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Short communication

Safety and efficacy of Coronary Sinus Reducer implantation at 2-year follow-up

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ABSTRACT

Introduction: Coronary Sinus Reducer emerged as promising therapeutic option for patients with refractory angina. While recent literature reports short-term benefits of Reducer implantation, there is paucity of evidence regarding its safety and efficacy at longer follow-up.
Methods: In the original cohort of 50 refractory angina patients treated with Reducer at San Raffaele Hospital (Milan, Italy) between March 2015 and August 2016, we reassessed angina symptoms, quality of life and recorded adverse events at 2-year (mean ± SD: 748 ± 84 days) follow-up.
Results: Canadian Cardiovascular Society (CCS) score improved of ≥1 class in 34 patients (75.6%), and of ≥2 classes in 16 patients (35.6%), translating into a significant mean CCS score reduction at 2-year follow-up (1.74 ± 0.86 vs. 2.98 ± 0.52; $p < 0.001$). Four out of five Seattle Angina Questionnaire items improved significantly ($p < 0.001$ for all). Ten patients (22%) underwent percutaneous coronary intervention (PCI) during follow-up, three for acute coronary syndromes. Five patients died, two for cardiovascular causes (stroke and cardiac arrest).
Conclusions: Safety and efficacy observed in the short follow-up period after Reducer implantation are maintained at two years. Ten patients underwent PCI during follow-up, underlining that Reducer does not affect coronary artery disease progression.

1. Introduction

Coronary Sinus (CS) Reducer (Neovasc Inc., Richmond B.C., Canada) is a novel device designed to improve symptoms in patients with angina refractory to medical therapy and not amenable to further revascularization. It is a balloon-expandable, hourglass-shaped, stainless steel stent implanted percutaneously into the CS to create a controlled narrowing and establish a backward pressure gradient along the coronary tree [1,2].

In concordance with COSIRA randomized trial [3] and few other single-center experiences [4,5], our previous study demonstrated clinical safety and efficacy of Reducer implantation in 50 refractory angina patients treated at San Raffaele Hospital, Milan, Italy [6]. In this study, all patients were successfully treated, without procedural and device-related complications at 1-year follow-up. Patients experienced a significant reduction in angina burden, and improvements in both quality of life and functional capacity.

To date, safety and efficacy of Reducer implantation at the long-term (beyond 1-year) has been only reported in a small series of 10 patients [7]. Herewith, we provide 2-year follow-up of the largest single-center experience of patients with refractory angina treated with CS Reducer implantation.

2. Methods

This was a single center, prospective, observational study including 50 consecutive refractory angina patients with evidence of inducible myocardial ischemia treated with CS Reducer at San Raffaele Hospital, Milan, Italy, between March 2015 and August 2016. Criteria for patient selection were previously described [6]. All the patients underwent thorough clinical assessments including Canadian Cardiovascular Society (CCS) class evaluation, Seattle Angina Questionnaire (SAQ), New York Heart Association (NYHA) functional class and current anti-ischemic medical therapy before the procedure and at serial follow-ups. Adverse events at follow-up were also collected. One-year follow-up results were previously reported [6].

Device safety was defined as absence of device-related events during follow-up. Information on death, myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary artery by-pass graft, cardiac tamponade, life-threatening arrhythmias and respiratory failure needing invasive ventilation were also recorded. The clinical efficacy endpoints included CCS angina class and SAQ score at 2-year follow-up. NYHA score and antianginal therapy at follow-up were also evaluated.

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2.1. Statistical analysis

Continuous variables are described as mean ± standard deviation (SD) or as median (interquartile range [IQR]). Normality of distribution was tested by the Kolmogorov-Smirnov test. Categorical variables are expressed as proportions. The baseline and follow-up measurements were compared using a paired Student's *t*-test or the 1-sided Wilcoxon signed rank test, as appropriate. A p value <0.05 was considered to indicate statistical significance.

3. Results

Baseline characteristics of the study population (61 ± 9 years, 78% males, 85% three-vessel disease) were previously reported [6].

Mean 2-year follow-up was assessed at 748 ± 84 days. No device-related complications were observed at 2-year follow-up. Two patients

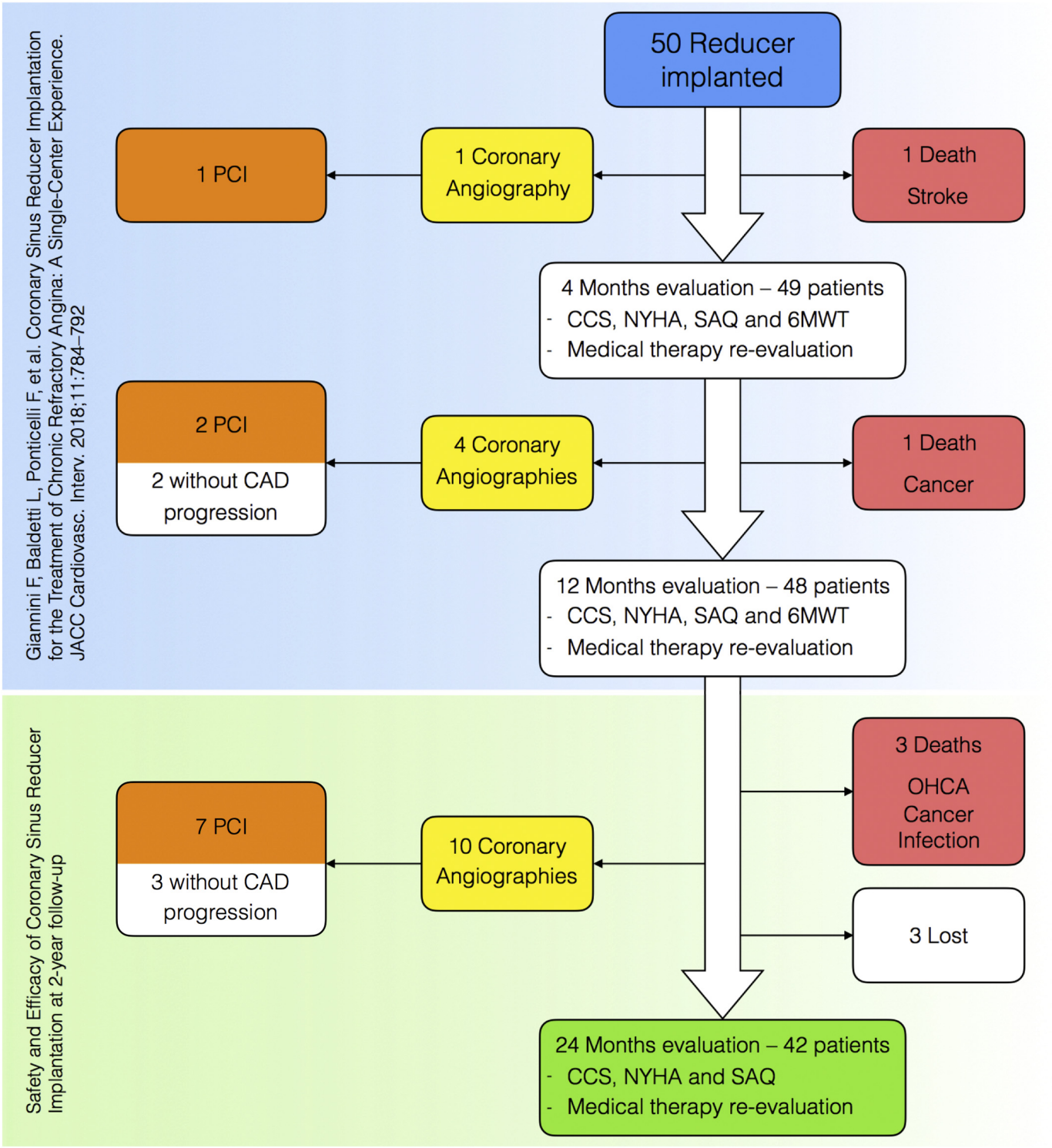

Fig. 1. Reducer protocol at San Raffaele Hospital. Of the 50 patients implanted, 2 died during the first year of ischemic stroke and urological malignancy. At 2 years, 3 patients were lost at follow-up, and 3 patients died of out-of-hospital cardiac arrest, pulmonary malignancy and nosocomial infection, respectively. We evaluated Canadian Cardiovascular Society (CCS) and New York Heart Association (NYHA) scores, Seattle Angina Questionnaire (SAQ) and medical therapy at all time points. At 2 years, 13 patients underwent a total of 15 further coronary angiographies: 9 patients required 10 further percutaneous coronary interventions (two patients underwent 2 further angiographies each, one of them required 2 PCIs), while from 5 angiographies there was no evidence of coronary artery disease (CAD) progression.

died during the first 12 months, due to an ischemic stroke and a urological malignancvy, respectively. Following the first year, three patients died because of out-of-hospital cardiac arrest, pulmonary malignancy, and nosocomial infection during a hospitalization for heart failure, respectively.

Data for the efficacy endpoint was available for 42 of the 45 living patients (93%), while 3 were unreachable by means of telephone calls or emails and were thus considered lost at follow up. Among them, 13 patients (31%) required a total of 15 clinically-driven coronary angiographies (two patients underwent two angiographies); 9 patients (21%) underwent a total of 10 PCIs (3 for myocardial infarctions, 7 for progression of coronary artery disease [CAD]), while from 5 angiographies there was no evidence of CAD progression (Fig. 1).

Angina burden was significantly reduced at 2-year follow-up as compared to baseline (CCS class 1.74 ± 0.86 vs. 3.00 ± 0.51, $p < 0.001$), and the benefit in CCS class observed at 1-year was maintained at 2-year follow-up (1.74 ± 0.86 vs. 1.73 ± 0.82, $p = 0.69$). The NYHA class improvement achieved at four months and maintained at one year as compared to baseline (1.2 ± 0.65 vs. 1.67 ± 0.72 $p < 0.001$), was lost at 2-year follow-up (1.68 ± 0.73 vs. 1.67 ± 0.72; $p = 1$, for 2-year vs. baseline).

At 2 years, all SAQ domains but angina stability remained significantly higher than baseline: physical limitation, 67.10 ± 13.79 vs. 47.85 ± 14.72 ($p < 0.001$); angina stability, 45.24 ± 14.01 vs. 39.76 ± 11.98 points ($p = 0.08$); angina frequency, 69.02 ± 15.07 vs. 44.43 ± 19.2 ($p < 0.001$); treatment satisfaction, 74.02 ± 8.43 vs. 37.89 ± 14.74 ($p < 0.001$) and quality of life, 58.76 ± 18.08 vs. 25.67 ± 12.35 ($p < 0.001$) (Fig. 2).

The number of antianginal drugs at 2-year follow-up was not significantly different when compared to baseline or 1-year follow-up [median number of drugs at 2-year: 3 (IQR: 2 to 4) vs. baseline: 3 (IQR: 2 to 4) ($p = 0.101$); 2-year: 3 (IQR: 2 to 4) vs. 1-year: 3 (IQR: 2 to 3.25) ($p = 0.484$)] (Fig. 2).

4. Discussion

The main findings of our study are the following:

1. Reducer remains safe in the long-term with no device-related adverse events at the two years follow up.
2. The reduction of angina symptoms and the improvement of quality of life observed after Reducer therapy are maintained at 2-year follow-up.
3. About one out of three patients underwent coronary angiography within 2 years from Reducer implantation, with half of them requiring PCI due to CAD progression.

Chronic refractory angina is a disabling condition, affecting between 5 and 10% of the stable CAD population [8]. As a consequence of population aging and reduction of CAD-related mortality, a higher number of

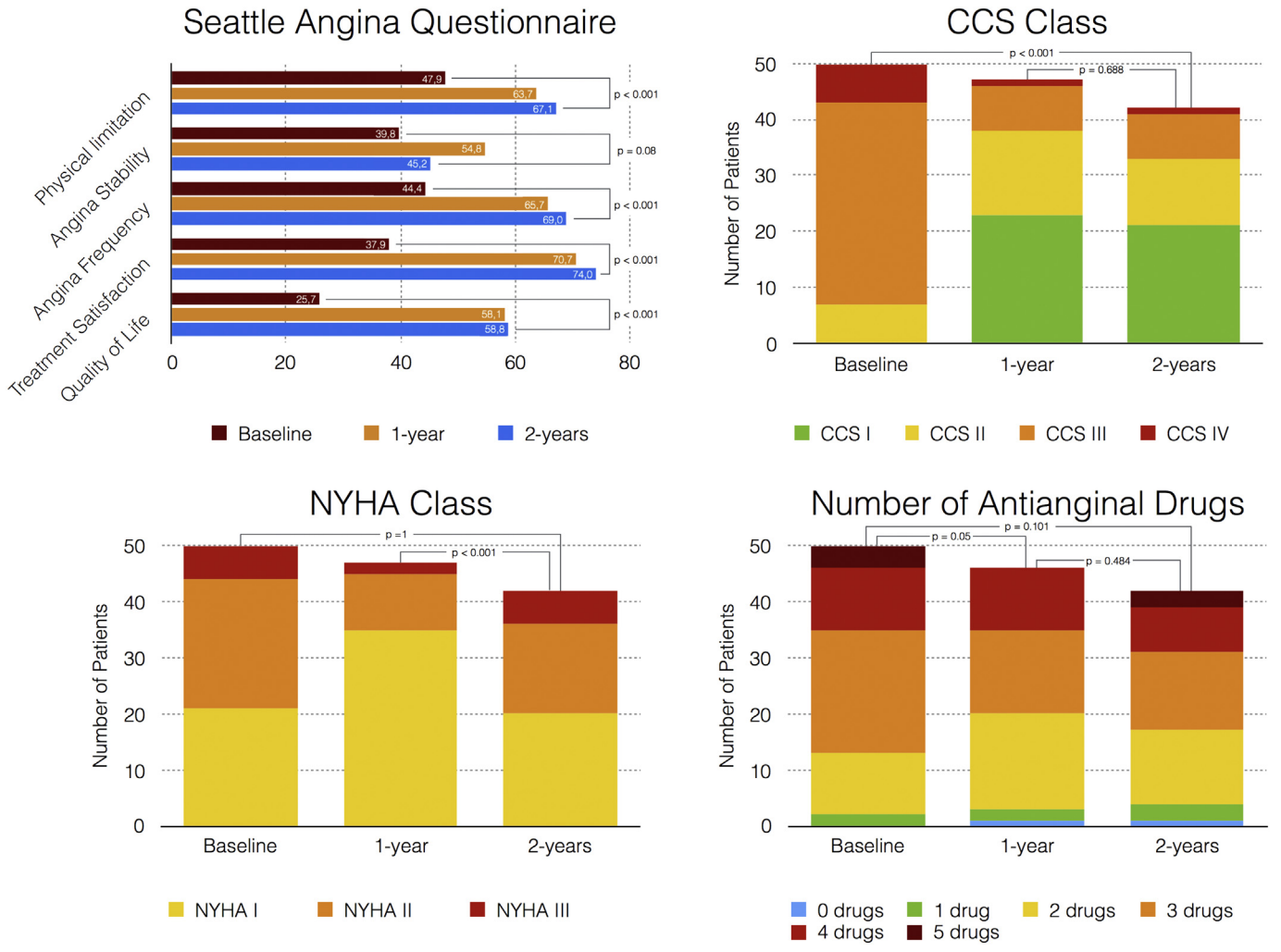

Fig. 2. Comparison between SAQ, CCS score, NYHA class, and number of drugs at baseline, 1 year and 2 years from Reducer implantation. All SAQ fields, but angina stability were improved significantly ($p < 0.001$) at 2 years as compared to baseline. Mean CCS class maintained the improvement described at 12 month, with reduction from 3.00 ± 0.51 to 1.74 ± 0.86 at 2 years ($p < 0.001$). No difference is observed between baseline and 2 years NYHA class, with loss of the improvement reported at 1 year.

patients are expected to present refractory angina. Indeed, there is a compelling need of alternative strategies to achieve symptom control for this population with currently limited therapeutic options [9].

The concept of CS narrowing for treatment of angina was first described in 1955 by Claude Beck, who demonstrated that partial surgical ligation of the CS led to quality of life improvement and mortality reduction in patients with angina [10]. With a similar rationale, CS Reducer recently emerged as promising technique for this challenging population [2].

International experience with this device is growing, with the largest multicenter clinical registry (REDUCE-Study) reporting improvements of CCS class, symptoms and quality of life at 1-year from the procedure [11], and few single center studies describing similarly favorable clinical outcomes in comparable time frames [4–6].

At two years from the implantation procedure, we observed maintained benefits on anginal symptoms and quality of life, similar to those reported at one year [6], confirming a lower burden of angina after treatment with Reducer system. These results provide further basis to support the very long-term positive outcomes of the 10 patients belonging to the first-in-human Reducer study recently reported by Parikh and colleagues [7].

While significant reduction in antianginal therapy was achieved at 1 year when compared to baseline [6], a trend of reduction was still present at 2-year compared to baseline evaluations, but was not significant. Although the burden of symptoms and quality of life remained improved after two years, few patients experienced worsening of angina related to CAD progression, requiring PCI. This finding might explain the mild increase of number of antianginal medications observed at 2-year follow up as compared to 1-year.

The substantial rate of angina-driven revascularization observed within the 2 years from Reducer implantation is not surprising: the diagnosis of “refractory” angina, labeling CAD as “not amenable to further revascularization”, is based on a single-point evaluation [8], rather than considering the dynamic and progressive nature of atherosclerotic disease [12,13]. The observed PCI rate is comparable to that of refractory angina patients not treated with Reducer [13]. Indeed, by acting from within the coronary venous system, the anti-ischemic effect of Reducer scaffold is not bound to a concomitant effect on CAD progression.

This observation has also important clinical implications, suggesting that physicians should consider patients with refractory angina for further evaluation and revascularization when needed, in case of recurrence or worsening of symptoms [13].

In conclusion, CS Reducer is safe and effective over the two-year follow-up. These findings further support consideration of Reducer as a therapeutic option to be considered in a population with limited therapeutic options. Further studies assessing the device safety at the long term, will further support the wider device application in this steadily increasing patient population.

Declaration of Competing Interest

F. Giannini is consultant for Neovasc Inc. All other authors report no relationships that could be construed as a conflict of interest.

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