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EDITORIAL

Predictors of re-hospitalization in patients with chronic heart failure

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Abstract

Heart failure (HF) is a chronic, progressive illness that is highly prevalent in the United States and worldwide. This morbid illness carries a very poor prognosis, and leads to frequent hospitalizations. Repeat hospitalization in HF is both largely burdensome to the patient and the healthcare system, as it is one of the most costly medical diagnoses among Medicare recipients. For years, investigators have strived to determine methods to reduce hospitalization rates of HF patients. Despite such efforts, recent reports indicate that re-hospitalization rates remain persistently high, without any improvement over the past several years and thus, this topic clearly needs aggressive attention. We performed a key-word search of the literature for relevant citations. Published articles, limited to English abstracts indexed primarily in the PubMed database through the year 2011, were reviewed. This article discusses various clinical parameters, serum biomarkers, hemodynamic parameters, and psychosocial factors that have been reviewed in the literature as predictors of re-hospitalization of HF patients. With this information, our hope is that the future holds better risk-stratification models that will allow providers to identify high-risk patients, and better customize effective interventions according to the needs of each individual HF patient.

Key words: Heart failure; Readmission; Predictors; Re-hospitalization; Chronic heart failure; Hospitalization

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INTRODUCTION

Heart failure (HF) is a prevalent and morbid chronic illness. According to the European Society of Cardiology and the American Heart Association, HF affects approximately 15 million Europeans and over 5 million Americans[1,2]. HF is not only taxing to the patient, but also to the healthcare system. Studies evaluating the economic burden of HF among several countries reveal estimated direct HF costs of 1%-2% of total healthcare expenditures, with approximately two-thirds of costs attributable to hospitalization[3]. While HF poses a significant burden to healthcare systems worldwide, the most abundant data and literature comes from the United States. In the United States a reported $37.2 billion was spent in direct and indirect costs in 2009, with $20.1 billion dollars of the expenditure relating to hospitalization[2]. Repeat hospitalization contributes significantly to the hospitaliza-

tion expenditure as HF patients are re-hospitalized at an alarmingly high rate, with approximately 50% of patients requiring readmission in the 6 mo after initial hospitalization[4]. Reports from the Medicare Payment Advisory Commission reported that Medicare expenditures for potentially preventable re-hospitalizations may be as high as $12 billion a year[5]. Public reports from Medicare data reported by Ross *et al*[6] revealed that all-cause 30-d readmission rates after HF hospitalization have shown no improvement over the past several years with rates of 23.0% in 2004, 23.3% in 2005, and 22.9% in 2006, indicating that this persistent public health problem must be addressed more aggressively. In this article, we aim to discuss the predictors of re-hospitalization in patients with chronic HF, with the hope that providers will better be able to identify their patients who are at highest risk of repeat hospitalization, and customize their care accordingly.

PREDICTORS OF HEART FAILURE HOSPITAL READMISSIONS

Numerous studies have been conducted in order to identify factors associated with readmission of HF patients. In order to identify such relevant studies, we performed a key-word literature search using the PubMed database. Examples of key words used were "heart failure", "heart failure readmission", "heart failure hospitalization", "predictors of heart failure". Only English citations were searched and reviewed through 2011. We found that with the vast and diverse HF population as well as the differences in study characteristics, many predictors have been identified, however not all factors have been consistently found to be predictors among all studies. Several groups of investigators have presented statistical models and risk scores in order to determine patient risk of readmission after HF hospitalization[7-11]. Identifying predictors among HF patients will help physicians to improve risk stratification and to determine the optimal post discharge plan for preventing readmission. Many predictors of readmission have been recognized and can be organized into (1) clinical parameters; (2) serum biomarkers; (3) hemodynamic parameters; and (4) psychosocial factors.

Clinical parameters

Patients with chronic HF may present to the hospital with various symptoms that represent volume overload and/or hypoperfusion. One study found several clinical predictors of early re-hospitalization (within 30 d) including angina, lower systolic blood pressure, and more extensive edema, while clinical predictors of later (within 90 d) of re-hospitalization included pulmonary rales, high jugular venous pressure, depressive symptoms and old age[12]. Coronary heart disease and prior pacemaker implantation were also predictors of 90-d readmission[12]. Implantable cardioverter-defibrillator (ICD) insertion and ICD firing has also been found by several groups to be a predictor of re-hospitalization[13,14]. The Multicenter Automatic Defibrillator Implantation Trial Ⅱ randomized control trial also found atrial fibrillation and diabetes to be predictors of HF re-hospitalization as well as a prolonged QT interval, and elevated heart rate[13]. Female sex and age have also been found to be predictors of re-hospitalization[15,16]. Muzzarelli *et al*[12] highlighted that patients with chronic HF have significant comorbidities and demonstrated that 45% of re-hospitalization was secondary to non-cardiovascular conditions. According to a Medicare analysis reported by Aranda *et al*[17], HF accounted for 28% of all hospital readmissions in the 6-9 mo following the initial (index) HF hospitalization, followed by pneumonia and chronic obstructive pulmonary disease. Patients who were readmitted had more diabetes, peripheral vascular disease and stroke when compared with HF patients who were not readmitted after their index hospitalization[17]. These studies indicate that comorbid conditions may be significant predictors of repeat hospitalization of HF patients.

Several studies have shown that previous hospitalization is a powerful independent predictor of readmission[4,7,16-19]. One study from Japan showed that prior hospitalization was the strongest predictor of HF re-hospitalization in a mixed population of HF with preserved and depressed ejection fraction patients[16]. Medicare data reveals average initial HF hospitalization as 5.5 ± 5.4 d[17], although there exists some variation, longer hospital stays were commonly described as more than 7 d. Increased length of initial hospital stay has been shown to be a predictor of future readmission[4,17,18]. Both length of hospital stay and repeat hospitalization worsened prognosis and increased risk of mortality[20,21]. Findings from the CHARM program reported that the risk of dying increased with each additional HF hospitalization[20]. After discharge from a second or third hospitalization there was an associated 30% cumulative incremental risk of death[20]. Reports also indicate that the risk of death was highest in the immediate post-discharge period, with an estimated 6-fold excess risk in the first month after discharge compared to a 2-fold increased risk of death 2 years after discharge[20]. These reports not only highlight the morbidity and mortality associated with hospitalization but also suggest an important role for increased surveillance in the immediate post-discharge period.

The etiology of worsened prognosis with hospitalization itself has not been fully elucidated. Some attribute the worsened prognosis to the use of intravenous diuretics and catecholamine release[21], while others have proposed that hospitalization leads to deconditioning and decreased exercise tolerance, which have been associated with increased likelihood of re-hospitalization and poorer prognosis[22,23]. A recent prospective study among African American patients with acute decompensated HF revealed that a distance of less than 200 m on the 6-min walk test was found to be a strong and independent predictor of mortality and HF re-hospitalization[24].

Serum biomarkers

Studies have shown that renal function worsens dur-

ing hospitalization[25,26]. Findings from Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) demonstrate that during hospitalization, 39% of HF patients had greater than 25% increase in blood urea nitrogen (BUN) and 12% had greater than a 25% decrease in estimated glomerular filtration rate (eGFR)[27]. Worsening renal function during hospitalization has been associated with increased HF hospitalizations[28,29]. Decreased renal function at the time of admission, defined as GFR less than 45 mL/min per 1.73 m^2, has also been found to be an independent predictor of re-hospitalization[16,30]. One study reported that at 1 year, 67% of HF patients with preserved renal function remained hospitalization-free compared with only 42.5% of HF patients with renal dysfunction[16].

Patients with HF suffer from vasomotor nephropathy, which can be defined as renal dysfunction that results from afferent/efferent arteriolar perfusion mismatch. In HF patients, this cardiorenal interaction at least in part occurs as a result of a distinct neurohormonal activation. While decreased renal function characterized by increased creatinine levels and lower eGFR have been associated with poor outcome[16,31,32], findings from the ACTIV in CHF study and OPTIME-CHF indicate that the BUN level is a better predictor of both mortality and re-hospitalization at 60 d[27,33]. BUN is likely a better prognostic indicator because it is more indicative of vasomotor nephropathy rather than an actual measure of renal dysfunction[34]. In HF, the renin-angiotensin-aldosterone system and sympathetic nervous system are activated, causing afferent arteriolar vasoconstriction and resulting reduction in renal perfusion pressure and increase in water reabsorption. This results in more filtered urea being absorbed along with water and sodium in the proximal tubule of the nephron. Vasopressin release also causes increased urea reabsorption in the distal nephron. These changes result in elevated BUN often independently of changes in GFR[35,36], as creatinine is secreted and not reabsorbed by the kidney.

Activation of the renin-angiotensin-aldosterone system may also explain the low serum sodium levels, defined as ≤ 134 mEq/L, seen in HF patients. The increased proximal tubular sodium and water retention that occurs as a compensatory mechanism for decreased renal perfusion, results in decreased sodium and water delivery to the collecting duct of the nephron, which, combined with resistance to the action of natriuretic peptides, results in impairment of free-water excretion and hyponatremia[35]. Increased vasopressin levels in HF contribute to the development of hyponatremia by increasing the number of aquaporin water channels in the collecting duct of the kidney[35]. While studies have shown that baseline admission serum sodium have been associated with poor prognosis and increased mortality[37], findings from the ESCAPE trial indicate that only persistent hyponatremia predicts both 6-mo mortality and re-hospitalization when compared to patients with corrected hyponatremia or normonatremia[38]. The poor prognosis may also be explained by the correlation of low serum sodium with ventricular ectopy[39], increased sudden death[40], and increased in-hospital mortality[41].

Anemia, defined by the World Health Organization as hemoglobin (Hb) < 12 g/dL in females and < 13 g/dL in males, is quite prevalent in HF patients. Studies have demonstrated varying prevalence, ranging from 4% to 50%[42,43]. Low serum Hb in HF patients is likely related to hemodilution secondary to volume overload. This patient population suffers from a high number of comorbid chronic diseases, which also likely contribute to the high prevalence of anemia. Findings from the OPTIME-CHF study, which reported a prevalence of anemia of 49%, show that, after adjusting for confounding variables associated with volume overload, anemia remained an independent predictor of death or re-hospitalization[42]. These investigators reported a 12% increase in the probability of death or re-hospitalization within 60 d for every 1 g/dL decrease in admission Hb[42].

B-type natriuretic peptide (BNP) is a commonly measured serum biomarker that is released from the cardiac ventricles and promotes vasodilatation, natriuresis, and diuresis in response to pressure and volume overload[44]. BNP has been used to help distinguish between cardiac *vs* pulmonary etiologies of dyspnea as well as to act as a guide for therapy in patients with chronic HF. Predischarge BNP has been shown by numerous studies to be a predictor of readmission[19,44-46].

Cardiac troponin T has also been used as a prognostic cardiac biomarker as it represents cardiomyocyte injury. In patients with HF, cardiac troponins are often found to be detectable, and elevated values have been associated with poor prognosis in both ambulatory and hospitalized patients[47-49], and have also been found to be independent predictors of readmission[45].

Cystatin, which is a serum marker for renal function has been shown to be an independent predictor of HF readmission[45]. Serum cystatin C concentrations have been shown to correlate with serum creatinine and eGFR[45]. Reports show that this marker predicts prognosis better than creatinine and the Modification of Diet in Renal Disease equation in HF patients[45,50], perhaps because this serum marker appears to be independent of age, sex and muscle mass and is able to detect early renal dysfunction. Reports have shown that HF patients with elevated cystatin C levels exhibited higher cardiac event rates compared with patients with normal cystatin C levels, even in patients with normal serum creatinine[45,51].

Several studies have assessed multiple cardiac biomarkers simultaneously in order to gain complementary prognostic information that could be used to improve risk stratification of HF patients. A recent prospective study incorporated NT-pro BNP, cardiac troponin T and cystatin C and, after multivariate regression analysis, found that independent and complementary prognostic information was gained[45]. A significant gradual in-

creased risk of mortality and/or readmission was reported as the number of elevated biomarkers increased[45]. The prognostic value of the multi-marker approach was found to be more powerful that the single-marker approach[45]. Another recent prospective study evaluated the incremental usefulness of multiple conventional biomarkers that have been known to have prognostic value in HF patients including elevated BNP, uric acid, high sensitivity C-reactive protein, decreased levels of serum sodium and Hb, and renal insufficiency[52]. Patients were given 1 point for each abnormal biomarker, then organized into 3 strata according to multi-marker score. Patients in the high strata (5-7 abnormal biomarkers) were found to have significantly higher rates of re-hospitalization than those in the low strata (0-3 abnormal biomarkers). After multivariate Cox proportional hazard regression analysis, only multimarker score was found to be an independent predictor of cardiac death or re-hospitalization among all the variables[52]. These findings suggest that the multi-marker approach may be a simple, objective way to improve risk stratification of HF patients for the prediction of readmission.

Hemodynamic predictors

HF patients commonly are readmitted with signs and symptoms of volume overload. While clinical parameters and laboratory findings are useful, these values are not always specific thus several studies have sought to investigate more accurate ways to determine volume status in an effort to prevent premature hospital discharges and reduce readmissions. Invasive measurements of right heart pressures and pulmonary capillary wedge pressures are gold standard methods of determining intravascular volume status but are not always practical for most patients. Conventional echocardiographic parameters that are measured in HF are left ventricular ejection fraction (LVEF) and mitral flow, which is an index of left ventricular filling pressure. LVEF has been an inconsistent predictor of readmission, with some studies suggesting patients with lower LVEF were more likely to be readmitted[19,53], while others showed no difference[46,54,55]. One novel study performed comprehensive 2-dimensional echo-Doppler examination prior to discharge and found that early diastolic velocity/tissue Doppler early diastolic mitral annular velocity (E/Ea), as a measure of left ventricular filling pressure, in combination with elevated pre-discharge BNP levels were powerful and incremental predictors of cardiac death or re-hospitalization for HF, to which the conventional predictors did not add[19]. Because of the cost and inconvenience of large full-featured ultrasound platforms, a more recent study evaluated the use of hand-carried ultrasound devices. In addition to pre-discharge BNP, this prospective study evaluated pre-discharge inferior vena cava size and collapsibility as these are known predictors of right atrial pressure[56]. Patients requiring repeat hospitalization were found to have abnormal inferior vena cava diameter (> 2.0 cm) and collapsibility indices (< 50%), 3 times and 1.5 times as often, respectively, when compared with patients who did not require hospitalization[46].

Most recently, investigators have been evaluating the effect of implantable hemodynamic devices that detect rising intracardiac pressures and therefore help predict future hospitalization, allowing the provider the chance to titrate diuretics and neurohormonal antagonists prior to clinical deterioration and hospitalization. Retrospective analysis of data from the COMPASS-HF trial which evaluated the impact of continuous monitoring of the Chronicle® device has shown a 36% prolongation in the time to first HF hospitalization[57]. Data from the HOMEOSTASIS trial, which evaluated the impact of the left atrial HeartPOD® device, found improvement in hemodynamics, symptoms, quality of life, as well as reduction in death and decompensated HF events, once left atrial-pressure guided therapy was initiated[58]. Results from the CHAMPION trial, which evaluated the effect of the CardioMEMS® Heart Sensor, demonstrated a 30% reduction in HF hospitalizations at 6 mo of follow-up[59]. The recent Partners HF study evaluated patients with cardiac resynchronization therapy implantable cardioverter-defibrillators which have been programmed with a diagnostic algorithm on an independent dataset[14]. They found that a positive diagnostic algorithm corresponded to a 5-fold increased risk of HF hospitalization within the following month[14]. These devices may be beneficial options in ambulatory HF patients with advanced symptoms that are refractory to optimal medical therapy and are at high risk for re-hospitalization as well as those with co-morbidities such as pulmonary disease or morbid obesity.

Psychosocial parameters

The morbidity associated with HF causes significant psychological distress, thought to be associated with changes in functional status, work status, and increased relationship strains[60-62]. Studies have demonstrated the prevalence of depression among HF patients to be quite high, ranging from 9%-60%, with large variation likely owing to the method of diagnosis, with prevalence estimates being lower with medical record diagnosis *vs* diagnosis via patient questionnaires[63]. One study showed that patients with major depression, diagnosed by initial screening with the Beck Depression Inventory followed by an interview using a modified National Institute of Mental Health Diagnostic Interview Schedule, had readmission rates 3 times that of patients with only mild depression or no depression[64]. Similarly, findings from OPTIMIZE-HF analysis show that depression was associated with increased mid (3-6 mo after discharge) and late (1 year after discharge) re-hospitalization, but not early re-hospitalization (within 3 mo of discharge), likely indicating that hospitalization immediately post discharge can be attributed to other factors[65]. In an effort to link depression with the increased morbidity associated with HF, investigators have demonstrated that depression increases neurohormonal activation, proinflammatory cy-

Table 1 Risk stratificatio

Predictors	Re-hospitalization risk		
	High risk	Intermediate risk	Low risk
Clinical parameters	3	2	1
Previous hospitalization			
Long hospital stay			
Age			
Sex			
Clinical symptoms			
Low blood pressure			
Comorbid conditions			
ICD, ICD firing			
QRS prolongation			
Elevated heart rate			
Serum biomarkers	3	2	1
Impaired renal function			
BUN			
Persistent hyponatremia			
Anemia			
Pre-discharge BNP			
Cardiac troponin T			
Cystatin			
Hemodynamic parameters	3	2	1
Pre-discharge elevated E/Ea			
IVC > 2.0 cm, collapsibility < 50%			
Abnormalities in implantable intracardiac device parameters			
Psychosocial parameters	3	2	1
Major depression			
Lack of emotional support			
Single marital status			
No occupation			
Race			
Education			
Poor follow-up			
Low income			
Intensity of multidisciplinary support/follow-up/therapy/education	3	2	1

All heart failure patients should be risk-stratified based upon the number of predictors present (those with the highest number of predictors would be considered high risk while those with the lowest number would be low risk). 3 denotes patients with the highest risk or re-hospitalization; 2 denotes an intermediate risk; 1 denotes the lowest risk. While all heart failure patients require comprehensive, multidisciplinary support, the intensity should be adjusted according to their risk of re-hospitalization. 3 denotes that high risk patients should receive the highest intensity of support; 1 denotes that patients with the lowest risk of re-hospitalization should receive lowest intensity of support; and 2 denotes that intermediate risk patients should get intermediate intensity support relative to the highest and lowest risk patients. Also etiology of re-hospitalization must be taken into consideration when customizing intervention to the individual patient. BNP: B-type natriuretic peptide; E/Ea: Early diastolic velocity/tissue Doppler early diastolic mitral annular velocity; IVC: Inferior vena cava; BUN: Blood urea nitrogen; ICD: Implantable cardioverter-defibrillator.

tokines, hypercoagulability, and arrhythmias all of which may contribute to decompensation[60,61,66,67]. Depression may also contribute to poor medical and dietary compliance as well as deconditioning. Hospitalized patients with HF and depression have also been found to experience longer hospital stays and were less likely to receive cardiac procedures, components of HF education, and referral to outpatient disease management programs[65]. These findings together suggest a role for closer depression screening as well as optimized therapy for depression in HF patients.

A strong social network has also been shown to reduce readmission rates in cardiac patients[68]. Among elderly patients with HF, the lack of emotional support was found to be a strong independent predictor of death or re-hospitalization[69]. Correspondingly, single marital status has also been shown to be an independent correlate of readmission[9]. Another independent predictor of readmission was no occupation[18], perhaps owing to increased physical activity and younger age of patients who have an occupation. A recent study also found that low income was an independent predictor or re-hospitalization of HF patients[70]. Several studies have shown that there are differences in HF statistics depending on race[15]. African Americans have a 50% higher incidence of HF compared with the general population and also have higher risk of initial and repeat hospitalization[71]. Poor follow-up was also found to be a strong predictor of HF readmission, with studies showing patients with less follow-up had a 5-fold increase in the risk of HF readmission[18]. These findings highlight the interplay between the social and medical factors that lead to re-admissions as well as indicate the need for establishing adequate social support and medical follow-up for HF patients.

We feel that all patients that are hospitalized for HF should be risk stratified as high risk, intermediate risk, or low risk of re-hospitalization according to the number of predictors of re-hospitalization they possess (Table 1). Also, the etiology of re-hospitalization must be evaluated, addressed, and taken into consideration when determining re-hospitalization risk[72]. Those patients who are at highest risk for re-hospitalization should be given the highest intensity of multidisciplinary support, education, follow-up, therapy, and access to resources, while those at lower risk should be given less (Table 1). This customized approach is crucial when resources are sparse and finances limited and may lead to reduced re-hospitalization of HF patients.

CONCLUSION

As investigators gain a more complete understanding of the pathophysiology of HF, more novel predictors of poor outcome are being identified. Extensive research has revealed a variety of promising predictors of re-hospitalization in HF patients including clinical parameters, serum biomarkers, novel hemodynamic approaches, and psychosocial factors. We hope the future holds the development of an effective, universally applicable risk stratification model utilizing the numerous predictors of readmission that have been identified. Perhaps better risk models will allow providers to better tailor comprehensive HF management programs, therapies, follow-up, and allocation of resources according to the needs of each individual patient and thus lead to reduced re-hospitalization of patients with chronic HF.

REFERENCES

1 **Dickstein K**, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Strömberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K. 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

2 **Lloyd-Jones D**, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, Ford E, Furie K, Go A, Greenlund K, Haase N, Hailpern S, Ho M, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott M, Meigs J, Mozaffarian D, Nichol G, O'Donnell C, Roger V, Rosamond W, Sacco R, Sorlie P, Stafford R, Steinberger J, Thom T, Wasserthiel-Smoller S, Wong N, Wylie-Rosett J, Hong Y. Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009; **119**: e21-181

3 **Lee WC**, Chavez YE, Baker T, Luce BR. Economic burden of heart failure: a summary of recent literature. *Heart Lung* 2004; **33**: 362-371

4 **Krumholz HM**, Parent EM, Tu N, Vaccarino V, Wang Y, Radford MJ, Hennen J. Readmission after hospitalization for congestive heart failure among Medicare beneficiaries. *Arch Intern Med* 1997; **157**: 99-104

5 A path to bundled payment around a rehospitalization. In: Report to the Congress: reforming the delivery system. Washington DC: Medicare Payment Advisory Commission, 2005: 83-103

6 **Ross JS**, Chen J, Lin Z, Bueno H, Curtis JP, Keenan PS, Normand SL, Schreiner G, Spertus JA, Vidán MT, Wang Y, Wang Y, Krumholz HM. Recent national trends in readmission rates after heart failure hospitalization. *Circ Heart Fail* 2010; **3**: 97-103

7 **Krumholz HM**, Chen YT, Wang Y, Vaccarino V, Radford MJ, Horwitz RI. Predictors of readmission among elderly survivors of admission with heart failure. *Am Heart J* 2000; **139**: 72-77

8 **Philbin EF**, DiSalvo TG. Prediction of hospital readmission for heart failure: development of a simple risk score based on administrative data *Rev Port Cardiol* 1999; **18**: 855-856

9 **Chin MH**, Goldman L. Correlates of early hospital readmission or death in patients with congestive heart failure. *Am J Cardiol* 1997; **79**: 1640-1644

10 **Felker GM**, Leimberger JD, Califf RM, Cuffe MS, Massie BM, Adams KF, Gheorghiade M, O'Connor CM. Risk stratification after hospitalization for decompensated heart failure. *J Card Fail* 2004; **10**: 460-466

11 **Yamokoski LM**, Hasselblad V, Moser DK, Binanay C, Conway GA, Glotzer JM, Hartman KA, Stevenson LW, Leier CV. Prediction of rehospitalization and death in severe heart failure by physicians and nurses of the ESCAPE trial. *J Card Fail* 2007; **13**: 8-13

12 **Muzzarelli S**, Leibundgut G, Maeder MT, Rickli H, Handschin R, Gutmann M, Jeker U, Buser P, Pfisterer M, Brunner-La Rocca HP. Predictors of early readmission or death in elderly patients with heart failure. *Am Heart J* 2010; **160**: 308-314

13 **Goldenberg I**, Moss AJ, Hall WJ, McNitt S, Zareba W, Andrews ML, Cannom DS. Causes and consequences of heart failure after prophylactic implantation of a defibrillator in the multicenter automatic defibrillator implantation trial II. *Circulation* 2006; **113**: 2810-2817

14 **Whellan DJ**, Ousdigian KT, Al-Khatib SM, Pu W, Sarkar S, Porter CB, Pavri BB, O'Connor CM. Combined heart failure device diagnostics identify patients at higher risk of subsequent heart failure hospitalizations: results from PARTNERS HF (Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients With Heart Failure) study. *J Am Coll Cardiol* 2010; **55**: 1803-1810

15 **Howie-Esquivel J**, Dracup K. Effect of gender, ethnicity, pulmonary disease, and symptom stability on rehospitalization in patients with heart failure. *Am J Cardiol* 2007; **100**: 1139-1144

16 **Komukai K**, Ogawa T, Yagi H, Date T, Sakamoto H, Kanzaki Y, Shibayama K, Hashimoto K, Inada K, Minai K, Ogawa K, Kosuga T, Kawai M, Hongo K, Taniguchi I, Yoshimura M. Decreased renal function as an independent predictor of rehospitalization for congestive heart failure. *Circ J* 2008; **72**: 1152-1157

17 **Aranda JM**, Johnson JW, Conti JB. Current trends in heart failure readmission rates: analysis of Medicare data. *Clin Cardiol* 2009; **32**: 47-52

18 **Tsuchihashi M**, Tsutsui H, Kodama K, Kasagi F, Setoguchi S, Mohr M, Kubota T, Takeshita A. Medical and socioenvironmental predictors of hospital readmission in patients with congestive heart failure. *Am Heart J* 2001; **142**: E7

19 **Dokainish H**, Zoghbi WA, Lakkis NM, Ambriz E, Patel R, Quinones MA, Nagueh SF. Incremental predictive power of B-type natriuretic peptide and tissue Doppler echocardiography in the prognosis of patients with congestive heart failure. *J Am Coll Cardiol* 2005; **45**: 1223-1226

20 **Solomon SD**, Dobson J, Pocock S, Skali H, McMurray JJ, Granger CB, Yusuf S, Swedberg K, Young JB, Michelson EL, Pfeffer MA. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. *Circulation* 2007; **116**: 1482-1487

21 **Setoguchi S**, Stevenson LW, Schneeweiss S. Repeated hospitalizations predict mortality in the community population with heart failure. *Am Heart J* 2007; **154**: 260-266

22 **Piepoli MF**, Davos C, Francis DP, Coats AJ. Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH). *BMJ* 2004; **328**: 189

23 **Belardinelli R**, Georgiou D, Cianci G, Purcaro A. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. *Circulation* 1999; **99**: 1173-1182

24 **Alahdab MT**, Mansour IN, Napan S, Stamos TD. Six minute walk test predicts long-term all-cause mortality and heart failure rehospitalization in African-American patients hospitalized with acute decompensated heart failure. *J Card Fail* 2009; **15**: 130-135

25 **Butler J**, Forman DE, Abraham WT, Gottlieb SS, Loh E, Massie BM, O'Connor CM, Rich MW, Stevenson LW, Wang Y, Young JB, Krumholz HM. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. *Am Heart J* 2004; **147**: 331-338

26 **Forman DE**, Butler J, Wang Y, Abraham WT, O'Connor CM, Gottlieb SS, Loh E, Massie BM, Rich MW, Stevenson LW, Young JB, Krumholz HM. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol* 2004; **43**: 61-67

27 **Klein L**, Massie BM, Leimberger JD, O'Connor CM, Piña IL, Adams KF, Califf RM, Gheorghiade M. Admission or changes in renal function during hospitalization for worsening heart failure predict postdischarge survival: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF). *Circ Heart Fail* 2008; **1**: 25-33

28 **Damman K**, Navis G, Voors AA, Asselbergs FW, Smilde

TD, Cleland JG, van Veldhuisen DJ, Hillege HL. Worsening renal function and prognosis in heart failure: systematic review and meta-analysis. *J Card Fail* 2007; **13**: 599-608
29 **Smith GL**, Lichtman JH, Bracken MB, Shlipak MG, Phillips CO, DiCapua P, Krumholz HM. Renal impairment and outcomes in heart failure: systematic review and meta-analysis. *J Am Coll Cardiol* 2006; **47**: 1987-1996
30 **McAlister FA**, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. *Circulation* 2004; **109**: 1004-1009
31 **Akhter MW**, Aronson D, Bitar F, Khan S, Singh H, Singh RP, Burger AJ, Elkayam U. Effect of elevated admission serum creatinine and its worsening on outcome in hospitalized patients with decompensated heart failure. *Am J Cardiol* 2004; **94**: 957-960
32 **Dries DL**, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. *J Am Coll Cardiol* 2000; **35**: 681-689
33 **Filippatos G**, Rossi J, Lloyd-Jones DM, Stough WG, Ouyang J, Shin DD, O'connor C, Adams KF, Orlandi C, Gheorghiade M. Prognostic value of blood urea nitrogen in patients hospitalized with worsening heart failure: insights from the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure (ACTIV in CHF) study. *J Card Fail* 2007; **13**: 360-364
34 **Aronson D**, Mittleman MA, Burger AJ. Elevated blood urea nitrogen level as a predictor of mortality in patients admitted for decompensated heart failure. *Am J Med* 2004; **116**: 466-473
35 **Schrier RW**, Abraham WT. Hormones and hemodynamics in heart failure. *N Engl J Med* 1999; **341**: 577-585
36 **Schrier RW**. Role of diminished renal function in cardiovascular mortality: marker or pathogenetic factor? *J Am Coll Cardiol* 2006; **47**: 1-8
37 **Klein L**, O'Connor CM, Leimberger JD, Gattis-Stough W, Piña IL, Felker GM, Adams KF, Califf RM, Gheorghiade M. Lower serum sodium is associated with increased short-term mortality in hospitalized patients with worsening heart failure: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study. *Circulation* 2005; **111**: 2454-2460
38 **Gheorghiade M**, Rossi JS, Cotts W, Shin DD, Hellkamp AS, Piña IL, Fonarow GC, DeMarco T, Pauly DF, Rogers J, DiSalvo TG, Butler J, Hare JM, Francis GS, Stough WG, O'Connor CM. Characterization and prognostic value of persistent hyponatremia in patients with severe heart failure in the ESCAPE Trial. *Arch Intern Med* 2007; **167**: 1998-2005
39 **Dargie HJ**, Cleland JG, Leckie BJ, Inglis CG, East BW, Ford I. Relation of arrhythmias and electrolyte abnormalities to survival in patients with severe chronic heart failure. *Circulation* 1987; **75**: IV98-I107
40 **Saxon LA**, Stevenson WG, Middlekauff HR, Fonarow G, Woo M, Moser D, Stevenson LW. Predicting death from progressive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1993; **72**: 62-65
41 **Chin MH**, Goldman L. Correlates of major complications or death in patients admitted to the hospital with congestive heart failure. *Arch Intern Med* 1996; **156**: 1814-1820
42 **Felker GM**, Gattis WA, Leimberger JD, Adams KF, Cuffe MS, Gheorghiade M, O'Connor CM. Usefulness of anemia as a predictor of death and rehospitalization in patients with decompensated heart failure. *Am J Cardiol* 2003; **92**: 625-628
43 **Al-Ahmad A**, Rand WM, Manjunath G, Konstam MA, Salem DN, Levey AS, Sarnak MJ. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2001; **38**: 955-962
44 **Dunlay SM**, Gerber Y, Weston SA, Killian JM, Redfield MM, Roger VL. Prognostic value of biomarkers in heart failure: application of novel methods in the community. *Circ Heart Fail* 2009; **2**: 393-400
45 **Manzano-Fernández S**, Boronat-Garcia M, Albaladejo-Otón MD, Pastor P, Garrido IP, Pastor-Pérez FJ, Martínez-Hernández P, Valdés M, Pascual-Figal DA. Complementary prognostic value of cystatin C, N-terminal pro-B-type natriuretic Peptide and cardiac troponin T in patients with acute heart failure. *Am J Cardiol* 2009; **103**: 1753-1759
46 **Goonewardena SN**, Gemignani A, Ronan A, Vasaiwala S, Blair J, Brennan JM, Shah DP, Spencer KT. Comparison of hand-carried ultrasound assessment of the inferior vena cava and N-terminal pro-brain natriuretic peptide for predicting readmission after hospitalization for acute decompensated heart failure. *JACC Cardiovasc Imaging* 2008; **1**: 595-601
47 **Roger VL**, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, Jacobsen SJ. Trends in heart failure incidence and survival in a community-based population. *JAMA* 2004; **292**: 344-350
48 **Levy D**, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK, Murabito JM, Vasan RS. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med* 2002; **347**: 1397-1402
49 **Fonarow GC**. Epidemiology and risk stratification in acute heart failure. *Am Heart J* 2008; **155**: 200-207
50 **Shlipak MG**, Katz R, Fried LF, Jenny NS, Stehman-Breen CO, Newman AB, Siscovick D, Psaty BM, Sarnak MJ. Cystatin-C and mortality in elderly persons with heart failure. *J Am Coll Cardiol* 2005; **45**: 268-271
51 **Arimoto T**, Takeishi Y, Niizeki T, Takabatake N, Okuyama H, Fukui A, Tachibana H, Nozaki N, Hirono O, Tsunoda Y, Miyashita T, Shishido T, Takahashi H, Koyama Y, Kubota I. Cystatin C, a novel measure of renal function, is an independent predictor of cardiac events in patients with heart failure. *J Card Fail* 2005; **11**: 595-601
52 **Niizeki T**, Takeishi Y, Kitahara T, Suzuki S, Sasaki T, Ishino M, Kubota I. Combination of conventional biomarkers for risk stratification in chronic heart failure. *J Cardiol* 2009; **53**: 179-187
53 **Gackowski A**, Isnard R, Golmard JL, Pousset F, Carayon A, Montalescot G, Hulot JS, Thomas D, Piwowarska W, Komajda M. Comparison of echocardiography and plasma B-type natriuretic peptide for monitoring the response to treatment in acute heart failure. *Eur Heart J* 2004; **25**: 1788-1796
54 **Cheng V**, Kazanagra R, Garcia A, Lenert L, Krishnaswamy P, Gardetto N, Clopton P, Maisel A. A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure: a pilot study. *J Am Coll Cardiol* 2001; **37**: 386-391
55 **Logeart D**, Thabut G, Jourdain P, Chavelas C, Beyne P, Beauvais F, Bouvier E, Solal AC. Predischarge B-type natriuretic peptide assay for identifying patients at high risk of re-admission after decompensated heart failure. *J Am Coll Cardiol* 2004; **43**: 635-641
56 **Nagueh SF**, Kopelen HA, Zoghbi WA. Relation of mean right atrial pressure to echocardiographic and Doppler parameters of right atrial and right ventricular function. *Circulation* 1996; **93**: 1160-1169
57 **Bourge RC**, Abraham WT, Adamson PB, Aaron MF, Aranda JM, Magalski A, Zile MR, Smith AL, Smart FW, O'Shaughnessy MA, Jessup ML, Sparks B, Naftel DL, Stevenson LW. Randomized controlled trial of an implantable continuous hemodynamic monitor in patients with advanced heart failure: the COMPASS-HF study. *J Am Coll Cardiol* 2008; **51**: 1073-1079
58 **Ritzema J**, Troughton R, Melton I, Crozier I, Doughty R, Krum H, Walton A, Adamson P, Kar S, Shah PK, Richards M, Eigler NL, Whiting JS, Haas GJ, Heywood JT, Frampton CM, Abraham WT. Physician-directed patient self-manage-

ment of left atrial pressure in advanced chronic heart failure. *Circulation* 2010; **121**: 1086-1095

59 **Abraham WT**, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, Strickland W, Neelagaru S, Raval N, Krueger S, Weiner S, Shavelle D, Jeffries B, Yadav JS. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet* 2011; **377**: 658-666

60 **MacMahon KM**, Lip GY. Psychological factors in heart failure: a review of the literature. *Arch Intern Med* 2002; **162**: 509-516

61 **Bosworth HB**, Steinhauser KE, Orr M, Lindquist JH, Grambow SC, Oddone EZ. Congestive heart failure patients' perceptions of quality of life: the integration of physical and psychosocial factors. *Aging Ment Health* 2004; **8**: 83-91

62 **Rozzini R**, Sabatini T, Frisoni GB, Trabucchi M. Depression and major outcomes in older patients with heart failure. *Arch Intern Med* 2002; **162**: 362-364

63 **Rutledge T**, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *J Am Coll Cardiol* 2006; **48**: 1527-1537

64 **Jiang W**, Alexander J, Christopher E, Kuchibhatla M, Gaulden LH, Cuffe MS, Blazing MA, Davenport C, Califf RM, Krishnan RR, O'Connor CM. Relationship of depression to increased risk of mortality and rehospitalization in patients with congestive heart failure. *Arch Intern Med* 2001; **161**: 1849-1856

65 **Albert NM**, Fonarow GC, Abraham WT, Gheorghiade M, Greenberg BH, Nunez E, O'Connor CM, Stough WG, Yancy CW, Young JB. Depression and clinical outcomes in heart failure: an OPTIMIZE-HF analysis. *Am J Med* 2009; **122**: 366-373

66 **Joynt KE**, Whellan DJ, O'connor CM. Why is depression bad for the failing heart? A review of the mechanistic relationship between depression and heart failure. *J Card Fail* 2004; **10**: 258-271

67 **Parissis JT**, Adamopoulos S, Rigas A, Kostakis G, Karatzas D, Venetsanou K, Kremastinos DT. Comparison of circulating proinflammatory cytokines and soluble apoptosis mediators in patients with chronic heart failure with versus without symptoms of depression. *Am J Cardiol* 2004; **94**: 1326-1328

68 **Berkman B**, Dumas S, Gastfriend J, Poplawski J, Southworthe M. Predicting hospital readmission of elderly cardiac patients. *Health Soc Work* 1987; **12**: 221-228

69 **Krumholz HM**, Butler J, Miller J, Vaccarino V, Williams CS, Mendes de Leon CF, Seeman TE, Kasl SV, Berkman LF. Prognostic importance of emotional support for elderly patients hospitalized with heart failure. *Circulation* 1998; **97**: 958-964

70 **Philbin EF**, Dec GW, Jenkins PL, DiSalvo TG. Socioeconomic status as an independent risk factor for hospital readmission for heart failure. *Am J Cardiol* 2001; **87**: 1367-1371

71 **Alexander M**, Grumbach K, Remy L, Rowell R, Massie BM. Congestive heart failure hospitalizations and survival in California: patterns according to race/ethnicity. *Am Heart J* 1999; **137**: 919-927

72 **Zaya M**, Phan A, Schwarz ER. The dilemma, causes and approaches to avoid recurrent hospital readmissions for patients with chronic heart failure. *Heart Fail Rev* 2011 Jun 5; Epub ahead of print

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BRIEF ARTICLE

Abdominal aortic aneurysm screening during transthoracic echocardiography: Cardiologist and vascular medicine specialist interpretation

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Abstract

AIM: To study the interobserver variability between a cardiologist and vascular medicine specialist in the screening of the abdominal aorta during transthoracic echocardiography (TTE).

METHODS: Consecutive patients, > 55 years of age, underwent abdominal aortic imaging following standard TTE. Two cardiologists and one vascular medicine specialist performed a blinded review of the images. Interobserver agreement of abdominal aortic size was determined by the correlation coefficient and paired *t* test. Interobserver reliability for each cardiologist was assessed using Bland-Altman plots.

RESULTS: Ninety patients were studied. The mean age of patients was 72 ± 10 years and 48% were male. The mean aortic diameter was 2.31 ± 0.50 cm and 5 patients (5.5%) had an abdominal aortic aneurysm (AAA). The additional time required for the abdominal aortic images was 4.4 ± 0.9 min per patient. Interobserver agreement between the 2 cardiologist interpreters and the vascular medicine specialist was excellent ($P > 0.05$ for all comparisons). On Bland-Altman analysis of interobserver reliability, the 95% lower and upper limits for measurement by the cardiologists were 84% and 124% of that of the vascular specialist.

CONCLUSION: The assessment of the abdominal aorta during a routine TTE performed by a cardiologist is accurate in comparison to that of a vascular medicine specialist. In selected patients undergoing TTE, the detection rate of AAA is significant. Additional time and effort required to perform imaging of the abdominal aorta after TTE is less than 5 min.

Key words: Abdominal aorta diameter; Screening; Transthoracic echocardiography

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INTRODUCTION

Abdominal aortic aneurysms (AAA) affect approximately

5% of elderly men at risk factors of cardiovascular disease[1,2]. Most AAA are not detectable on physical examination and remain silent until discovered during radiologic testing for other reasons or when complications occur. The recommendation for abdominal aortic ultrasound screening for AAA by the United States Preventive Services Task Force in select populations (men, age > 64 years, history of tobacco use) and by several Vascular Societies are supported by evidence demonstrating a reduction in aneurysm-related mortality[3-6]. However, AAA screening has not been widely adopted due to differing criteria for screening and uncertainty about costs and insurance coverage[7-10]. Transthoracic echocardiography (TTE) is frequently performed in patients with atherosclerotic vascular disease who may be at risk for the development of AAA. Although not commonly appreciated, the equipment used for TTE is similar to that used for abdominal aortic ultrasound, and imaging of the abdominal aorta can easily be performed as an adjunct to a standard echocardiographic examination.

The prevalence of AAA detected during TTE is estimated as 0.8%-6.5% depending on the demographic characteristics of the population screened[11-17]. Furthermore, the additional time required for AAA screening after TTE is generally less than 5 min. However, little data is available on who should interpret the study. Therefore, we designed a protocol for screening the abdominal aorta during TTE with the primary objective of comparing the interobserver variability between a cardiologist and vascular medicine specialist (i.e., the "gold standard").

MATERIALS AND METHODS

Study design

We prospectively evaluated 90 consecutive patients (age > 55 years old) scheduled for a clinically indicated TTE at the Cleveland Clinic Florida between November 1, 2005 and April 1, 2006. The study was approved by the Institutional Review Board. Clinical and demographic data were extracted from the electronic medical record. It was not known to the sonographer or the investigators at the time of the study whether the patient had a history of AAA. The same sonographer, licensed in both cardiac and vascular imaging performed all studies. Patient data were recorded with patient identifier numbers for confidentiality, and a database was secured with access only to the principal investigator and co-investigators.

Ancillary abdominal aortic ultrasound

An ancillary aortic ultrasound was performed in all patients after the routine TTE images were completed and immediately after the subcostal images were obtained. A standard ultrasound machine with harmonic imaging mode and cardiac presets was utilized (Philips iE33; Philips Medical System, Andover MA or Sequoia C512; Acuson, Mountain View, CA). The transducer probe and frequency were not changed. Images of the proximal, mid and distal abdominal aorta in transverse and longitudinal planes were obtained (Figure 1). Images were digitally clipped and stored for future review and labeled with a study number. In a subgroup of 19 patients, the time taken to perform the additional abdominal aortic images was recorded.

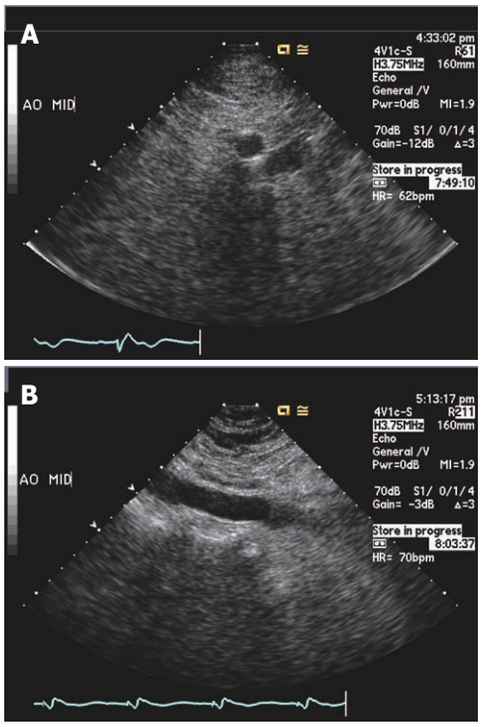

Figure 1 The mid abdominal aorta image obtained during transthoracic echocardiography. A: Transverse image; B: Longitudinal view.

Measurements

Two staff cardiologists (Novaro GM, Asher CR) and one vascular medicine specialist (Fernandez Jr BB) made off-line measurements of the abdominal aorta. Measurements were made in 10 patients (30 segments) using the outer-edge to outer edge convention of the proximal, mid and distal aortic transverse projection. The readers were blinded to patient information. For the purpose of the study, AAA was defined as a diameter $\geqslant$ 3 cm.

Statistical analysis

Comparisons were made between the cardiologists and vascular medicine specialist using paired *t* tests and Pearson's coefficient of correlation (*r*). Bland-Altman difference plots were constructed to evaluate interobserver agreement between each Cardiologist's interpretation compared with that of the vascular medicine specialist. These plots depict the mean of the aortic measurements on the x-axis, and the difference and 95% limit of agreement on the y-axis. $P < 0.05$ was considered statistically significant. We used SAS 9.1 (Cary, NC) and R 2.6.1 for all statistical analysis.

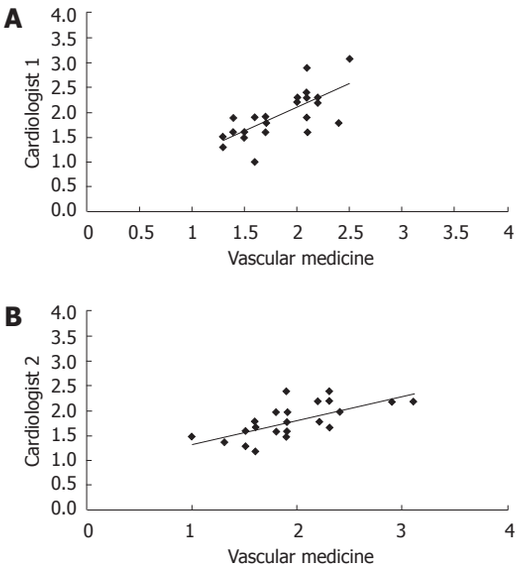

Figure 2 Linear regression analysis comparing aortic diameters measured in centimeters between cardiologists and a vascular medicine specialist. A: Between cardiologist 1 and vascular medicine specialist (r = 0.70); B: Between cardiologist 2 and vascular medicine specialist (r = 0.66).

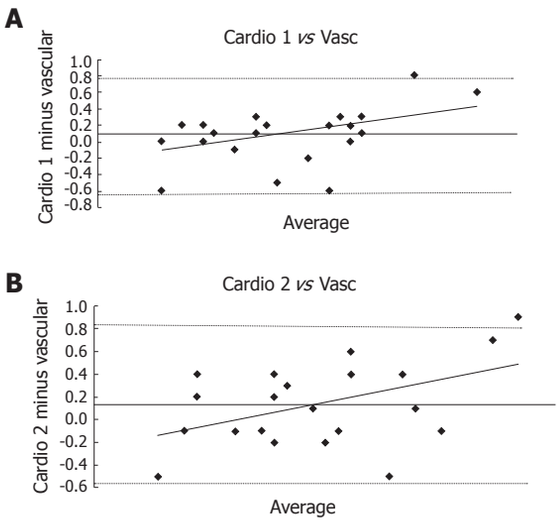

Figure 3 Bland-Altman plot of interobserver reliability showing 95% limits of agreement for measurement by cardiologists *vs* the vascular medicine specialist. The units on the y-axis are centimeters. A: Cardiologist 1 *vs* the vascular medicine specialist; B: Cardiologist 2 *vs* the vascular medicine specialist.

RESULTS

The study group comprised 90 patients, 43 men (48%), with an average age of 72 ± 10 years and body mass index (kg/m^2) of 26.4 ± 5.6, 57 (63%) hypertensive, 51 (57%) smokers, 29 (32%) with coronary artery disease and 16 (18%) with diabetes. All abdominal aorta segments (proximal, mid and distal) were visualized adequately for measurement in 77% of patients. The infrarenal segment was seen in 93%, with the distal abdominal aorta least often well seen. The mean aortic diameter was 2.31 ± 0.50 cm. Five patients (5.5%) had abdominal aortic aneurysms (defined as a diameter ⩾ 3.0 cm) ranging from 3.4 to 5.1 cm. Among the 5 patients with AAA, 2 were known and comparison computed tomography within 6 mo showed similar sizes (one patient had an AAA of 5.3 cm measured by computed tomography and of 5.1 cm measured by TTE and one patient had an AAA of 3.6 cm measured by computed tomography and of 3.9 cm measured by TTE). In 2 patients with small AAA, no confirmation was obtained due to advanced age and comorbid conditions. The additional time required for the abdominal aortic images was 4.4 ± 0.9 min per patient.

Interobserver agreement between the 2 cardiologist interpreters and the vascular medicine specialist was excellent (P > 0.05 for all comparisons; cardiologist 1 *vs* cardiologist 2, P = 0.531; cardiologist 1 *vs* vascular medicine, P = 0.728; cardiologist 2 *vs* vascular medicine, P = 0.432; Figure 2). Linear regression analysis showed a strong correlation at all 3 levels of aortic diameters. On Bland-Altman analysis of interobserver reliability, the 95% lower and upper limits for measurement by cardiologist 1 were 84.4% and 123.8% of that of the vascular medicine specialist and for cardiologist 2 they were 88.9% and 124.8% of that of the vascular medicine specialist. These differences were clinically insignificant with most measurements within 7 mm of the "gold standard" measurement (Figure 3).

DISCUSSION

In our study, we demonstrate that the interpretation of the abdominal aorta performed by a cardiologist during a TTE is accurate compared with that by a vascular medicine specialist. We found a similar prevalence of AAAs (5.5%) in a select group of patients 55 years of age and older as reported by previous studies and a limited (< 5 min) additional time required for abdominal imaging after a standard TTE.

AAA occur in 1-2% of the general population, most often in elderly man with a prior history of tobacco use or hypertension[1,2]. Current guidelines from the United States Preventive Services Task Force, Societies of Vascular Surgery and Medicine and Medicare recommend and support screening for AAA in selected groups of at-risk patients on the basis that screening is cost-effective and reduces aneurysm-related mortality[3-7]. Screening is underutilized because of the lack of consensus criteria and uncertain reimbursement[10]. Therefore, since the population of patients with cardiovascular disease undergoing TTE and those who are at risk for AAA have similar risk factors, abdominal aortic imaging during TTE is appealing and increasingly studied. Echocardiography continues to be a widely performed and reimbursable test particularly in patients with cardiovascular diseases such as coronary artery disease, hypertension, valvular heart disease and thoracic aortic disease.

The prevalence of AAA detected during supplementary imaging during TTE ranges from 0.8%-6.5%[11-17]. These studies have included both unselected and selected

populations of patients chosen for screening undergoing routine TTE examinations. Confirmatory testing has shown favorable accuracy for TTE screening compared with a gold standard test (computed tomography, magnetic resonance imaging or abdominal aortic ultrasound). Several studies have also demonstrated that imaging of the abdominal aorta can be performed with the same equipment and in limited time for most patients, usually less than 5 min[14,16].

Most studies on AAA screening during TTE do not identify the training of the sonographer performing the examinations or the background of the interpreting physician. Although, cardiologists routinely make measurements of the ascending aorta during TTE, they do no usually evaluate the abdominal aorta. Conventions for measuring the ascending aorta vary, including inner edge to inner edge and leading edge to leading edge techniques, differing from standard measurements made by vascular medicine specialists. In addition, the abdominal aorta has considerably more atheroma than the ascending aorta, which confounds measuring the outer edge of a blood vessel. Therefore, it is important to establish that cardiologists without vascular training can accurately measure the abdominal aorta and detect AAA. We utilized a sonographer with training in both cardiac and vascular imaging. It cannot be expected that a cardiac sonographer without vascular training can image the abdominal aorta with similar quality.

We did not systematically compare the measurement of the aorta made by TTE to a gold standard test and therefore sensitivity and specificity cannot be determined. Intraobserver variability was not performed.

The assessment of the abdominal aorta during a routine TTE performed by a cardiologist is accurate in comparison to that of a vascular medicine specialist. In selected patients that fit the criteria for AAA screening, TTE detection of AAA is significant. Additional time and effort required to perform imaging of the abdominal aorta after TTE is less than 5 min.

COMMENTS

Background

Most abdominal aorta aneurysm (AAA) are not detectable on physical examination and remain silent until discovered during radiologic testing for other reasons or when complications occur. Transthoracic echocardiography (TTE) is frequently performed in patients with atherosclerotic vascular disease who may be at risk for the development of AAA. Although not commonly appreciated, the equipment used for TTE is similar to that used for abdominal aortic ultrasound, and imaging of the abdominal aorta can easily be done as an adjunct to a standard echocardiographic examination. Furthermore, the additive time required for AAA screening after TTE is generally less than 5 min. However, little data is available on who should interpret the study.

Research frontiers

Most studies on AAA screening during TTE do not identify the training of the sonographer performing the examinations or the background of the interpreting physician. Although, cardiologists routinely make measurements of the ascending aorta during TTE they do no usually evaluate the abdominal aorta. Conventions for measuring the ascending aorta vary including inner edge to inner edge and leading edge to leading edge techniques, differing from standard measurements made by vascular medicine specialists. In addition, the abdominal aorta has considerably more atheroma than the ascending aorta which confounds measuring the outer edge of a blood vessel. Therefore, it is important to establish that cardiologists without vascular training can accurately measure the abdominal aorta and detect AAA. This research utilized a sonographer with training in both cardiac and vascular imaging.

Innovations and breakthroughs

In this study, authors investigated interobserver variability in the evaluation of TTE to assess the AAA. Two cardiologists and one specialist of vascular medicine were compared for their ability to accurately assess the TTE findings to diagnose AAA, since TTE is routinely used. They conclude that the diagnosis of AAA by routine TTE is as accurately done by a cardiologist as compared with a vascular medicine specialist.

Applications

The assessment of the abdominal aorta during a routine TTE performed by a cardiologist is accurate in comparison to a Vascular Medicine specialist. In selected patients that fit criteria for AAA screening, TTE detection of AAA is significant.

Peer review

This is an important work and it is well performed. The manuscript is well written and sufficiently well illustrated.

REFERENCES

1 **Bickerstaff LK**, Hollier LH, Van Peenen HJ, Melton LJ, Pairolero PC, Cherry KJ. Abdominal aortic aneurysms: the changing natural history. *J Vasc Surg* 1984; **1**: 6-12
2 **Scott RA**, Ashton HA, Kay DN. Abdominal aortic aneurysm in 4237 screened patients: prevalence, development and management over 6 years. *Br J Surg* 1991; **78**: 1122-1125
3 Screening for abdominal aortic aneurysm: recommendation statement. *Ann Intern Med* 2005; **142**: 198-202
4 **Kent KC**, Zwolak RM, Jaff MR, Hollenbeck ST, Thompson RW, Schermerhorn ML, Sicard GA, Riles TS, Cronenwett JL. Screening for abdominal aortic aneurysm: a consensus statement. *J Vasc Surg* 2004; **39**: 267-269
5 **Ashton HA**, Buxton MJ, Day NE, Kim LG, Marteau TM, Scott RA, Thompson SG, Walker NM. The Multicentre Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: a randomised controlled trial. *Lancet* 2002; **360**: 1531-1539
6 **Wilmink AB**, Quick CR, Hubbard CS, Day NE. Effectiveness and cost of screening for abdominal aortic aneurysm: results of a population screening program. *J Vasc Surg* 2003; **38**: 72-77
7 Multicentre aneurysm screening study (MASS): cost effectiveness analysis of screening for abdominal aortic aneurysms based on four year results from randomised controlled trial. *BMJ* 2002; **325**: 1135
8 **Lindholt JS**, Juul S, Fasting H, Henneberg EW. Hospital costs and benefits of screening for abdominal aortic aneurysms. Results from a randomised population screening trial. *Eur J Vasc Endovasc Surg* 2002; **23**: 55-60
9 **Wood S**. Proposed Medicare reimbursement for aortic aneurysm screening gains momentum and Congress support. Available from: URL: www.theheart.org [Heartwire > News]. Mar 29, 2004
10 **Federman DG**, Carbone VG, Kravetz JD, Kancir S, Kirsner RS, Bravata DM. Are screening guidelines for abdominal aortic aneurysms being implemented within a large VA primary health care system? *Postgrad Med* 2009; **121**: 132-135
11 **Schwartz KV**, Rashkow AM, Akella MS. Detection of Abdominal Aortic Aneurysm During Routine Echocardiography. *Echocardiography* 1996; **13**: 71-74
12 **Spittell PC**, Ehrsam JE, Anderson L, Seward JB. Screening for abdominal aortic aneurysm during transthoracic echocardiography in a hypertensive patient population. *J Am Soc Echocardiogr* 1997; **10**: 722-727
13 **Seelig MH**, Malouf YL, Klingler PJ, Oldenburg WA, Atkinson EJ. Clinical utility of routine screening for abdominal aortic aneurysm during echocardiography. *Vasa* 2000; **29**:

265-268
14 **Giaconi S**, Lattanzi F, Orsini E, Prosperi R, Tartarini G. Feasibility and accuracy of a rapid evaluation of the abdominal aorta during routine transthoracic echocardiography. *Ital Heart J Suppl* 2003; **4**: 332-336
15 **Bekkers SC**, Habets JH, Cheriex EC, Palmans A, Pinto Y, Hofstra L, Crijns HJ. Abdominal aortic aneurysm screening during transthoracic echocardiography in an unselected population. *J Am Soc Echocardiogr* 2005; **18**: 389-393
16 **Ruggiero M**, Lenti ML, Cavallari D, Dicillo CP, Mascolo AR, Musci S, Tota F, Sabato G, Tortorella C, Damiani D, Colonna P, Franchini G. Screening for abdominal aortic aneurysm during transthoracic echocardiography. A prospective study in 1202 consecutive patients at high risk: incidence, correlation with risk factors, feasibility, diagnostic accuracy, and increase in echocardiography time. *G Ital Cardiol* (Rome) 2006; **7**: 217-223
17 **Roshanali F**, Mandegar MH, Yousefnia MA, Mohammadi A, Baharvand B. Abdominal aorta screening during transthoracic echocardiography. *Echocardiography* 2007; **24**: 685-688

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BRIEF ARTICLE

Gender gap in acute coronary heart disease: Myth or reality?

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Abstract

AIM: To investigate potential gender differences in the prevalence of cardiovascular risk factors, cardiovascular disease (CVD) management, and prognosis in acute coronary syndrome (ACS).

METHODS: A systematic literature search was performed through Medline using pre-specified keywords. An additional search was performed, focusing specifically on randomized controlled clinical trials in relation to therapeutic intervention and prognosis. In total, 92 relevant articles were found.

RESULTS: Women with CVD tended to have more hypertension and diabetes at the time of presentation, whereas men were more likely to smoke. Coronary angiography and revascularization by percutaneous coronary intervention were performed more often in men. Women were at a greater risk of short-term mortality and complications after revascularization. Interestingly, women under 40 years presenting with ACS were at highest risk of cardiovascular death compared with men of the same age, irrespective of risk factors. This disadvantage disappeared in older age. The long-term mortality risk of ACS was similar in men and women, and even in favor of women.

CONCLUSION: Mortality rates are higher among young women with ACS, but this difference tends to disappear with age, and long-term prognosis is even better among older women.

Key words: Cardiovascular disease; Gender; Myocardial infarction; Coronary artery bypass grafting; Percutaneous coronary intervention; Postoperative complications; Mortality; Prognosis; Estrogens

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INTRODUCTION

Cardiovascular disease (CVD) is an important cause of death among both men and women. In women, CVD develops 7 to 10 years later than in men, potentially because of a protective effect of estrogens. However, CVD is the main cause of death among women and its occurrence narrows women's survival advantage over men[1]. In most parts of the world, the mortality rate has declined in the last 30 years, except for Eastern Europe and China[2]. In the

United States in 2007, 391 886 men died because of CVD, compared with 421 918 women[3], while 10 years previously the mortality rate of CVD in men was significantly higher in several countries[4]. Some studies have suggested gender differences in presentation and treatment of CVD and acute coronary syndrome (ACS), but there are many uncertainties and discrepancies between these studies[4,5]. Besides differences in presentation, women also seem to have different abnormalities with regard to electrocardiography and scintigraphy, compared with men[4]. The aim of this review is to provide an overview of what is known nowadays with respect to possible gender differences in cardiovascular risk factors, therapy and prognosis of ACS.

MATERIALS AND METHODS

A systematic literature search was performed through Medline using pre-specified keywords. The following keywords with synonyms were used for selecting relevant studies: CVD, coronary artery disease (CAD), ACS/event, ischemic heart disease, myocardial infarction (MI), gender, sex, women, men, differences, estrogens, hormone replacement therapy (HRT), coronary artery bypass surgery (CABG), percutaneous coronary intervention (PCI), revascularization, readmission, postoperative complications, outcome, and hospital mortality. Only studies that included both men and women were eligible for review. Of 2260 articles found, 199 articles appeared relevant after screening of the title and abstract. Furthermore, through a search of the references in the articles obtained by these keywords, 30 additional relevant articles were found.

A more focused exclusion of articles was then performed in relation to therapy and prognosis of ACS. Articles published before 2000 were excluded, because therapy, operative techniques and thereby prognosis have a high tendency to change over time. Selected articles included patients with ACS, unstable angina, acute MI, ST elevation MI (STEMI) and non-STEMI, and subsequently compared women with men. This provided 152 articles. After screening of the full text, a total of 92 articles were found to be relevant and valid.

RESULTS

Epidemiology

The prevalence of CVD increased with age and was higher among men. The prevalence of coronary heart disease (CHD) in the United States was 37.4% in men and 35.0% in women in 2008, with a mortality rate of 48.2% and 51.8% in men and women, respectively, in 2007. The prevalence of CHD in men and women of 20 years and older was 8.3% and 6.1%, respectively. When comparing different countries, France and Japan had the lowest prevalence of CHD for both men and women (Table 1)[3]. Although the incidence of CVD remained higher in men compared with women, figures of the last 30 years showed a declining incidence of CVD in men, while the incidence in women remained relatively stable. In North America CVD is the leading cause of hospital admission for both men and women. However, in women hospital stay tended to be longer and they experienced higher levels of pain, disability and discomfort, compared with men[2]. In the United States in 2007, one out of three deaths was caused by CVD and one out of six was due to CHD. However, the risk of heart disease in women often seemed to be underestimated, with CVD the major cause of death in women older than 75 years[3].

Table 1 Mortality rates of coronary heart disease per 100 000 population by gender[3]

Country	Year[1]	Men 35-74 yr	Women 35-74 yr
United States	2007	153.3	60.4
The Netherlands	2008	66.2	22.8
England/Wales	2007	138.3	43.4
Denmark	2006	84.8	32.4
France	2007	48.4	12.2
Germany	2006	125.3	38.2
Italy	2007	75.6	22.2
Russian Federation	2006	706.0	237.1
China	2000	108.3	71.9
Japan	2008	47.6	13.8
Australia	2006	88.9	26.8
New Zealand	2005	138.4	47.2
Argentina	1996	140.3	39.4

[1]Most recent year available.

Risk factors

The INTERHEART study identified nine different global risk factors for an acute MI, namely smoking, history of hypertension or diabetes, waist/hip ratio, dietary patterns, physical activity, consumption of alcohol, blood apolipoproteins, and psychosocial factors. Altogether, they could predict the risk of an acute MI as 90% in men and 94% in women. Although most of these classic risk factors were of equal clinical significance in both men and women[6], women who presented with ACS more often had hypertension[7-61], diabetes[7-10,12,13,15-17,20,22-25,27,28,30-32,34-36,38,39,41-43,45-47,49-54,57-66], hypercholesterolemia[7,9,10,13,15-17,21,22,26,28-30,35,36,50], and a history of angina[7,50], heart failure[7,45,47,52,53,59,60,63,64], and cerebrovascular events (CVA)[7,39,47,50,52,63,64] than men. On the other hand, men tended to smoke more[7-10,13-17,19-22,25,26,28,30,31,33-44,46,47,49-51,53-56,62,66] and were more likely to have a history of MI[7-9,14,16,18,19,21-23,28-32,36,39,41,43,45,47,51,53-56,58,64] and prior CABG[7-10,12,13,15-17,23,28,30,31,34,39,43,44,54,55,62-64,67] as shown in Table 2. Although women smoked less, the relative risk (RR) for developing a MI was 1.57 (95% CI: 1.25-1.97) among smoking women in comparison to smoking men and this increased risk was pronounced in women at younger age (< 55 years)[68]. The prevalence of fatal CHD was substantially higher in patients with diabetes, in comparison to patients without diabetes (5.4% *vs* 1.6%). Among women, this effect of diabetes on mortality was even stronger, with a RR of 3.50 (95% CI: 2.70-4.53), compared with a RR of 2.06 (95% CI: 1.81-2.34) among men with diabetes *vs* no diabetes[69]. Women with ACS more often had a family history of CAD[23,33,70]. However,

Table 2 Prevalence of cardiovascular risk factors and history of myocardial infarction and cardiac surgery stratified by gender

Author study/date	Design	Study population	Patients		Age (mean, yr)		*P*	Hypertension (%)		*P*	Diabetes (%)		*P*	Smoking (%)		*P*	History of MI (%)		*P*	History of cardiac surgery (%)			*P*
			Men	Women	Men	Women		Men	Women		Men	Women		Men	Women		Men	Women			Men	Women	
Reynolds *et al*[30] 2007	RCT	MI	12 498	4090	59.5	67.0	< 0.001	29.7	47.3	< 0.001	14.4	21.0	< 0.001	49.7	34.3	< 0.001	16.4	12.5	< 0.001	CABG	3.7	2.2	< 0.001
																				PCI	7.5	4.5	< 0.001
Moriel *et al*[28] 2005	Pros cohort	ACS	820	511	78	79	0.12	58	74	< 0.001	33	40	0.007	13	5	< 0.001	39	29	< 0.001	CABG	14	7	< 0.001
																				PCI	21	11	< 0.001
Herlitz *et al*[18] 2009	Retro cohort	AMI	835	588	72.7	79.2	< 0.0001	46	56	0.01	24	21	NS	22	16	NS	42	33	< 0.0001	CABG	10	7	0.06
																				PCI	7	5	0.32
Mehilli *et al*[54] 2002	Pros cohort	AMI	1435	502	60.7	70.3	< 0.001	61.0	72.9	< 0.001	18.0	25.3	< 0.001	43.1	25.9	< 0.001	22.1	16.3	0.001	CABG	6.1	3.4	0.02
																				PCI	10.7	7.6	0.04
Mueller *et al*[55] 2002	Pros cohort	MI	1033	417	64	68	0.01	60	72	0.01	19	23	0.15	33	21	0.01	37	24	0.01	CABG	17	6	0.01
																				PCI	24	21	0.20
Toumpoulis *et al*[34] 2006	Pros cohort	CABG	2598	1162	63.2	66.2	< 0.001	65.9	79.4	< 0.001	28.8	45.5	< 0.001	16.1	12.9	0.011	50.7	46.1	0.010	CABG	7.8	5.3	0.006
																				PCI	10.9	12.8	0.093
Dallongevillle *et al*[15] 2010	Pros cohort	ACS	6698	2268	62.2	65.8	< 0.0001	80.3	87.9	< 0.0001	33.6	38.4	0.009	19.3	11.0	< 0.0001	19.1	20.6	< 0.0001	CABG	20.4	17.2	< 0.0001
Anand *et al*[9] 2005	Trial	ACS	7726	4836	62.7	66.5	0.0001	53	68.8	0.0001	20.9	24.6	0.0001	76.4	37.4	0.0001	36.9	23.9	0.0001	CABG	13.3	6.8	0.0001
																				PCI	11.5	7.2	0.0001
Matsui *et al*[26] 2002	Retro cohort	AMI	346	136	62.9	70.4		44	54	0.047	25	33	0.078	60	19	0.001	18	15	0.517	CABG	1	1	0.556
																				PCI	12	4	0.016
Tizón-Marcos *et al*[33] 2009	RCT	PCI	1050	298	59.7	62.5		49	59	0.004	17	20	0.19	32	36	0.23	45	41	0.19	CABG	6.3	6.4	1.00
																				PCI	21	14	0.016
Reina *et al*[51] 2007	Pros cohort	AMI	4641	1568	64	71	< 0.01	41.0	61.1	< 0.01	25.5	41.2	< 0.01	53.6	15.7	< 0.01	16.6	13.0	< 0.01	Total	7.2	12.0	< 0.01
Thompson *et al*[53] 2006	Pros cohort	PCI	807	359	61.7	67.7	< 0.001	59.3	67.8	0.006	23.8	30.1	0.03	47.4	38.5	0.005	25.2	22.4	0.33	CABG	8.3	7.2	0.53
																				PCI	28.3	24.6	0.20
Lee *et al*[78] 2008	Pros cohort	STEMI	2954	1083	60.7	72.1	< 0.001	40.2	59.7	< 0.001	23.1	31.4	< 0.001	58.8	14.7	< 0.001	3.6	2.9	0.239	CABG	0.5	0.3	0.330
																				PCI	4.3	2.8	0.023
Jankowski *et al*[46] 2007	Pros cohort	CAD + PCI	738	187	57.5	60.6	< 0.001	72.6	87.8	< 0.001	14.5	21.3	< 0.05	13.6	6.4	< 0.01	63.2	66.0	NS	CABG	1.5	0.5	NS
																				PCI	8.8	8.5	NS
Duvernoy *et al*[43] 2010	Pros cohort	PCI	14848	7877	61.9	66.9	< 0.001	71.0	82.5	< 0.001	29.2	38.5	< 0.001	27.3	21.7	< 0.001	36.0	32.6	< 0.001	CABG	21.5	17.4	< 0.001
																				PCI	41.8	38.9	< 0.001
Lansky *et al*[22] 2005	RCT	AMI + PTCA	1520	562	57.0	66.0	< 0.001	29.0	59.3	< 0.001	14.0	25.7	< 0.001	45.3	37.4	0.001	15.7	8.4	< 0.001	PCI	12.7	7.1	< 0.001
Lansky *et al*[67] 2009	RCT	PCI	687	314	61.8	65.9	< 0.0001	72.7	81.5	0.0026	25.7	36.3	0.0007	24.0	21.2	0.3711	21.9	13.6	0.0022	Total	34.1	25.5	0.0066
De Luca *et al*[41] 2004	Pros cohort	STEMI	1195	353	59	66	< 0.001	24	39	< 0.001	8.7	15.8	< 0.001	52.1	42.7	0.002	11.6	7.1	0.014	CABG	2.1	1.7	NS
																				PCI	5.3	1.7	0.004
De Luca *et al*[42] 2010	Trail	STEMI	1283	379	59	67	< 0.001	39.1	52.5	< 0.001	15.3	22.4	< 0.001	56	36.9	< 0.001	9.2	7.7	0.35	Total	7.7	7.6	0.93
Bufe *et al*[62] 2010	Pros cohort	STEMI + PCI	376	124	58	65	< 0.001	66	54.8	0.055	11.2	24.2	< 0.001	67.3	40.3	< 0.001	11.7	8.9	0.479	CABG	5.6	0.8	0.046
																				PCI	5.6	4.0	0.658
Carrabba *et al*[40] 2004	Pros cohort	STEMI	627	293	67.7	76.3	0.001	45.3	60.1	< 0.001	22.7	25.3	0.385	34.1	14.3	< 0.001	17.2	14.7	0.331	CABG	2.6	1.0	0.129
																				PCI	5.9	2.1	0.010

Lawesson *et al*[24] 2010	Retro cohort	STEMI aged < 46	1748	384	40.8	40.4	0.14	13.9	21.7	< 0.001	12.4	18.5	0.002	58.0	63.9	0.04	6.6	5.2	0.30	CABG PCI	0.8 2.5	0.3 1.9	0.25 0.46
Berger *et al*[10] 2006	Pros cohort	PCI	2953	1331	61.9	66.8	< 0.001	66	78	< 0.001	22	36	< 0.001	15	10	< 0.001	36	33	0.08	CABG PCI	19 26	14 24	0.001 0.137
Chiu *et al*[13] 2004	Pros cohort	PCI	12 738	5301	62.3	66.5	< 0.001	58	71	< 0.001	24	34	< 0.001	21	20	0.01	43	42	0.29	CABG PCI	30 6	21 4	< 0.001 < 0.001
Koch *et al*[20] 2003	Pros cohort	CABG	1588	460				51.7	70.2	0.0001	22.5	36.3	0.0001	71.5	49.6	0.0001	14.3	10.7	0.044	CABG PCI	14.4 15.4	7.0 16.3	0.0001 0.6249
Setoguchi *et al*[31] 2008	Pros cohort	AMI	317	1308	80	82	< 0.001	71	80	0.001	33	39	0.03	15	10	0.01	52	37	< 0.001	CABG PCI	18 13	13 9	0.03 0.02

MI: Myocardial infarction; AMI: Acute myocardial Infarction; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; ACS: Acute coronary syndrome; STEMI: ST elevation MI; CAD: Coronary artery disease; NS: Not significant.

a family history of premature CAD was not a risk factor overall for in-hospital mortality[71]. The cardiovascular risk burden tended to be higher in women aged younger than 46 years, compared with men of the same age. Of all patients younger than 46 years presenting with ACS, 78.5% and 25.3% of women, respectively, had one or more than one risk factor for ACS, compared with 71.8% and 17.2%, respectively, among men ($P = 0.008$ and $P < 0.001$, respectively)[24]. Peirera *et al*[72] studied differences in hypertension between men and women as an important risk factor for CVD. Apart from the fact that women received treatment more often, they also had a greater awareness of the risk of hypertension for CVD. In both developing and developed countries, awareness, control and treatment of hypertension was significantly higher in women, compared with men. On the other hand, women were categorized at high-risk of CVD in risk assessment programs if a history of diabetes, stroke or chronic kidney disease was present[73], and all these conditions were generally more prevalent in women, compared with men, as noted above.

Interventions

In the evaluation of CVD, coronary angiography (CAG) was less often performed in women than in men[9,11,18,30,44,49,60]. Age might be an important confounding factor in this regard, because women present with an ACS 10 years later than men, and CAGs were less likely to be performed in the elderly[28]. Age was found to be a predictor for undergoing PCI, with an odds ratio (OR) of 0.98 (95% CI: 0.97-0.98) for each additional year[51,60,74]. Nevertheless, even after adjustment for age[18] and other cardiovascular risk factors[9,11], women with ACS were still less likely to have CAG or PCI[45,47,49] (OR, 0.70; 95% CI: 0.64-0.76)[75]. In men and women younger than 46 years, no differences were seen in the number of performed angiograms[24]. In ACS patients who underwent CAG, an equal number of men and women received a PCI afterwards[18,30,60,66]. In STEMI patients, results were inconsistent. Some studies found no significant differences in the number of CAGs and PCIs performed after adjustment for age[40,44,50,51], while Radovanovic *et al* found that women with both STEMI and non-STEMI underwent primary PCI less often (30.9% and 22.0%, respectively) compared with men (40.3% and 30.9%, respectively). This difference persisted after adjustment for cardiovascular risk factors (OR, 0.70) and after adjustment for age alone (OR, 0.71; 95% CI: 0.63-0.80)[58,74].

The mortality rate for ACS was highest among female patients who did not undergo a CAG; 12.9% *vs* 4.7% in those who underwent a CAG, compared with 5.6% and 2.9%, respectively, in men[30]. A higher mortality rate among women compared with men was also reported in patients who suffered a STEMI. A possible explanation may be the higher rate of comorbidity in women and a greater delay between onset of complaints and arrival at the emergency department compared with men. At 6 mo follow-up, no significant differences in mortality were present[28].

Several studies compared the coronary anatomy of men and women presenting with ACS. In general, women tended to have a smaller diameter of coronary arteries, in proportion with the lower body surface area, and this was associated with a higher mortality rate[13,16,20,22,34,36,43,53,75,76]. Women more often had one-vessel disease[8,19,23,24,34,43,52,62,67] and less often three-vessel disease[8,9,19,23-25,34,43,55,66,67] as shown in Table 3. Multiple vessel disease was associated with a higher mortality rate[77]. In addition, women with ACS had less extensive obstructive CAD, whereas men not only had more lesions, but also lesions of greater length and complexity[23]. Nevertheless, among patients who underwent PCI no differences were seen between men and women in the number of stents placed; 69% *vs* 66%[19] and 77% *vs* 77%[10]. Furthermore, no differences were found in length or diameter of the stents placed, nor in success rate of the performed PCI[25,41,43,46,48,53,56,57,59,78]. It remains uncertain whether women would benefit as much as men from early invasive strategy in the case of an ACS, because the power of the different studies was limited[14,21].

Table 3 Extent of coronary artery disease stratified by gender

Author study/date	Design	Study population	Patients		Age (mean, yr)		*P*	1 vessel disease (%)		*P*	3 vessel disease (%)		*P*
			Men	Women	Men	Women		Men	Women		Men	Women	
Lansky *et al*[22] 2005	RCT	AMI + PTCA	1520	562	57.0	66.0	< 0.001	51.1	51.6	NS	15.7	15.3	NS
Lansky *et al*[67] 2009	RCT	PCI	687	314	61.8	65.9	< 0.0001	61.3	74.2	< 0.0001	11.5	4.5	0.0002
Tizón-Marcos *et al*[33] 2009	RCT	PCI	1050	298	59.7	62.5		58	65	0.066	9.8	7.4	0.066
Hirakawa *et al*[19] 2007	Pros cohort	AMI	2048	566	62.92	71.08	< 0.01	60.1	56.0	< 0.05	34.8[1]	40.1[1]	< 0.05
Mueller *et al*[55] 2002	Pros cohort	MI	1033	417	64	68	0.01	24	26	0.45	42	29	0.01
Duvernoy *et al*[43] 2010	Pros cohort	PCI	14 848	7877	61.9	66.9	< 0.001	49.4	55.0	< 0.001	22.8	18.0	< 0.001
Liu *et al*[25] 2008	Pros cohort	STEMI + PCI	143	116	68.1	68.7	0.61	14.7	10.3	0.29	48.2	61.2	0.03
Jibran *et al*[81] 2010	Retro cohort	ACS + PCI	331	137	60.7	66.1	< 0.00001	41.1	48.9	0.3	22.7	12.4	0.3
De Luca *et al*[41] 2004	Pros cohort	STEMI	1195	353	59	66	< 0.001	47.9	43.8	NS	20.7	22.3	NS
Bufe *et al*[62] 2010	Pros cohort	STEMI + PCI	376	124	58	65	< 0.001	48.1	54.0	0.031	24.2	21.8	0.667
Lawesson *et al*[24] 2010	Retro cohort	STEMI aged < 46	1748	384	40.8	40.4	0.14	59.3	72.9	< 0.001	33.6	19.2	< 0.001
Berger *et al*[10] 2006	Pros cohort	PCI	2953	1331	61.9	66.8	< 0.001	48	50	0.195	18	17	NS
Toumpoulis *et al*[34] 2006	Pros cohort	CABG	2598	1162	63.2	66.2	< 0.001	4.6	7.3	0.001	73.7	69.3	0.005
Tillmanns *et al*[32] 2005	Pros cohort	STEMI	513	178	60	66	< 0.0001	43	44	NS	57[1]	56[1]	NS
Vakili *et al*[57] 2001	Retro cohort	PTCA first MI	727	317	59	65	< 0.005	56	59	NS	15	12	NS

[1]More than single vessel disease. MI: Myocardial infarction; CABG: Coronary artery bypass grafting; STEMI: ST elevation MI; NS: Not significant.

Table 4 Percentage of performed revascularizations stratified by gender

Author study/date	Design	Study population	Patients		Age (mean, yr)		*P*	CABG (%)		*P*	PCI (%)		*P*
			Men	Women	Men	Women		Men	Women		Men	Women	
Reynolds *et al*[30] 2007	RCT	MI	12 498	4090	59.5	67.0	< 0.001	3.4	3.1	0.45	27.4	23.6	< 0.01
Matsui *et al*[26] 2002	Retro cohort	AMI	346	136	62.9	70.4	0.01	4	7	0.179	95	84	0.001
Moriel *et al*[28] 2005	Pros cohort	ACS	820	511	78	79	0.12	7	6	0.47	32	28	0.06
Herlitz *et al*[18] 2009	Retro cohort	AMI	835	588	72.7	79.2	< 0.0001	9	2	< 0.0001	15	7	NS
Setoguchi *et al*[31] 2008	Pros cohort	AMI	317	1308	80	82	< 0.001	3	3	0.73	10	12	0.40
Tillmanns *et al*[32] 2005	Pros cohort	STEMI	513	178	60	66	< 0.0001	3	2	NS	95.1	93.8	
Toumpoulis *et al*[34] 2006	Pros cohort	CABG	2598	1162	63.2	66.2	< 0.001	100	100		1.6	3.1	0.002
Berger *et al*[10] 2006	Pros cohort	PCI	2953	1331	61.9	66.8	< 0.001	0.1	0.0	0.179	100	100	
Alfredsson *et al*[11] 2007	Pros cohort	Unstable/NSTEMI	34020	19761	69	73	< 0.001	7	5		18	14	
Lagerqvist *et al*[21] 2001	RCT	AMI	1708	749	64	68	< 0.001	30	24		34	28	
SoS[37] 2004	RCT	Multivessel disease	782	206	60.6	64.7	< 0.001	50.1	52.4		49.9	47.6	
Singh *et al*[79] 2008	Retro cohort	PCI	7616	3365	64.7	69.4		0.8	0.8		100	100	
Liu *et al*[25] 2008	Pros cohort	STEMI + PCI	143	116	68.1	68.7	0.61				85.3	84.3	NS

MI: Myocardial infarction; CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention; ACS: Acute coronary syndrome; STEMI: ST elevation MI; NS: Not significant.

Table 5 Percentage of peri-procedural complications during index admission stratified by gender

Author study/date	Design	Study population	Patients		Age (mean, yr)		*P*	Complications < admission (%)			*P*
			Men	Women	Men	Women			Men	Women	
Lansky *et al*[22] 2005	RCT	AMI + PTCA	1520	562	57.0	66.0	< 0.001	MACE	3.2	6.4	0.002
								Bleeding	2.0	5.2	0.0003
Lansky *et al*[67] 2009	RCT	PCI	687	314	61.8	65.9	< 0.0001	MACE[1]	1.3	3.2	0.0766
								Vascular[1]	0.6	1.0	0.6844
								MI[1]	1.0	2.9	0.0526
Tizón-Marcos *et al*[33] 2009	RCT	PCI	1050	298	59.7	62.5	< 0.0001	MACE[1]	3.9	3.4	0.86
								Bleeding[1]	1.1	2.4	0.16
								MI[1]	3.5	3.0	0.86
Thompson *et al*[53] 2006	Pros cohort	PCI	807	359	61.7	67.7	< 0.0001	MACE	2.7	3.9	0.29
								Vascular	4.2	12.0	< 0.0001
Jibran *et al*[81] 2010	Retro cohort	ACS + PCI	331	137	60.7	66.1	< 0.0001	MACE[1]	3.9	2.9	0.8
								Access site[1]	1.5	6.2	0.02
								MI[1]	1.5	0.7	1.0
Duvernoy *et al*[43] 2010	Pros cohort	PCI	14 848	7877	61.9	66.9	< 0.001	MACE	4.48	5.19	< 0.001
								Vascular	1.02	3.34	< 0.001
								MI	1.60	1.66	0.70
Bufe *et al*[62] 2010	Pros cohort	STEMI + PCI	376	124	58	65	< 0.001	Shock	10.1	11.3	0.838
								Renal failure	1.3	1.6	0.835
Reynolds *et al*[30] 2007	RTC	MI	12 498	4090	59.5	67.0	< 0.001	CVA[1]	0.2	0.6	< 0.01
								Heart failure	4.0	6.7	< 0.001
								Re-MI	2.7	3.5	0.004
Matsui *et al*[26] 2002	Retro cohort	AMI	346	136	62.9	70.4		Heart failure	16	26	0.013
								Re-MI	5	6	0.568
Moriel *et al*[28] 2005	Pros cohort	ACS	820	511	78	79	0.12	CVA	2	1	0.79
								Heart failure	21	21	0.86
								Re-MI	15	14	0.61
Uva *et al*[35] 2009	RCT	CABG	1485	481	64.7	69.0	0.001	MACE	3.9	6.6	NS
								CVA	0.7	1.2	0.2
								MI	0.7	1.3	0.08
Herlitz *et al*[18] 2009	Retro cohort	AMI	835	588	72.7	79.2	< 0.0001	Re-MI	4	2	0.02
Toumpoulis *et al*[34] 2006	Pros cohort	CABG	2598	1162	63.2	66.2	< 0.001	CVA	2.8	4.2	NS
								Bleeding	1.8	1.5	0.592
								MI	0.6	0.7	0.657
Liu *et al*[25] 2008	Pros cohort	STEMI + PCI	143	116	68.1	68.7	0.61	MACE	4.2	6.0	0.50
Berger *et al*[10] 2006	Pros cohort	PCI	2953	1331	61.9	66.8	< 0.001	MACE	2.9	3.0	0.922
								CVA	0.1	0.2	0.905
								MI	1.6	1.7	NS
								Access site	0.0	0.3	0.018
Chiu *et al*[13] 2004	Pros cohort	PCI	12 738	5301	62.3	66.5	< 0.001	Transfusion	4	12	< 0.001
								Haematoma	5	6	0.568
Setoguchi *et al*[31] 2008	Pros cohort	AMI	317	1308	80	82	< 0.001	CVA	3	4	0.57
Singh *et al*[79] 2008	Retro cohort	PCI	7616	3365	64.7	69.4	0.48	CVA	0.5	0.9	0.29
								MI	1.1	1.4	0.44
Tillmanns *et al*[32] 2005	Pros cohort	STEMI	513	178	60	66	< 0.0001	Re-MI	3	2	NS

[1]After 30 d. MI: Myocardial infarction; CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention; ACS: Acute coronary syndrome; STEMI: ST elevation MI; NS: Not significant; CVA: Cerebrovascular accident; MACE: Major adverse cardiac events.

The proportion of men and women undergoing CABG was equal[10,11,26,28,30-32,37,79] as shown in Table 4. In women undergoing CABG, the internal mammary artery was used less often than in men. The usage of this artery was associated with a decrease in mortality after CABG[16]. Furthermore, women underwent surgery more commonly on an urgent basis than men[12,16,20,34,36,63,75].

Prognosis

Many discrepancies existed between the different studies investigating the prognosis of men and women with an ACS. Some studies showed that women had more complications during hospital admission compared with men[7,9,13,18,22,30,36,53,61,64,78,80], while others showed no differences[23,25,28,33-35,38,40,44,46,48,54,56-58,62,81] (Table 5). Particularly at younger ages, women tended to have a greater risk for cardiac events compared with men at the same age[64,82]. This difference disappeared in patients older than 65 years[82,83].

Many discrepancies existed in the short-term mortality rate of patients with ACS. Some studies revealed

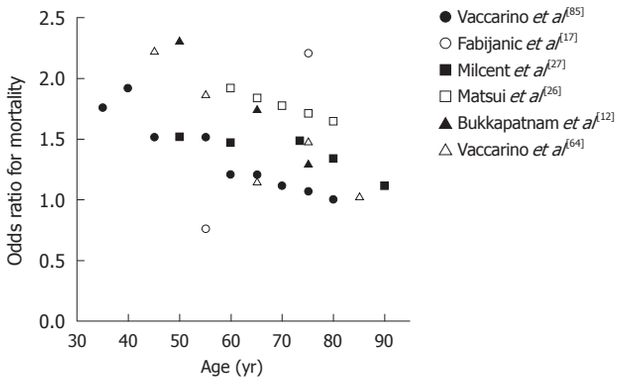

Figure 1 Gender differences in mortality after a myocardial infarction among different age categories. An odds ratio higher than one indicates an increased mortality after a myocardial infarction in women in comparison to men.

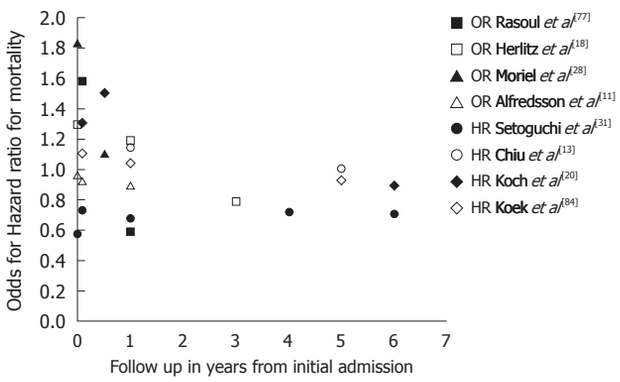

Figure 2 Gender differences in mortality risk in patients with coronary artery disease. An odds/hazard ratio higher than one indicates an increased mortality in women in comparison to men. OR: Odds ratio; HR: Hazard ratio.

a higher short-term mortality risk among women[7,12,17,22,24,27,28,35,36,57,64,78], while others did not[9-11,16,18,26,32-34,46,48,54,59,65,81] (Table 6). As discussed above, older age at presentation was an important confounding factor in this regard[29,39,54,58,75,77,84].

An important finding was that women with ACS had an increased mortality risk at younger ages compared with men of the same age[39,45,52,64]. Figure 1 illustrates the gender differences in mortality after a MI among different age categories. As shown in this Figure, the difference in mortality risk was reduced in older age[12,26,27,64,83,85].

Independent predictors of mortality were old age[20,29,39-41,49,50,54,59,75,77,84], with an OR of 1.06 (95% CI: 1.05-1.07) for each additional year[40,74], diabetes[20,24,29,49,54,62,74,77,84], heart failure[20,29,39], CAD[29], duration of ischemia, multiple vessel disease, history of MI, hypertension[41,77], CVA[77], anemia[20], cardiogenic shock, peripheral vascular disease[39], and ST-elevation[74]. Whether female gender can be considered as an independent risk factor remains unclear. Some studies claimed it could[24,27,51,55,57,75,77], but others showed no significant association after adjustment for risk factors[16,22,29,34,38-40,42-46,49,50,53,54,58,59,61,62,66,80,82,84]. After adjustment for several risk factors, female gender persisted as a risk factor for in-hospital mortality in ACS only for patients aged 51-60 years (OR, 1.78; 95% CI: 1.04-3.04)[74]. After adjustment for age and cardiovascular risk factors, the long-term mortality rate was equal for both men and women[13,20,22-24,29,31,32,40,41,44-46,48,49,58-60,62,65,79] or even in favor of women[10,31,34,42,54,55,63,77,84], as shown in Table 6 and Figure 2.

In the past 20-25 years the mortality rate at 30 d after PCI or CABG has declined equally in both men and women[76,79]. Data were inconsistent on the differences between men and women in the number of readmissions[86-88] and the number of second PCIs[10,18,21,23-26,28,33,35]. Interestingly, differences were found in the restenosis rates after PCI. In the first 6 mo after coronary stenting, restenosis was found in 28.9% of the women, compared with 33.9% of men (P = 0.01)[60,89]. After adjustment of gender, age and multiple risk factors, women showed a 23% risk reduction in angiographic restenosis compared with men (OR, 0.77; 95% CI: 0.63-0.93). Diabetes and small vessel size were identified as the most important predictors of restenosis. However, despite the higher prevalence of diabetes in women and smaller vessel size, women tended to have a lower incidence of restenosis[89]. Whether this can be explained by the protective mechanism of estrogens in women is still unknown. Estrogens were shown to have an antiinflammatory effect on the vessel wall and induce vasodilatation in coronary arteries[1]. However HRT in post-menopausal women did not lower the risk of mortality from CVD after adjustment for other risk factors[90-92]. HRT is therefore not recommended as primary or secondary prevention of CVD in women[73].

DISCUSSION

Women with CVD tended to have more cardiovascular risk factors such as diabetes, hypertension, and hypercholesterolemia when presenting with ACS. More importantly, women with an ACS at a young age had a higher mortality rate during index hospitalization and during 30 d of follow-up compared with men[24]. A possible explanation could be that pre-menopausal women enjoyed some protection against ACS from estrogens and those women who developed ACS despite this hormonal protection were more likely to have a higher cardiovascular risk factor burden leading to a more severe clinical presentation and worse outcome. None of the discussed studies adjusted for the use of hormone therapy among women. This might lead to information bias, because hormone therapy could influence the outcome of women with ACS. In the elderly, the long-term mortality rate was equal for both men and women, and even slightly in favor of women[13,20,22-24,29,31,32,79]. This small advantage in survival might possibly be due to the greater awareness and control of hypertension in women, compared with men, as hypertension is an important risk factor for CVD[72].

Study results were inconsistent, but it seems that an angiogram was less often performed in women than in men. This phenomenon could partly be explained by the higher average age of women as fewer diagnostic CAG

Table 6 Mortality rates in male and female patients with coronary artery disease at admission, at thirty days and after one-year of follow-up

Author study/ date	Design	Study population	Patients		Age (mean, yr)		*P*	Mortality < admission (%)		*P*	Mortality < 30 d (%)		*P*	Mortality < 1 year (%)		*P*
			Men	Women	Men	Women		Men	Women		Men	Women		Men	Women	
Lansky *et al*[22] 2005	RCT	AMI + PTCA	1520	562	57.0	66.0	< 0.001	1.0	3.4	0.0003	1.1	4.6	< 0.001	3.0	7.6	< 0.001
Singh *et al*[79] 2008	Retro cohort	PCI	7616	3365	64.7	69.4	0.48	1.8	2.5	0.38	2	3	0.25	4	4	0.490
Alfredsson *et al*[11] 2007	Pros cohort	Unstable/ NSTEMI	34 020	19 761	69	73	< 0.001	5	7		7	9		16	19	
Setoguchi *et al*[31] 2008	Pros cohort	AMI	317	1308	80	82	< 0.001	14.5	13.9		9.8	8.6		21.5 24.3[3]	18.2 25.0[3]	
Matsui *et al*[26] 2002	RCT	MI	346	136	62.9	70.4		4	4	0.851	4	10	0.013			
Uva *et al*[35] 2009	RCT	CABG	1485	481	64.7	69.0	0.001	0.8	2	0.01	1.2	2.3	0.09			
Toumpoulis *et al*[34] 2006	Pros cohort	CABG	2598	1162	63.2	66.2	< 0.001	2.7	2.9	0.639	3.7	3.9	0.747			
Moriel *et al*[28] 2005	Pros cohort	ACS	820	511	78	79	0.12	7	12	0.007				19[1]	21[1]	0.480
Herlitz *et al*[18] 2009	Retro cohort	AMI	835	588	72.7	79.2	< 0.0001	12	14	NS				18	22	0.040
Lawesson *et al*[24] 2010	Retro cohort	STEMI aged < 46	1748	384	40.8	40.4	0.14	1.0	2.9	0.005				2.2	3.7	0.010
Berger *et al*[10] 2006	Pros cohort	PCI	2953	1331	61.9	66.8	< 0.001	0.5	0.5	0.918				8.9[2]	10[2]	0.197
Liu *et al*[25] 2008	Pros cohort	STEMI + PCI	143	116	68.1	68.7	0.61	2.8	5.2					0	3.4	
Anand *et al*[9] 2005	Trial	ACS	7726	4836	62.7	66.5	0.0001				4.9	4.4	0.23[5]	11.1	9.7	0.040
Tizón-Marcos *et al*[33] 2009	RCT	PCI	1050	298	59.7	62.5	< 0.0001				0.2	0	1.00	0.8	1.0	0.720
Tillmanns *et al*[32] 2005	Pros cohort	STEMI	513	178	60	66	< 0.0001				6	6.2	NS	9 12[2]	12.5 18[2]	0.600 0.070
Lansky *et al*[67] 2009	RCT	PCI	687	314	61.8	65.9	< 0.0001				0	0		1.0	0.3	0.447
Koch *et al*[20] 2003	Pros cohort	CABG	1588	460							2.5	3.4	0.29	4.2[1] 15.8[4]	7.1[1] 19.6[4]	0.020 0.030
Lagerqvist *et al*[21] 2001	RCT	AMI	1708	749	64	68	< 0.001							5.7	7.2	NS
Chiu *et al*[13] 2004	Pros cohort	PCI	12 738	5301	62.3	66.5	< 0.001							5	7	< 0.001

[1]After 6 mo; [2]After 3 years; [3]After 4 years; [4]After 5 years; [5]Adjusted for age, diabetes, smoking, history of cardiovascular disease, increased cardiac enzymes, region and received therapy. MI: Myocardial infarction; CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention; ACS: Acute coronary syndrome; STEMI: ST elevation MI; NS: Not significant.

were performed in both male and female patients of older age. However, where a CAG was performed, women and men received the same therapy for similar vessel disease[9,11,18,24,28,30]. No differences between genders were found in the number of performed CABGs.

The current review has several limitations. Most included studies were retrospective in nature and performed a *post hoc* analysis by stratifying by gender. Included studies were hard to compare due to different patient characteristics; some studies included patients with STEMI, while others also included non-STEMI or patients with unstable angina. Another important limitation is the large difference in mean age between the included men and women across the different studies. Consequently, a comparison between the two genders was very difficult and no firm conclusion can be drawn. In addition, women are still underrepresented in most studies (inclusion rate < 30%). Due to the relatively low incidence of outcomes (e.g. complications, death), greater statistical power is needed to reach statistical significance. Therefore, large prospective observational cohort studies are needed in the future to provide sufficient power to answer the question whether female gender is an independent risk factor for cardiovascular morbidity and mortality.

CVD is the main cause of death among women. The prevalence of CVD is higher among men, but this gap narrows after the menopause. Women present approximately 10 years later with ACS than men, and at the time of presentation have a higher cardiovascular risk factor burden. Women are less often assigned to receive a CAG and subsequently less PCIs are performed. In addition, women have more complications and a higher short-term mortality after revascularization. Finally, mortality rates are higher among young women with ACS, but this difference tends to disappear with age, and long-term prognosis is even better among older women during long-term follow-up.

COMMENTS

Background

Cardiovascular disease (CVD) is the main cause of death among women and its occurrence narrows women's survival advantage over men. Many studies investigated gender differences in CVD, but results were inconsistent due to several limitations. Women were generally underrepresented in mainly retrospective studies and a true comparison between genders was difficult due to large differences in age at presentation between the included men and women.

Research frontiers

It is important to clarify possible differences between men and women in a large prospective cohort study, with equal numbers of male and female patients. Furthermore, as age is an important confounding factor, men and women of similar age should be compared. A systematic literature search was performed to assess the current state of knowledge on possible gender differences in CVD.

Innovations and breakthroughs

In the short-term, women with CVD seem to have a worse outcome compared with men. In particular, young women have an increased mortality risk, but this disadvantage disappears at older age. Moreover, long-term mortality is slightly better in elderly women compared with men.

Peer review

This is an interesting meta-analysis on putative gender differences in cardiovascular care.

REFERENCES

1 **Maas AH**, Appelman YE. Gender differences in coronary heart disease. *Neth Heart J* 2010; **18**: 598-603

2 **Pilote L**, Dasgupta K, Guru V, Humphries KH, McGrath J, Norris C, Rabi D, Tremblay J, Alamian A, Barnett T, Cox J, Ghali WA, Grace S, Hamet P, Ho T, Kirkland S, Lambert M, Libersan D, O'Loughlin J, Paradis G, Petrovich M, Tagalakis V. A comprehensive view of sex-specific issues related to cardiovascular disease. *CMAJ* 2007; **176**: S1-S44

3 **Roger VL**, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, de Simone G, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Greenlund KJ, Hailpern SM, Heit JA, Ho PM, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, McDermott MM, Meigs JB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Rosamond WD, Sorlie PD, Stafford RS, Turan TN, Turner MB, Wong ND, Wylie-Rosett J. Heart disease and stroke statistics--2011 update: a report from the American Heart Association. *Circulation* 2011; **123**: e18-e209

4 **Quyyumi AA**. Women and ischemic heart disease: pathophysiologic implications from the Women's Ischemia Syndrome Evaluation (WISE) Study and future research steps. *J Am Coll Cardiol* 2006; **47**: S66-S71

5 **Alexander KP**, Peterson ED. Medical and surgical management of coronary artery disease in women. *Am J Manag Care* 2001; **7**: 951-956

6 **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

7 **Hochman JS**, Tamis JE, Thompson TD, Weaver WD, White HD, Van de Werf F, Aylward P, Topol EJ, Califf RM. Sex, clinical presentation, and outcome in patients with acute coronary syndromes. Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIb Investigators. *N Engl J Med* 1999; **341**: 226-232

8 **Rosengren A**, Wallentin L, K Gitt A, Behar S, Battler A, Hasdai D. Sex, age, and clinical presentation of acute coronary syndromes. *Eur Heart J* 2004; **25**: 663-670

9 **Anand SS**, Xie CC, Mehta S, Franzosi MG, Joyner C, Chrolavicius S, Fox KA, Yusuf S. Differences in the management and prognosis of women and men who suffer from acute coronary syndromes. *J Am Coll Cardiol* 2005; **46**: 1845-1851

10 **Berger JS**, Sanborn TA, Sherman W, Brown DL. Influence of sex on in-hospital outcomes and long-term survival after contemporary percutaneous coronary intervention. *Am Heart J* 2006; **151**: 1026-1031

11 **Alfredsson J**, Stenestrand U, Wallentin L, Swahn E. Gender differences in management and outcome in non-ST-elevation acute coronary syndrome. *Heart* 2007; **93**: 1357-1362

12 **Bukkapatnam RN**, Yeo KK, Li Z, Amsterdam EA. Operative mortality in women and men undergoing coronary artery bypass grafting (from the California Coronary Artery Bypass Grafting Outcomes Reporting Program). *Am J Cardiol* 2010; **105**: 339-342

13 **Chiu JH**, Bhatt DL, Ziada KM, Chew DP, Whitlow PL, Lincoff AM, Ellis SG, Topol EJ. Impact of female sex on outcome after percutaneous coronary intervention. *Am Heart J* 2004; **148**: 998-1002

14 **Clayton TC**, Pocock SJ, Henderson RA, Poole-Wilson PA, Shaw TR, Knight R, Fox KA. Do men benefit more than women from an interventional strategy in patients with unstable angina or non-ST-elevation myocardial infarction? The impact of gender in the RITA 3 trial. *Eur Heart J* 2004; **25**: 1641-1650

15 **Dallongevillle J**, De Bacquer D, Heidrich J, De Backer G, Prugger C, Kotseva K, Montaye M, Amouyel P. Gender

differences in the implementation of cardiovascular prevention measures after an acute coronary event. *Heart* 2010; **96**: 1744-1749
16 **Ennker IC**, Albert A, Pietrowski D, Bauer K, Ennker J, Florath I. Impact of gender on outcome after coronary artery bypass surgery. *Asian Cardiovasc Thorac Ann* 2009; **17**: 253-258
17 **Fabijanic D**, Culic V, Bozic I, Miric D, Stipic SS, Radic M, Vucinovic Z. Gender differences in in-hospital mortality and mechanisms of death after the first acute myocardial infarction. *Ann Saudi Med* 2006; **26**: 455-460
18 **Herlitz J**, Dellborg M, Karlsson T, Evander MH, Hartford M, Perers E, Caidahl K. Treatment and outcome in acute myocardial infarction in a community in relation to gender. *Int J Cardiol* 2009; **135**: 315-322
19 **Hirakawa Y**, Masuda Y, Kuzuya M, Iguchi A, Kimata T, Uemura K. Impact of gender on in-hospital mortality of patients with acute myocardial infarction undergoing percutaneous coronary intervention: an evaluation of the TAMIS-II data. *Intern Med* 2007; **46**: 363-366
20 **Koch CG**, Weng YS, Zhou SX, Savino JS, Mathew JP, Hsu PH, Saidman LJ, Mangano DT. Prevalence of risk factors, and not gender per se, determines short- and long-term survival after coronary artery bypass surgery. *J Cardiothorac Vasc Anesth* 2003; **17**: 585-593
21 **Lagerqvist B**, Säfström K, Ståhle E, Wallentin L, Swahn E. Is early invasive treatment of unstable coronary artery disease equally effective for both women and men? FRISC II Study Group Investigators. *J Am Coll Cardiol* 2001; **38**: 41-48
22 **Lansky AJ**, Pietras C, Costa RA, Tsuchiya Y, Brodie BR, Cox DA, Aymong ED, Stuckey TD, Garcia E, Tcheng JE, Mehran R, Negoita M, Fahy M, Cristea E, Turco M, Leon MB, Grines CL, Stone GW. Gender differences in outcomes after primary angioplasty versus primary stenting with and without abciximab for acute myocardial infarction: results of the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. *Circulation* 2005; **111**: 1611-1618
23 **Lansky AJ**, Mehran R, Cristea E, Parise H, Feit F, Ohman EM, White HD, Alexander KP, Bertrand ME, Desmet W, Hamon M, Stone GW. Impact of gender and antithrombin strategy on early and late clinical outcomes in patients with non-ST-elevation acute coronary syndromes (from the ACUITY trial). *Am J Cardiol* 2009; **103**: 1196-1203
24 **Lawesson SS**, Stenestrand U, Lagerqvist B, Wallentin L, Swahn E. Gender perspective on risk factors, coronary lesions and long-term outcome in young patients with ST-elevation myocardial infarction. *Heart* 2010; **96**: 453-459
25 **Liu Y**, Wang LF, Yang XF, Ge YG, Wang HG, Xu L, Li WM, Ni ZH, Xia K, Chi YH, Li Q, Zhang DP, Wu XQ, Sun H, Guo ZS. Gender differences in efficacy of primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction. *Chin Med J* (Engl) 2008; **121**: 2374-2378
26 **Matsui K**, Fukui T, Hira K, Sobashima A, Okamatsu S, Hayashida N, Tanaka S, Nobuyoshi M. Impact of sex and its interaction with age on the management of and outcome for patients with acute myocardial infarction in 4 Japanese hospitals. *Am Heart J* 2002; **144**: 101-107
27 **Milcent C**, Dormont B, Durand-Zaleski I, Steg PG. **Gender** differences in hospital mortality and use of percutaneous coronary intervention in acute myocardial infarction: microsimulation analysis of the 1999 nationwide French hospitals database. *Circulation* 2007; **115**: 833-839
28 **Moriel M**, Behar S, Tzivoni D, Hod H, Boyko V, Gottlieb S. Management and outcomes of elderly women and men with acute coronary syndromes in 2000 and 2002. *Arch Intern Med* 2005; **165**: 1521-1526
29 **Pearte CA**, Furberg CD, O'Meara ES, Psaty BM, Kuller L, Powe NR, Manolio T. Characteristics and baseline clinical predictors of future fatal versus nonfatal coronary heart disease events in older adults: the Cardiovascular Health Study. *Circulation* 2006; **113**: 2177-2185
30 **Reynolds HR**, Farkouh ME, Lincoff AM, Hsu A, Swahn E, Sadowski ZP, White JA, Topol EJ, Hochman JS. Impact of female sex on death and bleeding after fibrinolytic treatment of myocardial infarction in GUSTO V. *Arch Intern Med* 2007; **167**: 2054-2060
31 **Setoguchi S**, Solomon DH, Levin R, Winkelmayer WC. Gender differences in the management and prognosis of myocardial infarction among patients & gt; or = 65 years of age. *Am J Cardiol* 2008; **101**: 1531-1536
32 **Tillmanns H**, Waas W, Voss R, Grempels E, Hölschermann H, Haberbosch W, Waldecker B. Gender differences in the outcome of cardiac interventions. *Herz* 2005; **30**: 375-389
33 **Tizón-Marcos H**, Bertrand OF, Rodés-Cabau J, Larose E, Gaudreault V, Bagur R, Gleeton O, Courtis J, Roy L, Poirier P, Costerousse O, De Larochellière R. Impact of female gender and transradial coronary stenting with maximal antiplatelet therapy on bleeding and ischemic outcomes. *Am Heart J* 2009; **157**: 740-745
34 **Toumpoulis IK**, Anagnostopoulos CE, Balaram SK, Rokkas CK, Swistel DG, Ashton RC, DeRose JJ. Assessment of independent predictors for long-term mortality between women and men after coronary artery bypass grafting: are women different from men? *J Thorac Cardiovasc Surg* 2006; **131**: 343-351
35 **Uva MS**, Freitas S, Pedro A, Matias F, Mesquita A, Bau J, Pinho J, Fernandes J, Magalhães MP. **Off-pump coronary** artery bypass surgery in women. *Rev Port Cardiol* 2009; **28**: 813-824
36 **Woods SE**, Noble G, Smith JM, Hasselfeld K. The influence of gender in patients undergoing coronary artery bypass graft surgery: an eight-year prospective hospitalized cohort study. *J Am Coll Surg* 2003; **196**: 428-434
37 **Zhang Z**, Weintraub WS, Mahoney EM, Spertus JA, Booth J, Nugara F, Stables RH, Vaccarino V. Relative benefit of coronary artery bypass grafting versus stent-assisted percutaneous coronary intervention for angina pectoris and multivessel coronary disease in women versus men (one-year results from the Stent or Surgery trial). *Am J Cardiol* 2004; **93**: 404-409
38 **Antoniucci D**, Valenti R, Moschi G, Migliorini A, Trapani M, Santoro GM, Bolognese L, Dovellini EV. **Sex-based** differences in clinical and angiographic outcomes after primary angioplasty or stenting for acute myocardial infarction. *Am J Cardiol* 2001; **87**: 289-293
39 **Berger JS**, Brown DL. Gender-age interaction in early mortality following primary angioplasty for acute myocardial infarction. *Am J Cardiol* 2006; **98**: 1140-1143
40 **Carrabba N**, Santoro GM, Balzi D, Barchielli A, Marchionni N, Fabiani P, Landini C, Scarti L, Santoro G, Valente S, Verdiani V, Buiatti E. In-hospital management and outcome in women with acute myocardial infarction (data from the AMI-Florence Registry). *Am J Cardiol* 2004; **94**: 1118-1123
41 **De Luca G**, Suryapranata H, Dambrink JH, Ottervanger JP, van 't Hof AW, Zijlstra F, Hoorntje JC, Gosselink AT, de Boer MJ. Sex-related differences in outcome after ST-segment elevation myocardial infarction treated by primary angioplasty: data from the Zwolle Myocardial Infarction study. *Am Heart J* 2004; **148**: 852-856
42 **De Luca G**, Gibson CM, Gyöngyösi M, Zeymer U, Dudek D, Arntz HR, Bellandi F, Maioli M, Noc M, Zorman S, Gabriel HM, Emre A, Cutlip D, Rakowski T, Huber K, van't Hof AW. Gender-related differences in outcome after ST-segment elevation myocardial infarction treated by primary angioplasty and glycoprotein IIb-IIIa inhibitors: insights from the EGYPT cooperation. *J Thromb Thrombolysis* 2010; **30**: 342-346
43 **Duvernoy CS**, Smith DE, Manohar P, Schaefer A, Kline-Rogers E, Share D, McNamara R, Gurm HS, Moscucci M. Gender differences in adverse outcomes after contemporary percutaneous coronary intervention: an analysis from the Blue Cross Blue Shield of Michigan Cardiovascular Consor-

tium (BMC2) percutaneous coronary intervention registry. *Am Heart J* 2010; **159**: 677-683.e1
44 **Halvorsen S**, Eritsland J, Abdelnoor M, Holst Hansen C, Risøe C, Midtbø K, Bjørnerheim R, Mangschau A. Gender differences in management and outcome of acute myocardial infarctions treated in 2006-2007. *Cardiology* 2009; **114**: 83-88
45 **Heer T**, Schiele R, Schneider S, Gitt AK, Wienbergen H, Gottwik M, Gieseler U, Voigtländer T, Hauptmann KE, Wagner S, Senges J. Gender differences in acute myocardial infarction in the era of reperfusion (the MITRA registry). *Am J Cardiol* 2002; **89**: 511-517
46 **Jankowski P**, Kawecka-Jaszcz K, Czarnecka D, Bryniarski L, Brzozowska-Kiszka M, Kieć-Wilk B, Dymek G, Kopacz E, Królikowski T, Dudek D. Gender does not influence event-free survival in patients with ischaemic heart disease undergoing non-emergency coronary angiography. A single centre analysis. *Kardiol Pol* 2007; **65**: 475-484; discussion 485
47 **Jneid H**, Fonarow GC, Cannon CP, Hernandez AF, Palacios IF, Maree AO, Wells Q, Bozkurt B, Labresh KA, Liang L, Hong Y, Newby LK, Fletcher G, Peterson E, Wexler L. Sex differences in medical care and early death after acute myocardial infarction. *Circulation* 2008; **118**: 2803-2810
48 **Kralev S**, Hennig O, Lang S, Kälsch T, Borggrefe M, Dempfle CE, Süselbeck T. Sex-based differences in clinical and angiographic outcomes in patients with ST-elevation myocardial infarction treated with concomitant use of glycoprotein IIb/IIIa inhibitors. *Cardiol J* 2010; **17**: 580-586
49 **Lee LC**, Poh KK, Tang TP, Tan YL, Tee HW, Tan HC. The impact of gender on the outcomes of invasive versus conservative management of patients with non-ST-segment elevation myocardial infarction. *Ann Acad Med Singapore* 2010; **39**: 168-172
50 **Park JS**, Kim YJ, Shin DG, Jeong MH, Ahn YK, Chung WS, Seung KB, Kim CJ, Cho MC, Jang YS, Park SJ, Seong IW, Chae SC, Hur SH, Choi DH, Hong TJ. Gender differences in clinical features and in-hospital outcomes in ST-segment elevation acute myocardial infarction: from the Korean Acute Myocardial Infarction Registry (KAMIR) study. *Clin Cardiol* 2010; **33**: E1-E6
51 **Reina A**, Colmenero M, Aguayo de Hoyos E, Arós F, Martí H, Claramonte R, Cuñat J. Gender differences in management and outcome of patients with acute myocardial infarction. *Int J Cardiol* 2007; **116**: 389-395
52 **Srinivas VS**, Garg S, Negassa A, Bang JY, Monrad ES. Persistent sex difference in hospital outcome following percutaneous coronary intervention: results from the New York State reporting system. *J Invasive Cardiol* 2007; **19**: 265-268
53 **Thompson CA**, Kaplan AV, Friedman BJ, Jayne JE, Gerling BR, Niles NW, Hettleman BD, Robb JF. Gender-based differences of percutaneous coronary intervention in the drug-eluting stent era. *Catheter Cardiovasc Interv* 2006; **67**: 25-31
54 **Mehilli J**, Kastrati A, Dirschinger J, Pache J, Seyfarth M, Blasini R, Hall D, Neumann FJ, Schömig A. Sex-based analysis of outcome in patients with acute myocardial infarction treated predominantly with percutaneous coronary intervention. *JAMA* 2002; **287**: 210-215
55 **Mueller C**, Neumann FJ, Roskamm H, Buser P, Hodgson JM, Perruchoud AP, Buettner HJ. Women do have an improved long-term outcome after non-ST-elevation acute coronary syndromes treated very early and predominantly with percutaneous coronary intervention: a prospective study in 1,450 consecutive patients. *J Am Coll Cardiol* 2002; **40**: 245-250
56 **Trabattoni D**, Bartorelli AL, Montorsi P, Fabbiocchi F, Loaldi A, Galli S, Ravagnani P, Cozzi S, Grancini L, Liverani A, Leon ME, Robertson C, Boyle P. Comparison of outcomes in women and men treated with coronary stent implantation. *Catheter Cardiovasc Interv* 2003; **58**: 20-28
57 **Vakili BA**, Kaplan RC, Brown DL. Sex-based differences in early mortality of patients undergoing primary angioplasty for first acute myocardial infarction. *Circulation* 2001; **104**: 3034-3038
58 **Heer T**, Gitt AK, Juenger C, Schiele R, Wienbergen H, Towae F, Gottwitz M, Zahn R, Zeymer U, Senges J. Gender differences in acute non-ST-segment elevation myocardial infarction. *Am J Cardiol* 2006; **98**: 160-166
59 **Cantor WJ**, Miller JM, Hellkamp AS, Kramer JM, Peterson ED, Hasselblad V, Zidar JP, Newby LK, Ohman EM. Role of target vessel size and body surface area on outcomes after percutaneous coronary interventions in women. *Am Heart J* 2002; **144**: 297-302
60 **Chang WC**, Kaul P, Westerhout CM, Graham MM, Fu Y, Chowdhury T, Armstrong PW. Impact of sex on long-term mortality from acute myocardial infarction vs unstable angina. *Arch Intern Med* 2003; **163**: 2476-2484
61 **Cheng CI**, Yeh KH, Chang HW, Yu TH, Chen YH, Chai HT, Yip HK. Comparison of baseline characteristics, clinical features, angiographic results, and early outcomes in men vs women with acute myocardial infarction undergoing primary coronary intervention. *Chest* 2004; **126**: 47-53
62 **Bufe A**, Wolfertz J, Dinh W, Bansemir L, Koehler T, Haltern G, Guelker H, Füth R, Scheffold T, Lankisch M. Gender-based differences in long-term outcome after ST-elevation myocardial infarction in patients treated with percutaneous coronary intervention. *J Womens Health* (Larchmt) 2010; **19**: 471-475
63 **Guru V**, Fremes SE, Austin PC, Blackstone EH, Tu JV. Gender differences in outcomes after hospital discharge from coronary artery bypass grafting. *Circulation* 2006; **113**: 507-516
64 **Vaccarino V**, Abramson JL, Veledar E, Weintraub WS. Sex differences in hospital mortality after coronary artery bypass surgery: evidence for a higher mortality in younger women. *Circulation* 2002; **105**: 1176-1181
65 **Lansky AJ**, Mehran R, Dangas G, Cristea E, Shirai K, Costa R, Costantini C, Tsuchiya Y, Carlier S, Mintz G, Cottin Y, Stone G, Moses J, Leon MB. Comparison of differences in outcome after percutaneous coronary intervention in men versus women & lt; 40 years of age. *Am J Cardiol* 2004; **93**: 916-919
66 **Woods SE**, Chandran P, Levin L. Does the patient's sex influence cardiovascular outcome after acute myocardial infarction? *J Fam Pract* 2002; **51**: 237-240
67 **Lansky AJ**, Ng VG, Mutlu H, Cristea E, Guiran JB, Midei M, Newman W, Sanz M, Sood P, Doostzadeh J, Su X, White R, Cao S, Sudhir K, Stone GW. Gender-based evaluation of the XIENCE V everolimus-eluting coronary stent system: clinical and angiographic results from the SPIRIT III randomized trial. *Catheter Cardiovasc Interv* 2009; **74**: 719-727
68 **Prescott E**, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. *BMJ* 1998; **316**: 1043-1047
69 **Huxley R**, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ* 2006; **332**: 73-78
70 **Chua TP**, Saia F, Bhardwaj V, Wright C, Clarke D, Hennessy M, Fox KM. Are there gender differences in patients presenting with unstable angina? *Int J Cardiol* 2000; **72**: 281-286
71 **Shaw LJ**, Shaw RE, Merz CN, Brindis RG, Klein LW, Nallamothu B, Douglas PS, Krone RJ, McKay CR, Block PC, Hewitt K, Weintraub WS, Peterson ED. Impact of ethnicity and gender differences on angiographic coronary artery disease prevalence and in-hospital mortality in the American College of Cardiology-National Cardiovascular Data Registry. *Circulation* 2008; **117**: 1787-1801
72 **Pereira M**, Lunet N, Azevedo A, Barros H. Differences in prevalence, awareness, treatment and control of hypertension between developing and developed countries. *J Hypertens* 2009; **27**: 963-975
73 **Mosca L**, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, Newby LK, Piña IL, Roger VL, Shaw LJ,

Zhao D, Beckie TM, Bushnell C, D'Armiento J, Kris-Etherton PM, Fang J, Ganiats TG, Gomes AS, Gracia CR, Haan CK, Jackson EA, Judelson DR, Kelepouris E, Lavie CJ, Moore A, Nussmeier NA, Ofili E, Oparil S, Ouyang P, Pinn VW, Sherif K, Smith SC, Sopko G, Chandra-Strobos N, Urbina EM, Vaccarino V, Wenger NK. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American Heart Association. *J Am Coll Cardiol* 2011; **57**: 1404-1423

74 **Radovanovic D**, Erne P, Urban P, Bertel O, Rickli H, Gaspoz JM. Gender differences in management and outcomes in patients with acute coronary syndromes: results on 20,290 patients from the AMIS Plus Registry. *Heart* 2007; **93**: 1369-1375

75 **Blankstein R**, Ward RP, Arnsdorf M, Jones B, Lou YB, Pine M. Female gender is an independent predictor of operative mortality after coronary artery bypass graft surgery: contemporary analysis of 31 Midwestern hospitals. *Circulation* 2005; **112**: I323-I327

76 **Humphries KH**, Gao M, Pu A, Lichtenstein S, Thompson CR. Significant improvement in short-term mortality in women undergoing coronary artery bypass surgery (1991 to 2004). *J Am Coll Cardiol* 2007; **49**: 1552-1558

77 **Rasoul S**, Ottervanger JP, de Boer MJ, Dambrink JH, Hoorntje JC, Marcel Gosselink AT, Zijlstra F, Suryapranata H, van 't Hof AW. Predictors of 30-day and 1-year mortality after primary percutaneous coronary intervention for ST-elevation myocardial infarction. *Coron Artery Dis* 2009; **20**: 415-421

78 **Lee KH**, Jeong MH, Ahn YK, Kim JH, Chae SC, Kim YJ, Hur SH, Seong IW, Hong TJ, Choi D, Cho MC, Kim CJ, Seung KB, Chung WS, Jang YS, Cho JG, Park SJ. Gender differences of success rate of percutaneous coronary intervention and short term cardiac events in Korea Acute Myocardial Infarction Registry. *Int J Cardiol* 2008; **130**: 227-234

79 **Singh M**, Rihal CS, Gersh BJ, Roger VL, Bell MR, Lennon RJ, Lerman A, Holmes DR. Mortality differences between men and women after percutaneous coronary interventions. A 25-year, single-center experience. *J Am Coll Cardiol* 2008; **51**: 2313-2320

80 **Akhter N**, Milford-Beland S, Roe MT, Piana RN, Kao J, Shroff A. Gender differences among patients with acute coronary syndromes undergoing percutaneous coronary intervention in the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). *Am Heart J* 2009; **157**: 141-148

81 **Jibran R**, Khan JA, Hoye A. Gender disparity in patients undergoing percutaneous coronary intervention for acute coronary syndromes - does it still exist in contemporary practice? *Ann Acad Med Singapore* 2010; **39**: 173-178

82 **Cartier R**, Bouchot O, El-Hamamsy I. Influence of sex and age on long-term survival in systematic off-pump coronary artery bypass surgery. *Eur J Cardiothorac Surg* 2008; **34**: 826-832

83 **Glaser R**, Selzer F, Jacobs AK, Laskey WK, Kelsey SF, Holper EM, Cohen HA, Abbott JD, Wilensky RL. Effect of gender on prognosis following percutaneous coronary intervention for stable angina pectoris and acute coronary syndromes. *Am J Cardiol* 2006; **98**: 1446-1450

84 **Koek HL**, de Bruin A, Gast F, Gevers E, Kardaun JW, Reitsma JB, Grobbee DE, Bots ML. Short- and long-term prognosis after acute myocardial infarction in men versus women. *Am J Cardiol* 2006; **98**: 993-999

85 **Vaccarino V**, Krumholz HM, Yarzebski J, Gore JM, Goldberg RJ. Sex differences in 2-year mortality after hospital discharge for myocardial infarction. *Ann Intern Med* 2001; **134**: 173-181

86 **Hannan EL**, Racz MJ, Walford G, Ryan TJ, Isom OW, Bennett E, Jones RH. Predictors of readmission for complications of coronary artery bypass graft surgery. *JAMA* 2003; **290**: 773-780

87 **Stewart RD**, Campos CT, Jennings B, Lollis SS, Levitsky S, Lahey SJ. Predictors of 30-day hospital readmission after coronary artery bypass. *Ann Thorac Surg* 2000; **70**: 169-174

88 **Steuer J**, Blomqvist P, Granath F, Rydh B, Ekbom A, de Faire U, Ståhle E. Hospital readmission after coronary artery bypass grafting: are women doing worse? *Ann Thorac Surg* 2002; **73**: 1380-1386

89 **Mehilli J**, Kastrati A, Bollwein H, Dibra A, Schühlen H, Dirschinger J, Schömig A. Gender and restenosis after coronary artery stenting. *Eur Heart J* 2003; **24**: 1523-1530

90 **Hulley S**, Grady D, Bush T, Furberg C, Herrington D, Riggs B, Vittinghoff E. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA* 1998; **280**: 605-613

91 **Grady D**, Herrington D, Bittner V, Blumenthal R, Davidson M, Hlatky M, Hsia J, Hulley S, Herd A, Khan S, Newby LK, Waters D, Vittinghoff E, Wenger N. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). *JAMA* 2002; **288**: 49-57

92 **Hsia J**, Langer RD, Manson JE, Kuller L, Johnson KC, Hendrix SL, Pettinger M, Heckbert SR, Greep N, Crawford S, Eaton CB, Kostis JB, Caralis P, Prentice R. Conjugated equine estrogens and coronary heart disease: the Women's Health Initiative. *Arch Intern Med* 2006; **166**: 357-365

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CASE REPORT

Percutaneous panvascular intervention in an unusual case of extensive atherosclerotic disease

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Abstract

It is common to see patients with atherosclerotic coronary disease and peripheral arterial disease in routine clinical practice. One needs to have a comprehensive and integrated multi-speciality approach and panvascular revascularization in such patients. We report a 54-year-old diabetic hypertensive male with extensive atherosclerotic coronary and peripheral arterial disease, who presented with congestive heart failure, claudication of both lower limbs and mesenteric ischemia. He underwent successful percutaneous panvascular revascularization of coronary, renal, mesenteric, aorto-iliac and superficial femoral arteries. Long-term patency of all the stents was also documented.

Key words: Atherosclerosis; Aorto-iliac bifurcation; Coronary artery disease; Chronic mesenteric ischemia; Contrast induced nephropathy; C-reactive protein; Inferior mesenteric artery; Peripheral arterial disease; Stents

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INTRODUCTION

Atherosclerosis is a systemic disease, which can have varied clinical presentation with involvement of multiple vascular beds. It is common to come across patients with concomitant coronary artery disease (CAD) and peripheral arterial disease (PAD), in whom panvascular revascularization is required. As they are high-risk patients with poor clinical outcome, their management requires a comprehensive multi-specialty approach. Following improvement in technical skills and hardware for percutaneous interventions in recent years, more complex lesions with adverse clinical situations can undergo intervention by a cardiologist/vascular interventionist. We hereby report a case with CAD and PAD, who underwent successful complex coronary and multiple peripheral interventions for his symptomatic disease.

CASE REPORT

A 54-year-old hypertensive, diabetic male and chronic smoker presented in February 2008 with symptoms of dyspnea on exertion, New York Heart Association class Ⅲ for 1 year, orthopnea and paroxysmal nocturnal dyspnea for 1 mo, and 6-mo bilateral lower limb claudication on walking 50 m. There was no history of angina, syncope or lower limb ulceration/discoloration. A general physical examination revealed a blood pressure of 130/90 mmHg in the right upper limb, feeble bilateral

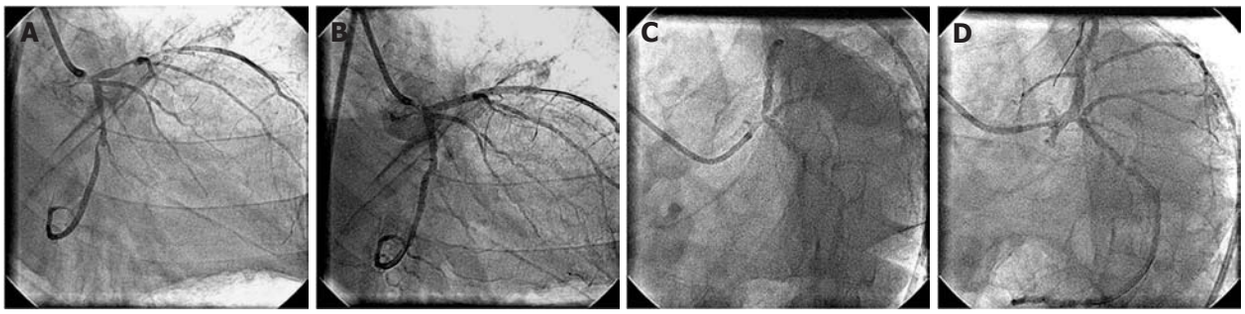

Figure 1 Coronary angiogram. A: 90% diffuse stenosis of proximal left anterior descending artery (LAD) and 90% tubular stenosis of the distal left circumflex artery (LCx); B: No residual stenosis following proximal LAD and distal LCx stenting; C: At 15 mo of follow-up, showing patent LAD and LCx stents. There is new 70% bifurcation stenosis of the left main coronary arterywith osteal LAD stenosis. The LCx ostium is normal without any stenosis; D: No residual stenosis and normal LCx ostium following left main coronary artery crossover stenting.

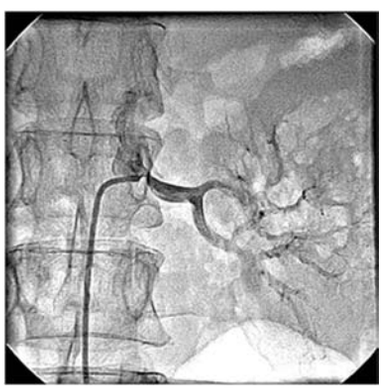

Figure 2 Left renal angiogram showing 75% osteal stenosis of renal artery.

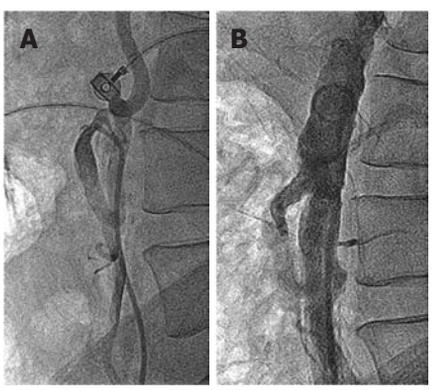

Figure 3 Inferior mesenteric artery angiogram. A: 50% osteal stenosis of the inferior mesenteric artery (IMA); B: Post-IMA osteal stenting with a 7 mm x 18 mm balloon-expandable stent, at 15 mo follow-up, showing no residual IMA stenosis.

femoral arterial pulse, dependent pitting edema of the feet, and raised jugular venous pressure. Systemic examination revealed a left ventricular third heart sound, bilateral crepitations in half of the basal lung fields. Ankle brachial pressure index (ABPI) was 0.54 on the right and 0.68 on the left side. Blood investigations revealed hemoglobin (Hb) 10.9 g/dL, urea 94 mg/dL, creatinine 1.9 mg/dL, and fasting blood sugar 250 mg/dL. The fasting lipid profile was total cholesterol 151 mg/dL, high density lipoprotein cholesterol (HDL) 38 mg/dL, low density lipoprotein cholesterol (LDL) 81 mg/dL, and triglycerides 137 mg/dL. Electrocardiography showed a poor R wave in V_1-V_4 chest leads, with the rest within normal limits. Two-dimensional echocardiography revealed global left ventricular hypokinesia, an ejection fraction of 0.30, mild tricuspid regurgitation, and an estimated pulmonary artery systolic pressure of 65 mmHg. Peripheral ultrasound Doppler revealed focal stenosis of the left superficial femoral artery (SFA) in the mid thigh.

After adequate decongestive therapy and glycemic control, the patient underwent contrast angiography of the coronary and peripheral vasculature. The coronary angiogram revealed 100% block of the proximal nondominant right coronary artery, 90% diffuse stenosis of the proximal left anterior descending artery (LAD) (Figure 1A), 90% tubular stenosis of the distal left circumflex artery (LCx) (Figure 1A), and a left dominant circulation. The left main coronary artery was normal and obtuse marginal-3 was occluded from its origin. Left ventricular end diastolic pressure was 50 mmHg. Peripheral angiography revealed 75% osteal stenosis of the left renal artery (Figure 2), 50% osteal stenosis of the right renal artery, a normal celiac trunk, 100% osteal block of the superior mesenteric artery (SMA), 50% osteal stenosis of the inferior mesenteric artery (IMA) (Figure 3A), diffuse narrowing of the infra-renal abdominal aorta, and more than 50% bilateral stenosis of the common iliac artery (right > left) (Figure 4A).

Following a detailed discussion about percutaneous/surgical revascularization for his extensive CAD and PAD, he gave written informed consent for percutaneous intervention. After a gap of a week, he underwent percutaneous intervention. Bilateral femoral arterial access was achieved with a 7 F sheath. The left coronary artery was cannulated with Judkins Left 3.5, 7 F guide catheter, and a 0.014 inch All Track Wire (ATW) (Cordis Corp., Miami, Florida) was inserted into the proximal LAD lesion. After pre-dilation with a 2.5 × 15 mm Sprinter balloon (Medtronic, Inc., Minneapolis, Minnesota), a sirolimus-eluting Cypher 3 × 33 mm stent (Cordis) was deployed. Then a 0.014 inch ATW wire (Cordis) was inserted into the distal LCx lesion, which was pre-dilated with 2.5 mm × 15 mm Sprinter balloon (Medtronic), and a Cypher 2.75 mm × 28 mm stent (Cordis) was deployed (Figure 1B). After coronary intervention, the left renal

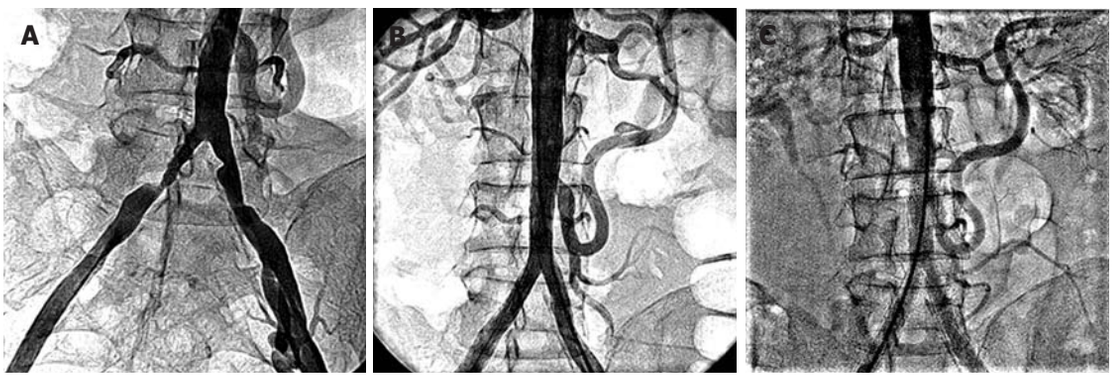

Figure 4 Abdominal aortogram. A: Bilateral common iliac artery stenosis; B: No residual stenosis following left renal and aorto-bilateral iliac artery stenting. A big inferior mesenteric artery collateral "arch of Riolan" supplies the occluded superior mesenteric artery; C: At 30 mo follow-up, showing patent left renal and aorto-bilateral iliac stents.

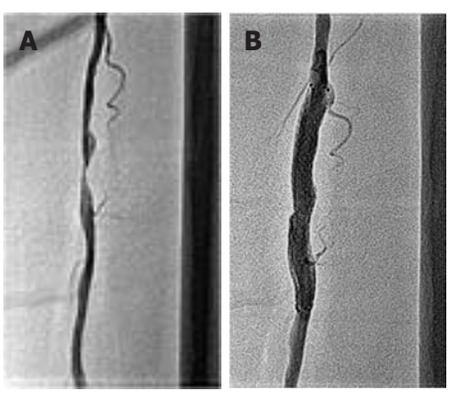

Figure 5 Left superficial femoral artery angiogram. A: At 3 mo follow-up, showing 90% discrete stenosis in the mid part; B: Following 7 mm x 60 mm self-expanding stent deployment, there is no residual stenosis.

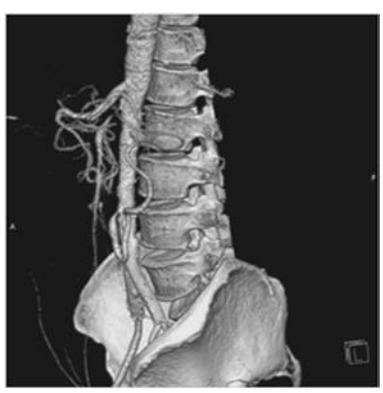

Figure 6 Computed tomography. Image of the abdominal aorta at 9 mo follow-up, showing 90% stenosis of the inferior mesenteric artery (IMA) ostium. The totally occluded superior mesenteric artery at the ostium is filled retrogradely *via* the arch of Riolan from the IMA.

artery was cannulated with a 7 F renal guide catheter (*Medtronic*) and a 7 mm × 15 mm Genesis™ balloon expandable stent (Cordis) was deployed across the ostium, resulting in brisk flow (Figure 4B). Then, for aorto-iliac intervention, a 0.018 inch Roadrunner floppy tip guide wire (Cook, Bloomington, Indiana, United States) was positioned across both iliac arteries, extending into the aorta. An 8 mm × 80 mm SMART™ control Nitinol self-expanding stent (Cordis) was directly deployed from the infra-renal abdominal aorta to the right iliac artery. It was post-dilated with an 8 mm × 60 mm OPTA®Pro Peripheral balloon (Cordis). Then, another 8 mm × 80 mm SMART™ control stent (Cordis) was deployed from the infra-renal abdominal aorta to the left iliac artery. It was post-dilated with a 5 × 20 mm and then an 8 × 60 mm OPTA®Pro Peripheral balloon (Cordis). An abdominal aortogarm showed brisk flow through the left renal artery and aorto-iliac arteries with no residual stenosis (Figure 4B). In total, 150 mL of iodixanol contrast agent and 20.7 min of fluoroscopy time was used for all these interventions. The patient had an uneventful recovery and was discharged on day 4 after the intervention. The pre-discharge serum creatinine was 1.9 mg/dL.

At 3-mo follow-up, the patient was admitted for left SFA intervention. This time the claudication distance of the left lower limb was 500 mm while there was no claudication in the right lower limb. A 6 F sheath was placed in the left femoral artery after a retrograde puncture. A 0.014 inch ATW wire (Cordis) was inserted into 90% of the stenosed SFA lesion (Figure 5A), pre-dilated with a 3 × 30 mm coronary angioplasty balloon, and a 7 × 60 mm Zilver self-expanding stent (Cook) was deployed. It was post-dilated with a 6 × 20 mm OPTA®Pro peripheral balloon (Cordis); a brisk flow was achieved in the SFA (Figure 5B).

At 9-mo follow-up, the patient was relatively asymptomatic. Congestive heart failure had improved; echocardiography showed a left ventricular ejection fraction of 0.40. There was no claudication in the lower limbs, and bilateral ABPI was 0.98. Glycemia was controlled with insulin and oral hypoglycaemic agents. Serum urea and creatinine were 52 and 1.6 mg/dL, respectively. Computed tomography showed patent left renal, bilateral aorto-iliac and left SFA stents. There was 90% osteal stenosis of the IMA; a 100% occluded SMA at the ostium showed retrograde filling through an arch of Riolan, which received a collateral from the IMA (Figure 6). There were no symptoms of chronic mesenteric ischemia despite underlying SMA and IMA stenosis.

At 15-mo follow-up, the patient started having pain in the upper abdomen 1.5-2 h following a meal and

lasting for about 1 h. This complaint was of 3 wk duration. There was no history of hematemesis or blood in the stool. Abdominal pain did not improve despite treatment with proton pump inhibitors and antacids. Abdominal ultrasound did not show any free fluid or dilated bowel loops suggestive of mesenteric infarction. Upper gastrointestinal endoscopy was within normal limits. In view of the typical postprandial abdominal pain of underlying mesenteric artery disease, a diagnosis of mesenteric ischemia was made. There was no cardiac angina, worsening heart failure, claudication, significant weight loss, hematemesis or occult blood in stool. His urea, creatinine and fasting blood sugar were 50 mg/dL, 1.6 mg/dL and 144 mg/dL, respectively. He was scheduled for percutaneous mesenteric revascularization. A 6 F sheath was placed in the right femoral artery for angiographic check of the stented coronary and peripheral arteries; a 7 F sheath was placed in the right brachial artery for IMA intervention. To our surprise, coronary angiography revealed 70% stenosis of the left main artery extending from the ostium to the bifurcation and to the osteal LAD; the Lcx ostium was normal (Figure 1C). Previously deployed stents in the proximal LAD and distal LCx were patent. Left renal and bilateral aorto-iliac stents were also patent. The IMA had 90% osteal stenosis. The right renal artery showed non-progressed 50% osteal stenosis. In view of significant left main coronary artery disease, informed written consent was obtained for both left main coronary artery and IMA stenting. In the same operation, the left coronary artery was cannulated with a Judgkins Left 3.5, 6F coronary guide catheter *via* the trans-femoral route. Both the LAD and LCx had a 0.014 inch ATW wire (Cordis) inserted. The left main coronary artery and osteal LAD were predilated with a 2.5 × 15 mm Sprinter balloon (Medtronic). A 3.5 cm × 18 mm Cypher stent (Cordis) was deployed from the ostium of the left main coronary artery to the proximal LAD, crossing the LCx ostium. After stenting, there was TIMI-3 flow in the left main coronary artery, LAD and LCx; the LCx ostium was normal with no stenosis (Figure 1D). Then, the IMA was cannulated with a Judgkins Right 3.5, 7 F coronary guide catheter *via* the right brachial route. A 0.014 inch ATW wire (Cordis) was inserted into the IMA lesion and a 7 mm × 18 mm Genesis balloon-expandable stent (Cordis*)* was deployed across the ostium of the IMA. Brisk flow was achieved in the IMA (Figure 3B). During this intervention, the fluoroscopy time was 24.5 min and 200 mL of iodixanol contrast agent was used. After the procedure, the creatinine at 72 h was 1.58 mg/dL. Repeat biochemistry revealed total cholesterol of 142 mg/dL, HDL 35 mg/dL, LDL 72 mg/dL and triglycerides 150 mg/dL; other parameters included lipoprotein(a) 37.3 mg/dL, high-sensitive c-reactive protein (hsCRP) 6.73 mg/L, homocysteine 15.86 μmol/L and HbA1c 10.10% The patient had an uneventful recovery and was discharged on day 4 following the intervention. There were no further symptoms of post-prandial abdominal pain at follow-up.

At 30-mo follow-up, the patient was asymptomatic and underwent an angiogram for academic reasons. It revealed a patent left main coronary artery, LAD and LCx stents; and left renal artery (Figure 4C), bilateral aorto-iliac (Figure 4C), IMA (Figure 4C) and left SFA stents.

During each session of angiography and/or intervention, adequate hydration was maintained, N-acetyl cysteine was given and the procedure was performed with the minimum permitted amount of iodixanol contrast agent to avoid contrast-induced nephropathy. At 40-mo follow-up in July 2011, he was asymptomatic and was on dual anti-platelet therapy, atorvastatin 40 mg, ramipril 10 mg, β-blockers and insulin and diuretics. His fasting blood sugar and creatinine were 110 mg/dL and 1.6 mg/dL, respectively.

DISCUSSION

Physicians frequently see patients with both CAD and PAD in routine clinical practice. In a study of 28 649 patients of angiography-proven CAD, 9% of patients were found to have associated PAD[1]. On the other hand, in an another study of 110 patients with abdominal aneurysm, 71% of patients had associated CAD[2]. Although there has been a significant improvement in CAD-associated morbidity and mortality following advanced percutaneous therapeutic interventions in recent years, concomitant PAD poses a therapeutic challenge. Coronary intervention is associated with improved myocardial function and survival, while peripheral interventions are associated with different clinical outcomes, for example in the carotid artery it is associated with reduced stroke rate, in the renal artery with reduced need for renal replacement and blood pressure therapy, in the mesenteric artery with decrease mesenteric ischemia, and in the ilio-femoral and femoro-popliteal arteries with improved functional status and reduced amputation rate[3]. Hence, there has to be an integrated and comprehensive multidisciplinary approach for therapeutic intervention in patients with CAD and PAD. The index diabetic case, who had renal, aorto-iliac, mesenteric and SFA stenosis, in addition to triple vessel CAD, had undergone multi-vascular interventions for improvement in cardiac function, claudication, renal function, hypertension and symptomatic mesenteric ischemia. He was a high-risk case for percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), because of associated risk factors such as triple vessel disease, diabetes, uremia, congestive heart failure, left ventricular systolic dysfunction, and associated PAD[4,5]. The option of PCI instead of CABG in this patient was more appropriate because of low ejection fraction, impaired renal function and associated PAD. Multi-vessel coronary revascularization with sirolimus drug-eluting stent as in the index case, has shown comparable long-term mortality and major adverse cardiac event rate with CABG in both normal and severe left ventricular dysfunction patients[6,7]. Accelerated atherosclerosis and need for repeat revascularization of left main coronary artery stenosis at 15 mo of follow-up can be explained by diabetes mellitus, uncon-

trolled glycemia (HbA1c 10.10%)[8], and raised hsCRP[9]. hs-CRP is a marker of inflammation and is a strong and independent predictor for future risk of myocardial infarction, stroke, PAD and sudden cardiac death in healthy population[10]. Amano *et al*[11] observed that post-PCI patients with elevated CRP frequently undergo non-culprit lesion revascularization at follow-up. Also, PAD patients undergoing PCI have higher in-hospital major cardiovascular complications and non-favorable long-term outcomes[12,13]. Wildman *et al*[14] also demonstrated that the CRP level is independently associated with PAD. A high level of hs-CRP, i.e., 6.73 mg/L in the index case, was associated with extensive atherosclerotic CAD and PAD. More aggressive statin therapy in CAD patients with high CRP levels is associated with a better clinical outcome[15,16], and therefore the index case was put on atorvastatin 40 mg/d throughout his follow-up course. The single stent technique as performed in the index case for the left main coronary artery bifurcation lesion has shown more favorable long-term clinical outcomes in comparison with the two-stent technique[17].

Risk factors such as diabetes, raised creatinine of >1.5 mg/dL, anemia, congestive heart failure and left ventricular dysfunction, present in the index case, are associated with contrast-induced nephropathy and adverse clinical outcomes following contrast load[18]. As per the recommendation for contrast-induced nephropathy prevention[19,20], we maintained adequate hydration by adjusting diuretic therapy, used N-acetyl cysteine and iodixanol contrast agent. According to the American College of Cardiology/American Heart Association (ACC/AHA) recommendations, asymptomatic bilateral renal artery stenosis (≥ 50% stenosis) as in the index case is a class Ⅱb indication for percutaneous revascularization[21]. Renal dysfunction with creatinine of 1.9 mg/dL can be explained by diabetic nephropathy and bilateral renal artery stenosis. Progression to total occlusion is more common in renal arteries with more severe stenosis, which may result into worsening renal function and the need for renal replacement therapy[22,23]. In the index case, we performed renal stenting in only the left kidney which had 75% stenosis, but did not intervene in the 50% stenosed right renal artery. A stabilized/decreased serum creatinine of 1.6 mg/dL at 40-mo follow-up can be explained by percutaneous left renal intervention and non-progression of right renal artery stenosis, though these points can be debated.

Symptomatic chronic mesenteric ischemia usually manifests when at least 2 of 3 mesenteric arteries, i.e., the celiac trunk, SMA and IMA, have proximal atherosclerotic stenosis[21]. A lack of clinical manifestation involving only one vessel is because of extensive interconnected collateral formation, though there can be an exception with the SMA[21,24]. The index case was initially asymptomatic despite 100% occlusion of the SMA, because of good retrograde filling *via* the arch of Riolan, which received collaterals from the IMA. There is no randomized trial or clinical guideline for revascularization in such a situation, when there is asymptomatic two-vessel involvement[21,25]. With progression of osteal stenosis of the IMA from 50% at baseline to 90% at 15-mo follow-up, the patient became symptomatic with classical postprandial abdominal pain of mesenteric ischemia, for which he underwent successful endovascular mesenteric revascularization. Endovascular treatment for chronic mesenteric ischemia is considered to be a primary therapeutic strategy in most instances[26]. Silva *et al*[24], in his series of 59 patients with chronic mesenteric ischemia treated with percutaneous intervention, had shown a procedural success rate of 96% with no procedural mortality and 80% 5-year symptom-free survival. Isolated IMA revascularization is useful in relieving symptoms and may improve mortality, when revascularization of other visceral arteries is technically not feasible and there is an extensive and intact collateral supply from the IMA[27]. The index patient also improved following partial mesenteric revascularization by performing isolated IMA intervention, as there was a well formed arch of Riolan supplying the SMA. No intervention in the chronically occluded SMA was performed because of the technical difficulty[28], expected symptomatic improvement following isolated IMA intervention[27], and the risk of contrast-induced nephropathy in this high-risk patient. Although surgical revascularization of the isolated IMA has been reported[27], there is no published report of isolated IMA stenting for chronic mesenteric ischemia management, and the index case is first one in the published literature. An interesting observation in this case, which is again not reported, is an increase in IMA diameter following SMA occlusion, for which we could deploy a 7 mm diameter balloon-expandable stent. According to ACC/AHA recommendations, symptomatic focal aorto-iliac and femoro-popliteal disease is a class 1 indication for endovascular interventions[21]. In this case, we performed bifurcation kissing stenting of the aorto-iliac lesion and focal stenting of the left SFA lesion, and demonstrated their long-term patency. Various authors have demonstrated about an 80% patency rate at 60 mo of follow-up for aorto-iliac stenting[29].

Patients with extensive atherosclerotic CAD and PAD require a comprehensive multi-specialty approach for management[30,31]. The index case was treated by a team of cardiologists, and an expert opinion was sought in between from various specialties such as nephrology, gastroenterology, diabetes care and radiology.

In conclusion, we hereby report an unusual case of extensive, atherosclerotic CAD and PAD with comorbid illness, who received successful percutaneous panvascular revascularization and had a favorable long-term outcome.

REFERENCES

1 **Makowsky MJ**, McAlister FA, Galbraith PD, Southern DA, Ghali WA, Knudtson ML, Tsuyuki RT. Lower extremity peripheral arterial disease in individuals with coronary artery disease: prognostic importance, care gaps, and impact of therapy. *Am Heart J* 2008; **155**: 348-355

2 **Sukhija R**, Aronow WS, Yalamanchili K, Sinha N, Babu S. Prevalence of coronary artery disease, lower extremity peripheral arterial disease, and cerebrovascular disease in 110 men with an abdominal aortic aneurysm. *Am J Cardiol* 2004;

94: 1358-1359
3 **Bittl JA**, Hirsch AT. Concomitant peripheral arterial disease and coronary artery disease: therapeutic opportunities. *Circulation* 2004; **109**: 3136-3144
4 **Singh M**, Rihal CS, Lennon RJ, Spertus J, Rumsfeld JS, Holmes DR. Bedside estimation of risk from percutaneous coronary intervention: the new Mayo Clinic risk scores. *Mayo Clin Proc* 2007; **82**: 701-708
5 **Singh M**, Gersh BJ, Li S, Rumsfeld JS, Spertus JA, O'Brien SM, Suri RM, Peterson ED. Mayo Clinic Risk Score for percutaneous coronary intervention predicts in-hospital mortality in patients undergoing coronary artery bypass graft surgery. *Circulation* 2008; **117**: 356-362
6 **Serruys PW**, Daemen J, Morice MC, De Bruyne B, Colombo A, Macaya C, Richardt G, Fajadet J, Hamm C, Dawkins KD, Vranckx P, Bressers M, van Domburg R, Schuijer M, Wittebols K, Pieters M, Stoll HP. Three-year follow-up of the ARTS-II# - sirolimus-eluting stents for the treatment of patients with multivessel coronary artery disease. *EuroIntervention* 2008; **3**: 450-459
7 **Gioia G**, Matthai W, Gillin K, Dralle J, Benassi A, Gioia MF, White J. Revascularization in severe left ventricular dysfunction: outcome comparison of drug-eluting stent implantation versus coronary artery by-pass grafting. *Catheter Cardiovasc Interv* 2007; **70**: 26-33
8 **Stolar MW**. Defining and achieving treatment success in patients with type 2 diabetes mellitus. *Mayo Clin Proc* 2010; **85**: S50-S59
9 **Pearson TA**, Mensah GA, Alexander RW, Anderson JL, Cannon RO, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, Rifai N, Smith SC, 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
10 **Ridker PM**. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. *Circulation* 2003; **107**: 363-369
11 **Amano T**, Matsubara T, Uetani T, Kato M, Kato B, Yoshida T, Harada K, Kumagai S, Kunimura A, Shinbo Y, Ishii H, Murohara T. Lipid-rich plaques predict non-target-lesion ischemic events in patients undergoing percutaneous coronary intervention. *Circ J* 2010; **75**: 157-166
12 **Singh M**, Lennon RJ, Darbar D, Gersh BJ, Holmes DR, Rihal CS. Effect of peripheral arterial disease in patients undergoing percutaneous coronary intervention with intracoronary stents. *Mayo Clin Proc* 2004; **79**: 1113-1118
13 **Saw J**, Bhatt DL, Moliterno DJ, Brener SJ, Steinhubl SR, Lincoff AM, Tcheng JE, Harrington RA, Simoons M, Hu T, Sheikh MA, Kereiakes DJ, Topol EJ. The influence of peripheral arterial disease on outcomes: a pooled analysis of mortality in eight large randomized percutaneous coronary intervention trials. *J Am Coll Cardiol* 2006; **48**: 1567-1572
14 **Wildman RP**, Muntner P, Chen J, Sutton-Tyrrell K, He J. Relation of inflammation to peripheral arterial disease in the national health and nutrition examination survey, 1999-2002. *Am J Cardiol* 2005; **96**: 1579-1583
15 **Ridker PM**, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, Pfeffer MA, Braunwald E. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med* 2005; **352**: 20-28
16 **Morrow DA**, de Lemos JA, Sabatine MS, Wiviott SD, Blazing MA, Shui A, Rifai N, Califf RM, Braunwald E. Clinical relevance of C-reactive protein during follow-up of patients with acute coronary syndromes in the Aggrastat-to-Zocor Trial. *Circulation* 2006; **114**: 281-288
17 **Kim WJ**, Kim YH, Park DW, Yun SC, Lee JY, Kang SJ, Lee SW, Lee CW, Park SW, Park SJ. Comparison of single- versus two-stent techniques in treatment of unprotected left main coronary bifurcation disease. *Catheter Cardiovasc Interv* 2011; **77**: 775-782
18 **Mehran R**, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, Mintz GS, Lansky AJ, Moses JW, Stone GW, Leon MB, Dangas G. A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. *J Am Coll Cardiol* 2004; **44**: 1393-1399
19 **Caixeta A**, Mehran R. Evidence-based management of patients undergoing PCI: contrast-induced acute kidney injury. *Catheter Cardiovasc Interv* 2010; **75** Suppl 1: S15-S20
20 **Kelly AM**, Dwamena B, Cronin P, Bernstein SJ, Carlos RC. Meta-analysis: effectiveness of drugs for preventing contrast-induced nephropathy. *Ann Intern Med* 2008; **148**: 284-294
21 **Hirsch AT**, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, Hiratzka LF, Murphy WR, Olin JW, Puschett JB, Rosenfield KA, Sacks D, Stanley JC, Taylor LM, White CJ, White J, White RA, Antman EM, Smith SC, Adams CD, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Hunt SA, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation* 2006; **113**: e463-e654
22 **Schreiber MJ**, Pohl MA, Novick AC. The natural history of atherosclerotic and fibrous renal artery disease. *Urol Clin North Am* 1984; **11**: 383-392
23 **Pearce JD**, Craven BL, Craven TE, Piercy KT, Stafford JM, Edwards MS, Hansen KJ. Progression of atherosclerotic renovascular disease: A prospective population-based study. *J Vasc Surg* 2006; **44**: 955-962; discussion 962-963
24 **Silva JA**, White CJ, Collins TJ, Jenkins JS, Andry ME, Reilly JP, Ramee SR. Endovascular therapy for chronic mesenteric ischemia. *J Am Coll Cardiol* 2006; **47**: 944-950
25 **Wilson DB**, Mostafavi K, Craven TE, Ayerdi J, Edwards MS, Hansen KJ. Clinical course of mesenteric artery stenosis in elderly americans. *Arch Intern Med* 2006; **166**: 2095-2100
26 **Sivamurthy N**, Rhodes JM, Lee D, Waldman DL, Green RM, Davies MG. Endovascular versus open mesenteric revascularization: immediate benefits do not equate with short-term functional outcomes. *J Am Coll Surg* 2006; **202**: 859-867
27 **Schneider DB**, Nelken NA, Messina LM, Ehrenfeld WK. Isolated inferior mesenteric artery revascularization for chronic visceral ischemia. *J Vasc Surg* 1999; **30**: 51-58
28 **Ayers NP**, Zacharias SJ, Abu-Fadel MS, Hennebry TA. Successful use of blunt microdissection catheter in a chronic total occlusion of a celiomesenteric artery. *Catheter Cardiovasc Interv* 2007; **69**: 546-549
29 **Pulli R**, Dorigo W, Fargion A, Innocenti AA, Pratesi G, Marek J, Pratesi C. Early and long-term comparison of endovascular treatment of iliac artery occlusions and stenosis. *J Vasc Surg* 2011; **53**: 92-98
30 **White CJ**, Ramee SR, Collins TJ, Jenkins JS. Global revascularization: the role of the cardiologist. *Int J Cardiovasc Intervent* 2000; **3**: 71-79
31 **Vijayvergiya R**, Kubba S, Grover A. Concomitant congenital, atherosclerotic coronary and peripheral artery disease: managed with percutaneous interventions. *Int J Cardiol* 2006; **112**: e69-e73

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Events Calendar 2012

January 18-21, 2012
Ninth Gulf Heart Association Conference
Muscat, Oman

January 27, 2012
ESC Global Scientific Activities at the 23rd Annual Conference of the Saudi Heart Association
Riyadh, Saudi Arabia

January 29–31, 2012
Integrated management of acute and chronic coronary artery disease
Innsbruck, Austria

January 30, 2012
Webinar on "Best of Euroecho 2011"
Sophia Antipolis, France

February 1-3, 2012
American Heart Association and American Stroke Association International Stroke Conference 2012
New Orleans, Louisiana, United States

February 3-5, 2012
6th Asian-Pacific Congress Of Heart Failure 2012
Chiang Mai, Thailand

February 9, 2012
4th British Society for Heart Failure Medical Training Meeting
London, United Kingdom

February 23–25, 2012
Advanced Invasive Cardiac Electrophysiology
Sophia Antipolis, France

February 24–26, 2012
International Congress of Cardiology
Hong Kong, China

February 28, 2012
Echocardiography evaluation of patient with multivalvular disease
Sophia Antipolis, France

February 29-March 3, 2012
Winter ISHNE 2012
Zakopane, Poland

March 8–10, 2012
Cardiac Pacing, ICD and Cardiac Resynchronisation
Vienna, Austria

March 8–10, 2012
24th Colombian Congress of Cardiology and Cardiovascular Surgery
Cali, Colombia

March 10-11, 2012
23rd International Meeting "Cardiology Today"
Limassol, Cyprus

March 14-18, 2012
Ninth Mediterranean Meeting on Hypertension and Atherosclerosis
Antalya, Turkey

March 15-17, 2012
e-Cardiology 2012
Osijek, Croatia

March 15-18, 2012
China Interventional Therapeutics 2012-CIT
Beijing, China

March 16-17, 2012
12th Annual Spring Meeting on Cardiovascular Nursing
Copenhagen, Denmark

March 16-17, 2012
3rd European Meeting: Adult Congenital Heart Disease
Munich, Germany

March 16-18, 2012
JCS2012 - The 76th Annual Scientific Meeting
Fukuoka, Japan

March 20–23, 2012
32nd International Symposium on Intensive Care and Emergency Medicine
Brussels, Belgium

March 25-29, 2012
16th International Symposium On Atherosclerosis 2012
Sydney, Australia

March 28–31, 2012
Rome Cardiology Forum 2012
Rome, Italy

March 28–31, 2012
Annual Spring Meeting of the Finnish Cardiac Society 2012
Helsinki, Finland

March 30-April 1, 2012
Frontiers In CardioVascular Biology 2012
London, United Kingdom

April 5-7, 2012
EAE Teaching Course on New echocardiographic techniques for myocardial function imaging
Sofia, Bulgaria

April 12-14, 2012
Cardiovascular Risk Reduction: Leading The Way In Prevention 2012
National Harbor, MD, USA

April 12-15, 2012
NHAM Annual Scientific Meeting 2012
Kuala Lumpur, Malaysia

April 18-21, 2012
World Congress of Cardiology Scientific Sessions 2012
Dubai, United Arab Emirates

April 19-21, 2012
Delivering Patient Care in Heart Failure
Sophia Antipolis, France

April 20-22, 2012
7th Clinical Update on Cardiac MRI and CT
Cannes, France

April 25-27, 2012
Angioplasty Summit 2012
Seoul, South Korea

April 25-28, 2012
The 61st International Congress of the European Society of Cardiovascular and Endovascular Surgery
Dubrovnik, Croatia

April 28-29, 2012
24th Annual Scientific Meeting of the SCS
Singapore, Singapore

May 3–5, 2012
EuroPRevent 2012
Dublin, Ireland

May 15–18, 2012
EuroPCR Congress 2012
Paris, France

May 17-20, 2012
2nd International Meeting On Cardiac Problems In Pregnancy 2012
Berlin, Germany

May 19-22, 2012
Heart Failure 2012
Belgrade, Serbia

May 23-26, 2012
46th Annual meeting of the Association for European Pediatric and Congenital Cardiology
Istanbul, Turkey

May 26-27, 2012
Cardiovascular Spring Meeting 2012
Vienna, Austria

June 7–9, 2012
6th Congress of Asian Society of Cardiovascular Imaging
Bangkok, Thailand

June 7-9, 2012
6th Congress of Asian Society of Cardiovascular Imaging 2012
Bangkok, Thailand

June 15–17, 2012
13th Annual Cardiology Update
Bhurban, Pakistan

June 21-24, 2012
10th International Pulmonary Hypertension Conference and Scientific Sessions 2012
Orlando, Florida, United States

July 19-22, 2012
13th Annual South African Heart Congress
Sun City, South Africa

August 16-19, 2012
60th annual scientific meeting of CSANZ
Brisbane, Australia

August 25-29, 2012
ESC Congress 2012
Munich, Germany

September 29-October 4, 2012
International Society of Hypertension 24th Annual Scientific Meeting 2012
Sydney, Australia

October 4-6, 2012
Magnetic Resonance in Cardiology
Riva Del Garda, Italy

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INSTRUCTIONS TO AUTHORS

GENERAL INFORMATION

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h,

blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

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Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
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