

Five-Year Outcome after Off-Pump or On-Pump Coronary Artery Bypass Grafting in Elderly Patients

Running Title: *Diegeler et al.; GOPCABE Five Year Outcome*

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Abstract

Background: The 30 days and one-year follow-up analysis of the German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients (GOPCABE) trial revealed no significant difference in the composite endpoint consisting of death, stroke, myocardial infarction, new renal replacement therapy or repeat revascularization. The five-year follow-up data of this trial are reported here.

Methods: From June 2008 to September 2011 a total of 2539 patients aged 75 years or older were randomly assigned to undergo off-pump or on-pump coronary artery bypass grafting (CABG) at 12 centers in Germany. The primary outcome was all-cause mortality at 5 years. The secondary five-year outcomes were a composite of death, myocardial infarction and repeat revascularization. Furthermore the impact of complete versus incomplete revascularization was assessed.

Results: After a median follow-up of five years 361 patients (31%) assigned to off-pump CABG and 352 patients (30%) assigned to on-pump CABG had died (hazard ratio off-pump/on-pump CABG, 1.03; 95% confidence interval [CI], 0.89 to 1.19; $P=0.71$). The composite outcome of death, myocardial infarction and repeat revascularization occurred in 397 (34%) after off-pump and in 389 (33%) after on-pump CABG (hazard ratio 1.03; 95% CI, 0.89 to 1.18; $P=0.704$). Incomplete revascularization occurred in 403 (34%) patients randomized to off-pump and 354 (29%) patients randomized to on-pump CABG ($p < 0.001$). Five-year survival rates were 72% [95% CI; 67 to 76] with incomplete versus 76% [95% CI, 74 to 80] with complete revascularization (log-rank test: $P=0.02$) after off-pump CABG and 72% [95% CI; 67 to 76] vs. 77% [95% CI, 74 to 80] after on-pump CABG (log-rank test: $P=0.03$), respectively. Cox regression analysis revealed a hazard ratio incomplete/complete revascularization of 1.19 [95% CI, 1.01 to 1.39; $P=0.04$].

Conclusions: In elderly patients ≥ 75 years, the five-year survival rates as well as the combined outcome of death, myocardial infarction and repeat revascularization were similar after on-pump and off-pump CABG. Incomplete revascularization was associated with a lower five-year survival rate, irrespective of the type of surgery.

Clinical Trial Registration: URL: <https://www.clinicaltrials.gov> Unique identifier: NCT00719667

Key Words: off-pump surgery; coronary artery bypass graft surgery; long-term outcome

Clinical Perspective

What is new?

- Off-pump and on-pump CABG provide similar long-term outcomes in elderly patients.
- Incomplete revascularization was associated with a lower five-year survival rate, irrespective of the type of surgery.

What are the clinical implications?

- In elderly patients with coronary heart disease undergoing CABG, the operative technique is not decisive, either for short-term or for long-term outcomes.
- Incomplete revascularization, however, may be associated with reduced late survival.



Circulation

Introduction

Numerous studies have compared on-pump and off-pump coronary artery bypass grafting (CABG). These efforts eventually culminated in three large-scale trials [1 - 3], totaling nearly 10,000 randomized patients. All three trials found no difference in outcomes after off-pump compared to on-pump CABG, with similar rates of death, myocardial infarction, stroke, new dialysis or repeat revascularization within 30 days and one year after surgery, respectively. After five years, two trials reported conflicting results with respect to survival and major adverse events [4, 5]. A consistent feature of all three trials was that patients who were operated off-pump received fewer grafts than the respective on-pump cohort. In the German off-pump Coronary Artery Bypass Grafting in Elderly Patients (GOPCABE) trial a higher number of patients in the off-pump group received fewer coronary grafts than initially planned [3]. This raises questions about the clinical long-term efficacy and durability of off-pump CABG. Extended follow-up of the GOPCABE study population should clarify the long-term impact of the operative technique and the completeness of revascularization.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Oversight

The GOPCABE trial has been described in detail previously [3]. In brief: The GOPCABE trial was a prospective, randomized multicenter trial conducted at 12 German institutions. These study centers were all proponents of off-pump CABG and nominated surgeons experienced with both surgical techniques in order to ensure the best medical outcome. For the enrollment of

patients planned for surgical revascularization, the qualifying criterion was age of at least 75 years. A unique feature of the trial was that neither morphologic characteristics like small, diffusely diseased vessels nor impaired left ventricular function were exclusion criteria. During the study period all potentially eligible patients were registered in a study log, resulting in an "all-comers" study design with a well-defined, representative patient sample. A certified ethics committee and the local institutional review board of each participating center approved the study protocol. All patients gave written, informed consent, which included the collection of prolonged follow-up information.

Follow-up Outcome

Follow-up information was obtained by telephone call from patients, their next of kin or their primary care physicians. Study sites were encouraged to acquire follow-up information on a yearly basis but at least once at five years after surgery. Data collection and data clearing were performed at the Herz- und Gefäß-Klinik GmbH, Bad Neustadt Germany.

For the five year follow-up study, the primary endpoint was all-cause mortality. Additional outcome events were the rate of myocardial infarction and repeated coronary revascularization.

There was no external funding to support the follow-up but the corresponding author received an internal institutional grant for data management and trial organization.

Completeness of Revascularization

Prior to randomization, the anticipated number of grafts and information about the corresponding target vessels were required to be entered into the data template. Revascularization was defined as complete when the number of performed coronary anastomoses was equal or higher than the number of anticipated anastomoses. Vice versa, when the performed number of coronary anastomoses was lower than expected, myocardial revascularization was recorded as incomplete.

Statistical Analysis

The initial study population consisted of 2403 randomized patients. The study population for this analysis included all randomized patients with available data one year after randomization (2370 patients; 98.6% of the initial study population). Analysis was performed according to the intention to treat.

Overall survival rates were analyzed using Kaplan-Meier plots and a comparison between on-pump and off-pump CABG was performed with the log-rank test. Long-term outcomes for complete versus incomplete revascularization are reported as time-to-event analysis using Cox regression, after testing the assumption of proportional hazards. The treatment effect is expressed as the hazard ratio with 95% confidence intervals, derived from the Cox proportional hazard model.

Results

Enrollment, Randomization and Follow-Up

Enrollment, randomization and follow-up of the GOPCABE study population has been described previously [3] and is shown in supplemental figure 1 (supplementary appendix). From June 2008 to September 2011, 2539 patients were randomly assigned to on-pump or off-pump CABG. Between randomization and surgery 136 patients were excluded because of the unavailability of the designated study surgeon for an urgent operation, a necessary additional cardiovascular procedure or withdrawn patient consent. Allocated surgery by a designated study surgeon was performed in 2403 patients. For 2394 patients the primary endpoint, a combination of death, myocardial infarction, stroke, new renal replacement therapy or repeat revascularization within 30 days after surgery could be evaluated. One year after surgery, the data of 2370 patients were

available for analysis of the primary endpoint. Baseline characteristics of these patients are shown in supplemental table 1 (supplementary appendix). Follow-up information after five years or longer regarding the vital status and eventually the date of death could be obtained in 2206 patients, representing 92% of the entire study population. The trial observed 11 260 patient-years with an average mortality rate of 6.3% per year (95% CI, 5.9 to 6.8). The deceased 713 patients had a median survival period of 3.3 years, the remaining surviving patients a median follow-up time of 5.3 years.

Survival

During follow-up, 361 patients assigned to off-pump and 352 patients assigned to on-pump died. Five-year survival of the entire cohort was 75.4% (95% CI, 74 to 77), 75.4% (95% CI, 73 to 78) for the off-pump group and 75.5% (95% CI, 73 to 78) for the on-pump group, respectively. The hazard ratio for off-pump versus on-pump CABG was 1.03 (95% CI, 0.89 to 1.19; $P=0.71$) (Table 1, Fig. 1).

Myocardial Infarction and Repeat Revascularisation

During follow-up, 36 myocardial infarctions and 77 repeat revascularizations were recorded, with no significant differences between the groups (table 1).

Completeness of Revascularization

Incomplete revascularization with fewer anastomoses than anticipated occurred more often in patients assigned to off-pump CABG (34% vs. 29%; $p<0.001$). In 403 of the 1187 patients (34%) assigned to off-pump CABG, fewer coronary anastomoses were performed than anticipated. The survival rate of this subgroup was 72% (95% CI, 67 to 76) versus 76% (95% CI, 74 to 80) of the group with complete revascularization (log-rank test $P=0.02$) (Fig. 2).

In the on-pump group, 354 of the 1207 patients (29%) were revascularized with fewer grafts than anticipated. Their survival was 72% (95% CI, 67 to 76) vs. 77% (95% CI, 74 to 80) for the group of patients with a complete revascularization (log-rank test: $P=0.03$) (Fig. 2).

In both groups, patients with complete and incomplete revascularization were structurally different with unevenly distributed baseline characteristics. In the off-pump group (supplemental Table 2, see supplementary appendix), the incompletely revascularized patients were more often male, older, had a higher logistic EuroSCORE [6], a higher percentage of an impaired left ventricular function and pulmonary hypertension. In the on-pump cohort (supplemental Table 3, see supplementary appendix), patients with incomplete revascularization had a higher logistic EuroSCORE, a higher proportion of peripheral arterial disease, insulin-dependent diabetes and a recent myocardial infarction.

Incomplete revascularization was associated with decreased long-term survival with similar survival curves for both operative techniques (Fig. 2). For the entire patient cohort, Cox regression analysis for all-cause mortality revealed a hazard ratio regarding incomplete/complete revascularization of 1.19 (95% CI, 1.01 to 1.39; $P=0.04$).

Discussion

The GOPCABE trial compared off-pump CABG with on-pump CABG in 2394 elderly patients who were at least 75 years old. Five years after surgery there was no significant difference between the groups regarding death, myocardial infarction and repeat revascularization. It seems intuitive that avoidance of the extracorporeal circulation may offer a benefit early after the CABG procedure with less inflammation and embolization. On the other hand, the technique of an arrested heart may result in a better quality of each single anastomosis and more complete

revascularization, which may lead to a better short- and long-term outcome. None of these possible consequences were apparent in the GOPCABE trial.

The currently published evidence on long-term outcome following off-pump versus on-pump CABG is inconclusive. A propensity-matched study using data of the New York State's Cardiac Surgery reporting system found a lower risk of death within 30 days for off-pump CABG but no significant difference between on-pump and off-pump CABG after seven years [7]. A comparable analysis using data from a Korean registry revealed similar 30 day and one year survival rates for on-pump and off-pump CABG, but a survival disadvantage for off-pump CABG after a median follow-up of 6.4 years [8]. One meta-analysis of 11 randomized controlled trials with follow-up time ranging from 1 to 6 years found a survival disadvantage for off-pump CABG [9].

Comparing our results with the recent large-scale multicenter studies of off-pump CABG versus on-pump CABG, [4,5], equivalent five-year survival is in line with the CORONARY trial [4]. However, it is contrary to the findings of the ROOBY trial, in which an increased mortality and higher rate of graft failure were observed in patients undergoing off-pump CABG [5]. The most cited limitation of the ROOBY trial addressed the level of experience of the participating surgeons [10]. The median pre-study off-pump CABG experience of the surgeons who had participated in the GOPCABE trial was 322 procedures, compared to more than 100 procedures in the CORONARY and a median of only 50 off-pump procedures in the ROOBY trial.

At five years, the mortality rate in the GOPCABE study population was higher than the respective rates of death in the CORONARY [4] and ROOBY [5] trial (25.4% versus 14.1% and 13.6%, respectively). GOPCABE exclusively enrolled elderly patients with a mean age of 78

years versus 68 years in the CORONARY trial and 63 years in the ROOBY trial, respectively. Thus, a higher all-cause mortality rate was expected. Comparison of the survival curves of the GOPCABE population with an age and sex-matched population (Fig. 3) demonstrates an increased risk of death shortly after surgery. Thereafter, the GOPCABE survival curve followed a flattened course, crossing the survival curve of the general population at 1.5 years and showing a higher survival rate within the next five to six years. This is consistent with a recent publication from a Swedish registry showing superior life expectancy in CABG patients above 55 years compared to the general population [12]. This survival benefit for patients undergoing CABG is remarkable, considering that patients with coronary heart disease treated medically or with percutaneous coronary intervention (PCI) had a similar mid-term survival as the general population [13].

The second important finding in the GOPCABE trial is that patients who received fewer revascularized coronary vessels than initially planned showed an inferior survival during the 5-year follow-up. Interestingly, this was irrespective of the operative technique. There are many definitions characterizing complete or incomplete revascularization [14]. The absence of a universal definition makes comparisons among studies examining completeness of revascularization challenging. However, a similar definition for the completeness of revascularization was used in one study investigating the SYNTAX trial population [15]. In this analysis, patients were categorized as incompletely revascularized if the number of treated coronary segments was lower than anticipated. Incomplete revascularization was more common in patients treated by PCI (PCI 43%; CABG 37%). Incompletely revascularized patients had a lower, albeit not significantly different three year survival rate and a higher rate of major adverse cardiovascular events in the PCI arm.

Incomplete revascularization according to our applied definition occurred in 29% of all patients assigned to on-pump and in 34% of those assigned to off-pump CAGB. This absolute 5% difference is likely to be the result of the more challenging off-pump technique. However, incomplete revascularization was a rather common event in both groups and occurred in one third of all patients, irrespective of the operative technique. Various reasons may be responsible for an incomplete revascularization: 1. preoperative misjudgment of the number of necessary and graftable vessels; 2. calcified target vessels; 3. target vessels that cannot be identified (e.g. because of an intramuscular course); 4. difficult exposure (e.g. because of hemodynamic instability) and 5. target vessel corresponding to an infarcted scar area without reasonable viable myocardium. Only two reasons (3 and 4) can be related to the applied surgical method, namely off-pump. In contrast all reasons from 2 to 5 are related to the pre operative morbidity of the patient. To which extent, pre-existing factors or the incomplete revascularization itself leads to the final result of reduced survival cannot be determined. It is, however, reasonable to assume that incomplete revascularization reflects to some degree, the severity of coronary heart disease and hence it may be a surrogate marker for a worse prognosis. Both subgroups of patients with incomplete revascularization showed significant differences in baseline characteristics. Taken together, incomplete revascularization characterized a structurally different patient group, with incomplete revascularization occurring in sicker patients. The difference in baseline characteristics and the bias in favor of complete revascularization is well known from analysis of multiple trials and registries [14]. All efforts to adjust for these differences with multivariate regression are limited and no propensity matching would be able to eliminate the bias of additional confounders when one patient group is obviously sicker than the other. Accordingly the inability to achieve a complete revascularization may be considered as the manifestation

rather than the cause of a worse patient prognosis. However, given the worse prognosis that was observed, every effort should be undertaken to achieve a complete revascularization whenever possible.

Limitations

The study results were based on information provided by the telephonically performed follow-up five years after surgery. Practical problems in communicating with the large number of elderly, chronically ill patients as well as financial restrictions rendered a more frequent follow-up or an actual follow-up patient visit not feasible. No attempt was made to differentiate between cardiac and non-cardiac causes of death because of the inherent difficulties to determine the cause of death in an elderly patient population. Although a recall bias for events like myocardial infarction and repeat revascularization is possible, it would have similarly affected both groups. Furthermore such a bias is unlikely for all-cause mortality. Finally, the present analysis does not allow a causal conclusion, whether incomplete revascularization per se or preexisting morbidity precluding complete revascularization is responsible for the reduced survival.

In summary, the five-year GOPCABE follow-up found a similar outcome in elderly patients with coronary heart disease randomly assigned to on-pump or off-pump CABG. Neither an adverse effect nor an advantage of the respective operative technique was detected. Incomplete revascularization, though more frequent with off-pump CABG, was a common event in both groups and was associated with an inferior survival. CABG in general appeared to confer a mid-term survival benefit as compared to an age and sex-matched general population.

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Disclosures

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Circulation

Table 1. Five year outcome events

Outcome	off-pump CABG	on-pump CABG	hazard ratio (95% CI)	p-value
Death	361/1179 (31%)	352/1191 (30%)	1.03 (0.89 - 1.19)	0.71
Myocardial infarction	21/993 (2.1%)	15/991 (1.5%)	1.69 (0.78 - 3.7)	0.181
Repeat revascularization	43/1025 (4.1%)	34/1023 (3.2%)	1.34 (0.83 - 2.15)	0.228
Composite*	397/1179 (34%)	389/1191 (33%)	1.03 (0.89 - 1.18)	0.704

Data are shown as number/total number (%);

*: composite outcome consisting of death, myocardial infarction and repeat revascularization within 5 years after surgery



Circulation

Figure Legends

Figure 1. Long-term survival after on-pump or off-pump CABG

Kaplan-Meier survival curves of patients scheduled to off-pump (red line) or on-pump (blue line) CABG.

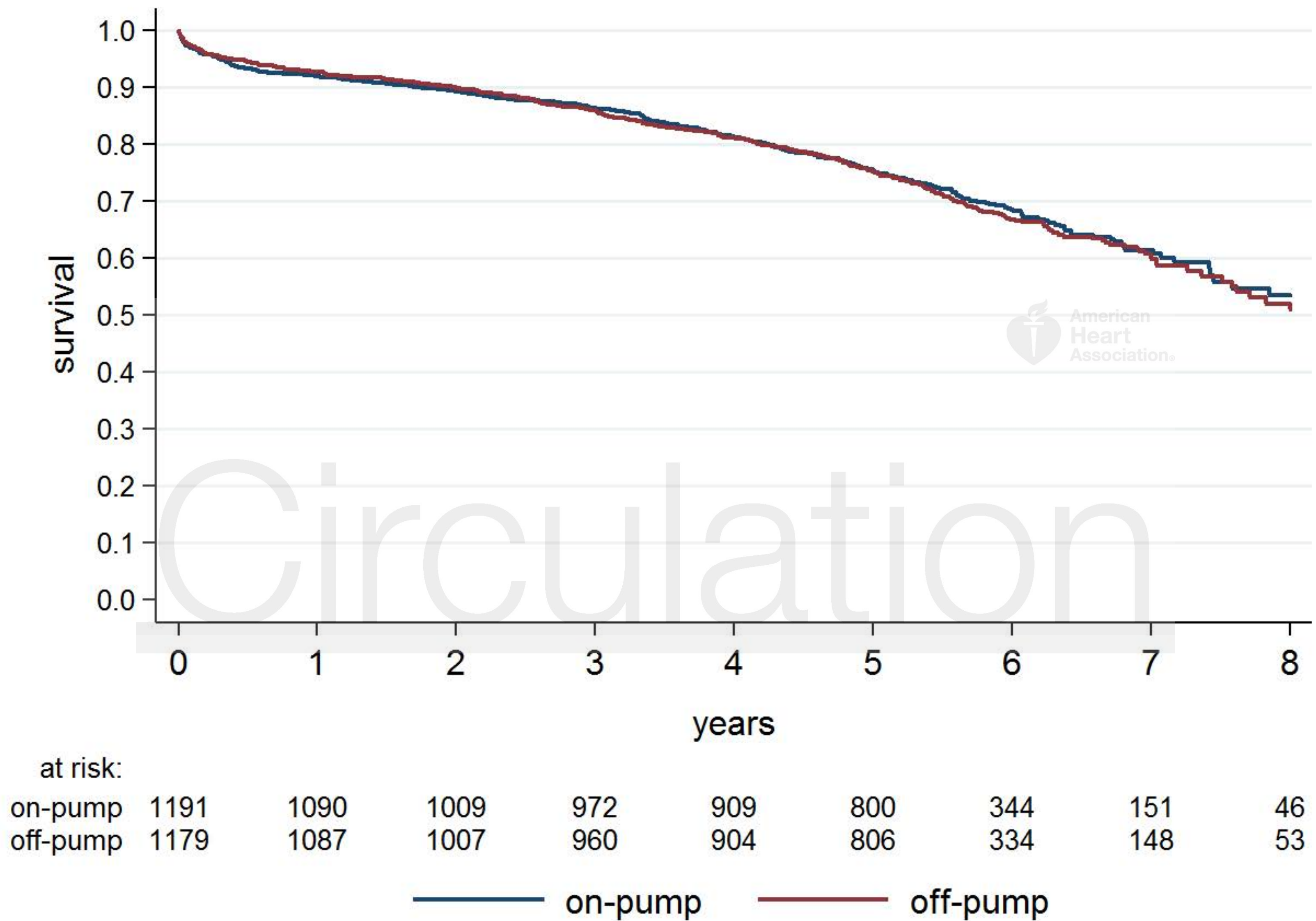
Figure 2. Survival after complete and incomplete revascularization

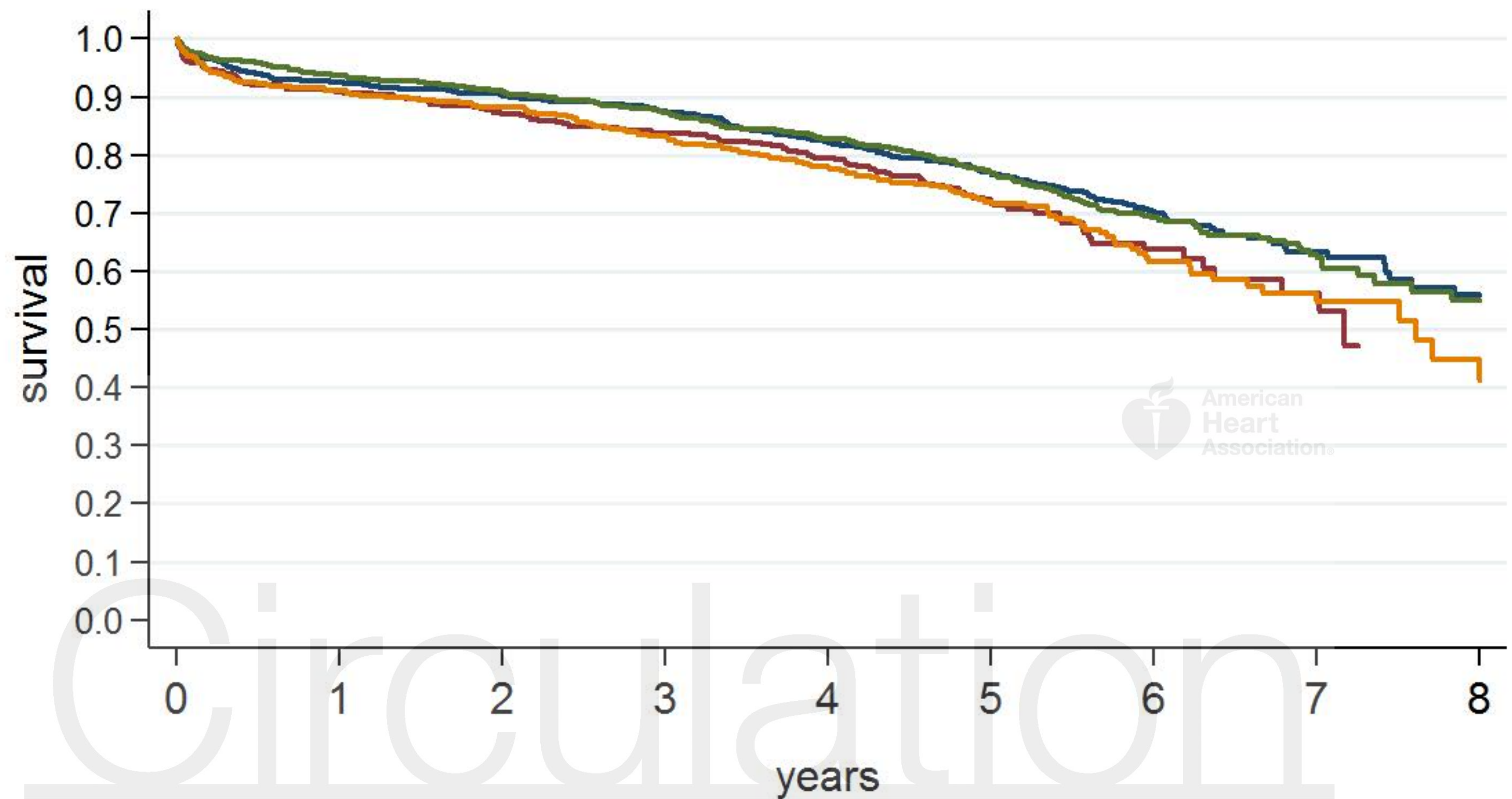
Kaplan-Meier survival curves of patients scheduled to off-pump or on-pump CABG with either complete or incomplete revascularization.



Figure 3. Survival of the GOPCABE patient population in comparison to the general population.

Kaplan-Meier survival curve of the whole GOPCABE study cohort with 95% confidence intervals (blue line) and the expected survival rate of an age and sex-matched German population (orange line), calculated according to the mortality table derived from the Bundesamt für Statistik [11].



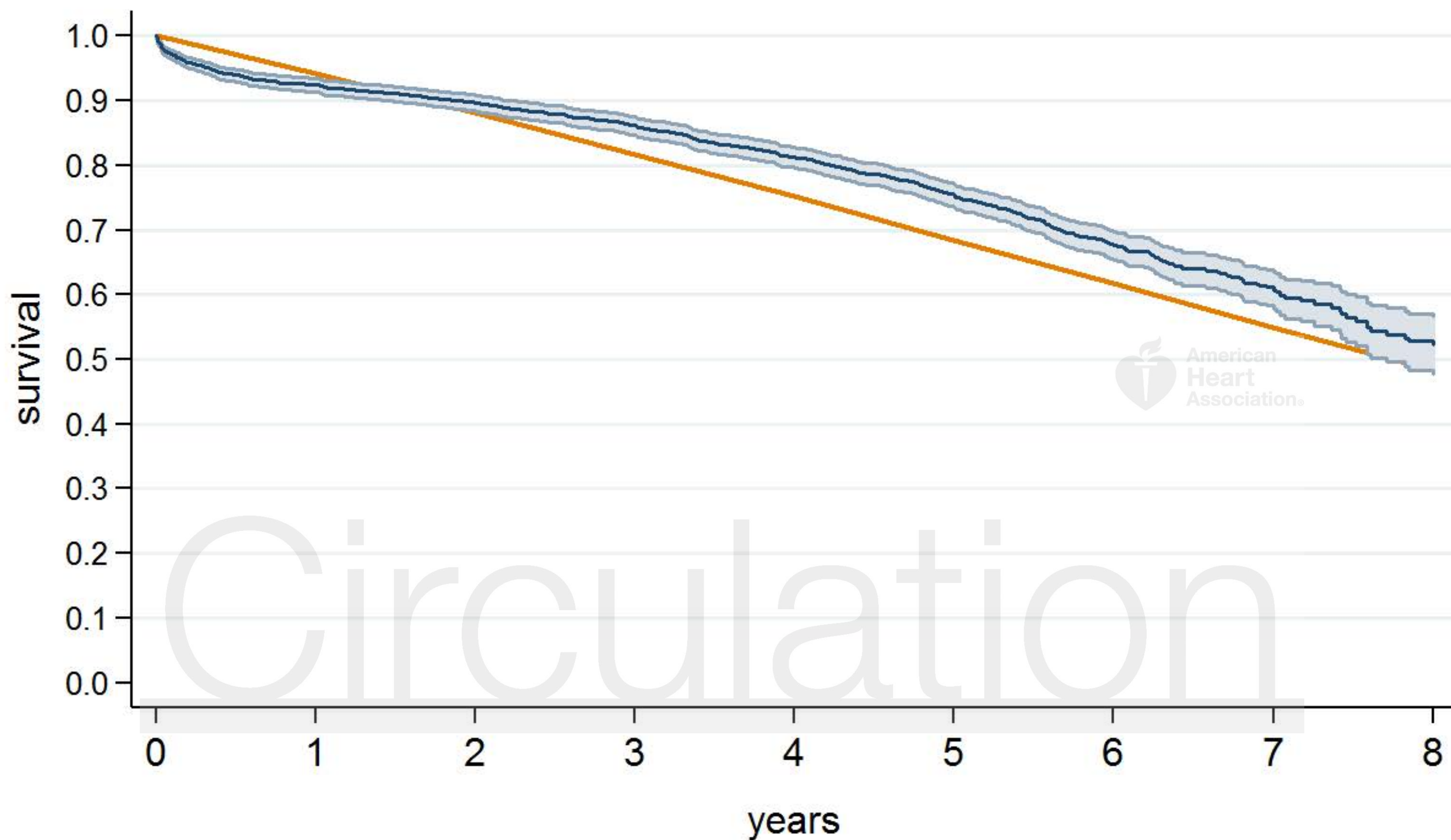


at risk:

on (complete)	841	774	712	686	639	567	279	128	42
on (incomplete)	350	316	297	286	270	233	65	23	4
off (complete)	781	726	671	643	608	538	246	105	40
off (incomplete)	398	361	336	317	296	268	88	43	13

— on-pump (complete)
— off-pump (complete)

— on-pump (incomplete)
— off-pump (incomplete)



at risk:

2370

2177

2016

1932

1813

1606

678

299

99

— GOPCABE

— matched German population