventricle. An alternative to wall motion analysis by visual interpretation is strain imaging (see also "Other risk markers" below).

Reduced LV contraction and increased LV filling pressure are one reason for impaired diastolic function with a restrictive filling pattern. Another type of diastolic dysfunction, with impaired LV relaxation, is often seen with LV hypertrophy, regardless of whether it is due to hypertension or aortic stenosis, and it is found in ischemic heart disease without severe systolic dysfunction.[96]

Diastolic dysfunction can be assessed by Doppler echocardiography of mitral and pulmonary venous (PV) flow and divided into four categories: [97, 98]

- Grade 1 = impaired relaxation pattern with normal filling pressure
  - 1a = impaired relaxation pattern with increased filling pressure
- Grade 2 = pseudonormalized pattern
- Grade 3 = reversible restrictive pattern
- Grade 4 = irreversible restrictive pattern

A restrictive filling pattern in particular has been shown to be an important independent predictor of LV dilation and CV mortality in patients with MI.[99-101] Patients with a restrictive filling pattern also have a higher incidence of CHF after an MI.[102] Papillary muscle dysfunction or rupture (emergency) may occur with an acute MI and result in mitral regurgitation, which may be severe. A large infarct, with the remodeling and dilation of the left ventricle, may cause dilation or a more rounded shape of the mitral annulus, also leading to mitral regurgitation. The abnormal position of the papillary muscles due to myocardial damage may cause restrictive motion of the mitral leaflets and subsequent mitral regurgitation.[103, 104] Mitral regurgitation is more frequent among patients with MI and has been shown in several studies to be a powerful indicator of increased risk of mortality and CV events [105-108] Few studies have focused on the prognostic value of mitral regurgitation in ACS, including patients with UAP.[108]

One of the first cardiac structures to be examined and analyzed by echocardiography was the left atrium (LA). [76] The atria act as reservoirs during ventricular systole and as a conduit during early diastole. [109] In late diastole, they function as muscle pumps to complete the ventricular filling before the start of ventricular contraction and atrioventricular valve closure. Today, the left atrium, especially the volume indexed for body size, is an important prognostic index in patients with heart diseases and even in the general population.[110-112] Mitral valve disease imposes a load on the left atrium, with an increase in its volume as a defense mechanism against the increased pressure or blood volume. Without mitral valve disease, and the absence of atrial fibrillation, which is another cause of atrial dilation, a left atrial enlargement may indicate LV impairment with chronically elevated LV filling pressure.[110, 113]

Clinical risk evaluation in ACS

The prognosis after a MI/coronary event is largely determined by the extent of myocardial damage and its location,[114] but previous events/damage, clinical risk factors and persistent ischemia are also factors that have to be taken into account when assessing future risk.[115, 116] The clinical risk factors that play a major role in the outcome include age, gender, smoking, blood pressure, previous history of ischemic heart disease and so on. In the very early risk stratification/evaluation of patients with ACS for the determination of acute treatment strategies and short-term prognosis, ECG and biochemical markers of myocardial necrosis are of major importance.[117, 118] Several different

combinations of these two variables and clinical risk factors have been presented as risk scores and have been used for the prediction not only of hospital mortality but also of long-term outcome. [119-122] The majority of these risk models have been derived from selected patient groups included in clinical studies.[119-122] In contrast, the recently created Global Registry of Acute Coronary Event-GRACE risk score was developed in a multinational observational registry of patients with ACS, which includes patients in all risk strata and is therefore representative of ACS patients in the real world.[116, 123] The GRACE risk score has become widely accepted as a prognostic tool in ACS and its introduction has been seen as an opportunity to stratify clinical risk factors in a uniform manner throughout the world. Two versions of the score have been developed and recommended from the GRACE Registry Group, one originally developed for the prediction of in-hospital mortality and the other for use as a predictor of 6-month mortality post discharge.[124, 125] After minor modification, the first has recently been shown to predict the development of MI and death up to five years after admission.[115] The latter has been shown by several external groups to predict long-term mortality as well.[62]

Other risk markers

The question of whether it is possible to improve the prediction of risk in ACS beyond what is achieved by clinical factors has been tested with different types of additional risk markers.[126-128] The present thesis is focused on the possibility to perform risk evaluation of cardiac function by ultrasound and BNP in a way that can be easily implemented in the clinical routine. Other factors related to risk of future events are myocardial ischemia and inflammation. Given the fact that atherosclerosis is an inflammatory disease,[16] a number of biomarkers of inflammation have been tested during the last decade as tools for a refined estimation of risk.[129, 130] Such markers, e.g. C-reactive protein (CRP), interleukin-6 (IL-6), phospholipase A2 (PLA2), osteoprotegerin (OPG), CXCL16, and interleukin-18 (IL-18) have also been studied in the current population of ACS patients.[131-134] However, they have not been incorporated among the factors of risk in the present thesis, in which the aim was to explore the benefit of readily available echocardiography and BNP in patients with ACS.

Residual myocardial ischemia as well as the extent of damaged myocardium are important prognostic factors. Area at risk and definite infarct area may best be determined by scintigraphy or magnetic resonance imaging.[135] Although infarct size and myocardial ischemia can also be evaluated

by echocardiographic contrast perfusion,[136, 137] wall motion analysis or strain imaging,[138-141] such techniques were not attempted in the present thesis. The extent of MI was assumed to give a reasonable imprint on global measures of LV function, and myocardial ischemia was assumed to be ruled out by bicycle exercise test or when present treated by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Further, the availability of modalites such as magnetic resonance imaging and scintigraphy is limited. The same is true for the more advanced forms of echocardiography. In the daily clinical care of ACS patients, in smaller hospitals as well as large university hospitals, echocardiography is the preferred technique, and we wanted to study ACS patients in the "real world".

Aims

In this prospective study of consecutive patients with different types of ACS, the following aims were selected for the present thesis:

- To assess the relationship between subacute plasma NT-proBNP levels and long-term mortality in patients with ACS
- To investigate whether NT-proBNP is related to mortality in ACS patients with no evidence of clinical CHF
- To evaluate whether there is a place for mitral regurgitation in the assessment of risk of future mortality in ACS and whether mitral regurgitation provides prognostic information above and beyond BNP and conventional clinical risk factors
- To determine the predictive value of a series of echocardiographic variables from a single, rapidly obtainable, echocardiographic view, regarding long-term all-cause mortality, CV mortality and rehospitalization due to CHF
- To investigate whether a restrictive filling pattern and elevated BNP levels in patients with ACS are associated with increased all-cause mortality, CV mortality and rehospitalization for CHF during long-term follow-up and whether these variables, alone or in combination, provide independent information when clinical variables have been taken into account by the GRACE risk score
- To determine the possible incremental yield of other echocardiographic variables over and above BNP levels, restrictive filling and the GRACE risk score

Material and Methods

Study population

Consecutive patients admitted to the coronary care unit (CCU) at Sahlgrenska University Hospital, Gothenburg, Sweden, with a suspicion of ACS were evaluated for participation in a study of prognosis and its prediction in ACS in real life (Prognosis and Risk of ACS in Sweden, PRACSIS; patient inclusions September 1995 - February 2001).[142] To enable long-term follow-up and repeat visits to our outpatient clinic, only patients under the age of 80 and living within the hospital's catchment area were eligible. Patients transferred from other hospitals for tertiary care were not included and neither were patients with ACS who were treated outside the CCU. Patients with an obvious acute MI or chest pain or other symptoms suggestive of myocardial ischemia were eligible for inclusion. The suspicion of myocardial ischemia had to be supported by:

- ECG changes on admission (ST-segment elevation ≥0.1 mV (0.2 mV in V1-V4) or ST depression ≥ 0.1 mV or T-wave inversion in at least two adjacent leads) and/or
- Biochemical markers of myocardial necrosis above the upper reference level (CK-MB >5μg/L and/or troponin T ≥0.05 μg/L) or
- previously recognized coronary artery disease, such as MI, prior PCI or CABG, stable or unstable angina pectoris with significant angiographic changes, or an exercise test suggestive of ischemia.

The main exclusion criteria were severe non-coronary artery disease associated with a life expectancy of less than one year or unwillingness to participate. A patient could only be included once.

Information on earlier hospital admission, risk factors and medication was collected from hospital medical records. During the hospital stay, the patients also took part in a detailed interview conducted by an experienced study nurse. If the information obtained in these interviews differed from that in the medical records, a thorough work-up was done to resolve the discrepancies. The patients were prospectively classified according to maximum Killip class on admission and during primary hospitalization. A detailed recording of complications, including arrhythmias, medical treatment and investigations, was made during in-hospital care. In-hospital mortality was recorded. Survival status and date of death were obtained from the Swedish National Population Registry and

information on CV mortality was obtained from the Swedish National Cause of Death Register. Rehospitalization for CHF was obtained from the Swedish Hospital Discharge Register. In Paper I the patients were followed until September 15, 2001, in Paper II until January 1, 2008 and in Papers III and IV until January 1, 2007. During the follow-up, eighteen patients were lost due to emigration. The study was approved by the local ethics committee at Gothenburg University and the patients gave their informed consent to participate.

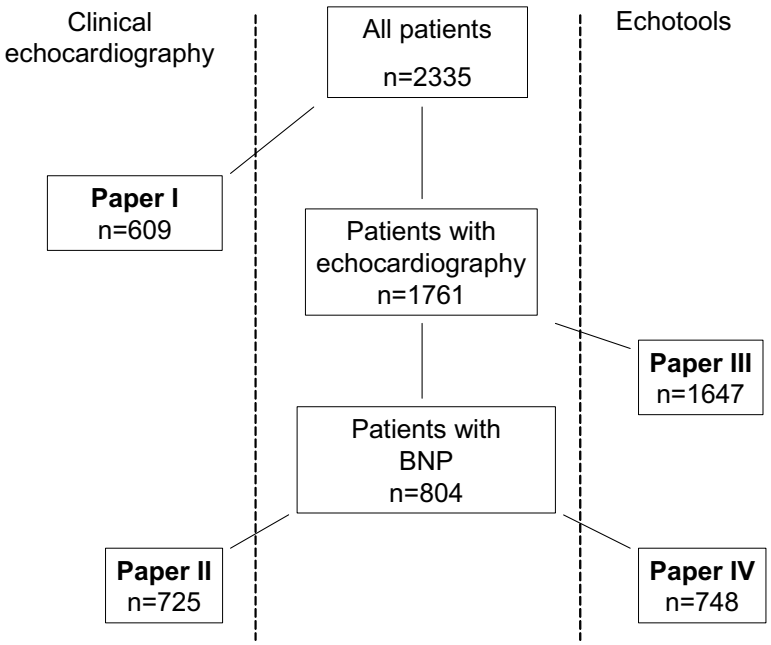


Figure 2. Flow chart illustrating patient selections for each paper.

Altogether 1,761 of the 2,335 patients in the PRACSIS study with a definite diagnosis of UAP or acute MI had an echocardiographic examination, see Figure 2. Out of these 1,761 patients 1,647 suitable Doppler echocardiography recordings were identified, while those from 5 patients could not be analyzed due to technical problems, 5 due to poor quality and 11 due to only a transesophageal approach, and in 93 patients the original recordings could not be traced. This thesis deals mainly with patients selected from the 1,647 with proper echocardiographic recordings; however another 206

patients with values of NT-proBNP from the sub-acute phase but no echocardiographic recording were included in Paper I. This paper comprised 609 patients with blood sampling for NT-proBNP assessments (and in 403 patients also echocardiography) in the sub-acute phase (median 3 days), included between September 1995 and February 2000. Paper II comprised 725 patients (included between December 1996 and March 2001) with blood sampled and BNP assessed in the acute phase (day 1) and an echocardiographic recording in which an evaluation of mitral regurgitation was possible. Paper III involved the 1,647 patients with available Doppler echocardiographic recordings, and Paper IV comprised those who also had BNP determined in the acute phase (day 1, n=748). The inclusion period was between September 1995 and March 2001 in Paper III and between December 1996 and March 2001 in Paper IV.

Blood samples

Peripheral blood samples were obtained in the acute phase within 24 hours of hospital admission and after two to five days (median 3 days, sub-acute phase) by the direct venipuncture of an antecubital vein after the patient had been in a supine position for longer than 30 minutes. The samples were drawn into serum tubes and chilled EDTA tubes. The EDTA tubes were immediately placed on ice and cold centrifuged at 3000 rpm within 1 hour. Serum tubes were placed at room temperature for 30 minutes and then centrifuged at 3000 rpm. EDTA plasma and serum samples were aspirated and stored at -70˚C until analysis.

NT-proBNP and BNP analyses

Our assay for NT-proBNP (Paper I) was based on the non-competitive NT-proBNP assay described by Karl et al. [143] Peptides corresponding to the N-terminal (amino acids 1 to 12) and C-terminal (amino acids 65 to 76) of the human NT-proBNP were used to raise rabbit polyclonal antibodies. IgG from the sera was purified on protein A sepharose columns. The C-terminal-directed antibody (0.5 μg in 100 μL for each well) was immobilized onto ELISA plates. The N-terminal antibody was affinity purified and biotinylated using biotin-X-N-hydroxysuccinimide ester (Calbiochem).[144] Aliqouts (20 μL) of samples or NT-proBNP standards were incubated in the C-terminal antibody-coated wells with the biotinylated antibody for 24 hours at 4˚C. Elisa plates were washed with 0.1% Tween in phosphate buffered saline buffer (PBS) and streptavidin (Chemicon International Ltd) labeled with methyl-acridinium ester ($5*10^6$ relative light units/mL) was added to each well.[145] Plates were read on a Dynatec MLX Luminometer, with sequential injections of 100 μL of 0.1 mol/L nitric

acid (with H_2O_2), followed by100 μL of NaOH (with cetyl ammonium bromide).[144] The lower limit of detection was 14.4 fmol/mL of unextracted plasma. Within and between assays, coefficients of variation were acceptable at 2.3% and 4.8% respectively. There was no cross-reactivity with ANP or BNP.

C-terminal BNP (Papers II and IV) was analyzed by fluorescence immunoassay from Biosite Diagnostics (San Diego, California, USA). Inter- and intra-assay coefficients of variation for BNP measurements were 9-12% in the low, medium and high ranges.

Echocardiography

Two-dimensional echocardiography - recording and on-line measurement of LVEF

Doppler echocardiography was performed using commercially available ultrasound machines by an experienced operator within five days (Papers I and II) of admission. In 166 patients, the examination was made for logistical reasons after discharge, median 22 days (Papers III and IV) after hospital admission. The examinations were performed in a standardized way (according to the recommendations of the American Society of Echocardiography).[146] In most cases harmonic tissue imaging was applied as previously described.[147] Patients were investigated at rest in the left lateral position on a couch with a mattress cutout for optimal apical access. In Papers I and II, LVEF was calculated by the biplane disc sum method (Simpson's) from the 4-chamber and 2-chamber views whenever possible. Accuracy was checked in motion mode. When tracing of the endocardial border was uncertain in one plane we used the other, and in some cases without reliable outlining, we used M-mode, according to Teichholtz,[146] when wall motion was homogenous enough, otherwise visual estimation.[148-150] All the examinations were primarily stored on S-VHS or an MO disk. In Papers III and IV, the LVEF and a number of other variables were calculated off-line from a monoplane 4-chamber view, see below.

Doppler - recording and on-line evaluation

The patients were examined using color Doppler, as well as pulsed- and continuous-wave Doppler. Blood flow velocity in the LV outflow tract (LVOT) was recorded by pulsed-wave Doppler from a tilted apical 4-chamber view. The flow velocity at the tips of the mitral valve in the 4-chamber view was recorded. The pulmonary venous flow velocity was obtained from the upper right pulmonary vein.

The grade of mitral regurgitation was determined from colour and continuous wave Doppler recordings, based on the regurgitation flow intensity and classified into five grades. [151] Grade 0 denoted no regurgitation or regurgitation limited to a small part of early systole, grade 1 indicated mild regurgitation weakly visible during the whole of systole, grade 2 was moderate regurgitation clearly visible throughout systole, grade 3 was defined by large regurgitation intensely visible during whole systole, grade 4 signified severe regurgitation as found, for example in chordal rupture, with a large intensity and altered shape of the spectral Doppler profile (sharp and often a visible V wave effect, rather than a rounded profile). In grades 3-4, the regurgitation usually reaches the roof of the left atrium and particularly in grade 4 swirls around. In grade 3-4 there is also usually a volume load on the left ventricle and reversed systolic pulmonary venous flow.

Echotools-computed measurements

In Papers III and IV, the systolic and diastolic phases of the left ventricle, interventricular septum (IVS) and both atria, as well as pulsed Doppler curves, were obtained from recordings of the apical 4-chamber view, directly stored digitally in DICOM format or digitized to the TIF format fro m videotape (Matrox Inspector 8.0©). Measurements were performed using a specially designed computer program (Echotools, Gothenburg, Sweden).

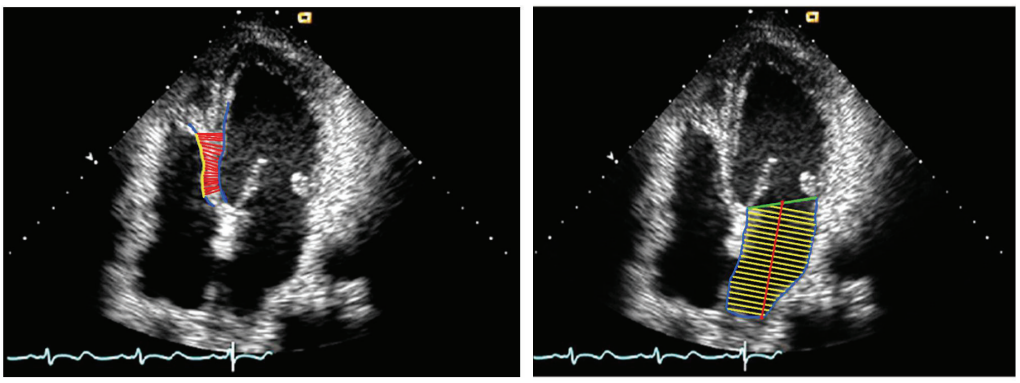


Figure 3. Outline of the interventricular septum and left atrium in Echotools.

The areas of the left ventricle and both atria were traced in diastolic and systolic stop frames. Both sides of the IVS were traced in diastole and the program calculated the average diameter of the mid 3

cm of the IVS, Figure 3. The Doppler curves (mitral, aortic and pulmonary) were digitized and measured in one of three similar beats. From the mitral flow velocity tracing, the early flow velocity (E), the deceleration time of the E wave and the peak velocity of the A wave were measured, Figure 4. From the LVOT velocity spectrum, the velocity time integral (VTI) was calculated, as were the peak velocities during systole (s) and diastole (d) in the pulmonary venous flow curve.

The LV and atrial volume indexes were calculated as the respective volumes divided by the body surface area (BSA). The BSA was calculated according to the duBois formula: BSA (m^2) = 0.007184 x Height (cm)$^{0.725}$ x Weight(kg).$^{0.425}$

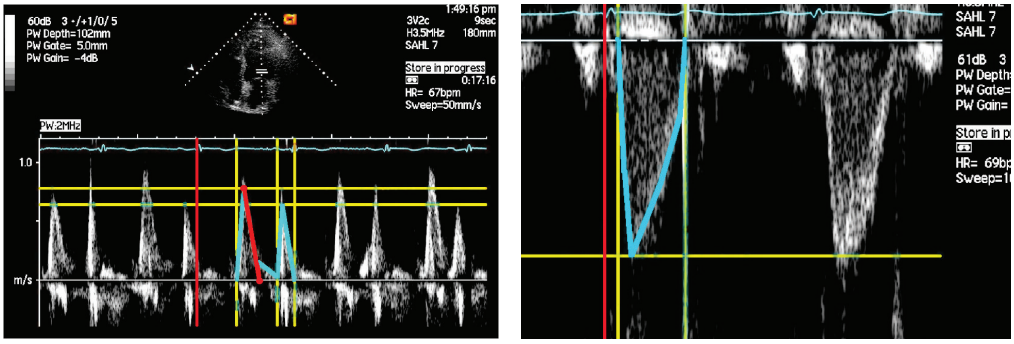


Figure 4. Mitral and LV outflow tract pulsed wave Doppler are outlined in the designed computer program Echotools for measurement. The vertical lines indicate some of the time intervals that are calculated.

The modified myocardial performance index (MPI) (also called the TEI index), an indicator of combined ventricular systolic and diastolic function, was also evaluated according to Tei's formula (Figure 5).[152] As a global index of systolic function, the pre-ejection period divided by the LV ejection time (PEP/LVET) was calculated. To evaluate LV remodeling and the importance of LV sphericity, we calculated the sphericity index as the ratio between the LV volume and the volume of a sphere with the same diameter as the LV long axis using the following formula: 6 * LV volume/(π * L3), where L is the measured LV length.[153]

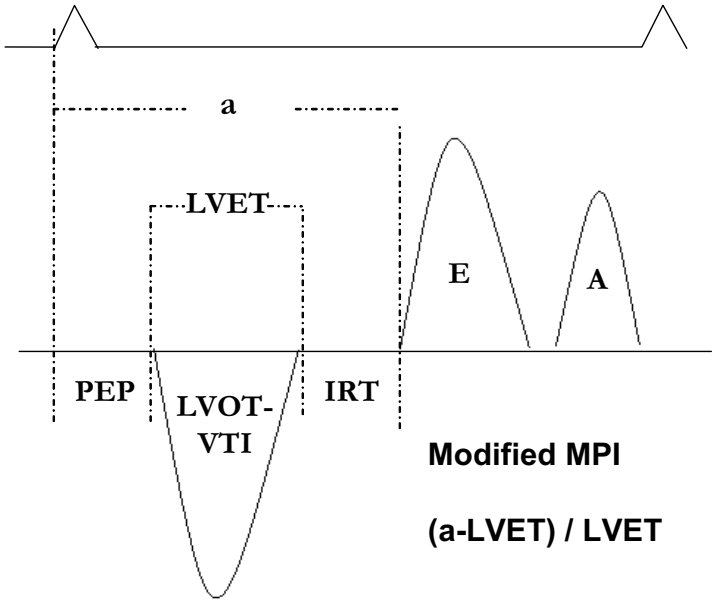


Figure 5. Illustration of the modified myocardial performance index (MPI), left ventricular ejection time (LVET), isovolumic relaxation time (IRT) and pre-ejection period (PEP).

To reduce inter-observer variability, all measurements in Papers III and IV were made by a single experienced observer (AP) and the intra-observer coefficients of variation at repeated measurements were assessed in 50 randomly selected patients. The intra-observer variation was 2.0-10.6% in measurements from Echotools, see Table 1. To validate Echotools, we used a commercial workstation (EchoPAC, General Electric) and the coefficients of variation between Echotools and EchoPAC are shown in Table 2. Due to the technical specifications in our EchoPAC system, not all the Echotool variables could be validated against EchoPAC.

Table 1. Reproducability for measurements of Doppler echocardiographic variables.

Coefficients of variation (%)							
LVd-D	4.7	LAd-D	3.6	RAd-L	3.8	PVs	4.2
LVs-D	4.1	LAs-D	3.3	RAs-L	3.1	PVd	4.2
LVd-L	2.1	LAd-L	4.0	RAd-A	5.2	PV-s/d	4.4
LVs-L	2.1	LAs-L	2.3	RAs-A	4.3	PEP	1.8
LVd-A	4.6	LAd-A	4.9	RAd-V	8.7	LVET	10.6
LVs-A	5.9	LAs-A	3.7	RAs-V	7.4	MVQ-Ewave	2.0
LVd-V	7.7	LAd-V	7.3	MV-E	2.8	LVOTmaxvel	1.8
LVs-V	9.6	LAs-V	5.8	MV-A	3.3	LVOT-VTI	3.4
IVSd-mean	5.6	RAd-D	4.8	MV-EA	3.4		
		RAs-D	4.7	MV-dectime	6.1		

A, area; D, diameter; d, diastolic; IVS, interventricular septum; L, length; LA, left atrium; LV, left ventricular; LVET, left ventricular ejection time; LVOT, left ventricular outflow tract; MV, mitral flow velocity; PEP, pre-ejection period; PV, pulmonary venous flow velocity; RA, right atrium; s, systolic; V, volume; vel, velocity; VTI, velocity time integral

Table 2. The coefficients of variation between Echotools and EchoPAC.

Coefficients of variation (%)					
LVd-L	2.2	RAd-A	5.3	MV-dectime	17.3
LVs-L	7.7	RAs-A	4.3	PVs	2.0
LVd-V	6.1	RAd-L	3.2	PVd	3.4
LVs-V	8.8	RAs-L	2.1	PV-s/d	3.4
LAd-A	2.7	IVSd-mean	6.4	PEP	8.0
LAs-A	7.7	MV-E	1.9	LVET	13.6
LAd-L	3.2	MV-A	2.5	MV Q-Ewave	11.1
LAs-L	3.0	MV-EA	1.6	LVOTmaxvel	1.1
				LVOT-VTI	10.1

Abbreviations, see Table 1.

Statistical methods

A summary of the chosen statistical methods is presented below. For further details regarding statistics, see the individual papers.

The Mann-Whitney U test was used for two-group comparisons of continuous/ordered variables in all four papers.

The Kruskal-Wallis test was used for comparisons of diagnosis groups in Paper III in terms of continuous variables.

Fisher's exact test was used for group comparisons of categorical variables in all four papers.

Kaplan-Meier plots were generated to visualize the relationship between selected variables and outcome in all four papers.

The log rank test was used for univariate comparisons of outcome.

Cox's proportional hazards regression was applied for the calculation of crude and adjusted hazard ratios (HR) with corresponding 95% confidence intervals (CI) and p-values in all papers and it was also used, in a forward stepwise selection mode, to identify predictors of outcome in Papers III and IV. In Paper I adjustment was made for the clinical variables that separately decreased the risk ratio for supramedian NT-proBNP levels by at least 10% (age, Kllip class and LVEF). In Papers II and III the following clinical confounders were adjusted for: age, gender, smoking, diabetes, hypertension, hypercholesterolaemia, prior MI, prior angina, prior CHF, prior PCI/CABG, estimated glomerular filtration rate and index diagnosis. In Paper IV adjustments were made for the GRACE risk score.[124] A total risk score was created for each patient by summing the individual scores for the nine variables in the risk model: age (0-100 points), history of CHF (24 points) and MI (12 points), heart rate (0-43 points), systolic blood pressure (24-0 points), and ST-segment depression (11 points) at admission, elevated biomarkers of myocardial necrosis (15 points), baseline creatinine level (1-20 points), and no PCI during index hospitalisation (14 points).

All tests are two-sided and p-values of < 0.05 were considered statistically significant. The statistical software packages SPSS v.17 and SAS v.9.1 were used for the analyses.

Results

Paper I

Blood samples for NT-proBNP were obtained in 204 patients with STEMI, 220 with NSTEMI and 185 with UAP. During the 51 months of follow-up, 86 patients died and the median NT-proBNP levels were significantly higher in these patients compared with the levels in long-term survivors (1306 vs. 442 pmol/L, $p<0.0001$). Supramedian NT-proBNP levels were associated with higher Killip class, lower LVEF, ST-segment deviation, Q-wave abnormalities and anterior wall ECG changes.

In a multivariate analysis, higher NT-proBNP levels remained significantly associated with a higher risk of mortality when adjusting for age, LVEF and Killip class on admission. NT-proBNP was also a predictor of mortality after adjustment for the same three confounders in patients with Killip I, both on admission and during hospitalization, i.e. patients with no clinical signs of CHF.

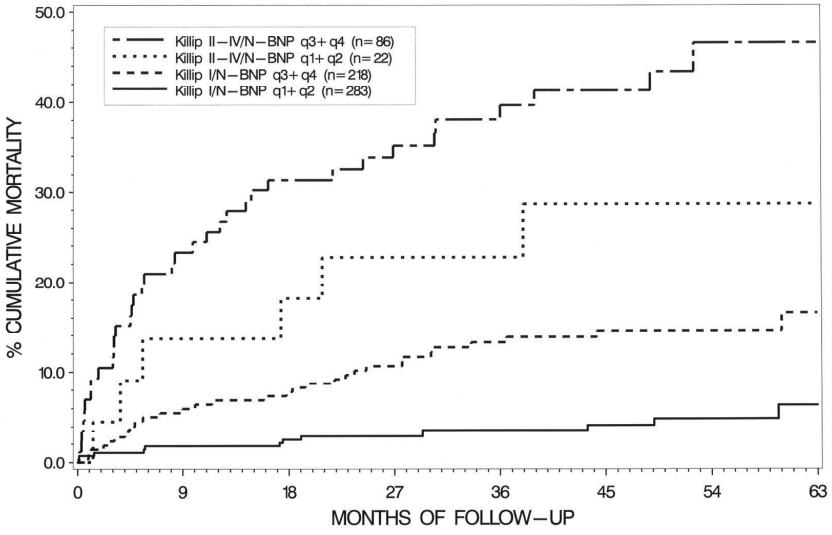


Figure 6. Mortality in relation to Killip class (I or II-IV) and NT-proBNP (=N-BNP) levels (q1-2 or q3-4). In Killip class I, NT-pro-BNP groups differed ($p=0.0001$), while they did not in Killip > I ($p=0.18$).

Paper II

Seven-year-mortality was significantly increased in patients with reduced LVEF, high BNP levels and mitral regurgitation.

These three factors all remained significant predictors of mortality when included in the same analysis. In multivariate models, each independently predicted death, even when all three were forced into the same model together with clinical confounders (HR for mitral regurgitation 1.53, 95% CI 1.06 to 2.19, p=0.02, HR for LVEF 1.94, 95% CI 1.38 to 2.73, p=0.0001, and HR for BNP 1.45, 95% CI 1.06 to 1.99, p=0.02). In the same type of multivariate model, both mitral regurgitation and LVEF were predictors of readmission to hospital for CHF, while there was a trend in the same direction for BNP (HR for mitral regurgitation 2.08, 95% CI 1.29 to 3.35, p=0.003, HR for LVEF 3.41, 95% CI 2.14 to 5.42, p<0.0001, and HR for BNP 1.51, 95% CI 0.96 to 2.38, p=0.07).

A composite score (0,1,2-3), with each of LVEF, BNP and mitral regurgitation outside the cut-off limits yielding 1 point, is illustrated in Figure 7, where mortality increased with a higher score. Even without BNP (Figure 2B in Paper II), the LVEF and mitral regurgitation score (0-1-2) was strongly associated with both mortality (HR 1.73, 95% CI 1.38 to 2.17, p<0.0001) and rehospitalization for CHF (HR 2.66, 95% CI 1.94 to 3.65, p<0.0001).

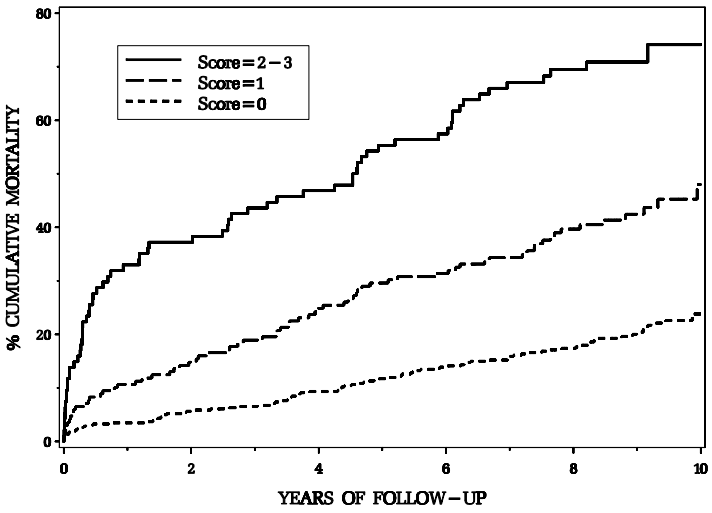


Figure 7. Cumulative incidence of death in relation to risk score 0, 1 and 2-3, where mitral regurgitation grade > 1, left ventricular ejection fraction < 0.40 and BNP > 373 pmol/L (75th percentile) yielded one score point each.

Paper III

Among our patients with ACS and an echocardiographic examination, the three diagnostic groups differed significantly in terms of several echocardiographic variables. Fourteen of 18 echocardiographic variables differed significantly between those who died and those who survived during a median follow-up of 7.3 years. The univariate relationships of all-cause mortality and CHF with 12 of the 18 variables are shown in Table 3.

Table 3. The unadjusted association between echocardiographic variables and long-term prognosis.

	All-cause mortality HR (95% CI)	**p**	**Rehospitalization due to CHF HR (95% CI)**	**p**
LVEF (q1 vs q2-4)	2.64 (2.22,3.14)	<0.0001	3.10 (2.39,4.02)	<0.0001
LVvolume index, d (q4 vs q1-3)	1.56 (1.29,1.88)	<0.0001	2.40 (1.84,3.12)	<0.0001
LVvolume index, s (q4 vs q1-3)	2.42 (2.01,2.90)	<0.0001	3.82 (2.94,4.97)	<0.0001
LV mass index (q4 vs q1-3)	1.40 (1.15,1.71)	0.0007	1.49 (1.12,1.99)	0.006
LA volume index, s (q4 vs q1-3)	1.60 (1.33,1.93)	<0.0001	2.16 (1.67,2.80)	<0.0001
RA volume index, s (q4 vs q1-3)	1.29 (1.06,1.56)	0.01	1.40 (1.06,1.85)	0.02
IVSd (q4 vs q1-3)	1.19 (0.98,1.45)	0.08	1.43 (1.08,1.89)	0.01
MV-E/A (q4 vs q1-3)	1.28 (1.06,1.54)	0.01	2.01 (1.55,2.62)	<0.0001
MV-Dec time (q1 vs q2-4)	1.01 (0.83,1.22)	0.94	1.28 (0.97,1.69)	0.08
PV-s/d (q1 vs q2-4)	1.86 (1.52,2.26)	<0.0001	3.25 (2.47,4.29)	<0.0001
LVET (q1 vs q2-4)	1.41 (1.18,1.69)	0.0002	1.45 (1.11,1.90)	0.007
LVOT-VTI (q1 vs q2-4)	2.54 (2.15,3.01)	<0.0001	2.42 (1.87,3.12)	<0.0001

d, diastole; Dec, deceleration; E/A, early/atrial; IVS, interventricular septum; LA, left atrium; LV, left ventricular; LVEF, left ventricular ejection fraction; LVET, left ventricular ejection time; LVOT, left ventricular outflow tract; MV, mitral valve; PV, pulmonary venous; q, quartile; RA, right atrium; s, systole; VTI, velocity time integral.

Results

When adjusting for clinical confounders, 9 of the 18 variables were associated with an increased risk of all-cause mortality, 10 with a risk of CV mortality and 11 with rehospitalization for CHF. In a multivariate analysis including only patients who had all 18 variables measured, considering not only clinical information but also all echocardiographic information, 6 remained as predictors of outcome events; 4 of these predicted all-cause mortality, all 6 CV mortality and 3 rehospitalization due to CHF, Figure 8. Two variables, LVVIs index and PV-s/d, were independent predictors of all three end-points. Cut-off values (25th or 75th percentile) for the six variables in Figure 8 were: LVVIs > 38.1 ml/m^2, IVSd > 1.12 cm, MV-A wave > 0.75 m/s, PV-s/d < 0.90, LVOT-VTI < 14.3 cm, and LVEF < 36.7%.

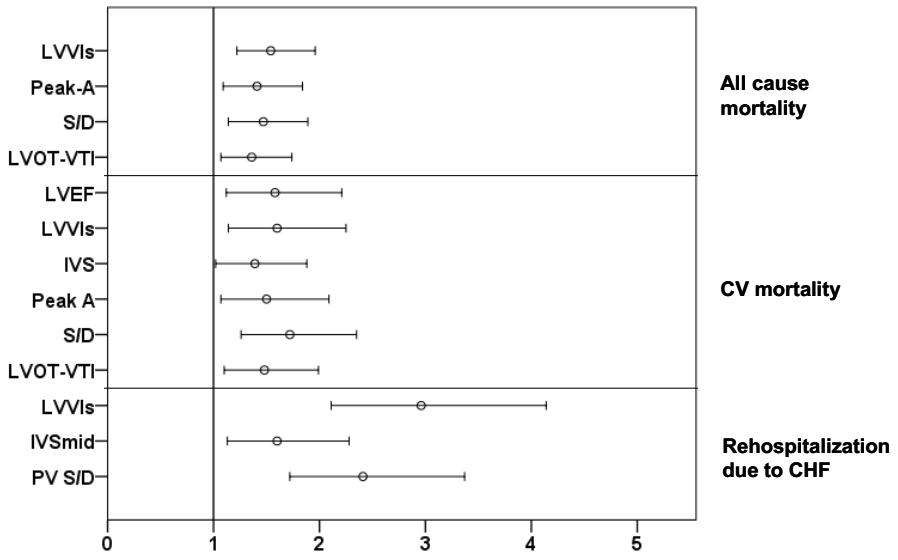


Figure 8. The echocardiographic variables that were independently associated with all-cause or cardiovascular (CV) mortality, or rehospitalization due to congestive heart failure (CHF). For other abbreviations, see the text, or the abbreviation list.

Paper IV

BNP levels and echocardiographic variables were available in 748 patients with ACS. A restrictive filling pattern was present in 13.5% of the patients and high BNP levels (4th quartile) in 187 patients, of whom 43 (23%) also had a restrictive filling pattern. The BNP level was associated with age, body size, previous hypertension, MI, angina, CHF and atrial fibrillation, as well as heart rate at admission, coronary interventions, the GRACE score and ACS type. A restrictive filling pattern was associated with CHF, previous revascularization, atrial fibrillation, CK-MB, creatinine, the GRACE score and BNP but not with ACS type. BNP was associated with 14 of 18 echocardiographic variables, and restrictive filling with all but two of the 18 variables.

In univariate analyses, both high levels of BNP and restrictive filling were strongly associated with all-cause mortality, CV mortality and rehospitalization for CHF, with hazard ratios between 2.29 and 3.86 (see Paper IV, Table 3). High BNP and restrictive filling remained as significant predictors of all three end-points in a multivariate model and they did so also when adjusting for the GRACE score, Figure 9.

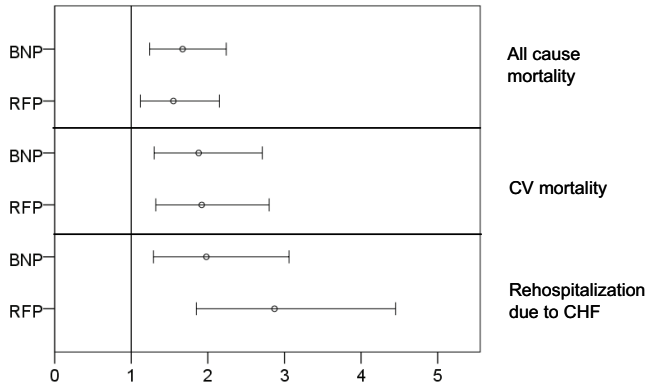


Figure 9. Hazard ratios for B-type natriuretic peptide (BNP) and restrictive filling pattern (RFP) and their associations with all-cause and CV mortality and congestive heart failure (CHF).

Finally, we included all the echocardiographic variables that were not part of the definition of restrictive filling in a stepwise selection model. After adjustment for BNP, LV filling pattern and the GRACE score, we found an independent association between LVOT-VTI and all three outcomes. In addition to LVOT-VTI, the LVEF predicted mortality and LVVIs predicted rehospitalization due to CHF.

Discussion

This thesis focused on the long-term prognosis in patients covering the entire spectrum of ACS and the question of whether echocardiographic variables and natriuretic peptides, in addition to clinical risk factors, are useful tools in the prediction of mortality and rehospitalization for CHF.

General comments

The definition of MI in this study was that applied as a clinical routine at Sahlgrenska University Hospital when the study was conducted relying mainly on serial measurements of CK-MB. The assessment of troponin was slowly introduced during the course of the study, but the new MI criteria, with cardiac troponin as the preferred biomarker and a lower decision level for the diagnosis of MI, as suggested in 2000,[11] were not fully implemented at our CCU until inclusion in the study had been completed. A reclassification of our patients according to modern criteria was unfortunately not possible, since serial measurements of troponin are lacking in too many patients, mainly those included during the first years of the study. Had today's criteria been applied, a substantial number of our patients who were diagnosed with UAP would instead have been given a diagnosis of NSTEMI. It is also possible that some patients who were excluded from participation because of a lack of objective signs of myocardial ischemia would have qualified today, due to a troponin value just above the detection level. The overall effect on the composition of our study population in comparison with a contemporary group of patients with ACS is that our patients were slightly more ill.

We started to include patients in our study in the mid-1990s. At that time, thrombolysis was the treatment of choice in patients with STEMI, but, towards the end of the study, primary PCI was preferred in many STEMI patients. During the course of the study, there was also a gradual increase in the number of patients with NSTEMI and UAP who underwent coronary angiography with subsequent coronary reperfusion therapy during hospitalization. The extent and the exact manner in which this change in treatment strategies has influenced the result of this thesis is impossible to judge.

It is always possible to discuss whether patients with atrial fibrillation should be included in a study focusing on echocardiography, such as ours. There are some variables that can only be calculated if the patient is in regular sinus rhythm. We chose to measure everything that was possible in each patient. This means that all patients, including those with atrial fibrillation, were included in

the univariate analysis whenever information was available. Since their deceleration time could be measured, they were also included in the restrictive versus non-restrictive groups and the subsequent analyses. It has been shown that a restrictive filling pattern, if anything, is a more ominous prognostic sign in patients with atrial fibrillation.[154] In the final multivariate models, when all the variables were required (Papers III and IV), only patients with 100% data took part; in practice, this means that no patient with atrial fibrillation was included. The number of patients with atrial fibrillation was small (12 in Paper III and 6 in Paper 4), and it is unlikely that their exclusion had a significant impact on our results.

The echocardiographic examinations were performed according to a detailed scheme, and stored on S-VHS tape, and in a large part also on MO-discs. In the initial part of the study, patients were not routinely referred for echocardiography if they did not have clinical signs of CHF and some patients, particularly those with UAP, were discharged before we could trace them to perform an echocardiogram. This explains why the proportion of patients with UAP within the echocardiographic substudy is somewhat smaller than in the main study. During the study period referral for echocardigraphy became more or less an integrated part of the CCU program.

Several experienced investigators at the Department of Clinical Physiology determined the ejection fraction for Papers I and II, and the degree of mitral regurgitation in Paper II. However, all measurements performed for Papers III and IV were made by a single observer (AP). Due to either a missing 4-chamber view or the poor quality of available projections, 7% of all patients with an echocardiographic examination could not be analyzed for Papers III-IV.

Blood sampling was scheduled for the first morning in the CCU, if within 24 hours of symptom onset, and 2-5 days after arrival. Some patients were originally admitted to other medical wards or the intensive care unit and transferred to the CCU after more than 24 hours had passed, while others were already discharged after a couple of days. Other reasons why blood sampling was missed were logistics, such as the patient being away for coronary angiography/other examinations, a shortage of staff, unwillingness on the patient's part, death within 24 hours or too poor a condition to justify extra blood sampling. So, for the reasons described, the sub-populations of patients in this thesis are not fully representative of the entire PRACSIS population. The most important consequence of our less than 100% sampling would be that our ACS patients constituted a somewhat healthier group than the background population.

In comparision with other studies of ACS we have a good, almost complete, follow-up and the only reason why patients were lost was due to emigration. One enormous strength of the study is the

fact that the same experienced study nurse collected all the clinical data throughout the whole 6 and a half year long inclusion period and conducted a personal interview with all patients.

Clinical predictors of risk

Many clinical prediction models have lately been developed to predict the outcome in patients with ACS.[120-122, 125] Their complexity varies and consequently also their usefulness in the clinical setting. They all include various combinations of baseline characteristics, presenting symptoms and signs, hospital procedures and medical treatment. These type of variables have repeatedly been shown to explain a large part of the outcome events in ACS, with a fairly limited contribution from additional risk markers.[155] The adjustment for clinical confounders is therefore of utmost importance in studies such as ours, where the additional benefit of more sophisticated measurements are evaluated. Various models for this adjustment can be applied. In our first paper we conducted exploratory analyses to identify confounders and included only the most important factors in our final multivariate model. In Papers II and III we made no attempt to evaluate the contribution from each of the presumed confounders, but ensured that their number was reasonable in relation to the number of outcome events. Finally, in Paper IV we used the recently developed GRACE score, which from a statistical point of view has the advantage of being a single factor.[124] Another reason for choosing the Grace score was its widespread use, thereby facilitating comparisons between our study and others. Since the Grace score was developed in an unselected population of ACS patients, and therefore with similar risk profile as ours, it should be valid in our patients. [116] We made no attempt to apply the GRACE score in the first three papers as well. It seem unlikely though that this would have changed our results to any significant degree.

NT-proBNP and BNP

BNP has been shown to have great clinical potential for diagnosis, prognosis and treatment options, particularly in patients with CHF,[51, 156-160] and it has been proven to be a valuable predictor of mortality in patients with MI, in both the short and the long term.[53, 161, 162] There are a growing number of studies regarding the role of BNP as a risk marker in the whole spectrum of ACS and it appears to have great potential in these populations as well. de Lemos et al demonstrated that a single measurement of BNP within the first day after the onset of ischemic symptoms had a prognostic value in the risk stratification among patients with ACS.[50] These findings were confirmed by more recent reports [163-168] as well as by our findings with measurements from the sub-acute

phase.[59] In contrast to the de Lemos study, the present one was not a sub-study of a multicenter, clinical drug trial, but rather a view of the "real world". The most exciting part of our results was that BNP was a significant predictor of future risk, even in patients with no signs or symptoms of CHF. Similar results have been presented by others, which support the notion that the release of BNP is more complex than originally thought and that ischemia constitutes a potent stimulus.[36, 50]

When it comes to the sampling and analysis of BNP and NT-proBNP, it has been shown that EDTA should be added to the tubes, together, if possible, with protease inhibitors.[40, 169] At the commencement of this study, our knowledge of protease inhibition was incomplete, whereas the value of EDTA was recognized and it was therefore used from the very outset of the study. Similarly, when the study started, there was incomplete information on the effects of long-term storage on the stability of BNP. This issue was studied during the course of our study by others and also by ourselves.[169] In a recent trial, it was shown that BNP stored at -20ºC had fairly good stability.[170] We found a weak inverse relationship between BNP levels and the time from sampling to analysis (Paper II). The extent to which this might have influenced our results is difficult to evaluate. The blood samples were stored at -70ºC. By analysis on one occasion in our study we minimized the methodological differences, however, even if there were some reduction of marker levels over time, those from a specific year should also be influenced to the same extent. Thereby the analytical conditions will be similar for patients included at a specific period in time, and we included the full spectrum of ACS throughout the study. We therefore believe that storage time should not have affected our results in any important way.

Echocardiography

Echocardiography has become a very useful instrument for the bedside evaluation of the extent of myocardial damage in MI patients and a valuable tool in the clarification of various other aspects of cardiac structure and function in ACS. The rationale behind echocardiographic examination at an early stage in ACS is to determine whether the patient is at high or low risk for future events. Although coronary angiography is increasingly performed, LV angiography is less frequently used. While coronary angiography visualizes the anatomy of the coronary arteries and shows whether a thrombus is present or not, echocardiography provides a valuable estimation of the overall cardiac function.

Discussion

Remodeling of the heart begins within hours of a heart attack, and is brought about by the sudden increase in loading conditions caused by loss of myocardium.[171] The final impact of the process is not seen until several weeks have passed,[172] and during the initial weeks after ACS treatment by angiotensin converting enzyme inhibition may be successful to prevent remodeling and reduce mortality as demonstrated in the CONSENSUS II and SAVE trials.[85, 89, 90, 93, 173] In our study, we examined patients at a median of 3 days after arrival at the hospital, thus well before remodeling had been completed. Despite this, mortality and rehospitalization for CHF were predicted by several of our echocardiographic variables, probably reflecting an injured or stunned myocardium with impaired diastolic function or reduced contractile performance. Moreover, an altered myocardial function due to previous MI or CHF may contribute to the predictive value of echocardiography. While an optimal strategy might have been to have an echocardiographic examination as soon as possible after admission and a subsequent one in a stable phase close to discharge,[100, 174] we invested our resources to get one optimized echocardiogram in the subacute phase around day 3-5. Our main ambition was to obtain predictive variables as early as possible during the course of the acute event, and by this approach we probably captured the very early form of remodeling, i.e. the "self defense" that occurs as a response to mechanical alterations and neurohormonal activation.

In numerous studies, an association has been demonstrated between outcome in terms of death or CHF and functional data in terms of LVEF, left atrial volume, wall motion index (WMI), and more complex variables obtained by tissue Doppler and stress echocardiography.[94, 111, 175-178] The majority of these studies have included populations with acute MI,[176] CHF or stable coronary artery disease,[179] and have not covered the entire register of ACS. More advanced techniques such as stress echocardiography,[175] although informative and valuable in a stable phase, are fairly time consuming and less feasible in an acute situation. Stevens et al.[179] studied partly similar variables as us but in a population with stable coronary artery disease. Other differences are a smaller percentage of patients with previous hypertension (41% vs. 71%) and previous MI (22% vs. 54%) in our study. These differences may explain why in their study LVMI was clearly the most significant predictor of CHF during follow-up, and together with LAVI and restrictive filling the only significant variables. In univariate analysis we also found, despite less prevalent hypertension, LVMI to be predictive of all-cause mortality and CHF with HR 1.4 (95% CI 1.15-1.71); p=0.0007 and 1.49 (1.12-1.99); p= 0.006, as was LAVI with HR 1.6 (1.33-1.93); p<0.0001 and 2.16 (1.67-2.80); p<0.0001. After

adjustment not only for age as in the study by Stevens et al, but for a number of other clinical variables, LVMI tended to be significantly associated to rehospitalization for CHF (p=0.06) and LAVI was significantly so (p=0.007). When adjusting for another 17 Doppler echocardiographic variables, we found no significant association of LVMI or LAVI with all-cause mortality, and neither with CHF. However, a component of LVMI, the septal thickness, was still associated with rehospitalization for CHF. A putative reason for this is the association between diastolic function and symptoms, which is stronger than association between diastolic function and mortality.[180] In the study by Stevens et al,[179] a restrictive filling pattern was independently associated with future CHF, and we found rehospitalization for CHF to be associated, after adjustment for clinical variables, both with the PV-s/d ratio in Paper III, and with a restrictive filling pattern in Paper IV, in the latter also when accounting for BNP.

Mitral regurgitation

It is well known that mitral regurgitation can occur after an acute MI due to ischemic injury to the papillary muscle apparatus as well as LV dilation. [103-107, 181, 182] In cases without valve pathology as an obvious cause, and with no previous echocardiogram, it is often difficult to determine whether mitral regurgitation in ACS is newly developed or was already present before the acute event. In our study, we did not attempt to differentiate between new and old mitral regurgitation. Although a potential limitation, it is a general problem, as discussed by Bursi et al.,[104] in a report on a cohort study of patients with acute MI. There are many ways to quantitate mitral regurgitation, and which one is most correct is debatable.[183, 184] We used continuous Doppler together with color Doppler to classify regurgitation into five grades.[151] Other studies have measured the regurgitant volume and fraction by using a volumetric method or mitral regurgitation index.[107, 108, 185, 186]

The exact mechanism by which BNP/NT-proBNP is activated in patients with mitral regurgitation is unknown. Detaint et al.[187] compared the BNP activation in patients with organic and functional mitral regurgitation and found that the release of BNP was larger in functional than organic regurgitation of the same degree, and that LV end-systolic volume rather than the magnitude of the regurgitation, was the major determinant.

The important finding in our study was that the presence of a significant mitral regurgitation confers an increased risk on patients with ACS and it should therefore not be forgotten in an evaluation of the patient's total risk burden.

Discussion

Restrictive filling pattern

Several recent studies have shown that disturbances of the diastolic function are associated with an adverse outcome in different patient categories. This has been demonstrated in CHF and acute MI patients, in whom a restrictive filling pattern of the left ventricle was associated with increased mortality and morbidity in the long term.[100-102, 154, 188-191] As yet, there are no conclusive data from the whole spectrum of ACS.

There is no uniform definition of a restrictive filling pattern. We chose a combination of an increased E/A ratio and a shortened deceleration time, since this approach has been used by many other groups. In order not to exclude any patient with a disturbed filling pattern, we opted for a broad rather than a narrow definition of shortened deceleration time (140 ms). As previously mentioned we also measured the deceleration time in our patients with atrial fibrillation. However, in the final multivariate analyses of Papers III and IV patients with atrial fibrillation were not included since these analyses required presence of all our Doppler echocardiographic variables.

We analysed the value of echocardiographic measurements from a single view, while Nijland et al[100] examined, in serial studies from multiple views the LV wall motion index and volume index as well as the restrictive filling in patients with acute MI. Restrictive filling was the single predictor of all-cause mortality in their study, and our data confirm in ACS the importance of a restrictive filling pattern as predictor of mortality and future CHF episodes, even when adjusting for BNP and the GRACE score. The association between BNP and restrictive filling has been studied from a pathophysiological point of view and, in several reports, elevated BNP levels have been shown to mirror diastolic LV abnormalities. [54, 192] In line with these findings our patients with a restrictive filling pattern had significantly higher BNP levels than those without signs of restriction.

In a meta-analysis of MI patients, 19.7% were defined as restrictive.[101] The corresponding percentage in our population was 13.5%, reflecting the fact that we studied the entire spectrum of ACS and not just MI patients. In accordance with other studies,[100, 193] we found only limited differences between patients with or without a restrictive-filling pattern regarding clinical characteristics. In contrast, echocardiographic measurements related to systolic structure and function were significantly more pathological in the restrictive patients, again confirming prior findings of an association between restrictive filling pattern and impaired systolic function.[101] Consequently, does systolic impairment have an important prognostic role when filling pattern is known? In the study by Steven et al, [179] impaired systolic function in terms of a reduced LVOT-VTI

indicating a low stroke volume was found to have borderline independent relation to future CHF development in patients with stable coronary heart disease. However, in our ACS patients a low LVOT-VTI was indepently associated with future rehospitalization for CHF as well as with all-cause and CV mortality even when considering BNP, filling pattern and the GRACE score (Paper IV).

A low PV-s/d may be found in young subjects, just as a third heart sound, a rapid filling wave in an apex cardiogram and a high mitral flow E/A ratio. However, in adults, a low PV-s/d ratio indicates increased LV filling pressure or a restrictive filling pattern.[194] In Paper III we found a low PV-S/D to be predictive of mortality as well as rehospitalization for CHF. However, when patients were classified as having a restrictive filling pattern or not by means of the mitral flow profile, to our surprise a low PV-S/D was not an additional ominous sign but indicated if anything a reduced mortality, Paper IV. Hypothetically, since a high PV-s/d ratio may indicate an increased risk associated with hypertension and myocardial hypertrophy,[195] a low PV-s/d ratio without restrictive filling pattern might indicate less likelihood of an hypertrophic ventricle and its associated risk. However, also in hypertensives, a low PV-s/d ratio may indicate tendency for CHF, [196] and the interpretation of our finding regarding PV-s/d in Paper IV is an open question.

The MV-E divided by the tissue Doppler E velocity (E/é) has been widely used as an index of of restrictive LV filling or filling pressure.[197] In an early part of the PRACSIS study, we performed tissue Doppler imaging and made some interesting observations.[198] However, a methodological study, which was part of a previous thesis,[199] did not show convincing data on the value of E/é, [200] and tissue Doppler data was not collected systematically for the remainder of our study.

The combination of BNP, echocardiography and clinical risk factors

Efforts to improve risk stratification in CV disease are constantly ongoing and novel markers of risk are continuously considered for addition to existing risk scores.[64, 201, 202] Various combinations of already established risk factors could be another way forward, which the results of this thesis suggest, since we have been able to show that our studied variables have an independent association with risk. In Paper IV, we showed that the risk information provided by BNP was independent of that obtained by the GRACE score, which corroborates the findings by some other groups. [53, 166, 203] In some studies NT-proBNP/BNP has provided unique information also when C-reactive protein has been simultaneously assessed. [63, 65] In Papers I, II and IV NT-proBNP or BNP were predictors of risk when LVEF had been taken into account, together with clinical confounders. In fact, we adjusted not only for LVEF, but measured systolic LV function in a number of ways, including

LVOT-VTI, LVVIs and time intervals. While the latter did not contribute independent information, both LVVIs and LVOT-VTI did so. The lack of independent information from time intervals is likely due to strong prognostic power in our other variables, since time intervals have also been shown to contain important information. Tei et al proposed the myocardial performing index (MPI), a combination of diastolic and systolic LV performance, as a measure of global cardiac function. [152] Recent studies have shown that MPI predicts cardiac death after a first MI,[204] and is also a markers of outcome in patients with restrictive and dilated cardiomyopathies.[152, 205] In contrast to these results we did not find any differences in MPI between patients with or without a restrictive filling pattern, nor in patients with high or low levels of BNP. One reason for this discrepancy could be the heterogeneity of our patients, some with unstable angina and very small deviations in cardiac function and others with large MI and major abnormalities. As expected the isovolumic relaxation time (IRT) was decreased in our restrictive patients secondary to the increased left atrial pressure and a decreased LV compliance. The ratio of PEP/LVET was increased in the groups with a restrictive filling pattern or high BNP levels (Paper IV) and as individual variables they were significantly associated with both mortality and rehospitalization due to CHF (Paper III).

BNP and NT-proBNP are related to an impaired LV function but, in most studies, in agreement with ours, they provide prognostic information independent of LVEF, indicating that the risk in the elevated BNP levels is not only a reflection of a disturbed systolic LV function. [206, 207] Richards et al showed already in 1998 that BNP, or NT-proBNP, and LVEF were complementary independent predictors of mortality and proposed to combine them in the risk stratification of patients with MI. [207] In a small study of CHF patients, BNP was a strong predictor of short-term outcome in patients with a restrictive filling pattern.[208] The incremental prognostic value of BNP to clinical information and a comprehensive echocardiogram, including an assessment of LV filling, was recently demonstrated in 400 MI patients.[176] Our Paper IV extends this information by showing that BNP provided independent and incremental prognostic information to restrictive filling and clinical data across the entire spectrum of ACS.

Future implications

Treatment strategies for patients with ACS have changed markedly since the first patient was included in our study. Current guidelines offer strict recommendations on in-hospital treatment, invasive or non-invasive, and on pharmacological therapies at discharge,[9, 10] but data on in-hospital

management shows a treatment-risk paradox, with less high risk than low risk patients subjected to evidence based pharmacological therapies.[209] Physicians seem to fail to identify strong adverse predictors of risk and do not take them into account in their overall risk assessment. [210] Very little is known about risk stratification of patients in connection with discharge in the clinical routine. According to personal communications a systematic calculation of risk in ACS patients is a rare phenomenon among cardiologists in Sweden, and in clinical practice all ACS patients are treated with similar approaches to therapy, irrespective of tremendous variability in risk. Current optimal medical therapy consists of five drug classes; aspirin, β-adrenoreceptor antagonists, angiotensin converting enzyme inhibitors/angiotensin receptor antagonists, clopidogrel and statins, which according to guidelines should be given to all patients.[9, 10] It has been shown that optimal treatment improves prognosis,[211, 212] but adherence to guidelines is variable and far from complete in many hospitals. Organized approaches to improvement have been carried out by several groups and been reported successful. [213, 214] A decline in the use of drugs appears to occur during the year following discharge, [211]indicating that the transition of patients back to primary care might be a critical point.

Given the established routines for treatments of patients with ACS, one could argue that risk stratification at discharge is meaningless since it would not lead to any changes in therapy. However, although long-term case fatality after hospitalization for acute MI has decreased, out-of-hospital morbidity and mortality continue to be higher than in the general population, including in patients with UAP,[115, 215, 216] indicating that improvements in the secondary prevention are necessary. This notion is supported by a recent Swedish report showing marked limitations in risk factor control in post MI patients.[217] It is logical to believe that efforts to identify the patients with highest risk would be an efficient use of available resources. A focus on those who have the most to gain, with attempts to obtain a perfect control of all manageable risk factors, should result in an increased survival and a reduced morbidity in ACS patients. We believe that the risk factors that have been investigated in the present thesis could be useful tools in the evaluation of ACS patients at discharge. Ideally, the factors should be tested in a new population of ACS patients to verify their predictive power. Our data do not allow us to recommend their routine use in all patients. However, the data indicate that all echocardiographic examinations, should be carefully evaluated, taking into consideration other variables than LVEF, and whenever available, incorporation of BNP levels in the evaluation of risk seems valuable. The ultimate answer regarding the usefulness of our variables in risk evaluation would require a randomized study with patients at higher risk referred to either usual or special care with aggressive risk factor control in the latter group.

Conclusions

- The biochemical marker NT-proBNP predicted long-term mortality in our population and added prognostic information above Killip class, age and LVEF.
- NT-proBNP was an independent predictor of mortality even in patients with max. Killip I on admission and during hospitalization, i.e. without any clinical signs of CHF.
- Mitral regurgitation, BNP and LVEF, individually and combined in a score system, provided prognostic information on both mortality and rehospitalization due to CHF.
- A score including only mitral regurgitation and LVEF provided information similar to the score that also took BNP into account.
- From a single-view echocardigraphic examination, LVVIs and PV-s/d were the two variables that were associated with not only all-cause mortality but also CV mortality and rehospitalization for CHF.
- A restrictive filling pattern and high BNP levels were associated with a poor prognosis, even after adjustment for the GRACE risk score.
- LV systolic function added significantly to risk prediction.

To summarise, we conclude that both BNP levels and echocardiographic variables are strongly associated with the long-term prognosis in ACS indicating an important role for risk stratification in these patients.

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References

1. Fox KA, Steg PG, Eagle KA, Goodman SG, Anderson FA, Jr., Granger CB, Flather MD, Budaj A, Quill A, Gore JM. Decline in rates of death and heart failure in acute coronary syndromes, 1999-2006. *JAMA*. 2007;297:1892-1900
2. The National Board of Health and Welfare. Myocardial infarctions in Sweden 1987-2007. Stockholm: Official statistics of Sweden. *Health and Medical Care*. 2009
3. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med*. 2010;362:2155-2165
4. The National Board of Health and Welfare. Causes of Death 2008. Stockholm: Offical statistics of Sweden. *Health and Medical Care*. 2010
5. Fox KA. Coronary disease. Acute coronary syndromes: presentation--clinical spectrum and management. *Heart*. 2000;84:93-100
6. Kumar A, Cannon CP. Acute coronary syndromes: diagnosis and management, part I. *Mayo Clin Proc*. 2009;84:917-938
7. Falk E. Pathogenesis of atherosclerosis. *J Am Coll Cardiol*. 2006;47:C7-12
8. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med*. 2005;352:1685-1695
9. Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernandez-Aviles F, Fox KA, Hasdai D, Ohman EM, Wallentin L, Wijns W. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J*. 2007;28:1598-1660
10. Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, Filippatos G, Fox K, Huber K, Kastrati A, Rosengren A, Steg PG, Tubaro M, Verheugt F, Weidinger F, Weis M. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J*. 2008;29:2909-2945
11. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol*. 2000;36:959-969
12. Thygesen K, Alpert JS, White HD, Jaffe AS, Apple FS, Galvani M, Katus HA, Newby LK, Ravkilde J, Chaitman B, Clemmensen PM, Dellborg M, Hod H, Porela P, Underwood R, Bax JJ, Beller GA, Bonow R, Van der Wall EE, Bassand JP, Wijns W, Ferguson TB, Steg PG, Uretsky BF, Williams DO, Armstrong PW, Antman EM, Fox KA, Hamm CW, Ohman EM, Simoons ML, Poole-Wilson PA, Gurfinkel EP, Lopez-Sendon JL, Pais P, Mendis S, Zhu JR, Wallentin LC, Fernandez-Aviles F, Fox KM, Parkhomenko AN, Priori SG, Tendera M, Voipio-Pulkki LM, Vahanian A, Camm AJ, De Caterina R,

Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Widimsky P, Zamorano JL, Morais J, Brener S, Harrington R, Morrow D, Lim M, Martinez-Rios MA, Steinhubl S, Levine GN, Gibler WB, Goff D, Tubaro M, Dudek D, Al-Attar N. Universal definition of myocardial infarction. *Circulation*. 2007;116:2634-2653

13. Horowitz RS, Morganroth J, Parrotto C, Chen CC, Soffer J, Pauletto FJ. Immediate diagnosis of acute myocardial infarction by two-dimensional echocardiography. *Circulation*. 1982;65:323-329

14. Sabia P, Afrookteh A, Touchstone DA, Keller MW, Esquivel L, Kaul S. Value of regional wall motion abnormality in the emergency room diagnosis of acute myocardial infarction. A prospective study using two-dimensional echocardiography. *Circulation*. 1991;84:I85-92

15. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. *Arterioscler Thromb Vasc Biol*. 2003;23:168-175

16. Libby P, Ridker PM, Hansson GK. Inflammation in atherosclerosis: from pathophysiology to practice. *J Am Coll Cardiol*. 2009;54:2129-2138

17. Tabas I, Williams KJ, Boren J. Subendothelial lipoprotein retention as the initiating process in atherosclerosis: update and therapeutic implications. *Circulation*. 2007;116:1832-1844

18. Thim T, Hagensen MK, Bentzon JF, Falk E. From vulnerable plaque to atherothrombosis. *J Intern Med*. 2008;263:506-516

19. Kramer MC, Rittersma SZ, de Winter RJ, Ladich ER, Fowler DR, Liang YH, Kutys R, Carter-Monroe N, Kolodgie FD, van der Wal AC, Virmani R. Relationship of thrombus healing to underlying plaque morphology in sudden coronary death. *J Am Coll Cardiol*. 2010;55:122-132

20. Shah PK. Mechanisms of plaque vulnerability and rupture. *J Am Coll Cardiol*. 2003;41:15S-22S

21. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. *J Am Coll Cardiol*. 2006;47:C13-18

22. Davies MJ. The pathophysiology of acute coronary syndromes. *Heart*. 2000;83:361-366

23. Giroud D, Li JM, Urban P, Meier B, Rutishauer W. Relation of the site of acute myocardial infarction to the most severe coronary arterial stenosis at prior angiography. *Am J Cardiol*. 1992;69:729-732

24. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation*. 2002;105:1135-1143

25. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937-952

26. Anand SS, Islam S, Rosengren A, Franzosi MG, Steyn K, Yusufali AH, Keltai M, Diaz R, Rangarajan S, Yusuf S. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. *Eur Heart J*. 2008;29:932-940

27. Burke AP, Farb A, Malcom G, Virmani R. Effect of menopause on plaque morphologic characteristics in coronary atherosclerosis. *Am Heart J*. 2001;141:S58-62

28. de Bold AJ, Borenstein HB, Veress AT, Sonnenberg H. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. *Life Sci*. 1981;28:89-94

29. Levin ER, Gardner DG, Samson WK. Natriuretic peptides. *N Engl J Med*. 1998;339:321-328

30. Clerico A, Emdin M. Diagnostic accuracy and prognostic relevance of the measurement of cardiac natriuretic peptides: a review. *Clin Chem*. 2004;50:33-50

31. Mair J. Biochemistry of B-type natriuretic peptide--where are we now? *Clin Chem Lab Med*. 2008;46:1507-1514

32. Nishikimi T, Maeda N, Matsuoka H. The role of natriuretic peptides in cardioprotection. *Cardiovasc Res*. 2006;69:318-328

33. de Lemos JA, McGuire DK, Drazner MH. B-type natriuretic peptide in cardiovascular disease. *Lancet*. 2003;362:316-322

34. Munagala VK, Burnett JC, Jr., Redfield MM. The natriuretic peptides in cardiovascular medicine. *Curr Probl Cardiol*. 2004;29:707-769

35. Wilkins MR, Redondo J, Brown LA. The natriuretic-peptide family. *Lancet*. 1997;349:1307-1310

36. Goetze JP, Christoffersen C, Perko M, Arendrup H, Rehfeld JF, Kastrup J, Nielsen LB. Increased cardiac BNP expression associated with myocardial ischemia. *FASEB J*. 2003;17:1105-1107

37. Lam CS, Burnett JC, Jr., Costello-Boerrigter L, Rodeheffer RJ, Redfield MM. Alternate circulating pro-B-type natriuretic peptide and B-type natriuretic peptide forms in the general population. *J Am Coll Cardiol*. 2007;49:1193-1202

38. Martinez-Rumayor A, Richards AM, Burnett JC, Januzzi JL, Jr. Biology of the natriuretic peptides. *Am J Cardiol*. 2008;101:3-8

39. van Kimmenade RR, Januzzi JL, Jr., Bakker JA, Houben AJ, Rennenberg R, Kroon AA, Crijns HJ, van Dieijen-Visser MP, de Leeuw PW, Pinto YM. Renal clearance of B-type natriuretic peptide and amino terminal pro-B-type natriuretic peptide a mechanistic study in hypertensive subjects. *J Am Coll Cardiol*. 2009;53:884-890

40. Belenky A, Smith A, Zhang B, Lin S, Despres N, Wu AH, Bluestein BI. The effect of class-specific protease inhibitors on the stabilization of B-type natriuretic peptide in human plasma. *Clin Chim Acta*. 2004;340:163-172

41. Ordonez-Llanos J, Collinson PO, Christenson RH. Amino-terminal pro-B-type natriuretic peptide: analytic considerations. *Am J Cardiol*. 2008;101:9-15

42. Apple FS, Wu AH, Jaffe AS, Panteghini M, Christenson RH. National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines: analytical issues for biomarkers of heart failure. *Clin Biochem*. 2008;41:222-226

43. Tang WH, Francis GS, Morrow DA, Newby LK, Cannon CP, Jesse RL, Storrow AB, Christenson RH. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: clinical utilization of cardiac biomarker testing in heart failure. *Clin Biochem*. 2008;41:210-221

44. Apple FS, Panteghini M, Ravkilde J, Mair J, Wu AH, Tate J, Pagani F, Christenson RH, Jaffe AS. Quality specifications for B-type natriuretic peptide assays. *Clin Chem*. 2005;51:486-493

45. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC, Jr. Plasma brain natriuretic peptide concentration: impact of age and gender. *J Am Coll Cardiol*. 2002;40:976-982

46. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Wilson PW, Vasan RS. Impact of obesity on plasma natriuretic peptide levels. *Circulation*. 2004;109:594-600

47. Bruins S, Fokkema MR, Romer JW, Dejongste MJ, van der Dijs FP, van den Ouweland JM, Muskiet FA. High intraindividual variation of B-type natriuretic peptide (BNP) and amino-terminal proBNP in patients with stable chronic heart failure. *Clin Chem*. 2004;50:2052-2058

48. Alehagen U, Lindstedt G, Levin LA, Dahlstrom U. Risk of cardiovascular death in elderly patients with possible heart failure. B-type natriuretic peptide (BNP) and the aminoterminal fragment of ProBNP (N-terminal proBNP) as prognostic indicators in a 6-year follow-up of a primary care population. *Int J Cardiol*. 2005;100:125-133

49. Daniels LB, Maisel AS. Natriuretic peptides. *J Am Coll Cardiol*. 2007;50:2357-2368

50. de Lemos JA, Morrow DA, Bentley JH, Omland T, Sabatine MS, McCabe CH, Hall C, Cannon CP, Braunwald E. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. *N Engl J Med*. 2001;345:1014-1021

51. Jourdain P, Jondeau G, Funck F, Gueffet P, Le Helloco A, Donal E, Aupetit JF, Aumont MC, Galinier M, Eicher JC, Cohen-Solal A, Juilliere Y. Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. *J Am Coll Cardiol*. 2007;49:1733-1739

52. Linssen GC, Bakker SJ, Voors AA, Gansevoort RT, Hillege HL, de Jong PE, van Veldhuisen DJ, Gans RO, de Zeeuw D. N-terminal pro-B-type natriuretic peptide is an independent predictor of cardiovascular morbidity and mortality in the general population. *Eur Heart J*. 2010;31:120-127

53. Lorgis L, Zeller M, Dentan G, Sicard P, Buffet P, L'Huillier I, Beer JC, Vincent-Martin M, Makki H, Gambert P, Cottin Y. Prognostic value of N-terminal pro-brain natriuretic peptide in elderly people with acute myocardial infarction: prospective observational study. *BMJ*. 2009;338:b1605

54. Lubien E, DeMaria A, Krishnaswamy P, Clopton P, Koon J, Kazanegra R, Gardetto N, Wanner E, Maisel AS. Utility of B-natriuretic peptide in detecting diastolic dysfunction: comparison with Doppler velocity recordings. *Circulation*. 2002;105:595-601

55. Maisel A, Mueller C, Adams K, Jr., Anker SD, Aspromonte N, Cleland JG, Cohen-Solal A, Dahlstrom U, DeMaria A, Di Somma S, Filippatos GS, Fonarow GC, Jourdain P, Komajda M, Liu PP, McDonagh T, McDonald K, Mebazaa A, Nieminen MS, Peacock WF, Tubaro M, Valle R, Vanderhyden M, Yancy CW, Zannad F, Braunwald E. State of the art: using natriuretic peptide levels in clinical practice. *Eur J Heart Fail*. 2008;10:824-839

56. Maisel AS, Koon J, Krishnaswamy P, Kazenegra R, Clopton P, Gardetto N, Morrisey R, Garcia A, Chiu A, De Maria A. Utility of B-natriuretic peptide as a rapid, point-of-care test for screening patients undergoing echocardiography to determine left ventricular dysfunction. *Am Heart J*. 2001;141:367-374

57. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AH, Clopton P, Steg PG, Westheim A, Knudsen CW, Perez A, Kazanegra R, Herrmann HC, McCullough PA. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med*. 2002;347:161-167

58. Parekh N, Maisel AS. Utility of B-natriuretic peptide in the evaluation of left ventricular diastolic function and diastolic heart failure. *Curr Opin Cardiol*. 2009;24:155-160

59. Omland T, Persson A, Ng L, O'Brien R, Karlsson T, Herlitz J, Hartford M, Caidahl K. N-terminal pro-B-type natriuretic peptide and long-term mortality in acute coronary syndromes. *Circulation*. 2002;106:2913-2918

60. Palazzuoli A, Calabria P, Vecchiato L, Quatrini I, Carrera A, Bruni F, Puccetti L, Pastorelli M, Pasqui AL, Auteri A. Plasma brain natriuretic peptide levels in coronary heart disease with preserved systolic function. *Clin Exp Med*. 2004;4:44-49

61. Palazzuoli A, Deckers J, Calabro A, Campagna MS, Nuti R, Pastorelli M, Pasqui AL, Bruni F, Auteri A, Puccetti L. Brain natriuretic peptide and other risk markers for outcome assessment in patients with non-ST-elevation coronary syndromes and preserved systolic function. *Am J Cardiol*. 2006;98:1322-1328

62. Eggers KM, Kempf T, Venge P, Wallentin L, Wollert KC, Lindahl B. Improving long-term risk prediction in patients with acute chest pain: the Global Registry of Acute Coronary Events (GRACE) risk score is enhanced by selected nonnecrosis biomarkers. *Am Heart J*. 2010;160:88-94

63. James SK, Lindahl B, Siegbahn A, Stridsberg M, Venge P, Armstrong P, Barnathan ES, Califf R, Topol EJ, Simoons ML, Wallentin L. N-terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable coronary artery disease: a Global Utilization of Strategies To Open occluded arteries (GUSTO)-IV substudy. *Circulation*. 2003;108:275-281

64. Melander O, Newton-Cheh C, Almgren P, Hedblad B, Berglund G, Engstrom G, Persson M, Smith JG, Magnusson M, Christensson A, Struck J, Morgenthaler NG, Bergmann A,

Pencina MJ, Wang TJ. Novel and conventional biomarkers for prediction of incident cardiovascular events in the community. *Jama*. 2009;302:49-57

65. Sabatine MS, Morrow DA, de Lemos JA, Gibson CM, Murphy SA, Rifai N, McCabe C, Antman EM, Cannon CP, Braunwald E. Multimarker approach to risk stratification in non-ST elevation acute coronary syndromes: simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide. *Circulation*. 2002;105:1760-1763

66. Bando M, Ishii Y, Sugiyama Y, Kitamura S. Elevated plasma brain natriuretic peptide levels in chronic respiratory failure with cor pulmonale. *Respir Med*. 1999;93:507-514

67. ten Wolde M, Tulevski, II, Mulder JW, Sohne M, Boomsma F, Mulder BJ, Buller HR. Brain natriuretic peptide as a predictor of adverse outcome in patients with pulmonary embolism. *Circulation*. 2003;107:2082-2084

68. Zakynthinos E, Kiropoulos T, Gourgoulianis K, Filippatos G. Diagnostic and prognostic impact of brain natriuretic peptide in cardiac and noncardiac diseases. *Heart Lung*. 2008;37:275-285

69. Richards M, Nicholls MG, Espiner EA, Lainchbury JG, Troughton RW, Elliott J, Frampton CM, Crozier IG, Yandle TG, Doughty R, MacMahon S, Sharpe N. Comparison of B-type natriuretic peptides for assessment of cardiac function and prognosis in stable ischemic heart disease. *J Am Coll Cardiol*. 2006;47:52-60

70. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K, Vahanian A, Camm J, De Caterina R, Dean V, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J*. 2008;29:2388-2442

71. Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, Marino P, Smiseth OA, De Keulenaer G, Leite-Moreira AF, Borbely A, Edes I, Handoko ML, Heymans S, Pezzali N, Pieske B, Dickstein K, Fraser AG, Brutsaert DL. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J*. 2007;28:2539-2550

72. Morrow DA, Cannon CP, Jesse RL, Newby LK, Ravkilde J, Storrow AB, Wu AH, Christenson RH. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: Clinical characteristics and utilization of biochemical markers in acute coronary syndromes. *Circulation*. 2007;115:e356-375

73. Edler I, Hertz C. The use of ultrasonic reflectoscope for the continuous recording of the movements of heart walls *Kungl Fysiogr Sällsk i Lund Förhandl*. 1954;24:1-19

74. Edler I, Hertz CH. The use of ultrasonic reflectoscope for the continuous recording of the movements of heart walls (Reproduction of orignal article from 1954). *Clin Physiol Funct Imaging*. 2004;24:118-136

75. Edler I, Lindstrom K. The history of echocardiography. *Ultrasound Med Biol*. 2004;30:1565-1644

76. Feigenbaum H. Role of M-mode technique in today's echocardiography. *J Am Soc Echocardiogr*. 2010;23:240-257; 335-247

77. Gowda RM, Khan IA, Vasavada BC, Sacchi TJ, Patel R. History of the evolution of echocardiography. *Int J Cardiol*. 2004;97:1-6

78. Picard MH, Popp RL, Weyman AE. Assessment of left ventricular function by echocardiography: a technique in evolution. *J Am Soc Echocardiogr*. 2008;21:14-21

79. Jensen JA. Medical ultrasound imaging. *Prog Biophys Mol Biol*. 2007;93:153-165

80. Roguin A. Christian Johann Doppler: the man behind the effect. *Br J Radiol*. 2002;75:615-619

81. Pearlman AS, Scoblionko DP, Saal AK. Assessment of valvular heart disease by Doppler echocardiography. *Clin Cardiol*. 1983;6:573-587

82. Hatle L, Angelsen BA, Tromsdal A. Non-invasive assessment of aortic stenosis by Doppler ultrasound. *Br Heart J*. 1980;43:284-292

83. Sanderson JE, Wang M, Yu CM. Tissue Doppler imaging for predicting outcome in patients with cardiovascular disease. *Curr Opin Cardiol*. 2004;19:458-463

84. Smiseth OA, Stoylen A, Ihlen H. Tissue Doppler imaging for the diagnosis of coronary artery disease. *Curr Opin Cardiol*. 2004;19:421-429

85. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. *Circulation*. 1990;81:1161-1172

86. Ahnve S, Gilpin E, Henning H, Curtis G, Collins D, Ross J, Jr. Limitations and advantages of the ejection fraction for defining high risk after acute myocardial infarction. *Am J Cardiol*. 1986;58:872-878

87. Ahnve S, Gilpin E, Dittrich H, Nicod P, Henning H, Carlisle J, Ross J, Jr. First myocardial infarction: age and ejection fraction identify a low-risk group. *Am Heart J*. 1988;116:925-932

88. Mollema SA, Nucifora G, Bax JJ. Prognostic value of echocardiography after acute myocardial infarction. *Heart*. 2009;95:1732-1745

89. Bonarjee VV, Carstensen S, Caidahl K, Nilsen DW, Edner M, Berning J. Attenuation of left ventricular dilatation after acute myocardial infarction by early initiation of enalapril therapy. CONSENSUS II Multi-Echo Study Group. *Am J Cardiol*. 1993;72:1004-1009

90. St John Sutton M, Pfeffer MA, Moye L, Plappert T, Rouleau JL, Lamas G, Rouleau J, Parker JO, Arnold MO, Sussex B, Braunwald E. Cardiovascular death and left ventricular remodeling two years after myocardial infarction: baseline predictors and impact of long-term use of captopril: information from the Survival and Ventricular Enlargement (SAVE) trial. *Circulation*. 1997;96:3294-3299

91. White HD, Norris RM, Brown MA, Brandt PW, Whitlock RM, Wild CJ. Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation*. 1987;76:44-51

92. Caidahl K, Svardsudd K, Eriksson H, Wilhelmsen L. Relation of dyspnea to left ventricular wall motion disturbances in a population of 67-year-old men. *Am J Cardiol*. 1987;59:1277-1282

93. Carstensen S, Bonarjee VV, Berning J, Edner M, Nilsen DW, Caidahl K. Effects of early enalapril treatment on global and regional wall motion in acute myocardial infarction. CONSENSUS II Multi Echo Study Group. *Am Heart J*. 1995;129:1101-1108

94. Moller JE, Hillis GS, Oh JK, Reeder GS, Gersh BJ, Pellikka PA. Wall motion score index and ejection fraction for risk stratification after acute myocardial infarction. *Am Heart J*. 2006;151:419-425

95. Skali H, Zornoff LA, Pfeffer MA, Arnold MO, Lamas GA, Moye LA, Plappert T, Rouleau JL, Sussex BA, St John Sutton M, Braunwald E, Solomon SD. Prognostic use of echocardiography 1 year after a myocardial infarction. *Am Heart J*. 2005;150:743-749

96. Redfield MM, Jacobsen SJ, Burnett JC, Jr., Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *Jama*. 2003;289:194-202

97. Nishimura RA, Tajik AJ. Evaluation of diastolic filling of left ventricle in health and disease: Doppler echocardiography is the clinician's Rosetta Stone. *J Am Coll Cardiol*. 1997;30:8-18

98. Oh J, Seward J, Tajik AJ. *The Echo Manual*. Philadelphia: Lippincott Williams & Wilkins; 2007.

99. Moller JE, Pellikka PA, Hillis GS, Oh JK. Prognostic importance of diastolic function and filling pressure in patients with acute myocardial infarction. *Circulation*. 2006;114:438-444

100. Nijland F, Kamp O, Karreman AJ, van Eenige MJ, Visser CA. Prognostic implications of restrictive left ventricular filling in acute myocardial infarction: a serial Doppler echocardiographic study. *J Am Coll Cardiol*. 1997;30:1618-1624

101. Moller JE, Whalley GA, Dini FL, Doughty RN, Gamble GD, Klein AL, Quintana M, Yu CM. Independent prognostic importance of a restrictive left ventricular filling pattern after myocardial infarction: an individual patient meta-analysis: Meta-Analysis Research Group in Echocardiography acute myocardial infarction. *Circulation*. 2008;117:2591-2598

102. Somaratne JB, Whalley GA, Gamble GD, Doughty RN. Restrictive filling pattern is a powerful predictor of heart failure events postacute myocardial infarction and in established heart failure: a literature-based meta-analysis. *J Card Fail*. 2007;13:346-352

103. Bursi F, Enriquez-Sarano M, Jacobsen SJ, Roger VL. Mitral regurgitation after myocardial infarction: a review. *Am J Med*. 2006;119:103-112

104. Bursi F, Enriquez-Sarano M, Nkomo VT, Jacobsen SJ, Weston SA, Meverden RA, Roger VL. Heart failure and death after myocardial infarction in the community: the emerging role of mitral regurgitation. *Circulation*. 2005;111:295-301

105. Feinberg MS, Schwammenthal E, Shlizerman L, Porter A, Hod H, Friemark D, Matezky S, Boyko V, Mandelzweig L, Vered Z, Behar S, Sagie A. Prognostic significance of mild mitral regurgitation by color Doppler echocardiography in acute myocardial infarction. *Am J Cardiol*. 2000;86:903-907

106. Lamas GA, Mitchell GF, Flaker GC, Smith SC, Jr., Gersh BJ, Basta L, Moye L, Braunwald E, Pfeffer MA. Clinical significance of mitral regurgitation after acute myocardial infarction. Survival and Ventricular Enlargement Investigators. *Circulation*. 1997;96:827-833

107. Lehmann KG, Francis CK, Dodge HT. Mitral regurgitation in early myocardial infarction. Incidence, clinical detection, and prognostic implications. TIMI Study Group. *Ann Intern Med*. 1992;117:10-17

108. Perez de Isla L, Zamorano J, Quezada M, Almeria C, Rodrigo JL, Serra V, Garcia Rubira JC, Ortiz AF, Macaya C. Prognostic significance of functional mitral regurgitation after a first non-ST-segment elevation acute coronary syndrome. *Eur Heart J*. 2006;27:2655-2660

109. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440-1463

110. Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tajik AJ, Tsang TS. Left atrial size: physiologic determinants and clinical applications. *J Am Coll Cardiol*. 2006;47:2357-2363

111. Moller JE, Hillis GS, Oh JK, Seward JB, Reeder GS, Wright RS, Park SW, Bailey KR, Pellikka PA. Left atrial volume: a powerful predictor of survival after acute myocardial infarction. *Circulation*. 2003;107:2207-2212

112. Tsai CT, Hwang JJ, Shih YC, Chiang FT, Lai LP, Lin JL. Evolution of Left Atrial Systolic and Diastolic Functions in Different Stages of Hypertension: Distinct Effects of Blood Pressure Control. *Cardiology*. 2007;109:180-187

113. Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as a morphophysiologic expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. *Am J Cardiol*. 2002;90:1284-1289

114. Norris RM, Barnaby PF, Brandt PW, Geary GG, Whitlock RM, Wild CJ, Barratt-Boyes BG. Prognosis after recovery from first acute myocardial infarction: determinants of reinfarction and sudden death. *Am J Cardiol*. 1984;53:408-413

115. Fox KA, Carruthers KF, Dunbar DR, Graham C, Manning JR, De Raedt H, Buysschaert I, Lambrechts D, Van de Werf F. Underestimated and under-recognized: the late

consequences of acute coronary syndrome (GRACE UK-Belgian Study). *Eur Heart J*. 2010;31:2755-2764

116. Fox KA, Eagle KA, Gore JM, Steg PG, Anderson FA. The Global Registry of Acute Coronary Events, 1999 to 2009--GRACE. *Heart*. 2010;96:1095-1101

117. Diderholm E, Andren B, Frostfeldt G, Genberg M, Jernberg T, Lagerqvist B, Lindahl B, Venge P, Wallentin L. The prognostic and therapeutic implications of increased troponin T levels and ST depression in unstable coronary artery disease: the FRISC II invasive troponin T electrocardiogram substudy. *Am Heart J*. 2002;143:760-767

118. Holmvang L, Luscher MS, Clemmensen P, Thygesen K, Grande P. Very early risk stratification using combined ECG and biochemical assessment in patients with unstable coronary artery disease (A thrombin inhibition in myocardial ischemia [TRIM] substudy). The TRIM Study Group. *Circulation*. 1998;98:2004-2009

119. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, Braunwald E. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. *Jama*. 2000;284:835-842

120. Lagerqvist B, Diderholm E, Lindahl B, Husted S, Kontny F, Stahle E, Swahn E, Venge P, Siegbahn A, Wallentin L. FRISC score for selection of patients for an early invasive treatment strategy in unstable coronary artery disease. *Heart*. 2005;91:1047-1052

121. Morrow DA, Antman EM, Charlesworth A, Cairns R, Murphy SA, de Lemos JA, Giugliano RP, McCabe CH, Braunwald E. TIMI risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: An intravenous nPA for treatment of infarcting myocardium early II trial substudy. *Circulation*. 2000;102:2031-2037

122. Yan AT, Yan RT, Tan M, Casanova A, Labinaz M, Sridhar K, Fitchett DH, Langer A, Goodman SG. Risk scores for risk stratification in acute coronary syndromes: useful but simpler is not necessarily better. *Eur Heart J*. 2007;28:1072-1078

123. Steg PG, Goldberg RJ, Gore JM, Fox KA, Eagle KA, Flather MD, Sadiq I, Kasper R, Rushton-Mellor SK, Anderson FA. Baseline characteristics, management practices, and in-hospital outcomes of patients hospitalized with acute coronary syndromes in the Global Registry of Acute Coronary Events (GRACE). *Am J Cardiol*. 2002;90:358-363

124. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, Goodman SG, Granger CB, Steg PG, Gore JM, Budaj A, Avezum A, Flather MD, Fox KA. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *Jama*. 2004;291:2727-2733

125. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van De Werf F, Avezum A, Goodman SG, Flather MD, Fox KA. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med*. 2003;163:2345-2353

126. James SK, Lindahl B, Timmer JR, Ottervanger JP, Siegbahn A, Stridsberg M, Armstrong P, Califf R, Wallentin L, Simoons ML. Usefulness of biomarkers for predicting long-term mortality in patients with diabetes mellitus and non-ST-elevation acute coronary syndromes (a GUSTO IV substudy). *Am J Cardiol*. 2006;97:167-172

127. Mockel M, Danne O, Muller R, Vollert JO, Muller C, Lueders C, Stork T, Frei U, Koenig W, Dietz R, Jaffe AS. Development of an optimized multimarker strategy for early risk assessment of patients with acute coronary syndromes. *Clin Chim Acta*. 2008;393:103-109

128. Tello-Montoliu A, Marin F, Roldan V, Mainar L, Lopez MT, Sogorb F, Vicente V, Lip GY. A multimarker risk stratification approach to non-ST elevation acute coronary syndrome: implications of troponin T, CRP, NT pro-BNP and fibrin D-dimer levels. *J Intern Med*. 2007;262:651-658

129. Blake GJ, Ridker PM. Inflammatory bio-markers and cardiovascular risk prediction. *J Intern Med*. 2002;252:283-294

130. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, 3rd, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC, Jr., Taubert K, Tracy RP, Vinicor F. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation*. 2003;107:499-511

131. Hartford M, Wiklund O, Hulten LM, Persson A, Karlsson T, Herlitz J, Hulthe J, Caidahl K. Interleukin-18 as a predictor of future events in patients with acute coronary syndromes. *Arterioscler Thromb Vasc Biol*. 2010;30:2039-2046

132. Hartford M, Wiklund O, Mattsson Hulten L, Perers E, Person A, Herlitz J, Hurt-Camejo E, Karlsson T, Caidahl K. CRP, interleukin-6, secretory phospholipase A2 group IIA, and intercellular adhesion molecule-1 during the early phase of acute coronary syndromes and long-term follow-up. *Int J Cardiol*. 2006;108:55-62

133. Jansson AM, Aukrust P, Ueland T, Smith C, Omland T, Hartford M, Caidahl K. Soluble CXCL16 predicts long-term mortality in acute coronary syndromes. *Circulation*. 2009;119:3181-3188

134. Omland T, Ueland T, Jansson AM, Persson A, Karlsson T, Smith C, Herlitz J, Aukrust P, Hartford M, Caidahl K. Circulating osteoprotegerin levels and long-term prognosis in patients with acute coronary syndromes. *J Am Coll Cardiol*. 2008;51:627-633

135. Sorensson P, Heiberg E, Saleh N, Bouvier F, Caidahl K, Tornvall P, Ryden L, Pernow J, Arheden H. Assessment of myocardium at risk with contrast enhanced steady-state free precession cine cardiovascular magnetic resonance compared to single-photon emission computed tomography. *J Cardiovasc Magn Reson*. 2010;12:25

136. Dijkmans PA, Senior R, Becher H, Porter TR, Wei K, Visser CA, Kamp O. Myocardial contrast echocardiography evolving as a clinically feasible technique for accurate, rapid, and safe assessment of myocardial perfusion: the evidence so far. *J Am Coll Cardiol*. 2006;48:2168-2177

137. Gaibazzi N, Rigo F, Reverberi C. Detection of coronary artery disease by combined assessment of wall motion, myocardial perfusion and coronary flow reserve: a multiparametric contrast stress-echocardiography study. *J Am Soc Echocardiogr*. 2010;23:1242-1250

138. Madler CF, Payne N, Wilkenshoff U, Cohen A, Derumeaux GA, Pierard LA, Engvall J, Brodin LA, Sutherland GR, Fraser AG. Non-invasive diagnosis of coronary artery disease by quantitative stress echocardiography: optimal diagnostic models using off-line tissue Doppler in the MYDISE study. *Eur Heart J*. 2003;24:1584-1594

139. Bjork Ingul C, Rozis E, Slordahl SA, Marwick TH. Incremental value of strain rate imaging to wall motion analysis for prediction of outcome in patients undergoing dobutamine stress echocardiography. *Circulation*. 2007;115:1252-1259

140. Reant P, Labrousse L, Lafitte S, Bordachar P, Pillois X, Tariosse L, Bonoron-Adele S, Padois P, Deville C, Roudaut R, Dos Santos P. Experimental validation of circumferential, longitudinal, and radial 2-dimensional strain during dobutamine stress echocardiography in ischemic conditions. *J Am Coll Cardiol*. 2008;51:149-157

141. Voigt JU, Exner B, Schmiedehausen K, Huchzermeyer C, Reulbach U, Nixdorff U, Platsch G, Kuwert T, Daniel WG, Flachskampf FA. Strain-rate imaging during dobutamine stress echocardiography provides objective evidence of inducible ischemia. *Circulation*. 2003;107:2120-2126

142. Perers E, Caidahl K, Herlitz J, Sjolin M, Karlson BW, Karlsson T, Hartford M. Spectrum of acute coronary syndromes: history and clinical presentation in relation to sex and age. *Cardiology*. 2004;102:67-76

143. Karl J, Borgya A, Gallusser A, Huber E, Krueger K, Rollinger W, Schenk J. Development of a novel, N-terminal-proBNP (NT-proBNP) assay with a low detection limit. *Scand J Clin Lab Invest Suppl*. 1999;230:177-181

144. Hughes D, Talwar S, Squire IB, Davies JE, Ng LL. An immunoluminometric assay for N-terminal pro-brain natriuretic peptide: development of a test for left ventricular dysfunction. *Clin Sci (Lond)*. 1999;96:373-380

145. Hart RC, Taaffe LR. The use of acridinium ester-labelled streptavidin in immunoassays. *J Immunol Methods*. 1987;101:91-96

146. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, Gutgesell H, Reichek N, Sahn D, Schnittger I, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr*. 1989;2:358-367

147. Caidahl K, Kazzam E, Lidberg J, Neumann Andersen G, Nordanstig J, Rantapaa Dahlqvist S, Waldenstrom A, Wikh R. New concept in echocardiography: harmonic imaging of tissue without use of contrast agent. *Lancet*. 1998;352:1264-1270

148. McGowan JH, Cleland JG. Reliability of reporting left ventricular systolic function by echocardiography: a systematic review of 3 methods. *Am Heart J*. 2003;146:388-397

149. Rich S, Sheikh A, Gallastegui J, Kondos GT, Mason T, Lam W. Determination of left ventricular ejection fraction by visual estimation during real-time two-dimensional echocardiography. *Am Heart J*. 1982;104:603-606

150. Shahgaldi K, Gudmundsson P, Manouras A, Brodin LA, Winter R. Visually estimated ejection fraction by two dimensional and triplane echocardiography is closely correlated

with quantitative ejection fraction by real-time three dimensional echocardiography. *Cardiovasc Ultrasound*. 2009;7:41

151. Waagstein F, Caidahl K, Wallentin I, Bergh CH, Hjalmarson A. Long-term beta-blockade in dilated cardiomyopathy. Effects of short- and long-term metoprolol treatment followed by withdrawal and readministration of metoprolol. *Circulation*. 1989;80:551-563

152. Tei C, Dujardin KS, Hodge DO, Kyle RA, Tajik AJ, Seward JB. Doppler index combining systolic and diastolic myocardial performance: clinical value in cardiac amyloidosis. *J Am Coll Cardiol*. 1996;28:658-664

153. Wong SP, French JK, Lydon AM, Manda SO, Gao W, Ashton NG, White HD. Relation of left ventricular sphericity to 10-year survival after acute myocardial infarction. *Am J Cardiol*. 2004;94:1270-1275

154. Raunso J, Moller JE, Kjaergaard J, Akkan D, Hassager C, Torp-Pedersen C, Kober L. Prognostic importance of a restrictive transmitral filling pattern in patients with symptomatic congestive heart failure and atrial fibrillation. *Am Heart J*. 2009;158:983-988

155. Abu-Assi E, Ferreira-Gonzalez I, Ribera A, Marsal JR, Cascant P, Heras M, Bueno H, Sanchez PL, Aros F, Marrugat J, Garcia-Dorado D, Pena-Gil C, Gonzalez-Juanatey JR, Permanyer-Miralda G. "Do GRACE (Global Registry of Acute Coronary events) risk scores still maintain their performance for predicting mortality in the era of contemporary management of acute coronary syndromes?". *Am Heart J*. 2010;160:826-834 e821-823

156. Cioffi G, Tarantini L, Stefenelli C, Azzetti G, Marco R, Carlucci S, Furlanello F. Changes in plasma N-terminal proBNP levels and ventricular filling pressures during intensive unloading therapy in elderly with decompensated congestive heart failure and preserved left ventricular systolic function. *J Card Fail*. 2006;12:608-615

157. Hartmann F, Packer M, Coats AJ, Fowler MB, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Anker SD, Amann-Zalan I, Hoersch S, Katus HA. Prognostic impact of plasma N-terminal pro-brain natriuretic peptide in severe chronic congestive heart failure: a substudy of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial. *Circulation*. 2004;110:1780-1786

158. Miller WL, Hartman KA, Burritt MF, Grill DE, Rodeheffer RJ, Burnett JC, Jr., Jaffe AS. Serial biomarker measurements in ambulatory patients with chronic heart failure: the importance of change over time. *Circulation*. 2007;116:249-257

159. Miller WL, Hartman KA, Grill DE, Burnett JC, Jr., Jaffe AS. Only large reductions in concentrations of natriuretic peptides (BNP and NT-proBNP) are associated with improved outcome in ambulatory patients with chronic heart failure. *Clin Chem*. 2009;55:78-84

160. Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. *Heart*. 2006;92:843-849

161. Arakawa N, Nakamura M, Aoki H, Hiramori K. Plasma brain natriuretic peptide concentrations predict survival after acute myocardial infarction. *J Am Coll Cardiol*. 1996;27:1656-1661

162. Khan SQ, Quinn P, Davies JE, Ng LL. N-terminal pro-B-type natriuretic peptide is better than TIMI risk score at predicting death after acute myocardial infarction. *Heart*. 2008;94:40-43

163. Galvani M, Ottani F, Oltrona L, Ardissino D, Gensini GF, Maggioni AP, Mannucci PM, Mininni N, Prando MD, Tubaro M, Vernocchi A, Vecchio C. N-terminal pro-brain natriuretic peptide on admission has prognostic value across the whole spectrum of acute coronary syndromes. *Circulation*. 2004;110:128-134

164. Heeschen C, Hamm CW, Mitrovic V, Lantelme NH, White HD. N-terminal pro-B-type natriuretic peptide levels for dynamic risk stratification of patients with acute coronary syndromes. *Circulation*. 2004;110:3206-3212

165. Jernberg T, Stridsberg M, Venge P, Lindahl B. N-terminal pro brain natriuretic peptide on admission for early risk stratification of patients with chest pain and no ST-segment elevation. *J Am Coll Cardiol*. 2002;40:437-445

166. Khan SQ, Narayan H, Ng KH, Dhillon OS, Kelly D, Quinn P, Squire IB, Davies JE, Ng LL. N-terminal pro-B-type natriuretic peptide complements the GRACE risk score in predicting early and late mortality following acute coronary syndrome. *Clin Sci (Lond)*. 2009;117:31-39

167. Jarai R, Wojta J, Huber K. Circulating B-type natriuretic peptides in patients with acute coronary syndromes. Pathophysiological, prognostical and therapeutical considerations. *Thromb Haemost*. 2005;94:926-932

168. Weber M, Bazzino O, Navarro Estrada JL, Fuselli JJ, Botto F, Perez de Arenaza D, Mollmann H, Nef HN, Elsasser A, Hamm CW. N-terminal B-type natriuretic peptide assessment provides incremental prognostic information in patients with acute coronary syndromes and normal troponin T values upon admission. *J Am Coll Cardiol*. 2008;51:1188-1195

169. Murdoch DR, Byrne J, Farmer R, Morton JJ. Disparity between studies of the stability of BNP in blood: comparison of endogenous and exogenous peptide. *Heart*. 1999;81:212-213

170. Pereira M, Azevedo A, Severo M, Barros H. Long-term stability of endogenous B-type natriuretic peptide during storage at -20 degrees C for later measurement with Biosite Triage assay. *Clin Biochem*. 2007;40:1104-1107

171. Mann DL, Bogaev R, Buckberg GD. Cardiac remodelling and myocardial recovery: lost in translation? *Eur J Heart Fail*. 2010;12:789-796

172. Opie LH, Commerford PJ, Gersh BJ, Pfeffer MA. Controversies in ventricular remodelling. *Lancet*. 2006;367:356-367

173. Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ, Jr., Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med*. 1992;327:669-677

174. Visser CA, Kan G, Meltzer RS, Koolen JJ, Dunning AJ. Incidence, timing and prognostic value of left ventricular aneurysm formation after myocardial infarction: a prospective, serial echocardiographic study of 158 patients. *Am J Cardiol*. 1986;57:729-732

175. Dawson D, Kaul S, Peters D, Rinkevich D, Schnell G, Belcik JT, Wei K. Prognostic value of dipyridamole stress myocardial contrast echocardiography: comparison with single photon emission computed tomography. *J Am Soc Echocardiogr*. 2009;22:954-960

176. Kruszewski K, Scott AE, Barclay JL, Small GR, Croal BL, Moller JE, Oh JK, Hillis GS. Noninvasive assessment of left ventricular filling pressure after acute myocardial infarction: a prospective study of the relative prognostic utility of clinical assessment, echocardiography, and B-type natriuretic peptide. *Am Heart J*. 2010;159:47-54

177. Muscholl MW, Oswald M, Mayer C, von Scheidt W. Prognostic value of 2D echocardiography in patients presenting with acute chest pain and non-diagnostic ECG for ST-elevation myocardial infarction. *Int J Cardiol*. 2002;84:217-225

178. Romano S, Dagianti A, Penco M, Varveri A, Biffani E, Fedele F. Usefulness of echocardiography in the prognostic evaluation of non-Q-wave myocardial infarction. *Am J Cardiol*. 2000;86:43G-45G

179. Stevens SM, Farzaneh-Far R, Na B, Whooley MA, Schiller NB. Development of an echocardiographic risk-stratification index to predict heart failure in patients with stable coronary artery disease: the Heart and Soul study. *JACC Cardiovasc Imaging*. 2009;2:11-20

180. Rihal CS, Nishimura RA, Hatle LK, Bailey KR, Tajik AJ. Systolic and diastolic dysfunction in patients with clinical diagnosis of dilated cardiomyopathy. Relation to symptoms and prognosis. *Circulation*. 1994;90:2772-2779

181. Birnbaum Y, Chamoun AJ, Conti VR, Uretsky BF. Mitral regurgitation following acute myocardial infarction. *Coron Artery Dis*. 2002;13:337-344

182. Calvo FE, Figueras J, Cortadellas J, Soler-Soler J. Severe mitral regurgitation complicating acute myocardial infarction. Clinical and angiographic differences between patients with and without papillary muscle rupture. *Eur Heart J*. 1997;18:1606-1610

183. Gelfand EV, Hughes S, Hauser TH, Yeon SB, Goepfert L, Kissinger KV, Rofsky NM, Manning WJ. Severity of mitral and aortic regurgitation as assessed by cardiovascular magnetic resonance: optimizing correlation with Doppler echocardiography. *J Cardiovasc Magn Reson*. 2006;8:503-507

184. Shanks M, Siebelink HM, Delgado V, van de Veire NR, Ng AC, Sieders A, Schuijf JD, Lamb HJ, Ajmone Marsan N, Westenberg JJ, Kroft LJ, de Roos A, Bax JJ. Quantitative assessment of mitral regurgitation: comparison between three-dimensional transesophageal echocardiography and magnetic resonance imaging. *Circ Cardiovasc Imaging*. 2010;3:694-700

185. Grigioni F, Detaint D, Avierinos JF, Scott C, Tajik J, Enriquez-Sarano M. Contribution of ischemic mitral regurgitation to congestive heart failure after myocardial infarction. *J Am Coll Cardiol*. 2005;45:260-267

186. Pellizzon GG, Grines CL, Cox DA, Stuckey T, Tcheng JE, Garcia E, Guagliumi G, Turco M, Lansky AJ, Griffin JJ, Cohen DJ, Aymong E, Mehran R, O'Neill WW, Stone GW. Importance of mitral regurgitation inpatients undergoing percutaneous coronary intervention for acute myocardial infarction: the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. *J Am Coll Cardiol*. 2004;43:1368-1374

187. Detaint D, Messika-Zeitoun D, Avierinos JF, Scott C, Chen H, Burnett JC, Jr., Enriquez-Sarano M. B-type natriuretic peptide in organic mitral regurgitation: determinants and impact on outcome. *Circulation*. 2005;111:2391-2397

188. Independence of restrictive filling pattern and LV ejection fraction with mortality in heart failure: an individual patient meta-analysis. *Eur J Heart Fail*. 2008;10:786-792

189. Cerisano G, Bolognese L, Buonamici P, Valenti R, Carrabba N, Dovellini EV, Pucci PD, Santoro GM, Antoniucci D. Prognostic implications of restrictive left ventricular filling in reperfused anterior acute myocardial infarction. *J Am Coll Cardiol*. 2001;37:793-799

190. Whalley GA, Gamble GD, Doughty RN. Restrictive diastolic filling predicts death after acute myocardial infarction: systematic review and meta-analysis of prospective studies. *Heart*. 2006;92:1588-1594

191. Whalley GA, Gamble GD, Doughty RN. The prognostic significance of restrictive diastolic filling associated with heart failure: a meta-analysis. *Int J Cardiol*. 2007;116:70-77

192. Yu CM, Sanderson JE, Shum IO, Chan S, Yeung LY, Hung YT, Cockram CS, Woo KS. Diastolic dysfunction and natriuretic peptides in systolic heart failure. Higher ANP and BNP levels are associated with the restrictive filling pattern. *Eur Heart J*. 1996;17:1694-1702

193. Temporelli PL, Giannuzzi P, Nicolosi GL, Latini R, Franzosi MG, Gentile F, Tavazzi L, Maggioni AP. Doppler-derived mitral deceleration time as a strong prognostic marker of left ventricular remodeling and survival after acute myocardial infarction: results of the GISSI-3 echo substudy. *J Am Coll Cardiol*. 2004;43:1646-1653

194. Rossvoll O, Hatle LK. Pulmonary venous flow velocities recorded by transthoracic Doppler ultrasound: relation to left ventricular diastolic pressures. *J Am Coll Cardiol*. 1993;21:1687-1696

195. Iwashima Y, Horio T, Kamide K, Rakugi H, Ogihara T, Kawano Y. Pulmonary venous flow and risk of cardiovascular disease in essential hypertension. *J Hypertens*. 2008;26:798-805

196. Masuyama T, Lee JM, Yamamoto K, Tanouchi J, Hori M, Kamada T. Analysis of pulmonary venous flow velocity patterns in hypertensive hearts: its complementary value in the interpretation of mitral flow velocity patterns. *Am Heart J*. 1992;124:983-994

197. Rivas-Gotz C, Khoury DS, Manolios M, Rao L, Kopelen HA, Nagueh SF. Time interval between onset of mitral inflow and onset of early diastolic velocity by tissue Doppler: a novel index of left ventricular relaxation: experimental studies and clinical application. *J Am Coll Cardiol*. 2003;42:1463-1470

198. Guron CW, Hartford M, Persson A, Herlitz J, Thelle D, Caidahl K. Timing of regional left ventricular lengthening by pulsed tissue Doppler. *J Am Soc Echocardiogr*. 2004;17:307-312

199. Guron C. Pulsed tissue Doppler and left ventricular filling in acute coronary syndromes. *Cardiovascular Institute*. 2005;MD:92

200. Guron CW, Persson A, Wikh R, Caidahl K. Can the left ventricular early diastolic tissue-to-blood time interval be used to identify a normal pulmonary capillary wedge pressure? *Eur J Echocardiogr*. 2007;8:94-101

201. Beygui F, Silvain J, Pena A, Bellemain-Appaix A, Collet JP, Drexler H, Bhatt D, Vicaut E, Montalescot G. Usefulness of biomarker strategy to improve GRACE score's prediction performance in patients with non-ST-segment elevation acute coronary syndrome and low event rates. *Am J Cardiol*. 2010;106:650-658

202. Zethelius B, Berglund L, Sundstrom J, Ingelsson E, Basu S, Larsson A, Venge P, Arnlov J. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. *N Engl J Med*. 2008;358:2107-2116

203. Ang DS, Wei L, Kao MP, Lang CC, Struthers AD. A comparison between B-type natriuretic peptide, global registry of acute coronary events (GRACE) score and their combination in ACS risk stratification. *Heart*. 2009;95:1836-1842

204. Moller JE, Sondergaard E, Poulsen SH, Egstrup K. The Doppler echocardiographic myocardial performance index predicts left-ventricular dilation and cardiac death after myocardial infarction. *Cardiology*. 2001;95:105-111

205. Dujardin KS, Tei C, Yeo TC, Hodge DO, Rossi A, Seward JB. Prognostic value of a Doppler index combining systolic and diastolic performance in idiopathic-dilated cardiomyopathy. *Am J Cardiol*. 1998;82:1071-1076

206. Ang DS, Kong CF, Kao MP, Struthers AD. Serial bedside B-type natriuretic peptide strongly predicts prognosis in acute coronary syndrome independent of echocardiographic abnormalities. *Am Heart J*. 2009;158:133-140

207. Richards AM, Nicholls MG, Espiner EA, Lainchbury JG, Troughton RW, Elliott J, Frampton C, Turner J, Crozier IG, Yandle TG. B-type natriuretic peptides and ejection fraction for prognosis after myocardial infarction. *Circulation*. 2003;107:2786-2792

208. Feola M, Aspromonte N, Milani L, Bobbio M, Bardellotto S, Barro S, Giovinazzo P, Noventa F, Valle R. Plasma brain natriuretic peptide predicts short-term clinical outcome in heart failure patients with restrictive filling pattern. *J Card Fail*. 2008;14:420-425

209. Yan AT, Yan RT, Tan M, Fung A, Cohen EA, Fitchett DH, Langer A, Goodman SG. Management patterns in relation to risk stratification among patients with non-ST elevation acute coronary syndromes. *Arch Intern Med*. 2007;167:1009-1016

210. Yan AT, Yan RT, Huynh T, Casanova A, Raimondo FE, Fitchett DH, Langer A, Goodman SG. Understanding physicians' risk stratification of acute coronary syndromes: insights from the Canadian ACS 2 Registry. *Arch Intern Med*. 2009;169:372-378

211. Bramlage P, Messer C, Bitterlich N, Pohlmann C, Cuneo A, Stammwitz E, Tebbenjohanns J, Gohlke H, Senges J, Tebbe U. The effect of optimal medical therapy on 1-year mortality after acute myocardial infarction. *Heart*. 2010;96:604-609

212. Carlhed R, Bojestig M, Peterson A, Aberg C, Garmo H, Lindahl B. Improved clinical outcome after acute myocardial infarction in hospitals participating in a Swedish quality improvement initiative. *Circ Cardiovasc Qual Outcomes*. 2009;2:458-464

213. Lewis WR, Peterson ED, Cannon CP, Super DM, LaBresh KA, Quealy K, Liang L, Fonarow GC. An organized approach to improvement in guideline adherence for acute myocardial infarction: results with the Get With The Guidelines quality improvement program. *Arch Intern Med*. 2008;168:1813-1819

214. Peterson A, Carlhed R, Lindahl B, Lindstrom G, Aberg C, Andersson-Gare B, Bojestig M. Improving guideline adherence through intensive quality improvement and the use of a National Quality Register in Sweden for acute myocardial infarction. *Qual Manag Health Care*. 2007;16:25-37

215. Dudas K, Lappas G, Rosengren A. Long-term prognosis after hospital admission for acute myocardial infarction from 1987 to 2006. *Int J Cardiol*. 2010

216. Perers E, Caidahl K, Herlitz J, Karlsson T, Hartford M. Impact of diagnosis and sex on long-term prognosis in acute coronary syndromes. *Am Heart J*. 2007;154:482-488

217. Heart-Lung Foundation. Hjärtrapporten. *Report (www.hjart-lungfonden.se)*. 2010:17-24

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