I. Introduction

The societies are steadily aging in developed countries, especially in Japan. More than 40% of the elderly population in these countries reportedly suffers from cardiac disease, and these patients may become candidates for cardiac surgery. The actual number of cardiovascular operations is still continuously increasing, as presented in the annual report of the Japanese Association of Thoracic Surgery, particularly among elderly patients. However, there has been a decrease in the number of ischemic heart surgeries over the last decade, possibly due to the emergence of the drug-eluting stent (DES), which have proven effective treatment for coronary artery disease. Especially in Japan, there has been an extreme shift toward percutaneous coronary intervention (PCI) rather than coronary bypass artery grafting (CABG), and the ratio of PCI to CABG has been reported to be 7:1. Otherwise, in 2012, the Japanese guideline for myocardial revascularization to treat stable ischemic heart disease was revised, leading to CABG as the primary indication for high-risk patients with more complex left main trunk disease and/or triple-vessel disease. This revision resulted in a slight increase in the number of isolated CABG surgeries in 2012, including those performed in elderly patients. In addition, the high successful rate of off-pump CABG has particularly been reported in Japan, being 60.9% among cases of isolated CABG in 2016, which kept over 60% among all isolated CABG cases in the past decade.

Off-pump CABG has the greater benefit to high-risk patients, and enabled surgery to be performed in elderly patients with acceptable perioperative mortality and morbidity rates.

According to the aging procession, a certain rate of elderly population with some cognitive disorders has also been increasing. In 2013 the Ministry of Health, Labor and Welfare of Japan reported that the population of dementia patients was estimated to be 4.62 million, and a quarter of the elderly population had some form of cognitive disorder, including from mild cognitive impairment (MCI) to dementia. Clinicians can diagnose the symptoms of dementia based on the standard criteria of the fifth...
In brief, the DSM-5 diagnosis of “dementia”, which corresponds to “major neurocognitive disorder”, requires substantial impairment to be present in one or more cognitive domains, to the extent that the impairment interferes with the independence in everyday activities. “Mild neurocognitive disorder” is defined as the symptomatic pre-dementia stage on the continuum of cognitive decline, characterized by objective impairment in cognition that is not sufficient to require help with usual activities of daily living, which corresponds to “mild cognitive impairment (MCI)”. Such cognitive decline and dementia are known to be associated with cardiovascular risk factors. Additionally, low levels of cognitive function have long been associated with worsened cardiac mortality rates.

The ideal strategy for cardiovascular surgery including CABG for the elderly patients, especially with some form of cognitive disorder, remains controversial, because of their higher-risk for surgery. Few studies have focused on CABG in dementia patients, therefore, the present report reviews the strategies and outcomes of CABG in elderly patients, including those with cognitive disorders, accompanied the institutional study at our facility.

II. Coronary revascularization for general elderly patients

The number of patients with ischemic heart disease is increasing as the population ages, and more elderly patients are referred for revascularization. Recently, improved outcomes of revascularization for elderly patients have been reported with the advances in devices and surgical techniques, and several randomized trials have compared the outcomes of CABG and medical treatment.

A randomized trial of invasive versus medical therapy (Trial of Invasive versus Medical therapy in Elderly patients with chronic symptomatic coronary artery disease [TIME]) found that 305 patients with >75 years of age benefited more from revascularization than from optimized medical therapy in terms of symptom relief and their quality of life. The APPROACH (The Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease) trial was a large, population-based, clinical registry that captured all patients undergoing cardiac catheterization and revascularization, comparing the crude and risk-adjusted survival by each treatment (CABG, PCI, or medical therapy) among patients with <70 years (15,392 patients), 70 to 79 years (5,198 patients), and ≥80 years of age (983 patients). The 4-years result of CABG in the elderly was associated with significantly better survival than PCI and medical therapy alone in all age groups (Fig. 1). In addition, in the ≥80 years old group, CABG resulted in significantly better outcomes than PCI.}

**Fig. 1** APPROACH trial: Kaplan-Meier plots of the patient survival overtime for each of three age groups. The differences in survival according to treatment strategy were significant in all age groups (P<0.0001 for each group).

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ger late survival comparison was reported in the registries of the Northern New England Cardiovascular Disease Study Group (NNECDSG) between CABG and PCI among 1,693 octogenarians16. Although the in-hospital mortality was 3.0% for PCI and 5.9% for CABG, the 8-year survival was significantly better with CABG than PCI for the group (p<0.005).

The recent improvement in the outcomes of CABG in elderly population might be due to the increased prevalence of off-pump CABG (OPCAB). Puskas et al reported that the OPCAB was associated with lower operative mortality than CABG on cardio-pulmonary bypass for high-risk patients8. Additionally, this mortality benefit was increased with higher operative-risk patients. Panesar et al performed meta-analysis comparing the early outcomes in the elderly patients (>70 years of age) between OPCAB and on-pump CABG27. That study included 14 non-randomized studies with 4,921 patients, showing a significantly lower incidence of death in the OPCAB group in the on-pump CABG group (odds ratio [OR] 0.48, 95% confidence interval [CI] 0.28 to 0.84).

III. Preoperative dementia in CABG candidates

Although CABG on elderly patients has been studied with the outcomes found to be largely satisfactory as mentioned above, the discussion on CABG candidates with dementia remains insufficient, probably because patients with dementia are more likely to be excluded from the indications for surgery. There are several examinations evaluating of cognitive function, representative as Revised Hasegawa’s Dementia Scale (HDS-R)27, Mini-Mental State Examination (MMSE)10, Montreal Cognitive Assessment (MoCA)18, Mini-Cog20, and Clinical Dementia Rating (CDR)21, along with other examinations worldwide.

In 2018, we analyzed the outcomes of cardiovascular surgery for patients with preoperative dementia and reported the optimal strategy evaluating by MMSE score21. The study group included 490 elderly patients, and the preoperative cognitive status was evaluated using MMSE, which had maximum score of 30 points, assessing cognitive functions in orientation, registration, attention, calculation, recall and language20. To evaluate the dementia severity, the relationship between the MMSE score and the Clinical Dementia Rating (CDR) categories has been reported, and the standard criteria values have been verified as follows: MMSE score 20–23 equates to mild dementia, 10–19 to moderate dementia, and <10 to severe dementia21,26. An analysis between the dementia group (n=51) and non-dementia group (n=439) revealed that the hospital mortality rate in dementia group was significantly higher than non-dementia group (11.8% vs 2.1%, P=0.002). Regarding post-operative morbidity, the incidences of cerebrovascular disorder (P=0.001), pneumonia (P=0.039), delirium (P=0.004), and wound infection (P=0.006) were more frequent in dementia group than non-dementia group (Table 1). Furthermore, the more severe outcomes were indicated in the group of MMSE <20, along with higher rate of hospital mortality (25%) and post-operative delirium (58%).

A multivariate logistic regression analysis revealed that MMSE score <24 was an independent risk factor for hospital death and post-operative delirium. Based on these findings, surgical intervention in patients diagnosed as moderate dementia (MMSE score <20) remains controversial due to the high rates of mortality and morbidity, although surgery for patients with MMSE score <24 may be considerable with less invasive strategy.

Focusing on CABG in our report, 122 CABG patients were included, divided into 12 (9.8%) dementia patients and 110 non-dementia patients. OPCAB was performed for 6 in dementia group (50%), and 41 in non-dementia group (37.3%) (P=0.534). There was no marked difference in the number of bypass grafting (dementia: 2.58±1.08, non-dementia: 2.76±0.91; P=0.516). Regarding the hospital mortality, there was 1 death with preoperative MMSE score 19 in dementia group (8.3%) and none in non-dementia group (P=0.098). Operative morbidity indicated no differences between the groups. Although hospital transfers for rehabilitation were necessary for 1 dementia patient and 9 non-dementia patients, all of them were ultimately able to be discharged to home.

A certain proportion of dementia patients seemed consisted in the CABG studies for elderly population. Jensen et al have reported that a surprising 20% of CABG candidates with >55 years of age had some preoperative dementia with MMSE score <2427. Recently, Yoshimoto et al have studied for perioperative cognitive changes in cardiovascular surgery candidates, and 11 preoperative dementia patients were observed in 52 elderly patients with ≥75 years of age, accounting for 9.6% of all patients (11/115) and consisting 21.2% of the elderly patients group20. The perioperative cognitive function of the patients was evaluated individually using HDS-R and MMSE, resulting that the dementia group showed statistically significant decline at cognitive score comparing with non-dementia group.

IV. Preoperative MCI in CABG candidates

Regarding for preoperative mild cognitive impairment (MCI) status, several reports have shown that a relatively large number of CABG candidates have MCI, which corresponds to CDR score of 0.5 or MMSE score of 24–27.20,26. In the ROOBY trial, preoperative baseline cognitive analyses were performed, and more than 20% of patients showed MCI. Additionally in this study, less than 10% of patients were diagnosed as dementia at baseline26, which was similar to the reported ratio of dementia in the study by Yoshimoto and our own institution20,26. Silbert et al reported that some cognitive impairment was presented in ap-
approximately 35% of patients prior to CABG. Similarly, the prospective longitudinal study showed that preexisting cognitive impairment was identified in 105 of 326 (32.2%) patients at baseline.

These preoperative low cognitive functions have the association with mortality and morbidity after CABG. Poole et al have examined the relationship between the preoperative cognitive functioning and the postoperative inflammatory and neuroendocrine response in patients undergoing CABG. The study resulted in the association between MCI and the negative pattern of biological response to surgery, concretely the elevation of IL-6 and cortisol output, followed by poorer physical recovery. Furthermore, cognitive impairment increases risk of delirium after CABG, which portends increased mortality and re-admission rates, poorer quality of life, and post-operative complications including atrial fibrillation, pneumonia, need for re-intubation.

Oldham et al reported that preoperative MCI could predict post-operative delirium and delirium severity, suggesting that diagnosis of MCI on CDR scoring by MMSE might be important for evaluating the functional status before CABG.

V. Early and late post-operative cognitive decline

The issue of post-operative cognitive decline (POCD) after CABG has been widely investigated and well defined. Early cognitive decline after CABG typically appears in the first few days or weeks and is basically characterized by memory difficulties and decreased visual attention. The highest rates of POCD (approximately 50% of patients) have been observed in the early weeks, followed by a significant reduction in incidence over the first 6 months. The risk factors occurring POCD have been analyzed, and preoperative cognitive decline, older age were found to be predictive factors for POCD.

Another issue concerning POCD is the effect of the cardiopulmonary bypass (CPB) on CABG. It had been hypothesized that an off-pump approach would avoid central nervous system sequelae associated with CABG. Several studies have assessed the cognitive outcomes after off-pump versus on-pump CABG. There were some off-pump reports indicating the improvement of cognitive performance within 6 months after CABG. Otherwise, in their randomized control trial of 281 patients, Van Dijk et al compared the effect of CABG with and without CPB, resulting that POCD occurred in 21% in off-pump and 29% in the on-pump group (P=0.15). The improvement of cognitive performance at 3 months was significantly better in off-pump group than on-pump (P=0.03), nevertheless no significant differences were observed in quality of life, stroke rate and mortality at 3 and 12 months. Jensen et al reported the comparison of cognitive outcomes in elderly high-risk patients 1 year after CABG with or without CPB, finding no significant differences in the cognitive decline, although patients with dementia were ex-

Table 1 Surgical outcomes of dementia and non-dementia groups including all cardiovascular surgeries

|                         | Dementia group (n=51) | Non-dementia group (n=439) | P value |
|-------------------------|-----------------------|----------------------------|---------|
| 30-days mortality       | 3 (5.9%)              | 5 (1.1%)                   | 0.041   |
| Hospital mortality      | 6 (11.8%)             | 9 (2.1%)                   | 0.002   |
| Operation time (min)    | 414 ± 152             | 390 ± 136                  | 0.247   |
| CPB time (min)          | 191 ± 79              | 191 ± 78                   | 0.975   |
| Ventilation time (hours)| 5009 ± 8896           | 3887 ± 9442                | 0.412   |
| ICU stay (days)         | 7.4 ± 11.1            | 4.7 ± 7.1                  | 0.102   |
| Hospital stay (days)    | 36.1 ± 27.2           | 26.8 ± 25.1                | 0.014   |
| Transfer to recuperating hospital | 16 (31.4%)          | 64 (14.6%)                 | 0.005   |

Morbidities

|                        | Dementia group (n=51) | Non-dementia group (n=439) | P value |
|------------------------|-----------------------|----------------------------|---------|
| Arrhythmia             | 27 (53%)              | 178 (41%)                  | 0.098   |
| Cerebrovascular disorder | 9 (18%)              | 19 (4%)                    | 0.001   |
| Pneumonia              | 9 (18%)               | 36 (8%)                    | 0.039   |
| Dysphagia              | 9 (18%)               | 33 (7%)                    | 0.259   |
| Wound infection        | 7 (14%)               | 9 (2%)                     | 0.006   |
| Bleeding               | 2 (4%)                | 11 (2%)                    | 1.000   |
| Delirium               | 18 (35%)              | 84 (19%)                   | 0.004   |

Data are shown as the number (%) or mean ± standard deviation.

CPB: cardiopulmonary bypass, ICU: intensive care unit

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cluded in that study. In the ROOBY trial, including more than 20% of either group had MCI at baseline, the preoperative lower cognitive function, older age, lower education and ethnicity were predictive factors of POCD after CAGB\(^\text{29}\). However this study also found no convincing evidence regarding 1-year post-CABG cognitive decline for either on- or off-pump treatments.

Some observational studies have reported a late cognitive decline occurring several years after CABG. Newman et al found that relatively high as 42% of their patients had lower cognitive performance at 5 years of follow-up than before surgery. They investigated predictors of cognitive decline, and the cognitive function at discharge was a significant predictor of the long-term function\(^\text{30}\). Evered et al followed up patients for 7.5 years after CABG, reported that dementia developed in 30.8%, which was significantly higher rate than the background prevalence of general population (9%)\(^\text{31}\). Impaired cognition before surgery or the presence of cardiovascular disease were associated with an increased risk of long-term dementia. In the Cardiovascular Health Study with follow-up for a median of 6 years, the risk of dementia in patients with CABG history was approximately doubled in their analysis compared with those with no CABG history\(^\text{32}\). Their Kaplan-Meier curves for dementia indicated that the curve with CABG history began to diverge after 1 year from baseline, and kept greater increasing than that without CABG history for each year. Selnes et al reported 6-year cognitive outcomes after CABG comparing with the coronary artery disease (CAD) patients who did not undergo CABG and the healthy subjects with no risk factors for CAD\(^\text{33}\). The overall cognitive performance at baseline was lower in all groups with CAD than in the group of healthy subjects, and it remained lower throughout the follow-up period. Each group of CAD patients had some cognitive decline between 12 and 72 months, although the degree of decline did not differ significantly among nonsurgical, CAGB and OPCAB groups. Thus, the risk of cognitive decline after CABG appears to be related to the mechanisms other than surgical procedure itself and cardiopulmonary bypass. Additionally, late cognitive decline is likely associated with the progression of underlying cerebrovascular disease, therefore, more consistent postoperative control for cardiovascular and cerebrovascular disease, as well as use of lipid-lowering agents and \(\beta\)-blockers, might reduce the risk of long-term cognitive changes\(^\text{34}\).

VI. Conclusion

Although CAD patients are becoming to the elderly population, the appropriate strategies should be considered including off- and on-pump CAGB. The presence of preoperative dementia affects the surgical outcomes with regard to hospital death and delirium, thus, attentive preoperative assessment represented by MMSE should be performed. Because the existence of the use of cardiopulmonary bypass seems not affecting the late cognitive outcomes, the strategy of pump use should be determined based on each patient’s various risk factors. The preoperative evaluation of an individual cognitive function may substantially contribute to appropriate postoperative management, reduce the incidence of delirium and improve the overall surgical outcome, in addition to improving the cost-efficacy.

Disclosures

The authors declare no conflicts of interest.

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