Journal of Geriatric Cardiology (2012) 9: 197–208

Review · Open Access ·

Depression, anxiety, and cardiac morbidity outcomes after coronary artery bypass surgery: a contemporary and practical review

Phillip J Tully[1,2,3,4], Robert A Baker[1]

[1]*Department of Surgery, Flinders Medical Centre and Flinders University of South Australia, 3 Flinders Drive, Bedford Park, SA 5042, Australia*
[2]*School of Psychology,University of Adelaide Hughes Building, North Terrace, Adelaide, SA 5005, Australia*
[3]*Discipline of Psychiatry, The University of Adelaide, Eleanor Harold Building, Frome Road, Adelaide, SA 5005, Australia*
[4]*Heart Failure Self Management Program, Ambulatory and Primary Healthcare Directorate, Hampstead Rehabilitation Centre, 207 Hampstead Road, Northfield, SA 5085, Australia*

Abstract

Research to date indicates that the number of coronary artery bypass graft (CABG) surgery patients affected by depression (i.e., major, minor, dysthymia) approximates between 30% and 40% of all cases. A longstanding empirical interest on psychosocial factors in CABG surgery patients highlights an association with increased risk of morbidity in the short and longer term. Recent evidence suggests that both depression and anxiety increase the risk for mortality and morbidity after CABG surgery independent of medical factors, although the behavioral and biological mechanisms are poorly understood. Though neither depression nor anxiety seem to markedly affect neuropsychological dysfunction, depression confers a risk for incident delirium. Following a comprehensive overview of recent literature, practical advice is described for clinicians taking into consideration possible screening aids to improve recognition of anxiety and depression among CABG surgery patients. An overview of contemporary interventions and randomized, controlled trials are described, along with suggestions for future CABG surgery research.

J Geriatr Cardiol 2012; 9: 197–208. doi: 10.3724/SP.J.1263.2011.12221

Keywords: Depression; Depressive disorder; Coronary artery bypass; Coronary artery disease; Antidepressive agents; Anxiety

1 Introduction

The benefits of coronary artery bypass graft (CABG) surgery with respect to survival, improved ventricular function, freedom from angina and re-stenosis in coronary artery disease (CAD) populations are well established.[1] With an estimated 408,000 CABG surgery procedures performed in the USA alone, evidence suggests that between 30% and 40% of CABG surgery patients experience a form of psychological depression immediately leading up to and after surgery.[2–6] The longstanding focus on psychosocial factors in CABG patients has highlighted an association with increased risk of morbidity in the short and longer term. This contemporary review describes the prevalence of depression and anxiety symptoms, and disorders, among CABG surgery patients. Practical advice is described for clinicians taking into consideration potential screening aids to improve identification of anxiety and depression among CABG patients. An overview of research documenting the deleterious impact of psychosocial factors upon cardiac and neuropsychological morbidity and mortality within the acute peri-operative period, and in the longer term, is then covered, describing possible pathophysiological mechanisms. Finally, current treatment intervention studies are described along with suggestions for future CABG surgery research.

2 Depression among CABG surgery patients

Unipolar depression is characterized by depressed mood and/or loss of interest or pleasure, among other symptoms. The reported 15% to 20% prevalence of uni-polar depression among CABG surgery patients is consistent with that found generally among cardiac patients.[7] Comparatively, the point prevalence among the general population is 5% to 9% for females and 2% to 3% among males[8] suggesting CABG surgery patients have higher prevalence of depression than community samples. Though CABG surgery is indicated for increasingly older patients with substantial co-morbidity in contemporary surgical practice, depression has surprisingly

Correspondence to: Robert A Baker, PhD, Cardiac and Thoracic Surgical Unit, Flinders Medical Centre, 3 Flinders Drive, Bedford Park, SA 5042, Australia. E-mail: Rob.Baker@health.sa.gov.au
Telephone: +61-88404-2015 **Fax:** +61-88404-2019
Received: December 22, 2011 **Revised:** March 6, 2012
Accepted: March 13, 2012 **Published online:** May 30, 2012

been associated with patients of younger age,[9] and female gender.[6] Far less research has been devoted to minor depressive episodes and dysthymia, with the latter reported between 13% and 18% of CABG surgery patients.[4,5] Collectively, research to date indicates the number of patients affected by any depression (i.e., major, minor or dysthymia) is approximately between 30% and 40% of CABG surgery patients, a summary of which is provided in Table 1. Studies thus far reporting depression prevalence are not without limitations and could be improved. Connerney and colleagues[2] employed a modified diagnostic criteria based on only several days of symptoms immediately post-CABG, thereby potentially inflating prevalence estimates. Other studies employing diagnostic criteria have rarely recruited more than 100 patients[3,6,10] while others less than 50 patients,[4,5,11] suggesting larger samples are required.

Studies employing self-reported depression measurements suggest up to 50% of patients experience depression symptoms.[12–15] Wide variations in the choice of self-reporting measures and dichotomous cut-points to establish depression cases highlight how heterogeneity has contributed to unwieldy estimates. Studies employing self-reported measurements do not reflect a clinical diagnosis of depression, but rather depression symptoms. A lower level of depression symptoms after surgery may reflect the upturn in mood associated with improvements in physical condition from revascularization.[15] However, some patients may develop new depressive symptoms over the course of recovery from surgery.[16] McKhann *et al*.[15] showed between 13% and 9% of 124 CABG patients at one month and twelve month follow up, respectively, reported clinically relevant depressive symptoms not evident at the time of surgery. Peterson *et al*.[16] explain newly developed depressive symptoms resulting from the stressors of surgery that can produce an adjustment response, or reactive type depression. In any case, as described below, identifying depression in the CABG surgery patient is complicated by the somatic symptoms experienced in CAD and the physical stressors of surgery.

3 Anxiety among CABG surgery patients

Self-reporting estimates of anxiety are also variable. Anxiety is particularly high for CABG patients while on the waiting list with an unknown surgery date.[17] Fear of dying before, rather than during surgery, has been highlighted as a pervasive and anxious preoccupation.[17,18] Anxiety also manifests as an autonomic symptom that can exacerbate CAD symptoms.[19] After surgery, while anxiety may decrease to below pre-operative levels, the severity of anxiety does not necessarily remit to below sub-clinical levels and may warrant intervention.[20] Like depression, complicating and accurate identification of anxious patients over the course of surgery recovery is the finding that autonomic-arousal symptoms significantly increase after CABG.[21] This is hardly surprising given the overlap and seemingly indistinguishable nature of CAD and somatic anxiety symptoms (e.g., breathlessness, increased heart rate). A caveat of research to date is the use of non-specific self-reporting measurements that do not reflect the characteristics of any particular anxiety disorder, but rather a nebulous, often ill-defined, construct, similar to "stress".[22]

The most common anxiety disorders appear to be generalized anxiety disorder (GAD), a disorder marked by pervasive worry, and panic disorder, a disorder marked by recurrent panic attacks. Both GAD and panic disorder are variably reported from zero prevalence to nearly 11% of CABG surgery patients (see Table 1).[4,5,11,23] To date, emphasis on panic disorder and GAD is possibly the result of recognition of their higher prevalence, and also, that each disorder is generally associated with adverse cardiac outcomes among CAD patients.[24,25] With respect to other anxiety disorders in CABG patients, it is estimated that between 2.5% and

Table 1. CABG studies reporting prevalence of depression and anxiety with structured diagnostic interview.

Reference	Sample characteristics	Diagnosis	Timing of assessment	Major depression (%)	Dysthymia (%)	PTSD (%)	GAD (%)	Panic (%)
Connerney, *et al*[2]	309 CABG, USA	NIMH	Pre	20.0	-	-	-	-
Kazmierski, *et al*[10]	260 CABG, Poland	MINI	Pre	6.2	-	-	-	-
Tully, *et al*[3,23]	158 CABG ± valve, Australia	MINI	Pre	17.1	-	0.6	10.2	10.8
Mitchell, *et al*[6]	124 CABG, Canada	MINI	Pre	28.2	-	-	-	-
Fraguas, *et al*[4]	50 CABG, Brazil	CIS	Pre	8.0	6.0	-	2.0	-
Rafanelli, *et al*[5]	47 CABG, Italy	SCID	Post (1 month)	10.6	12.8	-	-	0.0
Rothenhausler, *et al*[11]	34 CABG, Germany	SCID	Pre	2.9	17.6*	8.8	5.9	-

*Minor depression and dysthymia. CABG: coronary artery bypass graft; CIS: clinical interview schedule; GAD: generalized anxiety disorder; MINI: Mini-international neuropsychiatric interview; NIMH: national institute of mental health; Pre: preoperative period; Post: postoperative period; PTSD: post traumatic stress disorder; SCID: structured clinical interview for DSM disorders.

4.3% meet the criteria for social phobia;[5,23] and between 0.6% and 2.1% meet criteria for obsessive compulsive disorder.[5,23] Less is known regarding phobic disorders among CABG patients and only one study reported 1.3% prevalence of specific phobia.[23] The above mentioned literature highlights the requirement for rigorous psychiatric evaluation among larger CABG surgery samples to determine the prevalence of anxiety disorders.

Recently, particular research interest has focused on post-traumatic stress disorder (PTSD) in CAD and CABG surgery patients. One of the unique diagnostic features of PSTD is subjective experience or witness to, an extremely traumatic event.[8] An audit of 62,665 electronic medical records suggested post-traumatic stress disorder was prevalent in 14.7% of CABG patients.[26] Prospective studies with structured psychiatric assessments have reported far lower pre-operative levels of PTSD, varying between 0.6% before surgery[23] and 9.0% at one month post-operatively.[5] PTSD symptomatology, including traumatic memories related to CABG surgery, was evident in up to 18% of 148 patients at six month follow-up.[27] As most PTSD symptoms were incident cases, the data suggest that exposure to the CABG surgical procedures and in-hospital stressors may contribute to PTSD etiology.[27] That being said, research among 63 Holocaust survivors with PTSD symptoms at the time of CABG has suggested that such individuals can also achieve improvements in quality of life despite significant preexisting PTSD symptoms.[28]

4 Identifying depression and anxiety

A survey of 796 cardiovascular physicians determined 71.2% of respondents asked fewer than half of their patients with CAD about depression.[29] Some authors have recommended depression screening following CABG surgery as a way to improve pathways to recovery,[30] though the American College of Cardiology and American Heart Association 2004 guideline update on CABG surgery[19] highlight that pre-operative screening may simply sensitize staff and family members to post-operative distress and mood changes. The American Heart Association recently indicated that evidence exists for depression screening in CAD patients,[31] stating it is reasonable in instances where patients have access to case management, in collaboration with their primary care physician, and a mental health specialist. Thus, we strongly recommended that suitable follow-up, referral and psychosocial intervention pathways are in place prior to commencing with routine screening among CABG surgery patients. As such, not every cardiac surgery unit or medical centre could feasibly adopt a routine depression screening and follow-up protocol. Also, current evidence seems premature to support the premise that routine depression screening in CAD leads to an improvement in cardiac outcomes and furthermore no such evidence exists for anxiety. Clinicians are encouraged to prudently use their own judgment to consider psychiatric intervention for depression and anxiety disorders once identified in the CABG surgery patient, or any other CAD patient, regardless of impact upon cardiac prognosis.

The American Heart Association has recommended self-reporting measures to aid rapid identification of likely depressed patients.[32] The Patient Health Questionnaire (PHQ)[33] is one such depression assessing measurement, available in English and Spanish, as a two-item screener (PHQ-2), to tap into the two requisite symptoms for a depression or major depressive episode diagnosis, i.e., (1) little interest or pleasure in doing things, (2) feeling down, depressed, or hopeless. In its expanded form, the PHQ-9 covers the full spectrum of symptoms reflective of major depression as depicted in Table 2. As Carney and Freedland point out,[34] many different combinations of symptoms fulfill criteria for a major depressive episode. Certainly, close monitoring and follow-up for patients describing thoughts of death or self harm is strongly recommended. Shemesh *et al*.[35] reported that more than 12% of cardiovascular patients require immediate evaluation of suicidal thoughts and intent, reiterating the practical requirements for appropriate referral pathways following assessment.

It has been suggested that a positive response to either of the PHQ-2 questions should be followed up with administration of the PHQ-9, with scores of $\geq$ 10 on the PHQ-9 requiring an even more comprehensive assessment, such as by a psychiatrist or psychologist.[32] As previously mentioned,

Table 2. Core depression symptoms assessed by PHQ-9.

Over the past two weeks, how often have you been bothered by any of the following problems?
1. Little interest or pleasure in doing things.
2. Feeling down, depressed, or hopeless.
3. Trouble falling or staying asleep, or sleeping too much.
4. Feeling tired or having little energy.
5. Poor appetite or overeating.
6. Feeling bad about yourself-or that you are a failure or have let yourself or your family down.
7. Trouble concentrating on things, such as reading the newspaper or watching television.
8. Moving or speaking so slowly that other people could have noticed? Or the opposite–being so fidgety or restless that you have been moving around a lot more than usual.
9. Thoughts that you would be better off dead of or hurting yourself in some way.

Questions are scored: not at all = 0; several days = 1; more than half the days = 2; nearly every day = 3. Refer to references [33,38]. PHQ: Patient health questionnaire.

the somatic laden, depression diagnostic criteria overlap CAD symptoms. Specifically, fatigue, loss of appetite, psychomotor retardation, insomnia, and difficulty concentrating can be the direct physiological response to a medical illness and hospitalization[36] and have been documented to significantly increase in the first month after CABG surgery.[37] Brief psychological reactions to the impending stressors of surgery and the post-operative recovery period may spontaneously remit over time, thus requiring no further intervention. Watchful waiting, monitoring and brief support of suspected depressed patients might serve as a useful strategy before implementing psychological intervention. To aid clinicians, the developers of the PHQ-9 have described their own recommendations for what constitutes depression remission and treatment efficacy in primary care populations.[38] With respect to depression identification from self-reporting symptoms *vs*. structured psychiatric interview, the only study to employ receiver operating characteristics (a type of statistical analysis) in CABG surgery patients showed that a measure of depression yielded an area-under curve of 0.811 and 70.4% for sensitivity and 77.1% for specificity in the detection of major depression.[39] Without more research, the utility of self-reporting measures to identify depression in CABG populations remains largely unknown.

Identification of anxiety disorders, such as GAD, panic disorders and PTSD, is more complicated as each is demarcated by specific criteria of symptoms[8] which are currently under revision in anticipation of the fifth Diagnostic and Statistical Manual of Mental Disorders. The group that developed the PHQ also developed a measurement with items closely matching diagnostic criteria for GAD.[40] Scores of ≥ 10 on the GAD-7 were likely to yield a positive diagnosis. The GAD-7 also demonstrated sensitivity and specificity for identification of a range of other anxiety disorders in primary care patients, such as PTSD and panic disorder.[41] Moreover, the group further described a single question pertaining to panic attacks with sufficient sensitivity and specificity for primary care populations.[41] The question was "In the last four weeks, have you had an anxiety attack-suddenly feeling fear or panic?".[41] As mentioned above, self-reporting measures are typically non-specific and do not relate to any particular anxiety disorder. Despite an availability of a multitude of anxiety questionnaires, few have been validated as screening tools to identify anxiety disorders in CAD. Favorable sensitivity (90.7%) and specificity (61.4%) was reported for the Hospital Anxiety and Depression Scale anxiety subscale scores of ≥ 8 to detect GAD.[25] A study among CABG surgery patients showed superior receiver operating characteristics (75.0% sensitivity, 72.5% specificity; area-under curve of 0.795) in detection of GAD when the general distress scale of the Mood Anxiety Symptom Questionnaire was used.[39] Conversely, panic disorder was best predicted by somatic anxiety (75.0% sensitivity, 68.5% specificity; area-under curve of 0.784). Apart from a multitude of self-reporting anxiety measurements, more time intensive structured, clinical interviews are also available for a range of anxiety disorders that can be undertaken by a psychiatrist or psychologist.

5 Depression, anxiety and morbidity after CABG surgery

Comprehensive cardiac research has included meta-analyses detailing etiological and prognostic associations between depression, in particular, and CAD outcomes.[42,43] Recent depression research among CABG surgery patients are described in Table 3. Several earlier studies corroborate the association between depressive symptoms upon mortality in the longer term.[2,13] In a study of 309 patients at one year follow-up, Connerney *et al*.[2] reported that major depression, but not depressive symptoms, were associated with cardiac events. The authors found a more than two-fold greater risk for cardiac events [risk ratio = 2.31, 95% confidence interval (CI) 1.17–4.56] after adjustment for ejection fraction, female, gender, extended length of hospital stay, New York Heart Association class and number of revascularized vessels and living alone. Follow-up of these patients at ten years showed both depression symptoms and major depression increased the risk for cardiac mortality. A similar finding attributable to depression symptoms was reported by Blumenthal *et al*.[44] who excluded patients with a major depression and psychiatric diagnosis, but nevertheless found that moderate to severe depression symptoms were associated with increased mortality risk (hazard ratio = 2.4, 95%CI 1.2–4.2). Evidence also extends to non-fatal morbidity outcomes, where depression symptoms reportedly increase the risk for unplanned hospital readmissions,[12,45–47] cardiac events[2,48] and poorer quality of life.[49] Scheier *et al*.[50] reported depressive symptoms associated with surgery, CAD and wound infection resulted in hospital readmissions among 309 patients at six month follow-up. Patients reporting depressive symptoms one month after cardiac surgery were found to have a greater proportion of arrhythmias and return of angina symptoms at five year follow-up.[14] In a study of 963 CABG patients, improvements in physical health at six month follow up were lower among patients with depressive symptoms after adjustment for cardiac severity and baseline health.[51] A systematic comparison of depression, anxiety and stress suggested that only depression was consistently associated with quality of life domains tapping into vitality, social role functioning, physical and general health.[49]

Table 3. Association between depression and mortality or cardiac outcome after cardiac surgery.

Reference	Sample	Age(% female)	F/U	Outcome, *n*(%)	Depression measures	Prevalence preop/postop	Adjustment	Critical value HR/ OR/RR (95%CI)
Baker, *et al*[13]	158 CAG ± valve, AUS	64.6 (25.3)	Median 2 years	All-cause mortality, 6 (3.8)	DASS ≥ 10	1 day preop, 15.2%	-	Unadjusted OR = 6.24 (95%CI 1.18–32.98); $P < 0.05$
Blumenthal, *et al*[44]	817 CAG, USA	61 (27)	Mean 5.2 years	All-cause mortality, 122 (15)	CES-D 16–26 (mild)	1 day preop, 26.1% mild preop	Cigarette smoking, LVEF, sex, age, grafts 4 *vs*. 2, DM, previous MI	Adjusted moderate-severe HR = 2.37 (95%CI 1.40–4.00); $P = 0.001$
					CES-D ≥ 27 (moderate to severe)	11.9% moderate to severe preop		Adjusted mild HR = 1.08 (95% CI 0.70–1.67); $P = 0.723$
Burg, *et al*[55]	89 CAG, USA	66.3 (0)	2 years	Cardiovascular mortality, 5 (5.6)	BDI > 10	< 1 week preop 28.1%	Tu score (age, gender, LV function, urgency, redo)	Adjusted OR = 23.16 (95%CI 1.38–389.08); $P = 0.03$
Burg, *et al*[45]	89 CAG, USA	65.9 (0)	6 months	Hospitalization for MI or unstable angina, 8 (9)	BDI ≥ 10	< 1 week 28.1% preop	History of MI, chronic renal insufficiency	$\chi^2 = 4.24$, $P = 0.039$
Connerney, *et al*[2]	309 CAG, USA	63.1 (33)	12 months	MI, PCTA, redo, cardiac arrest, death due to cardiac causes, rehospitalization for angina, CHF; 42 (14)	BDI ≥ 10	4–10 days postop, 28%	MDD, LVEF, sex, living alone, LOS, NYHA class, CAG/valve, vessels	Adjusted RR = 1.62 (95%CI 0.83–3.16), P = NR
Connerney, *et al*[2]	309 CAG, USA	63.1 (33)	12 months	MI, PCTA, redo, cardiac arrest, death due to cardiac causes, rehospitalization for angina, CHF; 42 (14)	DIS	4–10 days postop, 20.4%	LVEF, sex, living alone, LOS, NYHA class, CAG/valve, vessels	Adjusted RR = 2.31(95%CI 1.17–4.56), $P = 0.01$
Connerney, *et al*[48]	309 CAG, USA	63.1 (33)	Median 9.3 years	Cardiac mortality, 62 (20.1)	DIS	4–10 days postop, 20.4%	Female sex, age, LVEF, DM	Adjusted HR 1.78 (95%CI 1.04–3.04), $P = 0.04$
Connerney, *et al*[48]	309 CAG, USA	63.1 (33)	Median 9.3 years	All cause mortality, 117 (37.9)	DIS	4–10 days postop, 20.4%	Female sex, age, LVEF, DM	Adjusted HR 1.19 (95%CI 0.78–1.82), $P = 0.42$
Oxlad, *et al*[46]	119 CAG ± valve, AUS	63.3 (16.0)	6 months	CHD or surgery related readmission, 21 (17.9)	DASS-D ≥ 10	5–6 days postop, 15.7%	CPB time	Adjusted preop HR 5.15 (95%CI 1.45–18.28), $P = 0.01$
								Adjusted postop HR = 0.97 (95%CI 0.25–3.79), $P = 0.96$
Oxman, *et al*[101]	232 CAG, AVR, CAG ± AVR, USA	Age not reported (28)	6 months	In-hospital and post-operative all-cause mortality, 21 (9.1)	HAM-D ≥ 9	1–2 week preop 21.6%	-	χ^2 $P = 0.07$
Phillips-Bute, *et al*[102]	427 CAG, USA	61 (30)	2 years	Repeat CAG, PCI, MI, cardiac arrest, all-cause mortality; *n* = not stated	CES-D >16	1 day preop 36.8%	None	Adjusted OR = 2.6 (95%CI 1.6–4.3), $P < 0.05$
Szekley, *et al*[103]	180 CAG/valve, HUN	57.9 (33.9)	4 years	All-cause mortality, 17 (9.4)	BDI > 10	1–5 days preop 44%	-	Not reported
Szekley, *et al*[103]	180 CAG/valve, HUN	57.9 (33.9)	4 years	Cardiac death, hospitalization for angina, CHF, MI, PTCA, cardiac arrest; 48 (26.2)	BDI > 10	1–5 days preop 44%	DM, postop infection, ICU ds, preoperative and post discharge 6th month STAI-T, 6 month BDI scores	Adjusted HR = 0.980 (95% CI 0.917–1.047), $P = 0.544$

(Table 3. Conti)

Reference	Sample	Age(% female)	F/U	Outcome, *n*(%)	Depression measures	Prevalence preop/postop	Adjustment	Critical value HR/ OR/RR (95%CI)
Tully, *et al*[53]	440 CAG ± valve, AUS	64 (20)	Median 5 years 10 months	All-cause mortality, 67 (15.2)	DASS-D ≥ 10	< 1 week preop 20%	Age, renal disease, Valve procedure, CVD, PVD	Adjusted HR = 1.61 (95% CI 0.91–2.85), *P* = 0.10
Tully, *et al*[12]	226 CAG, AUS	63 (17)	6 months	Cardiovascular/ surgery readmission, 72 (32)	DASS-D ≥ 10	< 1 week preop 20.1%	Anxiety, stress, age, sex, LVEF, urgency, lung disease, CHF,	Adjusted preop HR = 0.80 (95% CI 0.38–1.68), *P* = 0.56
						4 days postop 23.5%	DM, PVD, renal disease, MI < 90 ds, HTN, CCS, psychoactive medication use	Adjusted postop HR = 2.06 (95% CI 0.97–4.40), *P* = 0.06
Tully, *et al*[52]	226 CAG, AUS	63 (17)	Median 4.9 year	MI, unstable angina, revascularization, CHF, sustained arrhythmia, stroke/CVA, LV failure, cardiac mortality, 65 (28.8)	BDI-II Cognitive factor	4 days postop	LVEF, age, respiratory disease, CHF, renal disease, DM	Adjusted HR = 1.36 (95% CI 1.02–1.82), *P* = 0.04

AUS: Australia; BDI: beck depression inventory; CAG: coronary artery graft; CCS: Canadian Cardiovascular Society; CES-D: Centre for Epidemiological Studies-Depression; CHD: coronary heart disease; CHF: congestive heart failure; CI: confidence interval; CPB: cardiopulmonary bypass time; CVA: cerebrovascular accident; DASS: depression, anxiety and stress scales; DIS: diagnostic interview schedule; DM: diabetes mellitus; HAM-D: Hamilton rating scale for depression; HR: hazard ratio; HUN: Hungary; HTN: hypertension; ICU: intensive care unit; LOS: length of stay; LV: left ventricular; LVEF: left ventricular ejection fraction; MDD: major depressive disorder; MI: myocardial infarction; NYHA: New York Heart Association; OR: odds ratio; PCI: percutaneous coronary intervention; PCTA: percutaneous coronary transluminal angioplasty; PVD: peripheral vascular disease; RR: risk ratio; STAI-T: State Trait Anxiety Inventory-Trait; Preop: preoperation; Postop: postoperation.

Depression sub-types have also been investigated. Extrapolating whether the timing and course of depression influences post-CABG morbidity, some evidence supports that new onset[16,48] and persistent *vs.* remitted depression symptoms assessed by self-reporting questionnaires[44] pose a greater risk for mortality and cardiac morbidity than brief periods of depression at the time of surgery. With respect to specific clusters of depression symptoms, two recent studies support a prognostic association between cognitive depression symptoms (e.g., pessimism, past-failure, self-criticalness, worthlessness) with nearly a two-fold greater risk of cardiac morbidity and mortality after CABG surgery.[48,52] These findings curiously suggest that the adverse effects of depression after CABG are independent of any somatic depressive symptoms, or medical related co-morbidity. However, current evidence summarized by Carney and Freedland[34] generally does not confirm that any particular subtype of depression confers greater CAD morbidity risk.

Depression appears to contribute only partly to increased risk for subsequent morbidity after CABG surgery. Not surprisingly, research also implicates anxiety in CABG surgery outcomes,[56–58] as depression and anxiety frequently occur in the same individual concurrently and across the lifespan. A study among 62,665 CABG patients showed that 9% of cases with co-morbid PTSD and major depression diagnosis had a greater risk of in-hospital mortality than patients with either PTSD, or major depression alone.[26] However, electronic medical records were employed for a limited range of psychiatric disorders that were not verified with structured psychiatric interview. By contrast, studies that simultaneously assessed both depression and anxiety symptoms, reported that each negative emotional state portended nearly two-fold increased risk of unplanned hospital readmissions.[43,59] Recently, our group showed pre-operative anxiety was associated with greater all-cause mortality [hazard ratio = 1.88, 95%CI 1.12–3.17] and independent of age, renal disease, concomitant valve procedure, cerebrovascular disease and peripheral vascular disease.[53] Taking these findings further, we showed that anxiety increases odds for incident atrial fibrillation after CABG surgery.[54] Additionally, we found that GAD, but not major depression or panic disorder, was associated with acute in-hospital morbidity events, such as stroke, myocardial infarction and renal failure.[23] Together the results seem to suggest that both depression and anxiety have a role in post-CABG morbidity. However, focusing solely on depression, rather than general psychiatric distress and anxiety, might pose as a barrier to the identification of CABG surgery patients at risk of morbidity and requiring psychological intervention.

Studies to date are not without their limitations. Like depression-CAD studies elsewhere,[42] lack of adjustment for conventional cardiac risk factors, such as left ventricular function, pose a serious caveat to interpreting the role of psychosocial factors upon post CABG functioning. It is likely that adjustment for non-psychological morbidity risk factors is limited by the low number of actual morbidity events experienced among typically small samples with short follow-up.[48] Some studies have also excluded patients with a depression or anxiety diagnosis,[42,61] thereby precluding examination of a dose-response effect among the more distressed patients. Unfortunately, these practices tend to bias the results in favor of rejecting the null hypothesis and the resultant wide confidence intervals,[13,46,55] obscure the effect of study size and the biological plausibility of an effect for depression and anxiety. Research could be improved by addressing the known risk factors for postoperative morbidity and mortality, such as those identified by the Society of Thoracic Surgeons,[56] extending the length of patient follow-up, recruiting more patients, and employing structured psychiatric assessments alongside self-reported distress measurements.

6 Depression, anxiety and neuropsychological morbidity after CABG surgery

Systematic reviews have also identified depression as a predisposing factor to increase the risk for delirium among cardiac surgery populations.[57] In the hospitalized patient, a delirious state may manifest itself as a fluctuating course of disorientation to time, place and persons, perceptual disturbances and hallucinations. Delirium is the most common psychiatric disorder observed upon admission to healthcare settings.[58] The incidence of delirium after cardiac surgery is reportedly between 3.1% and 50%,[10,59–64] depending on the timing and criteria for diagnosis. McAvay and colleagues[65] showed that dysphoric mood and hopelessness and depressive symptoms were associated with incident delirium after hospitalization. A prognostic study for 158 CABG patients showed that even when diagnostic criteria for delirium is modified to reduce bias from overlapping delirium-depression symptoms, pre-operative major depression remained associated with incident delirium after CABG surgery.[3] In explaining recent findings, Davydow[66] suggested a bidirectional relationship whereby persons may develop subsequent distress as a response to in-hospital delirium. Surprisingly, related research concerning depression and anxiety in post-CABG neuropsychological functions has produced predominantly null findings from relatively small samples. Though post-operative neuropsychological dysfunction has been exhaustively documented,[15,67,68] only weak correlations have been reported between depression, anxiety and cognitive function in the short term[18,55] and long term.[15,69] At six month and five year follow-up, neither depression, anxiety, or stress was consistently associated with neuropsychological dysfunction in regression analysis among 75 CABG surgery and 36 control patients.[69] The above results suggest that while psychological factors, such as depression might play a role in delirium, these are not consistently associated with neuropsychological functions.

7 Mechanisms of cardiopathogenesis

An increased risk in CAD morbidity attributable to emotional distress is likely explained by both behavioral and biological mechanisms. With respect to the former, epidemiological surveys suggest that affective disorders are associated with larger body mass index, hypertension, hypercholesterolemia, diabetes,[70] physical inactivity[71] and regular smoking and nicotine dependence.[65,66] Despite a greater proportion of co-morbidity and clinical risk factors, patients with emotional distress and co-morbid CAD are also less likely to comply with prescribed medications, such as aspirin.[72] Psychological distress has also been associated with less concordance to exercise regimens and smoking cessation four months after myocardial infarction.[73]

The biological mechanisms of cardio-pathogenesis attributable to depression and anxiety are multifactorial and include the dysregulation of the hypothalamic-pituitary-adrenal axis,[69–71] reduced heart-rate-variability,[72–74] altered serotonergic pathways, inflammatory response[74] and altered platelet aggregability.[75] An earlier review suggested 20% of variability in CAD and depressive symptoms was attributable to common genetic factors and the authors speculated these could be related to inflammation and serotonin.[76] The association between depression and delirium is explained, in part, by common patho-physiological pathways via the limbic-hypothalamic-pituitary-adrenal-axis, sympathetic nervous system and inflammatory responses suspected to affect cognition, mood and motivation and induce fatigability, anhedonia and reduced appetite.[77]

8 Intervention and treatment

An encouraging 2006 survey of cardiovascular physicians reported nearly 50% of respondents treat the symptoms of depression once identified in patients with CAD.[29] With respect to pharmacological management, clinicians should be aware of the possible pro-arrhythmic and cardio-toxic effects of tricyclic anti-depressants in cardiac patients.[78,79] Selective serotonin re-uptake inhibitors (SSRI), on the other

hand, have been hypothesized as safe among cardiac patients due to the serotonin transporter affinity and attenuation of platelet functioning. Safety, tolerability and efficacy of SSRIs among cardiac patients have been reported in some studies,[80,81] but not others.[82–84] The possible risks attributable to SSRIs for CABG surgery patients specifically include increased bleeding, but has not been consistently supported.[85,86] One study suggested an increased mortality and readmission risk after CABG surgery attributable to SSRIs.[87] Another recent study indicated greater renal morbidity and ventilation times, but not greater mortality risk.[88] Two recent systematic reviews of randomized, controlled trials (RCT) in CAD patients both corroborated SSRI *vs.* placebo were not associated with reductions or increased risk in mortality and differential findings were reported with respect to hospital readmissions. One found a reduced odds [pooled odds ratio (OR) = 0.58, 95%CI 0.39–0.85],[89] whereas another review did not when applying a stringent criteria for properly randomized studies (risk ratio = 0.74, 95%CI 0.44–1.23).[90] Depression symptom efficacy for SSRI *vs.* placebo was supported by a pooled standardized mean differences of -0.24 (95%CI: -0.38 to -0.09).[89]

Depression is an important predictor of participation in, and completion of, cardiac rehabilitation among CABG surgery patients and thus may form a barrier to improvements in cardiac functioning.[91] A diverse range of behavioral and psychological RCT interventions have been reported and cognitive behavioral therapy or collaborative care constitutes Class IIa evidence (i.e., it is reasonable to administer treatment, additional studies with focused objectives are needed).[91] Prior to CABG surgery, interventions have typically focused on anxiety. A non-psychological educational intervention before surgery had little impact on anxiety and depression.[92] By contrast, an intervention consisting of information and emotional support was found to impact depression and anxiety in the longer term.[93] In a Canadian study,[94] eight weeks prior to CABG, an intervention consisting of nurse initiated education and support, in addition to exercise training (n = 113), was not associated with differences in pre-surgery anxiety versus usual care (n = 107). Post-operative interventions have typically focused on depression as the primary psychological factor.[95,96] Freedland *et al*.[95] compared cognitive behavior or supportive stress management *vs* usual care and found significant three month depression remission rates in the treatment arms (71%, 57%, and 33% respectively, P = 0.002). Group differences were sustained at nine month follow up while cognitive behavioral therapy intervention was found to be superior with respect to measures of anxiety, hopelessness, stress, and quality of life. An eight month, bi-weekly, nurse-led telephone delivered intervention for depressed patients reported modest effect sizes for mental health quality of life (0.30; 95%CI 0.17–0.52), but reported exceptionally low mental health service visits (4% intervention *vs.* 6% usual care).[96] Lie *et al*.[97] in a RCT reported no differences in quality of life or distress measures between patients receiving nurse-led education with psychological support intervention (n = 93) and patients receiving usual care (n = 92). However, the brief intervention was restricted to four home visits at two and four weeks post-operatively. Significantly lower depression levels among a control group (n = 90) compared to an exercise and behavior modification group (n = 94)[98] challenge the benefits of components, such as behavioral activation alone, for reducing depressive symptoms post CABG surgery.

The limitation of psychosocial RCTs among revascularization populations is that those patients experiencing significant post-operative morbidity are likely to be excluded from trial inclusion. Thus, less is potentially known with respect to the long term treatment outcomes for patients who experience stroke, deep sternal wound infection, sternal dehiscence, renal failure requiring dialysis and extended length of time on mechanical ventilation, or intensive care during their hospital stay. These moribund patients face high risks for developing or exacerbating psychological distress. Also, though treatment of affective distress is important in any context, it has not been sufficiently investigated whether interventions among cardiac patients can promote and maintain health related behavior change.[99] Finally, beyond clinical trials, potential barriers to the implementation of patient support, include hospital culture and psychiatry registrar or allied health professional workload, in addition to mental health service accessibility and cost, cardiologist and surgeon preference and overlap with cardiac rehabilitation services.

9 Conclusions and future research directions

How can prognostic studies using a once off assessment of psychiatric disorders and psychological distress show an increase in the risk for morbidity and mortality months and years after CABG surgery? The behavioral and physiological mechanisms, such as smoking, alcohol use, diet, compliance to medication and exercise regimes, along with inflammatory processes, are possible explanations warranting further research in CABG surgery cohorts. Unfortunately, contemporary understandings of the risks of depression and anxiety in CAD are constrained by a predominantly biomedical model. Further consideration for the interaction between these disorders and social factors, such as socio-economic status, ethnicity, living alone, social isolation, may improve our understandings and uncover fruitful avenues for intervention. Moreover, research to date appears too focused on depres-

sion, whereas the limited studies addressing depression and anxiety, simultaneously, warrants further research to acquire and extrapolate cumulative knowledge with respect to psychosocial risk.[100] Collaboration between psychologists and psychiatric specialists with cardiac surgeons, cardiologists and cardiac nurses will enhance the research base and may lead to improved patient outcomes.

In conclusion, between 30% and 40% of CABG surgery patients experience depression and anxiety disorders at rates significantly higher than prevalent in community samples. Both depression and anxiety appear to confer greater morbidity risks, though the behavioral and biological mechanisms are poorly understood. It is commonly hoped that psychosocial intervention might mitigate the deleterious impact of depression and anxiety upon subsequent morbidity and mortality. Accurate diagnosis and intervention among CABG surgery patients may impact upon distress levels and clinicians are encouraged to establish referral and treatment pathways for their own CAD patients.

References

1 Taggart DP. Thomas B. Ferguson lecture. Coronary artery bypass grafting is still the best treatment for multivessel and left main disease, but patients need to know. *Ann Thorac Surg* 2006; 82: 1966–1975.

2 Connerney I, Shapiro PA, McLaughlin JS, *et al*. Relation between depression after coronary artery bypass surgery and 12-month outcome: a prospective study. *Lancet* 2001; 358: 1766–1771.

3 Tully PJ, Baker RA, Winefield HR, *et al*. Depression, anxiety disorders and Type D personality as risk factors for delirium after cardiac surgery. *Aust N Z J Psychiatry* 2010; 44: 1005–1011.

4 Fraguas JR, Ramadan ZB, Pereira AN, *et al*. Depression with irritability in patients undergoing coronary artery bypass graft surgery: the cardiologist's role. *Gen Hosp Psychiatry* 2000; 22: 365–374.

5 Rafanelli C, Roncuzzi R, Milaneschi Y. Minor depression as a cardiac risk factor after coronary artery bypass surgery. *Psychosomatics* 2006; 47: 289–295.

6 Mitchell RH, Robertson E, Harvey PJ, *et al*. Sex differences in depression after coronary artery bypass graft surgery. *Am Heart J* 2005; 150: 1017–1025.

7 Gehi A, Haas D, Pipkin S, *et al*. Depression and medication adherence in outpatients with coronary heart disease: findings from the Heart and Soul Study. *Arch Intern Med* 2005; 165: 2508–2513.

8 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-IV-TR*, 4th Edition; Amer Psychiatric Pub: Washington DC, USA, 2000.

9 Fraguas R Jr, Iosifescu DV, Alpert J, *et al*. Major depressive disorder and comorbid cardiac disease: is there a depressive subtype with greater cardiovascular morbidity? Results from the STAR*D study. *Psychosomatics* 2007; 48: 418–425.

10 Kazmierski J, Kowman M, Banach M, *et al*. Preoperative predictors of delirium after cardiac surgery: a preliminary study. *Gen Hosp Psychiatry* 2006; 28: 536–538.

11 Rothenhausler HB, Grieser B, Nollert G, *et al*. Psychiatric and psychosocial outcome of cardiac surgery with cardiopulmonary bypass: a prospective 12-month follow-up study. *Gen Hosp Psychiatry* 2005; 27: 18–28.

12 Tully PJ, Baker RA, Turnbull D, *et al*. The role of depression and anxiety symptoms and hospital readmissions after cardiac surgery. *J Behav Med* 2008; 31: 281–290.

13 Baker RA, Andrew MJ, Schrader G, *et al*. Preoperative depression and mortality in coronary artery bypass surgery: Preliminary findings. *ANZ J Surg* 2001; 71: 139–142.

14 Borowicz L Jr, Royall R, Grega M, *et al*. Depression and cardiac morbidity 5 years after coronary artery bypass surgery. *Psychosomatics* 2002; 43: 464–471.

15 McKhann GM, Borowicz LM, Goldsborough MA, *et al*. Depression and cognitive decline after coronary artery bypass grafting. *The Lancet* 1997; 349: 1282–1284.

16 Peterson JC, Charlson ME, Williams-Russo P, *et al*. New postoperative depressive symptoms and long-term cardiac outcomes after coronary artery bypass surgery. *Am J Geriatr Psychiatry* 2002; 10: 192–198.

17 Koivula M, Tarkka MT, Tarkka M, *et al*. Fear and anxiety in patients at different time-points in the coronary artery bypass process. *Int J Nurs Stud* 2002; 39: 811–822.

18 Fitzsimons D, Parahoo K, Richardson SG, *et al*. Patient anxiety while on a waiting list for coronary artery bypass surgery: a qualitative and quantitative analysis. *Heart Lung* 2003; 32: 23–31.

19 Eagle KA, Guyton RA, Davidoff R, *et al*. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: summary article. A report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2004; 44: E213–E310.

20 Krannich JH, Weyers P, Lueger S, *et al*. Presence of depression and anxiety before and after coronary artery bypass graft surgery and their relationship to age. *BMC Psychiatry* 2007; 12: 47.

21 Andrew MJ, Baker RA, Kneebone AC, *et al*. Mood state as a predictor of neuropsychological deficits following cardiac surgery. *J Psychosom Res* 2000; 48: 537–546.

22 Bunker SJ, Colquhoun DM, Esler MD, *et al*. "Stress" and coronary heart disease: psychosocial risk factors. *Med J Aust* 2003; 178: 272–276.

23 Tully PJ, Pedersen SS, Winefield HR, *et al*. Cardiac morbidity risk and depression and anxiety: a disorder, symptom and trait analysis among cardiac surgery patients. *Psychol Health Med* 2011; 16: 333–345.
24 Chen YH, Tsai SY, Lee HC, *et al*. Increased risk of acute myocardial infarction for patients with panic disorder: a nationwide population-based study. *Psychosom Med* 2009; 71: 798–804.
25 Frasure-Smith N, Lesperance F. Depression and anxiety as predictors of 2-year cardiac events in patients with stable coronary artery disease. *Arch Gen Psychiatry* 2008; 65: 62–71.
26 Dao TK, Chu D, Springer J, *et al*. Clinical depression, post-traumatic stress disorder, and comorbid depression and post-traumatic stress disorder as risk factors for in-hospital mortality after coronary artery bypass grafting surgery. *J Thorac Cardiovasc Surg* 2010; 140: 606–610.
27 Schelling G, Richter M, Roozendaal B, *et al*. Exposure to high stress in the intensive care unit may have negative effects on health-related quality-of-life outcomes after cardiac surgery. *Crit Care Med* 2003; 31: 1971–1980.
28 Schreiber S, Soskolne V, Kozohovitch H, *et al*. Holocaust survivors coping with open heart surgery decades later: post-traumatic symptoms and quality of life. *Gen Hosp Psychiatry* 2004; 26: 443–452.
29 Feinstein RE, Blumenfield M, Orlowski B, *et al*. A national survey of cardiovascular physicians' beliefs and clinical care practices when diagnosing and treating depression in patients with cardiovascular disease. *Cardiol Rev* 2006; 14: 164–169.
30 Charlson ME, Isom OW. Clinical practice. Care after coronary-artery bypass surgery. *N Engl J Med* 2003; 348: 1456–1463.
31 Smith SC Jr, Benjamin EJ, Bonow RO, *et al*. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. *J Am Coll Cardiol* 2011; 58: 2432–2446.
32 Lichtman JH, Bigger JT Jr, Blumenthal JA, *et al*. Depression and coronary heart disease: recommendations for screening, referral, and treatment: a science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Psychiatric Association. *Circulation* 2008; 118: 1768–1775.
33 Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *JAMA* 1999; 282: 1737–1744.
34 Carney R, Freedland K. Is there a high-risk subtype of depression in patients with coronary heart disease? *Curr Psychiatry Rep* 2012; 14: 1–7.
35 Shemesh E, Annunziato RA, Rubinstein D, *et al*. Screening for depression and suicidality in patients with cardiovascular illnesses. *Am J Cardiol* 2009; 104: 1194–1197.
36 Koenig HG, George LK, Peterson BL, *et al*. Depression in medically ill hospitalized older adults: prevalence, characteristics, and course of symptoms according to six diagnostic schemes. *Am J Psychiatry* 1997; 154: 1376–1383.
37 Contrada RJ, Boulifard DA, Idler EL, *et al*. Course of depressive symptoms in patients undergoing heart surgery: confirmatory analysis of the factor pattern and latent mean structure of the Center for Epidemiologic Studies Depression Scale. *Psychosom Med* 2006; 68: 922–930.
38 The MacArthur Initiative on Depression in Primary Care, Use of the PHQ-9 to make a tentative diagnosis (symptomatology and functional impairment), 2011. Http://www.depression-primarycare.org/clinicians/toolkits/materials/forms/phq9/(Access on May 28, 2012).
39 Tully PJ, Penninx BW. Depression and anxiety among coronary heart disease patients: can affect dimensions and theory inform diagnostic disorder based screening? *J Clin Psychol* 2012; 68: 448–461.
40 Spitzer RL, Kroenke K, Williams JB, *et al*, A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006; 166: 1092–1097.
41 Kroenke K, Spitzer RL, Williams JB, *et al*. The Patient Health Questionnaire Somatic, Anxiety, and Depressive Symptom Scales: a systematic review. *Gen Hosp Psychiatry* 2010; 32: 345–359.
42 Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146538 participants in 54 observational studies. *Eur Heart J* 2006; 27: 2763–2774.
43 Suls J, Bunde J. Anger, anxiety, and depression as risk factors for cardiovascular disease: the problems and implications of overlapping affective dispositions. *Psychol Bull* 2005; 131: 260–300.
44 Blumenthal JA, Lett HS, Babyak MA, *et al*. Depression as a risk factor for mortality after coronary artery bypass surgery. *The Lancet* 2003; 362: 604–609.
45 Burg MM, Benedetto MC, Rosenberg R. Presurgical depression predicts medical morbidity 6 months after coronary artery bypass graft surgery. *Psychosom Med* 2003; 65: 111–118.
46 Oxlad M, Stubberfield J, Stuklis R, *et al*. Psychological risk factors for cardiac-related hospital readmission within 6 months of coronary artery bypass graft surgery. *J Psychosom Res* 2006; 61: 775–781.
47 Saur CD, Granger BB, Muhlbaier LH, *et al*. Depressive symptoms and outcome of coronary artery bypass grafting. *Am J Crit Care* 2001; 10: 4–10.

48 Connerney I, Sloan RP, Shapiro PA, *et al*. Depression is associated with increased mortality 10 years after coronary artery bypass surgery. *Psychosom Med* 2010; 72: 874–881.
49 Tully PJ, Baker RA, Turnbull DA, *et al*. Negative emotions and quality of life six months after cardiac surgery: the dominant role of depression not anxiety symptoms. *J Behav Med* 2009; 32: 510–522.
50 Scheier MF, Matthews KA, Owens JF, *et al*. Optimism and rehospitalization after coronary artery bypass graft surgery. *Arch Intern Med* 1999; 159: 829–835.
51 Mallik S, Krumholz HM, Lin ZQ, *et al*. Patients with depressive symptoms have lower health status benefits after coronary artery bypass surgery. *Circulation* 2005; 111: 271–277.
52 Tully PJ, Winefield HR, Baker RA, *et al*. Confirmatory factor analysis of the Beck Depression Inventory-II and the association with cardiac morbidity and mortality after coronary revascularization. *J Health Psychol* 2011; 16: 584–595.
53 Tully PJ, Baker RA, Knight JL. Anxiety and depression as risk factors for mortality after coronary artery bypass surgery. *J Psychosom Res* 2008; 64: 285–290.
54 Tully PJ, Bennetts JS, Baker RA, *et al*. Anxiety, depression, and stress as risk factors for atrial fibrillation after cardiac surgery. *Heart Lung* 2011; 40: 4–11.
55 Burg MM, Benedetto MC, Soufer R. Depressive symptoms and mortality two years after coronary artery bypass graft surgery (CABG) in men. *Psychosom Med* 2003; 65: 508–510.
56 Shahian DM, O'Brien SM, Filardo G, *et al*. The Society of Thoracic Surgeons 2008 Cardiac Surgery Risk Models: Part 1--Coronary Artery Bypass Grafting Surgery. *Ann Thorac Surg* 2009; 88(1 Suppl): S2–S22.
57 Sockalingam S, Parekh N, Bogoch II, *et al*. Delirium in the postoperative cardiac patient: a review. *J Card Surg* 2005; 20: 560–567.
58 Leentjens AF, Maclullich AM, Meagher DJ. Delirium, Cinderella no more...? *J Psychosom Res* 2008; 65: 205.
59 Norkiene I, Ringaitiene D, Misiuriene I, *et al*. Incidence and precipitating factors of delirium after coronary artery bypass grafting. *Scand Cardiovasc J* 2007; 41: 180–185.
60 Rolfson DB, McElhaney JE, Rockwood K, *et al*. Incidence and risk factors for delirium and other adverse outcomes in older adults after coronary artery bypass graft surgery. *Can J Cardiol* 1999; 15: 771–776.
61 Rudolph JL, Babikian VL, Birjiniuk V, *et al*. Atherosclerosis is associated with delirium after coronary artery bypass graft surgery. *J Am Geriatr Soc* 2005; 53: 462–466.
62 Rudolph JL, Jones RN, Grande LJ, *et al*. Impaired executive function is associated with delirium after coronary artery bypass graft surgery. *J Am Geriatr Soc* 2006; 54: 937–941.
63 Santos FS, Velasco IT, Fraguas R Jr. Risk factors for delirium in the elderly after coronary artery bypass graft surgery. *Int Psychogeriatr* 2004; 16: 175–193.
64 Yoon BW, Bae HJ, Kang DW, *et al*. Intracranial cerebral artery disease as a risk factor for central nervous system complications of coronary artery bypass graft surgery. *Stroke* 2001; 32: 94–99.
65 McAvay GJ, Van Ness PH, Bogardus ST Jr, *et al*. Depressive symptoms and the risk of incident delirium in older hospitalized adults. *J Am Geriatr* 2007; 55: 684–691.
66 Davydow DS. Symptoms of depression and anxiety after delirium. *Psychosomatics* 2009; 50: 309–316.
67 Rudolph JL, Schreiber KA, Culley DJ, *et al*. Measurement of post-operative cognitive dysfunction after cardiac surgery: a systematic review. *Acta Anaesthesiol Scand* 2010; 54: 663–677.
68 Tully PJ, Baker RA, Kneebone AC, *et al*. Neuropsychologic and quality of life outcomes following coronary artery bypass surgery with and without cardiopulmonary bypass: a prospective randomized trial. *J Cardiothorac Vasc Anesth* 2008; 22: 515–521.
69 Tully PJ, Baker RA, Knight JL, *et al*. Neuropsychological function five years after cardiac surgery and the effect of psychological distress. *Arch Clin Neuropsychol* 2009; 24: 741–751.
70 Barger SD, Sydeman SJ. Does generalized anxiety disorder predict coronary heart disease risk factors independently of major depressive disorder? *J Affect Disord* 2005; 88: 87–91.
71 Goodwin RD. Association between physical activity and mental disorders among adults in the United States. *Prev Med* 2003; 36: 698–703.
72 Carney RM, Freedland KE, Eisen SA, *et al*. Major depression and medication adherence in elderly patients with coronary artery disease. *Health Psychol* 1995; 14: 88–90.
73 Kuhl EA, Fauerbach JA, Bush DE, *et al*. Relation of anxiety and adherence to risk-reducing recommendations following myocardial infarction. *Am J Cardiol* 2009; 103: 1629–1634.
74 Frasure-Smith N, Lesperance F, Irwin MR, *et al*. Depression, C-reactive protein and two-year major adverse cardiac events in men after acute coronary syndromes. *Biol Psychiatry* 2007; 62: 302–308.
75 Soufer R, Arrighi JA, Burg MM. Brain, behavior, mental stress, and the neurocardiac interaction. *J Nucl Cardiol* 2002; 9: 650–662.
76 McCaffery JM, Frasure-Smith N, Dube MP, *et al*. Common genetic vulnerability to depressive symptoms and coronary artery disease: a review and development of candidate genes related to inflammation and serotonin. *Psychosom Med* 2006; 68: 187–200.
77 Maclullich AM, Ferguson KJ, Miller T, *et al*. Unravelling the pathophysiology of delirium: a focus on the role of aberrant stress responses. *J Psychosom Res* 2008; 65: 229–238.
78 Cohen HW, Gibson G, Alderman MH. Excess risk of myocardial infarction in patients treated with antidepressant medications: association with use of tricyclic agents. *Am J Med* 2000; 108: 2–8.
79 Ha JH, Wong CK. Pharmacologic treatment of depression in patients with myocardial infarction. *J Geriatr Cardiol* 2011; 8: 121–126.

80 Dowlati Y, Herrmann N, Swardfager WL, *et al*. Efficacy and tolerability of antidepressants for treatment of depression in coronary artery disease: a meta-analysis. *Can J Psychiatry* 2010; 55: 91–99.

81 Glassman AH, O'Connor CM, Califf RM, *et al*. Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA* 2002; 288: 701–709.

82 Veien KT, Videbaek L, Schou M, *et al*. High mortality among heart failure patients treated with antidepressants. *Int J Cardiol* 2011; 146: 64–67.

83 Von Ruden AE, Adson DE, Kotlyar M. Effect of selective serotonin reuptake inhibitors on cardiovascular morbidity and mortality. *J Cardiovasc Pharmacol Ther* 2008; 13: 32–40.

84 Tata LJ, West J, Smith C, *et al*. General population based study of the impact of tricyclic and selective serotonin reuptake inhibitor antidepressants on the risk of acute myocardial infarction. *Heart* 2005; 91: 465–471.

85 Kim DH, Daskalakis C, Whellan DJ, *et al*. Safety of selective serotonin reuptake inhibitor in adults undergoing coronary artery bypass grafting. *Am J Cardiol* 2009; 103: 1391–1395.

86 Andreasen JJ, Riis A, Hjortdal VE, *et al*. Effect of selective serotonin reuptake inhibitors on requirement for allogeneic red blood cell transfusion following coronary artery bypass surgery. *Am J Cardiovasc Drugs* 2006; 6: 243–250.

87 Xiong GL, Jiang W, Clare R, *et al*. Prognosis of patients taking selective serotonin reuptake inhibitors before coronary artery bypass grafting. *Am J Cardiol* 2006; 98: 42–47.

88 Tully PJ, Cardinal T, Bennetts JS, *et al*. Selective Serotonin Reuptake Inhibitors, Venlafaxine and Duloxetine are Associated With in Hospital Morbidity but Not Bleeding or Late Mortality After Coronary Artery Bypass Graft Surgery. *Heart Lung Circ* 2012; 21: 206–214.

89 Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with coronary artery disease. *Cochrane Database Syst Rev* 2011; 9: CD008012.

90 Pizzi C, Rutjes AW, Costa GM, *et al*. Meta-analysis of selective serotonin reuptake inhibitors in patients with depression and coronary heart disease. *Am J Cardiol* 2011; 107: 972–979.

91 Hillis LD, Smith PK, Anderson JL, *et al*. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery: Executive Summary A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the American Association for Thoracic Surgery, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2011; 58: 2584–2614.

92 Shuldham CM, Fleming S, Goodman H. The impact of preoperative education on recovery following coronary artery bypass surgery. A randomized controlled clinical trial. *Eur Heart J* 2002; 23: 666–674.

93 Sorlie T, Busund R, Sexton J, *et al*. Video information combined with individualized information sessions: Effects upon emotional well-being following coronary artery bypass surgery-A randomized trial. *Patient Educ Couns* 2007; 65: 180–188.

94 Arthur HM, Daniels C, McKelvie R, *et al*. Effect of a preoperative intervention on preoperative and postoperative outcomes in low-risk patients awaiting elective coronary artery bypass graft surgery. A randomized, controlled trial. *Ann Intern Med* 2000; 133: 253–262.

95 Freedland KE, Skala JA, Carney RM, *et al*. Treatment of depression after coronary artery bypass surgery: a randomized controlled trial. *Arch Gen Psychiatry* 2009; 66: 387–396.

96 Rollman BL, Belnap BH, LeMenager MS, *et al*. Telephone-delivered collaborative care for treating post-CABG depression: a randomized controlled trial. *JAMA* 2009; 302: 2095–2103.

97 Lie I, Arnesen H, Sandvik L, *et al*. Effects of a home-based intervention program on anxiety and depression 6 months after coronary artery bypass grafting: a randomized controlled trial. *J Psychosom Res* 2007; 62: 411–418.

98 Sebregts EH, Falger PR, Appels A, *et al*. Psychological effects of a short behavior modification program in patients with acute myocardial infarction or coronary artery bypass grafting. A randomized controlled trial. *J Psychosom Res* 2005; 58: 417–424.

99 Hermele S, Olivo EL, Namerow P, *et al*. Illness representations and psychological distress in patients undergoing coronary artery bypass graft surgery. *Psychol Health Med* 2007; 12: 580–591.

100 Smith TW, Cundiff JM. Aggregation of psychosocial risk factors: Models and methods. In *Handbook of cardiovascular behavioral medicine*; Waldstein SR, Kop WJ, Katzel LI, Eds., Springer: New York, 2011.

101 Oxman TE, Barrett JE, Freeman DH, *et al*. Frequency and correlates of adjustment disorder related to cardiac surgery in older patients. *Psychosomatics* 1994; 35: 557–568.

102 Phillips-Bute B, Mathew JP, Blumenthal JA, *et al*. Relationship of genetic variability and depressive symptoms to adverse events after coronary artery bypass graft surgery. *Psychosom Med* 2008; 70: 953–959.

103 Szekely A, Balog P, Benko E, *et al*. Anxiety predicts mortality and morbidity after coronary artery and valve surgery-a 4-year follow-up study. *Psychosom Med* 2007; 69: 625–631.