Comparison in Patients < 75 Years of Age - Versus − Those > 75 Years on One-year-Events With Atrial Fibrillation and Left Atrial Appendage Occluder (From the Prospective Multicenter German LAARGE Registry)

Aref El Nasasra, MD[a], Johannes Brachmann, MD[b], Thorsten Lewalter, MD[c,d], Ibrahim Akin, MD[d], Horst Sievert, MD[e], Christoph A. Nienaber, MD[f], Christian Wei, MD[g], Sven T. Pleger, MD[h], Hüseyin Ince, MD[i], Jens Maier, MD[j], Stephan Achenbach, MD[k], Holger H. Sigusch, MD[l], Matthias Hochadel, PhD[m], Steffen Schneider, PhD[m], Jochen Senges, MD[m], and Uwe Zeymer, MD[a,m,*]

Left atrial appendage closure (LAAC) is an alternative to oral anticoagulation therapy in patients with non-valvular atrial fibrillation for the prevention of embolic stroke and systemic embolism. Although elderly patients (>75 years) have both higher ischemic and bleeding risk as compared with younger patients, they benefit from optimal anticoagulation. The subanalysis aimed to assess the indications, the safety, efficacy, and 1-year outcomes of interventional LAAC in elderly patients (≥ 75 years) compared with younger (< 75 years) patients in clinical practice. We analyzed data from the prospective Left-Atrium-Appendage Occluder Registry Germany. A total of 638 patients were included in the registry, 402 (63%) were aged ≥ 75 years. Compared with younger subjects, patients aged ≥75 were more likely to have higher CHA2DS2-VASC and HAS-BLED scores. Procedural success rate was high und similar in both groups (97.6%). Periprocedural adverse events were not statistically significant in groups (11.9% in <75 years vs 12.9% in ≥75 years; p = 0.80). At 1 year follow-up, all-cause mortality was higher in patients aged ≥75 compared withwith younger group (13.0% vs 7.8 %,p = 0.04), mainly due to non-cardiovascular causes (10.6% vs 6.0%). No significant differences in major bleeding, stroke, systemic embolism were observed. In conclusion, LAAC is feasible and safe in patients with AF at high stroke risk and with contraindications for OAC and should be considered as candidates for LAA closure. Elderly patients often present these characteristics and could benefit from this novel therapy. **© 2020 Published by Elsevier Inc.** **(Am J Cardiol 2020;136:81−86)**

Atrial fibrillation (AF) is associated with a five-fold increased risk of ischemic stroke and becomes of special importance when patients reach older age, with an increasing incidence and prevalence of AF with advancing age.[1,2] Oral anticoagulation (OAC) is recommended for stroke prevention in patients with non-valvular AF and CHA_2DS_2-VASc score ≥ 2 in men and ≥ 3 in women, in all those who are eligible.[3] The left atrial appendage (LAA) seems to be the source of more than 90% of thrombi in cases of stroke in which the thrombus could be identified.[4] These data support that left atrial appendage closure (LAAC) may offer an alternative mechanical approach[5] to reduce cardioembolic risk in AF patients.[6] Compared with OAC therapy, LAAC reduced the risk of life-threatening bleeding events, such as

[a]Klinikum Ludwigshafen, Ludwigshafen, Germany; [b]Department of Cardiology, Angiology, and Pneumology, Second Medical Clinic, Coburg Hospital, Coburg, Germany; [c]Department of Medicine-Cardiology and Intensive Care, Hospital Munich-Thalkirchen, Munich, Germany; [d]First Department of Medicine,University Medical Centre Mannheim (UMM), Faculty of Medicine Mannheim, University of Heidelberg, and DZHK (German Center for Cardiovascular Research) partner site Heidelberg/Mannheim, Mannheim, Germany; [e]CardioVascular Center Frankfurt, Frankfurt, Germany and Anglia Ruskin University, Chelmsford, United Kingdom; [f]Cardiology and Aortic Center, Royal Brompton and Harefield NHS Foundation, Trust at Imperial College, London, United Kingdom; [g]Department of Cardiology, Klinikum Lüneburg, Lüneburg, Germany; [h]Department of Internal Medicine III, Division of Cardiology, University of Heidelberg, Heidelberg, Germany; [i]Clinic for Internal Medicine, University of Rostock, Rostock, Germany and Vivantesklinikum im Friedrichshain und Am Urban, Berlin, Germany; [j]Medical Department I, SLK-Kliniken Heilbronn GmbH, Klinikum Am Gesundbrunnen, Heilbronn, Germany; [k]Department of Medicine, University of Erlangen, Erlangen, Germany; [l]Clinic for Internal Medicine I, Heinrich-Braun-Klinikum Zwickau gGmbH, Zwickau, Deutschland; and [m]Stiftung Institut für Herzinfarktforschung, Ludwigshafen, Germany.. Manuscript received June 29, 2020; revised manuscript received and accepted September 1, 2020.

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*Corresponding author: Tel: +49 621 503 2941; fax: +49 621 503 4044.
E-mail address: Uwe.Zeymer@t-online.de (U. Zeymer).

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intracranial bleeding.[7,8] Multicenter randomized studies found the treatment to be safe, effective, and noninferior to vitamin K antagonists for stroke prevention,[9,10] whereas longer-term follow-up supports a potential for superiority and lower mortality of LAAC.[11] Elderly patients present a cohort with a greater risk of ischemic and bleeding events. The present study aimed to assess the indications, the 1-year outcome, the safety and efficacy of LAAC in elderly patients (≥75 years) compared with younger patients in clinical practice.

Methods

The German left atrial appendage occlusion registry (LAARGE) is a prospective, nonrandomized, multicenter real-world registry that encompasses consecutive patients with the indication to receive a LAAC from 38 voluntary participating centers. Recruitment into the registry started in July 2014 and ended in December 2015. Patients should have been treated according to current recommendations. [12] Patients ≥18 years planned for LAAC with all 3 types of non-valvular AF, a CHA_2DS_2-VASc score ≥2 and ineligibility for long-term OAC (previous bleeding events, labile INR, poor compliance, patient preferences, stroke/TIA although anticoagulation therapy) were included. Participating centers were encouraged to include all patients consecutively to avoid recruitment bias. The study was carried out according to the principles of the Declaration of Helsinki and was approved by the Landesärztekammer Rheinland-Pfalz in Mainz. Written informed consent was obtained from all study patients. The study is financed and conducted by the Stiftung Institut für Herzinfarktforschung, Ludwigshafen am Rhein, Germany.

The study aimed to assess the indications, the 1-year outcome, the safety and efficacy of LAAC in elderly patients (≥ 75 years) compared with younger (<75 years) patients in clinical practice. As described previously,[13-16] preprocedural screening, the conduction of the implantation procedure as well as postprocedural management including the antithrombotic treatment were at the discretion of the operating physician. Usually, suitable patients received a clinical examination, an electrocardiogram, a blood analysis, and a transesophageal echocardiography. After confirming the indication and the technical feasibility of the LAA (i.e., size, absence of thrombus, or sludge), the procedure was performed under conscious sedation or general anesthesia for specific cases. transesophageal echocardiography guiding or intracardiac echocardiography was used to rule out an intracardiac thrombus intraprocedurally and to facilitate transseptal puncture. Device implantation was performed taking into consideration the specific manufacturer's recommendations. After device releasing and sheath removal the venous access site was sealed at the discretion of the operator. All participating centers reported procedural data and intrahospital complications as well as discharge medication for all successfully implanted patients. Patients were prospectively followed until hospital discharge, and after 3- and 12-month. Patients were contacted directly or via phone call 1 year after the implantation procedure to assess survival and occurrence of complications. Furthermore, antithrombotic medication was registered. Distinctive scores, for example, the Bleeding Academic Research Consortium (BARC) score,[17] were used to grade event severity. Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina). Continuous data are presented as medians with interquartile ranges (25th and 75th percentiles), or as means with standard deviation, and categorical data as frequencies with group-related percentages.

Categorical variables were compared between the patient groups using the Pearson's chi-squared test, or by the Mann-Whitney-Wilcoxon test, as indicated in the tables. Metrical or ordinal variables were compared using the Mann-Whitney-Wilcoxon test. One-year mortality after the implantation procedure and the incidence of the combined event of death or stroke were evaluated by means of survival analysis. p-values <0.05 (two-tailed) were considered significant.

Results

A total 638 patients were included in the registry. Of them 402 (63%) were aged ≥ 75 years at the time of the procedure. Baseline characteristics of the study population stratified according to age group are presented in Table 1. Compared with patients < 75 years, patients aged ≥75 had a lower proportion of structural heart disease, a higher prevalence of coronary artery disease, higher prevalence of permanent atrial fibrillation, and higher CHA_2DS_2-VASC and HAS-BLED scores. There were no significant differences between groups in the prevalence of diabetes mellitus or previous cerebrovascular events.

The most common indication for LAAC was previous bleeding, as shown in Table 2. Patients aged ≥75 years had a higher prevalence of previous bleeding and labile INR (Table 2).

As presented in Table 3, LAAC has been successfully performed in 623 patients (97.6%).

Table 1
Baseline characteristics of the study population

p Value	≥ 75 years (n = 402)	<75 years (n = 236)	Variables
Age (years)	68.0± 6.6	80.6± 3.8	< 0.001
Female	84 (35.6%)	164 (40.8%)	0.19
Coronary artery disease	77 (32.6%)	215 (53.5%)	< 0.001
Diabetes mellitus	79 (33.5%)	138 (34.3%)	0.83
Valvular disease	38 (16.1%)	94 (23.4%)	0.028
No structural heart disease	74 (31.4%)	54 (13.4%)	< 0.001
Prior PVI	8 (3.4%)	9 (2.2%)	0.38
Prior pacemaker	15 (6.4%)	29 (7.2%)	0.68
Prior cerebrovascular event			
TIA	25 (10.6%)	27 (6.7%)	0.084
Stroke	61 (25.8%)	76 (19.0%)	0.041
CHA_2DS_2-VASc score	3.6±1.5	5.1±1.3	< 0.001
HAS-BLED score	3.5±1.2	4.1±1.0	< 0.001
HAS-BLED score ≥ 3	191 (82.3%)	382 (95.5%)	< 0.001
Type of AF paroxysmal	113 (47.9%)	161 (40.0%)	0.054
Persistent	48 (20.3%)	67 (16.7%)	0.24
permanent	75 (31.8%)	174 (43.3%)	0.004

Continuous data are presented as mean ± standard deviation. Categorical variables are presented as number (percentage). AF= atrial fibrillation; PVI= pulmonary vein isolation; TIA= transitory ischemic attack.

Table 2
Indications for left atrial appendage closure

Variables	< 75 years (n = 236)	≥ 75 years (n = 402)	p Value
Prior bleeding	173 (73.4%)	334 (82.9%)	0.003
Severe bleeding	103 (59.5%)	149 (44.6%)	
Moderate bleeding	47 (27.2%)	148 (44.3%)	
Mild bleeding	23 (13.3%)	37 (11.1%)	
Cerebrovascular event	77 (32.6%)	96 (23.9%)	0.016
Stroke	61 (25.8%)	76 (18.9%)	0.039
TIA	25 (10.6%)	27 (6.7%)	0.084
Labile INR	11 (4.7%)	43 (10.7%)	0.008
Contraindication for OAC	53 (22.5%)	68 (16.9%)	0.085
Non-compliance with OAC	13 (5.5%)	20 (5.0%)	0.77
Patient's preference	62 (26.3%)	99 (24.6%)	0.64
Others	24 (10.2%)	34 (8.5%)	0.47

Categorical variables are presented as presented in numbers (percentage). INR= international normalized ratio; OAC= oral anticoagulation; other abbreviations as in Table 1.

Table 3
Procedural data

Variables	≥ 75 years (n = 402)	< 75 years (n = 236)	p Value
Procedural success rates	229 (97.0%)	394 (98.0%)	0.43
Type of device, each			
Amplatzer cardiac plug	50 (21.3%)	127 (31.6%)	0.005
Amplatzer Amulet™	74 (31.5%)	89 (22.1%)	0.009
Watchman	101 (43.0%)	177 (44.0%)	0.80
Other	10 (4.3%)	9 (2.2%)	0.15
Sedation type			
Conscious sedation	186 (79.1%)	350 (87.1%)	0.008
General anesthesia	35 (14.9%)	38 (9.5%)	0.038
Total duration [min]	55 (42-75)	60 (44-82)	0.10
Fluoroscopy time [min]	10 (7-14)	10 (7-15)	0.42
TEE	231 (97.9%)	399 (99.3%)	0.13
Periprocedural anticoagulation			
UFH	223 (94.9%)	385 (95.8%)	0.61
LMWH	7 (3.0%)	6 (1.5%)	0.20
VKA	1 (0.4%)	2 (0.5%)	0.90
NOAC	2 (0.9%)	1 (0.2%)	0.28

Continuous data are presented as mean ± standard deviation or median (interquartile range). LMWH= low-molecular weight heparin; NOAC= non-vitamin K dependent oral anticoagulant; TEE= transesophageal echocardiography; UFH= unfractionated heparin; VKA= vitamin K antagonist.

There were no significant differences between groups in the procedural duration time or fluoroscopy time. Indeed, the periprocedural anticoagulation strategy was similar in groups.

The periprocedural adverse events were not statistically different in groups (Table 4). During the hospital stay 2 deaths occurred, 1 in each group (in the <75 group due to cardiovascular cause and in the ≥ 75 group, non-cardiovascular death). Severe bleeding events occurred in 6 and 1 patients (aged ≥75 and <75 years respectively) but none of these was fatal.

As presented in Table 5, at 1 year of follow-up, the all-cause mortality was higher in patients aged ≥75 compared with younger group (p = 0.04), mainly due to non-cardiovascular causes. No significant differences between groups in stroke and significant bleeding were observed. The same was seen for the rate of device complications and pericardial effusion.

The antithrombotic strategy is provided in Figure 1. Overall, the majority of patients were discharged on dual antiplatelet therapy in both groups. At 1-year follow-up, monotherapy antiplatelet was the main therapy in both groups. Only a few patients were without any antithrombotic therapy at 1 year.

Table 4.
Periprocedural adverse events

Variables		< 75 years (n = 236)	≥ 75 years (n = 402)	p Value
Mean hospital stay, days		2 (1-3)	2 (2-4)	0.004
Total complications		28 (11.9)	52 (12.9)	0.80
Major complication		11 (4.7%)	18 (4.5%)	1.00
MACCE		2 (0.85%)	1 (0.25%)	0.56
Death		1 (0.42%)	1 (0.25%)	1.00
Stroke		1 (0.42%)	0 (0.0%)	0.37
Myocardial infarction		1 (0.42%)	0 (0.0%)	0.37
Severe bleeding		1 (0.42%)	6 (1.49%)	0.27
AV fistula or pseudoaneurysm		3 (1.27%)	3 (0.75%)	0.68
Pericardial effusion requiring action	surgical	1 (0.42%)	1 (0.25%)	1.00
	interventional	4 (1.69%)	9 (2.24%)	0.78
Device- dislodgement requiring action	surgical	0 (0.0%)	0 (0.0%)	-
	interventional	1 (0.43%)	1 (0.25%)	1.00
Moderate complication		22 (9.3%)	40 (10.0%)	0.89
Successful CPR		2 (0.85%)	1 (0.25%)	0.56
TIA		0 (0.0%)	0 (0.0%)	-
Moderate bleeding		3 (1.27%)	9 (2.24%)	0.55
Access-site infection		1 (0.42%)	0 (0.0%)	0.37
Groin hematoma		7 (2.97%)	11 (2.74%)	1.00
Pericardial effusion – conservative treatment		3 (1.27%)	8 (1.99%)	0.75
Device-dislodgment – retraction during the same intervention		3 (1.28%)	4 (1.0%)	0.71

CPR= Cardiopulmonary resuscitation; MACCE= Major adverse cardiac and cerebrovascular event.

Table 5
One-year outcomes

Variables	< 75 years (n = 236)	≥ 75 years (n = 402)	p Value
Death	18 (7.8%)	51 (13.0%)	0.04
Cardiovascular	4 (1.8%)	8 (2.4%)	0.41
Non-cardiovascular	14 (6.0%)	43 (10.6%)	0.12
Non-fatal Stroke	3 (1.3%)	3 (0.7%)	0.67
Systemic embolism	1 (0.5%)	0 (0.0%)	0.40
Severe bleeding	3 (1.3%)	11 (2.7%)	0.27
Moderate bleeding	8 (3.4%)	23 (5.7%)	0.25
Myocardial infarction	2 (0.9%)	4 (1.0%)	1.00
Device dislocation	5 (2.1%)	10 (2.5%)	0.78

Discussion

The main findings of the present analysis are (1) the identical LAAC procedural success rates in patients aged ≥75 and <75 years, (2) similar rates of stroke and significant bleeding in both groups after 1 year, (3) a higher all-cause mortality triggered by a higher non-cardiovascular mortality rate in the elderly.

In PCI an age older than or equal to 75 years of age constitutes an independent high-risk variable (Bauer et al)[18] and the higher prevalence of cardiac and noncardiac diseases contribute to higher adverse event rates with advancing age. The risk of thromboembolism in AF increases sharply with age over 65 years, with the relative risk increasing approximately 1.45-fold per decade.[19] Although increasing age as a risk factor for AF and stroke is continuous, age ≥75 years is arbitrarily used to dichotomize risk in cohort analyses and systematic reviews.[19]

In the randomized controlled trials patients aged ≥75 were represented to a lesser extent. Although in the PROTECT-AF trial the mean age was 72 years (190/463, 41.0% aged ≥75) and approximately two-thirds of the patients had a $CHADS_2$ score of 1 or 2, the PREVAIL study had more patients ≥75 years (140/269, 52%) and the patients had higher $CHADS_2$ and CHA_2DS_2-VASc scores.[9,10]

Previous studies of LAAC procedure have included patients under 75 years old, but few examined the safety and efficacy of LAAC in patients over 75 years old.[20–23] There is 1 subanalysis showing higher bleeding events in patients ≥75 years after LAA occluder implantation compared with a younger group (4.4% vs 1.4%).[24]

NOACs have been introduced in the past few years and evaluated in large phase III randomized trials also in participants ≥75 years old and provide substantial evidence for their efficacy in this age group. Both doses of dabigatran in RE-LY were associated with a lower risk of major hemorrhage in patients <75 years, but this was not the case in those aged ≥75 years. The risk of major hemorrhage and extracranial hemorrhage rose more steeply with dabigatran than warfarin with increasing age.[25] In ROCKET AF, there was an increased risk of nonmajor clinically relevant bleeding in patients aged ≥75 years treated with rivaroxaban compared with warfarin.[26] In ARISTOTLE, apixaban was more effective in reducing strokes and all-cause mortality and had a lower risk of major bleeding with no significant age interaction when compared against warfarin.[27] When compared with aspirin, apixaban was superior in preventing stroke or systemic embolism in patients with AF, including those aged 75 years. There was no significant increase in risk of major bleeding in patients ≥75 years in the AVERROES study.[28]

Compared with previous studies, our results are remarkable for a few reasons. Firstly, we are the largest and first to present results of the LAAC procedure using a variety of endocardial devices, except Freixa X, et al[21], but they showed the results of 1 device (Amplatzer Cardiac Plug,St Jude, Minneapolis, Minnesota). Secondly, we present a mortality difference at 1-year follow-up between groups; this difference was not shown in previous studies. Importantly, there was no significant difference in bleeding rates in patients aged ≥75 and <75 years despite a greater HAS-BLED score in the older group, as study by Freixa X et al, showed.

In our registry, patients aged ≥75 years presented increased all-cause mortality, mainly a consequence of a

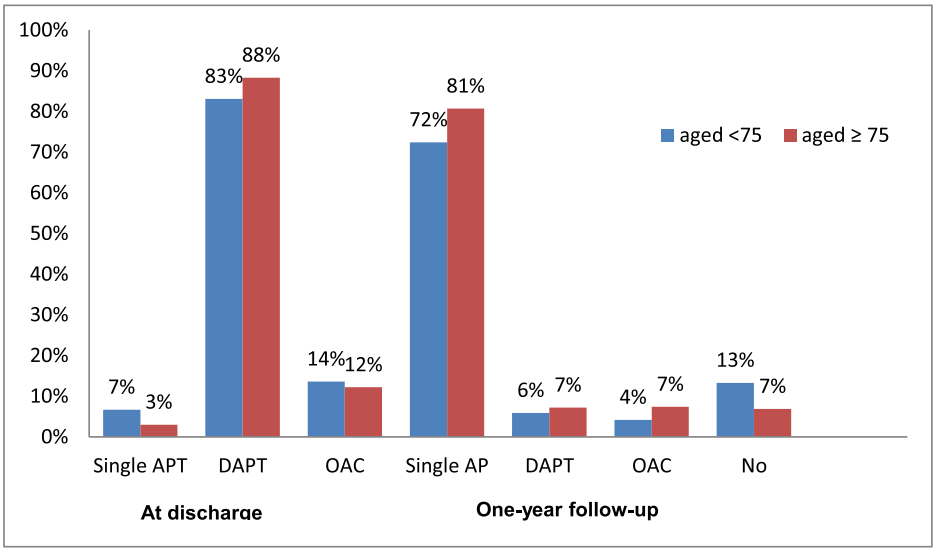

Figure 1. Antithrombotic therapy at discharge and at 1-Year follow-up. APT = antiplatlet therapy; DAPT = dual antiplatlet therapy; OAC = oral anticoagulation.

higher incidence of non-cardiovascular death. This finding is not unexpected and probably strengthens the power of our results as it exposes a natural outcome such as the higher risk of death in older patients. A meta-analysis of pooled, patient-level data from long-term follow-up of PROTECT-AF and the PREVAIL further assessed the outcomes of LAA closure with the Watchman compared with warfarin in AF patients suitable for long-term warfarin.[29] The rate of the primary efficacy end point (cardiovascular/unexplained death, stroke, or systemic embolism) was similar between device closure and warfarin therapy ($p = 0.27$), as was the rate of all-cause stroke and systemic embolism ($p = 0.87$). The rate of cardiovascular or unexplained death and the rate of all-cause mortality was both significantly lower with device therapy ($p = 0.027$ and $p = 0.035$).

A retrospective analysis of 351 patients with non-valvular AF and older than 75 years who underwent LAAC, most common with Watchman device, revealed no significant differences in procedure-related major complications within 7 days between the groups aged ≥ 75 years and aged < 75 years. However, after a nearly 2-year follow-up, there was an increased trend of major bleedings and all bleedings in the group aged ≥ 75 years without significant differences between both groups in all-cause death, cardiovascular death, stroke/TIA/system embolism, device thrombus, and device gap.[30] Recently, a multicenter, randomized trial, the PRAGUE-17, compared percutaneous LAA closure with direct oral anticoagulants in patients with nonvalvular AF at high risk for stroke. At median 19.9 months follow-up, the annual rates of the primary composite outcome (stroke, transient ischemic attack, systemic embolism, cardiovascular death, major or nonmajor clinically relevant bleeding, or procedural-/device related complications) were 10.99% with LAAC and 13.42% with direct oral anticoagulants ($p = 0.004$ for noninferiority).[31]

OAC therapy remains underutilized in elderly atrial fibrillation patients, and adherence to therapy is sometimes a challenge in this population. The frail patients are at increased risk of not only ischemic events but also serious bleeding. Therefore, interventional LAA occlusion is an alternative strategy in old patients, and implantation of this device could obviate the need for long-term OAC.

The present study has several limitations that should be acknowledged. The study is based on observational registry data, which included many large-volume centers. The major limitation for estimating the overall value of LAAC is the lack of a control group and only a calculated stroke or bleeding risk.

Conclusion

Therapies must be tailored to elderly patients, with particular attention to co-morbidities and bleeding risk. Elderly patients are at increased risk for thromboembolic events und thromboembolic protection is therefore of major importance in this population. LAAC should be kept as alternative in suitable patients and this study adds to the evidence that LAAC is effective in reducing the risk of stroke and major bleeding in AF with a low rate of complications also in the elderly population.

Authors contribution

Author agreement/statement: Aref El Nasasra,MD: writing original draft, completion final draft and editing. Johannes Brachmann, MD: writing review and editing. Thorsten Lewalter, MD: writing review; Ibrahim Akin, MD: writing review and editing; Horst Sievert, MD: writing review. Christoph A. Nienaber, MD: writing review. Christian Wei, MD: writing review. Sven T. Pleger, MD: writing review. Hüseyin Ince, MD: writing review. Jens Maier, MD: writing review. Stephan Achenbach, MD: writing review. Holger H. Sigusch, MD: writing review. Matthias Hochadel, PhD: writing review, statistical analysis. Steffen Schneider, PhD, statistical analysis, Jochen Senges, MD: writing review; Uwe Zeymer, MD: Conceptualization, Methodology, writing review and editing.

Conceptualization − Uwe Zeymer; Methodology − Aref El Nasara, Uwe Zeymer; Formal analysis − Matthias Hochadel; Resources − Uwe Zeymer, Jochen Senges; Data curation − Matthias Hochadel; Writing original draft − Aref El Nasasra, Uwe Zeymer; Writing − Review and Editing −Aref El Nasrasra, Uwe Zeymer; Visualization − Uwe Zeymer; Supervision − Uwe Zeymer; Project administration − Steffen Schneider.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

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