# Major adverse cardiac events after elective infrarenal endovascular aortic aneurysm repair

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## ABSTRACT

**Objective:** There is a significant cardiac morbidity and mortality after endovascular aneurysm repair (EVAR). However, information about long-term risk of cardiac events after EVAR and potential predictors is lacking. Therefore, the aim of this study was to determine incidence and predictors of major adverse cardiac events (MACE) at 1 and 5 years after elective EVAR for infrarenal abdominal aortic aneurysms.

**Methods:** Baseline, perioperative, and postoperative information of 320 patients was evaluated. The primary outcome was the incidence of MACE after EVAR, which was defined as acute coronary syndrome, unstable angina pectoris, de novo atrial fibrillation, hospitalization for heart failure, mitral valve insufficiency, revascularization (including percutaneous coronary intervention and coronary artery bypass grafting), as well as cardiovascular and noncardiovascular death. Kaplan-Meier analyses were performed to determine incidences of MACE, MACE excluding noncardiovascular death and cardiac events by excluding noncardiovascular and vascular death from MACE. Predictors of MACE were identified using univariate and multivariate binary regression analysis.

**Results:** Through 1 and 5 years of follow-up after EVAR, freedom from MACE was 89.4% (standard error [SE], 0.018) and 59.8% (SE, 0.033), freedom from MACE excluding noncardiovascular death was 94.7% (SE, 0.013) and 77.5% (SE, 0.030) and freedom from cardiac events was 96.0% (SE, 0.011) and 79.1% (SE, 0.030), respectively. Predictors for MACE within 1 year were American Society of Anesthesiologists (ASA) score of III or IV (odds ratio [OR], 3.17; 95% confidence interval [CI], 1.52-6.59) and larger abdominal aortic diameter (OR, 1.04; 95% CI, 1.01-1.08). A history of atrial fibrillation (OR, 0.14; 95% CI, 0.03-0.60) was a negative predictor factor. Predictors for MACE through 5 years were a history of heart failure (OR, 4.10; 95% CI 1.36-12.32) and valvular heart disease (OR, 2.31; 95% CI, 0.97-5.51), American Society of Anesthesiologists score of 3 or 4 (OR, 1.66; 95% CI, 0.96-2.88), and older age (OR, 1.04; 95% CI, 1.01-1.08).

**Conclusions:** MACE is a common complication during the first 5 years after elective EVAR. Cardiac diseases at baseline are strong predictors for long-term MACE and potentially helpful in optimizing future postoperative long-term follow-up. (J Vasc Surg 2022;76:1527-36.)

**Keywords:** MACE; AAA; EVAR; Heart failure

In past decades, endovascular aneurysm repair (EVAR) became the preferred treatment option for most abdominal aortic aneurysms (AAA) with a suitable anatomy, related to the early morbidity and survival benefit over open surgery.[1] However, there seems to be a significant cardiac morbidity and mortality after EVAR, ranging from 5% to 18%.[2-4]

More knowledge about postoperative cardiac complications after EVAR for AAA will help in weighting the benefits and risks of modern aneurysm treatment. Identifying predictive factors for cardiac events could be especially helpful to anticipate problems that may occur after EVAR. A few studies investigated multiple predictors for myocardial injury after EVAR, where the only shared predictor was an advancing age.[5-7] The occurrence of myocardial injury, comparable with other studies,[5-7] was also found to be significantly different between patients aged above and below

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75 years in a study, that mainly focused on the effect of single risk factors, like other studies,[8-14] on survival after aneurysm repair.[8] Other described predictors for myocardial injury after EVAR included the American Society of Anesthesiologists (ASA) score of IV,[7] diabetes mellitus,[7] different preoperative laboratory results such as haemoglobin[5] and creatinine,[7] and duration of surgery, as well as complications during or immediately after surgery.[6]

To date, the literature has focused mainly on myocardial infarction as predominant cardiac complication after EVAR. Complications such as new-onset atrial fibrillation (AF) and hospitalization for heart failure or specification of the required cardiac revascularization following myocardial infarction such as the need for a coronary artery bypass graft (CABG) or a percutaneous coronary intervention (PCI) after EVAR are rarely reported in literature.[15,16] However, studies have demonstrated that EVAR increases vascular stiffness,[17,18] which is related to cardiac events. A study by Takeda et al[18] linked this increased stiffness to induced left ventricular hypertrophy and diastolic dysfunction, which indicates that endograft placement may influence cardiac remodeling and function. Additionally, most available literature focusses on short-term complications only. There is a lack of information about the long-term risk of cardiac events after EVAR and potential predictors.[5-7] The aim of this study is to evaluate the risk and predictors of early and late major adverse cardiac events (MACE) after an elective infrarenal EVAR.

## METHODS

**Database.** This is a single-center, retrospective cohort study. All consecutively treated patients for an infrarenal AAA with elective EVAR, between January 1, 2011, and January 1, 2019, were included consecutively. Patients who underwent fenestrated EVAR, chimney EVAR, thoracic EVAR, endovascular aneurysm sealing, and those who were treated with an iliac branched device or underwent a reintervention after previous AAA repair were excluded, as were patients with a symptomatic or ruptured AAA.

**Ethical approval.** Retrospective research of patients' files is not in the scope of Dutch law for human research; investigational review board approval was, therefore, not required. However, a waiver (CMO 2018-4118) and local approval were obtained. As a consequence, informed consent from the patients was not obtained. Electronic hospital records were checked to ensure patients had no objection for the use of data in scientific research. Patients' data were analyzed anonymously. All authors had full access to all the data in the study and take responsibility for its integrity and data analysis. This study was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki.

### ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center, retrospective cohort study
- **Key Findings:** Major adverse cardiac events (MACE) were studied in 320 patients who were treated electively with endovascular aneurysm repair. Freedom from MACE was 89.4% and 59.8% through 1 and 5 years of follow-up. Cardiac disease at baseline, such as valvular heart disease and heart failure, were strong predictors.
- **Take Home Message:** MACE are common complications after endovascular aneurysm repair with cardiac disease at baseline as a strong predictor.

**Data extraction.** Data were extracted from electronic hospital records and entered into Research Manager (Deventer, the Netherlands). Baseline characteristics, medication, laboratory results, periprocedural information, follow-up information, and information on adverse events was collected up until August 2020, resulting in at least 1 year of follow-up information per patient. Data were extracted from Research Manager to IBM SPSS Statistics (SPSS version 25.0 for windows, IBM Corporation, Armonk, NY). Data were checked for outliers, which were then checked in hospital records. Any mistakes found this way were corrected.

**Outcomes.** Outcome parameters were classified according to the *International Classification of Disease*, 10th Revision (ICD-10). The primary outcome was MACE during follow-up. Outcomes were checked by a committee of three members and solved by consensus in case of discrepancies. MACE was defined as acute coronary syndrome (defined as ST-elevation myocardial infarction [ICD codes I21.0-I21.3, I21.9[19]], non-ST-elevation myocardial infarction [ICD code I21.4[19]], unstable angina pectoris [ICD code I20.0]), de novo AF (ICD codes I48.0-I48.2, I48.9), hospitalization for heart failure (ICD code I50),[20] mitral valve insufficiency (ICD codes I05, I34), and revascularization (including PCI and CABG), as well as cardiovascular and noncardiovascular death.[21-23] Hospital records were checked for MACE, which were compared with the definition according to the ICD-10 codes. The incidence of MACE was reviewed at 1 year and 5 years after intervention. Additionally, freedom from MACE excluding noncardiovascular death, cardiac events and freedom from all-cause death was investigated. As a secondary objective, the influence of cardiac history was investigated on the occurrence of MACE. Cardiac history was defined as any of the following in the medical history; myocardial infarction (ICD code I21), angina pectoris (ICD code I20), AF (ICD codes I48.0-I48.2, I48.9), coronary artery disease (ICD codes I24.0, I24.8, I25.1, I25.4), valvular heart disease (ICD codes I05-I09,

**Table I.** Baseline patient characteristics

| | Total | MACE | No MACE | *P* value |
|---|---|---|---|---|
| Age, years | 72.9 ± 8.1 | 75.2 ± 7.9 | 71.2 ± 7.9 | <.001 |
| Male gender | 275 (85.9) | 117 (87.3) | 158 (84.9) | .548 |
| Body mass index, kg/m$^2$ | 26.6 ± 4.2 | 26.4 ± 4.0 | 26.7 ± 4.3 | .529 |
| Systolic blood pressure, mm Hg | 142.3 ± 21.5 | 140.5 ± 22.9 | 143.6 ± 20.5 | .211 |
| Diastolic blood pressure, mm Hg | 80.6 ± 10.3 | 79.9 ± 10.8 | 81.1 ± 9.9 | .327 |
| Diabetes mellitus | 63 (19.7) | 35 (26.1) | 28 (15.1) | .015 |
| Smoking | 110 (34.4) | 40 (29.9) | 70 (37.6) | .205 |
| Hypertension | 233 (72.8) | 100 (74.6) | 133 (71.5) | .465 |
| Hyperlipidemia | 246 (76.9) | 96 (71.6) | 150 (80.6) | .687 |
| Pulmonary dysfunction | 68 (21.3) | 34 (25.4) | 34 (18.3) | .058 |
| Renal dysfunction | 102 (31.9) | 52 (38.8) | 50 (26.9) | .017 |
| ASA classification | | | | .017 |
| I or II | 153 (47.8) | 54 (40.3) | 99 (53.2) | |
| III or IV | 165 (51.6) | 80 (59.7) | 85 (45.7) | |
| SVS/AAVS score | | | | .022 |
| 1 Absent | 90 (28.1) | 26 (19.4) | 64 (34.4) | |
| 2 Mild | 154 (48.1) | 69 (51.5) | 85 (45.7) | |
| 3 Moderate | 38 (11.9) | 19 (14.2) | 19 (10.2) | |
| 4 Severe | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Cardiac history | | | | |
| Myocardial infarction | 78 (24.4) | 37 (27.6) | 41 (22.0) | .264 |
| Angina pectoris | 32 (10.0) | 17 (12.7) | 15 (8.1) | .172 |
| AF | 50 (15.6) | 22 (16.4) | 28 (15.1) | .772 |
| Coronary artery disease | 30 (9.4) | 16 (11.9) | 14 (7.5) | .187 |
| Valvular heart disease | 34 (10.6) | 23 (17.2) | 11 (5.9) | .001 |
| Heart failure | 25 (7.8) | 21 (15.7) | 4 (2.2) | <.001 |
| CABG | 40 (12.5) | 20 (14.9) | 20 (10.8) | .273 |
| Pacemaker/implantable cardioverter-defibrillator | 12 (3.8) | 7 (5.2) | 5 (2.7) | .259 |
| PCI | 54 (16.9) | 26 (19.4) | 28 (15.1) | .333 |
| Medication | | | | |
| Diabetic medication | 57 (17.8) | 34 (25.4) | 23 (12.4) | .805 |
| Hypertension medication | 230 (71.9) | 109 (81.3) | 121 (65.1) | .449 |
| Statin use | 248 (77.5) | 94 (70.1) | 154 (82.8) | .286 |
| Anticoagulants | 267 (83.4) | 111 (82.8) | 156 (83.9) | .276 |
| Aneurysm morphology | | | | |
| AAA maximum diameter | 59.7 ± 10.1 | 61.8 ± 11.2 | 58.2 ± 9.0 | .002 |
| Infrarenal aortic neck diameter | 24.1 ± 3.9 | 24.4 ± 3.7 | 23.9 ± 4.0 | .249 |
| Infrarenal aortic neck length | 28.6 ± 12.7 | 28.7 ± 13.0 | 28.5 ± 12.4 | .906 |
| Angle between AAA and neck | 42.8 ± 19.6 | 43.6 ± 21.3 | 42.4 ± 18.8 | .716 |
| Graft material | | | | .084 |
| PTFE | 118 (36.9) | 42 (31.3) | 76 (40.9) | |
| Polyester | 200 (62.5) | 91 (67.9) | 109 (58.6) | |
| Endograft type | | | | .090 |
| Medtronic Endurant | 191 (59.7) | 87 (64.9) | 104 (55.9) | |

*(Continued on next page)*

**Table I.** Continued.

| | Total | MACE | No MACE | *P* value |
|---|---|---|---|---|
| Gore Excluder | 94 (29.4) | 32 (23.9) | 62 (33.3) | |
| Endologix AFX | 22 (6.9) | 8 (6.0) | 14 (7.5) | |
| Other[a] | 13 (4.1) | 7 (5.2) | 6 (3.2) | |

Values are mean ± standard deviation or number (%).
*AAA*, Abdominal aortic aneurysm; *AF*, atrial fibrillation; *ASA*, American Society of Anesthesiologists Physical Status score; *CABG*, coronary artery bypass graft; *PCI*, percutaneous coronary intervention; *PTFE*, polytetrafluoroethylene; *SVS/ASVS*, Society for Vascular Surgery/American Association for Vascular Surgery score.
[a]Other specification: Medtronic EVO (n = 5), Cook Zenith (n = 4), TerumoAortic Anaconda (n = 2), Endologix Ovation (n = 2).

I34-I36), heart failure (ICD code I50), CABG, PCI, and/or pacemaker/implantable cardioverter-defibrillator. All events were peer reviewed by a cardiologist to determine whether the events needed to be scored as major.

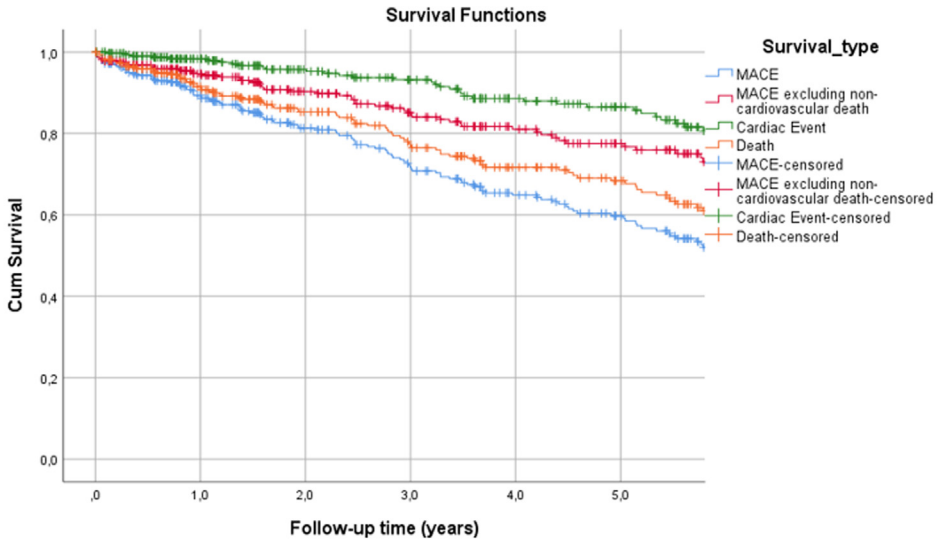
**Statistical analyses.** Continuous variables are presented as mean ± standard deviation if normally distributed or as median with interquartile range if applicable. Categorical and nominal data are presented as a number followed by percentage. Missing values were not replaced in order to provide unbiased and informative findings. Univariate logistic regression was used to identify univariate predictors. Variables with a *P* value of less than .050 were included for multivariate logistic regression analysis. Logistic regression backward method was used to identify the optimal set of predictors for MACE. A subanalysis was performed for development of MACE, excluding noncardiovascular death. Furthermore, subgroup analyses were performed for those with and without a predefined cardiac history. All variables were provided with reference values, if necessary. This study investigated the risk of presence of for example AF and heart failure compared with the absence of these parameters on developing MACE. Therefore, the absence of these parameters was chosen as reference category, so the odds ratio (OR) represents the risk of the presence of these conditions compared with those without these conditions. Correlations between the variables entered in the multivariate model were checked. Both the first and final model of multivariate regression were visualized with its corresponding univariate analysis results according to Field et al.[24] Model performances were described using the $\chi^2$ test, −2 log likelihood, Nagelkerke $R^2$, Hosmer and Lemeshow test, and percentage of correctly classified MACE of the total population; receiver operating characteristic curves were created for the final models. Freedom from MACE, MACE excluding noncardiovascular death, cardiac events, and death were analyzed using Kaplan-Meyer analyses. Noncardiovascular and vascular death were excluded from MACE to find the cardiac events for this analysis. Two-sided *P* values of less than .050 were considered significant. Statistical analysis were performed using IBM SPSS Statistics (SPSS version 25.0 for windows, IBM Corporation, Armonk, NY).

## RESULTS

**Baseline.** A total of 320 patients were included. Baseline characteristics are depicted in Table I. The mean patient age was 72.9 ± 7.9 years and males comprised 85.9% of patients. Most patients had a history of hyperlipidemia and hypertension and were classified with ASA score of II or III. Prior cardiovascular disease was present in 50.6% of patients. The maximum AAA diameter before EVAR was 59.7 ± 10.1 mm. A polyester and polytetrafluoroethylene endograft was implanted in 62.9% and 37.1% of patients, respectively (Table I). Furthermore, 47 patients (14.7%) required an AAA reintervention. Four patients (1.3%) presented with a ruptured AAA, all of whom underwent endovascular reintervention; one patient needed explantation related to prothesis infection.

**MACE and cardiac events.** The freedom from MACE was 89.4% (standard error [SE], 0.018) through 1 year and 59.8% (SE, 0.033) through 5 years follow-up (Fig). At both time points, noncardiovascular death constituted approximately 50% and cardiovascular death covered approximately 16.5% of MACE. The freedom from MACE excluding noncardiovascular death was 94.7% (SE, 0.013) and 77.5% (SE, 0.030) through 1 and 5 years of follow-up, respectively. There was a gradual increase in the incidence of MACE through 5 years of follow-up, where MACE occurred in 3.1% of patients in the first 30-days after surgery. The freedom from cardiac events at 1 and 5 years of follow-up was 96.0% (SE, 0.011) and 79.1% (SE, 0.030), respectively. De novo AF and myocardial ischemia-driven revascularization were the most common first cardiac events after EVAR (Table II).

The mean time to first MACE was 3.2 ± 2.4 years (Table III), without differences between those with and without cardiac disease in medical history. Patients with a cardiac history showed a trend to develop stroke or peripheral artery disease earlier in time compared with those without cardiac history. Furthermore, 22.3% of the patients who developed MACE within 5 years experienced more than one event, where 14.3%, 7.1%, and 0.9% developed, respectively, two, three, and four events.




| | 0 | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|
| **MACE** | | | | | | |
| Nr. at risk | 320 | 288 | 268 | 247 | 233 | 224 |
| MACE free survival (%) | 100 | 89.4 | 81.3 | 71.7 | 64.9 | 59.8 |
| SE | | 0.018 | 0.024 | 0.029 | 0.031 | 0.033 |
| **MACE excluding non-cardiovascular death** | | | | | | |
| Nr. at risk | 320 | 304 | 294 | 284 | 277 | 272 |
| Event free survival (%) | 100 | 94.7 | 90.3 | 85.1 | 81.0 | 77.5 |
| SE | | 0.013 | 0.018 | 0.024 | 0.027 | 0.030 |
| **Cardiac event** | | | | | | |
| Nr. at risk | 320 | 308 | 298 | 289 | 282 | 277 |
| Event free survival (%) | 100 | 96.0 | 91.5 | 86.8 | 82.7 | 79.1 |
| SE | | 0.011 | 0.018 | 0.023 | 0.026 | 0.030 |
| **Death** | | | | | | |
| Nr. at risk | 320 | 298 | 285 | 372 | 262 | 257 |
| Overall survival (%) | 100 | 92.6 | 87.3 | 81.2 | 75.9 | 72.9 |
| SE | | 0.015 | 0.020 | 0.025 | 0.028 | 0.030 |

**Fig.** Cumulative freedom from major adverse cardiac events (*MACE*) *(blue line),* MACE excluding non-cardiovascular death *(red line),* cardiac events (green line) and all-cause death (orange line) through 5-year follow-up after elective endovascular aneurysm repair (EVAR) for infrarenal aneurysms. Here, events and censored data are superimposed in each corresponding line as a vertical line. *SE,* Standard error.

**Survival.** Freedom of all-cause death after EVAR was 92.6% (SE, 0.015) and 72.9% (SE, 0.030) through 1 and 5 years of follow-up, respectively. Seventy percent of the patients who died within 5 years also suffered from heart failure before undergoing EVAR. Overall, 101 patients died during the follow-up, of which nine (six patients with and three patients without a cardiac history) were related to cardiac events. There were six patients, all with a cardiac history, who died from an AAA or procedure related event. Causes of death for these patients were AAA rupture (n = 2), renal failure (n = 2), autonomic failure (n = 1), and an infected prothesis (n = 1). Three patients had an AAA reintervention and four patients died within 2 months of their primary surgery or reintervention. Additionally, cerebrovascular events occurred in three patients with and one patient without a cardiac history. Furthermore, the 30-day results regarding survival after EVAR showed that three patients died, all of whom had a cardiac history (Supplementary Table I, online only).

**Predictors of MACE.** The resulting positive predictive factors for MACE within 1 year of follow-up were an ASA score of III or IV and larger abdominal aortic diameter (in mm), whereas a negative predictive factor was a history of AF (Table IV). Positive predictors of MACE within 5 years of follow-up were a history of heart failure and valvular heart disease before EVAR, an ASA score of III or IV and older age (in years). Model performances are described in Supplementary Table II (online only). Given the large number of noncardiovascular death events, another multivariate analysis was performed for MACE

**Table II.** Major cardiac adverse events (*MACE*), cardiovascular, and abdominal aortic aneurysm (*AAA*) related events during follow-up

| | | Cardiac history | | |
|---|---|---|---|---|
| | Events (n = 320) | Yes (n = 162) | No (n = 158) | *P* value |
| First MACE during 1-year follow-up | 44 (13.8) | 25 (15.4) | 19 (12.0) | .753 |
| Acute coronary syndrome | 3 (0.9) | 2 (1.2) | 1 (0.6) | |
| AF de novo | 6 (1.8) | 2 (1.2) | 4 (2.5) | |
| Heart failure hospitalization | 2 (0.6) | 1 (0.6) | 1 (0.6) | |
| Mitral valve insufficiency | 1 (0.3) | 1 (0.6) | 0 (0.0) | |
| Ischemia driven revascularization | 3 (0.9) | 2 (1.2) | 1 (0.6) | |
| Cardiovascular death | 7 (2.1) | 5 (3.0) | 2 (1.3) | |
| Noncardiovascular death | 22 (6.9) | 12 (7.4) | 10 (6.3) | |
| First MACE during 5-year follow-up | 112 (35.0) | 68 (42.0) | 44 (27.8) | .246 |
| Acute coronary syndrome | 7 (2.2) | 5 (3.1) | 3 (1.9) | |
| AF de novo | 10 (3.1) | 3 (1.9) | 7 (4.4) | |
| Heart failure hospitalization | 8 (2.5) | 5 (3.1) | 3 (1.9) | |
| Mitral valve insufficiency | 1 (0.3) | 1 (0.6) | 1 (0.6) | |
| Ischemia-driven revascularization | 9 (2.8) | 6 (3.7) | 6 (3.8) | |
| Cardiovascular death | 19 (5.9) | 15 (9.3) | 4 (2.5) | |
| Noncardiovascular death | 58 (18.1) | 35 (21.6) | 23 (14.6) | |
| Cardiovascular and AAA related events during total follow-up | | | | |
| All-cause death | 101 (31.6) | 64 (39.5) | 37 (23.4) | .002 |
| AAA event | 47 (14.7) | 28 (17.3) | 19 (12.0) | .168 |
| AAA reintervention | 47 (14.7) | 25 (15.4) | 22 (13.9) | .669 |
| Stroke | 21 (6.6) | 17 (10.5) | 4 (2.5) | .006 |
| Peripheral artery disease | 29 (9.1) | 15 (9.3) | 14 (8.9) | .873 |

*AAA*, Abdominal aortic aneurysm; *AF*, atrial fibrillation; *MACE*, major adverse cardiac events.

**Table III.** Overview of mean time to first event during follow-up in years followed by standard deviation

| | Total group | No cardiac history | Cardiac history | *P* value |
|---|---|---|---|---|
| Time to death | 3.7 ± 2.7 | 3.7 ± 3.0 | 3.7 ± 2.5 | .963 |
| Time to MACE | 3.2 ± 2.4 | 3.3 ± 2.7 | 3.2 ± 2.3 | .886 |
| Time to AAA event | 2.6 ± 2.3 | 2.8 ± 2.6 | 2.5 ± 2.2 | .639 |
| Time to AAA reintervention | 2.8 ± 2.3 | 2.7 ± 2.4 | 2.9 ± 2.2 | .825 |
| Time to stroke | 2.7 ± 2.5 | 3.1 ± 3.8 | 2.6 ± 2.3 | .830 |
| Time to peripheral artery disease | 3.2 ± 2.8 | 3.9 ± 2.8 | 2.4 ± 2.7 | .150 |

*AAA*, Abdominal aortic aneurysm; *MACE*, major adverse cardiac events.

excluding noncardiovascular death (Supplementary Table III, online only). Positive predictors for MACE excluding noncardiovascular death within 1 year of follow-up were the presence of typical angina pectoris and higher systolic blood pressure (in mm Hg). Positive predictors for MACE excluding noncardiovascular death within 5 years of follow-up were the presence of valvular heart disease, an ASA score of III or IV, and a higher diastolic blood pressure (in mm Hg).

Analyzing patients with and without a cardiac history separately showed nearly the same predictors as the predictors for MACE (Supplementary Tables IV and V, online only). Maximum AAA diameter was a positive predictor for MACE within 1 and 5 years of follow-up for patients without a cardiac history (Supplementary Table IV, online only). The presence of diabetes mellitus was also a positive predictor for MACE within 5 years of follow-up. A negative predictor within 1 year of follow-up for patients with cardiac history was AF, where older age was a positive predictor for MACE (Supplementary Table V, online only). A history of heart failure, older age, and a longer procedure time were positive predictors for MACE within

**Table IV.** Predictors for MACE within 1 (n[a] = 44) and 5 (n[a] = 112) years follow-up

| | Univariate regression | | | Multivariate regression: First model | | | Multivariate regression: Final model | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable, reference | β | OR [95% CI] | *P* value | β | OR [95% CI] | *P* value | β | OR [95% CI] | *P* value |
| One year | | | | | | | | | |
| ASA score of I or II | 1.039 | 2.827 [1.398-5.719] | .004 | 1.060 | 2.888 [1.371-6.085] | .005 | 1.153 | 3.168 [1.523-6.590] | .002 |
| AAA maximum diameter, mm | 0.047 | 1.048 [1.018-1.078] | .004 | 0.042 | 1.043 [1.012 -1.076] | .006 | 0.042 | 1.043 [1.012-1.075] | .006 |
| Procedure time, minutes | 0.007 | 1.007 [1.001-1.012] | .018 | 0.005 | 1.005 [0.999-1.010] | .113 | | | |
| AF, no | −1.52 | 0.219 [0.051-0.934] | .040 | −1.969 | 0.140 [0.031-0.623] | .010 | −1.998 | 0.136 [0.031-0.602] | .009 |
| Five years | | | | | | | | | |
| Heart failure, no | 1.928 | 6.8778 [2.660-17.787] | <.001 | 1.722 | 5.596 [1.716-18.250] | .004 | 1.411 | 4.099 [1.363-12.323] | .012 |
| Valvular heart disease, no | 1.237 | 3.444 [1.651-7.183] | .001 | 0.850 | 2.339 [0.955-5.728] | .063 | 0.839 | 2.314 [0.971-5.514] | .058 |
| ASA score of I or II | 0.841 | 2.319 [1.441-3.733] | .001 | 0.370 | 1.448 [0.781-2.685] | .240 | 0.507 | 1.661 [0.957-2.882] | .071 |
| SVS/AAVS score, 0 | 0.741 | 2.097 [1.167-3.769] | .013 | 0.135 | 1.144 [0.575-2.277] | .701 | | | |
| Diabetes mellitus, no | 0.739 | 2.093 [1.196-3.663] | .010 | 0.576 | 1.779 [0.805-3.496] | .095 | | | |
| Age, years | 0.064 | 1.066 [1.033-1.099] | <.001 | 0.039 | 1.040 [1.002-1.079] | .041 | 0.043 | 1.044 [1.009-1.082] | .015 |
| AAA maximum diameter, mm | 0.034 | 1.035 [1.011-1.059] | .003 | 0.022 | 1.023 [0.995-1.052] | .155 | | | |

*AAA*, Abdominal aortic aneurysm; *AF*, atrial fibrillation; *ASA*, American Society of Anesthesiologists Physical Status score; *AAA*, *CI*, confidence interval; *OR*, odds ratio.
*SVS/AAVS*, Society for Vascular Surgery/American Association for Vascular Surgery score.
[a]Number of patients with MACE at each time point.

5 years of follow-up. Additionally, the use of lipid medication was a negative predictor for MACE within 5 years of follow-up.

## DISCUSSION

The present study has shown that the freedom from MACE through 1 and 5 years of follow-up after EVAR are, respectively, 89.4% (SE, 0.018) and 59.8% (SE, 0.033), which is mostly driven by the incidence of noncardiovascular death. The freedom from MACE excluding noncardiovascular death was 94.7% (SE, 0.013) and 77.5% (SE, 0.030) and freedom from cardiac events was 96% (SE, 0.011) and 79.1% (SE, 0.030) through 1 and 5 years of follow-up, respectively, indicating that cardiac events are common and noncardiovascular death is very common after EVAR. Results from the present study emphasize the need to take the health-related characteristics, especially cardiac health, of patients into account to determine the risk for MACE and cardiac complications during follow-up after EVAR. These results help to improve the identification and medical management of these patients, where they may benefit from referral to and surveillance by cardiologists after EVAR. Patients with preexisting AF seem to be protected from developing MACE, which suggests better overall cardiovascular management compared with patients without preexisting AF. Because one-half of all MACE consisted of AF de novo, AF detection programs and better lipid management (although usual care for AAA patients) for patients without preexisting AF could help to prevent secondary damage by, for example cerebral vascular accident or heart failure, as result from AF.

In contrast with our study, previous studies have mainly focused on individual complications after EVAR, mostly myocardial injury.[5-7] To our knowledge, no other studies have investigated MACE after EVAR within the range of our definition. The observed incidence of acute coronary syndrome of 0.9% through 1 year of follow-up after EVAR is comparable with the incidence of postoperative myocardial injury, as described by Yang et al[6] and Bertges et al[7] of 1.4% and 1.0%, respectively, through 30 days of follow-up. Duceppe et al[5] found an incidence of postoperative myocardial injury of 6.7% at 30 days of follow-up, which is higher than current and other studies, despite comparable definitions for myocardial injury.

Patients with an ASA score of III or IV had an increased risk of developing MACE within both 1 and 5 years after EVAR. This risk is three-fold higher within 1 year of follow-up compared with those with a lower ASA score. Duceppe et al[5] described a lower (2.2 times higher) risk to develop myocardial injury in patients with ASA score of IV, however, in a shorter time period of 30 days. In contrast with the current study, Dijkstra et al[25] found that the Society for Vascular Surgery/American Association for Vascular Surgery medical comorbidity grading system, and not the ASA classification, is a useful tool

to predict the occurrence of major adverse events and 1-year survival in patients undergoing EVAR. Potentially, the ASA classification is more sensitive for cardiac events after EVAR compared with the Society for Vascular Surgery/American Association for Vascular Surgery medical comorbidity grading system, but this difference remains to be elucidated.

Valentine et al[26] demonstrated that the occurrence of de novo AF is not uncommon after EVAR, but that it is not associated with increased morbidity and mortality, like other studies.[5-7] The current study demonstrated that de novo AF covered one-quarter of the cardiac events after EVAR. A history of AF proved to be protective for MACE after EVAR, despite there being approximately the same number of patients with a history of AF at baseline in the group who developed MACE and those who did not. In contrast, Gonzalez-Guardiola et al[15] found an increased risk for patients with a history of AF as an independent predictor for MACE after EVAR. A possible explanation for the protective role of AF in current study could be that patients already diagnosed with AF receive more optimal medical treatment, including oral anticoagulation, whereas in the general AAA population a thrombocyte aggregation inhibitor is usually prescribed. In general, however, patient characteristics show a high use of lipid-lowering and antihypertensive medication at baseline. This finding is also consistent with current guidelines,[27] where it is recommended to prescribe all patients with AAA platelet aggregation inhibitors and statins.

Due to the strong protective role of AF for MACE, as well as the occurrence of AF within MACE, sensitivity analyses for AF were performed. Three models were created: predictors for MACE without patients with AF at baseline, and predictors for MACE without AF for the total population, and the population without patients with AF at baseline were analyzed. All three models showed approximately the same predictors (data not shown), which suggest no bias in the association found between AF and the occurrence of MACE within 1 year of EVAR. One could speculate that patients with AF at baseline may visit often for follow-up, which decreases their risk of developing MACE. However, this factor should be investigated in a prospective study.

In a review of the literature, Verhagen et al[28] found conflicting data on the impact of perioperative arrythmias on cardiac outcomes after various vascular procedures. However, Winkel et al[29] found an association between new-onset AF during vascular surgery and cardiovascular events through 1 year of follow-up. This finding suggests that vascular surgery, including EVAR, could be a trigger to develop arrhythmias and thereby impose a higher risk to develop MACE. Whether there is a difference between open surgery and the minimally invasive endovascular techniques remains to be studied. Also, regardless of the fact that most studies were published in the last decade, an improved cardiovascular risk management may change the described data.

AAA diameter was also a predictor of short-term MACE. A plausible explanation could be that a larger AAA diameter is a reflection of a more advanced stage of cardiovascular disease and that, consequently, the risk of MACE increases. In addition, cardiovascular risk is influenced by increased left ventricular load, resulting from a disturbed flow pattern, or increased inflammatory markers,[30,31] which are both related to AAA diameter.

A history of heart failure was another predictor of long-term MACE, possibly relating to alterations in vascular resistance and subsequent impact on cardiac loading conditions. This finding complements previous data from Bertges et al[7] showing that preexistent heart failure is a predictor for myocardial injury during hospitalization after EVAR. Heart failure is also a strong predictor for MACE in the general population.[32] This study demonstrated that patients with AAA with heart failure undergoing EVAR should be monitored carefully for developing MACE. Subsequently, the present study showed that a more advanced age was a positive predictor for only MACE through 5 years of follow-up, where other studies[5-7] found more advanced age to be a predictive factor for short-term myocardial injury. However, the mean age between studies was comparable with this study. Furthermore, presence of valvular heart disease had a strong positive predictive value for MACE during 5 years of follow-up. In general, valvular heart disease leads to abnormal cardiac loading conditions, which leads to other cardiac events (such as AF and heart failure).

Noncardiovascular death accounted for approximately one-half of the MACE in this study. Although it is common to include noncardiovascular death in the definition of MACE, this practice could affect the analysis to determine predictors for major cardiac events. Therefore, another multivariate analysis was also performed for MACE excluding noncardiovascular death, which revealed slightly different predictors. An ASA score of III or IV remained a predictor for MACE, excluding noncardiovascular death within 5 years of follow-up. However, systolic and diastolic blood pressures were predictors for MACE, excluding noncardiovascular death within 1 and 5 years of follow-up. Although this is measured at one time point, these results are in line with other studies showing a higher risk for cardiovascular events in patients with higher or uncontrolled blood pressure,[33-35] which is associated with diastolic dysfunction and long-term heart failure,[36] as well as with the development of AF.[37] One could imagine that when blood pressure control in patients after EVAR is suboptimal, their risk of MACE after EVAR is increased. Because high blood pressure does not necessarily result in noncardiovascular death, it seems logical that blood pressure is not a resulting predictor in the initial analysis for MACE. In the end,

valvular heart disease was also a predictor for MACE excluding noncardiovascular death within 5 years of follow-up, which is similar to the initial analysis for MACE. This finding implicates that cardiac health remains a good predictor of long-term MACE, whether noncardiovascular death is included or not, implying that the basic causes of cardiovascular disease should be well-monitored after EVAR.

This study demonstrated that the presence of a cardiac history increases the risk of developing MACE during follow-up. Although this may seem obvious, there is a paucity of data on this topic. A study by Gonzalez-Guardiola et al[15] did not find an association between a history of myocardial infarction, prior PCI, CABG, or stroke and the incidence of MACE. In contrast, a study by Bakker et al[38] found a positive association between a history of congestive heart failure with cardiovascular complications after vascular surgery. Onohara et al[39] found only a univariate correlation between a history of coronary artery disease, cardiovascular disease, and coronary revascularization with the incidence of MACE after EVAR, but no significant prognostic factors were present in the multivariate analysis.

The most novel finding of this study is the broad definition of MACE and the split analysis for patients with and without a cardiac history. Because there are multiple definitions of MACE used in the literature, these results could be difficult to compare with other studies.[40,41] A limitation of this study could be the focus on predictors for MACE at a certain time point by excluding the continual time aspect. As an extra check, a Cox regression analysis was performed, which resulted in the same predictors for MACE during 1 year of follow-up in combination with the glomerular filtration rate at baseline. Predictors for MACE during 5 years of follow-up were then limited to age and an ASA score of III or IV. Another limitation is the missing data on the presence of peripheral artery disease at baseline, which is also a well-known predictor of mortality. Unfortunately, this factor could not be extracted reliably from the database because imaging of the peripheral arteries is not part of the standard workup for patients undergoing EVAR in this institution. The retrospective nature is the main limitation of this study, making it susceptible to incomplete and missing data, which could have influenced the analysis. In particular, because the cause of death was not always known and verified by post mortem investigation, the incidence of cardiac-related death may well be underestimated. To minimize the impact of bias caused by the retrospective design we have used predefined definitions of cardiac events, which were evaluated by cardiologists.

## CONCLUSIONS

MACE are common complications during the first 5 years after elective EVAR for infrarenal AAA, with higher ASA scores being predictors of both short- and long-term MACE. The presence of cardiac disease at baseline, including heart failure and valvular heart disease, are strong predictors for long-term MACE. These predictors are potentially helpful in optimizing future postoperative long-term follow-up to determine which patients would benefit from surveillance after EVAR and thereby better treatment of their risk factors. However, more research is needed to conform these results in other prospective cohorts.

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## AUTHOR CONTRIBUTIONS

Conception and design: JV, MR, SH
Analysis and interpretation: ED, JV, RP, PS, MR, SH
Data collection: ED, JV
Writing the article: ED, JV, SH
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Final approval of the article: ED, JV, RP, PS, MR, SH
Statistical analysis: ED, JV, RP, SH
Obtained funding: MR, SH
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**Supplementary Table I (online only).** Major adverse cardiac events (*MACE*), cardiovascular and abdominal aortic aneurysm (*AAA*)-related events during 30 days of follow-up

| | | Cardiac history | | |
|---|---|---|---|---|
| | Events (n = 320) | Yes (n = 162) | No (n = 158) | *P* value |
| First MACE | 8 (2.5) | 5 (3.1) | 3 (12.0) | .285 |
| Acute coronary syndrome | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| AF de novo | 2 (0.6) | 1 (0.6) | 1 (0.6) | |
| Heart failure hospitalization | 2 (0.6) | 1 (0.6) | 1 (0.6) | |
| Mitral valve insufficiency | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Ischemia driven revascularization | 1 (0.3) | 0 (0.0) | 1 (0.6) | |
| Cardiovascular death | 2 (0.6) | 2 (1.2) | 0 (0.0) | |
| Noncardiovascular death | 1 (0.3) | 1 (0.6) | 0 (0.0) | |
| Cardiovascular and AAA-related events | | | | |
| All-cause death | 3 (0.9) | 3 (1.8) | 0 (0.0) | .025 |
| AAA event | 5 (1.5) | 4 (2.4) | 1 (0.6) | .371 |
| AAA reintervention | 3 (0.9) | 2 (1.2) | 1 (0.6) | 1.000 |

*AF*, Atrial fibrillation.
Values are number (%).

**Supplementary Table II (online only).** Model performances of the multivariate analysis final models for major adverse cardiac events (*MACE*) at 1 and 5 years of follow-up, with respectively 288 and 224 patients at risk

| | MACE during 1 year of follow-up | MACE during 5 years of follow-up |
|---|---|---|
| $\chi^2$ | 28.028 ($P < .001$) | 35.856 ($P < .001$) |
| −2 Log likelihood | 224.604 | 322.028 |
| Nagelkerke $R^2$ | 15.5% | 16.7% |
| Hosmer and Lemeshow test | 5.562 ($P = .696$) | 4.104 ($P = .848$) |
| Correctly classified MACE of the total population | 86.4% | 69.9% |
| Receiver operating characteristic area under the curve | 0.726 ($P < .001$) | 0.677 ($P < .001$) |

**Supplementary Table III (online only).** Predictive factors for major adverse cardiac events (*MACE*) excluding non-cardiovascular death within 1 (n[a] = 22) and 5 (n[a] = 54) years of follow-up

| Variable, reference | Univariate regression | | | Multivariate regression: First model | | | Multivariate regression: Final model | | |
|---|---|---|---|---|---|---|---|---|---|
| | β | OR [95% CI] | *P* value | β | OR [95% CI] | *P* value | β | OR [95% CI] | *P* value |
| One Year | | | | | | | | | |
| Typical angina pectoris, no | 1.621 | 5.059 [1.887-13.563] | .001 | 1.541 | 4.671 [1.675-13.026] | .003 | 1.541 | 4.671 [1.675-13.026] | .003 |
| Systolic blood pressure, mm Hg | 0.033 | 1.034 [1.013-1.055] | .001 | 0.032 | 1.032 [1.011-1.054] | 003 | 0.032 | 1.032 [1.011-1.054] | .003 |
| Five years | | | | | | | | | |
| Valvular heart disease, no | 1.304 | 3.684 [1.711-7.931] | .001 | 1.218 | 3.381 [1.513-7.559] | .003 | 1.187 | 3.276 [1.467-7.319] | .004 |
| ASA score of I or II | 0.641 | 1.899 [1.033-3.489] | .039 | 0.653 | 1.922 [0.989-3.736] | .054 | 0.737 | 2.090 [1.087-4.017] | .027 |
| Diastolic blood pressure, mm Hg | 0.030 | 1.031 [1.002-1.061] | .037 | 0.040 | 1.041 [1.010-1.072] | .009 | 0.041 | 1.042 [1.012-1.074] | .006 |
| Total procedure time, minutes | 0.005 | 1.005 [1.000-1.011] | .041 | 0.004 | 1.004 [0.999-1.010] | .124 | | | |

*ASA*, American Society of Anesthesiologists Physical Status score; *CI*, confidence interval; *OR*, odds ratio.
[a]Number of patients with MACE excluding noncardiovascular death at each time point.

**Supplementary Table IV (online only).** Predictive factors for major adverse cardiac events (*MACE*) within 1 (n[a] = 44) and 5 (n[a] = 112) years of follow-up for patients without cardiac history

| Variable, reference | Univariate regression | | | Multivariate regression: First model | | | Multivariate regression: Final model | | |
|---|---|---|---|---|---|---|---|---|---|
| | β | OR [95% CI] | *P* value | β | OR [95% CI] | *P* value | β | OR [95% CI] | *P* value |
| One year | | | | | | | | | |
| AAA maximum diameter, mm | 0.051 | 1.053 [1.004-1.104] | .032 | 0.051 | 1.053 [1.002-1.106] | .042 | 0.051 | 1.053 [1.004-1.103] | .033 |
| Total procedure time, minutes | 0.003 | 1.003 [0.994-1.012] | .534 | 0.002 | 1.002 [0.993-1.012] | .629 | | | |
| Age, years | 0.013 | 1.013 [0.954-1.075] | .680 | -0.002 | 0.998 [0.938-1.061] | .939 | | | |
| Five years | | | | | | | | | |
| Diabetes, no | 1.062 | 2.893 [1.165-7.185] | .022 | 1.534 | 4.636 [1.677-12.818] | .003 | 1.464 | 4.322 [1.615-11.566] | .004 |
| Lipid medication, no | −1.109 | 0.330 [0.040-2.708] | .302 | 0.819 | 2.269 [0.257-20.049] | .461 | | | |
| AAA maximum diameter, mm | 0.030 | 1.031 [0.994-1.070] | .106 | 0.037 | 1.038 [0.989-1.088] | .130 | 0.041 | 1.042 [0.995-1.090] | .080 |
| Age, years | 0.033 | 1.034 [0.990-1.080] | .137 | 0.026 | 1.027 [0.970-1.086] | .362 | | | |
| Total procedure time, minutes | 0.000 | 1.000 [0.992-1.008] | .958 | −0.001 | 0.999 [0.984-1.014] | .884 | | | |

*AAA*, Abdominal aortic aneurysm; *CI*, confidence interval; *OR*, odds ratio.
[a]Number of patients with MACE at each time point.

**Supplementary Table V (online only).** Predictive factors for major adverse cardiac events (*MACE*) within 1 (n[a] = 44) and 5 (n[a] = 112) years follow-up for patients with cardiac history

| | Univariate regression | | | Multivariate regression: First model | | | Multivariate regression: Final model | | |
|---|---|---|---|---|---|---|---|---|---|
| **Variable, reference** | **β** | **OR [95% CI]** | ***P* value** | **β** | **OR [95% CI]** | ***P* value** | **β** | **OR [95% CI]** | ***P* value** |
| One year | | | | | | | | | |
| Age, years | 0.096 | 1.101 [1.035-1.170] | .002 | 0.079 | 1.082 [1.006-1.164] | .033 | 0.106 | 1.112 [1.038-1.191] | .002 |
| AAA maximum diameter, mm | 0.042 | 1.043 [1.006-1.082] | .023 | 0.033 | 1.033 [0.986-1.083] | .174 | | | |
| Total procedure time, minutes | 0.009 | 1.009 [1.001-1.016] | .018 | 0.007 | 1.007 [0.999-1.014] | .091 | | | |
| AF, no | −2.656 | 0.009 [0.033-0.534] | .010 | −2.880 | 0.127 [0.007-0.469] | .008 | −2.833 | 0.059 [0.007-0.465] | .007 |
| Five years | | | | | | | | | |
| Heart failure, no | 1.718 | 5.573 [2.089-14.869] | .001 | 1.453 | 4.278 [1.314-13.925] | .016 | 1.450 | 4.263 [1.404-12.939] | .010 |
| Diabetes, no | 0.412 | 1.510 [0.737-3.094] | .260 | 0.573 | 1.773 [0.728-4.319] | .208 | | | |
| Valvular heart disease, no | 0.990 | 2.692 [1.236-5.866] | .013 | 0.052 | 1.053 [0.363-3.053] | .924 | | | |
| Age, years | 0.084 | 1.088 [1.039-1.139] | <.001 | 0.049 | 1.050 [0.987-1.117] | .124 | 0.066 | 1.068 [1.009-1.131] | .022 |
| AAA maximum diameter, mm | 0.035 | 1.035 [1.005-1.067] | .023 | 0.026 | 1.026 [0.985-1.070] | .216 | | | |
| Total procedure time, minutes | 0.010 | 1.010 [1.002-1.017] | .016 | 0.009 | 1.009 [1.001-1.016] | .025 | 0.008 | 1.009 [1.001-1.016] | .032 |
| Lipid medication, no | 1.997 | 7.364 [1.498-36.195] | .014 | −1.664 | 0.189 [0.034-1.055] | .058 | −1.586 | 0.205 [0.037-1.144] | .071 |

*AAA*, Abdominal aortic aneurysm; *AF*, atrial fibrillation; *CI*, confidence interval; *OR*, odds ratio.
[a]Number of patients with MACE at each time point.