No protection of heart, kidneys and brain by remote ischemic preconditioning before transfemoral transcatheter aortic valve implantation: Interim-analysis of a randomized single-blinded, placebo-controlled, single-center trial

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Abstract

Background: Remote ischemic preconditioning (RIPC) reduces myocardial injury and improves clinical outcome in patients undergoing coronary revascularization, but only in the absence of propofol-anesthesia. We investigated whether RIPC provides protection of heart, kidneys and brain and improves outcome in patients undergoing transfemoral transcatheter aortic valve implantation (TF-TAVI).

Methods: Patients undergoing TF-TAVI were randomized to receive RIPC (3 cycles of 5 min left upper arm ischemia and 5 min reperfusion) or placebo. The primary endpoint was myocardial injury, reected whether RIPC provides protection of heart, kidneys and brain and improves outcome in patients undergoing transfemoral transcatheter aortic valve implantation (TF-TAVI).

Results: 100 consecutive patients were enrolled between September 2013 and June 2015. There were no significant between-group differences in the primary endpoint of peri-interventional myocardial injury (ratio RIPC/placebo AUC-TnI: 0.87, 95% CI: 0.57–1.34, p = 0.53) or the secondary endpoints of cardiac, renal, and cerebral impairment. There was no significant treatment effect in subgroup-analyses of patients undergoing transfemoral cerebral MRI. Mortality and MACCE did not differ. No RIPC-related adverse events were observed.

Conclusions: RIPC did neither protect heart, kidneys and brain nor improve clinical outcome in patients undergoing TF-TAVI.
1. Introduction

Transcatheter aortic valve implantation (TAVI) has recently evolved as the method of choice to treat inoperable patients with severe, symptomatic native aortic valve stenosis [1] and is a viable alternative to surgical aortic valve replacement in high-risk patients [2]. TAVI, however, inflicts perioperative injury to the heart and other organs, especially the kidneys and the brain. Periprocedural myocardial injury [3], as reflected by increases of serum troponin concentrations, acute kidney injury [4] and periprocedural stroke [5] are all associated with increased morbidity and mortality. In addition, clinically silent cerebral embolization is a TAVI-inherent phenomenon [6], which may result in long-term neurocognitive impairment. A non-invasive, easily feasible, safe and inexpensive method such as remote ischemic preconditioning (RIPC) to induce multi-organ protection appears, therefore, particularly welcome in the elderly, multimorbid patients undergoing TAVI.

RIPC is the systemic response to brief episodes of ischemia/reperfusion of a peripheral tissue or organ and can provide protection to distant parenchymal organs such as heart, kidneys and brain [7,8]. RIPC reduces infarct size in patients with acute myocardial infarction treated by percutaneous intervention [9,10] or thrombolysis [11] and in patients undergoing elective interventional [12] or surgical coronary revascularization [13–15]. Also, better clinical short- [10,15] and long-term [14,16,17] outcomes have been reported as secondary endpoints in retrospective analyses. However, not all studies in humans demonstrated beneficial effects, and two recent phase III trials did not report reduced troponin release or improved clinical outcome in patients undergoing cardiac surgery [18,19]. Most likely the use of propofol anesthesia abrogated the cardioprotective effect of RIPC in these studies [8,20,21].

We, therefore, performed a randomized, controlled clinical trial to explore the potential protection of heart, kidneys and brain by RIPC in patients undergoing transfemoral TAVI (TF-TAVI). In this setting, there is no interference of general anesthesia with protection by RIPC, since TF-TAVI in our institution is usually performed under conscious sedation without the use of propofol. We now present the prespecified interim-analysis of the first 100 patients who completed 1-year follow-up.

2. Methods

2.1. Study design and participants

This prospective, randomized, single-blinded, placebo-controlled, single-center trial was conducted from September 2013 until June 2015 at the University Hospital of Essen, Germany. Adult patients hospitalized in the Departments of Cardiology or Thoracic and Cardiovascular Surgery of the West German Heart and Vascular Center were eligible when undergoing elective TAVI for severe, symptomatic native aortic valve stenosis and a prohibitive or high risk for surgical aortic valve replacement, as judged by the institutional multidisciplinary heart team from risk score and comorbidity assessment. Patients considered unlikely to benefit in their quality of life and to have a life expectancy of <1 year were excluded, as were patients with an unfavorable anatomy for TF-TAVI, left ventricular thrombus, active endocarditis or infection, acute ST-segment elevation myocardial infarction, hemodynamic instability or a preoperative serum troponin I concentration above the upper normal limit of 0.1 ng/mL. Patients with a history of stroke within the last 6 weeks and patients requiring acute or chronic hemodialysis were also excluded.

Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution’s human research committee (reference number 13–5355–BO). The trial is registered at ClinicalTrials.gov (NCT02080299).

2.2. Randomization and masking

Computer-generated codes in sealed envelopes were used to randomly allocate enrolled patients in a 1:1 ratio to undergo TF-TAVI with placebo or RIPC using block randomization in the first 100 patients. For each patient, the next available code was used, and a staff anesthetist without involvement in the study opened the envelope in the preparation room adjacent to the hybrid operating room where the TF-TAVI procedure was performed. Interventionalists/surgeons and physicians other than the attending anesthetist were unaware of patient allocation, as were study coordinators and outcome assessors.

2.3. Procedures

In our institution, TF-TAVI is predominantly performed under anesthetist-controlled conscious sedation with midazolam (0.05–0.10 mg/kg orally the evening and morning before TF-TAVI) and continuous intravenous infusion of remifentanil (0.01–2 μg/kg/min), with additional boli of midazolam (0.01–0.02 mg/kg) when appropriate during TF-TAVI. Only rarely, TF-TAVI is performed under general anesthesia with intravenous sufentanil (1 μg/kg), etomidate (0.2–0.5 mg/kg), rocuronium (0–6 mg/kg) and isoflurane (end-tidal, 0.6–1.0%).

RIPC was performed after the induction of conscious sedation (n = 47) or general anesthesia (n = 3) and was accomplished by 3 cycles of 5 min inflation of a blood pressure cuff on the left arm to 200 mm Hg with subsequent 5 min deflation. Per protocol, the time interval between the end of the last inflation and local groin anesthesia using mepivacaine chloride (400 mg) with subsequent arterial puncture was 30 min. In the placebo group, the blood pressure cuff remained uninflated after the induction of conscious sedation (n = 47, with conversion to general anesthesia in two patients during the procedure) or general anesthesia (n = 3) (Fig. 1A).

TF-TAVI was performed in a dedicated hybrid operating room by standard techniques using the balloon-expandable Sapien XT Edwards Lifesciences Inc., Irvine, CA, USA) or the next-generation Sapien 3 stent-valve bioprosthesis, which replaced the SAPIEN XT device after its CE-approval in February 2014. Procedures were conducted percutaneously with femoral artery access and closure using a suture-mediated vascular closure device (Perclose ProGlide, Abbott Vascular Inc., Redwood City, CA, USA). Preparatory balloon aortic valvuloplasty was performed in all cases, and the prosthesis was subsequently implanted by stepwise, slow balloon inflation under rapid right ventricular pacing at 160 to 200 bpm. Non-ionic, low-osmolar, monomeric contrast medium was used, either iomeprol (Imeron, Bracco Imaging S.P.A., Milan, Italy) or iopromide (Ultrascan 300, Bayer HealthCare Pharmaceuticals Inc., Germany).

Patients were on standard cardiac medications (e.g. beta-blockers, angiotensin-converting enzyme inhibitors, diuretics, acetylsalicylic acid, statins). Before the procedure, all patients received ceftriaxon (2 g) as single-shot antibiotic prophylaxis. Patients with an impaired renal function, defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m², received a continuous intravenous infusion of 0.9% saline (1 mL/kg/h) for 12 h before and up to 12 h after the procedure, and nephrotoxic drugs were withdrawn, if feasible. During the procedure, intravenous heparin was administered to achieve an activated clotting time > 250 s for the entire procedure; activated clotting time was measured every 30 min. Hemodynamic stability during the entire procedure was ensured by the attending anesthetist using a pulmonary artery catheter for invasive hemodynamic monitoring and intravenous epinephrine and/or norepinephrine for vasoactive support when required. After the procedure, dual anti-platelet therapy (acetylsalicylic acid 100 mg/day, clopidogrel 75 mg/day) was administered for 6 months, followed by acetylsalicylic acid alone for life. In patients with atrial fibrillation, phenprocoumon and clopidogrel were administered for 6 months and clopidogrel then exchanged for acetylsalicylic acid.

2.4. Blood sampling and analysis

Venous blood samples were drawn before the TF-TAVI procedure and at 1, 6, 12, 24, 48 and 72 h thereafter for measurement of serum concentrations of troponin I and creatinine. Serum troponin I concentrations were measured with a specific two-side immunoassay...
2.5. Outcomes

2.5.1. Cardioprotection

Primary endpoint was the extent of peri-interventional myocardial injury, as reflected by the area under the curve for serum troponin I concentrations (AUC-TnI over 72 h), calculated according to the trapezoidal rule. Secondary endpoints were periprocedural myocardial infarction according to valve academic research consortium 2 criteria (VARC-2) [22] and the incidence of cardiac arrhythmias, specifically new-onset atrial fibrillation and the need for permanent pacemaker implantation.

In a subgroup of patients, pre- and postinterventional cardiac magnetic resonance imaging (MRI) was performed and the prevalence and volume of delayed gadolinium enhancement was analyzed. Patients were selected to undergo cardiac MRI based on the absence of contraindications (e.g., permanent pacemaker), compliance to the examination and logistic feasibility (e.g., availability of the examination). MRI was performed on a 1.5 Tesla (Avanto or Aera, Siemens Healthcare, Erlangen, Germany, n = 52) or a 3 Tesla scanner (Magnetom Skyra or Biograph, Siemens Healthcare, Erlangen, Germany, n = 5) with late gadolinium-enhanced segmented two-dimensional inversion-recovery turbo fast low-angle shot sequences performed 10 min after contrast agent injection (Gadovist; Bayer Healthcare, Leverkusen, Germany), as described [23].

2.5.2. Nephroprotection

The maximum increase of serum creatinine concentrations and the maximum decrease in eGFR within the first week after TF-TAVI were secondary endpoints. Another secondary endpoint was the incidence of acute kidney injury, as defined according to VARC-2 criteria [22].
2.5.3. Cerebroprotection

A secondary endpoint was the incidence of peri-procedural stroke, as defined by VARC-2 criteria, with distinction between disabling and non-disabling strokes [22].

In a subgroup of patients, pre- and postinterventional cerebral MRI was performed at baseline and within the first week after TF-TAVI to detect clinically silent new foci of restricted diffusion [6]. Presence, number, and location of these cerebral lesions were analyzed. Patient selection was based on the same criteria as described for cardiac MRI. Cerebral MRI was performed on a 1.5-Tesla (Avanto or Aera, Siemens Medical Systems, Erlangen, Germany, n = 46) or 3 Tesla scanner (Magnetom Skyra or Biograph, Siemens Healthcare, Erlangen, Germany, n = 5) and included transversal fluid-attenuated inversion recovery sequences and transversal diffusion-weighted images of the whole brain, as described [6].

2.5.4. Clinical outcome

All-cause and cardiovascular mortality, first-time major adverse cardiac and cerebrovascular events (MACCE: cardiac death, non-fatal myocardial infarction, transient ischemic attack or stroke and heart failure requiring hospital admission) at 30 days, 3 months and 1 year were assessed. These data were reviewed by two consultant cardiologists who did not participate in the study (Theodor Baars and Amir Abbas Mahabadi) and assigned cardiovascular and non-cardiovascular causes of death.

2.6. Statistical analysis and sample size calculation

Since no data are currently available for the estimation of the protective effect of RIPC on heart, kidneys and brain during TF-TAVI and, consequently, for a power-analysis, this report presents a prespecified interim-analysis based on 50 patients per group, which was performed after the last patient had completed 1 year follow-up. The trial was halted after recruitment of these 100 patients.

Categorical variables, expressed as frequencies (%), were compared between groups with Fisher’s exact test or with Fisher-Freeman-Halton’s test, which was used for variables with more than two categories. Continuous variables, expressed as means ± standard deviation, were compared between groups with Welch’s t-test.

The AUC-TnI was log-transformed and analyzed with one-way analysis of variance (ANOVA). The ratios of AUC-TnI and peak serum troponin I (95% CI) for RIPC to placebo were obtained by back-transformation of the ANOVA results. Kaplan-Meier survival functions were compared with log-rank test. A post-hoc sensitivity analysis was performed with exclusion of patients in whom the primary endpoint was influenced by unexpected intra- or postinterventional complications. A post-hoc sample-size calculation was performed from the intention-to-treat and the post-hoc sensitivity analysis data. All statistical analyses were done with SAS (version 9.4).

3. Results

During the study period, 152 patients were scheduled for TF-TAVI and screened for the trial. After exclusion of 52 patients, 100 patients were randomized to RIPC (n = 50) or placebo (n = 50) and included in the intention-to-treat interim-analysis (Fig. 1B). The reasons for exclusion of 52 patients were: the TF-TAVI was performed for the treatment of a degenerated bioprosthesis (valve-in-valve) (n = 9), stenosed bicuspid valve (n = 1), aortic valve stenosis with concomitant hypertrophic obstructive cardiomyopathy (n = 1), or as bail-out after balloon-valvuloplasty in a patient with a large annulus (n = 1), with use of a different (i.e. not balloon-expandable) prosthesis (n = 3), a combination of the TF-TAVI procedure with an additional procedure (n = 3), or during hemodynamic instability (n = 3). In other patients, there was an increased serum troponin I concentration at baseline (n = 1), a history of stroke within the last 6 weeks (n = 3), the participation in another trial (n = 5), or the unwillingness to participate in the study (n = 22). Baseline characteristics (Supplemental Table 1) and procedural data (Supplemental Table 2) did not differ between the two groups. The calculation of AUC-TnI, serum creatinine, and eGFR was not possible in one patient of the RIPC group due to non-cardiovascular death <24 h after the procedure. This patient and four additional patients suffering unexpected intra- or postoperative complications with impact on the primary endpoint (i.e. myocardial perforation in three cases, coronary obstruction in one case) were excluded from the post-hoc sensitivity analysis. Fifty-seven patients underwent pre- and postinterventional cardiac (RIPC: n = 27, placebo: n = 30) and 51 patients pre- and postinterventional cerebral MRI (RIPC: n = 26, placebo: n = 25). Patients were followed up for at least 1 year, and at completion of the present interim-analysis follow-up data for 140 patient-years had been recorded with 100% completeness.

All baseline serum troponin I concentrations were lower than 0.1 ng/mL. RIPC was neither associated with reduced AUC-TnI (32.59 ng/mL over 72 h in the placebo group, 28.51 ng/mL over 72 h in the RIPC group) nor with reduced peak serum troponin I (1.11 ng/mL in the placebo group, 1.12 ng/mL in the RIPC group). The estimated ratio for RIPC to placebo for AUC-TnI was 0.87 (95% CI 0.57–1.34; p = 0.53) and that for peak serum troponin I (0.65–1.56; p = 0.97). In the post-hoc sensitivity analysis, the ratio for AUC-TnI was 0.81 (95% CI 0.55–1.19; p = 0.28) and that for peak serum TnI 0.93 (95% CI 0.63–1.39; p = 0.73). For the observed effects to be significantly different at a 5% level (two-sided), one would need approximately 950 patients per group for a power of 80%. Based on the observed effects in the post-hoc sensitivity analysis, approximately 300 patients per group would be needed.

The incidence of peri-procedural myocardial infarction according to VARC-2 criteria was not different between groups, nor was the occurrence of cardiac arrhythmias. New-onset atrial fibrillation was found in 10% of patients in each group, and permanent pacemaker implantation due to higher-degree atrioventricular block became necessary in 10% of patients in the RIPC group versus 6% of patients in the placebo group (p = 0.72) (Table 1). Of the 57 patients undergoing cardiac MRI, new delayed gadolinium enhancement was found in a single patient in each group (Table 2).

Both, the maximum increase of serum creatinine concentrations and the maximum decrease in eGFR within the first week after TF-TAVI did not differ between groups (Table 2), and there was no between-group difference regarding the incidence of acute kidney injury (Table 1). A sample size calculation based on the observed effects on peak serum creatinine concentration estimates approximately 350 patients per group for a power of 80%.

There was also no between-group difference in the incidence of neurological events after TF-TAVI, with similar rates of transient ischemic attack, disabling and non-disabling stroke (Table 1). Cerebral MRI did not reveal any significant differences in presence, number, size and location of clinically silent cerebral lesions (Table 2). If the sample size calculation would be based on the observed effects regarding the total lesion volume per patient, a power of 80% would be achieved with approximately 115 patients per group.

All-cause mortality did not differ between the RIPC and the placebo groups at 30 days, 3 months and 1 year (Fig. 2A), neither did cardiovascular mortality (Fig. 2B). MACCE rates were also similar in the RIPC and placebo groups at each time point (Fig. 2C).

No RIPC-related safety issues were observed.

4. Discussion

In the interim-analysis of the present single-center, single-blinded, placebo-controlled, randomized trial including 100 patients who underwent elective TF-TAVI, predominantly under conscious sedation and in the absence of propofol anesthesia, left upper arm RIPC as
Table 1
30-days clinical outcome.

<table>
<thead>
<tr>
<th></th>
<th>RIPC (n = 50)</th>
<th>Placebo (n = 50)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From any cause</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>1.00</td>
</tr>
<tr>
<td>From cardiovascular cause</td>
<td>0 (0)</td>
<td>2 (4)</td>
<td>0.49</td>
</tr>
<tr>
<td>MACCE</td>
<td>9 (18)</td>
<td>12 (24)</td>
<td>0.62</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>8 (16)</td>
<td>9 (18)</td>
<td>1.00</td>
</tr>
<tr>
<td>TIA</td>
<td>4 (8)</td>
<td>4 (8)</td>
<td>1.00</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disabling</td>
<td>1 (2)</td>
<td>3 (6)</td>
<td>0.62</td>
</tr>
<tr>
<td>Non-disabling</td>
<td>3 (6)</td>
<td>2 (4)</td>
<td>1.00</td>
</tr>
<tr>
<td>Periprocedural MI</td>
<td>2 (4)</td>
<td>1 (2)</td>
<td>1.00</td>
</tr>
<tr>
<td>Major vascular complications</td>
<td>1 (2)</td>
<td>5 (10)</td>
<td>0.20</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>8 (16)</td>
<td>5 (10)</td>
<td>0.30</td>
</tr>
<tr>
<td>II</td>
<td>0 (0)</td>
<td>3 (6)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>2 (4)</td>
<td>3 (6)</td>
<td></td>
</tr>
<tr>
<td>II + III</td>
<td>2 (4)</td>
<td>6 (12)</td>
<td>0.27</td>
</tr>
<tr>
<td>Bleeding complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life-threatening</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1.00</td>
</tr>
<tr>
<td>Major</td>
<td>5 (10)</td>
<td>4 (8)</td>
<td></td>
</tr>
<tr>
<td>New atrial fibrillation</td>
<td>5 (10)</td>
<td>5 (10)</td>
<td>1.00</td>
</tr>
<tr>
<td>New pacemaker</td>
<td>5 (10)</td>
<td>3 (6)</td>
<td>0.72</td>
</tr>
</tbody>
</table>

Values are n (%).

MI = myocardial infarction; TIA = transient ischemic attack.

Table 2
Laboratory and imaging parameters.

<table>
<thead>
<tr>
<th></th>
<th>RIPC</th>
<th>Placebo</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac MRI</td>
<td>n = 27</td>
<td>n = 30</td>
<td></td>
</tr>
<tr>
<td>Patients with new WMA</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>New gadolinum enhancement</td>
<td>1</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Cerebral MRI, silent lesions</td>
<td>n = 26</td>
<td>n = 25</td>
<td></td>
</tr>
<tr>
<td>Patients with new lesions</td>
<td>19 (73)</td>
<td>21 (84)</td>
<td>0.50</td>
</tr>
<tr>
<td>New lesions, total</td>
<td>78</td>
<td>109</td>
<td></td>
</tr>
<tr>
<td>New lesions per patient</td>
<td>4.11 ± 3.14</td>
<td>5.19 ± 3.67</td>
<td>0.32</td>
</tr>
<tr>
<td>Lesion location, No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACA</td>
<td>3</td>
<td>5</td>
<td>0.49</td>
</tr>
<tr>
<td>MCA</td>
<td>45</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>PCA</td>
<td>9</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>19</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Brainstem</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Average lesion volume, mm³</td>
<td>80.9 ± 89.9</td>
<td>90.9 ± 142.0</td>
<td>0.56</td>
</tr>
<tr>
<td>Average lesion volume per patient, mm³</td>
<td>86.20 ± 57.55</td>
<td>88.62 ± 93.20</td>
<td>0.92</td>
</tr>
<tr>
<td>Maximal lesion volume per patient, mm³</td>
<td>159.5 ± 137.2</td>
<td>231.4 ± 262.2</td>
<td>0.28</td>
</tr>
<tr>
<td>Total lesion volume per patient, mm³</td>
<td>332.1 ± 289.7</td>
<td>471.9 ± 458.1</td>
<td>0.32</td>
</tr>
<tr>
<td>Laboratory: Kidney</td>
<td>n = 49</td>
<td>n = 50</td>
<td></td>
</tr>
<tr>
<td>Maximum creatinine increase, mg/L</td>
<td>1.9 ± 5.2</td>
<td>2.9 ± 6.5</td>
<td>0.37</td>
</tr>
<tr>
<td>Peak creatinine, mg/L</td>
<td>14.3 ± 7.2</td>
<td>15.7 ± 6.3</td>
<td>0.30</td>
</tr>
<tr>
<td>Maximum eGFR decrease, mL/min/1.73m²</td>
<td>4.3 ± 8.6</td>
<td>6.6 ± 13.9</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%).

ACA = anterior cerebral artery; eGFR = estimated glomerular filtration rate; MCA = medial cerebral artery; PCA = posterior cerebral artery; WMA = wall motion abnormalities; MRI = magnetic resonance imaging.
RIPC can also protect the brain [30], a welcome effect since cerebral embolization is a TAVI-inherent phenomenon, which results in clinically overt stroke or in silent cerebral lesions on postprocedural MRI. However, we observed no reduction in clinically overt neurological events such as disabling stroke, non-disabling stroke and transient ischemic attack by RIPC. Again, our cohort was probably too small. In contrast, the incidence of clinically silent lesions on postprocedural cerebral MRI is high (>70%), and a positive effect of RIPC on this surrogate endpoint might be expected [31], but was not observed, in contrast to a recent trial, which reported a reduction of lesion number and size by a dedicated protection device [32]. The observed trends for protection of kidneys and brain by RIPC in our current study deserve further investigation in larger cohorts.

4.1. Limitations

No data are currently available for the estimation of a protective effect of RIPC during TF-TAVI, precluding a power-analysis. Hence, this report presents a prespecified interim-analysis based on 50 patients per group, which was performed after the last patient had completed 1 year follow-up. Due to the small number of patients, results have to be interpreted cautiously, and further recruitment of patients is mandatory to evaluate whether the beneficial trends seen in our prespecified interim-analysis become clinically relevant/meaningful in a larger cohort of patients. Additionally, there is a need to evaluate which confounders, specifically advanced age, comorbidities and comediations, potentially impair the efficacy of RIPC in different patient cohorts.

Fig. 2. Kaplan-Meier time-to-event curves in the interim-analysis of 100 patients. (A) All-cause mortality in the intention-to-treat cohort for the complete follow-up period. (B) Cardiovascular mortality in the intention-to-treat cohort for the complete follow-up period. (C) Major adverse cardiac and cerebrovascular events in the intention-to-treat cohort for the complete follow-up period. The inserted tables display the cumulative numbers of events at the prespecified time points 30 days, 3 months, and 1 year. d = days; mo = month; y = year.
5. Conclusion

In summary, RIPC in our interim-analysis of 100 typical TF-TAVI patients did not provide significant protection to heart, kidneys and brain. Even if we studied a substantially larger cohort of patients and achieved statistically significant results, the biological and clinical significance of the observed benefits would probably be minor. Therefore, our interim analysis does not support the routine use of RIPC in TF-TAVI patients.

Sources of funding and support

There was no funding source for this study.

Conflicts of interest

PKa and DW are clinical proctors for Edwards Lifesciences Inc. TR is clinical proctor for Medtronic. The other authors declare no conflicts of interest.

Acknowledgments

GH initiated the trial. PKa, GH, and PKl were the principal investigators and designed the trial. PKa, HAH, and PKl coordinated the trial. PKa, PCC, FA, RAJ, EK, UF, and JP performed the treatment protocol. PKa, HAH, MN, GH, and PKl analyzed the data. PKa, MN, TR, GH, and PKl interpreted the data. EK, UF, and HGJ were the senior anesthetists. DW, MT, and HGJ were the senior cardiothoracic surgeons. FN, TS, MS, and MF were the senior radiologists. The manuscript was written by PKa, MN, GH, and PKl.

All authors approved the final version of the manuscript. The corresponding author had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. We thank Theodor Baars and Amir Abbas Mahabadi, West-German Heart and Vascular Center Essen, Department of Cardiology and Vascular Medicine, Universitätsklinikum Essen, Essen, Germany, for reviewing the medical records, identifying and verifying the clinical outcome endpoints.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2016.12.005.

References

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