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Clinical

Long-Term Survival Following Transcatheter Mitral Valve Repair: Pooled Analysis of Prospective Trials with the Carillon Device

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ABSTRACT

Purpose: To report long-term survival and to identify potential determinants of survival among patients receiving treatment for functional mitral regurgitation (FMR) with the Carillon device.
Methods: This was a post hoc analysis in which we pooled prospectively collected data from three studies of the Carillon device with available long-term vital status data. Patient eligibility in these trials specified symptomatic congestive heart failure despite guideline-directed medical therapy, grade 2 to 4 FMR, left ventricular enlargement, and reduced ejection fraction. Echocardiographic parameters were available through the 12-month visit and vital status was available through 5 years. The association of patient characteristics and changes in echocardiographic parameters at 6 and 12 months with long-term survival was analyzed using Cox proportional hazards regression.
Results: A total of 74 patients (mean age 67 years, 72% male, 59% MR grade 3 or 4) were treated with the Carillon device. Over 1 year of follow-up, the New York Heart Association (NYHA) class decreased in 64% of patients, distance on the 6-minute walk test increased, and echocardiographic measures indicated significant decreases in MR grade and favorable left ventricular remodeling. The Kaplan-Meier survival rate was 83.6% at 1 year, 73.1% at 2 years, 67.9% at 3 years, and 56.2% at 4 and 5 years of follow-up. Primary determinants of long-term survival were a decrease in NYHA class, an increase in 6-minute walk test distance, and a decrease in regurgitant volume during the first year of follow-up.
Conclusions: Among patients with congestive heart failure and grade 2 to 4 FMR who were symptomatic despite guideline-directed medical therapy, transcatheter mitral valve repair with the Carillon device resulted in a favorable 5-year survival rate. The survival benefit was greatest among patients with improvement in clinical and hemodynamic parameters during the first year of follow-up.

1. Introduction

Patients with functional or secondary mitral regurgitation (MR) have an increased mortality risk, even when the MR is mild [1]. Guideline-directed medical therapy can reduce functional mitral regurgitation (FMR) [2,3] as can cardiac resynchronization therapy in appropriately selected individuals [4]. Historically, surgical annular reduction therapy has been applied, but remains unproven as a clinically effective treatment [5], and randomized trials have demonstrated high recurrence rates [6]. Consequently, less invasive transcatheter mitral valve repair techniques have been developed to correct MR, induce left ventricular (LV) remodeling, and improve health-related quality of life with less attendant morbidity. Recently, percutaneous leaflet clipping (MitraClip, Abbott, Abbott Park, IL) was evaluated in two randomized trials with conflicting results. Comparing patients treated with the MitraClip procedure versus those receiving medical therapy only, no survival benefit was realized after 1-year of follow-up in the COAPT trial [7] or the Mitra-Fr trial [8]. However, 2-year results from the

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COAPT trial demonstrated significantly greater survival rates with MitraClip, suggesting that longer follow-up duration may be needed to fully assess the potential survival benefit of FMR treatments.

The Carillon Mitral Contour System (Cardiac Dimensions, Kirkland, WA) is a percutaneous treatment for FMR that has been evaluated in several prospective trials [9–12]. Overall, these studies have demonstrated a consistent reduction in MR as assessed by independent echocardiographic core laboratories. In addition, favorable LV remodeling was evident at the 1-year follow-up visit in these studies. However, none of these trials were statistically powered for clinical endpoints and the duration of patient follow-up was variable. In the TITAN trial [10], patients were followed for 5 years whereas the TITAN II [11] and REDUCE FMR [12] trials specified 1 year of follow-up. Subsequently, a high-enrolling center evaluated the vital status of their patients that participated in the TITAN II and REDUCE FMR trials over 5 years. This provided an opportunity to provide a more robust evaluation of long-term survival with the Carillon device by performing a pooled analysis of these datasets that were derived from common protocols. Such an analysis is of considerable clinical interest since, to date, survival rates with the Carillon device have only been reported through 2 years of follow-up in the peer-reviewed literature [10]. Thus, the main objective of this study was to report long-term survival among patients receiving treatment for FMR with the Carillon device. A secondary objective of this analysis was to identify potential determinants of long-term survival in these patients.

2. Methods

This post hoc analysis pooled data from three trials of the Carillon device—TITAN, TITAN II, and REDUCE FMR. All patients from TITAN (n = 36), a multicenter trial of the Carillon device with 5-year patient follow-up, were included in this analysis. Additionally, a single high-enrolling site (Pôle Santé Republic, Claremont Ferrand, France) that enrolled 15 of 36 patients in the TITAN II trial and 23 of 73 patients in the REDUCE FMR trial tracked the vital status of their patients for 5 years. Overall, the pooled dataset included baseline patient characteristics, functional and echocardiographic results through 1 year of follow-up, and survival through final follow up. In each trial, ethics committees at each site approved the protocol and all patients provided written informed consent. Patients treated at Pôle Santé Republic provided consent for collection of long-term vital status data.

Patient eligibility in these trials specified symptomatic congestive heart failure despite guideline-directed medical therapy and grade 2+ to 4+ FMR. In addition, patients were required to have an enlarged LV (>5.5 cm left ventricular end-diastolic diameter [LVEDD]) and reduced ejection fraction (<40% in TITAN and TITAN II; <50% in REDUCE FMR). Detailed listings of patient eligibility criteria in each trial have been previously published [10–12].

All echocardiograms were read for quantitative parameters by independent echocardiographic core laboratories, and MR grading was based upon American Society of Echocardiography recommendations, rather than the more common clinical assessment of regurgitant jet area in the left atrium [13]. The procedure for Carillon device implantation has been described elsewhere [9] and involves placement of a device into the coronary sinus to allow approximation of the mitral valve leaflets, facilitated by the anatomical proximity of the coronary sinus to the posterior mitral annulus.

Baseline patient characteristics were reported as the mean and standard deviation for continuous outcomes and counts and percentage for categorical outcomes. The primary outcome of this analysis was the Kaplan-Meier survival estimate through 5 years of follow-up. The association of patient characteristics and changes in echocardiographic parameters over 1 year of follow-up with long-term survival was analyzed using a Cox proportional hazards model and reported as a hazard ratio (HR) and 95% confidence interval. The threshold for statistical significance was $p < 0.05$ and all tests were two-sided. Statistical analyses were performed using JMP v14.3 (SAS Institute, Cary, NC) and Stata v16 (StataCorp, College Station, TX).

3. Results

This pooled dataset included 74 patients treated with the Carillon device for FMR—36 who successfully received a Carillon device in the TITAN trial and 38 who successfully received a Carillon device at Pôle Santé Republic in the TITAN II and REDUCE FMR trials. Overall, mean age was 67 ± 11 years and 72% were male. The etiology of cardiomyopathy was ischemic in 72% of patients. Most patients (88%) were classified as NYHA class III or IV. Baseline ejection fraction was 31 ± 8% and the LV end-diastolic volume (LVEDV) was 194 ± 58 cc. The independent echocardiographic core laboratory categorized the MR grade at baseline as 3 or 4 in 59% of patients (Table 1).

Over 5 years of follow-up, 28 patients died, 8 were lost to follow-up, 17 have not completed follow-up through 5 years, and 21 returned for 5-year follow-up. A patient flow diagram is provided in Fig. 1. Functional improvement was rapid and durably maintained following treatment. The proportion of patients who improved by at least 1 NYHA class was 72% at 1 month, 64% at 6 months, and 64% at 1 year (Supplement Fig. 1). Distance on the 6-minute walk test increased from 311 ± 85 m at

Table 1
Baseline patient characteristics.[a]

Characteristic	All patients (n = 74)	MR grade 3 or 4[b] (n = 42)
Demographics		
Age (years)	67 ± 11 (74)	64 ± 13 (42)
Male sex	72% (53/74)	71% (30/42)
Body mass index (kg/m^2)	26 ± 4 (72)	25 ± 4 (42)
Medical and surgery history		
Cardiomyopathy etiology		
Ischemic	72% (53/74)	71% (30/42)
Nonischemic	28% (21/74)	29% (12/42)
HF hospitalization within 12 months	57% (38/74)	61% (22/42)
Atrial fibrillation	43% (32/74)	43% (18/42)
Implantable Cardioverter Defibrillator or Pacemaker	34% (25/74)	24% (10/42)
Diabetes mellitus	20% (15/74)	24% (10/42)
Functional assessment		
New York Heart Association classification		
II	12% (9/73)	5% (2/41)
III	81% (59/73)	83% (34/41)
IV	7% (5/73)	12% (5/41)
6-Minute walk test (meters)	311 ± 85 (72)	313 ± 82 (40)
Hemodynamic measures		
Heart rate (bpm)	75 ± 17 (71)	79 ± 18 (42)
Systolic blood pressure (mmHg)	113 ± 18 (72)	109 ± 16 (42)
Diastolic blood pressure (mmHg)	68 ± 11 (72)	66 ± 11 (42)
LV parameters		
LV ejection fraction (%)	31 ± 8 (65)	30 ± 9 (42)
LV end-diastolic diameter (cm)	6.5 ± 0.9 (70)	6.6 ± 0.9 (42)
LV end-systolic diameter (cm)	5.6 ± 1.0 (70)	5.7 ± 1.1 (42)
LV end-diastolic volume (cc)	194 ± 58 (65)	205 ± 61 (42)
LV end-systolic volume (cc)	137 ± 52 (65)	146 ± 55 (42)
Mitral valve parameters		
Regurgitant volume (ml)	34 ± 14 (67)	39 ± 13 (41)
Vena contracta (cm)	0.64 ± 0.16 (52)	0.70 ± 0.12 (36)
Effective regurgitant orifice area (cm^2)	0.23 ± 0.10 (68)	0.28 ± 0.10 (41)
MR jet area (cm^2)	10.6 ± 5.5 (56)	13.2 ± 5.0 (35)
MR grade		
1	11% (8/71)	0% (0/42)
2	30% (21/71)	0% (0/42)
3	42% (30/71)	71% (30/42)
4	17% (12/71)	29% (12/42)

LV, left ventricular; MR, mitral regurgitation.
[a] Values are mean ± SD (n) or percentage (n/N).
[b] MR grade 3 denotes moderate to severe MR and grade 4 denotes severe MR.

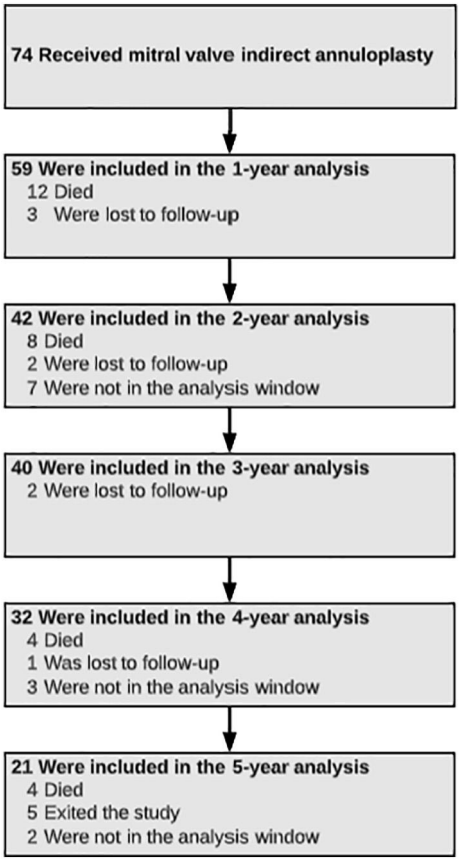


Fig. 1. Patient flow diagram.

baseline to 381 ± 133 m at 1 month, 417 ± 169 m at 6 months, and 399 ± 155 m at 1 year ($p < 0.001$ vs. baseline). Compared to the entire cohort, functional improvement was similar among patients with grade 3+ or 4+ MR with 79% improving by at least 1 NYHA class and with a 6-minute walk test distance improvement of 92 ± 168 m at 1 year ($p < 0.0001$ vs. baseline).

Treatment with the Carillon device was associated with significant decreases in MR grade in the entire cohort (Fig. 2). Significant decreases in LV volumes and increases in ejection fraction were noted at the 1-year follow-up visit (Fig. 3). Additional echocardiographic parameters including regurgitant volume, effective regurgitant orifice area, vena contracta, and MR jet area decreased by 34–41% over 1 year among the entire cohort as well as in the grade 3+ or 4+ MR subgroup. The change in LVESV was significantly associated with change in regurgitant

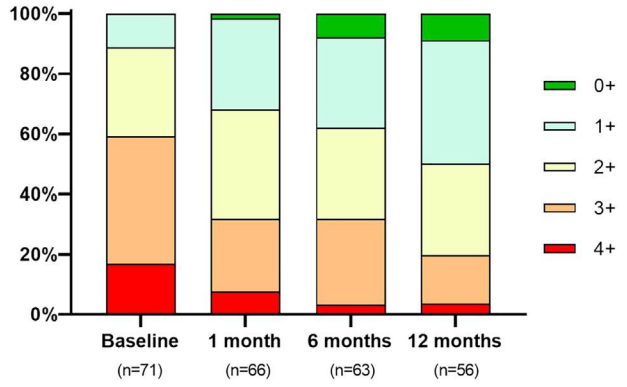


Fig. 2. Change in mitral regurgitation grade over 1 year of follow-up after implant with the Carillon device.

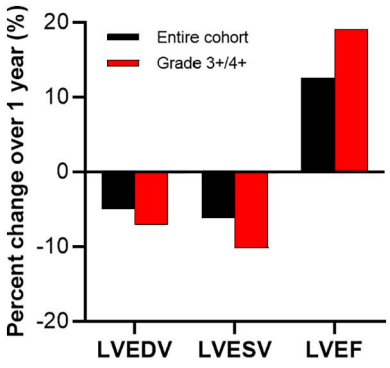


Fig. 3. Change in left ventricular echocardiographic parameters over 1 year of follow-up after implant with the Carillon device. LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction.

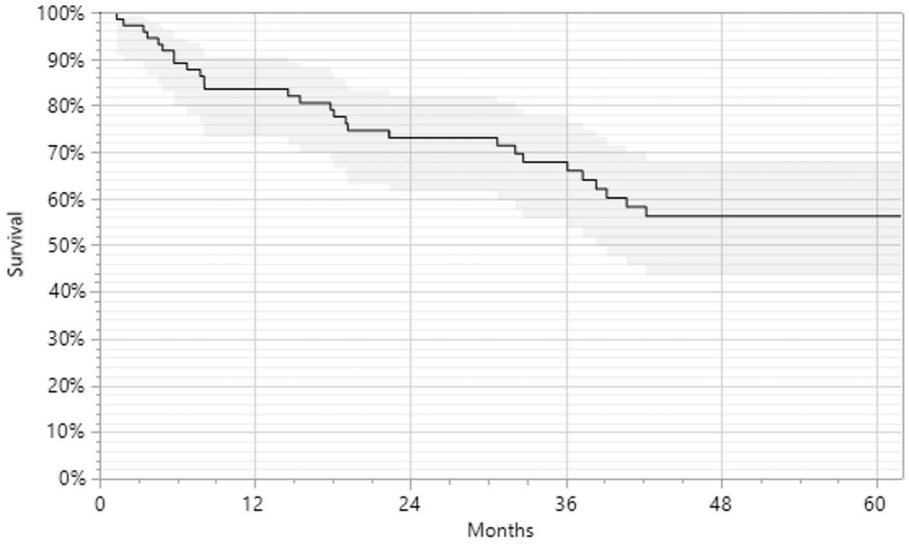
volume over 1 year of follow-up (Supplement Fig. 2, $r = 0.58$, $p < 0.001$).

The Kaplan-Meier survival rate was 83.6% at 1 year, 73.1% at 2 years, 67.9% at 3 years, and 56.2% at 4 and 5 years of follow-up (Fig. 4). Among patients with MR grade 3+ or 4+, survival rates were almost identical to those of the entire cohort—78.3% at 1 year, 75.5% at 2 years, 66.3% at 3 years, and 56.0% at 4 and 5 years of follow-up (Supplement Fig. 3). In a Cox proportional hazards model, no baseline characteristic was associated with post 1-year survival. However, when evaluating the change in key parameters after treatment, survival beyond 6 months of follow-up was higher in patients who experienced a decrease in NYHA class at 6 months (HR = 2.74 per 1 class decrease, $p = 0.001$). Among patients surviving for at least 1 year, an increase in the 6MWT (HR = 1.54 per 100-meter increase, $p = 0.03$), a decrease in NYHA class (HR = 2.56 per 1 class decrease, $p < 0.01$), and a decrease in regurgitant volume (HR = 1.24 per 10% decrease, $p = 0.02$) at the 1-year visit were significant predictors of long-term survival (Table 2). Although changes in LV volumes were not significantly associated with survival in these models, the associations approached statistical significance (all p-values 0.07 to 0.15). Comparing patients with vs. without favorable LV remodeling at 6 months, defined as decrease in LVESV at least 10%, survival was 83.3% vs. 57.9% (log rank $p = 0.11$).

4. Discussion

In a pooled analysis of 74 patients treated with the Carillon device for functional MR and with 5 years of vital status follow-up, there were several important findings. First, patients realized rapid functional improvement that was sustained over the first year after treatment, with clinically important improvements in NYHA class and 6-minute walk test distance. Second, patients treated with the Carillon device had significant decreases in MR grade, LV volumes, and other echocardiographic parameters such as regurgitant volume, effective regurgitant orifice area, vena contracta, and MR jet area. Third, the 5-year survival rate was 56.2% and represents the first time that long-term survival has been reported in patients treated with the Carillon device. Finally, we identified several factors that were associated with long-term survival including a decrease in NYHA class, an increase in 6MWT distance, and a decrease in regurgitant volume during the first year of follow-up.

Multiple studies have demonstrated that the Carillon device can significantly reduce MR and induce LV remodeling in symptomatic patients with congestive heart failure, ischemic or non-ischemic cardiomyopathy, and reduced ejection fraction [9–12]. However, none of these studies were powered for clinical events, and the primary endpoints were evaluated at no later than 1 year of follow-up. The CARILLON study (ClinicalTrials.gov NCT03142152) is an ongoing double-blind, sham-controlled, randomized trial with a 2-year hierarchical endpoint which will address the clinical impact of Carillon in



Timepoint	0	12	24	36	48	60
No at risk	74	59	45	37	26	16
P(survival)	100.0% ± 0.0%	83.6% ± 8.5%	73.1% ± 10.4%	67.9% ± 11.2%	56.2% ± 12.6%	56.2% ± 12.6%
P(death)	0.0% ± 0.0%	16.4% ± 8.5%	26.9% ± 10.4%	32.1% ± 11.2%	43.8% ± 12.6%	43.8% ± 12.6%

Fig. 4. Kaplan-Meier survival estimate over 5 years of follow-up after implant with the Carillon device. Survival was 56.2% at 5 years of follow-up.

the treatment of patients with symptomatic congestive heart failure and functional MR. Results from the current pooled analysis were used to help inform the design of the CARILLON study and to support the hypothesis that a survival benefit may be anticipated from that study.

Because there were no corresponding control patients for this examination, it was useful to assess this analysis in a context of historical controls. In a single center study of patients with HFrEF [14], the approximate 5 year mortality of all patients was 47%, with worse survival in those with important MR; specifically mortality rates were over 50% in patients with moderate MR and over 60% in those with severe MR. In the present analysis, mortality rates were lower at 43.8% in patients with similar degrees of MR.

The recent publication of the COAPT study [7] and subsequent 3-year follow up [15] provided a reference for comparison of mortality data among patients with a similar diagnosis. Therefore, we descriptively compared results of patients with baseline grade 3+ or 4+ MR from the Carillon studies to the published outcomes of the two MitraClip trials for FMR [7,8,16], which only enrolled patients with grade 3+ or 4+ MR. Forty-two of the 74 patients (57%) in the above Carillon datasets were included in this subset analysis. The 2-year mortality rate in the control arm of the COAPT study was 43% and increased in a linear fashion over the follow-up period to 55.5% at 3 years. In contrast, mortality in the intervention arm of COAPT was 28.2% at 2 years and 42.8% at 3 years. We observed a similar nonlinear mortality trend in the current analysis of patients with grade 3+ or 4+ MR treated with the Carillon device with mortality rates of 24.5% at 2 years and 33.7% at 3 years, with similar numbers if the entire cohort is evaluated (Supplement Fig. 4). These results suggest that the primary clinical benefit of

Table 2
Association of key change characteristics on post 6 or 12 month survival through final follow-up.[a]

Variable	Unit of measure	Hazard ratio	95% CI	p-Value
Change in 6-minute walk test distance				
-6 months	Per 100-meter increase	1.32	0.82, 2.12	0.26
-12 months	Per 100-meter increase	1.54	1.03, 2.30	0.03
Change in NYHA				
-6 months	Per 1 class decrease	2.74	1.47, 5.11	0.001
-12 months	Per 1 class decrease	2.56	1.39, 4.72	<0.01
Change in regurgitant volume				
-6 months	Per 10% decrease	1.14	0.98, 1.33	0.09
-12 months	Per 10% decrease	1.24	1.03, 1.49	0.02
Absolute change in LVESV				
-6 months	Per 5 ml decrease	1.13	0.99, 1.30	0.08
-12 months	Per 5 ml decrease	1.10	0.98, 1.23	0.10
Percent change in LVESV				
-6 months	Per 5% decrease	1.20	0.99, 1.45	0.07
-12 months	Per 5% decrease	1.13	0.98, 1.31	0.09
Absolute change in LVEDV				
-6 months	Per 5 ml decrease	1.09	0.98, 1.21	0.11
-12 months	Per 5 ml decrease	1.09	0.98, 1.21	0.13
Percent change in LVEDV				
-6 months	Per 5% decrease	1,17	0.95, 1.44	0.15
-12 months	Per 5% decrease	1,18	0.96, 1.45	0.12

LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association.
[a] 6-Month change values used to predict post 6-month survival through final follow-up. 12-month change values used to predict post 12-month survival through final follow-up.

percutaneous mitral valve repair may only be realized only after approximately 1 year, a delayed response consistent with the long-term benefits from a decrease in LV volume overload.

The Cox proportional hazards model in this pooled analysis suggests that several factors may contribute to survival but only after 12 months since no baseline patient characteristic was associated with post 12-month survival. A key criterion to long term survival was a decrease in regurgitant volume at 12 months. This supports the role of a mitral regurgitation both in pathogenesis and prognosis and also the potential of a targeted treatment to have a clinical impact. This hypothesis is supported further by the data describing that improved mitral regurgitation in the COAPT treated arm was associated with a mortality benefit, However, the treated arm in MITRA-FR, did not experience a significant reduction in MR or mortality. The current analysis also suggests that improvement in mitral regurgitation is closely associated with favorable left ventricular remodeling, which has consistently been associated with mortality benefits [17]. These important clinical benefits of the Carillon device will be better assessed in the prospective, pivotal, randomized, sham-controlled CARILLON study.

4.1. Limitations

This is the first report of long-term survival in patients treated with the Carillon device, however there are several important limitations of this study. Firstly, long-term survival data were not collected prospectively for patients receiving the Carillon device in TITAN II or REDUCE FMR except for patients treated at Pôle Santé Republic. It is possible therefore that inclusion of these data derived from a single site introduces bias due to patient characteristics or operator experience. Secondly, patients enrolled in these trials who ultimately did not receive a Carillon device owing to implantation failure or control group assignment were not followed over the long-term and, therefore, we were unable to make direct comparisons to a control group in this patient-level analysis. Unlike the recent REDUCE FMR trial, and the ongoing CARILLON trial, there was no randomized control arm in these prior studies. Consequently, comparisons of these survival outcomes with other therapies for MR should be made cautiously. Thirdly, while some patients from Pôle Santé Republic were enrolled in the blinded REDUCE FMR trial, most patients in this pooled analysis were aware of their treatment assignment. Fourth, 34% of patients were lost to follow-up or had not yet completed 5 years of follow-up. Finally, the comparisons with historical cohort data are limited by the confounder of treatment epochs, patient characteristics and the relatively small numbers in the present dataset.

5. Conclusions

Among patients with congestive heart failure and grade 2 to 4 FMR who were symptomatic despite guideline-directed medical therapy, transcatheter mitral valve repair with the Carillon device resulted in a favorable 5-year survival rate. The survival benefit was greatest among patients with improvement in clinical and hemodynamic parameters during the first year of follow-up.

CRediT authorship contribution statement

Janusz Lipiecki: Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing.**David M. Kaye:** Data curation. **Klaus K. Witte:** Data curation, Formal analysis, Writing - review & editing.**Michael Haude:** Data curation, Formal analysis, Writing - review & editing.**Samir Kapadia:** Formal analysis, Writing - review & editing.**Horst Sievert:** Data curation, Formal analysis, Writing - review & editing.**Steven L.Goldberg:** Conceptualization, Data curation, Formal analysis.**Wayne C.Levy:** Formal analysis, Writing - review & editing. **Tomasz Siminiak:** Data curation, Formal analysis, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carrev.2020.02.012.

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