ABSTRACT

Background: Cognitive impairments (CI) may limit uptake of secondary prevention in acute coronary syndrome (ACS) patients but is poorly understood, including in cardiac rehabilitation (CR) participants.

Aim: To explore CI in relation to psychological state in ACS patients over the course of CR and follow-up.

Methods: ACS patients without diagnosed dementia were assessed on verbal learning, processing speed, executive function and visual attention, at CR entry, completion and follow up and scores adjusted using normative data. The Hospital Anxiety and Depression Scale measured psychological state.

Results: Participants (n=40) had an average age of 66.2 (±8.22) years and were 70% male. Mild CI occurred at CR entry in single 62.5% and multiple domains 22.5% but was significantly less prevalent by CR completion (52.5% and 15.0%) and follow-up (32.5% and 7.0%). Domains most often impaired were verbal learning (52.5%) and processing speed (25.6%), again decreasing significantly with time (verbal learning CR completion 42.5%, follow-up 22.5%; processing speed CR completion 15.0%, follow-up 15.0%). A small group of patients had persistent multiple domain CI.

At CR entry patients with CI in processing speed, a single domain or multiple domains had more depression, and patients with CI in executive function had more depression and anxiety.

Conclusions: At CR entry, mild CI is very common in post-ACS patients and worse in patients who have depression or anxiety symptoms. CI decreases significantly by CR follow-up. A small proportion of patients have persistent, multiple domain CI flagging potential long-term changes and the need for further investigations and cognitive rehabilitation.

Keywords

Mild cognitive impairment, acute coronary syndrome, cardiac rehabilitation, anxiety, depression

Implications for practice

- Mild CI is very common in ACS patients attending CR and may create significant barriers to understanding and uptake of secondary prevention behaviours.
- Screening for mild CI in this population is recommended at CR entry so that education strategies may be modified, and repeated at CR discharge to identify persistent CI requiring further neurocognitive testing and/or intervention.
- Mild CI is strongly correlated with depression and anxiety and while no cause and effect can be presumed, screening, monitoring and referral for treatment should be instituted.

INTRODUCTION

Uptake of secondary prevention behaviours by acute coronary syndrome (ACS) patients is the cornerstone to limiting future coronary heart disease (CHD) events.[1] Despite this, ACS patients find initiation of secondary prevention behaviours challenging.[1-3] Six months post ACS only 22.5% of patients are achieving exercise guidelines[2] and 29% of patients are not taking their medications as prescribed.[3] ACS patients are often overwhelmed by their new diagnosis and may experience depression and mild cognitive impairment (CI).[3, 4] Comprehensive cardiac rehabilitation (CR) addresses many issues ACS patients face, and has well-established benefits for secondary prevention behaviours, mortality and readmissions.[5, 6] CR also has the potential to benefit cognitive outcomes in CHD patients because shared risk factors are addressed.

Cognitive impairment is common in CHD patients, potentially due to a shared pathway of systemic atherosclerosis and vascular CI.[7] However, the prevalence of CI in ACS survivors is uncertain; a recent systematic review reported widely disparate prevalence rates of 9-85%, although slightly less variable rates of CI of 11- 52% were reported during early recovery.[8] CI is important to detect in early recovery and manage and accommodate because even mild CI has the potential to interfere with learning, planning and execution of secondary prevention behaviours,[9] and of concern, 30% of mild CI cases will progress to dementia within 5 years.[7]

CR provides a potential platform to improve treatment of ACS patients and prevention of CI. Mild CI may be detected through screening at CR entry, and for those who screen positive, education strategies could be modified to improve effectiveness. Cognitive screening could be repeated at discharge, so that those with persistent CI could be referred for formal neuropsychological testing, other investigations (e.g. brain magnetic resonance imaging) or cognitive rehabilitation programs.[10, 11] CR is reported to improve attention, executive function and memory in a recent systematic review.[8] However, methodological limitations were common and included small sample sizes, combining ACS patients with other cardiac populations known to have more CI, such as cardiac surgery and heart failure patients, and failing to define mild CI. Furthermore, mild CI may

be directly related to psychological wellbeing including anxiety and depression,[12] aspects which tend to improve post ACS regardless of CR participation.

There is some indication that mild CI is prevalent in ACS patients attending CR and changes with time. The term 'Mild Cognitive Impairment' has been utilised throughout the ageing literature to document impairment occurring beyond an expected threshold (typically -1sd or -1.5sd) relative to a person's age and education level based on appropriate normative data.[12] This concept has been useful to identify individuals in a 'high risk' state, who are more likely to progress to dementia within five years. However, difficulties in interpretation of CI results occur in relation to CR due to the varied timing and duration of CR and lack of definitions of mild CI.[13] At CR entry, mild CI (defined as ≥-1sd) has been reported in 36% (two weeks post ACS) and at discharge in 33% (three weeks post ACS) of patients.[14] At CR entry (three months post ACS) the domains affected most often have been reported to be verbal fluency (84.5%), learning/memory (60.3%),[14] attention-executive-psychomotor (29.4%) and verbal memory (29.4%) domains, which improved significantly to 23.5% and 11.8% respectively at CR discharge (12-weeks post CR entry).[15] However, adjustment for known correlates of mild CI, such as age and education, via comparison with normative data (and the computation of *z*-scores) was rarely used. Similarly, only one study examined concurrently depression and anxiety, which are known correlates of CI.

Given the potential that CR offers to screen and support ACS patients who have CI, further exploration is warranted. This study aims to address the gaps in knowledge of mild CI in ACS patients attending CR by 1) determining the profile of CI at CR entry (2 weeks post ACS), CR completion (6 weeks post entry) and follow-up (8 weeks post completion) and 2) determining associations between mild CI and anxiety and depressive symptoms at CR entry.

METHODS

The study used a prospective descriptive design with measures taken at CR entry, completion and follow-up and data collection in 2017. The study conforms to the principles

outlined in the Declaration of Helsinki and was approved by the local health district Human Research Ethics Committee LNR/15/HAWKE/342.

Subjects and setting

The study was conducted at two university teaching hospitals in Sydney, Australia. CR programs at these sites have systematic referrals for all ACS patients. Programs typically begin 2-3 weeks post hospital discharge and include 6 weeks of individually-tailored supervised structured aerobic and resistance exercise sessions of 1- hour 1-2/week and a home-based program, which directs patients to achieve an accumulation of 30 minutes of exercise 5 days/week. Regular education sessions on diet, stress management, medications and exercise are included. Participants may choose to continue with exercise sessions alone for up to 16 weeks afterwards.

Participants were considered eligible if they 1) had commenced CR at either hospital, 2) were admitted for a diagnosis of ACS (unstable angina, ST- elevation and non ST-elevation myocardial infarction (STEMI and nSTEMI), primary percutaneous coronary intervention (PCI), 3) did not have known dementia or a neuropsychiatric diagnosis, 4) were fluent in English, and 5) were able to participate in the full 16 weeks of the study.

DATA COLLECTION

Cognitive Performance

A battery of five standardised neuropsychological tests was used including assessment of: 1) verbal learning by the Rey Auditory Verbal Learning Test (RAVLT), 2) processing speed by the Trail Making Test A (TMT–A) and Cogstate identification task (Cogstate ID), 3) executive function domain by the Trail Making Test B (TMT–B), and 4) visual attention by the Cogstate detection task (Cogstate DET). These tests were selected in consultation with a neuropsychologist (SN) due to their ability to detect very early changes in attention/processing speed, learning/memory and executive functions (areas most often effected by vascular-based brain changes).[16-18] The tests are brief to suit busy patient-care settings.[18, 19] The study research nurses received one-on-one training with a

neuropsychologist to administer all tests. The neuropsychological tests took an average 15-25 minutes to complete depending on the patient's level of impairment. The full detail of the tests including validity and reliability are provided in Supplementary Table 1 and a brief outline of each test is provided below. All tests are reported by both raw scores and education and/or age adjusted Z-scores.

The **RAVLT** was used to assess the ability to learn and then recall an unstructured list of 15 unrelated words in three trials.[16] The RAVLT has been used in cardiac surgical patients successfully.[20] While 5 trials are typically administered, we modified the test to administer only 3 trials. Lower scores indicate more impairment (potential range 0-45). An alternate form of the words was used at each time point.[21] In our study the modified RAVLT had good reliability (Cronbach's Alpha 0.90).

The **TMT-A** is a test of visuomotor speed, with participants asked to draw a continuous line connecting encircled numbers in numerical order (1-25) as quickly as possible while avoiding mistakes.[22] Longer time to complete reflects poorer cognitive function.[19] In heart failure patients TMT-A has reported reliability with test-retest (intra class correlation 0.79 and Cronbach's Alpha 0.89).[23]

Cogstate ID measures choice reaction time[17] with participants asked to indicate recognition of a flipped joker card on a computer screen for 30 correct trials. Longer reaction time indicates worse cognitive function.[22] The Cogstate ID has excellent reliability in cardiac patients (Intra class correlation 0.89).[25]

TMT–B measures executive function[18] and requires participants to draw a continuous line alternating between numbers and letters (1, A, 2, B etc.) until they reach the end of 25 circles. More time taken indicates more impairment. TMT-B has been shown to be reliable in a heart failure population with high test-retest values (intra class correlation 0.81 and Cronbach's Alpha 0.89).[24]

Cogstate DET task assesses visual attention[21] and participants are required to correctly identify when a playing card changes between red and black on a computer screen for 35 correct trials. More time taken indicates more impairment.[18] In a cardiac population, the Cogstate DET task demonstrated excellent reliability (Intra class correlation 0.91).[24]

Psychological State

Symptoms of anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS), selected due to its suitability for detecting psychological symptoms in the context of medical comorbidities.[26] HADS is a self-reported questionnaire of 14 items, half each for symptoms of depression and anxiety. Responses score 0 to 3 for a total of 0-21 for each subscale (depression and anxiety) with higher scores indicating more symptoms.[27] HADS has been used extensively in cardiac patient samples,[28] with good reliability in both the anxiety (Cronbach alpha 0.94) and depression subscales (Cronbach alpha 0.88).

Sample characteristics

Data were collected from the patient and extracted from the medical record for socio-demographics, anthropometrics (height, weight), medical history and CVD risk factors.

Procedure

Potential participants were screened for eligibility and approached to join the study at their initial CR assessment. Data was then collected from the patient or the medical record, and further data collected on the day of CR completion and at a follow-up clinic visit. Three phone call attempts were made, if no contact participants were considered lost to follow-up. Using these methods participants at each stage numbered (Figure 1) 55 screened, 40 enrolled at baseline (CR entry), 32 at CR completion and 30 at CR follow-up. There was no significant difference in drop-outs at CR completion or follow-up for CI at baseline for age, gender and cognitive profile.

Classification of CI

All cognitive test scores were converted to a *z*-score using age- and where applicable education-adjusted normative data. For each test, a participant was classified as having 'impairment' if their *z*-score fell below -1sd. Since this study sought to detect incipient CI in a high socioeconomic area of metropolitan Sydney, a more sensitive cut-off of *z*-score ≤-1 was utilised. This cut-point has also been used in studies screening cardiac populations for CI.[19]

If any individual demonstrated an impairment on only one test, they were classified as meeting impairment for single domain mild CI and multiple domain mild CI if there were impairments on at least two tests. For individuals that had impairments on both tests of processing speed, this was coded as only one impairment, not two.

Statistical Analysis

Data were analysed using SPSS, version 24. The sample characteristics, psychological status and prevalence of CI overall and in domains were described using means and standard deviations, number and percentages. Continuous data were assessed for normal distribution using the Shapiro-Wilk test and where this criterion was met, then changes in mean test scores, anxiety and depression were assessed using paired t-tests. For data that were categorical or proportions, Chi-squared or Fisher's Exact test were used for comparison. All tests were two-tailed and employed an alpha set at $p<0.5$.

RESULTS

The sample had a mean age of 66.2 (±SD 8.22) years, were primarily male (70%), 45% were employed and the average schooling was 16 (± SD 3.72) years (Table 1). The most common referral diagnosis was nSTEMI (57.5%). CVD risk factors were very common; the most prevalent being hypercholesterolaemia (87.5%), hypertension (50%), diabetes (22.5%), obesity (22.5%) and sedentary lifestyle (20%).

Patients screened positive for depression (12.5%) and anxiety (27.5%) symptoms at CR entry as detailed in Table 2. The proportion of patients screening positive for these symptoms decreased significantly by CR completion (9.4%, $p = .001$ and 25.0%, $p = .012$). However, at CR follow-up while the proportion of patients screening positive for anxiety continued to decrease significantly (24.1%, $p <.001$) the proportion screening positive for depression increased (17.2% $p = .01$).

Cognitive Performance

At CR entry 62.5% of participants had a single domain mild CI and 22.5% had multiple domain mild CI (Figure 1). The cognitive domain most often impaired at CR entry was

verbal learning (52.5%) followed by processing speed (25.6%) and executive function (12.8%) and the least common was visual attention (9.7%). and were associated with mild CI (Table 3). Patients who had executive dysfunction at CR entry had more depressive (p=.004) and anxiety symptoms (p=.004), and patients with slowed processing speed (p=.008), any (p=.043) or multiple domain impairments (p=.016) had more depressive symptoms.

Change in Cognitive Performance

The percentage of patients who screened positive for mild CI declined significantly from CR entry to completion for a single domain (62.5% to 52.5%, p = .002) and for multiple domains (22.5% to 15.0%, p = .021) and from CR completion to follow-up in a single domain (52.5% to 32.5%, p = .019) and for multiple domains (15.0% to 7.0%, p = .05) (Figure 2). CI persisting from CR entry to completion occurred in a single domain (42.5%) and in multiple domains (10%). CI persisting from CR completion to follow up occurred in a single domain (17.5%) and in multiple domains (2.0%).

The specific domains of cognitive impairments that declined significantly from CR entry to completion were verbal learning (52.5% to 42.5%, p =.002) and processing speed (25.6% to 15.0%, p = .006). From CR completion to follow up the specific domains of cognitive impairment that declined were verbal learning (42.5% to 22.5%, p = .013) and visual attention (15.0% to 10.0%, p = .002) (Supplementary Table 2).

DISCUSSION

The study results demonstrate mild CI is very common in ACS patients attending CR. At CR entry almost two-thirds had mild CI in a single domain (62.5%) and more than one in five had multiple domains (22.5%) affected, most often in the new verbal learning and processing speed domains. Impairment in these domains may create significant barriers to learning about secondary prevention. Depression and anxiety symptoms were also pronounced and associated with mild CI at this time. Greater depressive symptoms were evident in those with decrements in processing speed and executive function, which is

aligned with that found in the depression literature.[29] There was an unexpected increase in the proportion of patients meeting the HADS threshold for symptomatic depression at CR follow-up.

The study results contribute to emerging knowledge of mild CI in ACS patients. Our study results, at 62.5% for a single domain and 22.5% for multiple domain impairments are midway between previous reports of 36% (2 weeks post ACS)[30] and 85% (3 months post ACS).[8] Different scoring and score standardising methods and samples may have contributed to variations and make comparison difficult. Adjustment for age and education occurred in our study but may not have fully compensated for differences in study samples. Our study participants were much older, but also had substantially more education, particularly in comparison to Silva, Pereira [14] study participants who had less than 9 years education. Education has well-established neuroprotective benefits for cognitive performance, and is theorised to provide a cognitive reserve against brain degeneration, ostensibly meaning that those with more education or 'reserve' are more resilient to brain pathology and greater levels of pathology would be required in order to detect clinical deficits.[31]

Given that we employed only a limited test battery comprising five tests, it is likely that our screening test battery, whilst sensitive, may not have captured all impairments, and thus, may have under-estimated the rates of mild CI in our sample. On balance, however, we used a fairly liberal cut-score of -1sd to determine CI. Whilst we felt this was appropriate for a highly educated sample, it could have misclassified those in the Low Average IQ range as having impairments. Furthermore, it has been shown that multiple measures of a cognitive domain provide a more reliable estimate of a cognitive construct than any single measure.[32] Thus, studies requiring impairment in more than one test of any given domain may have produced different and more stable rates of cognitive impairment. Further work using a more comprehensive assessment of cognition and using more stringent cut-scores for mild CI is now required.

Interestingly, in this study, we found that mild CI may be transient as demonstrated by significant decreases in prevalence over the course of CR participation and follow-up. The prevalence of mild CI in our study decreased by 10% from CR entry to discharge of

a 6-week program, with significant improvements occurring in verbal learning and processing speed domains. Other studies have shown improvements in attentional abilities[33] and memory, including verbal learning, visuo-spatial memory and attention-executive-psychomotor domains[15] from CR entry to discharge of a12-week program. The exception to this trend of overall improvement in our study was a nonsignificant increase in impairment in visual attention at CR completion, which has not been reported previously and is worth further exploration, particularly in relation to individual's changes in CVD fitness.[34] It is unclear whether mild CI resolves spontaneously or the improvements can be attributed to CR participation. However, prior work has shown that improvements in CR fitness in terms of metabolic equivalents (METS) were related to improvements in verbal recall.[15] A further consideration is that our study uniquely assessed CI following CR discharge (8 weeks) and identified that further improvements occurred after CR completion in verbal learning, processing speed and visual attention domains.

Improvements in CI may result from the positive influence of CR on secondary prevention behaviours, which are sustained after CR completion, but may also result from resolution of other influences including anxiety and depression. Anxiety and depression are common following ACS, occurring in 38%[35] and associated with CI, particularly memory and executive function domains,[36] and anxiety is correlated with impairment in the visuo-spatial domain in CR participants post ACS.[14] Our findings are aligned with this prior work, where higher depression and anxiety symptoms at CR entry occurred in patients who had impaired executive function and for anxiety symptoms for impaired processing speed. Additionally, clinically relevant anxiety and depressive symptom prevalence reduced from CR entry to discharge and follow-up in a similar pattern to CI in our study, although there was an unexpected increase in the proportion of patients meeting suggested cutoffs for depression at follow-up. Further research that investigates cognitive status, anxiety and depression over time in post ACS patients who attend and do not attend CR is required.

The prevalence of mild CI at CR entry flags a potential barrier to learning, planning and uptake of secondary prevention behaviours in this high-risk post ACS population.[9] Screening for mild CI at CR entry is justified to ensure that appropriate accommodation

is made and alternative models of patient education considered and has been included in the scientific statements for the care of cardiovascular patients from the American Heart Association.[37] Screening is especially important for ACS patients who have experienced out of hospital cardiac arrest given the increased probability of neurological changes.[38]

Patient education strategies need to accommodate common impairments in auditory verbal learning, processing speed and visual attention, however, few evidence-based patient education strategies for CI are available in this population. Alternative models of delivery, including technology-based should be considered, that allow repetition, multiple learning styles and inclusion of visual and verbal content. This is especially important in patients with multiple persistent impairments. In our study a small number of patients fit this category indicating the need for rescreening at CR discharge and potentially referral for further testing and support.

Our findings have important clinical implications. Overall, they suggest that screening of ACS patients for mild CI and psychological status is warranted at CR entry, at the least to enable tailoring of education and support strategies. Mild CI may be transient or respond to CR participation in some ACS patients given significant decreases in prevalence over time. However, a small number of patients had persistent multiple domain CI at CR follow-up, indicating the need for rescreening at CR discharge and potentially for referral for further neuropsychological testing, other investigations and cognitive interventions. Given that Alzheimer's and vascular dementia increases considerably in those aged over 60 years[39] and that up to half of dementia risk is due to modifiable risk factors, early detection and intervention may assist in slowing cognitive decline, dementia, and associated disability.

LIMITATIONS

The study results may not be generalisable to the ACS population more widely due to the small, selected sample of CR participants. The study sample was small and not powered for multiple tests, thereby potentially increasing Type 1 error. The study should be repeated in a larger, more diverse sample. As noted, if we had used a more

comprehensive neuropsychological battery, further significant decrements may have been evident. We shortened the RAVLT for feasibility within the clinical environment so delayed recall memory storage (which is sensitive to hippocampal brain functioning), was not measured. Additionally, we did not examine visuospatial functions, working memory or more comprehensive components of executive functioning such as verbal fluency, areas which have been shown to be impaired in prior work.[14] Finally, there was a 25% drop-out at follow-up, although this is not particularly unusual in clinical studies such as these.

CONCLUSIONS

Mild CI is prevalent in post-ACS patients attending CR and is common in areas that affect their capacity to learn about secondary prevention and engage in necessary behaviours. Mild CI decreases significantly over the course of CR and follow-up, but it is unclear if this is a consequence of CR participation or improvement in other factors such as psychological status, as depression and anxiety and CI are associated. A small proportion of patients have persistent, multiple domain CI flagging potential long-term changes.

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CONFLICTS OF INTEREST

There are no potential conflicts of interest declared by authors in terms of the research, authorship and publication.

References:

1. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with st-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with st-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2017; 39: 119-177.

2. Chow CK, Redfern J, Hillis GS, et al. Effect of lifestyle-focused text messaging on risk factor modification in patients with coronary heart disease: a randomized clinical trial. *JAMA* 2015; 314: 1255-1263.

3. Mathews R, Peterson ED, Honeycutt E, et al. Early medication nonadherence after acute myocardial infarction: insights into actionable opportunities from the TReatment with ADP receptor iNhibitorS: Longitudinal Assessment of Treatment Patterns and Events after Acute Coronary Syndrome (TRANSLATE-ACS) Study. *Circ Cardiovasc Qual Outcomes* 2015; 8: 347-356.

4. McKee G, Mooney M, O'Donnell S, et al. A cohort study examining the factors influencing changes in physical activity levels following an acute coronary syndrome event. *Eur J Cardiovasc Nurs* 2018; 18: 57-66.

5. Anderson L, Oldridge N, Thompson DR, et al. Exercise-based cardiac rehabilitation for coronary heart disease. *J Am Coll Cardiol* 2016; 67: 1-12.

6. van Halewijn G, Deckers J, Tay HY, et al. Lessons from contemporary trials of cardiovascular prevention and rehabilitation: a systematic review and meta-analysis. *In J Cardiol* 2017; 232: 294-303.

7. Abete P, Della-Morte D, Gargiulo G, et al. Cognitive impairment and cardiovascular diseases in the elderly. A heart-brain continuum hypothesis. *Ageing Res Rev* 2014; 78: 41.

8. Zhao E, Lowres N, Woolaston A, et al. Prevalence and patterns of cognitive impairment in acute coronary syndrome patients: A systematic review. *Eur J Prev Cardiol* 2019; 27: 2047487319878945.

9. Salzwedel A, Heidler M-D, Haubold K, et al. Prevalence of mild cognitive impairment in employable patients after acute coronary event in cardiac rehabilitation.(original research)(report). *Vasc Health Risk Manag* 2017; 13: 55.

10. Mowszowski L, Batchelor J and Naismith SL. Early intervention for cognitive decline: can cognitive training be used as a selective prevention technique? *Int Psychogeriatr* 2010; 22: 537-548.

11. Mowszowski L, Lampit A, Walton C, et al. Strategy-based cognitive training for improving executive functions in older adults: a systematic review. *Neuropsychol Rev* 2016; 26: 252-270.

12. Petersen R, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. *Arch Neurol* 2001; 58: 1985-1992.

13. Alagiakrishnan K, Mah D and Gyenes G. Cardiac rehabilitation and its effects on cognition in patients with coronary artery disease and heart failure. *Expert Rev Cardiovasc Ther* 2018; 16: 645-652.

14. Silva M, Pereira E, Rocha A, et al. Neurocognitive impairment after acute coronary syndrome: prevalence and characterization in a hospital-based cardiac rehabilitation program sample. *J Cardiovasc Thorac Res* 2018; 10: 70-75.

15. Stanek KM, Gunstad J, Spitznagel MB, et al. Improvements in cognitive function following cardiac rehabilitation for older adults with cardiovascular disease. *Int J Neurosci* 2011; 121: 86-93.

16. Lezak MD. *Neuropsychological Assessment*. Oxford, New York: Oxford University Press, 2012.

17. Maruff P, Lim YY, Darby D, et al. Clinical utility of the cogstate brief battery in identifying cognitive impairment in mild cognitive impairment and Alzheimer's disease. *BMC Psychology* 2013; 1: 30.

18. McBride SJ, Szoeke CEI, Good NM, et al. A web-based normative data tool for assessing cognitive performance in healthy older Australians. *Med J Aust* 2011; 194: S12-S14.

19. Ashendorf L, Jefferson AL, O'Connor MK, et al. Trail making test errors in normal aging, mild cognitive impairment, and dementia. *Arch Clin Neuropsychol* 2008; 23: 129-137.

20. Selnes OA, Grega MA, Borowicz LM, et al. Cognitive changes with coronary artery disease: a prospective study of coronary artery bypass graft patients and nonsurgical controls. *Ann Thorac Surg* 2003; 75: 1377-1386.

21. Hawkins KA, Dean D and Pearlson GD. Alternative forms of the rey auditory verbal learning test: a review. *Behav Neurol* 2004; 15: 99-107.

22. Bowie CR and Harvey PD. Administration and interpretation of the trail making test. *Nat Protoc* 2006; 1: 2277.

23. Bauer L, Pozehl B, Hertzog M, et al. A brief neuropsychological battery for use in the chronic heart failure population. *Eur J Cardiovasc Nurs* 2012; 11: 223-230.

24. Silbert BS, Maruff P, Evered LA, et al. Detection of cognitive decline after coronary surgery: a comparison of computerized and conventional tests. *Br J Anaesth* 2004; 92: 814-820.

25. Kortte KB, Horner MD and Windham WK. The trail making test, part B: cognitive flexibility or ability to maintain set? *Appl Neuropsychol* 2002; 9: 106-109.

26. Zigmond AS and Snaith RP. The hospital anxiety and depression scale. *Acta psychiatrica scandinavica* 1983; 67: 361-370.

27. Ceccarini M, Manzoni GM and Castelnuovo G. Assessing depression in cardiac patients: what measures should be considered? *Depress Res Treat* 2014; 2014.

28. Smarr KL and Keefer AL. Measures of depression and depressive symptoms: Beck Depression Inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale

(CES-D), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), and Patient Health Questionnaire-9 (PHQ-9). *Arthritis Res Ther* 2011; 63.

29. Naismith SL, Norrie LM, Mowszowski L, et al. The neurobiology of depression in later-life: clinical, neuropsychological, neuroimaging and pathophysiological features. *Prog Neurobiol* 2012; 98: 99-143.

30. Jeffares I, Merriman NA, Rohde D, et al. A systematic review and meta-analysis of the effects of cardiac rehabilitation interventions on cognitive impairment following stroke. *Disabil Rehabil* 2019: 1-16.

31. Fichman HC, Dias LBT, Fernandes CS, et al. Normative data and construct validity of the rey auditory verbal learning test in a Brazilian elderly population. *Psychology & Neuroscience* 2010; 3: 79-84.

32. Bondi MW, Edmonds EC, Jak AJ, et al. Neuropsychological criteria for mild cognitive impairment improves diagnostic precision, biomarker associations, and progression rates. *J Alzheimers Dis*. 2014;42:275-289.

33. Gunstad J, Macgregor KL, Paul RH, et al. Cardiac rehabilitation improves cognitive performance in older adults with cardiovascular disease. *J Cardiopulm Rehabil* 2005; 25: 173-176.

34. Netz Y, Dwolatzky T, Khaskia A, et al. Cardiovascular fitness and neurocognitive performance among older adults in the maintenance stage of cardiac rehabilitation. *Isr J Psychiatry Relat Sci* 2015; 52: 55-63.

35. Norlund F, Lissaker C, Olsson EM, et al. P2509 Associations of emotional distress in patients with first myocardial infarction. Results from SWEDEHEART registry. *Eur Heart J* 2017; 38.

36. Yatawara C, Lim L, Chander R, et al. Depressive symptoms influence global cognitive impairment indirectly by reducing memory and executive function in patients with mild cognitive impairment. *J Neurol Neurosurg Psychiatry* 2016; 87.

36. Barnason PS, White-Williams LC, Rossi SL, et al. Evidence for therapeutic patient e7ucation interventions to promote cardiovascular patient self-management: a scientific statement for healthcare professionals from the American Heart Association. *Circ Cardiovasc Qual Outcomes* 2017; 10: 581–589.

38. Boyce LW and Goossens PH. Rehabilitation after cardiac arrest: integration of neurologic and cardiac rehabilitation. *Semin Neurol* 2017; 37: 94-102.

39. Mrcpsych PM, Franzcp CM and Mann CA. Risk factors for Alzheimer's disease and dementia: a case-control study based on the MRC elderly hypertension trial. *Neurology* 1994; 44: 97-104.