Review

Comorbidity in patients undergoing coronary artery bypass graft surgery: impact on outcome and implications for cardiac rehabilitation

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The increasing comorbid disease burden among patients undergoing coronary artery bypass graft surgery (CABG) and the improved operative survival are expanding the number of post-CABG patients living with prognostically significant comorbidities. In a large contemporary database, 29.9% of the patients receiving isolated CABG had diabetes mellitus, 16% peripheral vascular disease, 18.6% chronic obstructive pulmonary disease, and 27.5% renal dysfunction. Patients with comorbidity are more likely to be old and often female, may have special care-requirements early after discharge, and are at increased risk for adverse outcomes. Contemporary available evidence indicates that older individuals, women, and patients with comorbidities are significantly less likely to receive cardiac rehabilitation. In addition, compliance with proven atherosclerosis risk reduction strategies for CABG patients is suboptimal. In this article we will review the impact of comorbidity on short-term and long-term outcome after CABG and their implications for cardiac rehabilitation. *Eur J Cardiovasc Prev Rehabil* 15:379–385 © 2008 The European Society of Cardiology

Introduction

Despite an increasing severity of the risk profile of the patients undergoing coronary artery bypass graft surgery (CABG), operative mortality is declining owing to an increased experience in operating on high-risk patients over time and an improved surgical strategy [1]. This suggests that the proportion of patients who remain at increased risk of adverse outcome and have special-care requirements after discharge is increasing. Besides cardiac-related and operation-related factors, patient-related factors including advanced age, female sex, comorbidity, previous cardiac surgery, and clinical pre-operative situation can impact on the clinical outcome of post-CABG patients. In this article we will review the impact of comorbidities on short-term and long-term outcome of patients undergoing CABG and their implications for cardiac rehabilitation (CR).

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Prevalence and prognostic impact of comorbidities

Comorbidities are common among patients undergoing CABG. In a contemporary database encompassing 483 914 patients who received isolated CABG [2], 29.9% of the patients had diabetes mellitus (DM), 16% had peripheral vascular disease (PVD), 18.6% had chronic obstructive pulmonary disease (COPD), and 27.5% had moderate to severe renal dysfunction (RD), as defined by a glomerular filtration rate (GFR) less than $60 \, \text{ml/min/1.73 m}^2$ estimated from the simplified Modification of Diet in Renal Disease study equation [3]. It is relevant to note that even minor elevations of serum creatinine may be consistent with a substantial reduction in GFR [3]. The prevalence of previous cerebrovascular disease ranges from 6.7 [1] to 10.8% [4]. Comorbidity adversely affects the outcome of the patients undergoing CABG. In the European System for Cardiac Operative Risk Evaluation (EuroSCORE) database, COPD, extracardiac arteriopathy, and preoperative renal insufficiency were found to be robust risk factors for in-hospital [5] and long-term

mortality [6]. In additon, CABG patients with greater comorbid illness (Charlson score $\geq$ 2) experience a worse relative 30-day postdischarge survival [7]. Among comorbidities, PVD, COPD, RD, and DM do have the greatest impact on short-term and long-term outcome of patients undergoing CABG.

Peripheral vascular disease

In the Northern New England Study, patients with PVD (defined as prior cerebrovascular accidents, history of transient ischemic attacks, carotid stenosis, claudication, or prior vascular surgery) were 2.4 times more likely to die in hospital after CABG than those without PVD [8]. The patients with PVD were older and had more comorbidity and advanced heart disease than patients without PVD. However, the presence of PVD remained a strong independent risk factor for CABG-related death even after adjustment for these variables. The analysis of the New York State database encompassing 16 120 patients who underwent isolated CABG in 2002 confirmed the importance of PVD as a risk factor for in-hospital mortality [9]. In addition, severe systemic atherosclerosis was found to be predictive of neurocognitive deficit and stroke in the postoperative period [10]. Peripheral vascular disease is a diabetes-related comorbidity. Studies have shown that long-term cardiac-specific survival of post-CABG diabetic patients is greatly affected by associated PVD, defined as cerebrovascular and/or lower extremity disease. In the study of Leavitt *et al.* [11], the annual incidence rate of death for diabetic patients without PVD or renal insufficiency was 4.4 deaths per 100 person-years compared with 8.4 deaths per 100 person-years for diabetic patients with PVD. Moreover, PVD adversely impacts on the long-term survival of patients with severely depressed left ventricular function, with 3.2 times higher odds for 5-year mortality [12].

Chronic obstructive pulmonary disease

The adverse effect of COPD in patients undergoing general surgery is well-known. In cardiac surgery, sternotomy, and cardiopulmonary bypass further increase the prognostic burden of COPD by interfering with pulmonary function, alveolar stability, and immune response [13]. Patients with moderate to severe COPD are at an increased risk for operative mortality and postoperative complications. Fuster *et al.* [13] related the degree of preoperative pulmonary dysfunction, as assessed by the forced expiratory volume in the first second (FEV_1), to in-hospital occurrence of death and major complications. A FEV_1 less than 60% proved to be a powerful independent predictor of death, increasing mortality risk by more than five times. A FEV1 less than 40% identified an extremely high-risk subgroup. Pneumonia with subsequent sepsis was the most frequent cause of death (31%). The impact of COPD on outcome persists in the long-term. In the large study of Leavitt *et al.* [14], the presence of COPD significantly increased

the overall incidence rate of deaths per 100 person-years from 2.1 to 4.0. Sixty-four percent of the patients with COPD had $\geq$ 1 comorbidity (renal failure, DM, vascular disease, congestive heart failure, obesity, or ulcer peptic disease). The coexistence of $\geq$ 1 other comorbidity with COPD further increased the incidence rate of deaths per 100 person-years to 9.4 [14]. The proportion of patients surviving by 10 years was 77% for those with no comorbidity, 64% for those with COPD alone, 37% for patients with COPD plus other comorbidity, and 52% for patients with non-COPD disease [14].

Renal dysfunction

Mortality rates after CABG in patients with end-stage kidney disease are known to be higher [15]. Recent studies have, however, changed our understanding of the prognostic importance of RD by demonstrating that even lesser degrees of RD influence early mortality and long-term survival of patients undergoing CABG.

Among the 483 914 patients with isolated CABG encompassed in the Society of Thoracic Surgeons National Adult Cardiac database [2], 24% had moderate RD (GFR 30–59 ml/min/1.73 m^2) and 2% had severe RD without dialysis (GFR < 30 ml/min/1.73 m^2). After adjustment for diabetes and other variables, patients with moderate RD had 55% higher odds for in-hospital mortality compared with those with normal renal function. This rose to 2.87 times higher mortality risk among those with severe RD [2]. The risk for severe complications such as stroke, pulmonary insufficiency requiring ventilatory support for $\geq$ 48 h, and acute renal failure was also significantly higher. Acute renal failure is a serious complication of CABG that affects approximately 7% of the patients [16] and is associated with substantial in-hospital [16,17] and 90-day mortality [18]. On a positive note, a recent analysis of the National Inpatient Sample database has demonstrated that in-hospital mortality associated with acute renal failure after CABG declined from 39.5% in 1998 to 17.9% in 2003 [16].

After discharge, patients with RD continue to be at higher risk of death and recurrent hospitalization compared with those without RD [6,19–21]. In a study including 26 506 post-CABG patients, preoperative RD was the most significant independent predictor of mortality [19]. One-year postdischarge mortality was 16.6% in patients with a serum creatinine greater than 2.0 mg/dl, 6.4% with a serum creatinine 1.4–2.0 mg/dl, and 2.2% with normal renal function. Zakery *et al.* [20] studied 4403 consecutive CABG patients. A 3-year survival rate of the patients with a serum creatinine value ranging from 1.47 to 2.25 mg/dl was significantly lower than for patients with a creatinine level less than 1.47 (81 vs. 93%). Estimated GFR had a substantially better predictive power than creatinine alone; among

patients with a GFR less than 60 ml/min/1.73 m^2, a linear relationship between increasing mortality rates and decreasing GFR was observed. Furthermore, in the Bypass Angioplasty Revascularization Investigation study [21], a preoperative serum creatinine level of more than 1.5 mg/dl was independently associated with a markedly increased risk of death, both of all-cause and of cardiac causes, and recurrent hospitalization at 7 years. RD and diabetes worked synergistically to increase risk of adverse outcome. When both RD and diabetes were present, the 7-year mortality risk was additive at 70% [21]. Finally, postoperative acute renal failure has been shown to be a strong risk factor for long-term mortality increasing the risk by nine times [6]. RD is also one of the most powerful predictors of long-term mortality among patients with ischemic cardiomyopathy undergoing CABG. Among 379 patients with a left ventricular ejection fraction (LVEF) ≤ 35% who underwent isolated first CABG, preoperative RD was the strongest independent predictor of long-term mortality [22]. Patients with a GFR of less than 45 ml/min/1.73 m^2 (20%) were at particularly high risk, their 3-year survival rate was 68% compared with 90% of the patients with normal renal function. In this homogeneous patient group, LVEF was of no prognostic significance. In another recent study, renal insufficiency (creatinine > 1.5 mg/dl) increased the risk of long-term mortality by a larger magnitude than severely depressed LVEF [23]. Among patients with severely depressed LVEF, the presence of renal insufficiency was associated with a three times higher 5-year mortality.

The association between RD and adverse outcomes after CABG has multiple possible explanations. First, acute renal failure after CABG is more likely to occur in patients with preoperative RD than in those with normal renal function [2]. Second, RD is likely a direct risk factor for intraoperative and postoperative complications that lead to longer ventilation and operative times [2]. Third, patients with RD are older and have an increased prevalence of traditional and nontraditional risk factors, which may accelerate atherogenesis [2,21,24]. Consistently, a more extensive coronary artery disease (CAD) and a greater frequency of peripheral and cerebrovascular disease has been observed in post-CABG patients with even moderate RD compared with those with normal renal function [2,21]. It is also possible that, in the presence of RD, traditional risk factors may have a qualitatively and quantitatively different risk relationship with cardiovascular disease [24]. Finally, patients with RD are less likely to receive efficacious therapies [25].

In summary, recent studies have consistently demonstrated that even moderate RD is a major contributor to morbidity as well as short-term and long-term mortality after CABG. Across worsening RD categories, patients are more likely to have an increasingly poor prognosis.

Diabetes mellitus

DM has traditionally been associated with increased in-hospital morbidity and mortality in patients undergoing CABG. However, recent studies suggest that diabetic patients can be surgically revascularized with low morbidity and mortality owing to improved perioperative management [26]. Instead, the adverse effect of DM on the long-term mortality and morbidity remains a problem.

In a cohort of 146 786 patients undergoing CABG in 1997, DM significantly increased the 30-day risk for mortality and morbidity [27]. However, in two more recent series, the presence of DM was not found to be an independent predictor of hospital mortality [28,29] suggesting that DM may, in fact, no longer be a risk factor for early mortality after CABG surgery. It is worth noting that the in-hospital mortality rate in diabetic patients significantly decreased from 3.1% in 1998–2002 to 1.0% in 2003–2005 [12].

Two large studies addressed the impact of DM on long-term survival after CABG [11,30]. In the study of Mohammadi *et al.* [30], long-term cardiac-specific survival of diabetics was most negatively influenced by the need for insulin therapy and presence of diabetic-related comorbidities such as PVD and RD. In the absence of RD and PVD, the cardiac-specific survival of noninsulin-dependent diabetic patients was similar to but slightly less than that of nondiabetic patients for some years after CABG. Thereafter, it was significantly lower. The late divergence of the cardiac death risk curve in favor of nondiabetic patients could be related to the development of diabetic nephropathy or insulin requirement during the follow-up [30]. The annual mortality of diabetic patients with RD was three times that of nondiabetic individuals and twice that of diabetic individuals without RD [30]. Insulin-dependent diabetic patients, regardless of the presence of diabetes-related comorbidities, had a significantly poorer long-term survival than nondiabetic patients with a divergence of the risk curves occurring as early as 2 years after surgery [30]. These findings indicate that noninsulin-dependent DM by itself is not an independent risk factor for late cardiac death after CABG. The long-term cardiac-specific survival of post-CABG diabetic patients is determined by the presence of kidney disease and/or the need for insulin therapy.

Readmission after coronary artery bypass surgery

Readmission to hospital after CABG is common. In a study including 16 325 patients discharged alive in 1999, 15.3% were readmitted within 30 days, and 12.9% were readmitted for reasons directly related to CABG [31]. Older patients and women were more likely to be readmitted. RD, PVD, COPD, and diabetes were identified as significant independent predictors of

readmission. RD was also specifically predictive of readmission for heart failure. In another study, 39% of post-CABG patients were readmitted to hospital within 1 year; the risk was highest early after discharge and then gradually decreased [32]. Among other risk factors, old age, low LVEF, and advanced New York Heart Association class independently increased the likelihood of hospital readmission.

Implications for cardiac rehabilitation

Comprehensive CR is effective in prolonging survival and reducing morbidity and disability after a coronary event [33,34]. Therefore, it should be considered the standard of care after a myocardial infarction or coronary bypass surgery [33,34]. The core components of cardiac rehabilitation/secondary prevention programs have recently been updated [35]. However, only marginal recommendations concerning comorbidity are provided.

The increasing comorbid disease burden among patients undergoing CABG and the improved operative survival are expanding the number of post-CABG patients living with prognostically significant comorbidities. They are more likely to be old and female, are at increased risk for mortality, morbidity, rehospitalization, and disability, and may have special care-requirements after discharge. Thus, patients with comorbidities may potentially benefit the most from early CR, delivered in outpatient or inpatient settings depending on the functional and clinical risk status, assuring appropriate clinical management, proven risk reduction strategies, and programs aimed at promoting rapid functional recovery and therapeutic lifestyle changes. However, contemporary available evidence indicates that older individuals, women, and patients with comorbidities are significantly less likely to receive cardiac rehabilitation [33]. In addition, compliance at hospital discharge with proven atherosclerosis risk reduction strategies for CABG patients is still suboptimal [36]. In the Get With the Guideline database [36], ACE-inhibitors and statins were prescribed only to 57 and 77% of post-CABG eligible patients without contraindications, respectively.

Secondary prevention is a core component of cardiac rehabilitation. Post-CABG patients with concurrent PVD are at higher risk for fatal and nonfatal atherothrombotic events than those without PVD. Ample evidence confirms that aggressive comprehensive risk factor management improves survival, reduces recurrent events, and improves quality of life for patients with coronary artery and other atherosclerotic vascular disease [37].

Among patients with CAD, the prevalence of diabetes has increased sharply from 1994 to 2006 and its therapeutic management remains poor [38]. One-third of the patients undergoing CABG have diabetes and many of them have

the attendant comorbidities, kidney disease and PVD [2]. Thirty-two percent of the 144735 diabetic patients encompassed in the Society of Thoracic Surgeons National Adult Cardiac database [2] had a substantially decreased renal function (GFR $< 60\,ml/min/1.73\,m^2$). RD, whether preexistent or developing after surgery, PVD, and the need for insulin therapy have a strong negative impact on long-term cardiac-specific survival of post-CABG patients with diabetes [11,30]. In contrast, long-term survival for noninsulin-dependent diabetic patients without comorbidities is similar to that observed for nondiabetic patients. Therefore, in a clinical setting of CR, a major goal should be early recognition of the patients with kidney disease or PVD so that intensive preventive treatment can be instituted [37,39]. The National Kidney Foundation defines kidney disease as either (i) kidney damage, with or without a decrease in GFR, or (ii) GFR less than $60\,ml/min/1.73\,m^2$, with or without kidney damage [3]. Persistent albuminuria is the most common marker of kidney damage. Microalbuminuria, which may represent an early expression of diffuse vascular endothelial dysfunction in patients with diabetes as well as in those without diabetes, is a prominent marker for development of nephropathy in type 2 diabetes [39,40]. Macroalbuminuria identifies the patients with substantial histological damage and heralds a predictable linear decline in renal function [38]. As the stage of kidney disease is primarily determined by the level of kidney function [3] and a significant decline in renal function may be noted in patients with diabetes in the absence of increased urine albumin excretion [41], estimation of GFR is mandatory. Institution of intensive treatment at a point very early in the course of diabetic renal disease can have a very significant impact on the clinical course of this complication [42]. Use of renin–angiotensin system (RAS) inhibitors, lowering blood pressure to less than 130/80 mmHg, strict glycaemic control (HbA1c level $\leq 7.0\%$), smoking cessation, and dietary protein restriction in selected patients can delay the progression from microalbuminuria to macroalbuminuria, slow the decline in GFR in patients with macroalbuminuria, and improve cardiovascular outcome [39–42]. Attainment of all treatment targets is critical to achieve optimal outcome [41]. Unfortunately, although RAS inhibitors are used in almost all patients, good glycaemic control, cessation of smoking, and controlled hypertension are still achieved in only a subgroup of patients in clinical practice [38,43]. Continued surveillance to assess both response to therapy and progression of disease is also recommended [41]. Once GFR has fallen to less than $60\,ml/min/1.73\,m^2$, referral to a physician experienced in the care of diabetic renal disease may be indicated [42].

About 30% of post-CABG patients have moderate to severe RD (GFR $< 60\,ml/min/1.73\,m^2$) [2]. Post-CABG patients with impaired renal function are at higher risk for

cardiac-specific mortality, morbidity, and rehospitalization than those with preserved renal function and the risk of adverse outcome progressively increases with declining estimated GFRs [2,6,19–23]. Thus, RD should be recognized as a potent risk factor for adverse outcome after CABG, especially in the presence of left ventricular dysfunction [19]. Post-CABG patients with decreased GFR are older and more often female, have a substantially higher prevalence of traditional and nontraditional cardiovascular risk factors, and are less likely to receive therapies proven to be beneficial than patients without RD [2,25]. Comorbidities and extensive atherosclerosis as evidenced by the increased percentage of patients with concomitant PVD are also more prevalent among patients with RD [2]. Thus, they have the potential to gain a large benefit from comprehensive risk reduction programs [44]. Cardiovascular risk factor management and lifestyle changes are recommended for patients with chronic kidney disease, regardless of whether they have CAD or not. The Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Cardiovascular Diseases recommend that chronic kidney disease patients who qualify for CR be referred to a specialist [45]. Interestingly, a recent observational study suggests a survival benefit of CR for dialysis patients after CABG [46].

In the setting of CR, the ability to recognize even moderate RD through estimating GFR, which is a more sensitive indicator of renal function than serum creatinine concentration [3], should make clinicians more vigilant on postsurgery clinical management [47]. For clinical purposes, grading the severity of RD, determining whether renal function is stable or getting worse or better, and considering change from baseline are important features. As kidney disease worsens, the need for consultation and comanagement with nephrologists increases [3].

Patients with CAD and associated kidney disease are often undertreated with therapies proven to be beneficial in patients with normal renal function, especially RAS inhibitors, probably because of concern for adverse events and lack of evidence of benefit [25,37]. Indeed, despite the well-recognized link between abnormalities of kidney function and risk of adverse outcome in patients with CAD [48–51], major cardiovascular trials, especially those testing RAS inhibitors, frequently exclude patients with renal insufficiency and do not provide information on the effect of treatments on patients with kidney disease [52]. The interaction between renal function and effect of RAS inhibitor treatment in patients with CAD has been examined in secondary reports of some clinical trials [48–50]. It is notable that patients with stage 4 kidney disease (GFR of $15–30\,\text{ml/min/1.73}\,\text{m}^2$) were poorly represented in these studies. In the Survival and Ventricular Enlargement (SAVE) study [48], patients with a GFR less than $60\,\text{ml/min/1.73}\,\text{m}^2$ derived greater absolute benefit from captopril therapy than those without RD. In the Prevention of Events with ACE Inhibition (PEACE) trial [49], trandolapril therapy reduced mortality by 27% in patients with a GFR less than $60\,\text{ml/min/1.73}\,\text{m}^2$, but not in those with better levels of renal function. In the European Trial on Reduction of Cardiac Events with Perindopril study [50], treatment benefit by perindopril was substantial and consistent in patients with and without impaired renal function. Furthermore, it is relevant that RAS inhibitors confer substantial renal benefits in patients with stage 3 and 4 chronic kidney disease [53,54]. Taken together, these data demonstrate that RAS inhibitors can significantly improve kidney and cardiovascular outcomes of CAD patients with decreased GFR. Whether measuring GFR offers the opportunity to find patients most likely to derive a benefit from ACE-inhibitors, as suggested by the PEACE [50] trial, is less clear. Kidney damage, as confirmed by persistent proteinuria, with normal GFR is the earliest stage of kidney disease [3]. In a secondary report of the SAVE trial [55], proteinuria was an independent predictor of all-cause and cardiovascular mortality in patients with systolic dysfunction after myocardial infarction, independently of GFR. Patients with proteinuria appeared to have the greatest reduction in all-cause and cardiovascular mortality with captopril therapy, with a significant interaction between proteinuria and treatment assignment (placebo vs. captopril). Furthermore, in the PEACE trial [56], albuminuria, even in low levels within the normal range, and the progression of albuminuria over time were associated with increased risk for cardiovascular and all-cause mortality in low-risk patients with stable CAD, independent of GFR and diabetes. These findings strengthen the link between kidney disease and risk of adverse outcome in patients with CAD, and generate the hypothesis that the earliest stage of kidney disease may be a therapeutic target for stable CAD.

Conclusion

The aging of the patient population undergoing CABG and the increasing prevalence of significant comorbidities pose challenges to the achievement of optimal long-term outcomes and the application of clinical practice guidelines [57]. Indeed, while single-disease guidelines mention the problem of chronic comorbidities, they provide only marginal recommendations [57]. In contrast, there is little 'evidence' to base recommendations for chronic polymorbidities [57]. In view of the existing evidence, the presence of comorbidities should be considered as a major risk factor for adverse outcome after CABG. Greater awareness of the substantially increased risk for mortality, morbidity, and recurrent hospitalization among post-CABG patients with comorbidities should stimulate the development of 'tailored' care and surveillance strategies. Reasonably, such patients would more efficaciously be managed by a collaborative, multidisci-

plinary team. Cardiac rehabilitation/secondary prevention programs may play a key role in improving the process of care and outcome of this growing high-risk category of patients.

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