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Review

Natriuretic peptides for perioperative management of cardiac surgery

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ABSTRACT

Atrial natriuretic peptide (carperitide) is used to treat heart failure in Japan, while brain natriuretic peptide (nesiritide) is employed in Europe/USA.

Patients undergoing cardiac surgery have a complex underlying pathologic state that features increased levels of neurohumoral factors due to activation of the renin–angiotensin–aldosterone system and/or increased sympathetic activity. We considered that perioperative administration of carperitide could be beneficial for cardiac surgery patients, and we have conducted clinical investigations of its use. This article reviews the effects of natriuretic peptides in cardiac surgery patients based on our experience and on previous reports about perioperative management with carperitide or nesiritide.

Contents

Introduction

The natriuretic peptides include atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). Two of these hormones are produced by the heart, with ANP being secreted in response to atrial distention and BNP mainly being secreted in response to ventricular loading. CNP is a locally acting hormone synthesized in various tissues, including bone, where it is essential for endochondral bone growth. CNP is also a neuropeptide found in the central nervous system, and its expression by vascular endothelial cells and monocyte/macrophages has been detected as well [1–4]. ANP and BNP have natriuretic and vasodilatory effects, as well as inhibiting aldosterone secretion, myocardial hypertrophy, myocardial fibrosis, the neuroendocrine system, and inflammatory cytokines, resulting in a cardioprotective effect by modulation of vascular tone, renal and endothelial functions, and ventricular contractility [4]. Clinically, human ANP (hANP; carperitide) is used to treat heart failure in Japan, while BNP (nesiritide) is employed for this indication in Europe and the USA.

In Japan, carperitide is classified as a Class IIa treatment for heart failure in the Guidelines for Treatment of Acute Heart Failure published by The Japanese Circulation Society, based on available evidence of its efficacy [5–7] (http://www.j-circ.or.jp/guideline/pdf/JCS2011_izumi_h.pdf#search='JCS+2011'). The efficacy of

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carperitide for acute myocardial infarction has also been reported [8]. In contrast, a large-scale study of nesiritide in patients with acute heart failure (ASCEND-HF trial) found no difference in the rates of re-hospitalization and 30-day mortality rate between the nesiritide-treated and placebo groups [9]. The following reasons for these differing outcomes can be suggested. (1) Different administration methods: In the ASCEND-HF trial, a bolus dose of nesiritide was given to 38% of the subjects before continuous low-dose infusion, while bolus administration of carperitide is not performed in Japan. (2) Differences in the management of ischemic heart disease: While catheter-based therapy is frequently used for patients with ischemic heart disease and heart failure in Japan, adequate catheter therapy may not have been provided for the 60% of the patients with ischemic heart disease enrolled in the ASCEND-HF trial. (3) Different medical systems: Most patients with heart failure are not discharged from the hospital within 30 days of admission in Japan, while most patients with heart failure would have been discharged within that time in the ASCEND-HF trial because its primary endpoint was re-hospitalization for heart failure or death within 30 days. Therefore, it is possible that more favorable results would be obtained by using nesiritide in a similar manner to carperitide.

Patients undergoing cardiac surgery have a complex underlying pathologic state that features increased levels of neurohumoral factors due to activation of the renin–angiotensin–aldosterone system (RAAS) and/or increased sympathetic activity along with fluid retention. Catecholamines and loop diuretics are generally employed in the perioperative management of these patients. However, use of catecholamines and loop diuretics may be associated with a worse prognosis because of tachyarrhythmia, ischemia-reperfusion injury, RAAS activation, and deterioration of renal function leading to renal impairment [10,11]. During cardiac surgery, the activity of various neurohumoral factors (RAAS, catecholamines, antidiuretic hormone, and the sympathetic nervous system) is enhanced, the inflammatory response may be enhanced, coagulation can be activated, and third-space fluid retention and endothelial dysfunction can be induced by cardiopulmonary bypass. Such changes might have an adverse influence on cardiac and renal functions. We considered that perioperative administration of carperitide could be beneficial for this complicated pathophysiology associated with cardiac surgery, and we have conducted clinical research on low-dose continuous infusion of carperitide during cardiac surgery (NU-HIT trial) since 1997. At present, the number of hospitals that routinely use carperitide during cardiac surgery is increasing in Japan. Mitaka et al. reviewed 11 studies evaluating ANP and 4 studies evaluating BNP in patients undergoing cardiac surgery or abdominal aortic surgery. They concluded that infusion of either peptide increased the urine output and the creatinine clearance or glomerular filtration rate, and also reduced use of diuretics and the serum creatinine level [12].

This review of the effects of natriuretic peptides in patients with cardiac surgery is based on our experience and on previous reports about use of carperitide or nesiritide for perioperative management.

Material and methods

We searched PubMed for articles from February 1987 to March 2015 using the terms "carperitide" and "cardiac surgery," "hANP" and "cardiac surgery," "ANP" and "cardiac surgery," and "nesiritide" and "cardiac surgery." As a result, 1271 articles were extracted for "nesiritide" and "cardiac surgery," 309 for "ANP" and "cardiac surgery," 46 for "hANP" and "cardiac surgery," and 22 for "carperitide" and "cardiac surgery." Among these articles, we searched for English language reports on prospective randomized controlled trials performed in adult patients undergoing non-transplant cardiac surgery and found 14 reports on the use of carperitide and 7 reports on nesiritide. We reviewed the data in these reports and also included our report on carperitide (Table 1).

Cardiac protection by natriuretic peptides in cardiac surgery

In the field of cardiovascular medicine, it has been reported that carperitide reduces the levels of angiotensin-II, aldosterone, and endothelin-1 which accelerate myocardial fibrosis, ameliorates LV remodeling [13], decreases cardiac sympathetic nerve activity while inhibiting LV remodeling [14], and prevents ventricular arrhythmia and ischemia-reperfusion injury [15]. In a canine model of ischemia-reperfusion injury, carperitide was shown to inhibit the decrease of myocardial high-energy phosphates, prevent reperfusion arrhythmia, and increase cyclic guanosine monophosphate (cGMP), resulting in a cardioprotective effect [16].

In the field of cardiac surgery, our pilot study showed that low-dose intraoperative infusion of carperitide led to inhibition of the RAAS, an increase in urine volume, a decrease in the furosemide dose, and compensation for the adverse influence of cardiopulmonary bypass (CPB) [17]. In patients with LV dysfunction undergoing coronary artery bypass grafting (CABG), infusion of carperitide increased urine volume, decreased the furosemide dose, reduced cardiac death or cardiac events during long-term follow-up, and improved both serum BNP and the LV ejection fraction at 1 year after surgery. Thus, carperitide had a strong cardioprotective effect not only in the acute phase, but also over the long term [18]. In patients with acute coronary syndrome undergoing urgent CABG, carperitide decreased postoperative ischemia-reperfusion injury and prevented postoperative ventricular arrhythmia. At 1 month after surgery, the LV end-diastolic pressure, LV end-diastolic volume index, and the serum BNP level were significantly lower in the carperitide group. In addition, the risk factors for long-term cardiac events were non-use of perioperative carperitide and non-use of postoperative aldosterone blockers, suggesting that suppression of the RAAS by carperitide in the acute phase and by aldosterone blocker therapy over the long term had a strong positive influence on the prognosis [19–21]. In our clinical studies of carperitide, isosorbide dinitrate was also used by the majority of the subjects, while PDE III inhibitors were administered to about 30% of the patients from both groups in the NU-HIT trial for LVD. Thus, there was no difference in the use of isosorbide dinitrate or PDE III inhibitors between the groups with and without carperitide treatment in these studies. To evaluate the vasodilatory effect of each agent, carperitide should be compared directly with isosorbide dinitrate or a PDE III inhibitor and this has been done in two studies so far. In patients with acute heart failure, nitrate therapy significantly reduced the diastolic pulmonary arterial pressure and systemic vascular resistance index compared with carperitide, but there were no differences in clinical outcomes [22]. In the other study, carperitide significantly improved EF, LVEDVI, and LVESVI compared with nitroglycerin in AMI patients, indicating suppression of LV remodeling by carperitide [13]. However, further investigation is necessary because these effects of carperitide have not fully been examined and no studies have compared carperitide with PDE III inhibitors. In our clinical studies, treatment with carperitide also significantly reduced the use of furosemide because of its diuretic effect.

The good long-term results obtained after perioperative administration of carperitide for several days were consistent with the findings of the J-WIND study and the mechanisms involved are probably also similar [8]. It is probable that carperitide has a "legacy effect", i.e. prevention of LV remodeling in the acute phase by inhibition of the RAAS, particularly aldosterone, leads to a better long-term outcome. Another possible

Table 1
Randomized clinical trials of natriuretic peptides during cardiac surgery.

Author	Natriuretic peptide	Study target	Number of patients	Dose (μg/kg/min)	Duration	Superiority of carperitide and nesiritide versus placebo	
						Perioperative results	Long-term results (>6 months)
Sezai (2000) [17]	ANP	CABG	40	0.03 or 0.05	24 h	c-GMP, RAAS, UV, U-Na, respiratory index, reduction in the use of furosemide	–
Hayashida (2000) [38]	ANP	Mitral valve surgery	18	0.05	6 h	c-GMP, UV, FENa	–
Hayashi (2003) [40]	ANP	Cardiac surgery	30	0.025	24 h	Reduction in the use of furosemide and potassium, renin, ALD	–
Hayashi (2004) [41]	ANP	Mitral valve surgery	26	0.05	24 h	Renin, ALD	–
Swärd K (2004) [37]	ANP	AKI after cardiac surgery	61	0.05	ANP: 5.3 ± 0.8 days Placebo: 4.3 ± 0.7 days	Dialysis-free, CCr	–
Sezai (2007) [21]	ANP	CABG for ACS	124	0.02	–	Postoperative arrhythmias, CK-MB, lactate, sCr, f reduction in the use of furosemide, resp. time, ICU and hospital stay	Cardiac events (2 years), BNP (1 year), LVEDP (1 month)
Mentzer (2007) [28]	BNP	CABG with LVD	279	0.01	39.4 ± 21.6 h	UV, sCr, respiratory failure, hospital stay	180-day mortality
Chen (2007) [43]	BNP	CVS with CKD	40	0.005	24 h	cGMP, cystatin, ALD	–
Izumi (2008) [39]	ANP	CABG and valve surgery with CKD	18	0.01 or 0.02	5.2 ± 0.6 days	UV, U-NAG, sCr	–
Dyke (2008) [44]	BNP	Cardiac surgery with LVD and CKD	266	0.01	24–96 h	eGFR, postoperative renal function, sCr	–
Beaver (2008) [46]	BNP	Maze + mitral valve surgery	19	0.01	72 h	PaO_2/FiO_2	–
Sezai (2009) [30]		CABG with non-CKD	504	0.02	2.23 ± 0.82 days	UV, postoperative complications, hospital stay, sCr, RFI, RAAS, ICU and hospital stay	–
Ejaz (2009) [45]	BNP	High-risk cardiac surgery	94	0.01	5 days	Postoperative AKI, sCr, hospital stay	–
Sezai (2010) [18]	ANP	CABG with LVD	133	0.02	2.8 ± 1.1 days	Reduction in the use of furosemide and potassium, sCr, CK-MB, Ang-II, ALD, postoperative complications, postoperative arrhythmias, hospital stay	Cardiac death and cardiac events (12 years), BNP (1 year)
Sezai (2011) [32]	ANP	CABG with CKD	285	0.02	2.98 ± 1.93 days	cGMP, reduction in the use of furosemide, hospital stay, sCr	Dialysis-free rate (1 year) Cardiac events (1 year)
Hisatomi (2012) [42]	ANP	CVS using CPB	70	0.035 ± 0.0037	6.2 ± 3.7 days	sCr, reduction in the use of furosemide	–
Sezai (2013) [57]	ANP	High-risk CABG	367	0.02	–	Hospital stay, sCr	MACCE-free and dialysis-free rate (2 years), sCr (1 year), BNP (1 year)
Mori (2014) [49]	ANP	Aortic arch surgery	42	0.0125	24 h	UV, postoperative AKI	–
Chen (2014) [47]	BNP	PH after MVR	60	2 μg/kg (bolus) + 0.01	12 h	PAP, PCWP, PVRI	–
Shibasak (2015) [48]	ANP	Cardiac surgery	30	0.025	24 h	Albumin, UV, interleukin-6, renin	–

ACS, acute coronary syndrome; AKI, acute kidney injury; ALD, aldosterone; Ang-II, angiotensin-II; ANP, atrial natriuretic peptide (carperitide); BNP: brain natriuretic peptide (nesiritide); CABG, coronary artery bypass grafting; CCr, creatinine clearance; c-GMP, cyclic-guanosine monophosphate; CKD, chronic kidney disease; CK-MB, creatine kinase MB; CVS, cardiovascular surgery; eGFR, estimated Glomerular filtration rate; FENa, fractional sodium excretion; ICU, intensive care unit; LVEDP, left ventricular end-diastolic pressure; LVD, left ventricular dysfunction; major adverse cardiac and cerebrovascular event; P, placebo; PH, pulmonary hypertension; PVC, premature ventricular contraction; RAAS, renin–angiotensin–aldosterone system; RFI, renal failure index; sCr, serum; U-Na, urinary sodium; U-NAG, urinary N-acetyl-beta-D-glucosaminidase; UV, urine volume; VT, ventricular tachycardia; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVRI, pulmonary vascular resistance index.

mechanism would be the renoprotective effect of carperitide. While patients with heart disease have a risk of developing cardiac events during long-term follow-up, renal events are also common, and it is possible that protection of the kidneys by carperitide in the acute phase decreases renal events over the long term.

We developed a procedure for administering cardioplegia combined with carperitide (hANP shot: administration of 100 μg of carperitide into the ascending aorta during infusion of cardioplegia), and our investigations demonstrated that carperitide had a cardioprotective effect by maintaining myocardial ATP levels and inhibiting intracellular Ca overload during reperfusion, with electron microscopy revealing improved integrity of the mitochondria and myocardial fibers in the carperitide group [23–25]. A clinical trial of hANP shot confirmed its safety because no serious adverse events occurred and showed that the cardioprotective effect of carperitide was mediated via cGMP (a second messenger of carperitide), while inhibition of ischemia-reperfusion injury was revealed by measurement of biomarkers along with a decrease in postoperative arrhythmias [26]. Thus, hANP shot shows promise as a new cardioprotective technique for cardiac surgery. In this context, Tsuneyoshi et al. performed LV repair in a rat model of LV aneurysm and reported that intravenous carperitide had beneficial effects on postoperative LV remodeling, LV function, and fibrosis, suggesting that carperitide infusion could be useful after LV surgery [27].

With regard to nesiritide, Mentzer et al. reported that nesiritide treatment achieved a shorter hospital stay and lower 180-day mortality rate in patients with LV dysfunction undergoing CABG (NAPA trial) [28]. Lazar et al. performed a study of bolus and continuous nesiritide administration with cardioplegia in a porcine model, and they reported significantly smaller infarcts, better preservation of endothelial function, and less pulmonary edema in the animals receiving nesiritide [29]. Although there are only a few reports about good results with nesiritide in cardiac failure, it might be expected to improve the prognosis after cardiac surgery.

Renal protection by natriuretic peptides in cardiac surgery

In our trial of 504 patients without renal impairment who underwent CABG, the maximum postoperative serum creatinine (Cr) level and percent increase of Cr were significantly lower in the carperitide group. Four patients in the placebo group required hemodialysis versus none in the carperitide group, and the carperitide group showed lower fractional sodium excretion, a potent natriuretic action of carperitide, and inhibition of the RAAS, which prevented the deterioration of postoperative renal function [30,31]. In a randomized controlled trial of 303 patients with chronic kidney disease (CKD) who underwent CABG, the dialysis-free rate at 1 year postoperatively was 98.6% in the carperitide group versus 91.6% in the placebo group (being significantly higher in the carperitide group), and postoperative Cr was significantly lower in the carperitide group not only in the acute stage but also at 1 year [32]. Intravenous administration of carperitide to patients with CKD not only improved perioperative renal function, but also prevented the progression of CKD [33]. In this study, the postoperative dialysis-free rates for the carperitide and placebo groups were 99.3% and 91.6% at 1 year, 97.8% and 90.1% at 5 years, and 97.8% and 81.1% at 10 years, respectively, and these rates were significantly higher in the carperitide group ($p = 0.0014$) (Fig. 1). In dialysis patients, non-use of carperitide was a significant risk factor for early death and major adverse cardiovascular and cerebrovascular events (MACCE). No studies on the efficacy of carperitide in dialysis patients have been reported. While the renoprotective effect of carperitide has no meaning for dialysis patients, this research suggests the possibility of preventing the onset of MACCE not only in the early postoperative period but also over the long term by its cardioprotective effect [34]. In our clinical studies, the diuretic effect of carperitide led to a significant reduction in the use of furosemide, while furosemide may have had adverse effects on renal function via mechanisms such as RAAS activation in the group without carperitide.

Various effects of carperitide on the kidneys have been reported, and it is considered to act directly on the renal tubules (exhibiting a diuretic effect) to increase urinary sodium excretion, thereby maintaining the electrolyte balance and avoiding renal parenchymal damage caused by high-dose diuretics [35]. Valsson et al. administered carperitide for 30 min to patients with acute renal failure and heart failure after cardiac surgery, and found that the urine volume, glomerular filtration rate, and renal blood flow increased by 62%, 43%, and 38%, respectively, whereas renal vascular resistance decreased by 30% [36]. Their group also conducted a randomized clinical trial (RCT) in 61 patients with combined acute renal failure and heart failure after cardiac surgery, revealing that the requirement for hemodialysis was decreased by carperitide and dialysis-free survival was improved [37]. Hayashida and colleagues reported that their carperitide group had a significantly higher urine volume than the placebo group, as well as better hemodynamics and water balance [38]. Izumi investigated patients with CKD undergoing cardiac surgery, and reported a significant postoperative decrease of Cr, a

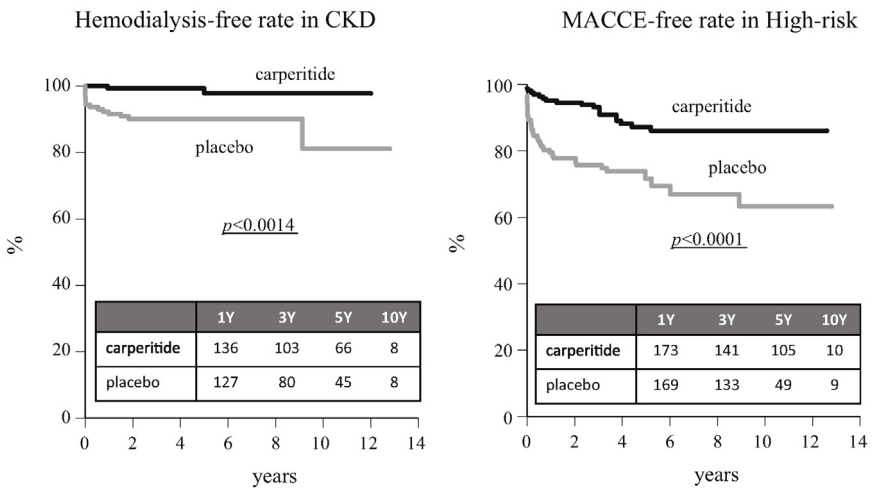

Fig. 1. (Left panel) Hemodialysis-free rate in patients with chronic kidney disease (CKD). (Right panel) Major adverse cardiovascular and cerebrovascular event (MACCE)-free rate in the high-risk group (EuroSCORE ≥6). The hemodialysis-free rate and MACCE-free rate were both significantly higher in the carperitide group than in the placebo group.

significant increase in the intraoperative urine volume, and an increase in the urinary N-acetyl-beta-D-glucosaminidase level in the carperitide group [39]. Hayashi et al. reported significantly lower total doses of furosemide and potassium chloride during the first 72 h after surgery in the carperitide group. On the first postoperative day, plasma renin activity and the plasma aldosterone level were also significantly lower in the carperitide group [40,41]. Hisatomi et al. performed a multicenter trial of carperitide in 88 patients with CKD undergoing cardiovascular surgery, reporting that postoperative Cr was significantly lower and creatinine clearance was significantly higher in the carperitide group than in the controls. One patient in the control group required hemodiafiltration, but no patient from the carperitide group required it [42].

In an investigation of nesiritide for patients with CKD undergoing cardiac surgery (NAPA trial), the plasma levels of cystatin and aldosterone, serum Cr, and estimated Ccr were all better in the nesiritide group [43]. Dyke et al. performed a subanalysis of this trial and reported that postoperative renal dysfunction was less frequent in the nesiritide group, particularly moderate or severe renal dysfunction [44].

Ejaz et al. reported that nesiritide did not reduce the incidence of dialysis and/or all-cause mortality. However, fewer patients receiving nesiritide had acute kidney injury compared with controls (2.2% versus 22.4%), and mean Cr was lower during the immediate postoperative period for patients undergoing high-risk cardiac surgery in the nesiritide group [45]. Beaver et al. studied 19 patients undergoing the maze procedure and mitral valve surgery, and reported that there were no differences in urine volume, PaO_2/FiO_2, endothelin-1, and sCr between those receiving placebo or nesiritide [46].

Pulmonary protection by natriuretic peptides in cardiac surgery patients

There have only been a few investigations into the effect of natriuretic peptides on the pulmonary circulation. Among them, Chen et al. performed an RCT that compared nesiritide, prostaglandin E_1 (PGE_1), and placebo in patients with pulmonary hypertension after mitral valve replacement. While they reported that both nesiritide and PGE_1 improved pulmonary hypertension, the effect of nesiritide was slower and weaker than that of PGE_1, suggesting that these two agents act on pulmonary arterial pressure via different pathways [47]. Shibasaki et al. found no difference in the pulmonary blood volume index, extravascular lung water index, and pulmonary vascular permeability index between the patients treated with carperitide or placebo, but urine volume was significantly higher and the interleukin-6 and albumin levels were significantly lower in the carperitide group. Accordingly, Shibasaki et al. concluded that carperitide reduces third-space fluid retention caused by CPB [48].

Other effects of natriuretic peptides

Thoracic aortic surgery

The only RCT on use of natriuretic peptides during thoracic aortic surgery was reported by Mori et al., who administered carperitide or placebo for 24 h from the induction of anesthesia in patients undergoing elective aortic arch surgery. They reported that intraoperative urine output was significantly higher in the carperitide group, while the incidence of postoperative acute kidney injury was 73% in the placebo group versus 30% in the carperitide group, being significantly lower in the carperitide group [49].

We conducted a retrospective investigation in patients undergoing surgery for thoracic aortic aneurysm using hypothermia and selective cerebral perfusion, which is the most stressful of the procedures employing CPB. The urine volume during CPB and that from weaning off CPB until the return to the intensive care unit was significantly larger in the carperitide group, while blood loss, blood transfusion volume, furosemide dose, and KCl dose were all significantly lower in the carperitide group. The peak lactate level was also significantly lower in the carperitide group, and these findings indicated that carperitide inhibited ischemia/reperfusion injury [50].

In a patient with acute aortic dissection complicated by the myonephropathic metabolic syndrome (MNMS), high-dose (0.1 μg/kg/min) carperitide improved postoperative MNMS without the need for hemodialysis. Although carperitide was originally investigated for heart failure, it has various pharmacologic effects, and MNMS may have been alleviated through a strong diuretic effect and prevention of ischemia/reperfusion injury [51]. Based on our experience with carperitide, a low infusion rate of 0.02 μg/kg/min is generally sufficient. At high doses, the risk of low blood pressure may outweigh the benefits of carperitide infusion. However, further investigation is necessary to find the optimal infusion rate for each condition, because infusion at a high rate of 0.1 μg/kg/min is beneficial for some patients, e.g. for improvement of reperfusion injury associated with MNMS as described above.

Postoperative atrial fibrillation

Postoperative atrial fibrillation (POAF) is the most common complication after cardiac surgery, with an incidence of 16–85% [52,53]. For prevention of this complication, amiodarone and beta-blockers are recommended [54,55]. In the NU-HIT study of LV dysfunction, carperitide was shown to reduce the incidence of POAF [18]. Among 668 patients undergoing CABG, POAF occurred in 41/335 patients (12.2%) from the carperitide group versus 110/333 patients (32.7%) from the placebo group ($p < 0.0001$). The mechanisms by which carperitide protects against POAF may include (1) RAAS inhibition, (2) an anti-ischemic effect, and (3) improvement in volume overload via its diuretic effect [56]. Since an anti-arrhythmic effect or suppression of atrial fibrillation by natriuretic peptides has not been reported previously, further investigation is needed.

High-risk patients

In 367 high-risk patients (total EuroSCORE ≥6 points) from the NU-HIT trial, the postoperative MACCE-free rate was significantly higher in the carperitide group than the placebo group, being 95.2% versus 79.6% at 1 year, 87.2% versus 71.7% at 5 years, and 86.1% versus 63.3% at 10 years ($p < 0.0001$) (Fig. 1). None of the patients from the carperitide group started hemodialysis after surgery versus 7 patients in the placebo group, and the dialysis rate was significantly lower in the carperitide group ($p = 0.0147$). MACCE was strongly associated with an age ≥75 years, CKD, hemodialysis, LV dysfunction, and non-use of carperitide [57] (Fig. 1).

Because we have demonstrated that carperitide inhibits RAAS activity, we consider that it is indicated for cardiac surgery using CPB. In addition, carperitide shows a stronger effect in high-risk patients, as noted above, and is not only beneficial in the acute perioperative phase but also over the long term.

Conclusion

Carperitide is already regarded as first-line therapy for heart failure in Japan, and it is also considered to be appropriate for use during cardiac surgery associated with neurohumoral activation based on the characteristics of this drug demonstrated by domestic clinical research. Similar to carperitide, nesiritide has been reported to achieve good long-term results in cardiac surgery patients, suggesting that natriuretic peptide therapy could be an important aspect of perioperative management due to its possible

cardioprotective and renoprotective effects, as well as compensating for CPB, preventing left ventricular remodeling, arrhythmias, and ischemia-reperfusion injury, and protecting major organs including the kidneys.

Conflict of interest statement

Akira Sezai has received lecture fees from Daiichi Sankyo Co., Ltd., and the coauthor has no conflicts of interest associated with this study.

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