

Cognitive function in patients with coronary artery disease: A literature review

Journal of International Medical Research

2018, Vol. 46(10) 4019–4031

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DOI: 10.1177/0300060517751452

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Abstract

Objective: Cognitive function impairment is a well-documented complication of cerebrovascular disease (CBVD). Less is known about what factors affect the deterioration of cognitive function in patients with coronary artery disease (CAD). The aim of this review is to explore recent studies investigating factors associated with cognitive function in patients with CAD.

Methods: Studies published from 2010 to 2016 were identified through a systematic search of MEDLINE/PubMed and were included if they addressed factors affecting cognitive function in the CAD population.

Results: Of the 227 publications identified, 32 were selected for the review. Five factors tentatively affecting cognitive function in patients with CAD were identified: coronary artery bypass grafting (CABG) surgery, apolipoprotein E4 (APOE4) genotype, left ventricular ejection fraction (LVEF), medication use, and various hormones and biomarkers.

Conclusion: New techniques in CABG surgery have proven to alleviate postoperative cognitive decline. Researchers are still debating the effects of APOE4 genotype, LVEF, and the use of cardiovascular medications on cognitive function. Thyroid hormones and biomarkers are associated with cognitive function, but the exact nature of the association is debatable. Longitudinal studies should clarify those associations. In addition, cross-sectional studies addressing other causes of cognitive decline in patients with CAD are warranted.

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Keywords

Cognitive function, coronary artery disease, coronary artery bypass grafting, APOE4 genotype, left ventricular ejection fraction, medication use, biomarkers

Date received: 26 July 2017; accepted: 11 December 2017

Background

Coronary artery disease (CAD) is one of the most common causes of death worldwide and is predicted to remain the most frequent cause of death for the next 20 years.¹ CAD shares mutual risk factors with cerebrovascular disease (CBVD). Such factors include age (men aged >45 years, women aged >55 years), sex (men > women), family history of heart disease, and race (African-American). Mutual modifiable risk factors include an elevated low-density lipoprotein cholesterol (LDL-C) level, hypertension, diabetes,² smoking, obesity, physical inactivity, metabolic syndrome, mental stress, depression, excess consumption of alcohol, and low or lack of regular physical activity.³

Both CBVD and CAD can severely affect cognitive function,^{4,5} which are internal mental processes underlying how people perceive, remember, speak, think, make decisions, and solve problems.⁶ Cognitive impairment is defined as a disruption of certain cognitive functions such as attention, planning, or memory.⁷ Many studies have investigated the association between cognitive impairment and CBVD or stroke,⁸⁻¹¹ whereas fewer have examined the link between cognitive function and CAD.⁴ Because of the well-documented role of vascular factors in cognitive decline, the term “vascular cognitive impairment” was recently introduced to better define causes of cognitive decline and develop new therapeutic strategies with a focus on the vasculature.¹² Indeed, global impairment of

vascular functioning (including the brain) is common in patients with CAD,^{13,14} suggesting that vascular impairment could be an important risk factor for cognitive decline in patients with established CAD. In contrast to CBVD, CAD has been linked with worsening of global cognitive function in few studies. Therefore, further research in this area is warranted.⁴ A study of 1101 patients with CAD aged >65 years showed significant levels of cognitive impairment; 24% had a mild form, 22% had a moderate form, and 16% had a severe form. In fact, among the patients with CAD aged >65 years without a history of stroke, the prevalence of cognitive dysfunction was 62%.¹⁵

Recent studies have demonstrated a direct link between CAD and impaired brain function. A cross-sectional study by Ottens et al.¹³ comparing 102 patients with CAD after revascularization with 48 control subjects confirmed that patients with CAD had worse cognitive function and greater cerebrospinal fluid volume, which was found to be an independent predictor of poor cognitive function.¹³ In subjects without dementia, cerebral white matter lesions were strongly associated with an increased risk of impaired cognitive performance.¹⁶ A cross-sectional study by Santiago et al.¹⁷ further exemplified these findings by analyzing 49 patients with CAD and showing that cerebral white matter microstructural integrity was associated with executive function impairment.¹⁷ Zheng et al.¹⁴ performed a prospective

multisite longitudinal study of 74 cognitively normal participants attending aging centers in California and found that CAD was linked to cognitive decline as evaluated using magnetic resonance imaging measures of subclinical vascular brain injury.¹⁴

A decline in cognitive function has also been shown to coexist with CAD, and cognitive impairment is a common complaint in these patients.¹⁸ Impaired adult cognition predicts a higher mortality risk¹⁹ and greater dependency on others to carry out activities of daily living.²⁰ Moreover, accelerated cognitive decline has been linked to dementia²¹ and reduced quality of life.²² Studies examining the cognitive function of patients with CAD are encouraged to better identify individuals at high risk for cognitive decline.²³

It is also important to determine which factors may be associated with cognitive function in this particular population. It has been stipulated that healthy cognition is linked with sociodemographic factors such as sex, age, and education. However, many other studies analyzing the CAD population have shown that these factors are not the strongest predictors of cognitive decline. Therefore, the aim of our study was to review recent research that investigated factors associated with cognitive function in patients with CAD. Because the major reviews of cognitive function in patients with CAD extend only through 2012,^{24–26} we performed this review to update the literature with the newest (2010–2016) emerging themes.

Material and method

An electronic search of the MEDLINE/PubMed database was conducted to identify relevant studies published from January 2010 to December 2016. The keywords “cognitive function” and “coronary artery disease” were used. Studies were included if they were published in English and

investigated factors affecting cognitive function in patients with CAD. We excluded studies that analyzed the cognitive function of patients without CAD as well as those whose primary aim was not to measure cognitive function. We also excluded reviews and opinion pieces. Because this study was a review, no ethics committee approval was needed.

Results

The search strategy returned 227 publications. After removing 94 titles from the review scope, 133 of the remaining records were screened for eligibility by the authors. The screening process of papers meeting the review criteria resulted in exclusion of 101 articles. Thus, the search produced 32 articles reporting studies suitable for review (Figure 1).

Characteristics of included studies

The age of participants across all analyzed studies ranged from 54 to 75 years, with a median age of 64 years. Two studies analyzing postoperative cognitive outcomes of CABG particularly aimed their investigation at relatively young adults with a mean age of 54 ± 8 years²⁷ and 56 ± 6 years.²⁸ Several studies focused on older adults with a mean age ranging from 71 ± 9 to 75 ± 8 years.^{29–31} Study samples ranged from 17 to 4752 patients with a median number of 101 participants. Eleven studies were described as cross-sectional studies,^{31–41} eight were comparative studies,^{42–49} five were randomized controlled trials,^{50–54} and two were retrospective cohort studies.^{30,55} The remaining studies were a prospective cohort study,²⁹ an observational study,²⁷ a follow-up study,²⁸ a case-control study,⁵⁶ a longitudinal study,⁵⁷ and an interventional study.⁵⁸

The studies employed various cognitive function measures. The tests used to examine

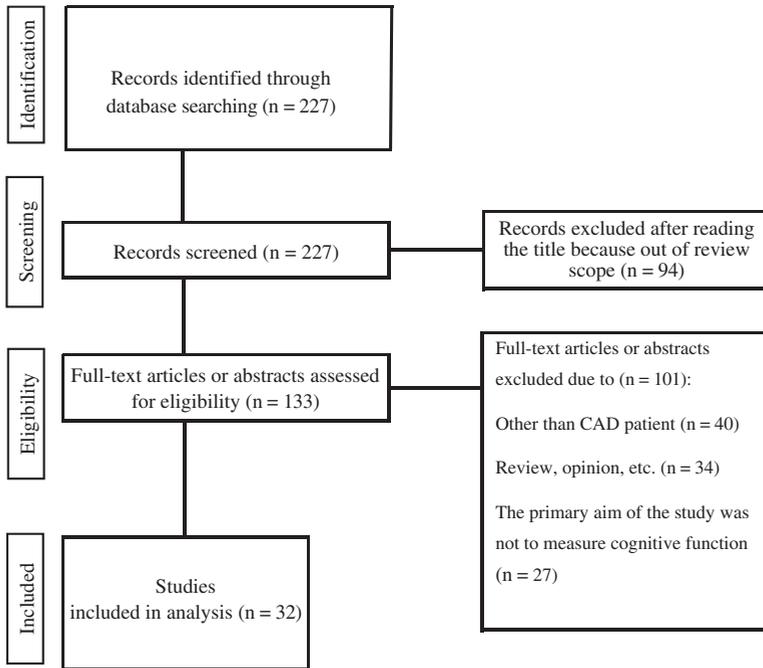


Figure 1. Identification of reviewed studies

the executive domain of cognitive function were the Trail Making Test,^{29,31,34–41,48,50,51,54,55,58} Digit Symbol Substitution Test,^{31,35–41,50,54,55} Digit Span Test,^{31,36,39,42,43,49,51–53,55} and Controlled Oral Word Association Test.^{29,31,35,37,38,43,45,51,54} Verbal memory was most commonly assessed using the California Verbal Learning Test.^{35,37,38,40,41,54} The global cognitive function measure used in most of the studies was the Mini-Mental State Examination.^{27–31,33,34,37,39,40–42,56}

The timing of cognitive outcome assessment varied greatly among the studies and ranged from 2 days^{28,33,43,44,46–49} to 7 years^{32,53} after the intervention. Similarly, there was a wide variability in the follow-up cognitive outcome assessment among all studies, ranging from 1 week to 60 months.

The definition of cognitive decline also varied across studies, and some studies did not present the used definition/construct of cognitive decline.^{29–31,36,37,47,54,57,59} However, most studies used the negative deviation from

the z-score of the cognitive functioning tests.^{27,34,35,38,41,44,45,49,51,55,58} Some studies focusing on CABG discussed their findings in light of postoperative cognitive decline (POCD),^{27,28,42–46,52,58} while others did not address this issue.^{47,50,51,53,59}

The reviewed studies mainly focused on the following risk factors for cognitive function in patients with CAD: CABG,^{27,28,32,42–48,50–53,58} apolipoprotein E4 (APOE4) genotype,^{29,33,55,56} left ventricular ejection fraction (LVEF),^{31,34,57} medication use,^{30,35–37,54} hormones and biomarkers,^{38,40,49} and other risk factors.^{39,41}

Discussion

CABG surgery

CABG is a procedure used to reduce mortality in patients with extensive CAD. As with any operation, CABG is associated with potential perioperative and long-term

complications. The effects of CABG on cognitive function are of clinical relevance and have been examined. Newman et al.⁶⁰ reported a decline in cognitive function among patients who underwent CABG. The risk factors for CAD also contribute to post-CABG cognitive outcomes. For example, Krannich et al.⁴⁷ found that patients with preexisting diabetes mellitus had decreased cognitive function after the operation.

Different approaches are used to reduce the burden of CABG on cognition. For example, antiplatelet therapy and an even more effective method, dual antiplatelet therapy, have been implemented. In a study by Holinski et al.,⁴⁴ dual antiplatelet therapy had a greater cerebrovascular protective effect and resulted in significantly lower decline in overall cognitive function compared with single antiplatelet therapy.

CABG can be performed using cardiopulmonary bypass (on-pump) or on the beating heart (off-pump). In the CABG Off or On Pump Revascularization Study (CORONARY) study, Lamy et al.⁵⁰ found less reduction in cognitive function in patients who underwent on-pump than off-pump CABG. However, no significant differences were found between the two groups at 30 days or 1 year postoperatively. Another long-term follow-up study⁵³ showed that after 7.5 years, patients who had undergone off-pump CABG showed better attention and were better at simultaneously tracking and manipulating information.

A more recent innovative technique, no-touch off-pump CABG, provides a more favorable prognosis for preserving cognition. In this approach, all manipulation of the ascending aorta is avoided. A study by Szwed et al.⁴³ showed better cognitive outcomes at discharge in patients who underwent no-touch than traditional off-pump CABG.

Conventional extracorporeal circulation systems have been modified to counteract brain hypoperfusion resulting from the use of a cardiopulmonary bypass pump. Anastasiadis et al.⁵² found that minimal extracorporeal circulation produced better cognitive results than conventional extracorporeal circulation. Another study showed that a roller pump used for cardiopulmonary bypass induced less cerebral damage and preserved cognitive function better than the standard centrifugal pump.⁴⁶

APOE4 genotype

Studies analyzing cognitive function in the general population have shown that the APOE4 genotype might be a predictor of cognitive decline over time. Lipnicki et al.⁶¹ analyzed 2 to 15 years of longitudinal data from 14 cohorts in different European, Asian, and North American countries involving a total of 42,170 individuals aged 54 to 105 years (42% male) and found that most cognitive measures of APOE4 genotype carriers declined slightly more rapidly than those of non-carriers, with processing speed showing the greatest difference. A meta-analysis of 77 studies representing 40,942 cognitively healthy adults showed that the APOE4 genotype carriers performed worse in tests measuring episodic memory, executive function, and overall global cognitive ability.⁶²

Studies of the APOE4 phenotype in the CAD population suggest similar results. A retrospective cohort study analyzing the data of 233 patients with CAD and 124 non-cardiac patients showed that the APOE4 genotype was associated with neurocognitive decline 5 years following cardiac surgery.⁵⁵ Another prospective cohort study examined the association between depressive symptoms and cognitive decline over the course of 30 months among 374 patients with CAD and explored whether any observed associations were related to

the APOE4 allele.²⁹ The study showed that persistent depressive symptoms were associated with significantly greater declines in all cognitive measures over a span of 12 to 30 months after adjusting for sociodemographic and clinical factors.

However, an even more significant decline in global cognition was evident for patients with persistent depressive symptoms and the APOEε4 allele. Cross-sectional studies have provided different results regarding the association of APOE4 and cognition in patients with CAD. For example, in a case-control study, Barekattain et al.⁵⁶ analyzed 40 patients with CAD with mild cognitive impairment and 40 patients with CAD with normal cognitive function and found no significant difference in the APOE4 plasma levels between the two groups. Similarly, another cross-sectional study comprising 123 patients with CAD revealed no differences in APOE plasma levels or APOE genotype frequencies among patients with mild/moderate or severe atherosclerosis.³³ However, global cognitive function was significantly lower than that in the normal population, irrespective of atherosclerosis.

LVEF

A low LVEF (<40%) is important for diagnosing and monitoring heart failure and has been linked to cognitive impairment. Jefferson et al.⁶³ found that a low LVEF in normally aging adults was associated with accelerated cognitive aging (mostly in the domains of executive function such as cognitive flexibility) and with impaired verbal memory, visuospatial memory, and visuospatial organization. Similarly, Gottesman et al.³⁴ found that a low LVEF was associated with worse cognitive performance, particularly among individuals with low mean arterial pressure. A very recent review provided a summary

of the association between LVEF and the executive domains of cognitive function.²⁵ However, more recent studies have failed to prove such associations.^{31,57} For example, in a longitudinal study, Almeida et al.⁵⁷ investigated whether adults with CAD and a reduced LVEF showed evidence of accelerated cognitive decline over a period of 2 years when compared with adults with a normal LVEF with and without a history of CAD. That study revealed that both groups of participants experienced similar changes in cognitive decline. The Cambridge Cognitive Examination of the Elderly test scores of participants with congestive heart failure showed a more rapid cognitive decline compared with controls without CAD over a period of 2 years; however, the difference in the LVEF could not explain the observed associations.⁵⁷

Medications

For many patients with CAD, the first line of treatment is medical therapy. Most of the studies that have examined the impact of CAD medication on cognition were recently published, and most focused on medications that are essential to CAD therapy or on drugs/supplements that are known to affect the nervous system and cognition in general.

Medications prescribed to control vascular risk factors often cross the blood-brain barrier and may interfere with cognitive performance by producing anticholinergic effects. Lanctot et al.³⁷ calculated the cumulative anticholinergic activity of all drugs taken by participants using the anticholinergic cognitive burden scale. Anticholinergic exposure was proven to be associated with poorer performance on the Trail Making Test and Animal Naming Test in patients with CAD.³⁷ Another study also showed that even a single group of anticholinergic medications, namely the beta-1-selective beta-blockers,

was associated with worse incidental learning independently of sociodemographic characteristics, clinical CAD severity, and depression/anxiety symptoms.³⁶

Lipid-lowering therapy is often necessary for patients with CAD. Statins limit cholesterol synthesis and increase LDL-C catabolism.⁶⁴ They have demonstrated clear benefits in reducing morbidity and mortality in the secondary prevention of CAD but have been thought to be associated with decreased cognition because of low concentrations of LDL-C. However, a recent study by Rej et al.³⁵ showed that low LDL-C levels were not associated with impairment in global cognition or individual cognitive domains. In their study, the use of high-dose statins was actually associated with higher scores on visuospatial memory and executive function tests.³⁵ In addition, Lilly et al.⁶⁵ showed that non-persistent statin use was associated with a greater likelihood of being diagnosed with psychotic or cognitive disorder within 4 years. Statin use has a benefit with respect to secondary prevention in patients with CAD.⁶⁶ In 2012, the United States Food and Drug Administration issued a statement raising awareness on potential adverse cognitive adverse effects, including memory loss and confusion, associated with statin use.⁶⁷ However, a recent study suggested a beneficial effect of combined statin use with exercise therapy on cognitive functioning in patients with CAD.⁶⁸ A pilot study of 43 consecutive patients with CAD with mild cognitive decline examined the potential synergistic effect of statin therapy and weekly in-hospital aerobic exercise for 5 months on cognitive functioning. Interestingly, the patients already on statin therapy at the beginning of the trial displayed a more significant improvement in cognitive function than statin-naïve patients, implying that exercise was beneficial for cognition in this intervention.⁶⁸

Supplements may affect cognition in patients with CAD. Studies have shown that omega-3 fatty acids may play a protective role in maintaining cognitive function and improve reference memory-related learning. Mazereeuw et al.⁵⁴ evaluated patients with CAD and found a significant protective effect of omega-3 long-chain polyunsaturated fatty acids (LCPUFAs) on cognitive function, particularly immediate verbal memory. However, these cognitive benefits were not observed in patients with comorbid depression.⁵⁴ However, another study showed no statistically significant effect of oral supplementation with omega-3 LCPUFAs on maintaining cognitive function.⁶⁹ Yagi et al.³⁰ assessed the levels of various omega-3 LCPUFAs in patients with CAD, including eicosapentaenoic acid, docosahexaenoic acid, dihomo-gamma-linolenic acid, and arachidonic acid. They found that a low eicosapentaenoic acid serum level was a risk factor for cognitive impairment (lower Mini-Mental State Examination score), although the levels of the other three omega-3 LCPUFAs were excluded from the statistical analysis.³⁰

Hormones and biomarkers

A reduced concentration of free triiodothyronine and increased concentrations of N-terminal pro-B-type natriuretic peptide, high-sensitivity C-reactive protein (hs-CRP), and interleukin-6 (IL-6) are very common in patients with CAD and are associated with an unfavorable CAD prognosis.^{70,71} However, the influence of these serum biomarkers on the cognitive function of patients with CAD is not well established. A large proportion of studies have focused on global cognitive function⁷² and its association with thyroid hormones and other biomarkers. However, a link between these markers and more specific cognitive domains remains to be identified because

only a few studies have attempted to analyze these associations. A comparative study by Hudetz et al.⁴⁹ documented recent memory impairment in patients with CAD with elevated hs-CRP and IL-6 levels compared with low hs-CRP and IL-6 levels. Another study showed that a decline in cognitive function of patients with CAD was associated with the serum BDNF concentration but not the IL-6 concentration, tumor necrosis factor- α concentration, or val66met genotype.⁴⁰ A cross-sectional study of 24 depressed patients with CAD by Mazereeuw et al.³⁸ showed that a greater abundance of platelet-activating factors was associated with poorer global cognitive performance.

Other ongoing or emerging themes

In addition to the identified emerging or ongoing research topics, we found some studies that offered new risk factors for cognitive decline in patients with CAD. In a cross-sectional observational study, Swardfager et al.⁴¹ examined cardiopulmonary fitness in 81 patients with CAD by measuring peak oxygen uptake in a standardized exercise stress test. The study showed an association between peak oxygen uptake and executive domain cognitive function scores.

Several studies have shown that patients with CAD commonly experience depression and anxiety, which place them at greater risk for both cognitive decline⁵⁷ and death.⁷³ A recent cross-sectional study by Burkauskas et al.³⁹ of 510 patients with CAD who had not undergone CABG demonstrated associations between depression symptoms and slower psychomotor function. Higher state anxiety scores were shown to be associated with worse auditory attention and processing speed. Moreover, a type D personality, which is defined by personal characteristics of negative

affectivity and social inhibition—was correlated with impaired global cognitive function.

Limitations of our review strategy include a lack of diverse search engines/databases, no predefined hypotheses, and heterogeneity across the studies.⁷⁴ However, we used a systematic approach to reduce the risk of selection bias.⁷⁵ We reviewed only recently published studies investigating cognitive function in patients with CAD with the goal of capturing emerging research themes in the field.

The reviewed studies were heterogeneous in their timing of cognitive outcome assessment and measures used. These methodological differences can at least partially explain the contradictory findings across the studies. Only some of the reviewed studies provided the definition of cognitive decline/POCD used in the study. Therefore, it is important to discuss the study findings in light of the assessment timing and instruments used, especially because recent studies consider that POCD is a reversible condition.⁵⁰ A recent meta-analysis showed that the incidence rate of POCD during the perioperative period (1–2 weeks) and at 3 months postoperatively was significantly greater following on-pump than off-pump CABG. However, no significant between-group differences were observed at the 6- or 12-month follow-ups.²⁶ These findings suggest that there are no convincing differences in long-term POCD between off-pump and on-pump CABG procedures.⁷⁶

Another important aspect of the reviewed studies is the variability of outcome measures. There are recommendations advising which cognitive function tests should be administered in these types of studies.⁷⁷ However, recent studies still lack a consensus on the use of standardized cognitive batteries for testing individuals with CAD.

As important new themes arise in the investigation of cognitive function in the CAD population, several issues might hinder our understanding of the impact of the problem. One such issue is the lack of consensus on the cognitive tests used.⁷⁸ Another potential problem is the lack of a definition or unified concept of cognitive decline.⁷⁹ Finally, substantial disagreement still exists regarding the statistical approach with which to define meaningful change in cognitive function.⁸⁰

Conclusions

The recent studies reviewed in this report suggest that cognitive function impairment in patients with established CAD is associated with CABG surgery, the APOE4 genotype, a low LVEF, anticholinergic medication use, and hormones and biomarkers. Further longitudinal studies should either confirm or refute whether these are indeed the risk factors for cognitive decline in patients with CAD. Studies aiming to identify neuroprotective interventions that could be used to prevent cognitive decline in patients with CAD are strongly encouraged, as are studies focused on identifying novel risk factors for cognitive decline.

Declaration of conflicting interests

Julius Burkauskas works as a consultant at Cogstate, Ltd. The other authors have no conflicts of interest to report.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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